Kidney International, Vol. 43 (1993), pp. 493–505

NEPHROLOGY FORUM

Renovascular disease in children

Principal discussant: JULIE R. INGELFINGER

Massachusetts General Hospital, Boston, Massachusetts

Case presentation

A 4-year-old girl with neurofibromatosis and a one-year history of hypertension was admitted for repeat renal arteriography and for renal vein renin determinations. Neurofibromatosis, manifested by café-au-lait spots, cutaneous neurofibromata, and neurolipomas, had been diagnosed at age 6 months during evaluation of a large head circumference without hydrocephalus. Physical examination and growth and development were otherwise normal. The family history was negative for neurofibromatosis and hypertension.

One year prior to admission, her blood pressure was 130–140/90 mm Hg during a routine checkup; she was asymptomatic at that time. Laboratory evaluation included normal urinalysis (specific gravity, 1.022; pH, 5.0; no albumin; no blood; no glucose; no ketones; and an unremarkable sediment). Urine culture showed no growth. Serum creatinine was 0.4 mg/dl; BUN, 12 mg/dl; sodium, 139 mEq/liter; potassium, 3.5 mEq/liter; chloride, 103 mEq/liter; carbon dioxide, 24 mmol/liter; calcium, 9.5 mg/dl; phosphate, 4.7 mg/dl; and blood sugar, 108 mg/dl. A radionuclide renal scan showed equal function bilaterally, and an ultrasound examination of her kidneys and suprarenal areas was normal. A "spot" VMA and plasma catecholamines also were normal; peripheral plasma renin activity was 4.0 ng/ml/hour. Renal arteriography revealed an ostial stenosis of the left renal artery. Renal vein renin levels were not obtained.

She was treated with a combination of hydralazine, nifedipine, and enalapril, but her blood pressure failed to return to normal. Accordingly, elective repair of the ostial stenosis was performed using a left end-to-side splenorenal artery shunt. Hypertension persisted despite the apparently satisfactory revascularization procedure. Blood pressure was controlled with a combination of enalapril, hydralazine, and nifedipine. Renal function and plasma catecholamines remained normal; a cerebral CT scan showed no hydrocephalus.

The patient was admitted to the hospital for further evaluation.

Presentation of this Forum is made possible by grants from Merck Sharp & Dohme International; Amgen, Incorporated; Dialysis Clinic, Incorporated; Parke-Davis, Incorporated; Marion Merrell Dow, Incorporated; and Sandoz, Incorporated.

Discussion

DR. JULIE R. INGELFINGER (*Co-Director, Pediatric Nephrology Unit, Massachusetts General Hospital, and Associate Professor of Pediatrics, Harvard Medical School, Boston, Massachusetts*): Primary hypertension is diagnosed in children more and more frequently now that blood pressure norms are available even for newborns. However, severe hypertension in a very young child, such as the little girl described here, is still much more likely to be due to a definable cause of hypertension than to represent so-called primary hypertension [1]. In the overall pediatric population [2], renal and renovascular diseases account for close to 90% of definable hypertension in the first years of life; the percentage actually might be even higher. For the current discussion, I will first focus on renovascular disease in early childhood and present the current knowledge about its cause, evaluation, and therapy. I will focus on the vascular changes that produce hypertension and will concentrate less on changes that result from elevated blood pressure. I then will discuss the development of the renal vasculature and factors that might be important in its normal growth and remodeling. Finally, I will consider briefly the specific abnormalities in the renal artery vasculature in patients with neurofibromatosis.

Etiology

A variety of diseases can lead to renal and renovascular hypertension, although only a few arterial lesions are common in children. In the late 1960s and early 1970s, McCormack and colleagues developed a classification based on the layer of the vascular wall involved; this classification scheme is the current framework used to describe renovascular lesions [3, 4]. Table 1 lists the common causes of renovascular hypertension; let me review these briefly.

The most frequent causes of renovascular hypertension in childhood are the various lesions that fall into the category fibromuscular dysplasia [5–7]. Lesions of the intima occasionally are seen [8–13]. The intimal lesion involved consists of a circumferential, often eccentric, accumulation of loose fibrous matrix with a moderate number of cells and without inflammatory change or lipid accumulation. Whereas the internal elastic lamellae sometimes show duplications, more often the lamellae are intact and normal. For reasons not understood, the findings in the small percentage of patients with congenital rubella, who may develop renovascular hypertension, most often fall into

Table 1. Causes of renovascular hypertension in childhood

Intrinsic lesions
Fibrous and fibromuscular dysplasia
Intima
Intimal fibroplasia
Media
Medial fibroplasia (+/− aneurysms)
Medial hyperplasia
Perimedial fibroplasia
Adventitia
Periarterial fibroplasia
Genetic disorders
NF1 (vascular neurofibromatosis)
Williams syndrome
Feuerstein-Mimms syndrome
Klippel-Trenaunay-Weber syndrome
Thromboembolism
Post-umbilical catheter
Post-angiography
Post-trauma
Inflammatory stenoses
Takayasu syndrome
Moyamoya syndrome
Sarcoidosis
Kawasaki syndrome
Aortitis
Atherosclerosis
Progeria
Hyperlipidemias
Post-transplant
Extrinsic lesions
Tumor
Wilms'
Neuroblastoma
Pheochromocytoma/ganglioneuroma
Lymphoma
Congenital fibrous band
Post-trauma
Hematoma
Retroperitoneal fibrosis
Lymphadenopathy

this category [8]. Intimal lesions also are common in children with Williams syndrome, also called idiopathic hypercalcemia of infancy, which is characterized by unusual (leprechaun-like) facies, developmental retardation, cardiac lesions, and multiple vascular stenoses [14–16].

Fibromuscular dysplasia involving the media, the most frequent cause of renal artery disease, can occur with or without aneurysms [4]. The main renal artery, segmental branches, or both can be involved, with the arterial wall manifesting focal areas of thickening alternating with very thin areas. Arteriography generally reveals a "string of beads" pattern; the media often is replaced by a collagenous and fibrous matrix and degenerated elastic fibers that displace and disorient smooth muscle cells. Elastic lamellae often are deficient in these areas of media. In patients with fibromuscular disease involving the media, the longitudinally oriented smooth muscle cells in adventitial regions appear hypertrophic. In contrast to the frequency of intimal and medial disease, adventitial periarterial fibroplasia is relatively rare and is characterized by the deposition of collagen in the adventitia and fibroplasia of the surrounding connective tissue [4]. This adventitial lesion is often characterized by chronic inflammation (lymphocytes and plasma cells) within the connective tissue surrounding the arteries; small vessels and capillaries also can be cuffed by inflammatory cells.

Genetic disorders associated with renovascular disease are fairly common causes of hypertension in children. In the pediatric population, the most common genetically determined renovascular disorder is neurofibromatosis (NF), a hereditary congenital dysplasia of ectodermal and mesodermal tissues characterized by vascular lesions [17–28]. In fact, a number of pathologic studies that have reviewed cases of fibromuscular dysplasia in children have found most of these cases to be in individuals who have neurofibromatosis. Almost all children with NF develop vascular lesions, which can occur in virtually any artery; NF-associated stenosis, however, most commonly affects the abdominal aorta, and the renal, internal carotid, and vertebral arteries. Arterial lesions in NF include: (*1*) pure intimal lesions; (*2*) advanced intimal lesions and medial changes; (*3*) nodular aneurysmal lesions with loss of media elements; (*4*) periarterial nodular abnormalities; and (*5*) epithelioid lesions with marked cellular proliferation [29]. The most common lesion in NF consists of fibrous thickening of the intima; small blood vessels (vasa vasorum) can be seen within the remaining slit-like lumens. The internal elastic membranes often are fragmented and duplicated. Nodular collections of cells, seen in junctional zones between the intima and muscularis, are thought to represent smooth muscle cells [23] or nodules of neural origin [29].

Children with other genetically based disorders, such as Williams syndrome [14–16], Klippel-Trenaunay-Weber syndrome [7], and Feuerstein-Mimms syndrome [7], may have renovascular hypertension. The renal lesions in these patients appear to be in the category of fibromuscular dysplasia. Patients with tuberous sclerosis, who often develop intrarenal cystic lipomatous lesions, occasionally also develop arteriovenous malformations, which are associated with hypertension [30].

Thromboembolic occlusion of renal vessels is the most common cause of acute hypertension in premature or ill neonates [31–35]. In the newborn period, umbilical arterial catheterization is the usual prelude to arterial thrombosis. Trauma to endothelium, platelet aggregation, and subsequent thrombus formation is the usual sequence of events. Thromboembolic renal artery lesions occur less frequently in older infants and children, and the index of suspicion for this diagnosis is heightened if a history of trauma or catheterization exists; confirmation of the diagnosis requires angiography. Renal artery thrombosis occasionally can occur in older children after angiography [36], but close monitoring and administration of anticoagulants when the renal vessels are manipulated usually averts this unfortunate event. Following blunt trauma, as in motor vehicle accidents, renal vessels can be occluded, and it is important to bear this possibility in mind.

Inflammatory renal artery stenosis related to a vasculitis, while rare, does occur in children. Takayasu arteritis [37–39], Moyamoya syndrome [40], and sarcoidosis [41, 42] all have been associated with renovascular hypertension. Occasional reports of renovascular hypertension following Kawasaki disease also have been published [43]. Arteriosclerosis, also rare in children, occurs virtually only in syndromes such as progeria or

the dyslipidemias [44–46]. Renovascular disease has been reported as part of a diffuse arterial calcified elastopathy. The pathogenesis has not been elucidated [47, 48].

Renal artery stenosis can occur in children who have undergone renal transplantation [49]. Post-transplant hypertension can result from a number of problems other than renovascular disease, and these disorders must be considered. Acute and chronic rejection, the presence of multiple kidneys, medication, hypercalcemia, pyelonephritis, hydronephrosis, and/or recurrent nephropathy all are associated with hypertension. The renal artery itself can be compromised due to intrinsic narrowing related to suture placement, rejection phenomena, neovascular changes, or scarring.

Extrinsic compression can account for post-transplant renal artery stenosis. This topic has been reviewed recently [49, 50]. Such extrinsic causes of renovascular narrowing can cause severe, acute hypertension [7, 51–55]. Conditions resulting in external compression include tumors (Wilms', neuroblastoma, pheochromocytoma, and lymphomas), congenital bands, and neurofibromas. Following trauma, hematomas also can compress the renal artery.

