REMISSION OF ESSENTIAL HYPERTENSION AFTER RENAL TRANSPLANTATION

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with comments by
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Abstract Six patients in whom "essential hypertension" led to nephrosclerosis and kidney failure received kidney transplants from normotensive donors. After an average follow-up of 4.5 years, all were normotensive and had evidence of reversal of hypertensive damage to the heart and retinal vessels. These six patients, all of whom were black, and six control subjects matched for age, sex, and race were admitted to the General Clinical Research Center for 11 days for observation of their blood pressure and their responses to salt deprivation and salt loading. Mean arterial pressure (± S.E.M.) among the patients who had previously had essential hypertension was similar to that of the normal controls (92±1.9 vs. 94±3.9; P not significant), and both groups had similar responses to salt deprivation and salt loading. Thus, essential hypertension in human beings is shown to be similar to the hypertension seen in spontaneously hypertensive rats in that both can be corrected by transplantation of a kidney from a normotensive donor. This observation supports the concept of the primacy of the kidney in causing essential hypertension. (N Engl J Med 1983; 309:1009–1015.)

Essential hypertension has a high prevalence among blacks,1 appears to have a genetic basis,2 and by definition, has no known cause. However, both Guyton3 and Bianchi et al.4 have suggested that the kidney is primarily at fault in essential hypertension. Essential hypertension tends to cause kidney damage (nephrosclerosis) more frequently among blacks than whites5 and may be responsible for the disproportionate numbers of blacks who have end-stage renal disease.6

Support has been lent to the theory of the primacy of the kidney in the pathogenesis of essential hypertension by the confirmed observation7,8 that spontaneously hypertensive rats will become normotensive after removal of their native kidneys and transplantation with a kidney from a normotensive rat. The purpose of the current report is to demonstrate that this phenomenon also occurs in human beings; thus, black patients with essential hypertension associated with nephrosclerosis and eventual renal failure can become and remain normotensive when they receive an immunologically well-tolerated kidney allograft from a normotensive donor.

Methods

Six patients were selected from our transplant clinic for detailed study in our General Clinical Research Center because there was good evidence that essential hypertension leading to nephrosclerosis was the cause of their renal failure. All six had their native kidneys removed before transplantation, and renal histology and tissue blocks were available for study. All patients subsequently received a renal transplant from a normotensive living related donor (two patients) or a cadaveric donor (four patients) that provided good long-term renal function, and eventually all became normotensive without antihypertensive medications.

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AUTHORS’ COMMENTARY


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During the 1970s, John Curtis and I were involved in studying mechanisms of hypertension in our post–renal transplantation patients at the University of Kentucky Medical Center. The population was predominantly Caucasian. At least 1 year after successful renal transplantation from a live related donor, patients who were receiving alternate-day steroids and who had a serum creatinine of <2 mg/dl and a bilateral nephrectomy had a prevalence of hypertension of only 6%, i.e., less than in the normal population. Thus, we were able to show that a well-tolerated transplanted kidney could sustain normotension (1). For all patients, prevalence of hypertension was approximately 50% and the causes of hypertension were—in order of importance—chronic rejection, the native kidneys (renin-dependent hypertension), allograft renal artery stenosis, and steroid therapy.

We were aware of Guyton’s work (2) suggesting the primacy of the kidney in causing essential hypertension via extracellular fluid volume expansion as the major mechanism for essential hypertension. Alternatively, one could restate the hypothesis that chronic hypertension would not be maintained in the presence of normal renal function and especially of normal excretion of sodium chloride. During
The four cadaveric donors were young (mean ± S.E.M., 28 ± 4 years), white, and normotensive. All four had had traumatic deaths. All six patients were black, four were men, and the group’s mean age was 40 ± 2 years. At the time of their studies at the clinical research center the patients were receiving azathioprine (125 ± 22 mg per day) and prednisone (16 ± 1 mg per day) and had been followed for an average of 4.5 ± 1.0 years (range, 1.3 to 8.0) after receiving a renal transplant.

In an effort to establish more accurately the timing of the onset of hypertension and the cause of the patients’ renal failure, all available records of previous hospital stays and emergency room and doctor’s office visits before transplantation at University Hospital were obtained and reviewed. The clinical histories of these six patients that led to the diagnosis of essential hypertension and nephrosclerosis are given in the Appendix. Important historical features and results of investigations that were consistent with the diagnosis of essential hypertension along with those of blood-pressure and renal-function studies the first time both were obtained simultaneously are shown in Table 1. All University Hospital admission records were also reviewed for the six patients, and chest x-ray films, electrocardiograms, funduscopic examination notes, and blood-pressure recordings from admissions before transplantation were reviewed.

