Micrograph of proliferative endarteritis in malignant hypertension (musculomucoid intimal hyperplasia). In malignant nephrosclerosis, the interlobular (cortical radial) arteries reveal characteristic lesions. These lesions are variously referred to as proliferative endarteritis, endarteritis fibrosa, musculomucoid intimal hyperplasia, or the onionskin lesion. The typical finding is marked thickening of the intima that obstructs the vessel lumen. In severely affected vessels the luminal diameter may be reduced to the caliber of a single erythrocyte. Occasionally, complete obliteration of the lumen by a superimposed fibrin thrombus occurs.

Traditionally, three patterns of intimal thickening have been described [15]. (1) The onionskin pattern consists of pale layers of elongated concentrically arranged myointimal cells along with delicate connective tissue fibrils that give rise to a lamellar appearance. The media often appears as an attenuated layer stretched around the expanded intima. (2) In the mucinous pattern, intimal cells are sparse. Seen is an abundance of foamy, faintly basophilic-staining amorphous material. (3) In fibrous intimal thickening, seen are few cells with an abundance of hyaline deposits, reduplicated bands of elastica, and coarse layers of collagen. The renal histology in Blacks with malignant hypertension demonstrates a characteristic finding in the larger arterioles and interlobular arteries known as musculomucoid intimal hyperplasia, with an abundance of cells and a small amount of myxoid material (that is light blue in color on hematoxylin and eosin staining) between the cells [16, 17]. These various intimal findings may represent progression over time from an initially cellular lesion to fibrosis of the intima. Electron microscopy demonstrates that in each type of intimal thickening the most abundant cellular element is a modified smooth muscle cell. This cell is called a myointimal cell. Proliferative endarteritis is thought to occur as a result of phenotypic modulation of medial smooth muscle cells that dedifferentiate from the normal contractile phenotype to acquire a more embryologic proliferative-secretory phenotype. It has been proposed that the endothelial injury in malignant hypertension results in attachment of platelets with release of platelet-derived growth factor (PDGF) that may induce the phenotypic change in smooth muscle cells. PDGF stimulates chemotaxis of medial smooth muscles to the intima, where they proliferate and secrete mucopolysaccharide and later collagen and other extracellular matrix proteins, resulting in proliferative endarteritis, musculomucoid hyperplasia, and ultimately fibrous intimal thickening. (Hematoxylin and eosin stain, original magnification × 100.)
Micrograph of hyaline arteriolar nephrosclerosis in benign hypertension. It is important to draw a clear distinction between malignant hypertension and benign hypertension with regard to renal histology and clinical renal involvement. In benign arteriolar nephrosclerosis caused by benign hypertension, the characteristic histologic lesion is hyaline arteriosclerosis. In hyaline arteriosclerosis there is expansion of the intima of afferent arterioles with hyaline material that stains a pale-pink color on periodic acid–Schiff staining (large arrow). Patchy (focal) ischemic atrophy of the glomeruli usually is seen. Many glomeruli appear normal, whereas some are completely hyalinized. Atrophic tubules (small arrows), sometimes filled with amorphous material, may be seen in the vicinity of ischemic glomeruli. The severity of the glomerular and tubular changes generally reflect the extent of vascular involvement with hyaline arteriosclerosis. On gross examination, the kidneys are small with a granular-appearing capsular surface (contracted granular kidney). The loss of renal mass primarily is due to a thinning of the cortex. In untreated malignant hypertension, relentless progression to end-stage renal disease (ESRD) occurs within a year. In contrast, in benign hypertension, without underlying renal disease or superimposed malignant hypertension, despite well-established folklore to the contrary, ESRD seldom develops [21,22]. In benign hypertension, there is a usually a long asymptomatic phase, with eventual complications resulting from cerebrovascular disease, atherosclerotic disease, or congestive heart failure, in the absence of significant renal impairment despite histologic