Clinical manifestations

The clinical manifestations of renovascular hypertension vary considerably [56–58]. Like the child presented here, however, most youngsters are asymptomatic. When symptoms occur, they range from mild to severe and include headaches, confusion, epistaxis, anorexia, failure to thrive, and those of heart failure; polyuria, polydipsia, and nocturia (manifestations of a renal concentrating defect); and Bell's palsy. Because renovascular hypertension accounts for a substantial number of definable causes of hypertension but is frequently silent, the physician must consider it strongly in any hypertensive youngster. Thus, young children with severe hypertension without a positive family history should have a complete evaluation for renovascular hypertension. Hypertension after trauma, marked and difficult-to-control hypertension, and hypertension with a change in renal function all are clinical features associated with renal artery stenosis and should lead the clinician to perform a complete renovascular evaluation. Physical examination also can be invaluable in providing hints as to the presence of renovascular hypertension. Obviously the features of systemic diseases such as NF and Williams syndrome must be sought; detection of an abdominal or flank bruit, especially one that is diastolic and lateral to the midline, hints at the presence of a renal artery lesion.

Diagnosis

Diagnostic studies intended to define renal and renovascular diseases are divided into phases or stages in the pediatric patient just as in the adult [1, 59]. Initial screening tests should, at a minimum, include urinalysis, urine culture, measures of renal function (at least BUN and serum creatinine), serum electrolytes, and an evaluation of cardiac status by echocardiography or electrocardiogram plus chest radiograph. Next, studies that raise or lower the index of suspicion about renovascular disease should be carried out. Several suggested tests include peripheral plasma renin activity (caval and renal vein sampling are done later), and cardiac and renal imaging [1, 58, 59].

Peripheral plasma renin activity is influenced by a variety of volume-related and hormonal factors as well as by dietary salt intake [60]. Many medications also can increase or decrease plasma renin activity [60]. Thus, it is not surprising that therapy of hypertensive children can interfere with assessing the plasma renin activity or concentration accurately. Nonetheless, controlling the patient's elevated blood pressure is of prime importance and takes precedence over any diagnostic study. A "random" plasma renin activity value, unless very high or very low, is not of much help.

I recommend obtaining an initial plasma renin activity value prior to the administration of a diuretic or first dose of an angiotensin-converting-enzyme inhibitor. I interpret the results of such pre-treatment renin activity on the basis of the normal renin activity for the age of a child, the norms for the laboratory being used, and the conditions of sampling [60–64].

Renal vein renin sampling, with or without the patient having been given a converting enzyme inhibitor, may help in determining whether vascular stenosis is the physiologic cause of hypertension [65–67]. Renin activity is determined in blood samples from the renal veins (or renal vein segments), and from the inferior vena cava both below and above the renal veins [52, 57]. To show renin dependence, this study should demonstrate hypersecretion of renin from the suspect region (V_1), suppression from the normal region (V_2), and decreased perfusion of the suspect area as demonstrated by an increased concentration of renal-vein renin compared to the inferior vena cava concentration (systemic). Thus, the ratios between the affected side and normal should be at least 1.5:1.0 if one is to predict improvement in blood pressure control with interventional radiologic procedures or surgery [66]. Increased renin flowing from a kidney (or a renal segment) with renovascular lesion(s) should suppress the renin secretion from the contralateral normal kidney to a level equal to that in the systemic circulation (V_2 − IVC = ~0); if the normal side is not suppressed, surgical cure is less likely [66]. Partial nephrectomy based on the results of a segmental renal vein renin sampling study has been helpful in curing children with renal artery disease [65].

The utility of renal imaging studies in the hypertensive pediatric population remains a subject of great debate. The accuracy of any given imaging method depends not only on the technique, but also on the experience of the center using that technique, especially the experience with children [1]. Refinements in ultrasonography [68] and the possible combination of that technique with Doppler flow [69–72] enables the evaluation of renal blood flow in more effective ways. The ultrasound examination gives a good view both of the kidneys and of the suprarenal areas, although adrenal evaluation is not complete with ultrasound. Using Doppler renal flow, one can examine the flow characteristics of the aorta as compared with the distal and proximal renal artery [72]. In addition, the Doppler probe can be placed over the cortex of the kidney (localized by ultrasound); subsequent wave form analysis indicates the level of renal blood flow. This technique can be very accurate, approaching about 90% agreement with the "gold standard," arteriography [61]. Furthermore, the addition of a converting enzyme inhibitor sometimes reduces renal blood flow and decreases renal function in the kidney with moderate to severe renal artery stenosis. In such a study, the routine determination for arterial flow is performed; then 0.3 mg/kg of captopril is

administered [73]. One hour after administration of the drug, the studies are repeated. Should renal blood flow decrease markedly, the patient is likely to have a significant stenosis of the renal artery [73]. This study has not been performed in large numbers of children [73]. Conventional ultrasound, in combination with radionuclide renal scanning, has a high sensitivity and specificity for finding renal artery disease [67, 73]. Ultrasonography should be done as a screening test in any youngster with persistent hypertension, as ultrasound at least defines renal location and configuration.

Let me inject a word about the intravenous pyelogram (IVP). This test permits the detection of asymmetry in renal size, persistent delay in excretion of radiocontrast material when there is unilateral renovascular disease, or persistent nephrogram on both sides when bilateral renovascular disease is present. When several films are taken shortly after the injection of contrast material, the procedure is called a "rapid-sequence" IVP. Unfortunately, just as in adults, the sensitivity of the rapid-sequence IVP in hypertensive children is low, at most 65% [74, 75]. When bilateral renovascular disease is present, this test is even less sensitive. For this reason, an IVP should be done only when other imaging tests are unavailable.

Computed axial tomography (CT scanning) is a good diagnostic test for renal parenchymal abnormalities but is limited in its ability to detect renovascular disease even when used with radiocontrast enhancement. Magnetic resonance imaging (MRI) has the potential to visualize renal vessels using flow-related angiography [76–78], but such studies are not yet widely available and are neither sensitive nor specific enough to be recommended for common use in children [36].

Radionuclide renal scans using several rapidly decaying isotopes—technetium-99m (^{99m}Tc), iodine-131 (^{131}I), and iodine-123 (^{123}I)—can be used to document renal flow and cortical function [79, 80]. So-called renal morphology agents, ^{99m}Tc-dimercaptosuccinate (DMSA) and ^{99m}Tc-glucoheptonate (^{99m}Tc-GHA) are used to obtain at least semi-quantitative estimates of renal function in the absence of obstruction [79, 80]. However, functional agents such as DTPA and ^{131}I-orthoiodohippurate provide excellent estimates of function [79, 80]. Preferable in the pediatric population, ^{123}I-orthoiodohippurate gives a lower radiation dose to kidneys, gonads, and the whole body [79, 80]. Recently, ^{99m}Tc-MAG3 (mercaptoacetyltriglycine) has been shown to be a superior agent to orthoiodohippurate in visualizing renal parenchyma and gives fine results in children [81]. The use of captopril as an aid to the renal scintiscan for detecting renovascular hypertension in children is becoming increasingly popular [82, 83]. Some centers obtain a pre-captopril renal scan, then administer the agent and obtain a second scan. Others prefer to get a single scan after using captopril for variable lengths of time.

The computerized collection, storage, and manipulation of angiographic data have substantially improved the value of renal arteriography because the data can be reconfigured in a number of ways for subsequent analysis following the study [84–86]. Standard cut film arteriography, digital subtraction angiography, and digital venous subtraction angiography (DVSA) all provide images of the renal vessels after contrast injection. Venous angiography combines central venous injection with computer-enhanced imaging over the region of interest. Obviously, this technique avoids arterial cannulation and the complications of direct arteriography. In DVSA, a centrally placed venous catheter is used to inject a large bolus of contrast medium into the superior vena cava or right atrium. The delayed enhanced images are collected over the abdominal aorta and kidneys, producing an angiogram that represents a subtraction, or difference, image. This image is formed by subtracting an unenhanced image prior to the arrival of contrast material from the enhanced image after the peak arrival of the bolus of full-strength contrast medium. The sensitivity and specificity of DVSA have been debated. Motion and artifact can result in a poor image, which will hinder accurate interpretation of the study. Because children can have segmental fibromuscular disease, DVSA often is not sensitive enough for accurate detection. In an older child, this method is helpful in ruling out main renal artery disease.

Arterial cannulation is necessary both for digital subtraction angiography (DSA) and conventional angiography [84–86] if segmental vessels are to be well visualized. In children less then 5 years old, direct angiography is best performed with general anesthesia with standard arteriographic technique. The origins of the renal arteries generally are best visualized with an oblique (15°) view. Views obscured due to overlapping vessels can often be improved with DSA, because images can be reformatted subsequently. Transient vascular spasm can occur after selective renal cannulation, and it is crucial to distinguish this phenomenon from fibromuscular disease. To determine whether an apparent narrowing represents true stenosis or vascular spasm, one should use either a second injection with lower volume and pressure, or a central injection.

Therapy

The objective of therapy of renovascular disease is both preservation of renal function and correction of hypertension. In the 1980s, the development of interventional techniques averting the need for surgery changed the approach to the therapy of renovascular disease in children [87, 88].

Many surgical techniques have long been available [73, 89–91]. Traditionally, first-choice surgery in pediatric patients has been a bypass graft from the aorta to the renal artery distal to the area of stenosis. In children, vessels are small and growing; thus autologous tissue, such as the internal iliac artery, is the preferred conduit. Using an autologous conduit, subsequent normal vascular growth without aneurysm dilation is likely. When an autologous artery is not available, a distal saphenous vein or a splenorenal bypass can provide an effective graft. Often, autotransplantation of the kidney after bench repair is successful [73]. Nephrectomy should be avoided whenever possible [56–58, 73, 89–91].

Transluminal angioplasty (TLA) has been used extensively in the therapy of atherosclerotic renal artery disease in adults [92–95]. The procedure recently has gained popularity in adults for the treatment of fibromuscular renal artery disease [92–95], and TLA has been used over the last decade in increasing numbers of children with renovascular disease [87, 96–104]. Renal artery stenosis in a transplanted kidney also is amenable to balloon dilation [87, 105]. Now that balloons of more resilient materials are available, the technical procedure is more effective. In performing TLA it is important that one select a balloon catheter that will slightly overstretch the stenotic segment.