Histologic studies of the native kidneys of the six patients were reviewed by one of us (M.K.) to confirm the diagnosis of nephrosclerosis that had been made by surgical pathologists at the time of nephrectomy. In all cases neither the light-microscopical nor the ultramicroscopical studies revealed evidence of primary renal disease other than nephrosclerosis, and all the findings were consistent with nephrosclerosis as a primary cause of renal failure (Fig. 1). The anatomic criteria for the pathological diagnosis of nephrosclerosis included generalized interstitial scarring that was accompanied by tubular loss or atrophy. The scarring was irregular, with focal large scars interspersed against a background of more diffuse scarring. The residual nephrons showed a spectrum of changes, ranging from hypertrophy to varying degrees of ischemic changes and sclerosis. The hypertrophied but otherwise normal glomeruli were associated with hyperplastic tubules, whereas sclerotic

Table 1. Clinical Characteristics and Results of Blood-Pressure and Renal-Function Studies the First Time Both Were Obtained Simultaneously in the Six Black Patients with a Family History of Hypertension (See Appendix).*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Blood Pressure</th>
<th>Serum BUN/Creatinine</th>
<th>Urinary Protein</th>
<th>No. of Years Before ESRO Therapy</th>
<th>ESRO end-stage renal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>M</td>
<td>240/170</td>
<td>13/1.3</td>
<td>100 mg/24 hr</td>
<td>4</td>
<td>100 mg/24 hr</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>F</td>
<td>180/130</td>
<td>23/1.7</td>
<td>Negative by dipstick</td>
<td>1.5</td>
<td>100 mg/24 hr</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>M</td>
<td>150/100</td>
<td>12/1.0</td>
<td>Negative by dipstick</td>
<td>5</td>
<td>100 mg/24 hr</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>F</td>
<td>185/120</td>
<td>35/1</td>
<td>Negative by dipstick</td>
<td>2</td>
<td>100 mg/24 hr</td>
</tr>
<tr>
<td>5</td>
<td>38</td>
<td>F</td>
<td>150/100</td>
<td>100.4</td>
<td>360 mg/24 hr</td>
<td>2</td>
<td>100 mg/24 hr</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>M</td>
<td>500/160 (during pregnancy)</td>
<td>Negative by dipstick</td>
<td>2</td>
<td>2</td>
<td>100 mg/24 hr</td>
</tr>
</tbody>
</table>

*BUN denotes blood urea nitrogen level, and ESRO end-stage renal disease. *Creatinine not measured.

Figure 1. Photomicrograph of the Nephrectomy Specimen from a Patient Typical of Those Considered to Have Nephrosclerosis.

The interlobular artery shows marked fibrous thickening of the intima, with narrowing of the lumen. Arterioles show hyaline change of the walls, and a portion of a sclerotic glomerulus is also seen. A hypertrophied residual nephron is present. Interstitial infiltrate is minimal. (Hematoxylin and eosin; original magnification, ×100).

his nephrology fellowship, Dr. Curtis had spent some time with Dr. Kincaid-Smith. She is opposed to the concept that nonmalignant essential hypertension leads to hypertensive nephrosclerosis and end-stage renal disease [ESRD] and believed that a primary renal disease was much more common and much more likely; this view was based mainly on a histologic approach. In the Renal Division at the University of Kentucky Medical Center, we had weekly renal rounds that were lively and controversial and were termed “rollerball” by the residents and fellows. We were fortunate to have in the division an excellent endocrinologist with a major interest in hypertension, Dr. Ted Kotchen. He was reluctant to accept the primacy of the kidney-causing essential hypertension! We were also very interested in recurrent renal disease after transplantation and noted that systemic diseases such as a connective tissue disorder or diabetes mellitus were not “cured” by successful renal transplantation. If essential hypertension was a systemic disease that secondarily involved the kidney, then a well-tolerated allograft would not cure that disease. In contrast, if essential hypertension was due to a renal abnormality that led to hypertension, hypertensive nephrosclerosis, and end-stage kidney disease, then transplantation of a kidney that did not cause hypertension could be associated with “cure” of hypertension. We were thus challenged to find patients whose original cause for progressive renal disease was essential hypertension and whose hypertension was cured by transplantation of a normal kidney. We could not prove this sequence in Kentucky.

