CHAPTER

86 Use of Drugs in Patients with Renal Failure

Ali J. Olyaei • Jessica L. Steffl • William M. Bennett

Chronic kidney disease (CKD) is associated with a great magnitude of morbidity and mortality in the United States. The recent data indicate that approximately 26 million Americans have CKD, including 350,000 patients with end-stage renal disease (ESRD) who require scheduled dialysis several times per week. Despite the advances in the field of dialysis and management of comorbid conditions in these patients, infections, cardiovascular complications, and adverse drug reactions are the most common cause of mortality in patients with CKD.[1,2] A number of studies have documented the role of medication dosing errors in the overall increase in mortality of patients with renal failure.[3–5] Although a number of algorithms and drug dosing recommendations have been proposed over the last two decades, most are not up-to-date, not adequately studied, and have not kept pace with new advances in the field of dialysis.[6] Acute or chronic renal insufficiency alters the pharmacokinetic and pharmacodynamic properties of most commonly used drugs significantly. Kidneys play an important role in the excretion of active drugs and their pharmacologically active metabolites. Drug accumulation and adverse drug reactions can develop rapidly if drug dosages are not adjusted according to reduced renal function in patients with CKD. Most drugs should be adjusted as renal function improves to ensure efficacy and dosage should be reduced if renal function continues to deteriorate. Even in drugs that are mostly metabolized through the liver, patients with renal failure are at greater risk of adverse drug reactions and toxicity.[7] Drug interactions are also a common problem in this population because most patients with renal insufficiency often have serious comorbid conditions requiring pharmacologic intervention.[8–20]

In addition, a large part of the difficulty in prescribing drugs for the rapidly growing numbers of older patients is due to age-related declines in renal function.[3] Finally, renal replacement therapies including hemodialysis are considered the treatment of choice in patients with ESRD. The effects of dialysis on drug elimination and the need for supplemental dosing must also be considered in patients receiving renal replacement therapy.[21–27]

In this chapter, the basic principles of pharmacokinetic modeling and drug dosing in patients with CKD or dialysis are reviewed. The changes in drug pharmacokinetics and pharmacodynamics are highlighted, and practical guidelines for drug dosing in these patients are provided. However, dialysis patients also face the risk of drug–drug and drug–disease interactions, thus, no specific dosing guideline can be given confidently because individual patient factors such as age, gender, nutrition, body fluid volume, and disease states may influence pharmacokinetic and pharmacodynamic parameters significantly. To provide safe and effective pharmacotherapy, the clinician must utilize clinical judgments, knowledge of altered pharmacokinetic properties, and the patient's specific physiologic status to administer drugs safely to a renal patient population. In order to optimize pharmacotherapy and avoid over- and undermedication, these factors should be taken into account and appropriate dosage adjustment should be considered.

PHARMACOKINETIC PRINCIPLES

The term pharmacokinetics refers to a mathematical model of the time course of drug concentration in a body compartment. Pharmacokinetic properties of a drug define or predict plasma concentrations and, therefore, drug activity or toxicity at the site of the action. Pharmacokinetics is the study of drug absorption, distribution, metabolism, and elimination. Pharmacokinetics can be thought of as the body's effect on the drug over time. A simplified scheme of drug pharmacokinetics is illustrated in Figure 86.1. The pharmacologic effect of any drug depends on the concentration of the unbound active drug or an active metabolite at the receptor site of action. The blood and tissue levels of a drug are functions of the administered dose, rate of its absorption, concentration, rate of metabolism or biotransformation, and rate of elimination.[9–13]

Drug Absorption

Following extravascular administration, drugs must be transported through a number of physiologic barriers

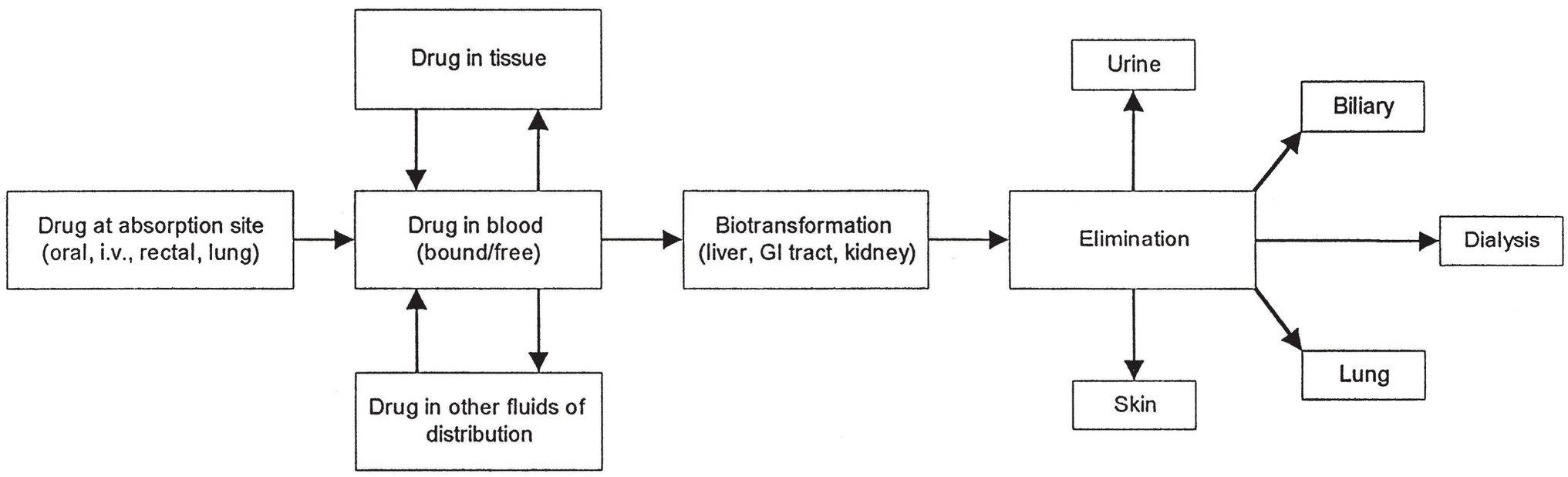


FIGURE 86.1 Pharmacokinetic factors involved in drug distribution.

before reaching the systemic circulation. Drug absorption and bioavailability relate to the amount of drug that reaches the systemic circulation after oral administration. The fraction or percent of administrated drug that reaches systemic circulation is known as bioavailability (F). These parameters are often highly specific for a given compound and vary with the physical and chemical properties of the drug, its formulation, the integrity of the absorptive surface, and the presence of other agents and/or food in the gastrointestinal tract. Absorption rates of most therapeutic agents are slow and unpredictable. Uremia-induced vomiting or sluggish peristalsis secondary to enteropathy may further reduce the onset of action of most agents. In patients with diabetes mellitus, the drug absorption is more variable due to autonomic neuropathy. Both calcium- and aluminum-containing phosphate binders may form insoluble complexes with certain drugs such as antibiotics or ferrous sulfate, thereby impeding absorption. Acidic drugs prefer an acidic environment for optimal absorption whereas weak basic drugs are better absorbed in a more alkalinized small intestine. Use of proton pump inhibitors or phosphate binders presumably reduces the rate of absorption of a number of acidic agents.[14–18] The gastrointestinal tract edema in patients with hypoalbuminemia may also diminish drug absorption.

Propranolol, morphine, and verapamil are examples of drugs that undergo first pass metabolism.[28,29] In first pass metabolism, a significant amount of the absorbed drug molecules are delivered to the liver via the portal vein. A drug is said to undergo significant first pass metabolism when it is metabolized in the liver so extensively upon absorption that only a small percentage of drug concentrations reaches the systemic circulation.[30,31] In addition many drugs may be metabolized via the cytochrome P-450 system in the gastrointestinal tract before reaching the systemic circulation. For example, it is well established that rifampin decreases and erythromycin increases the bioavailability of cyclosporine and calcium channel blockers by induction and inhibition of intestinal and hepatic cytochrome P-450 enzymes, respectively. Finally, patients with renal failure have a higher salivary urea concentration that increases the gastric ammonia levels and increases overall gastric pH. Drugs like iron and ketoconazole whose absorption is dependent on an acidic environment may have reduced bioavailability in renal failure.[29,32]

Volume of Distribution

The volume of distribution (Vd) for a specific drug is derived by dividing the fractional absorption of a dose by the plasma concentration.

$$\text{Volume of distribution (Vd)} = \frac{\text{Amount of drug in body}}{\text{Concentration of drug in plasma or blood (C)}} \qquad (86.1)$$

It is important to emphasize that Vd does not signify the total body fluid. Rather, it is an apparent volume needed for equal distribution of drug throughout the body compartment. For example, the plasma volume of a normal 70 kg man is approximately 3 to 3.5 L, whereas the Vd of 0.25 mg of digoxin to obtain a 0.7 ng per dL plasma level is 350 L, which is 10 times greater than the plasma volume. Therefore, Vd does not refer to a specific anatomic compartment per se. Instead, it is the volume of fluid in which the drug would need to be dissolved to give the observed plasma concentration.[33–35] A drug distributes in the body in a characteristic manner based on physiochemical properties of the drug and individual patient variables. Volume of distribution is used mathematically to determine the dose of a drug necessary to achieve a desired plasma concentration. Although the Vd is relatively constant for a given drug, many factors such as obesity, extracellular fluid volume status, age, gender, thyroid function, renal function, and cardiac output influence drug distribution. Volume of distribution echoes the water solubility and protein and tissue-binding characteristics of an individual agent. Drugs with a small Vd (Vd less than ~0.7 L per kg) are usually considered more water soluble. Highly lipid-soluble drugs have a large Vd with little retention of drug in the plasma because the drug tends to stay in the lipophilic tissue compartment. Drugs that are highly tissue bound, such as digoxin, will also have a large Vd. If

tissue binding of drugs is decreased by azotemia, a decrease in Vd results. Digoxin is highly bound to cardiac and other tissue Na^+–K^+–ATPase transporters, accounting for its large Vd of 300 to 500 L and very low plasma concentrations. Waste products that accumulate in the azotemic patient serve to displace digoxin from its tissue-binding sites and thus reduce its Vd. Further, such waste products cross-react with the antidigoxin antibody used in drug monitoring assays, producing "therapeutic" digoxin levels in patients not even taking the drug. Insulin and methotrexate similarly have diminished Vd in the uremic state. As a general rule, plasma concentrations of a drug correlate inversely with its Vd.[3,29,36]

Protein Binding

The third important pharmacokinetic concept is protein binding. Only unbound drug or unbound active drug metabolites are able to exert any pharmacologic effects. Disease states that affect total body proteins may significantly alter free drug concentration and increase the risk of drug toxicity. Quantity (binding site) and quality (affinity) of protein binding are substantially altered in patients with renal failure.[37–39] Specifically, uremic toxins may decrease the affinity of albumin for a variety of drugs. Organic acids that accumulate in renal failure compete with acidic drugs for protein binding sites. This results in a larger fraction of acidic compounds existing in the unbound or active state. Conversely, basic drugs bind more readily to nonalbumin serum proteins such as α_1-acid glycoprotein and may demonstrate increased protein binding because this acute phase reactant is often elevated in patients with acute disease states including renal impairment. Malnutrition and proteinuria lower serum protein levels, which may increase the free fraction of a compound as well. Alterations in a drug's protein binding and subsequent effects on drug disposition may be difficult to predict. Drugs that are highly protein bound (>80%) are not removed very effectively during dialysis. In general, drugs that are highly protein bound are largely confined to the vascular space and thus have a Vd of 0.2 L per kg or less. Generally, the Vd for a given agent increases as its protein binding decreases and diminishes as its protein-bound fraction increases.[37–39]

Drug Metabolism or Biotransformation

The total body clearance of a drug is equal to the sum of renal clearance plus nonrenal clearance. Obviously, in patients with renal insufficiency, the contribution of renal clearance to total body clearance will be reduced. Nonrenal clearance, however, may be increased, decreased, or unchanged in such patients. Specifically, hepatic pathways of drug metabolism or biotransformation including acetylation, oxidation, reduction, and hydrolysis may be slowed or accelerated depending on the drug under consideration.[40,41] Sulfisoxazole acetylation, propranolol oxidation, hydrocortisone reduction, and cephalosporin hydrolysis are all slowed in uremic patients. Most drugs undergo biotransformation to more polar but less pharmacologically active compounds that require intact renal function for elimination from the body.[7,42,43] Active or toxic metabolites of parent compounds may accumulate in patients with renal failure. The antiarrhythmic agent procainamide is metabolized to N-acetylprocainamide, which is excreted by the kidney. Thus, the antiarrhythmic properties and toxicity of procainamide and its active metabolite are additive, particularly in patients with renal failure. Meperidine, a commonly used narcotic, is biotransformed to normeperidine, which undergoes renal excretion. Although normeperidine has little narcotic effect, it lowers the seizure threshold as it accumulates in uremic patients.[44,45]

Renal Elimination

The most important route of drug elimination is the kidney. Specific processes involved in the renal handling and elimination of drugs include glomerular filtration, tubular secretion and reabsorption, and renal epithelial cell metabolism.[46] All of these functions can be directly or indirectly influenced by renal impairment. Because plasma proteins are too large to pass through a normal glomerulus, only unbound compounds will be freely filtered across this barrier. When proteinuria exists, protein-bound molecules may move into the tubular fluid and be eliminated from the circulation. Changes in renal blood flow may affect both drug reabsorption and secretion. Drugs that are highly protein bound can be eliminated without exerting any pharmacologic effects. For example, binding of furosemide to intraluminal albumin in nephrotic states may contribute to the diuretic resistance characteristic of such conditions. When renal disease reduces nephron numbers, the kidneys' ability to eliminate drugs declines in proportion to the decline in glomerular filtration rate (GFR). As patients progress toward dialysis dependency, drugs usually filtered and excreted begin to accumulate, leading to a high prevalence of adverse reactions unless dosage adjustments are instituted.[47–50]

Drugs that are extensively bound to protein either have a low renal clearance or enter the filtrate by tubular secretion. Tubular handling of a drug is an energy-requiring, active transport process and involves two separate and distinct pathways in the proximal tubule that are used for the secretion and reabsorption of organic acids and bases.[51] These processes are dependent on renal blood flow but not GFR. Accumulation of organic acids in the setting of renal failure competes with acidic drugs for tubular transport and secretion into the urinary space. This, in turn, may lead to drug accumulation and adverse reactions as serum concentrations of agents such as methotrexate, sulfonylureas, penicillins, and cephalosporins rise. Diuretics gain access to their intraluminal sites of action via organic acid secretory pumps. Competition for these secretory

pathways by accumulated uremic wastes results in diuretic resistance and necessitates increased diuretic doses to elicit the desired natriuretic effect.