Many children have bilateral disease, and in such circumstances it is best to manipulate one side at a time to avoid the possible complication of bilateral thrombosis.

Hypertension usually improves after TLA. However, about one-third of patients develop a subsequent stenosis. Various series have reported disparate results. The success of TLA depends on the location of the renal artery disease; the most successful results generally are achieved with short stenotic lesions [87]. Lesions at the origin of the renal artery, or lesions in which long segments of the renal artery are stenosed (often seen in neurofibromatosis) are particularly refractory to dilation [98]. A review of several reports comparing small numbers of pediatric patients treated with TLA suggests that this technique should be used when the arterial lesion is in a favorable location [105]. Long-term followup is not yet available, nor has a standardized approach to prevention of clot formation following the procedure emerged.

The successful use of intravascular stents or baffles for correcting renal artery stenosis has now been reported in adults [106]. The use of such devices in children is still theoretical. Stints remain in situ permanently after their placement, so it is important that the stint be of the caliber ultimately expected for the fully developed renal vessel.

Transcatheter ablation of renal tissue has been suggested for some forms of renal hypertension not easily treated with surgery or transluminal angioplasty [107–110]. For instance, a segmental artery stenosis that cannot be dilated or resected might be approached by selective infarction. A variety of agents have been utilized for renal ablation including gelfoam sponge, polyvinyl alcohol, ethanol, stainless steel minicoils, and autologous clot. A co-axial catheter system is used for placement of the ablating material. The important procedural concerns are the prevention of larger embolization than planned, the avoidance of infection, and the control of post-procedural pain, which can be severe. As experience is limited in the pediatric population, medical ablation should be used only in children who are very poor risks for other procedures.

Pharmacotherapy in children with hypertension follows the same basic principles as that in adults, that is, monotherapy should be used when possible and other agents added stepwise as needed [111–117]. Pharmacologic therapy of children with severe hypertension due to renovascular disease is now far simpler with the availability of many new, potent, and more specific medications. However, most newer drugs are not tested specifically in young children, and the caveat, "safety and efficacy in children is not known," generally appears in the manufacturer's literature. Particular concerns in the pediatric patient include unique aspects of pharmacokinetics, untoward side effects, and drug toxicity. The pharmacokinetics of hypotensive agents may be different in children compared to adults. For example, the half-life of renally excreted agents is longer in infants, in whom glomerular filtration rate is relatively decreased. Substantial experience has been documented in children in the use of angiotensin converting enzyme (ACE) inhibitors, calcium antagonists, newer beta blockers, and the combined alpha/beta blocker labetalol, yet none of these agents is formally approved for use in children. The doses used generally are obtained by scaling down the adult doses and starting at a minimal dose, as shown in Table 2. Specific problems in treating children with renovascular disease include a decrease in renal function with potent agents such as ACE inhibitors and the need for polypharmacy in severe hypertension.

Development and remodeling of renal and intrarenal arteries

Before closing by briefly commenting on the abnormal vasculature in neurofibromatosis, let me review the growth and development of the renal vasculature. The morphology of the renal vasculature in the human follows a set pattern in the maturing metanephros, well described in Jean Oliver's landmark tome published nearly 25 years ago [118]. After the ureteral bud first divides, arteries from the aorta and veins from the vena cava are visible next to the primitive ureter. These vessels give rise to branches traversing the metanephric blastema, which surrounds the ampullae. The terminal branches of these newly formed arteries and veins extend to the periphery and there anastomose into a subcapsular network. By 14 or 15 weeks of intrauterine life, the vascular pattern of the fetal kidney resembles that of the mature kidney. At this time, branches of arteries near the future corticomedullary junction start to elongate parallel to this zone, becoming arcuate arteries. When development is complete, the glomeruli in the outer ⅔ to ¾ of the cortex will be supplied by branches of the interlobular arteries; the juxtamedullary glomeruli are supplied directly by branches of the arcuate, oblique, or interlobular vessels. Although this architectural blueprint is known, the factors that specifically lead to normal or abnormal renovascular development are understood far less well. What is known about vascular development, however, together with some lessons concerning renal vascular development in abnormal states, permits us to make several statements concerning renovascular disease in children.

Angiogenesis is a major part of embryogenesis. During development, cells in the vasculature organize into layers, each derived from mesenchyme. These are the tunica intima, made up of endothelial and smooth muscle cells; the tunica media, made up of multiple layers of smooth muscle cells; and the tunica adventitia, made up of loose connective tissue containing small vessels and nerves. All blood vessels, even capillaries, have a lining of polarized endothelial cells. The luminal surface of these cells has nonthrombogenic properties; the antiluminal surface produces basement membrane substances. Other cell types that are part of the vessel wall—pericytes, smooth muscle cells and adventitial fibroblasts—are recruited during vascular development, in large part by signaling from the endothelial cells.

Two disparate mechanisms appear to be involved in the growth of the vasculature during embryonic development. First, blood vessels develop from endothelial cells of blood islands that differentiate in situ, a process referred to as vasculogenesis [119]. Vasculogenesis is distinguished from angiogenesis, or the sprouting of capillaries from existing vessels. The initial step in the development of the vascular system is the induction of so-called blood islands, or hemangioblasts; this step seems to require endoderm-mesoderm interaction. Vasculogenesis is the process by which blood vessels develop from differentiating endothelial cells from the blood islands. A variety of factors, "angiogenesis factors," appear to be important in the embryonic development of blood vessels. Such factors include acidic and basic FGF, TGF-α, TGF-β, TNF, adipocyte

Table 2. Medications for treatment of chronic hypertension[a]

Drug	Initial daily dose	Maximum daily dose	Frequency	Available formulation
Diuretics				
Hydrochlorothiazide	1.0 mg/kg (60 mg/m^2)	100 mg	bid	50 mg/5 ml solution
	3.0 mg/kg (<6 mo of age)	37.5 mg	bid	25, 50, 100 mg tablets
Chlorothiazide	20 mg/kg (600 mg/m^2)	1000 mg	bid	250 mg/5 ml solutions
	30 mg/kg (<6 mo of age)	375 mg (up to 2 yrs)	bid	250, 500 mg tablets
Furosemide	1–2 mg/kg	320 mg or 4 mg/kg	bid, qd	40 mg/5 ml, 10 mg/ml solutions; 20, 40, 80 mg tablets
β-Adrenergic antagonists				
Nonselective				
Propranolol	1–2 mg/kg	8 mg/kg	bid	20 mg/5 ml solution 10, 20, 40, 60, 80 mg tablets
Nadolol	40 mg[b]	640 mg	qd	20, 40, 80, 120 mg tablets
Selective				
Atenolol	50 mg[b]	100 mg	qd	25, 50, 100 mg tablets
Metoprolol	100–200 mg[b]	450 mg	qd, bid	50, 100 mg tablets
Acebutolol	200–400 mg[b]	1200 mg	qd	200, 400 mg tablets
Complex adrenergic antagonists				
Labetalol	50–100 mg[b]	1200–2400 mg	bid	100, 200, 300 mg tablets
Central sympatholytics				
Alpha methyldopa	10 mg/kg (300 mg/m^2)	65 mg/kg (2g/m^2)	bid, tid, qid	250 mg/5 ml solution, 125, 250, 500 mg tablets
Clonidine	0.05–0.1 mg tablet	2.4 mg by mouth	bid, tid	0.1, 0.2, 0.3 mg tablets
	0.1 mg/day patch	0.6 mg by patch	q week	0.1, 0.2, 0.3 mg patches
Guanabenz	0.08–0.2 mg/kg (>12 yrs)	64 mg	bid	4, 8 mg tablets
Direct vasodilators				
Hydralazine	0.5–1.0 mg/kg (25 mg/m^2)	4–8 mg/kg (200 mg)	tid, qid	10, 25, 50 mg tablets
Minoxidil	0.1 mg/kg	1 mg/kg (50 mg)	bid, qd	2.5, 10 mg tablets
Calcium-channel blockers				
Nifedipine	0.25 mg/kg	1–2 mg/kg (180 mg)	tid, qid	10, 20 mg capsules
Extended release		1–2 mg/kg (90 mg)	qd	30, 60, 90 mg tablets
Diltiazem	60–120 mg[b]	360 mg	bid, qd	60, 90, 120 mg tablets
Verapamil	120–240 mg[b]	480 mg	bid, qd	120, 240 mg tablets
Peripheral alpha blockade				
Prazosin	1–2 mg	20 mg	bid, tid	1, 2, 5 mg tablets
Angiotensin-converting-enzyme inhibitors				
Captopril	0.05–0.1 mg/kg	4 mg/kg (200 mg)	bid, tid	12.5, 25, 50, 100 mg tablets
Enalapril	1.25–2.5 mg[b]	40 mg	bid, qd	2.5, 5, 10, 20 mg tablets
Lisinopril	2.5 mg[b]	20 mg	bid, qd	5, 10, 20, 40 mg tablets

[a] Adapted from Jung FF and Ingelfinger JR, *Hypertension in Childhood and Adolescence, Pediatrics in Review*, Boston, Blackwell Scientific Publications, Inc.

[b] Pediatric dose is not established. This table is not an exhaustive list, but it is intended as a reference of most drugs currently used.

lipids, angiogenin, and various prostaglandins [119–123]. These factors affect endothelial cell proliferation and motility. The subsequent development of larger vessels involves endothelial cell secretion of chemotactic factors, as well as mechanical factors present as embryonic blood circulates [119–123]. Fetal blood vessels are surrounded by a vascular extracellular matrix that contains much fibronectin and laminin. Factors that form the renal vasculature in utero are incompletely understood. However, studies of microvasculature suggest that cells at the distal tip of an angiogenic "sprout" express features both of endothelial and smooth muscle cells, while endothelial cells more proximal to the "potential" vessel show a more characteristic "endothelial" phenotype. The extracellular matrix modulates microvascular migration in culture. For instance, TGF-β reduces mesangial cell migration; this migration is increased by laminin, fibronectin, and types I, IV, and V collagen [120, 121].