We were able to support this hypothesis strongly after we moved to the University of Alabama at Birmingham and began working there in Dr. Arnold Diethem’s very successful and active renal transplant program. Dr. Curtis and I had never seen so many young African American patients with what clearly seemed to be essential hypertension with various stages of progression of hypertensive nephrosclerosis. Indeed, more African American patients with ESRD have received renal transplants at that medical center than anywhere else in the world. As is often the case in clinical research, we required a unique alignment of the stars in the firmament to prove the hypothesis. In addition to the large number of African American patients with well-documented essential hypertension, many of these patients had bilateral nephrectomy before transplantation. Cyclosporine was not yet in routine use; had it been, we might not have been able to carry out this study successfully because of the high prevalence of cyclosporine-induced hypertension when this agent is used after transplantation. Dr. Harriet Dustin, the famous cardiologist, was setting up a hypertension center at about this time. Dr. Curtis composed a protocol for the GCRC. Dr. Dustin’s pithy review stated that "Dr. Curtis thinks about hypertension like a nephrologist.” We are uncertain whether she meant this as a compliment or not! Nevertheless, Dr. Dustin enthusiastically engaged in our research, and we used her protocol to compare the response of the easily found and documented normotensive transplant patients (who had previously had essential hypertension and hypertensive nephrosclerosis) to handle sodium restriction and loading as compared with normal control subjects. The final link in our studies was the availability of histology on the removed native kidneys and of a superb nephropathologist to prove that these kidneys on detailed histologic study did not have a primary renal disease. Dr. Michael Kashgarian at Yale ably filled this role.
Our study patients had an average mean arterial pressure of 168±9 mm Hg recorded during their first University Hospital admission before renal transplantation, at a time when each was receiving at least four different antihypertensive medications. Mean arterial pressure on Day 1 of the General Clinical Research Center admission (4.5 years after transplantation) was 92±1.9 mm Hg (P<.001), and none of the patients was receiving antihypertensive therapy. This mean arterial pressure was not different from that of the control subjects (94±3.9 mm Hg). Both groups had normal blood-pressure recordings throughout the research-center admission, even after the three days of intravenous sodium loading (94 mmol of sodium for 24 hours) and at least three glomeruli were examined by electron microscopy. No evidence of glomerular damage, other than that attributable to ischemia, was found in any of the patients.

Six age-matched (40±0.5 years) and sex-matched (four men and two women), black, healthy control subjects volunteered to be admitted to the clinical research center for control studies of renal responses to salt deprivation and salt loading. All six control subjects had normal physical examinations and were taking no medications. The patients and controls gave written informed consent for the 11-day admission to the center. The purposes of this admission were to monitor blood pressure over a prolonged period and to compare the responses to high, normal, and low sodium intakes in patients who had received transplants with those in matched normal subjects. The patients and controls were placed sequentially on diets containing 150 mmol of sodium for three days (normal sodium), 9 mmol of sodium for four days (low sodium), and 9 mmol of dietary sodium plus infusions of 3.6 mmol of intravenous sodium per kilogram of body weight for three days (high sodium).

At the end of each salt-intake period the following investigations were performed: plasma renin activity was measured by radioimmunoassay in the supine position and after a 30º head-up tilt; plasma aldosterone, norepinephrine, and epinephrine levels were measured in the supine position and after a 30º head-up tilt, using a radioenzymatic assay; body weight was measured; plasma volume was measured from the volume of distribution of human serum albumin, using 2.5 µCi of 125I-labeled human serum albumin and a 10-minute equilibrium period; 24-hour creatinine clearance and urinary sodium excretion were measured daily. Mean arterial pressure was calculated daily from the diastolic blood pressure plus one third of the pulse pressure obtained from the blood-pressure measurements in the supine position. All patients also had electrocardiography and chest radiography performed during their stay in the research center. Clinical records were reviewed for three blood-pressure measurements (immediately before dialysis) of patients one month after nephrectomy while the patients were undergoing long-term hemodialysis therapy. The average of these three measurements was used as the anephric blood pressure. As noted in the Appendix, our six study patients all had their native kidneys removed shortly after nephrectomy; dialysis was used to control vascular volume and hypertension during this period.

Statistical analysis was performed by means of the paired or unpaired Student’s t-test, as appropriate. A P value of less than 0.05 was considered significant.

RESULTS

The table patients had an average mean arterial pressure of 168±9 mm Hg recorded during their first University Hospital admission before renal transplantation, at a time when each was receiving at least four different antihypertensive medications. Mean arterial pressure on Day 1 of the General Clinical Research Center admission (4.5 years after transplantation) was 92±1.9 mm Hg (P<.001), and none of the patients was receiving antihypertensive therapy. This mean arterial pressure was not different from that of the control subjects (94±3.9 mm Hg). Both groups had normal blood-pressure recordings throughout the research-center admission, even after the three days of intravenous sodium loading (patients, 94±3.0 mm Hg, and controls, 94±6.1).

Comparison of electrocardiograms and chest x-ray films obtained before and after transplantation showed significant resolution of cardiac hypertrophy (Table 2). Medical records...
minute as compared with 113 epinephrine values were not altered by sodium intake and were there were no significant differences between groups. Plasma restriction and loading and to the tilt procedure as expected, and low-sodium diet (Table 3). Both groups responded to sodium after a 30º head-up tilt while the subjects were receiving the epinephrine levels during the different sodium-intake periods and periods, as did plasma renin activity and aldosterone and norepinephrine and natriuresis relationship, will in the long run override all extrarenal BP and volume-regulating mechanisms. It follows that irrespective of the primary disturbance leading to hypertension, BP cannot increase unless the renal BP natriuresis relationship is altered. The primary defect in essential hypertension has not been clarified, but according to Guyton, functional or structural (3) abnormalities of the kidney must play a central role.