Drug metabolism occurs in the kidney due to a high parenchymal concentration of cytochrome P-450 enzymes. Endogenous vitamin D metabolism and insulin catabolism are examples of processes that decline as renal failure progresses.[35,39–41]

First-order pharmacokinetics describes the manner in which most drugs and their metabolites are eliminated from the body. Specifically, the amount of drug eliminated over time is a fixed proportion of the body stores. The half-life ($t_{½}$) of a given agent is most commonly used to express its elimination rate from the body and equals the time required for the drug's plasma concentration to fall by 50%. Half-life can be expressed mathematically as follows:

$$t_{½} = \frac{0.693}{Kr + Knr} \qquad (86.2)$$

where Kr represents the renal elimination rate constant and Knr represents the nonrenal elimination rate constant. As renal elimination declines with renal function, $t_{½}$ is prolonged.

DOSAGE ADJUSTMENT FOR THE PATIENT WITH CHRONIC KIDNEY DISEASE

The following outline provides a stepwise approach to prescribing drug therapy for patients with renal failure. Again, it must be emphasized that these steps simply provide a framework for dosage adjustments in patients with renal impairment and must be modified on a case-by-case basis.

Initial Assessment

A history and physical examination constitute the first step in assessing dosimetry in any patient but particularly in those with renal impairment. Kidney injury should be defined as acute or chronic and the cause ascertained if possible. In addition, a history of previous drug intolerance or toxicity should be determined. The patient's current medication list must be reviewed, including both prescription as well as nonprescription and herbal formulations to identify potential drug interactions and nephrotoxins. Calculation of ideal body weight will be based on physical examination findings. For men, the ideal body weight is 50 kg plus 2.3 kg for each 2.54 cm (1 inch) over 152 cm (5 feet). For women, the formula is 45.5 kg plus 2.3 kg per 2.54 cm over 152 cm. An assessment of extracellular fluid volume is also key because significant shifts can affect the Vd of many pharmacologic agents. The presence of hepatic dysfunction may also require additional dosage adjustments.

Calculating Creatinine Clearance

The rate of drug excretion by the kidney is proportional to the GFR. Therefore, it is important to accurately assess renal function and GFR. Serum creatinine alone is an unreliable marker of renal function. Although it overestimates GFR, calculated creatinine clearance (Ccr) more accurately approximates the GFR than serum creatinine and can be estimated conveniently by the Cockcroft and Gault (CG) equation:

$$Ccr = \frac{(140 - age)\ (ideal\ body\ weight\ in\ kg)}{72 \times serum\ creatinine\ in\ mg/dL} \qquad (86.3)$$

For women, the calculated value is multiplied by 0.85. The use of this formula implies that the patient is in a steady-state with respect to serum creatinine. There is no accurate method to quantify GFR when renal function is rapidly changing, and as such, it is best to assume a GFR value of less than 10 mL per minute in acute renal failure to avoid drug accumulation and toxicity.[52]

Measured GFR is another method of renal assessment. Inulin is an ideal agent for measuring GFR. Following administration, inulin is filtered by the glomerulus and, in contrast to creatinine, inulin is not secreted, reabsorbed, or metabolized by the kidney. Like other exogenous substances, the inulin test is costly and time consuming and is not available for routine clinical use. Today, isotope tests (51Cr-EDTA, 99Tc-DTPA) have replaced the inulin clearance test for measuring GFR.[53]

Other methods have been suggested to estimate GFR to improve accuracy and reduce estimation errors.[54] However, all newer methods are serum creatinine–based equations and are subject to the same systemic errors as CG method. The Modification of Diet in Renal Disease (MDRD) equation was derived from the 1,628 patients involved in the MDRD study group.[55] In this study, subjects underwent GFR measurement using 125 I-iothalamate, 24–hour creatinine clearance urine collection, and a single measurement of serum creatinine. Multiple variables (i.e., weight, height, sex, ethnicity, diabetes, etc.) were used to determine the most accurate assessment of GFR. Initially, a six-variable equation was determined by the study group. Upon further study, the four-variable equation was found to be as accurate as the six-variable equation. Adding albumin and urea as variables did not improve accuracy or reduces errors.

MDRD6 Equation*

$$GFR = 170 \times [Pcr]^{-0.999} \times [Age]^{-0.176} \times [0.762\ \text{if patient is female}] \times [1.180\ \text{if patient is black}] \times [SUN]^{-0.170} \times [Alb]^{0.318}$$

*Pcr, serum creatinine concentration; SUN, serum urea nitrogen concentration; Alb, serum albumin concentration

MDRD4 Equation

$$GFR = 186 \times Scr^{-1.154} \times age^{-0.203} \times 0.742 \text{ [if female]} \times 1.21 \text{ [if black]}$$

The U.S. Food and Drug Administration (FDA) released "Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis and Impact on Dosing and Labeling" in 2010, recommending the CG or MDRD4 equations as the method for assessing renal function in pharmacokinetic studies.[56] It is important to emphasize that all different methods of GFR estimation and equations for drug dosing in CKD have small biases when comparing CG to other methods.[57]

Choosing a Loading Dose

Loading doses are intended to achieve a therapeutic steady-state drug level within a short period of time. As such, the loading dose generally is not reduced in the setting of renal failure. Loading doses can be calculated if the Vd and desired peak level are known, as is discussed later. If extracellular volume depletion exists, the Vd may be reduced for certain pharmacologic agents, and slight reductions in the loading dose would be prudent. Specifically, drugs with narrow therapeutic–toxic profiles such as digoxin and ototoxic aminoglycosides should be administered with a 10% to 25% reduction in their loading dose when volume contraction is present in patients with renal failure.

Choosing a Maintenance Dose

Maintenance doses of a drug ensure steady-state blood concentrations and lessen the likelihood of subtherapeutic regimens or overdosage. In the absence of a loading dose, maintenance doses will achieve 90% of their steady-state level in three to four half-lives. One of two methods can be used to adjust maintenance doses for patients with renal insufficiency. The "dosage reduction" method involves reducing the absolute amount of drug administered at each dosing interval proportional to the patient's degree of renal failure. The dosing interval remains unchanged, and more constant drug concentrations are achieved. The "interval extension" method involves lengthening the time period between individual doses of a drug, reflecting the extent of renal insufficiency. This method is particularly useful for drugs with a wide therapeutic range and long half-life.

Monitoring Drug Levels

Blood, serum, and plasma drug concentrations may not be equivalent. As a result, drug levels can only be interpreted if the dosage schedule is known, including the dose administered, timing, and route of administration. A peak level is usually obtained 30 minutes following intravenous administration and 60 to 120 minutes after oral ingestion. It reflects the maximum level achieved after the rapid distribution phase and before significant elimination has occurred. A trough level is obtained just prior to the next dose, reflects total body clearance, and may be a marker of drug toxicity. If the concentration of a drug and its Vd are known, the dose required to achieve a desired therapeutic level can be calculated by the following formula where Vd in L per kilogram is multiplied by ideal body weight (IBW) in kilograms and the desired plasma concentration in milligrams per L (Cp):

$$\text{Dose} = \text{Vd} \times \text{IBW} \times \text{Cp} \quad (86.4)$$

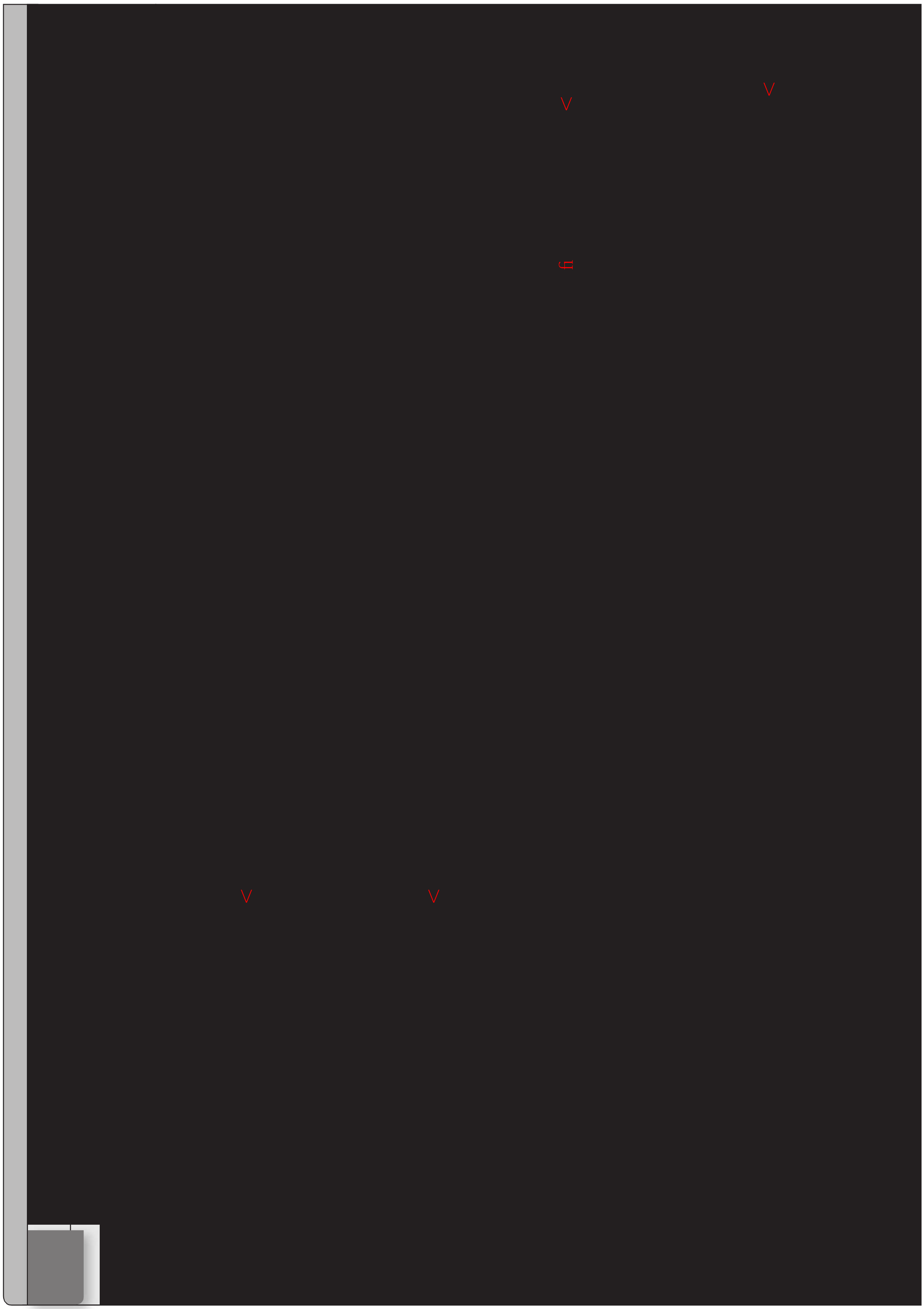
Drug level monitoring is a clinically useful tool when used appropriately. Clinical judgment is paramount because drug failure or toxicity can occur within "therapeutic concentrations." For example, digitalis intoxication can occur in the presence of therapeutic serum levels if hypokalemia or metabolic alkalosis coexists. Phenytoin toxicity is a common problem in patients with renal failure and hypoalbuminemia because of an increase in the unbound or biologically active fraction of phenytoin despite a low total phenytoin plasma concentration. In this setting phenytoin levels should be adjusted for reduced protein binding and the effect of renal failure on phenytoin distributions (Table 86.1).