The direction of blood flow in the developing vasculature appears to change direction several times. The development of larger vessels in the embryo is thought to be influenced not only by the secretion of chemotactic factors, which attract cells to the vascular wall, but by physical forces and mechanical stresses imposed by blood flow in the fetus [119].

Some evidence indicates that the number of smooth muscle layers in larger arteries is predetermined and already present at birth [124]. Subsequent medial thickening, then, is due to increased production of connective tissue, cell mass, or cell number—not to the number of cell layers. There are differences in the vascular development of spontaneously hypertensive rat embryos as compared with vascular growth in normotensive rats [125, 126]. Evidence suggests that while endothelial cell migrate into developing anlage, smooth muscle cells are locally derived [122]. Schwartz et al have suggested that implicit in this concept is the possibility that smooth muscle cells within the vasculature can have different origins, depending both on their location within organs and tissues and on signaling factors that

can attract them during vascular development [122]. Possibly, various growth factors of the endothelium act both by modulating the matrix and thus cell-to-substrate interactions within vessels and by modulating cell-to-cell interactions. Such a concept allows for the possibility that there exists a common action for growth factors as morphogens and as mitogens. It is interesting to speculate that the changes in the vasculature seen in certain inherited systemic diseases associated with renovascular hypertension such as vascular NF-1 or Williams syndrome may be influenced by changes in endothelial cell signaling resulting in pathogenic cell:matrix or cell:cell interaction. We can also hypothesize a similar pathogenesis for acquired renovascular lesions.

In the kidney, certain vasoactive substances affect the vasculature. The developmental expression of one of these substances, renin, is different in the fetus from that in the mature organism [127, 128]. In the case of renin, there is a far wider expression of both its mRNA and protein in the fetal vasculature. In the fetus, renin-producing cells are found in large amounts in the afferent and efferent arteriole, and the expression regresses with development [129]. Animals transgenic for the renin promoter attached to the large T antigen of the SV40 virus develop a pathologic vasculature [130]. Other animals transgenic for other aspects of the renin-angiotensin system also have an aberrant renovascular development [131].

Let's return to today's patient. The repeat arteriogram revealed bilateral renal artery stenosis and stenosis of a branch of the right renal artery, as well as superior mesenteric artery stenosis. Thus, her vasculopathy was progressive. How might the vasculature in neurofibromatosis, as seen in this little girl, have become abnormal? This child has probable neurofibromatosis type 1 (NF–1), for which the gene (a transcript encoding 13 kilobases) was recently isolated using positional cloning [132, 133]. Several point mutations and deletions have been described in this gene on the long arm of chromosome 17. The presumed NF–1 gene product appears to be a polypeptide of 2818 amino acids, a GAP (guanosine triphosphatase [GTP]-activating protein) that controls or is controlled by the *ras* oncogene [134–136]. The *ras* oncogene is important in growth, and an abnormality in its control obviously could affect growth, development, and differentiation. Indeed, in the human, the *ras* gene products appear to function as coupling proteins between mitogen receptors and effector molecules [121]. It is intriguing to speculate that the underlying defect in NF–1 results in a long-term potential for abnormal vascular development and remodeling, ultimately culminating in renal arterial disease and hypertension.

Questions and answers

DR. JOHN T. HARRINGTON (*Chief of Medicine, Newton-Wellesley Hospital, Newton, Massachusetts*): Dr. Ingelfinger, what do we know about the specific abnormalities in the vessels of patients with neurofibromatosis? Can one see changes in the peculiar collagen fibers that are formed? Perhaps you could expand on what you already have told us.

DR. INGELFINGER: The question as to whether biochemical changes occur in or around the vasculature unique to neurofibromatosis is an interesting one. It would appear that the protein product of the NF–1 gene on chromosome 17q11.2 is related to regulators of *ras* proteins [134, 135]; a portion of NF–1 that is homologous to the *ras* GTPase-activating protein, that is, GAP, encodes a similar protein. It is not fully understood how the abnormal gene product in neurofibromatosis affects the vasculature. What is known is that the cellular differentiation and expression of matrix genes in NF–1 vasculature can be abnormal [136], with changes in the amount of type-IV collagen and fibronectin detected immunocytochemically. Studies do suggest that the NF cells are freely accessible to various plasma proteins, including growth factors, which in turn could influence the development of the lesions [136]. However, the vessels that have been examined in NF-1 are those within neurofibromas, not the renal arteries themselves.

DR. HARRINGTON: Are there any similarities between the neurofibromata per se and the vessel lesions? Are the collagen fibers similar, or are these totally different expressions of the same disease?

DR. INGELFINGER: I cannot really answer this question directly, but by deduction, I would guess that the answer may be yes. While a small study comparing pediatric renal artery dysplasia in patients with and without NF showed no difference in the histologic lesions observed [17], the renovascular abnormalities in NF have been thought to have some neural elements. As I mentioned earlier, a spectrum of renal vascular lesions has long been described in neurofibromatosis, including adventitial neurofibromas, which can cause external compression of renal vessels or coarctation of the aorta [18, 29, 137, 138]; intimal hyperplasia consisting of concentric intimal proliferation of spindle cells with atrophy and thinning of media and elastica; intimal-aneurysmal lesions with marked fibrous thickening with irregular loss of medial smooth muscle and elastic fragmentation; lesions with fusocelluar nodules found between media and adventitia; and epithelioid lesions. Such lesions, which have proliferative foci or aspects have been variously considered as having connective tissue origin, endothelial origin, or Schwann cell origin. Vascular elements also can be abnormal. For example, in a recent case report, smooth muscle proliferation of spindle-shaped cells in arteries, arterioles, and veins of all calibers throughout the renal parenchyma supported the existence of vasculopathic lesions in NF separate from lesions in association with abnormal proliferation of cells derived from the neural crest [18].

DR. RONALD D. PERRONE (*Division of Nephrology, New England Medical Center, Boston, Massachusetts*): Several recent studies have suggested that there is activation of the renin-angiotensin system in autosomal dominant polycystic kidney disease [139, 140]. Can you give us any information about angiogenesis and polycystic kidney disease?

DR. INGELFINGER: There are not, to my knowledge, any studies directly addressing the question of PKD and angiogenesis within the kidney in autosomal dominant polycystic kidney disease (ADPKD). However, cystic renal disease is associated with cardiovascular abnormalities [141]. Experimental steroid-induced polycystic kidney disease induced by methylprednisolone in newborn rabbits is associated with a vasculopathy in which multiple microvascular changes, such as multiple afferent and efferent arterioles in glomeruli, poor development of glomerular tufts, and persistence of sinusoidal vascular cortical plexus, occurred [142]. These vascular changes did not correlate with the number or stages of cysts, and these alterations were interpreted as a separate process [142].

DR. ANDREW KING (*Division of Nephrology, New England Medical Center*): I'm interested in renal artery stenosis in very young children. Is there any structural abnormality in the kidney, such as small glomeruli? If so, when blood flow is restored, do these children have normal growth patterns? Finally, do either DuP 753 (losartan) or ACE inhibitors impair renal growth in these patients?

DR. INGELFINGER: We do not know whether there are unique structural or pathologic features within the renal parenchyma in pediatric renovascular disease. Presumably, as in the two-kidney, one-clip model of hypertension, the kidney ipsilateral to a stenotic lesion is relatively protected, while the opposite side is subject to the effects of systemic hypertension [143, 144]. Very little is known concerning the histology of pediatric kidneys following successful repair of renal artery stenosis in a main renal artery or branch. Whether revascularization leads to normal or supranormal renal growth in the previously hypoperfused kidney is not known, although the anecdotal and undocumented impression is that both renal and somatic growth improve. More is known about segmental renal abnormalities. For example, many children with the entity of segmental renal hypoplasia, or Ask-Upmark kidney (which is characterized by a dysplastic renal segment with atrophic tubules, sparse glomeruli, and frequently disordered vasculature) are thought to be hypertensive [145]. Segmental hyperreninemia is often present in the abnormal segment of an Ask-Upmark kidney, and partial nephrectomy usually cures the hypertension [145].

I have the clinical impression that when renal artery disease is successfully repaired in children, it can take a substantial period of time for blood pressure to normalize, and that renal function in such individuals may not remain normal. Like many of you in this audience, I have followed several young people who underwent technically successful repair of bilateral renal artery stenosis and in whom both kidneys appeared to have been protected from systemic hypertension, and yet in whom long-term renal dysfunction developed insidiously, over a number of years.

You ask whether the angiotensin II receptor (AT_1) antagonist losartan (DuP 753) or converting enzyme inhibitors impair renal growth in children with renovascular disease. Again, the answer is unclear. Experience with losartan in children is minimal at present. However, the use of ACE inhibitors in children with complex renovascular disease (bilateral renal artery stenosis or renal artery stenosis in a single kidney) is associated with decreases in renal function [116, 146, 147]. Nonetheless, many pediatric nephrologists still use ACE inhibitors in such situations [50]. To my knowledge, there are no reports about ACE inhibitor use and renal growth in children per se. We have observed a case in which renal perfusion and size was decreased while a child with multiple renal arterial stenosis received the agent, and was improved upon discontinuation of the agent (unreported case).

DR. RICHARD LAFAYETTE (*Division of Nephrology, New England Medical Center*): Does the presence of pediatric hypertension as you have defined it, greater than the 95th percentile, predict essential hypertension in adults?

DR. INGELFINGER: The answer is not as clear as one would hope. The concept of blood pressure "tracking" along the same percentile throughout growth and development so that a child with blood pressure at the fiftieth percentile will remain or "track" at that level, while another at the 95th percentile will "track" along that curve, has much epidemiologic support [1, 148, 149]. Unfortunately, tracking does not necessarily predict essential hypertension. One of the larger available studies of teenagers with mild or labile hypertension in which subjects were examined 5 years later showed that about one-third had the same blood pressure, one-third had lower blood pressure, and another third had established hypertension [150]. Nonetheless, I would agree with the recommendation of the Pediatric Task Force for following blood pressure closely in children with a family history of essential hypertension whose blood pressure is at the 90th to 95th percentiles [1].

DR. LAFAYETTE: Previous studies have examined the familial nature of hypertension and have found cosegregation of certain genotypes, for example, the renin gene, with adult hypertension. Have any similar studies been conducted in children?