This idea gained further momentum when transplantation experiments in animals showed that BP “goes with the kidney” (4,5). These experiments are technically very demanding, because the outcome is easily confounded by arterial or ureteral stenosis, ischemia reperfusion injury, or immune damage to the graft. The most convincing evidence had come from the study of Rettig et al. (6), who transplanted kidneys of spontaneously hypertensive rats (SHR) into hybrid recipients that were unable to mount a rejection against the graft. In the recipients, the central and peripheral nervous system, the volume-regulatory systems, the heart, and the vascular system all were genetically programmed for normotension.

Nevertheless, the presence of a kidney that was genetically programmed for hypertension was able to override all control systems and impose hypertension on an originally normotensive recipient. These results are particularly impressive, because, at least in later studies, hypertension-induced damage of the graft had been carefully avoided by antihypertensive treatment of the prehypertensive donor animals starting from weaning. It proved more difficult to show that transplantation of a graft derived from a normotensive donor rat is able to lower BP in a hypertensive rat, but, ultimately, this also has been documented (7).
similar for both groups (40.0±1.6 vs. 24.3±5.5 pg per milliliter; P not significant). Both groups also responded to the tilt procedure with similar increases in plasma epinephrine levels (+16.5±5.6 vs. +16.8±7.8 pg per milliliter; P not significant).

**Discussion**

We have described six patients who had strong clinical and histologic evidence of essential hypertension and nephrosclerosis as a cause of end-stage renal disease, along with evidence of other end-organ damage from the hypertension. One to eight years after successful transplantation, all had blood-pressure measurements that, despite prednisone therapy, were not different from those of six normotensive subjects. Moreover, all had evidence of reversal of end-organ damage. We believe that these observations support Guyton’s and Bianchi’s contention that, at least in some patients, the kidney is primarily at fault in essential hypertension.3,4

We and others13–15 have previously reported the dramatic reversal of hypertension that occurs in some patients with end-stage renal disease after successful renal transplantation. However, there was no documentation in these reports that the patient’s original disease was essential hypertension and nephrosclerosis. Nephrosclerosis is a diagnosis that is not easily documented.16 Since hypertension develops in most patients with other forms of primary renal disease (so-called secondary hypertension) and since most nephrologists do not perform renal biopsies in patients in whom they suspect nephrosclerosis, it is difficult to prove that some other occult primary renal disease was not the true cause of both the hypertension and renal failure. Our six patients were selected because all had histologic examinations of their native kidneys and strong clinical histories to support the diagnosis of nephrosclerosis and to rule out other causes of renal failure. Only black patients whose age at onset of hypertension was characteristic of that for essential hypertension were selected. Moreover, all were documented to have low levels of urinary protein excretion that were consistent with essential hypertension, and most were observed to have hypertension at a time when renal function, at least as judged by levels of blood urea nitrogen and creatinine, was normal. In each instance there was a family history of hypertension, and all physicians who managed their cases believed that—compared with normal controls—graft recipients had similar responses to salt deprivation and salt loading. Curtis et al. had remained appropriately cautious as to the exact cause, i.e., whether the primary defect is intrinsic to the kidney or the result of faulty interaction of the kidney with extrarenal signals, e.g., hypothalamic natriuretic substances.

The general conclusion of Curtis et al. that renal functional abnormalities must play a role in the genesis of essential hypertension is in line with some studies that documented abnormalities of renal hemodynamics in “prehypertensive” individuals, i.e. offspring of hypertensive parents who had not (yet) developed hypertension (14,15). Unfortunately, these studies differ in important details, so their interpretation is difficult.

| Table 3. Plasma Renin Activity, Aldosterone and Norpinephrine Levels, and Volume Measured in Six Patients and Six Controls during Periods of Three Different Levels of Sodium Intake and after a 30° Head-up Tilt. |

<table>
<thead>
<tr>
<th>INDEX</th>
<th>NORMAL</th>
<th>HIGH</th>
<th>LOW</th>
<th>LOW, WITH HEAD-UP TILT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma renin activity (ng/ml)</td>
<td>0.3±0.2</td>
<td>0.1±0.09</td>
<td>2.9±3.3</td>
<td>3.0±1.1</td>
</tr>
<tr>
<td>Controls</td>
<td>0.4±0.2</td>
<td>0.1±0.04</td>
<td>2.7±1.3</td>
<td>3.5±1.6</td>
</tr>
<tr>
<td>Plasma aldosterone (pg/ml)</td>
<td>82±6</td>
<td>61±17</td>
<td>461±84</td>
<td>572±86</td>
</tr>
<tr>
<td>Patients</td>
<td>84±27</td>
<td>85±17</td>
<td>433±75</td>
<td>511±56</td>
</tr>
<tr>
<td>Plasma norpinephrine (pg/ml)</td>
<td>202±24</td>
<td>236±29</td>
<td>447±125</td>
<td>629±105</td>
</tr>
<tr>
<td>Control</td>
<td>275±56</td>
<td>232±51</td>
<td>381±46</td>
<td>537±40</td>
</tr>
<tr>
<td>Plasma volume (liters/m²)</td>
<td>1.5±0.06</td>
<td>1.7±0.09</td>
<td>1.3±0.06</td>
<td>1.3±0.06</td>
</tr>
<tr>
<td>Patients</td>
<td>1.4±0.08</td>
<td>1.7±0.1</td>
<td>1.3±0.06</td>
<td>1.3±0.06</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