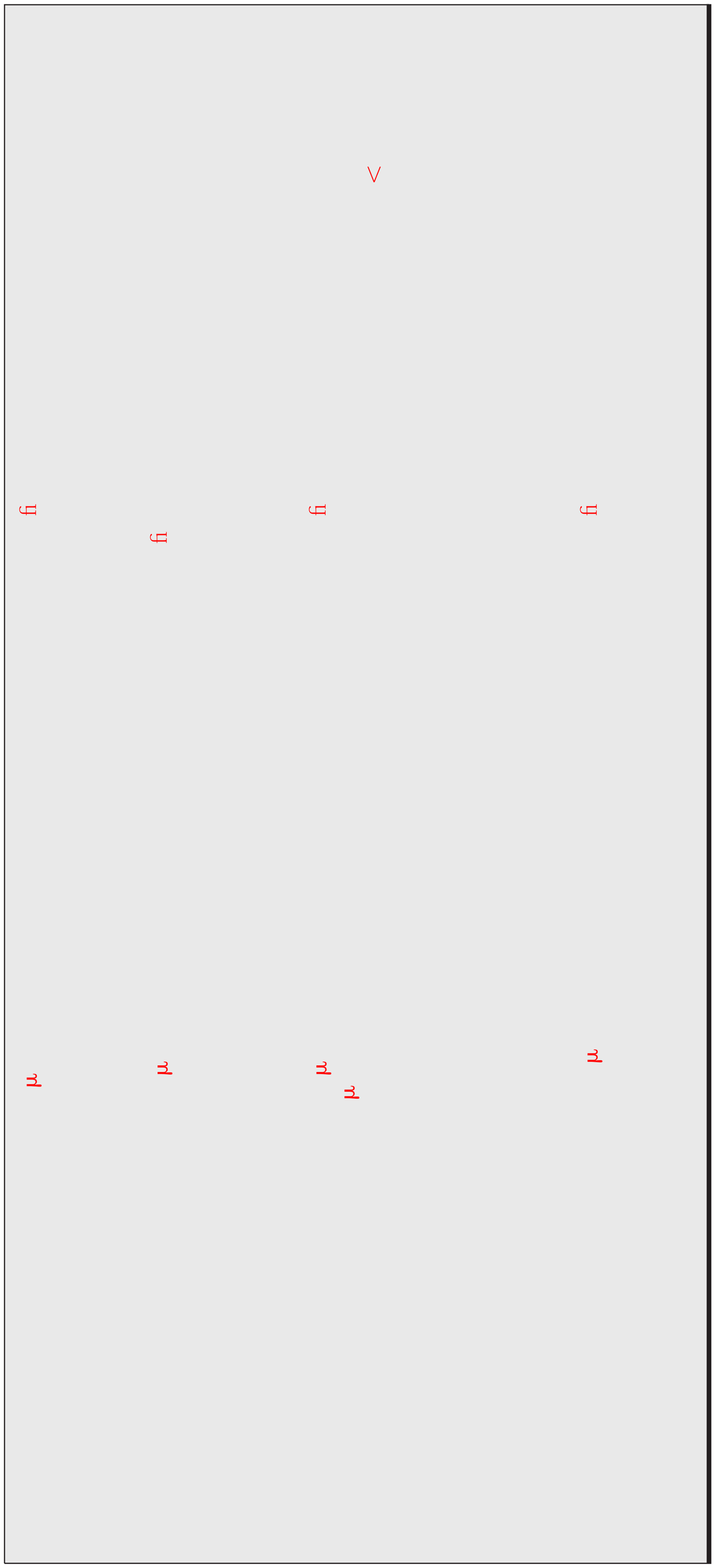
DIALYSIS AND DRUG DOSING

Patients undergoing renal replacement therapy (dialysis therapy) require special attention in terms of dosage adjustment because dialysis membranes significantly remove many therapeutic agents. An array of modalities including high efficiency, high flux, continuous, and conventional hemodialysis exist and differ from one another based on membrane porosity, surface area, and blood as well as dialysate flow rates. These differences, in turn, affect drug removal. In Table 86.2 are summarized drug properties and dialysis parameters that determine dialytic clearance of pharmacologic agents. In general, in thrice weekly intermittent hemodialysis (IHD), the drug removal is affected by blood and dialysate flow rate, molecular weight (MW) of the drug, fraction of protein binding, and dialyzer surface area. Drugs with MW greater than 500 D and that are highly protein bound (80%), highly tissue bound, and lipophilic are poorly dialyzed by conventional IHD. However, drugs with small MW, low protein binding, small volume of distribution, and of a hydrophilic character are effectively removed by IHD.[58–61]

Drug Properties Affecting Dialytic Clearance

A drug's molecular weight is a major determinant of its dialyzability. Specifically, drugs larger than 500 D are primarily cleared by convection as opposed to diffusion. If too large to pass through a given membrane, the drug will not

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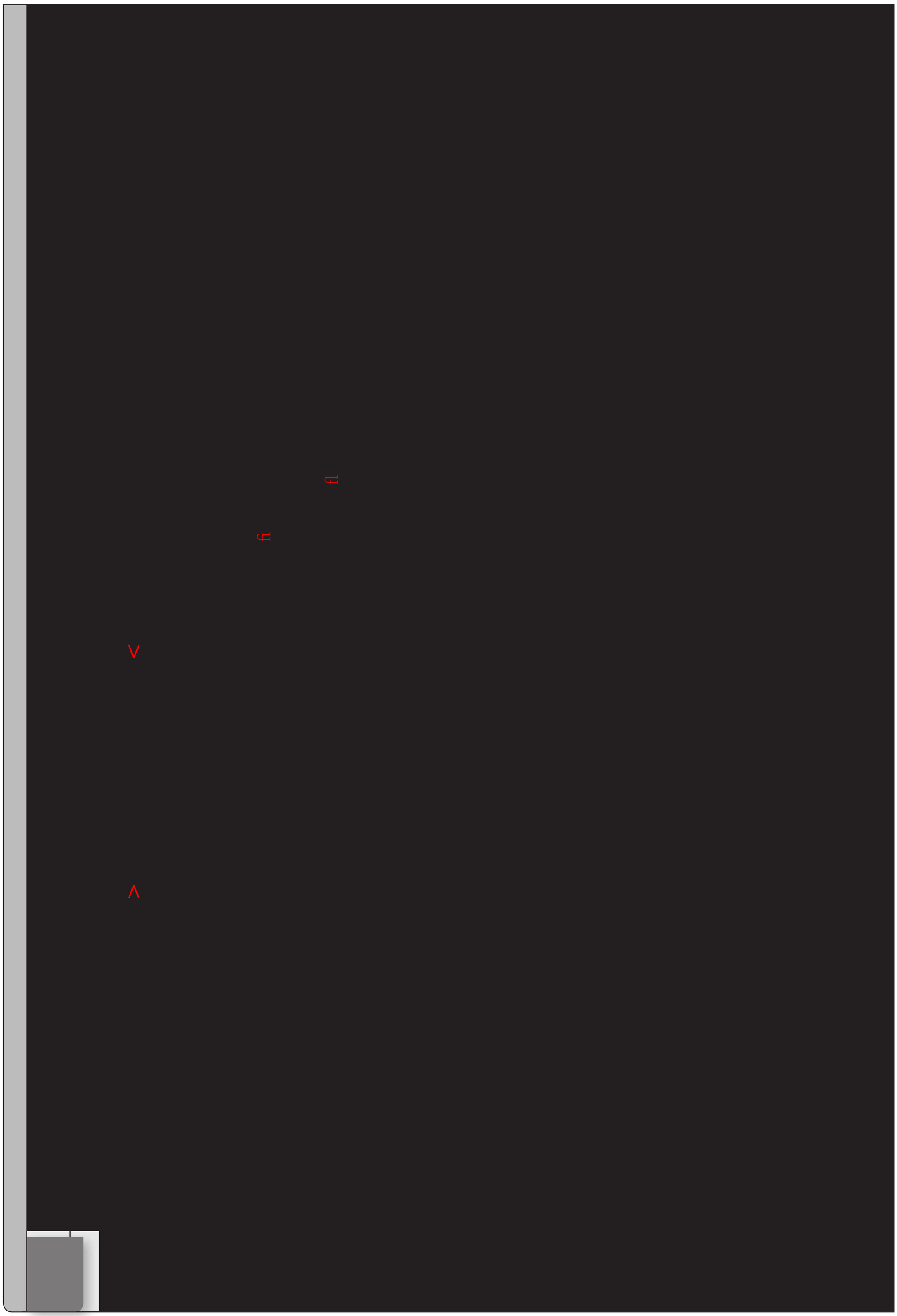
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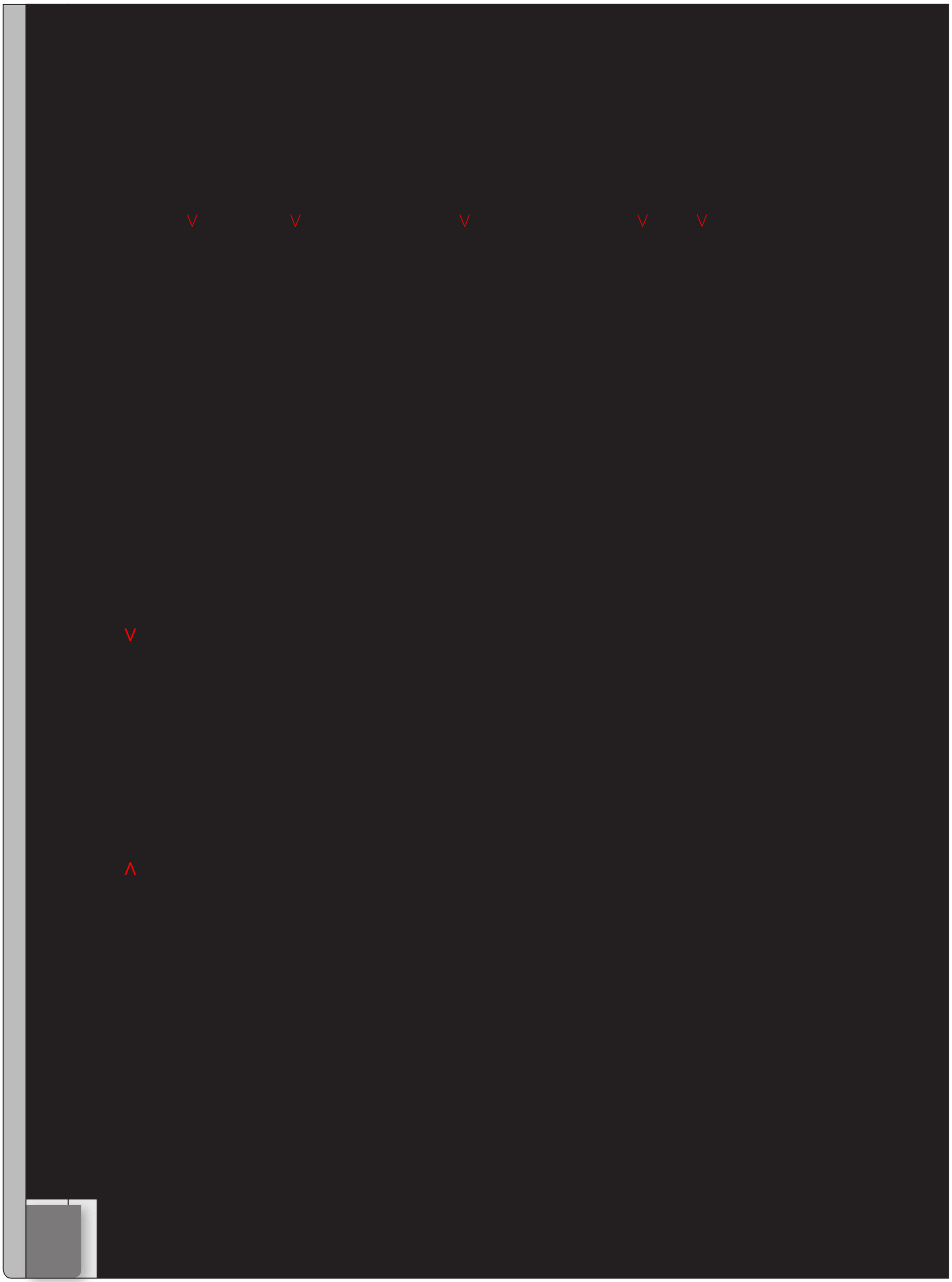