DR. INGELFINGER: In my opinion, studies in which RFLP studies of kindreds with hypertension using candidate genes such as the renin gene thus far have failed to show a clear association [151, 152]. There are no specifically pediatric studies using such an approach as yet, although some of the subjects in the RFLP studies were adolescents. It is especially exciting that recent studies, albeit in rats, using reverse genetics [153, 154] have implicated an area on the tenth chromosome of the rat close to or congruent with the ACE gene, which may be associated with hypertension. Future studies examining the analogous area in the human genome will be of great interest and value.

DR. HARRINGTON: What is Williams syndrome? You described it briefly in your discussion. What should we know about it?

DR. INGELFINGER: Williams syndrome, also known as idiopathic hypercalcemia of infancy or the supravalvular aortic stenosis complex, is associated with multisystem abnormalities including multiple vascular stenoses. Williams syndrome is characterized by a constellation of features including hypercalcemia in infancy; short stature; "elfin" facies; mental retardation; and stenoses of the aorta (supravalvular aortic stenosis, coarctation), pulmonary arteries, and peripheral systemic arteries [16, 155]. Since hypertension often accompanies the vascular abnormalities, physicians evaluating hypertension in children must be aware of this syndrome. Occasionally, proteinuria and renal functional impairment also occur in Williams syndrome, and we have found a higher-than-expected incidence of single kidney [15]. The underlying abnormality accounting for both aberrant calcium metabolism and the systemic manifestations has not been determined. Vitamin D metabolism is normal. However, calcitonin secretion may be deficient, and recent data suggest that the calcitonin-gene-related peptide might be responsible for some the manifestations of the syndrome [16]. It is also worth noting the existence of an active Williams Syndrome Association. This group of more than 1700 members provides information and support to patients and families, and helps investigators learn more about the syndrome (Membership, Sally Meersman, 2841 Highridge Road, LaCrescenta, California, 91214, USA).

DR. JAMES STROM (*Chief of Nephrology, St. Elizabeth's Hospital, Brighton, Massachusetts*): Would you give us the latest estimates on the incidence in non-referred populations of

renal artery stenosis as a cause of adolescent hypertension both in boys and girls?

DR. INGELFINGER: It is not possible to provide accurate incidence in unselected adolescent populations, but it is safe to guess that the actual number is small. Most teenagers with elevated blood pressure turn out to have mild elevation due to essential hypertension. Among those youngsters with definable causes of hypertension, only about 10% have renovascular disease [2], and these individuals usually have marked hypertension that is often difficult to control.

DR. AJAY SINGH (*Division of Nephrology, New England Medical Center*): Are there any racial differences in the onset, natural history, and response to treatment in pediatric patients with essential hypertension?

DR. INGELFINGER: This is an interesting question with a surprising answer. While hypertension is more common in black Americans than in whites, the Second Task Force on Blood Pressure Control in Children did not find any differences when they pooled compatible studies to create norms for American children [1]. Clearly there are racial influences on variables related to blood pressure control, but the prevalence of demonstrable hypertension does not appear to correlate with race until adulthood [156].

In my experience, black adolescents with presumed primary hypertension appear to respond very well to nonpharmacologic therapy, especially salt reduction. A variety of hypotensive agents have been used to treat primary hypertension in children, but no racial influence has been reported.

DR. HARRINGTON: What is the role of the recently discovered endothelial hormones, EDRF and endothelin, in renovascular hypertension?

DR. INGELFINGER: The possible roles of endothelin and EDRF in renovascular hypertension are only beginning to be explored, and no data in children are yet available to my knowledge. Experimental data from two-kidney, one-clip rats suggest that renovascular hypertension leads to impairment of endothelium-derived relaxing factors and sensitivity to endothelin-1 in resistance (mesenteric) arteries [157]. Spontaneously hypertensive rats may have a greater renal artery vasoconstrictive response to endothelin than do Wistar-Kyoto rats [158]. Plasma endothelin levels in adults with atherosclerosis, including some with renovascular lesions, appear to be elevated compared with controls [159]. However, it will be some time before pediatric data are available.

DR. BRIAN PEREIRA (*Division of Nephrology, New England Medical Center*): Moyamoya disease in the brain is postulated to be a consequence of arterial stenosis early in life, which leads to a "lacy pattern" in cerebral angiograms. Is a similar pattern observed in renal artery stenosis in infants and children?

DR. INGELFINGER: Renovascular disease in patients with Moyamoya syndrome is increasingly reported [40, 160], but the pattern of the renovascular lesion is not "lacy."

DR. PEREIRA: I am also interested in your comments on Takayasu's disease. In adults, although idiopathic aortoarteritis or "Takayasu's disease" is one of the leading causes of renovascular hypertension in eastern populations, this disease is uncommon in the west. Is the same distribution observed in the pediatric population?

DR. INGELFINGER: Yes.

DR. MICHAEL LINSHAW: (*Chief, Division of Pediatric Nephrology, New England Medical Center*): If a renal artery lesion is present in a solitary kidney that is small in size for age, would you recommend that we repair the lesion or treat with antihypertensive agents?

DR. INGELFINGER: There is no "right" answer for this question. However, the finding of a single kidney that is smaller than it should be suggests inadequate growth. Will correcting the vascular lesion enhance growth? Will medical therapy delay or prevent growth? One would need long-term data on single kidneys in which hypertension was controlled medically or corrected with angioplasty or surgery. No such outcome studies are available, and any recommendation is based on individual case reports. We do know that the use of ACE inhibition experimentally in renovascular hypertension models prevents renal hypertrophy [161–163]. One can control the blood pressure medically in a child with renal artery stenosis in a transplanted or native single kidney. My experience is that renal function in such a child often is adversely affected, at least temporarily, by complete normalization of blood pressure. If a renovascular lesion in a single kidney is repairable, I would repair such a lesion if it were easily approachable.

DR. HARRINGTON: What percentage of neonates who have umbilical catheters develop hypertension later? Have any good, long-term studies on these children been performed?

DR. INGELFINGER: The incidence of hypertension in newborns ranges from 0.7% to 3.0% overall. The incidence of neonates with umbilical artery catheters developing hypertension is low, although clinically inapparent and asymptomatic thrombi have been detected in 24% to 91% of catheters when angiography has been performed [31]. However, neonatal renal artery thromboembolism is one of the most common causes of hypertension in the neonatal period [31]. The majority of children who suffer this complication do very well indeed, with normalization of blood pressure and discontinuation of antihypertensive medications by one year of age. Redeveloping hypertension appears to be relatively uncommon [31, 32, 164].

Long-term followup studies on small cohorts of such infants reveal that more than 90% appear to have no clinical problems with hypertension. In a study by Adelman, all 10 infants who had catheter-related thromboembolic events had normal blood pressure an average of 5.75 years later (range 1 to 13 years) [32]. However, unilateral renal atrophy or abnormal radionuclide scans are observed in the majority, so as the years go by, more followup studies will be needed.

Acknowledgments

The author thanks Ms. Elaine Bubrzycki for help in typing the manuscript, and Drs. Johann Blickman, Flavia Jung, and Shiow-Shih Tang for helpful discussions. The work described in this Forum was supported in part by NIH grant HL 40210, The Juvenile Diabetes Foundation International, and Merck Sharp & Dohme Research Laboratories.

Reprint requests to Dr. J. Ingelfinger, Pediatric Nephrology Unit, Massachusetts General Hospital, Boston, Massachusetts 02114, USA

References

1. REPORT OF THE SECOND TASK FORCE ON BLOOD PRESSURE CONTROL IN CHILDREN. National Heart, Lung, and Blood Institute. *Pediatrics* 79:1–25, 1987