that in humans, “BP goes with the kidney” as well. This observation was different from attempts to show that recipients of grafts from donors with presumed hypertension (8) or from donors coming from families with known essential hypertension (9) caused more severe hypertension in the recipient. These early observations were not simple and clearcut; they were confounded by variable renal function and use of antihypertensive agents in the recipients. Although persuasive, they failed to provide the definitive evidence.

Curtis et al. took the opposite, more straightforward approach of looking at whether transplantation of a kidney coming from a normotensive donor caused normotension in a genetically hypertensive graft recipient. The authors very carefully ensured (to the extent that this is possible in the absence of a diagnostic marker of essential hypertension) that the recipients had essential hypertension and failed to have primary renal disease. The recipients’ own kidneys were subjected to careful histologic analysis, which failed to show anything but nonspecific nephrosclerosis.

The study of Curtis was carried out in the nick of time, because after the early 80s, BP in graft recipients is usually elevated to some extent because of the use of calcineurin inhibitors, which cause hypertension even in recipients of nonrenal grafts (10). However, the use of a kidney graft is not as clearcut a model as one would like to have it. Denervation of the graft is a potential confounder. Experimental (11) and clinical (12) studies showed that in the damaged kidney, activation of chemoreceptors and/or mechanoreceptors generates stimulatory signals that activate the hypothalamus and increase effenter sympathetic traffic. The potential role of renal nerves on the development of hypertension has been shown in elegant denervation experiments in models of hypertension that do not involve renoparenchymal damage (13).

Against the background of Guyton’s hypothesis (1), Curtis et al. went to great lengths to show that handling of salt and volume loads was normal in the recipients of the normotensive grafts. They provided convincing evidence that—compared with normal controls—graft recipients had similar responses to salt deprivation and salt loading. Curtis et al. had remained appropriately cautious as to the exact cause, i.e., whether the primary defect is intrinsic to the kidney or the result of faulty interaction of the kidney with extrarenal signals, e.g., hypothalamic natriuretic substances.

The general conclusion of Curtis et al. that renal functional abnormalities must play a role in the genesis of essential hypertension is in line with some studies that documented abnormalities of renal hemodynamics in “prehypertensive” individuals, i.e. offspring of hypertensive parents who had not (yet) developed hypertension (14,15). Unfortunately, these studies differ in important details, so their interpretation is difficult.

There is another aspect to the observation of Curtis et al. that deserves comment. The idea has been advanced that once hypertension has been sufficiently severe and has been present for a prolonged time, vascular remodeling will raise peripheral vascular resistance and maintain elevated BP, providing an element of self-perpetuating hypertension (16). The observation of Curtis et al. is encouraging in this respect by showing that, at least in the long run and in relatively young individuals, such vascular adaptations are functionally reversible.
of nephrosclerosis was less certain. One patient was a white
woman, 38 years of age, with clinical and histologic evidence
of essential hypertension; she was excluded for epidemiologic
reasons. The other two were black men with strong clinical
histories who were thought by our surgical pathologists to have
nephrosclerosis; however, one of us (M.K.), in reviewing their
renal histologic studies, believed that some form of occult, pri-
mary, interstitial renal disease could not absolutely be exclud-
ated, since a diffuse infiltrate of lymphocytes was present.

Thus, this study provides no estimate of the fraction of
patients with essential hypertension and nephrosclerosis who
become normotensive after renal transplantation. Although we
attempted to select for our study only black patients with
strong clinical histories of nephrosclerosis who had renal tis-

eue available for study and excellent allograft function, this
does not necessarily mean that the diagnosis of nephroscle-
rosis in our other patients was wrong. We have been following
360 patients in our renal-transplant clinic, and 81 of these (22
per cent) were said to have nephrosclerosis as their original
disease. Of these 81 patients, 33 had been followed at this writ-

ing for at least one year after transplantation, had had their
native kidneys removed, and had well-functioning allografts
(serum creatinine < 2.0 mg per deciliter [180 μmol per liter]).
Of these 33 patients with the clinical diagnosis of nephroscle-
rosis, 8 (24 per cent) still required antihypertensive medica-
tions, and the other 25 (76 per cent) were normotensive. This
is the same percentage (24 per cent) of hypertensive patients
that we observed previously15 in a group of transplant recipi-
ents with primary renal disease, although the groups are not
directly comparable. Although the clinical diagnosis of
nephrosclerosis in this group of 33 may not be as certain as in
our six study patients, they do provide an estimate of the per-
centage of such patients who become normotensive after suc-

cessful transplantation.