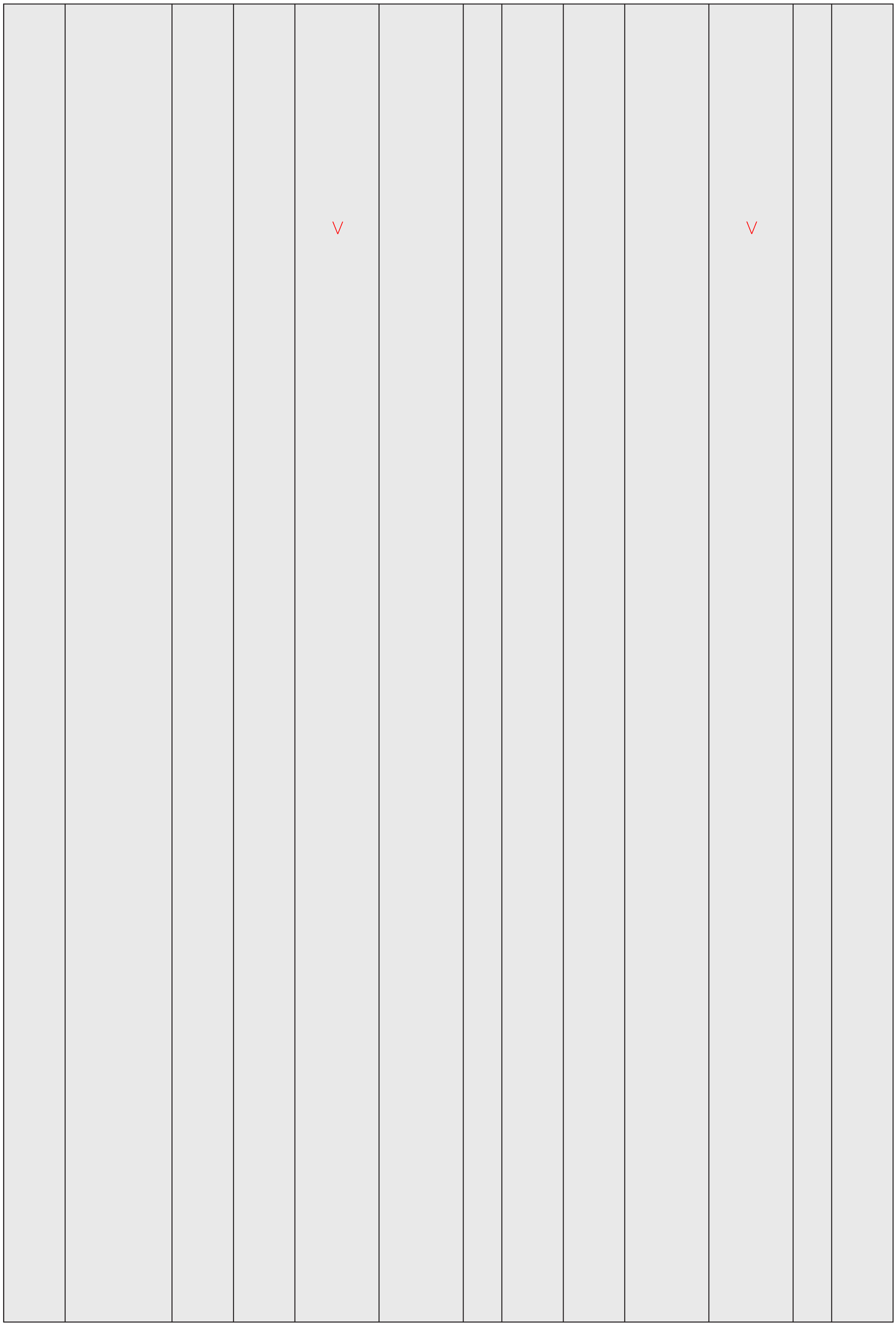

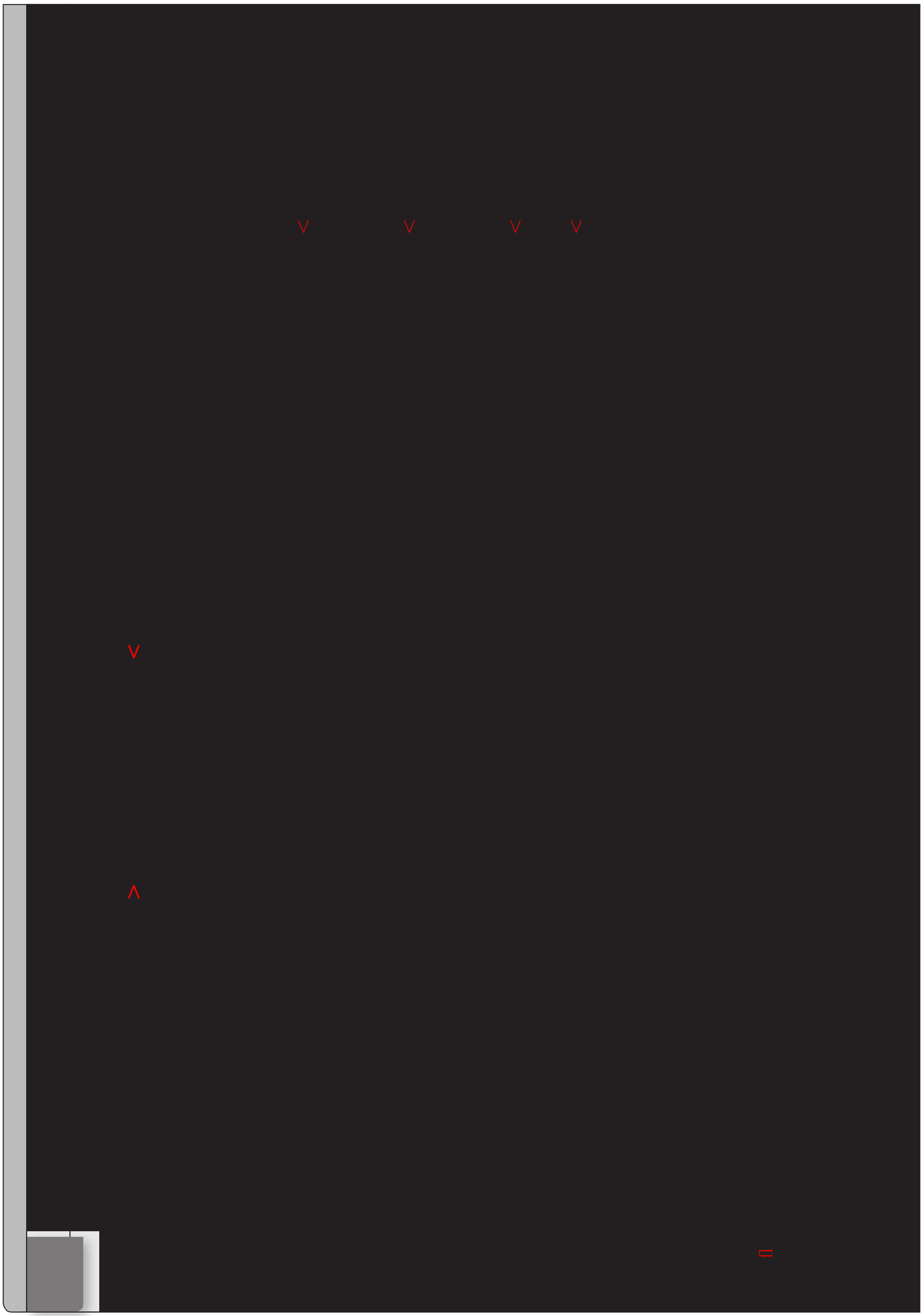

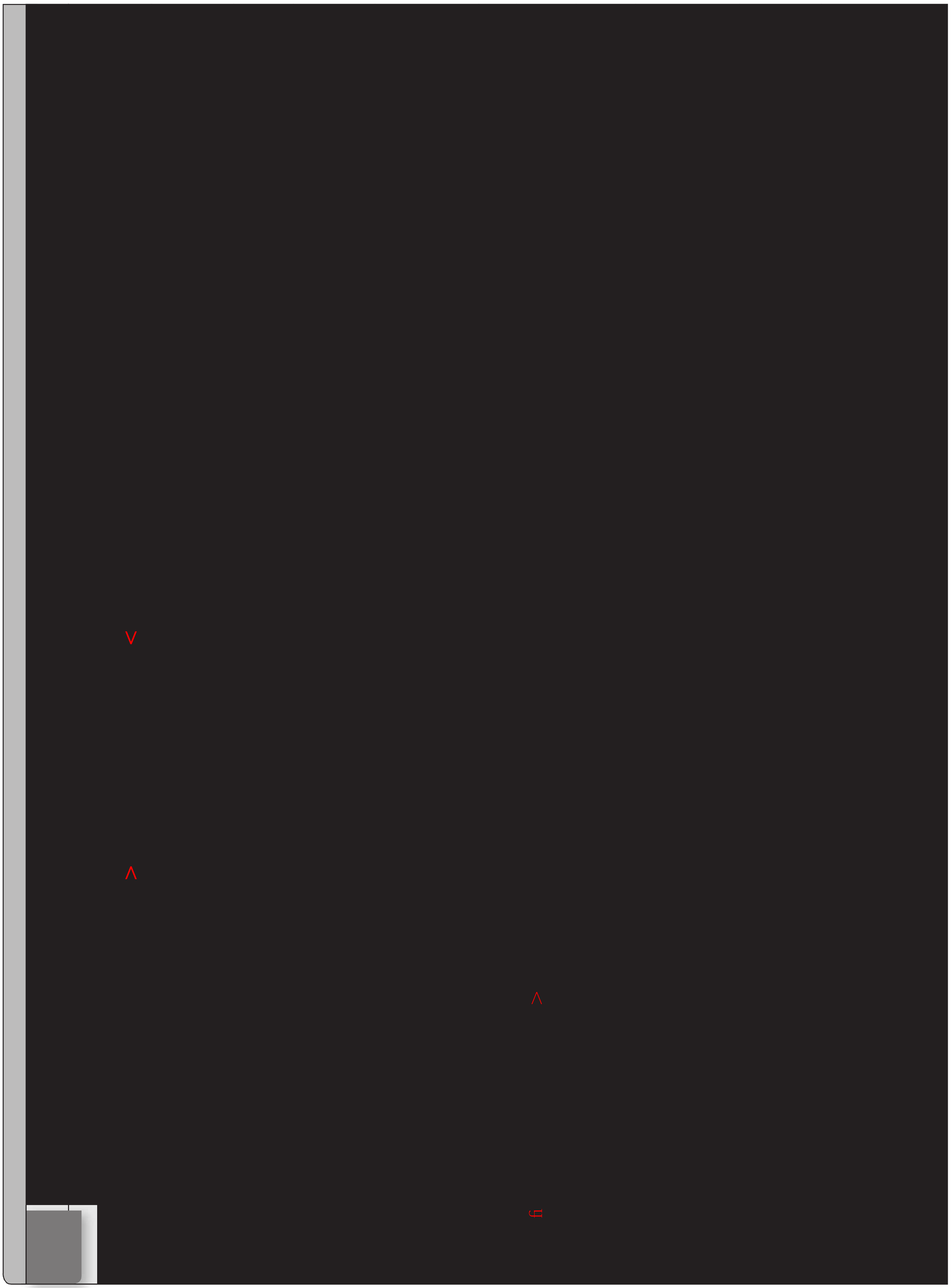

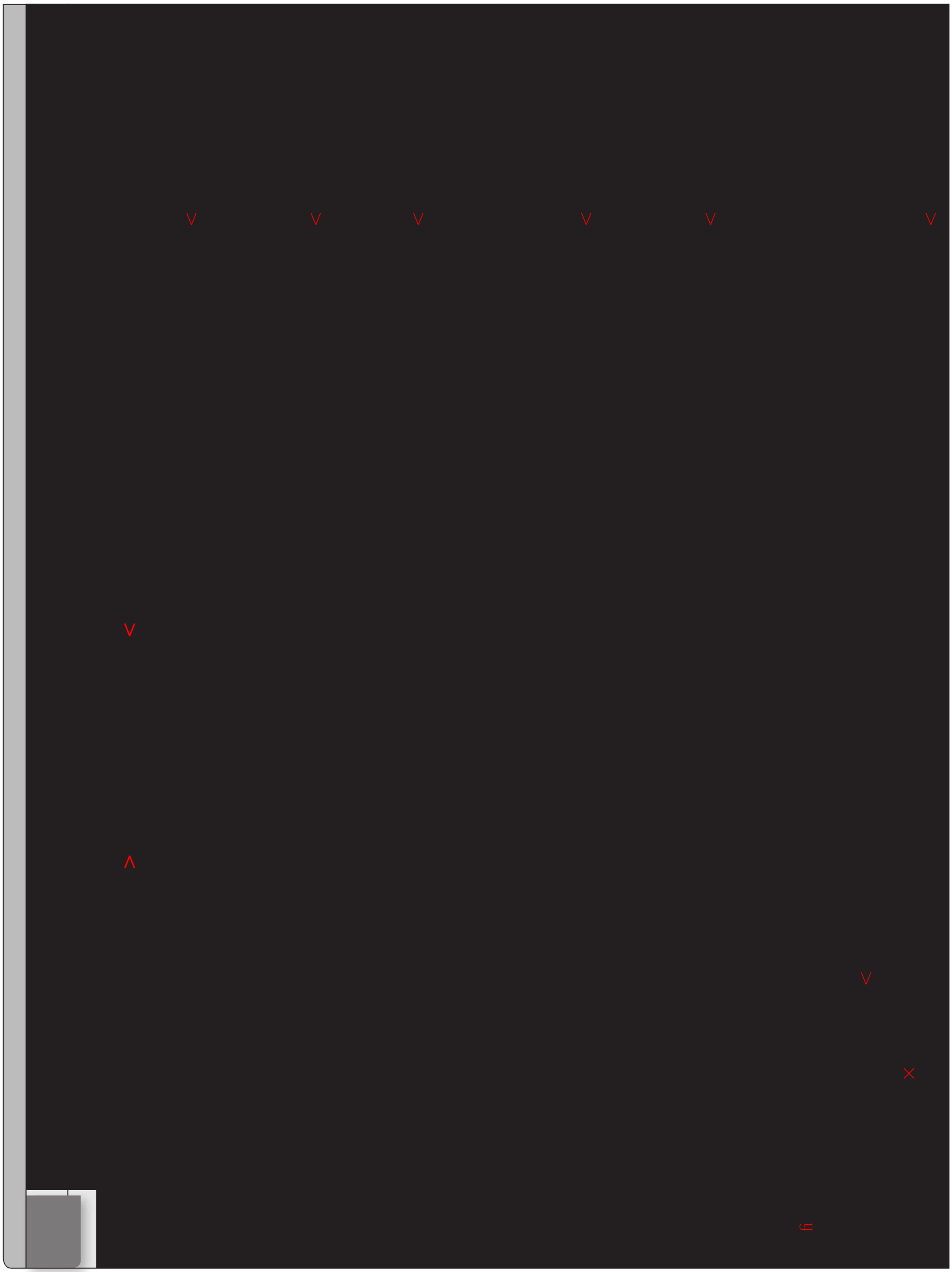

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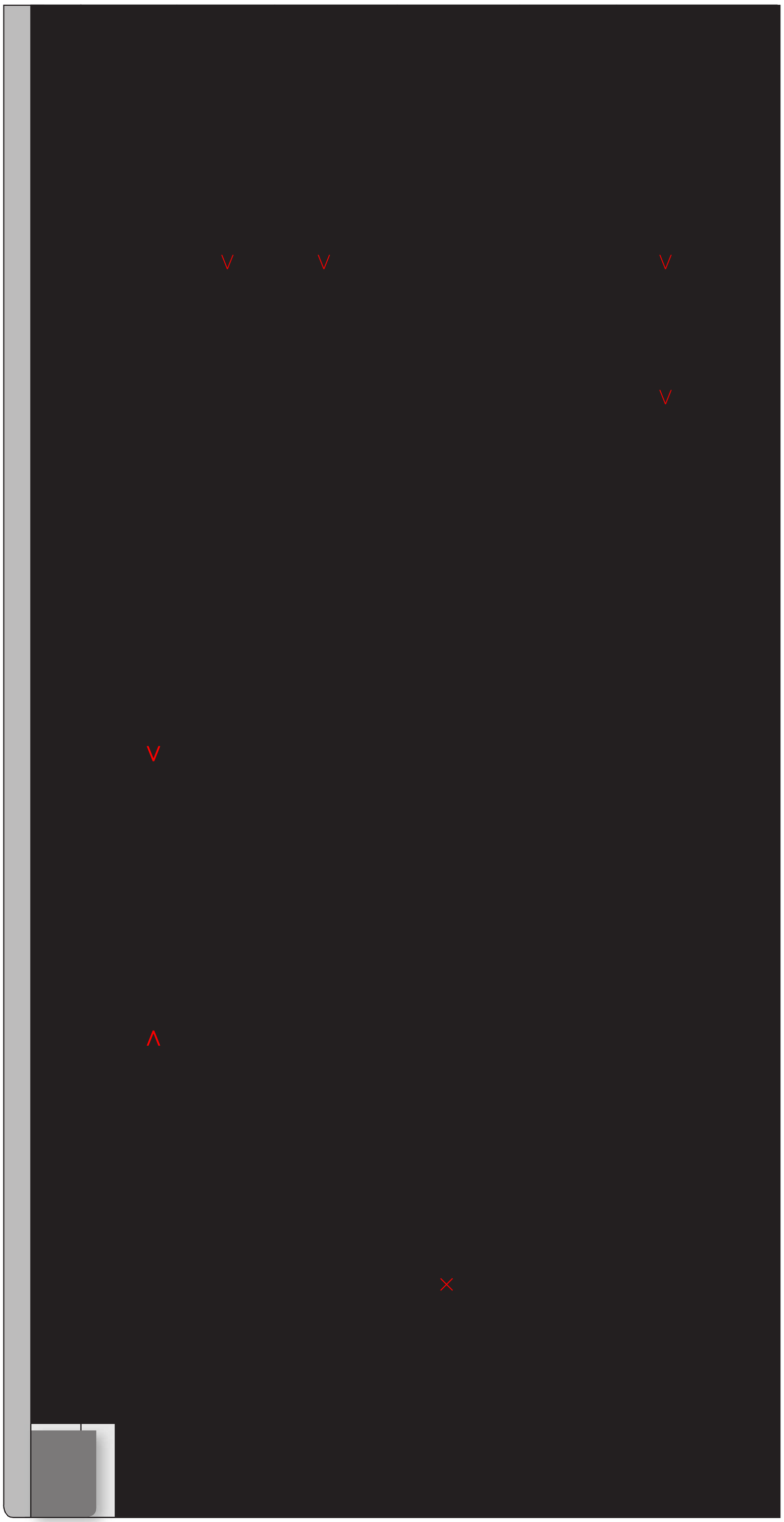


be cleared from the circulation. An inverse semilogarithmic relationship exists between molecular weight and dialysis clearance.

Protein binding represents another major determinant of drug dialyzability. Compounds that are highly protein bound have a smaller fraction of unbound drug available for removal by dialysis. Because heparin stimulates lipoprotein lipase, free fatty acid levels may increase during dialysis. Free fatty acid levels may displace sulfonamides, salicylates, and phenytoin from their protein binding sites, resulting in increased free fractions of each drug. In contrast, free fatty acids can increase protein binding of certain cephalosporins. The free fraction of phenytoin is increased by free fatty acids.

As discussed previously, drugs with a large Vd (greater than 2 L per kg) tend to have low concentrations in the intravascular space and are thus not readily dialyzable. The lower the Vd (less than 1 L per kg), the greater the drug's availability to the circulation and, similarly, to the dialyzer.

Larger molecular weight compounds do not equilibrate rapidly between the extracellular and intracellular compartments during dialysis—little change is detected in intracellular concentrations whereas extracellular levels may fall significantly. As such, postdialysis rebound may occur in which pharmacologic agents move down their concentration gradients into the extracellular space. Rebound can be sizable as well as highly unpredictable in its time course, as demonstrated by vancomycin. Ultrafiltration raises the hematocrit, which can influence the dialytic clearance of drugs that partition into red blood cells. Drugs such as ethambutol, procainamide, and acetaminophen partition into red blood cells and demonstrate decreased dialytic clearance due to hemoconcentration following dialysis ultrafiltration.

Thus, parent compounds and their metabolites will be eliminated by dialysis to a greater extent if they possess a low molecular weight, limited Vd, and are water soluble. An increase in drug clearance of 30% or greater by dialytic therapy is considered significant and may warrant supplemental dosing following dialysis.

Dialytic Factors Affecting Drug Clearance

Dialysis membranes, dialysate flow rates, and the dialytic technique used can significantly alter drug clearance (Table 86.3).[62] A wide variety of membranes have been developed including cellulose, cellulose acetate, polysulfone, polyamide, polyacrylonitrile (PAN; AN69), and polymethylmethacrylate (PMMA) in an effort to improve membrane permeability for larger uremic toxins. Similarly, albumin can cross polysulfone membranes to a limited extent.[63] Vancomycin clearance is significantly increased when polysulfone or PAN membranes are used.[59,60] Likewise, cuprammonia rayon membranes allow greater aminoglycoside removal compared to cellulose fibers.[44] Two endogenous compounds that are poorly dialyzed, phosphate and

86.3 Factors Affecting Drug Removal During Dialysis

Drug Properties	Dialysis System Properties
Renal clearance	Filter properties
Volume of distribution	Blood flow, dialysate flow, and ultrafiltration rates
Water and lipid solubility	
Protein binding	
Drug charge	
Molecular weight	

β_2-microglobulin, undergo enhanced clearance when PAN, PMMA, and polysulfone membranes are used due to the increased surface area of these membranes.[64] The electrical charge of a dialysis membrane as well as the drug may help or hinder clearance. Like charges will repel one another, whereas opposite charges between membrane and drug may lead to drug adsorption to the membrane, ultimately reducing clearance.[65,66]