2. LONDE S: Causes of hypertension in the young. *Pediatr Clin North Am* 25:55–65, 1978
3. HARRISON EG JR, MCCORMACK LJ: Pathologic classification of renal arterial disease in renovascular hypertension. *Mayo Clin Proc* 46:161–167, 1971
4. MCCORMACK LJ, DUSTAN HP, MEANEY TF: Selected pathology of the renal artery. *Semin Roentgenol* 2:126–138, 1967
5. DANIELS SR, LOGGIE JMH, SCHWARTZ DC, STRIFE JL, KAPLAN S: Systemic hypertension secondary to peripheral vascular anomalies in patients with Williams syndrome. *J Pediatr* 106:249–251, 1985
6. DESCHENES G, ZITECK M, GUBLER MC: Renal artery pathology and its therapeutic indications in the child. *Ann Pediatr* (Paris) 38:387–392, 1991
7. BLACKBURN WR, COOLEY NR JR: Vascular pathology in hypertensive children, in *Pediatric and Adolescent Hypertension*, edited by LOGGIE JMH, Boston, Blackwell Scientific, 1992, pp 378–397
8. ESTERLY JR, OPPENHEIMER EH: Vascular lesions in infants with congenital rubella. *Circulation* 36:544–554, 1967
9. MENSER MA, DORMAN DC, REYE RDK, REID RR: Renal artery stenosis in the rubella syndrome. *Lancet* 1:790–792, 1966
10. FORMBY D, EMERY JL: Intimal hyperplasia of the aorta and renal vessels in an infant with hypertension. *J Pathol* 98:205–208, 1969
11. HUGHES FWT, PERRY CB: Senile arterial changes in a child aged 7 weeks. *Bristol Med Chir J* 46:219–222, 1929
12. ROBERTSON JH: The significance of intimal thickening in the arteries of the newborn. *Arch Dis Child* 35:588–590, 1960
13. SCHMIDT DM, RAMBO ON JR: Segmental intimal hyperplasia of the abdominal aorta and renal arteries producing hypertension in an infant. *Am J Pathol* 44:546–555, 1965
14. INO T, NISHIMOTO K, IWAHARA M, AKIMOTO K, TOKITA A, KANEKO K, YABUTA K: Progressive vascular lesions in Williams syndrome (letter). *J Pediatr* 107:826, 1985
15. INGELFINGER JR, NEWBURGER JW: Spectrum of renal anomalies in patients with Williams syndrome. *J Pediatr* 119:771–773, 1991
16. JONES LK: Williams syndrome: an historical perspective of its evolution, natural history and etiology. *Am J Med Genet (suppl)* 6:89–96, 1990
17. DEVANEY K, KAPUR SP, PATTERSON K, CHANDRA RS: Pediatric renal artery dysplasia: a morphologic study. *Pediatr Pathol* 11: 609–621, 1991
18. FINLEY JL, DABBS DJ: Renal vascular smooth muscle proliferation in neurofibromatosis. *Hum Pathol* 19:107–110, 1988
19. CLINICOPATHOLOGIC CONFERENCES OF THE MASSACHUSETTS GENERAL HOSPITAL. *N Engl J Med* 314:1304–1311, 1986
20. SUPERNEAU DW, WERTELECKI W, BLACKBURN WR, RIDDICK L: The occurrence of vascular occlusion in neurofibromatosis, in *Proceedings of the Greenwood Genetics Center*, edited by SAUL RA, Clinton, SC, Jacobs Press, 1983, pp 112–113
21. WERTELECKI W, SUPERNEAU DW, BLACKBURN WR, VARAKIS JN: Neurofibromatosis, skin hemangiomas, and arterial disease, in *Birth Defects: Original Article Series*, edited by NYHAN WL, JONES KL, New York, Alan R. Liss, 1982, pp 29–41
22. HOLT JF: Neurofibromatosis in children. *Am J Roentgenol* 130: 615–639, 1978
23. GREENE JF JR, FITZWATER JE, BURGESS J: Arterial lesions associated with neurofibromatosis. *Am J Clin Pathol* 62:481–487, 1974
24. HALONEN H, HALONEN V, DONNER M, IIVANAINEN M, VUOLIO M, MAKINEN J: Occlusive disease of intracranial main arteries with collateral networks in children. *Neuropaediatrie* 4:187–206, 1973
25. TILFORD DL, KELSCH RC: Renal artery stenosis in childhood neurofibromatosis. *Am J Dis Child* 126:665–668, 1973
26. FIENMAN NL, YAKOVAC WC: Neurofibromatosis in childhood. *J Pediatr* 76:339–346, 1970
27. GRAD E, RANCE CP: Bilateral renal artery stenosis in association with neurofibromatosis (Recklinghausen's disease): report of two cases. *J Pediatr* 80:804–808, 1972
28. ITZCHAK Y, KATZNELSON D, BOICHIS H, JONAS A, DEUTSCH V: Angiographic features of arterial lesions in neurofibromatosis. *Am J Roentgenol* 122:643–647, 1974
29. FEYRTER F: Uber die vasculare Neurofibromatose, nach Untersuchnungen am menschlichen Magen-Darmschlauch. *Virchows Arch Pathol Anat Physiol Clin Med* 317:221–265, 1949
30. ANDERSON D, TANNEN RL: Tuberous sclerosis and chronic renal failure. Potential confusion with polycystic kidney disease. *Am J Med* 47:163–168, 1969
31. PERLMAN JM: Hypertension in newborn infants, in *Pediatric and Adolescent Hypertension*, edited by LOGGIE JMH, Boston, Blackwell Scientific, 1992, pp 347–356
32. ADELMAN RD: Long-term followup of neonatal renovascular hypertension. *Pediatr Nephrol* 1:35–41, 1987
33. VAILAS GN, BROUILLETTE RT, SCOTT JP, SHKOLNIK A, CONWAY J, WIRINGA K: Neonatal aortic thrombosis: recent experience. *J Pediatr* 109:101–108, 1986
34. FISHBACK H, RIEMENSCHNEIDER T, MENTZEL H: Morphologic aspects of Goldblatt hypertension in a newborn infant. *Clin Nephrol* 17:41–45, 1982
35. ADELMAN RD: Neonatal hypertension. *Pediatr Clin North Am* 23:99–110, 1978
36. BALL WS JR: Radiographic evaluation and intervention in the child with hypertension related to renal disease, in *Pediatric and Adolescent Hypertension*, edited by LOGGIE JMH, Boston, Blackwell Scientific, 1992, pp 264–287
37. SHARMA S, RAJANI M, SHRIVASTAVA S, KAUL U, KAMALAKAR T, TALWAR KK, SAXENA A: Non-specific aorto-arteritis (Takayasu's disease) in children. *Br J Radiol* 64:690–698, 1991
38. DANARAY TJ, ONG WH: Primary arteritis of abdominal aorta in children causing bilateral stenosis of renal artery and hypertension. *Circulation* 20:856–863, 1959
39. VINIJCHAIKUL K, BLACKBURN WR: Takayasu's arteriopathy. *Int Pathol Bull* 10:3–8, 1969
40. JANSEN JN, DONKER AJ, LUTH WJ, SMIT LM: Moyamoya disease associated with renovascular hypertension. *Neuropediatrics* 21:44–47, 1990
41. GROSS KR, MALLESON PN, CULHAM G, LIRENMAN DS, MCCORMICK AQ, PETTY RE: Vasculopathy with renal artery stenosis in a child with sarcoidosis. *J Pediatr* 108:724–726, 1986
42. MILLER JJ: Early-onset "sarcoidosis" and "familial granulomatous arthritis (arteritis)": the same disease. *J Pediatr* 109:387–388, 1986
43. INOUE O, AKAGI T, ICHINOSE E, KATO H: Systemic artery involvement in Kawasaki disease (*abstract*). *Circulation* 78:II440, 1988
44. HIGGINBOTTOM MC, GRISWOLD WR, JONES KL, VASQUEZ MD, MENDOZA SA, WILSON CB: The Cockayne syndrome: an evaluation of hypertension and studies of renal pathology. *Pediatrics* 64:929–934, 1979
45. HENRIKSEN T, MAHONEY EM, STEINBERG D: Interactions of plasma lipoproteins with endothelial cells. *Ann NY Acad Sci* 401:102–116, 1982
46. NEILL CA, DINGWALL MM: A syndrome resembling progeria: a review of two cases. *Arch Dis Child* 25:213–23, 1950
47. ANTIGNAC C, GUBLER MC, GAREL L, DECHAUX M, LENOIR G, HABIB R, BROYER M: Diffuse arterial calcified elastopathy. *Arch Mal Couer Vaiss* 78:1701–1705, 1985
48. GUBLER MC, ANTIGNAC C, BROYER M, GAREL L, LENOIR G, NIAUDET P, DECHAUX M, HABIB R: Diffuse arterial calcified elastopathy—a new cause of renovascular hypertension in children. *Int J Pediatr Nephrol* 6:47–54, 1985
49. ROSENBLUM ND, INGELFINGER JR: Hypertension in children with chronic renal insufficiency, in *Pediatric and Adolescent Hypertension*, edited by LOGGIE JMH, Boston, Blackwell Scientific, 1992, pp 239–251
50. INGELFINGER J, BREWER ED: Pediatric post-transplant hypertension: a review of current standards of care. *Child Nephrol Urol* 12:139–146, 1992
51. SUKAROCHANA K, TOLENTINO W, KIESWETHER WB: Wilms' tumor and hypertension. *J Pediatr Surg* 7:573–578, 1972
52. NAIDICH TP, SPRAYREGAN S, GOLDMAN AG, SPIEGELMAN SS: Renal artery alterations associated with pheochromocytoma. *Angiology* 23:488–499, 1972
53. SILVER D, CLEMENTS JB: Renovascular hypertension from renal