The observation that a number of patients with nephroscle-
rosis remain hypertensive after transplantation would not in-
validate this report, since it has been well documented that
even in the unusual patients who never had hypertension
before transplantation, hypertension may develop after trans-
plantation.15 The causes of such post-transplant hypertension
include chronic rejection of the allograft,17 stenosis of the
transplanted renal artery,18 steroid therapy,19 and the presence
of native, diseased kidneys.20 Reports of the likelihood that
hypertension will develop after transplantation suggest no cor-
relation with the original kidney disease.21–23 Thus, only the
finding of normal blood pressure in patients in whom end-
stage renal disease developed because of nephrosclerosis is
useful in support of Guyton’s hypothesis; the finding of hyperten-
sion would neither support nor detract from the proposition.

Bright was the first to suggest that the kidney was the organ
primarily responsible for causing damage to other organs
through a mechanism about which he hesitated to speculate.24
At the time neither the concept of measuring blood pressure
nor the means to do so were available. Forty-five years later,
Mahomed described “chronic Bright’s disease without albu-
minuria.”25 In 1911 Frank coined the term “essential hyperten-
sion” to describe the condition of similar patients.26 Since no
obvious renal disease (albuminuria) was seen in these patients,
Bright’s suggestion that the kidney was the organ primarily
responsible for causing damage to the others was given less
weight, and many saw the kidney as just another “end organ”
that was being damaged by the hypertension. A recent study by
Feld et al.27 in which medical treatment was used to prevent
the development of hypertension in spontaneously hypertensive

What are the implications for hypertension in renal dis-

case? Although numerous studies in essential hypertension
document abnormalities in the function of the CNS, the activ-
ity of the sympathetic and parasympathetic autonomous nerve
system, or the function of volume control, the study of Curtis
et al. proves that the kidney is both necessary and sufficient to
cause hypertension or normotension, respectively. If the kid-
ney is indispensable for the development of essential hyper-
tension in individuals without intrinsic renal disease, then it is
less surprising that hypertension is such an early (17) and
constant feature in patients with primary renal disease.

What is the general relevance of the observation of Curtis
today? One of the most important functions of the clinical
investigator is to provide robust data based on which he can
formulate plausible working hypotheses on potential patho-
mechanisms. Although the observation of Curtis did not
directly identify a smoking gun, it identified faulty renal
mechanisms as a necessary step in the genesis of essential
hypertension. This allows one to propose, for instance, one
realizable testable working hypothesis, i.e., that the epithe-

ilial sodium channel malfunction may be involved in the gen-
essis of essential hypertension. In this context, it is of inter-
est that all monogenic forms of hypertension identified so
far concern renal tubular sodium transport. In this perspec-
tive, the study of Curtis et al. is an illustration of the more
general principle of how medical progress is achieved. The
facts must be firmly established by careful observations and

testable working hypotheses must be formulated, and these
in turn must be subjected to falsification (or lack thereof) by
appropriate experiments—a scientific strategy brilliantly
outlined by the late philosopher Karl Popper (1902–1994).

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rats demonstrated that, despite control of blood pressure, renal lesions eventually developed in such rats that were identical to those that developed in spontaneously hypertensive rats that were allowed to become hypertensive. The authors concluded that hypertension was not the cause of the renal lesions, but rather that they were due to a genetic defect in the vessels of the rats’ kidneys.

The present study also suggests that, at least in this subgroup of patients with essential hypertension, the primary defect must lie within the kidney or must involve some pathophysiologic relation between another organ, a humoral agent, or the sympathetic nervous system and the patient’s kidneys that does not exist with the transplanted kidney. Of course, our findings are limited, in that the longest patient follow-up has only been for eight years. It is possible that the pathogenetic mechanisms of essential hypertension are not found solely in the kidney, but require longer periods of follow-up to become evident again. However, these findings strongly support the need for a continuing search for early abnormalities of renal function or structure or both in essential hypertension.