Drug clearance is achieved primarily by two processes: diffusion and convection. Diffusion of a compound increases as its molecular weight decreases and is negligible when standard membranes are used for substances larger than 1,000 D.[21,67] Diffusion of a drug is enhanced when the concentration gradient between blood and dialysate is maximized by countercurrent flow and increased blood and dialysate flow rates. Flow rates have less impact on the diffusion of middle-sized and large molecules, but the surface area and hydraulic permeability of the membrane assume greater significance. Diffusion can be hindered, however, when high ultrafiltration rates lead to the mixing of dialysate and ultrafiltrate. This results in a decreased concentration gradient between blood and dialysate, reducing diffusive clearance.[68] Convection refers to the movement of solute by way of ultrafiltration, which affects molecules of all sizes but particularly large molecular weight substances, which diffuse poorly. To be removed by dialysis, compounds greater than 1,000 D require ultrafiltration when cellulose membranes are used, whereas those greater than 2,000 D demonstrate limited clearance. Ultrafiltration, and thus convection, can be reduced by protein binding to membrane surfaces during the dialytic procedure, which ultimately diminishes drug removal.[21,22]

Continuous Renal Replacement Therapies and Drug Removal

Critically ill patients may require continuous renal replacement therapies (CRRTs) such as hemofiltration or hemodialysis, and an awareness of drug handling by such procedures is crucial to the patient's outcome. Continuous hemofiltration removes solute by convection. The degree to which a

solute can convectively cross a membrane can be quantitated by its sieving coefficient (S), the ratio of solute concentration in the ultrafiltrate to solute concentration in the retentate (returning to the patient's circulation). This can be approximated by the formula:

$$S = UF/A[5] \quad (86.5)$$

where UF is ultrafiltrate and A is arterial concentrations of solute, which will remain relatively constant during hemofiltration because blood flow does not affect sieving. Clearance of a solute (drug) is determined by multiplying the ultrafiltration rate by the S for that substance. The sieving coefficient for a given molecule can change, however, when comparing different dialysis membranes and is likely due to drug–membrane binding. Sieving can also be reduced by negatively charged solutes, although exceptions to this exist.[23,25] Because inulin (5,200 D) can readily cross polysulfone hemofiltration membranes, nearly all therapeutic agents would be expected to permeate such membranes given molecular weights less than that of inulin. The drug's degree of protein binding will be the major limiting factor to drug removal during hemofiltration.

In contrast to hemofiltration, drug removal during continuous hemodialysis occurs primarily via diffusion rather than convection. Protein binding again plays a central role whereby unbound drug diffuses more readily than protein-bound drug and molecular weight correlates inversely with diffusion. It should be noted that during continuous hemodialysis with venovenous access and average blood flow rates of 200 mL per minute, a GFR of 20 to 30 mL per minute can be achieved, which may provide greater drug clearance than expected. As previously discussed, when supplemental dosing is indicated, the amount of drug required to achieve a desired blood level can be calculated by multiplying the drug's Vd by the patient's IBW and the difference between the desired drug concentration and the trough concentration.

Lastly, peritoneal dialysis generally provides minimal drug removal, as dialysate flow rates are significantly slower than other forms of dialytic therapy. Drugs that are dialyzable via peritoneal dialysis must be small in size and have a low Vd. Drugs that are highly protein bound, however, may undergo greater clearance with peritoneal dialysis versus hemodialysis given the large protein losses commonly seen with peritoneal therapy.

SPECIFIC CONSIDERATIONS FOR DRUG PRESCRIBING IN RENAL FAILURE

In this section, the effects of renal insufficiency on drug pharmacokinetics and pharmacodynamics are reviewed and dosage adjustment guidelines are provided. It is imperative to reiterate that the following recommendations provide a framework for dosage adjustments that must be applied to individual patients with caution. Continual monitoring and modification of drug therapy are required by concurrent illnesses, clinical response, and side effects present in the individual patient. Drugs are listed in tabular form (Tables 86.3 through 86.13) by generic name in alphabetical order and are grouped into categories based on therapeutic effect. General comments about each group precede the individual dosing table. For reference, the standard dose given to patients with normal renal function is included. Specific dosing guidelines are provided for each drug based on the patient's level of renal function in terms of GFR. It should be remembered that creatinine clearance always overestimates true GFR.