artery compression by congenital bands. *Ann Surg* 183:161–165, 1976
54. Spark RF, Berg S: Renal trauma and hypertension. *Arch Intern Med* 136:1097–1100, 1976
55. Castle CH: Iatrogenic renal hypertension: two unusual complications of surgery for familial pheochromocytoma. *JAMA* 225: 1085–1088, 1973
56. Daniels SR, Loggie JMH, McEnery PT, Towbin RB: Clinical spectrum of intrinsic renovascular hypertension in children. *Pediatrics* 180:698–704, 1987
57. Makker ST, Moorthy B: Fibromuscular dysplasia of renal arteries: an important cause of renovascular hypertension in children. *J Pediatr* 95:940–945, 1979
58. Lawson JD, Boerth R, Foster JG, Dean RH: Diagnosis and management of renovascular hypertension in children. *Arch Surg* 112:1307–1316, 1977
59. Sinaiko AB: General considerations and clinical approach to the management of hypertension, in *Pediatric and Adolescent Hypertension*, edited by Loggie JMH, Boston, Blackwell Scientific, 1992, pp 119–126
60. Sealey JE, Laragh JH: The renin-angiotensin-aldosterone system for normal regulation of blood pressure and sodium and potassium homeostasis, in *Hypertension: Pathophysiology, Diagnosis and Management*, edited by Laragh JH, Brenner BM, New York, Raven Press, 1990, pp 1329–1348
61. Wilson DM, Stevenson DK, Luetscher JA: Plasma prorenin and renin in childhood and adolescence. *Am J Dis Child* 142:1070–1072, 1988
62. Dillon MJ, Smellie JM: Peripheral plasma renin activity, hypertension and renal scarring in children. *Contrib Nephrol* 39:68–80, 1984
63. Hiner LB, Gruskin AB, Baluarte HJ, Cote ML: Plasma renin activity in normal children. *J Pediatr* 89:258–261, 1976
64. Kotchen TA, Strickland AL, Rice TW, Walters DR: A study of the renin-angiotensin system in newborn infants. *J Pediatr* 80:938–946, 1972
65. Parrott TS, Woodard JR, Trulock TS, Glenn JF: Segmental renal vein renins and partial nephrectomy for hypertension in children. *J Urol* 131:736–739, 1984
66. Dillon MJ, Gordon I, Shah V: 99m-Tc-DMSA scanning and segmental renal vein renin estimations in children with renal scarring. *Contrib Nephrol* 39:20–27, 1984
67. Stringer DA, deBruyn R, Dillon MJ, Gordon I: Comparison of aortography, renal vein renin sampling, radionuclide scans, ultrasound and the IVU in the investigation of childhood renovascular hypertension. *Br J Radiol* 57:11–12, 1984
68. Slovis TL: Pediatric renal anomalies and infections, in *Neonatal and Pediatric Ultrasonography*, edited by Babcock DS, New York, Churchill Livingstone, 1989, pp 157–145
69. Maia CR, Bittar AE, Goldani JC, Deital LM, Garcia VB: Doppler ultrasonography for the detection of renal artery stenosis in transplanted kidneys. *Hypertension* 19 (suppl 2):II207–II209, 1992
70. Sauvain JL, Bourscheid D, Pierrat V, Cuenin E, Chavanne C, Rocq B, Chapoutot J, Ory JP, Sol F: Duplex Doppler ultrasonography of intra-renal arteries. Normal and pathologic aspects. *Ann Radiol* (Paris) 34:237–247, 1991
71. Deeg KH, Nagler B, Schonau E, Ruder H: Color-coded Doppler sonography of the kidney blood vessels in childhood. II. Pathological findings. *Monatsschr Kinderheilkd* 138:337–348, 1990
72. Eidt JF, Fry RE, Clagett GP, Fisher DF Jr, Alway C, Fry WJ: Postoperative follow-up of renal artery reconstruction with duplex ultrasound. *J Vasc Surg* 8:667–673, 1988
73. Fry WJ, Daniels SR: Renovascular hypertension in the pediatric age group, in *Pediatric and Adolescent Hypertension*, edited by Loggie JMH, Boston, Blackwell Scientific, 1992, pp 252–263
74. Stanley P, Gypes MT, Olson DL, Gates GF: Renovascular hypertension in children and adolescents. *Radiology* 129:123–131, 1978
75. Korobkin M, Perloff DL, Palubinskas AJ: Renal arteriography in the evaluation of unexplained hypertension in children and adolescents. *J Pediatr* 88:388–393, 1976
76. Slavis SA, Geil GE, Martin DC: Extra-adrenal pheochromocytoma causing renal artery stenosis and implications of magnetic resonance imaging as diagnostic tool. *Urology* 35:276–278, 1990
77. Choyke PL, Pollack HM: The role of MRI in diseases of the kidney. *Radiol Clin North Am* 26:617–631, 1988
78. Mitchell DG, Tobin M, LeVeen R, Tomaczewski J, Alavi A, Staum M, Kundel H: Induced renal artery stenosis in rabbits: magnetic resonance imaging, angiography, and radionuclide determination of blood volume and blood flow. *Magn Reson Imaging* 6:113–124, 1988
79. Blaufox MD, Fine EJ: Role of nuclear medicine techniques for evaluating hypertensive disease, in *Hypertension: Pathophysiology, Diagnosis and Management*, edited by Laragh JH, Brenner BM, New York, Raven Press, 1990, pp 1509–1534
80. Heidenreich P, Lauer O, Fendel H, Oberdorfer M, Pabst HW: Total and individual renal function in children by means of 123-I-hippuran whole body clearance and scintillation camera. *Pediatr Radiol* 11:17, 1981
81. Dondi M: Captopril renal scintigraphy with ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG3) for detecting renal artery stenosis. *Am J Hypertens* 4 (12, pt 2):737s–740s, 1991
82. Geyskes GG, Oei HY, Puylaert CB, Dorhout Mees EJ: Renovascular hypertension identified by captopril-induced changes in the renogram. *Hypertension* 9:451–458, 1987
83. Fommei E, Bellina R, Bertelli P, Gazzetti P, Palla L, Ragazzini A, Ghione S: Interactive functional imaging of renal scintigraphy after captopril in the detection of global and segmental hypoperfusion. *Contrib Nephrol* 56:111–116, 1987
84. Tonkin IL, Stapleton FB, Roy S III: Digital subtraction angiography in the evaluation of renal vascular hypertension in children. *Pediatrics* 81:150–158, 1988
85. Busch HP, Strass LG, Hoevels J, Georgi M: Fibromuscular dysplasia, a pitfall in intravenous digital subtraction angiography. *Eur J Radiol* 4:42–43, 1984
86. Gomes AS, Pais SO, Barbaric L: Digital subtraction angiography in the evaluation of hypertension. *Am J Roentgenol* 140:779–783, 1983
87. Chevalier RL, Tegtmeyer CJ, Gomez RA: Percutaneous transluminal angioplasty for renovascular hypertension. *Pediatr Nephrol* 1:89–98, 1987
88. Watson AR, Balfe JW, Hardy BE: Renovascular hypertension in childhood: a changing perspective in management. *J Pediatr* 106:366–372, 1985
89. Stanley JC, Fry WJ: Pediatric renal artery occlusive disease and renovascular hypertension. *Arch Surg* 116:669–676, 1981
90. Vermeulen F, Stas F, Delegher L, Buyssens N, Stalpaert G, Praesmans W, Lauwers G, Sloof F, van Pelt L, van Gorp L: Surgical correction of renovascular hypertension in children. *J Cardiovasc Surg* 16:21–34, 1975
91. Fry WJ, Ernst CB, Stanley JC, Brink B: Renovascular hypertension in the pediatric patient. *Arch Surg* 107:692–698, 1973
92. Tegtmeyer CJ, Kellum CD, Ayers CR: Percutaneous transluminal angioplasty of the renal artery: results and long term follow-up. *Radiology* 153:77–84, 1984
93. Sos TA, Pickering DG, Sniderman KW, Saddekni S, Case DB, Silane MF, Vaughan ED, Laragh JH: Percutaneous transluminal renal angioplasty in renovascular hypertension due to atheroma or fibromuscular dysplasia. *N Engl J Med* 309:274–279, 1983
94. Tegtmeyer CJ, Elson J, Glass TA, Ayers CR, Chevalier RL, Wellons HA, Studdard WE Jr: Percutaneous transluminal angioplasty: the treatment of choice for renovascular hypertension due to fibromuscular dysplasia. *Radiology* 143:631–637, 1982
95. Martin EC, Mattern RF, Baer L, Fankuchen EI, Casarella WJ: Renal angioplasty for hypertension: predictive factors for long term success. *Am J Roentgenol* 137:921–924, 1981
96. Towbin RB, Ball WS Jr: Pediatric interventional radiology. *Radiol Clin North Am* 26:419–440, 1988
97. Mali WP, Puijlaert CB, Kouwenberg HJ, Klinge J, Donckerwolcke RAMG, Geijskes BG, Overbosch EH, Rosenbusch GJE, Ludwig WW, Feldberg MAM: Percutaneous transluminal renal angioplasty in children and adolescents. *Radiology* 165:391–394, 1987