**APPENDIX**

**Case 1**

The patient, a 39-year-old black man, was first told he had hypertension in 1971 but was not treated at that time. He had severe morning headaches beginning in 1972 and was admitted to University Hospital with a blood pressure of 240/170 mm Hg. After blood-pressure control, his hospital evaluation included chest radiography and angiography, the results of which suggested left ventricular hypertrophy. Funduscopic examination demonstrated the presence of arteriolar venous nicking, arteriolar narrowing, hemorrhages, and exudates but no papilledema. Urinalysis revealed that the urine had a specific gravity of 1.030 and was otherwise normal. The 24-hour urinary excretion of protein was 100 mg. The blood urea nitrogen level was 13 mg per deciliter (4.6 mmol per liter), and the creatinine 1.3 mg per deciliter (110 μmol per liter). Creatinine clearance was 90 mL per minute. The intravascular pyelograft and renal arteriogram were normal, as were the serum potassium level and the results of urine tests for malperinephrine. There was a family history of hypertension that included a father who had died at age 38 from “severe hypertension.” The patient’s mother was taking antihypertensive medications. The patient’s father died at the age of 35 (cause unknown), and his mother, who was hypertensive, died at 68. He began receiving long-term dialysis in 1975, two years after his first admission for hypertension. His native kidneys were removed because of hypertension. His blood pressure was much more easily managed after nephrectomy; mean arterial pressure was 75/50 mm Hg while the patient was undergoing long-term dialysis. In 1977 he received a cadaver renal transplant and did well. Five years after transplantation he was admitted to the clinical research center for studies. His blood pressure was 115/80 (mean arterial pressure, 91.7 mm Hg) without antihypertensive medications.

**Case 2**

The patient was a 44-year-old black man who was in apparent good health until 1973, when he became short of breath and entered a local hospital. He was found to have a blood pressure of 180/150 mm Hg. Clinical signs of congestive heart failure were present, and chest x-ray films and an electrocardiogram demonstrated the presence of left ventricular hypertrophy. The patient’s blood pressure was controlled, and his congestive heart failure improved. His hematocrit was 44 percent, his serum potassium was 4.4 mmol per liter, serum calcium 9 mg per deciliter (2.25 mmol per liter), and serum phosphorus 4.5 mg per deciliter (1.5 mmol per liter). The urine was normal (protein by dipstick), and serum albumin was 4 g per deciliter (580 μmol per liter). The blood urea nitrogen level was 23 mg per deciliter (8.2 mmol per liter), and the serum creatinine level was 1.7 mg per deciliter (150 μmol per liter). Hypertensive intravenous pyelography was performed with normal results. The patient was discharged and was followed by the clinic, but he did not return until one year later (1974), when he had nausea and vomiting and returned to the same hospital. At that time his blood pressure was 160/120, the blood urea nitrogen level was 70 mg per deciliter (25 mmol per liter), and the creatinine level was 12 mg per deciliter (106 μmol per liter). The 24-hour urinary excretion of protein was 600 mg. With blood-pressure control, renal function did not improve, and the patient was transferred to University Hospital for dialysis therapy. He had 11 siblings, 8 of whom were hypertensive and receiving medical therapy. His father died at the age of 35 (cause unknown), and his mother, who was hypertensive, died at 68. He began receiving long-term dialysis in 1975, two years after his first admission for hypertension. His native kidneys were removed because of hypertension. His blood pressure was much more easily managed after nephrectomy; mean arterial pressure was 76/55 mm Hg while the patient was undergoing long-term dialysis. In 1977 he received a cadaver renal transplant and did well. Five years after transplantation he was admitted to the clinical research center for studies. His blood pressure was 115/80 (mean arterial pressure, 91.7 mm Hg) without antihypertensive medications.

**Case 3**

The patient was a 38-year-old black woman who first noted to have hypertension during her fourth pregnancy in 1974. She required antihypertensive therapy during the pregnancy, which terminated in a stillbirth. Her physician directed her to take antihypertensive medications when she left the hospital. No record of renal-function tests during this hospitalization are available.

The patient reported that she did not take the prescribed antihypertensive medications, and one year later (1975) she saw another physician who noted that her blood pressure was 150/100 mm Hg. On that office visit she had a normal urinalysis, a blood urea nitrogen level of 12 mg per deciliter (4.3 mmol per liter), and a creatinine level of 1.0 mg per deciliter (88 μmol per liter). She again received prescriptions for antihypertensive medications, but she did not take the medications.