The maintenance dosage regimen may be modified by either extending the interval between doses, decreasing the individual dose while maintaining normal dosing intervals, or a combination of the two methods. As outlined previously, the variable interval method allows a more convenient and less costly dosing schedule but may result in periods of subtherapeutic drug levels. The variable dose method maintains more constant drug levels because the dosing interval remains unchanged but risks greater toxicity because the difference between peak and trough levels is diminished. When the interval extension method (I) is used, the dosing interval length (in hours) is indicated. When the dosage reduction method (D) is used, the percentage of the standard dose normally used is indicated.

The requirement for supplemental dosing after hemodialysis and special dosing considerations for peritoneal dialysis and continuous renal replacement therapies are also included. For many drugs, specific data are not available on dialytic drug clearance, and the likelihood of dialytic removal is based on molecular weight, Vd, and protein binding.

Antimicrobial Agents

Infection is the leading cause of morbidity and mortality in patients with renal failure. Many antibiotics require dosage adjustment in the setting of renal insufficiency due to alterations in pharmacokinetic and pharmacodynamic parameters. An increased incidence of extrarenal toxicity is also observed in patients with renal insufficiency due, in part, to accumulation of drug and/or active metabolites. Specific dosing guidelines for individual antimicrobial agents are provided in Table 86.2. One or more pharmacokinetic parameters may be altered in the patient with renal failure.[69,70] A number of oral antibiotics are now available for the treatment of infections in patients with renal impairments. However, a decreased absorption may occur for some agents such as tetracycline or ciprofloxacin.[71,72] Most antibiotics should be administrated at least 2 to 4 hours after iron and phosphate binder therapy. Although the majority of antibiotics are excreted partially

or completely by glomerular filtration, a number of antimicrobials such as trimethoprim–sulfamethoxazole or ciprofloxacin reach the urinary space by tubular secretion. This, in turn, achieves high urinary concentrations of such agents even though the GFR is diminished.[73] This feature is used to therapeutic advantage for treatment of urinary tract infections in patients with renal insufficiency or cyst infections in patients with polycystic kidney disease.

For most drugs, the loading dose will be the same as that used in patients with normal renal function because rapid achievement of therapeutic antibiotic levels are critical for life-threatening infections. Recently, the postantibiotic effect has been observed with a number of antimicrobials including aminoglycosides, newer macrolides, and the penems.[74,75] Clinically, the persistence of antibiotic activity beyond the time point at which blood levels fall below the minimum inhibitory concentration may be used to design extended and more convenient dosing intervals of antimicrobial agents without jeopardizing patient outcomes.

Peritoneal dialysis patients often use the intraperitoneal route of antibiotic administration for treatment of peritonitis. Detailed reviews of this therapeutic modality exist elsewhere, and intraperitoneal antibiotic dosing for peritonitis has been reviewed by Li and colleagues. Patients with renal dysfunction have an increased risk of antimicrobial-induced nephrotoxicity whereby dosage adjustments and close monitoring are required to minimize further renal injury, particularly with aminoglycosides.[55] Less predictably, acute interstitial nephritis often complicates courses of antimicrobial therapy, but no known risk factors or preventive measures exist. Spurious rises in serum creatinine may result when certain cephalosporins interfere with the creatinine assay or trimethoprim blocks tubular secretion of creatinine. Lastly, significant potassium and salt loads may accompany the administration of certain antibiotics, particularly penicillins.

Analgesics and Agents Used by Anesthesiologists

Opioid analgesics remain the primary pain modality for the treatment of pain in patients with renal failure.[76] In Table 86.4 dosage recommendations are summarized for analgesics and agents used by anesthesiologists. Most analgesics are metabolized by the liver and thus require little dosage adjustment, but renal failure tends to increase the sensitivity to the pharmacologic effects of these drugs.[77] Special attention needs to be paid when prescribing meperidine or propoxyphene for patients with reduced renal function. Normeperidine, a meperidine metabolite excreted by the kidneys, has central nervous system excitatory properties that can lower the seizure threshold in patients with renal failure. Similarly, the propoxyphene metabolite has cardiovascular toxicity. Because of these serious adverse effects, both meperidine and propoxyphene should be avoided in patients with renal problems.[76] Acetaminophen should be considered initially for mild or moderate pain. If not effective, opioid analgesics or non-opioid analgesic (tramadol) should be considered. Use of NSAIDs should be avoided or limited in patients with chronic kidney disease. Cyclooxygenase-2 inhibitors should be avoided in patients with ischemic heart disease because of its risk of cardiovascular complications.[78–80] Finally, many of the neuromuscular blocking agents are excreted by the kidney and thus may display prolonged action and depolarization in patients with impaired renal function as the effects of the antagonist dissipate.[26,81,82]

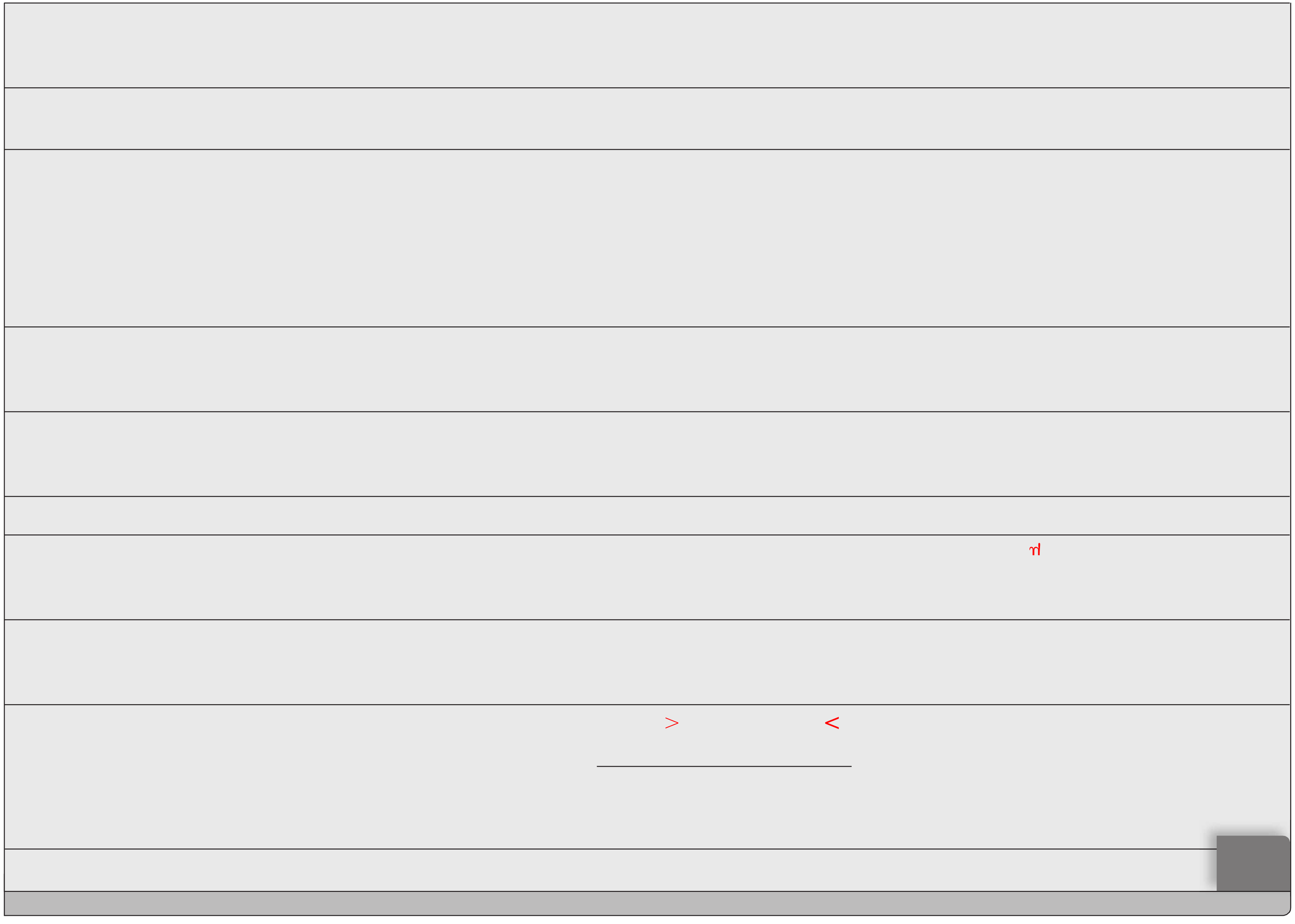
Antihypertensive and Cardiovascular Agents

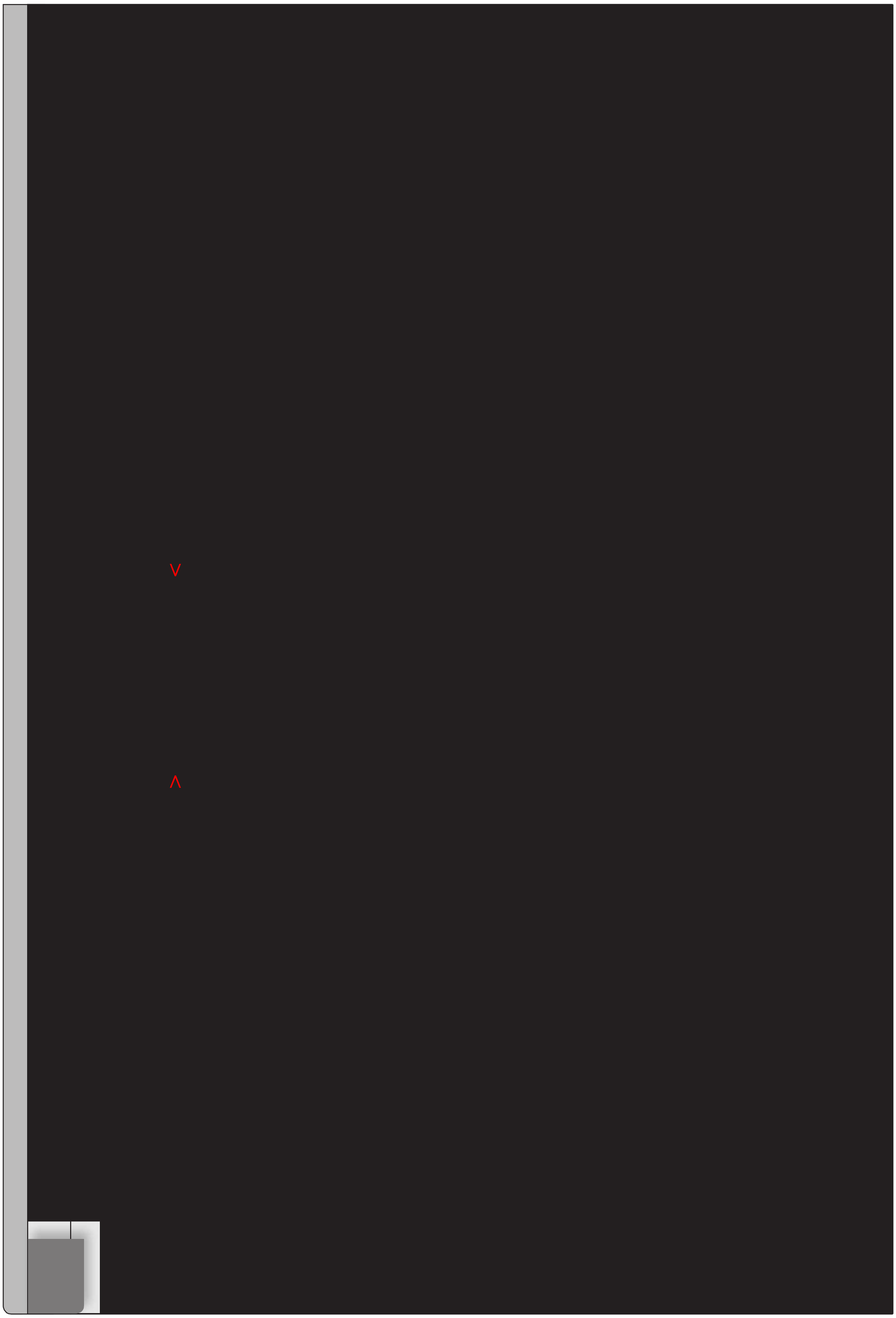
In Table 86.5 dosage recommendations are summarized for antihypertensive and cardiovascular agents. The most common cause of death in the ESRD population is cardiovascular disease. A number of factors contribute to cardiovascular diseases in patients with renal failure. The risk of cardiovascular diseases increases with age, hypertension, hyperlipidemia, smoking, and anemia. Unfortunately, most of the cardiovascular interventional studies have been done in patients with normal renal function and patients with serum creatinine greater than 2 mg per dL have been excluded. It is still strongly recommended to treat these risk factors aggressively. Hypertension complicates the management of most patients with renal insufficiency and impacts adversely on renal disease progression and increases the risk of cardiovascular events.[83]

Patients with renal disease, in particular diabetic patients and patients with the metabolic syndrome, have high serum levels of triglycerides, low-density lipoproteins (LDL), and total cholesterol. All patients with renal insufficiency should have an annual lipid panel and should be managed according to the new ATP III guideline.[84,85]