98. MALLMANN R, ROTH FJ: Treatment of neurofibromatosis associated renal artery stenosis with hypertension by percutaneous transluminal angioplasty. *Clin Exp Hypertens* 8:893–899, 1986
99. MILLER GA, FORD KK, BRAUN SD, NEWMAN GE, MOORE AV JR, MALONE R, DUNNICK NR: Percutaneous transluminal angioplasty versus surgery for renovascular hypertension. *Am J Roentgenol* 144:447–450, 1985
100. STANLEY P, HIESHINA G, MEHRINGER M: Percutaneous transluminal angioplasty for pediatric renovascular hypertension. *Radiology* 153:101–104, 1984
101. LUND G, SINAIKO A, CASTANEDA-ZUNIGA WR, CRAGG A, SALOMONOWITZ E, AMPLATZ K: Percutaneous transluminal angioplasty for treatment of renal artery stenosis in children. *Eur J Radiol* 4:254–257, 1984
102. STANLEY P, SENAC MO JR, BAKODY P, MALEKZADEH MH: Percutaneous transluminal dilatation for renal artery stenosis in a 22-month-old hypertensive girl. *Am J Roentgenol* 140:983–984, 1983
103. BARTH KH, BRUSILOW SW, KAUFMAN SL, FERRY FT: Percutaneous transluminal angioplasty of homographic renal artery stenosis in a 10 year old girl. *Pediatrics* 67:675–677, 1981
104. MCCOOK TA, MILLS SR, KIRKS DR, HEASTON DK, SEIGLER HG, MALONE RB, OSOFSKY SG: Percutaneous transluminal renal artery angioplasty in a 3½ year old hypertensive girl. *J Pediatr* 97:958–960, 1980
105. ROBINSON L, GEDROYE W, REIDY J, SAXTON HM: Renal artery stenosis in children. *Clin Radiol* 44:376–382, 1991
106. KUHN FP, KUTKUHN B, TORSELLO G, MODDER U: Renal artery stenosis: preliminary results of treatment with the Strecker stent. *Radiology* 180:367–372, 1991
107. TEIGEN CL, MITCHELL SE, VENBRUX AC, CHRISTENSON MJ, MCLEAN RH: Segmental renal artery embolization for treatment of pediatric renovascular hypertension. *J Vasc Interv Radiol* 3:111–117, 1992
108. WARREN WC, WARSHAW BL, HYMES LC, SONES PJ JR: Selective embolization of stenotic intrarenal artery for control of hypertension. *J Pediatr* 101:743–745, 1982
109. ELISCU EH, HAIRE HM, TEW FT, NEWTON LW: Control of malignant renovascular hypertension by percutaneous transluminal angioplasty and therapeutic renal embolization. *Am J Roentgenol* 134:815–817, 1980
110. ADLER J, EINHORN R, MCCARTHY J, GOODMAN A, SOLANGI K, VARANSI U, THELMO W: Gelfoam embolization of the kidneys for treatment of malignant hypertension. *Radiology* 128:45–48, 1978
111. GRUSKIN AB, LERNER GR, FLEISHMANN LE: Diuretic usage in hypertensive children, in *Pediatric and Adolescent Hypertension*, edited by LOGGIE JMH, Boston, Blackwell Scientific, 1992, pp 127–137
112. LERNER GR, GRUSKIN AB: Calcium channel antagonists and ACE inhibitors, in *Pediatric and Adolescent Hypertension*, edited by LOGGIE JMH, Boston, Blackwell Scientific, 1992, pp 159–177
113. DILLON MJ: Drug treatment of hypertension, in *Pediatric Nephrology* (2nd ed), edited by HOLLIDAY MA, BARRATT TM, VERNIER RL, Baltimore, Williams & Wilkins, 1988, pp 758–765
114. SIEGLER RL, BREWER ED: Effect of siblingual or oral nifedipine in the treatment of hypertension. *Pediatrics* 112:811–813, 1988
115. O'DEA RF, MIRKIN BL, ALWARD CT, SINAIKO AR: Treatment of neonatal hypertension with captopril. *J Pediatr* 113:403–406, 1988
116. MIRKIN BL, NEWMAN TJ: Efficacy and safety of captopril in the treatment of severe childhood hypertension: report of the international collaborative study group. *Pediatrics* 75:1091–1100, 1985
117. HRICIK DE, BROWNING PT, KOPELMAN R, GOORNO WE, MADIAS NE, DZAU VJ: Captopril induced functional renal insufficiency in patients with bilateral renal artery stenosis or renal artery stenosis in a solitary kidney. *N Engl J Med* 308:373–376, 1983
118. OLIVER J: *Nephrons and Kidneys: a Quantitative Study of Development and Evolutionary Mammalian Renal Architectonics*. New York, Harper and Row, 1968
119. RISAU W, DREXLER H, ZERWES H-G, SCHNURCH H, ALBRECHT U, HALLMANN R: Regulation of blood vessel growth and differentiation, in *Molecular Mechanisms in Cellular Growth and Differentiation*, edited by BELLVE AR, VOGEL AJ, New York, Academic Press, 1991, pp 207–222
120. MADRI JA, MARX M: Matrix composition, organization and soluble factors: modulators of microvascular cell differentiation in vitro. *Kidney Int* 41:560–565, 1992
121. PARKER PJ, KATAN M: Molecular biology of oncogenes and cell control mechanisms. *Ellis Horwood Series in Molecular Biology*, New York, Ellis Horwood Publishers, 1990, pp 1–181
122. SCHWARTZ SM, HEIMARK RL, MAJESKY MW: Developmental mechanisms underlying pathology of arteries. *Physiol Rev* 70: 1177–1209, 1990
123. FOLKMAN J, KLAGSBRUN M: Angiogenic factors. *Science* 235: 442–447, 1987
124. WOLINSKY H, GLAGOV S: A lamellar unit of aortic medial structure and function in mammals. *Circ Res* 20:99–101, 1967
125. ECCLESTON-JOYNER CA, GRAY SD: Arterial hypertrophy in fetal and neonatal spontaneously hypertensive rat. *Hypertension* 12: 513–518, 1988
126. GRAY SD: Anatomical and physiologic aspects of cardiovascular function in Wistar-Kyoto and spontaneously hypertensive rats at birth. *Clin Sci* 63 (suppl 8):383–385, 1982
127. DZAU VJ, GIBBONS GH, PRATT RE: Molecular mechanisms of vascular renin-angiotensin system in myointimal hyperplasia. *Hypertension* 18 (suppl II):II100–II105, 1991
128. KRIEGER JE, DZAU VJ: Molecular biology of hypertension. *Hypertension* 18 (suppl I):I3–I17, 1991
129. GOMEZ RA, LYNCH KR, STURGILL BC, ELWOOD JP, CHEVALIER RL, CAREY RM, PEACH MJ: Distribution of renin mRNA and its protein in the developing kidney. *Am J Physiol* 257:F850–F858, 1989
130. SIGMUND CD, JONES CA, JACOB HJ, INGELFINGER J, KIM U, GAMBLE D, DZAU VJ, GROSS KW: Pathophysiology of vascular smooth muscle in renin-promoter-T-antigen transgenic mice. *Am J Physiol* 260:F249–F257, 1991
131. BACHMANN S, PETERS J, ENGLER E, GANTEN D: Transgenic rats carrying the mouse renin gene—morphological characterization of a low-renin hypertension model. *Kidney Int* 41:24–36, 1992
132. ESTIVILL X, LAZARO C, CASALS T, RAVELLA A: Recurrence of a nonsense mutation in the NF1 gene causing classical neurofibromatosis type 1. *Hum Genet* 88:185–188, 1991
133. GOLDBERG NS, COLLINS FS: The hunt for the neurofibromatosis gene. *Arch Dermatol* 127:1705–1707, 1991
134. DECLUE JE, COHEN BD, LOWY DR: Identification and characterization of the neurofibromatosis type 1 protein product. *Proc Natl Acad Sci USA* 88:9914–9918, 1991
135. GUTMANN DH, WOOK DL, COLLINS FS: Identification of the neurofibromatosis type 1 gene product. *Proc Natl Acad Sci USA* 88:9658–9662, 1991
136. PELTONEN J, JAAKKOLA SD, LEBWOHL M, RENVALL S, RISTELI L, VIRTANEN I, UITTO I: Cellular differentiation and expression of matrix genes in type 1 neurofibromatosis. *Lab Invest* 59:760–771, 1988
137. VAALASTI A, SUOMALAINEN H, KUOKKANEN K, RECHARDT L: Neuropeptides in cutaneous neurofibromas of von Recklinghausen's disease. *J Cutan Pathol* 178:371–373, 1990
138. HALPERN M, CURRARINO G: Vascular lesions causing hypertension in neurofibromatosis. *N Engl J Med* 273:248–252, 1965
139. CHAPMAN AB, JOHNSON A, GABOW PA, SCHRIER RW: The renin-angiotensin-aldosterone system and autosomal dominant polycystic kidney disease. *N Engl J Med* 323:1091–1096, 1990
140. TORRES VE, TURNER ST, BURNETT JC JR, WILSON DM: Pathogenesis of hypertension in polycystic kidney disease (*abstract*). *J Am Soc Nephrol* 1:303, 1990
141. EVANS JA, STRANC LC: Cystic renal disease and cardiovascular anomalies. *Am J Med Genet* 33:398–401, 1989
142. ROS MA, OJEDA JL, GARCIA-PORRERO JA: Vascular architecture modifications in the steroid-induced polycystic kidney. *Nephron* 40:332–340, 1985
143. CROCKER DW, NEWTON RA, MAHONEY EM, HARRISON JH: Hypertension due to primary renal ischemia. A correlation of juxtaglomerular cell counts with clinicopathological findings in twenty-five cases. *N Engl J Med* 267:794–800, 1962
144. WILSON C, BYROM FB: The vicious circle in Bright's disease: experimental evidence from the hypertensive rat. *Q J Med* 10:65–93, 1941

145. ARANT BS JR, SOTELO-AVILA C, BERNSTEIN J: Segmental "hypoplasia" of the kidney (Ask-Upmark). *J Pediatr* 95:931–939, 1979
146. SINAIKO AR, MIRKIN BL, HENDRICK DA, GREEN TP, O'DEA FR: Antihypertensive effect and elimination kinetics of captopril in hypertensive children with renal disease. *J Pediatr* 103:799–805, 1983
147. BOUISSOU F, MEGUIRA B, ROSTIN M, FONTAINE C, CHARLET JP, BARTHE P: Long-term therapy by captopril in children with renal hypertension. *Clin Exp Hypertens A* 8:841–845, 1986
148. CLARKE WR, SCHROTT HG, LEAVERTON PE, CONNOR WE, LAUER RM: Tracking of blood lipids and blood pressures in school age children: the Muscatine study. *Circulation* 58:626–634, 1978
149. PRINEAS RJ, GOMEZ-MARIN O, GILLUM RF: Tracking of blood pressure in children and nonpharmacologic approaches to the prevention of hypertension. *Ann Behav Med* 7:25–29, 1985
150. KILCOYNE MM: Adolescent hypertension. II. Characteristics and response to treatment. *Circulation* 50:1014–1019, 1974
151. MORRIS BJ, GRIFFITHS LR: Frequency in hypertensives of alleles for a RFLP associated with the renin gene. *Biochem Biophys Res Comm* 150:219–224, 1988
152. NAFTALIN AJ, WILLIAMS R, BURT D, PAUL M, PRATT RE, HOBART P, CHIRGWIN J, DZAU VJ: A lack of genetic linkage of renin gene restriction fragment length polymorphisms with human hypertension. *Hypertension* 14:614–618, 1989
153. HILBERT P, LINDPAINTNER K, BECKMANN JS, SERIKAWA T, SOUBRIER F, DUBAY C, CARTWRIGHT P, DEGOUYON B, JULIER C, TAKAHASI S, VINCENT M, GANTEN D, GEORGES M, LATHROP GM: Chromosomal mapping of two genetic loci associated with blood-pressure regulation in hereditary hypertensive rats. *Nature* 353:521–529, 1991
154. JACOB JH, LINDPAINTNER K, LINCOLN SE, KUSUMI K, BUNKER RK, MAO Y-P, DZAU VJ, LANDER E: Genetic mapping of a gene causing hypertension in the stroke-prone spontaneously hypertensive rat. *Cell* 67:213–224, 1991
155. SMITH DW, JONES KL: The Williams elfin facies syndrome: a new perspective. *J Pediatr* 86:718–723, 1975
156. HEILICZER JD, MOORE ES: Hypertension in the black population, in *Pediatric and Adolescent Hypertension*, edited by LOGGIE JHM, Boston, Blackwell Scientific, 1992, pp 357–368
157. DOHI Y, CRISCIONE L, LUSCHER TF: Renovascular hypertension impairs formation of endothelium-derived relaxing factors and sensitivity to endothelin-1 in resistance arteries. *Br J Pharmacol* 104:349–354, 1991
158. LIN S-Y, CAI H, GONG Q-Y, YANG Z-C, ZHOU J-H, ZHANG D, ZHANG Z-K: Role of endothelin in the pathogenesis of hypertension in spontaneously hypertensive and 2 kidney, 1 clip rats. *Chin Med J* 103:748–753, 1990
159. LERMAN A, EDWARDS BS, HALLERT JW, HEUBLEIN DM, SANDBERG SM, BURNETT JC JR: Circulating and tissue endothelin immunoreactivity in advanced atherosclerosis. *N Engl J Med* 325:997–1001, 1991
160. HALLEY SE, WHITE WB, RAMSBY GR, VOYTOVICH AE: Renovascular hypertension in Moyamoya syndrome. Therapeutic response to percutaneous transluminal angioplasty. *Am J Hypertens* 1:348–352, 1988
161. JACKSON B, FRANZE L, SUMITHRAN E, JOHNSTON CI: Pharmacological nephrectomy with chronic angiotensin converting enzyme inhibitor treatment in renovascular hypertension in the rat. *J Lab Clin Med* 115:21–27, 1990
162. JACKSON B, JOHNSTON CI: Angiotensin converting enzyme inhibition in renal disease; contrasting effects on renal function in renal artery stenosis and progressive renal injury. *J Hum Hypertens* 3 (suppl 1):107–115, 1989
163. JACKSON B, FRANZE L, SUMITHRAN E, JOHNSTON CI: Chronic angiotensin converting enzyme inhibition in the two-kidney, one-clip hypertensive rat. *J Hypertens* Suppl 6:S408–S411, 1988
164. PAYNE RM, MARTIN TC, BOWER RJ, CANTER CE: Management and follow-up of arterial thrombosis in the neonatal period. *J Pediatr* 114:853–858, 1989