evidence of benign nephrosclerosis. In this regard, patients classified as having ESRD owing to “hypertensive nephrosclerosis” typically exhibit advanced disease initially, making the original process that initiated the renal disease difficult to detect. Moreover, significant racial bias may occur in the clinical diagnosis of the cause of ESRD [23]. Nephrologists presented with identical case histories of hypothetical patients with ESRD and hypertension in which the race is arbitrarily stated to be Black or White, tend to diagnose hypertensive nephrosclerosis in Blacks and chronic glomerulonephritis in Whites. It has been proposed that many of the patients presumed clinically to have ESRD owing to benign hypertension, actually have occult intrinsic renal disease with chronic glomerulonephritis, unrecognized bilateral atherosclerotic renal artery stenosis with ischemic nephropathy, atheroembolic renal disease, or episodes of malignant hypertension that had gone undetected [21,22]. (Periodic acid-Schiff stain, original magnification × 100.)
Malignant hypertension must be treated expeditiously to prevent complications such as hypertensive encephalopathy, acute hypertensive heart failure, and renal failure. The traditional approach to patients with malignant hypertension has been the initiation of potent parenteral agents. Listed are the settings in which parenteral antihypertensive therapy is mandatory in the initial management of malignant hypertension. Parenteral therapy generally should be used in patients with evidence of acute end-organ dysfunction or those unable to tolerate oral medications. Nitroprusside is the treatment of choice for patients requiring parenteral therapy. Diazoxide, employed in minibolus fashion to avoid sustained overshoot hypotension, may be advantageous in patients for whom monitoring in an intensive care unit is not feasible. It generally is safe to reduce the mean arterial pressure by 20% or to a level of 160 to 170 mm Hg systolic over 100 to 110 mm Hg diastolic. The use of a short-acting agent such as nitroprusside has obvious advantages because blood pressure can be stabilized quickly at a higher level if complications develop during rapid blood pressure reduction. When no evidence of vital organ hypoperfusion is seen during this initial reduction, the diastolic blood pressure can be lowered gradually to 90 mm Hg over a period of 12 to 36 hours. Oral antihypertensive agents should be initiated as soon as possible to minimize the duration of parenteral therapy. The nitroprusside infusion can be weaned as the oral agents become effective. The cornerstone of initial oral therapy should be arteriolar vasodilators such as calcium channel blockers, hydralazine, or minoxidil. Usually, β-blockers are required to control reflex tachycardia, and a diuretic must be initiated within a few days to prevent salt and water retention, in response to vasodilator therapy, when the patient’s dietary salt intake increases. Diuretics may not be necessary as a part of initial parenteral therapy because patients with malignant hypertension often present with volume depletion (Fig. 8-20).

Many patients with malignant hypertension definitely require initial parenteral therapy. However, some patients may not yet have evidence of cerebral or cardiac dysfunction or rapidly deteriorating renal function and therefore do not require instantaneous control of blood pressure. These patients often can be managed with an intensive oral regimen, often with a β-blocker and minoxidil, designed to bring the blood pressure under control within 12 to 24 hours. After the immediate crisis has resolved and the patient’s blood pressure has been controlled with initial parenteral therapy, oral therapy, or both, lifelong surveillance of blood pressure is mandatory. If blood pressure control lapses, malignant hypertension can recur even after years of successful antihypertensive therapy. Triple therapy with a diuretic, β-blocker, and a vasodilator often is required to maintain satisfactory long-term blood pressure control.

### FIGURE 8-19

**INDICATIONS FOR PARENTERAL THERAPY IN MALIGNANT HYPERTENSION**

- Hypertensive encephalopathy
- Rapidly failing vision
- Pulmonary edema
- Intracerebral hemorrhage
- Rapid deterioration of renal function
- Acute pancreatitis
- Gastrointestinal hemorrhage or acute abdomen from mesenteric vasculitis
- Patients unable to tolerate oral therapy because of intractable vomiting