Endocrine and Metabolic Agents

Dosage recommendations for endocrine and metabolic agents are provided in Tables 86.6, 86.7, and 86.8. Renal failure is associated with peripheral insulin resistance and decreased insulin metabolism by the kidney. In the presence of renal insufficiency, sulfonylureas that are excreted primarily by the kidney should be avoided, as prolonged hypoglycemia may result from the accumulation of such agents. Peritoneal dialysis allows for intraperitoneal insulin therapy, which has been shown to provide better overall control of plasma glucose when compared to standard subcutaneous injection therapy. Hyperlipidemia also complicates renal failure and adds to the increased risk of atherosclerotic complications in this population. Lipid-lowering agents such as bile acids can add to fluid overload and worsen acidosis in patients with renal failure, while other agents, such as lovastatin and clofibrate, have been associated with rhabdomyolysis.[86]





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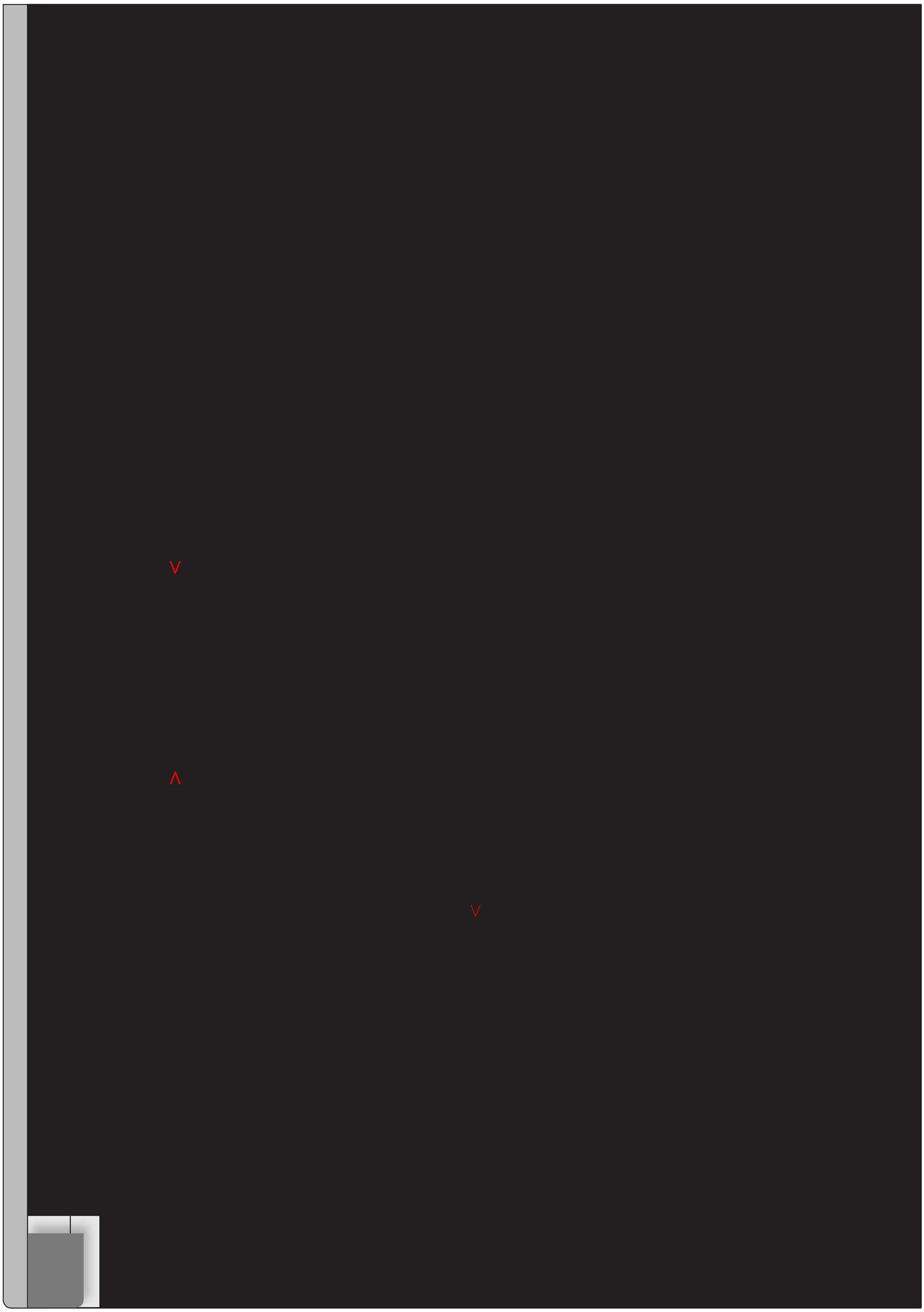

