Hypertension and the Kidney

8.4

FIGURE 8-3
Pathophysiology of malignant hypertension. The vicious cycle of malignant hypertension is best demonstrated in the kidneys. This cycle also applies equally well to the vascular beds of the retina, pancreas, gastrointestinal tract, and brain [1]. In this scheme, severe hypertension is central. Hypertension may be either essential or secondary to any one of a variety of causes. Because not all patients develop malignant hypertension despite equally severe hypertension, the interaction between the level of blood pressure and the adaptive capacity of the vasculature may be important. In this regard, chronic hypertension results in thickening and remodeling of arteriolar walls that may be an adaptive mechanism to prevent vascular damage from the mechanical stress of hypertension. However, when the blood pressure increases suddenly or increases to a critical level, these adaptive mechanisms may be overwhelmed, resulting in vascular damage. As a result of the mechanical stress of increased transmural pressure, focal segments of the arteriolar vasculature become dilated, producing a sausage-string pattern. Endothelial permeability increases in the dilated segments, leading to extravasation of fibrinogen, fibrin deposition in the media, and necrosis of smooth muscle cells (fibrinoid necrosis). Platelet adherence to damaged endothelium with release of platelet-derived growth factor induces migration of smooth muscle cells to the intima where they proliferate (neointimal proliferation) and produce mucopolysaccharide. These cells also produce collagen, resulting in proliferative endarteritis, musculomucoid hyperplasia, and eventually, fibrotic obliteration of the vessel lumen. Occlusion of arterioles leads to accelerated glomerular obsolescence and end-stage renal disease. Other factors may synergize with hypertension to damage the arterial vasculature. Renal ischemia leads to activation of the renin-angiotensin system that can cause further elevation of blood pressure and progressive vascular damage. Spontaneous natriuresis early in the course of malignant hypertension leads to volume depletion with activation of the renin-angiotensin system or catecholamines that further elevates blood pressure. It also is possible that angiotensin II may be directly vasculotoxic. Activation of the clotting cascade within the lumen of damaged vessels may lead to fibrin deposition with localized intravascular coagulation. Thus, microangiopathic hemolytic anemia is a common finding in malignant hypertension. Cigarette smoking and oral contraceptive use may contribute to development of malignant hypertension by decreasing prostacyclin production in the vessel wall and thereby inhibiting repair of hypertension-induced vascular injury. Low dietary intake of potassium may help promote vascular smooth muscle proliferation and therefore predisposes to the development of malignant hypertension in Blacks with severe essential hypertension. PDGF—platelet-derived growth factor.
Malignant hypertension is not a single disease entity but, rather, a syndrome in which the hypertension can be either primary (essential) or secondary to any one of a number of different causes [2]. Among Black patients the underlying cause is almost always essential hypertension. Chronic glomerulonephritis is thought to be the cause of malignant hypertension in up to 20% of cases. Unless a history of an acute nephritic episode or long-standing hematuria or proteinuria is available, the underlying glomerulonephritis may only become apparent when a renal biopsy is performed. Recently, immunoglobulin A (IgA) nephropathy has been reported as an increasingly frequent cause of malignant hypertension. In one series of 66 patients with IgA nephropathy, 10% developed malignant hypertension [3]. Chronic atrophic pyelonephritis is children, often a result of underlying vesicoureteral reflux, is the most common cause of malignant hypertension [4]. In Australia, malignant hypertension complicates up to 7% of cases of analgesic nephropathy [5]. Transient malignant hypertension responsive to volume expansion has been reported in analgesic nephropathy. It has been suggested that interstitial disease with salt-wasting is important in the pathogenesis by causing profound volume depletion with activation of the renin-angiotensin axis. Malignant hypertension is both an early and late complication of radiation nephritis that can occur up to 11 years after radiotherapy. Renovascular hypertension from either fibromuscular dysplasia or atherosclerosis is a well-recognized cause of malignant hypertension. In a series of 123 patients with malignant hypertension, renovascular hypertension was found in 43% of Whites and 7% of Blacks [6]. Among women of childbearing age, oral contraceptives can cause malignant hypertension [7]. In the absence of underlying renal disease, with discontinuation of the drug, long-term prognosis is excellent. Severe hypertension that may become malignant is a common complication of atherosclerotic renal disease. In patients presenting with malignant hypertension in the weeks to months after an arteriographic procedure, a careful history and physical should be performed to look for evidence of atheroembolism. Scleroderma renal crisis is the most life-threatening complication of progressive systemic sclerosis. Scleroderma renal crisis is characterized by hypertension that may enter the malignant phase. Even in the absence of hypertensive neuroretinopathy suggesting malignant hypertension, the renal lesion in scleroderma renal crisis is virtually indistinguishable from primary malignant nephrosclerosis [8]. Patients with antiphospholipid antibody syndrome, either primary or secondary to systemic lupus erythematosus, can develop malignant hypertension with renal insufficiency as a result of thrombotic microangiopathy [9]. The endocrine causes of hypertension only rarely lead to malignant hypertension. Pheochromocytoma can cause hypertensive crises owing to hypertensive encephalopathy or acute hypertensive heart failure in the absence of hypertensive neuroretinopathy (malignant hypertension).
Tertiary hyperaldosteronism after treatment of malignant hypertension. The diagnosis of primary hyperaldosteronism must be made with caution in patients with a history of malignant hypertension. After successful treatment of malignant hypertension, plasma renin activity rapidly normalizes, whereas aldosterone secretion may remain elevated for up to a year. This phenomenon has been attributed to persistent adrenal hyperplasia induced by long-standing hyperreninemia during the malignant phase [10]. During this phase of tertiary hyperaldosteronism, despite suppressed renin activity, hypokalemia, metabolic alkalosis, and aldosterone levels that are not suppressible, mimic primary hyperaldosteronism. Adrenal imaging studies reveal bilateral nodular adrenal hyperplasia. With continued long-term control of blood pressure this hyperaldosteronism remits spontaneously.