Five years later (1980), the patient had nausea and vomiting and was hospitalized in Selma, Alabama. She was found again to have hypertension and renal failure and was transferred to Montgomery, Alabama, for dialysis therapy. Several months later, she was referred to University Hospital for a bilateral excision of her native kidneys because her blood pressure was being poorly controlled with dialysis. She was also evaluated for a possible renal transplant on that admission. Her blood pressure on admission was 230/110 mm Hg; funduscopic examination revealed the presence of arteriolar venous nicking and copper-wire changes. An electrocardiogram and chest x-ray films demonstrated the presence of left ventricular hypertrophy. The urine was without abnormal protein, and 24-hour urinary excretion of protein was less than 100 mg. The patient’s father had been hypertensive and died at age 40 of a cerebral
vascular accident. Her mother was hypertensive and receiving therapy as well. She was told she had hypertension in 1966 during a physical examination for the armed forces. She did not receive therapy for her hypertension until 1976, when she was seen at a local emergency room for a laceration on her arm and was again found to be hypertensive. For six months his blood pressure was controlled with antihypertensive medications, but headaches developed and he was seen at a local emergency room with a blood pressure of 188/120 mm Hg. He was admitted to that hospital and found to have left ventricular hypertrophy by chest radiography and electrocardiogram; arteriolar narrowing and exudates were seen on funduscopic examinations. His serum potassium level was 4 mmol per liter, his blood urea nitrogen level was 35 mg per deciliter (15 mmol per liter), and a creatinine level of 19 mg per deciliter (1.7 mol per liter) exceeding the normal value of 14 mg per deciliter (1.2 mol per liter). After the transplantation, he was seen in consultation by members of the nephrology service. He stated that his long-standing hypertension and renal arteriography, the results of which was normal. The blood urea nitrogen level was 39 mg per deciliter (14 mmol per liter), and the patient was seen in consultation by members of the nephrology service, who thought his longstanding hypertension, low level of proteinuria, and normal-size kidneys were consistent with nephrosclerosis and recommended that he undergo renal biopsy. The patient’s mother and father were both hypertensive and required medication. One sister (age 30) was also taking antihypertensive medications and a brother (age 25) had been told he was hypertensive and given prescriptions for medications.

The patient’s antihypertensive medications were adjusted at Vanderbilt, and he was discharged in 1976 with a diagnosis of essential hypertension, to be followed by his local physician. In 1978 he saw his physician again, admitted he had not taken his medications, and was noted to have a blood urea nitrogen level of 129 mg per deciliter (46.3 mmol per liter) and a creatinine level of 19 mg per deciliter (1700 μmol per liter). His blood pressure was 200/130 mm Hg, and he was started on hemodialysis therapy. A bilateral nephrectomy was performed because the blood pressure could not be adequately controlled on dialysis. One month after nephrectomy, blood-pressure control was improved. Mean arterial pressure was 113 ± 3 mm Hg on long-term dialysis. One year later (1979), the patient received a cadaver renal transplant and did well. Three years later he was admitted to the clinical research center for studies. His blood pressure was 125/80 mm Hg (mean arterial pressure, 95 mm Hg) without antihypertensive medications.

Case 4

The patient was a 33-year-old black man who was first told he had hypertension in 1966. Despite antihypertensive therapy, blood pressure was 138/80 mm Hg. Despite her bilateral nephrectomy, the patient’s blood pressure proved difficult to control with long-term dialysis. One month after nephrectomy, the mean arterial pressure was 138 ± 4 mm Hg, despite therapy with propranolol (120 mg four times daily), hydralazine (50 mg three times daily), and dialysis.

In October 1980, a renal-transplant operation was performed with a kidney from the patient’s 31-year-old sister. The graft functioned well, and dialysis was not required. Eight months later, the patient was admitted to the clinical research center for studies; her blood pressure at that time was 125/75 mm Hg (mean arterial pressure, 91.7 mm Hg) without antihypertensive medications.

Case 5

The patient was a 45-year-old black woman who was first told she had hypertension in 1965 but was not given antihypertensive therapy at that time. Records of her sixth pregnancy were not available, but she was said to have become hypertensive without edema and had a “stillbirth.” She was admitted to University Hospital in 1975 during her seventh pregnancy when she was noted to have a blood pressure of 150/100 mm Hg. She was referred to Vanderbilt University Hospital for evaluation of the cause of his hypertension. At Vanderbilt, he underwent intravenous pyelography and renal arteriography, the results of which was normal. Urinalysis revealed trace protein, and the 24-hour urinary protein excretion was 500 mg. The 24-hour urinary excretion of catecholamines was also normal. The blood urea nitrogen level was 39 mg per deciliter (14 mmol per liter), and the patient was seen in consultation by members of the nephrology service, who thought his long-standing hypertension, low level of proteinuria, and normal-size kidneys were consistent with nephrosclerosis and recommended that he undergo renal biopsy. His blood pressure was 125/80 mm Hg (mean arterial pressure, 91.7 mm Hg) without antihypertensive medications. Despite therapy, the patient’s blood pressure proved difficult to control, and two months after the first onset of symptoms he was referred to University Hospital with a serum creatinine level of 30 mg per deciliter (2700 μmol per liter). The patient was treated with hemodialysis and required a bilateral nephrectomy for blood-pressure control one month after nephrectomy was performed and he was seen at a local emergency room for a laceration on his arm and was again found to be hypertensive. His blood pressure was 200/130 mm Hg, and he was started on hemodialysis therapy. A bilateral nephrectomy was performed because the blood pressure could not be adequately controlled on dialysis. One month after nephrectomy, blood-pressure control was improved. Mean arterial pressure was 113 ± 3 mm Hg on long-term dialysis. One year later (1979), the patient received a cadaver renal transplant and did well. Eight years later he was admitted to the clinical research center for studies with a blood pressure of 120/80 mm Hg (mean arterial pressure, 91.3 mm Hg) without antihypertensive medications.

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