Funduscopic findings are pivotal in the diagnosis of malignant hypertension. Keith and Wagener [11] graded retinal findings in hypertensive patients as follows: grade I, arteriolar narrowing; grade II, arteriovenous crossing changes; grade III, hemorrhages and exudates; grade IV, the changes in grade III plus papilledema. Although this classification of hypertensive retinopathy is of great historical importance, its clinical utility has several limitations, eg, it is extremely difficult to quantify arteriolar narrowing. In this regard, a tendency exists for significant observer bias such that patients with mild hypertension and questionable narrowing are invariably assigned to grade I. More importantly, this classification does not distinguish the retinal changes of benign and malignant hypertension. For example, the clinical significance of a cotton-wool spot appearing in the fundus of a young man with severe hypertension (diagnostic of malignant hypertension) is quite different from the clinical significance of a hard exudate in the fundus of a 60-year-old man with moderate hypertension. The prognostic and therapeutic implications of these two types of exudates clearly are different, although both would be classified as grade III. For this reason, the Keith and Wagener classification has been supplanted by the more clinically useful classification of hypertensive retinopathy shown here. This classification system draws a distinction between retinal arteriosclerosis with arteriosclerotic retinopathy, which is characteristic of benign hypertension, and hypertensive neuroretinopathy, which defines the existence of malignant hypertension [12,13]. Retinal arteriosclerosis, which is characterized histologically by the accumulation of hyaline material in arteries, occurs in elderly normotensive persons or in the setting of long-standing benign hypertension. Funduscopic findings reflecting retinal arteriosclerosis include arteriolar narrowing, arteriovenous crossing changes, perivasculitis, and changes in the light reflex with copper or silver wiring. Arteriosclerotic retinopathy manifests as solitary round hemorrhages in the periphery of the fundus and hard exudates. The finding of retinal arteriosclerosis is of no prognostic significance with regard to the risk of coronary atherosclerosis or cerebrovascular disease. The arteries visualized with the ophthalmoscope are technically arterioles with a diameter of 0.1 mm. Hyaline arteriosclerosis of the retinal vessels is a process entirely distinct from the atherosclerotic process that affects larger muscular arteries. Thus, the finding of retinal arteriosclerosis cannot predict the presence of atherosclerosis of the coronary or cerebral vessels. This lack of clinical significance of retinal arteriosclerosis in hypertensive patients contrasts dramatically with the importance and prognostic significance of the finding of hypertensive neuroretinopathy. This finding is the clinical sine qua non of malignant hypertension. The appearance of striate hemorrhages or cotton-wool spots with or without papilledema closely parallels the development of fibrinoid necrosis and proliferative endarteritis in the kidney and other organs. Thus, the presence of hypertensive neuroretinopathy predicts the development of end-stage renal disease, or other life-threatening hypertensive complications, within a year if adequate control of the blood pressure is not achieved.