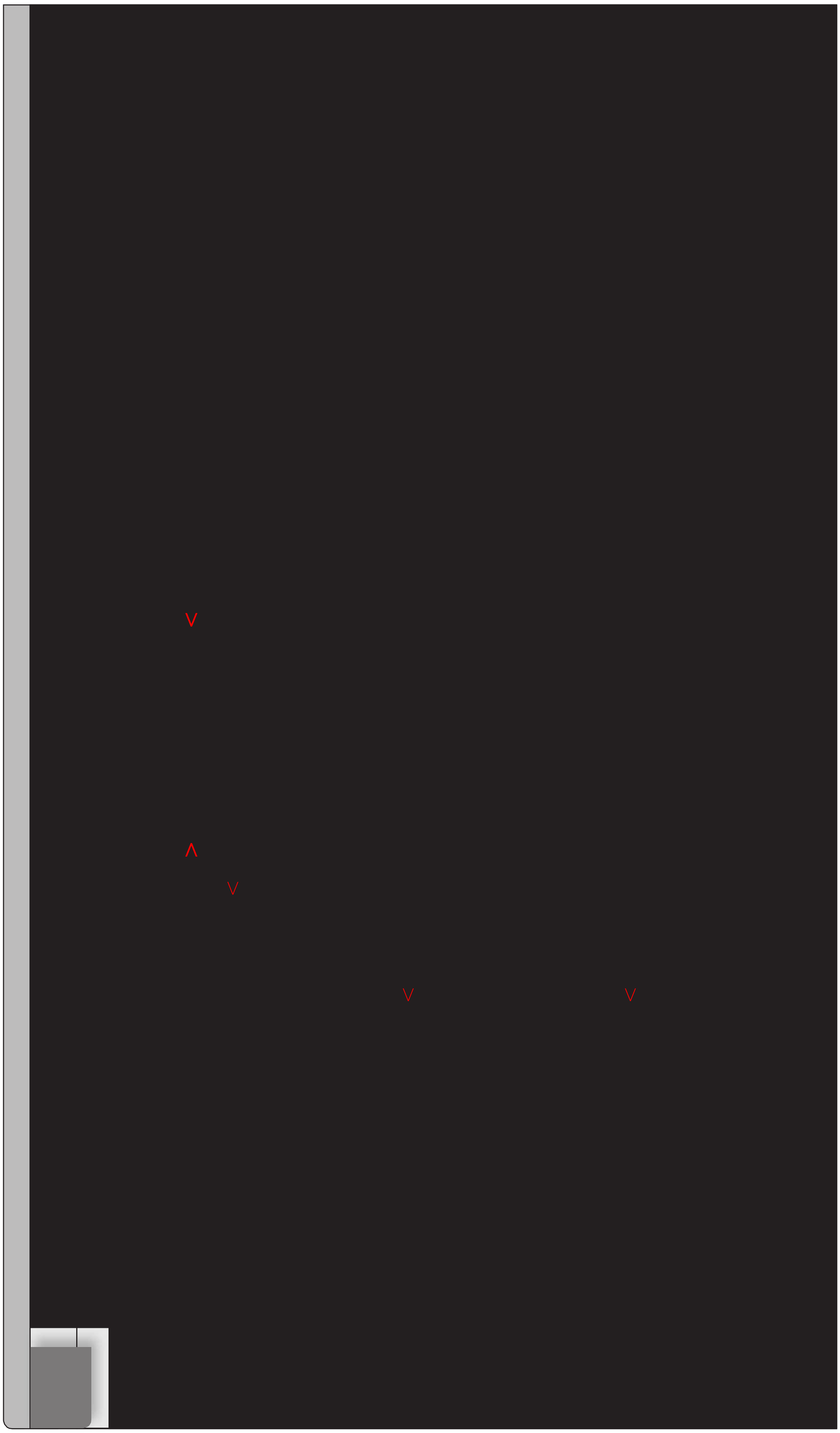

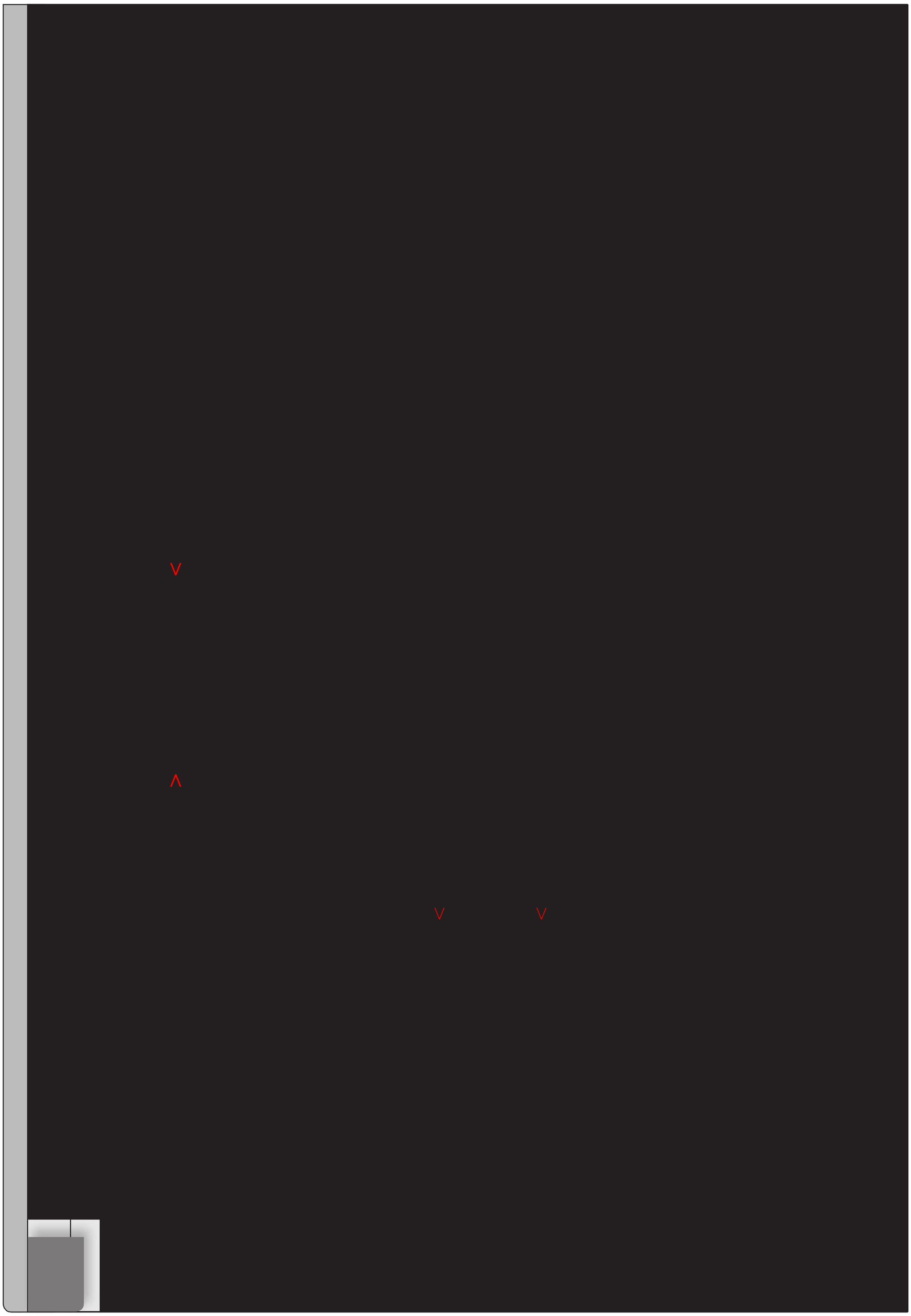

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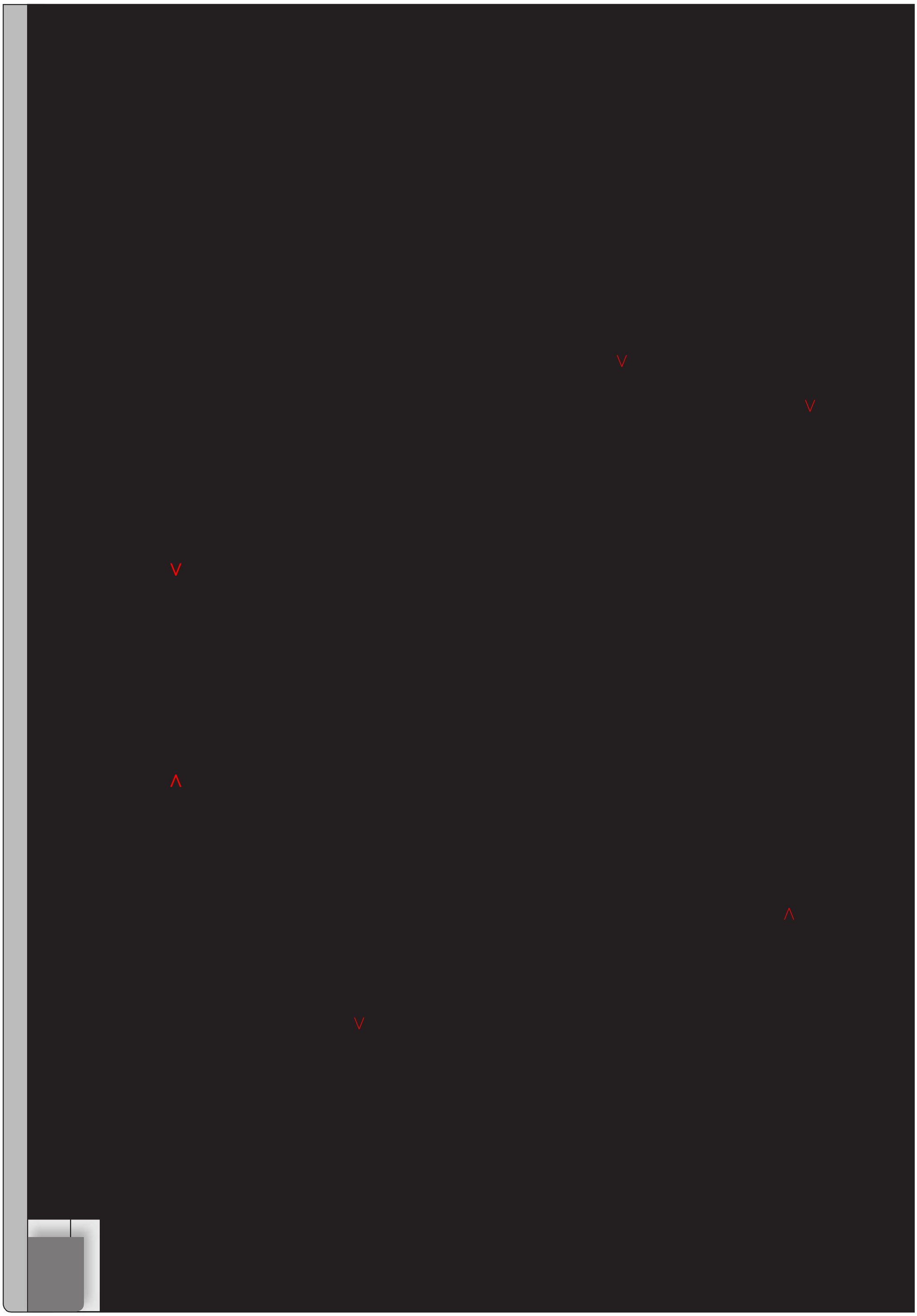
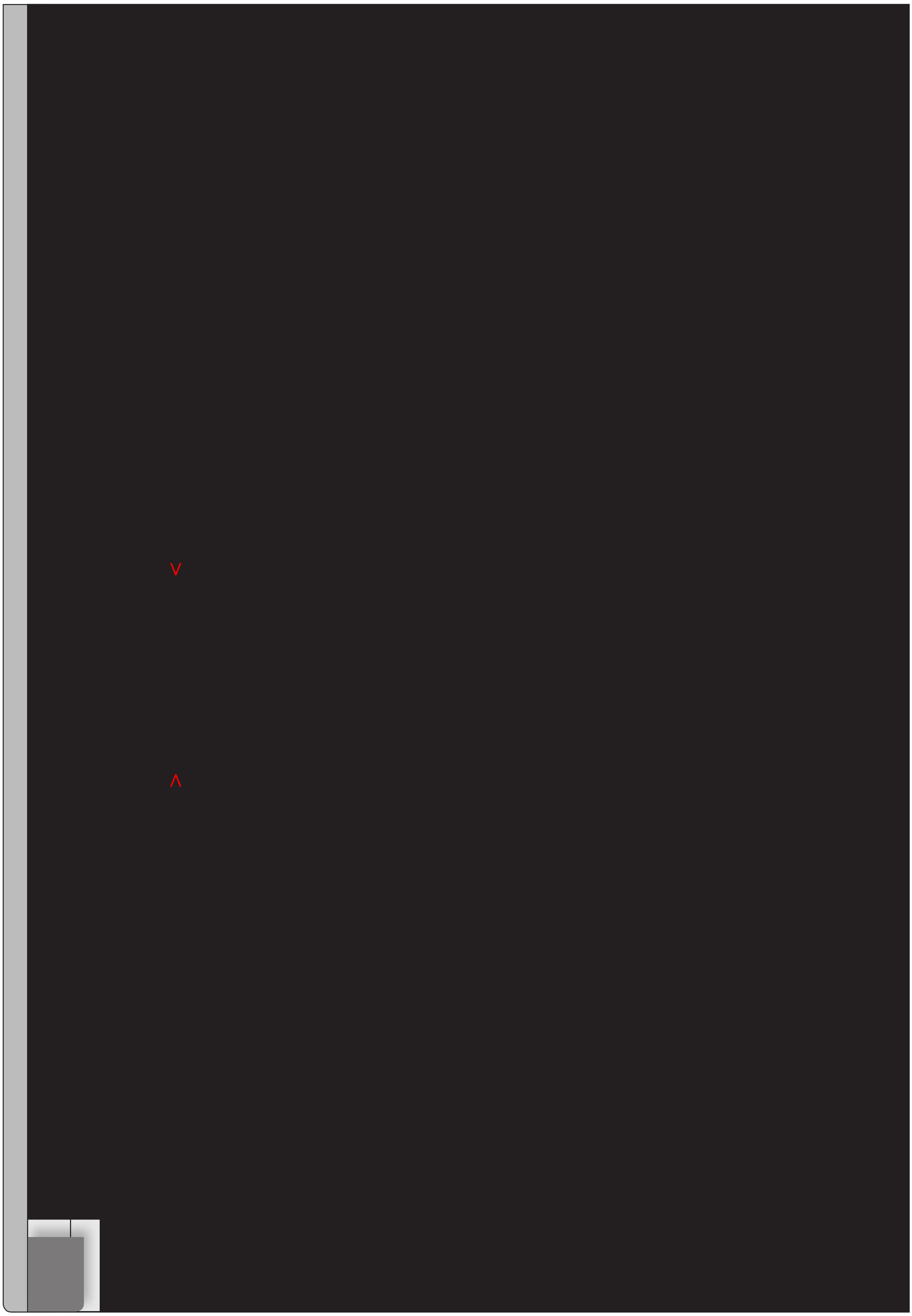
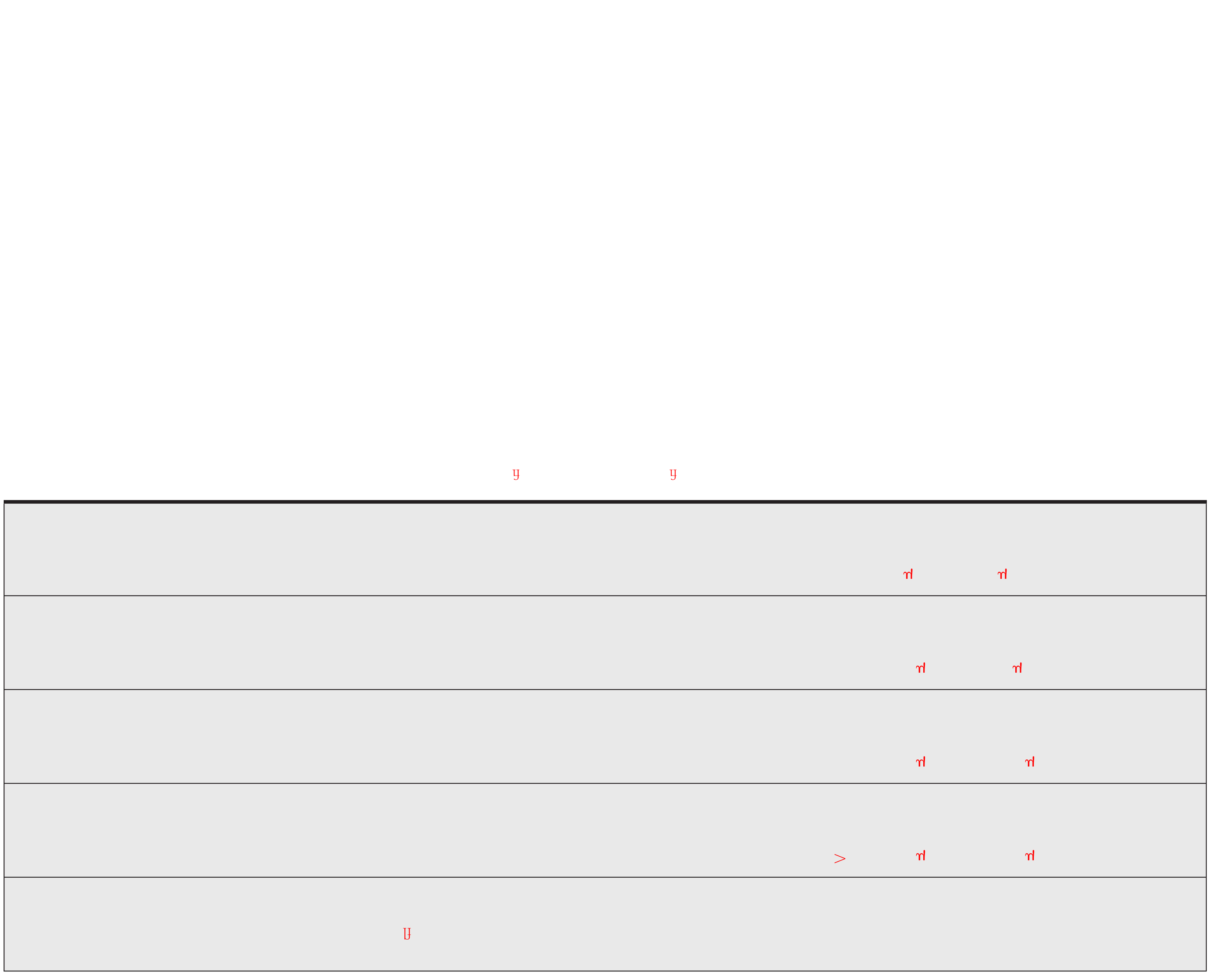






86.8 Antithyroid Dosing in Renal Failure

Antithyroid Drugs	Normal Dosage	% of Renal Excretion	Dosage Adjustment in Renal Failure: GFR > 50	GFR 10 to 50	GFR < 10	HD	CAPD	CVVH
Methimazole	5 to 20 mg tid	7	100%	100%	100%	No data	No data	Dose for GFR 10 to 50
Propylthiouracil	100 mg tid	<10	100%	100%	100%	No data	No data	Dose for GFR 10 to 50

GFR, glomerular filtration rate; HD, hemodialysis; CAPD, chronic peritoneal dialysis; CVVH, continuous venovenous hemofiltration; tid, three times a day.

Gastrointestinal Drugs

Table 86.9 summarizes dosage recommendations for gastrointestinal drugs. Patients with renal insufficiency experience gastrointestinal disorders more often than the general population, particularly peptic ulcer disease. Prior to the development of H_2 blockers, antacid therapy with compounds containing aluminum, calcium, magnesium, or bicarbonate was the mainstay. Excessive intake of calcium carbonate can result in the milk–alkali syndrome, characterized by hypercalcemia, metabolic alkalosis, and renal failure. Aluminum toxicity has been well described with chronic ingestion of aluminum-containing antacids in the setting of renal failure.

Neurologic Agents

Table 86.10 includes the dosage recommendations for neurologic agents. Unfortunately, seizure disorders complicate renal insufficiency and ESRD. Phenytoin is commonly used as an anticonvulsant, but in patients with renal impairment, its Vd increases while its degree of protein binding decreases. As a result, a low total plasma phenytoin level may not reflect subtherapeutic drug levels, as the "free phenytoin" level may be adequate. Following free or unbound phenytoin levels is prudent in patients with markedly reduced renal function.

Rheumatologic Agents

Summarized dosage recommendations for rheumatologic agents are in Table 86.11. Although dosage reductions of nonsteroidal anti-inflammatory drugs (NSAIDs) are generally not required in renal failure, several precautions must be considered. When renal perfusion is reduced as in congestive heart failure or cirrhotic patients, vasodilatory prostaglandins may be key in maintaining renal blood flow. NSAIDs in such settings may cause reversible abrupt declines in renal function due to prostaglandin inhibition. Impaired potassium, sodium, and water excretion have also been attributed to NSAID use.

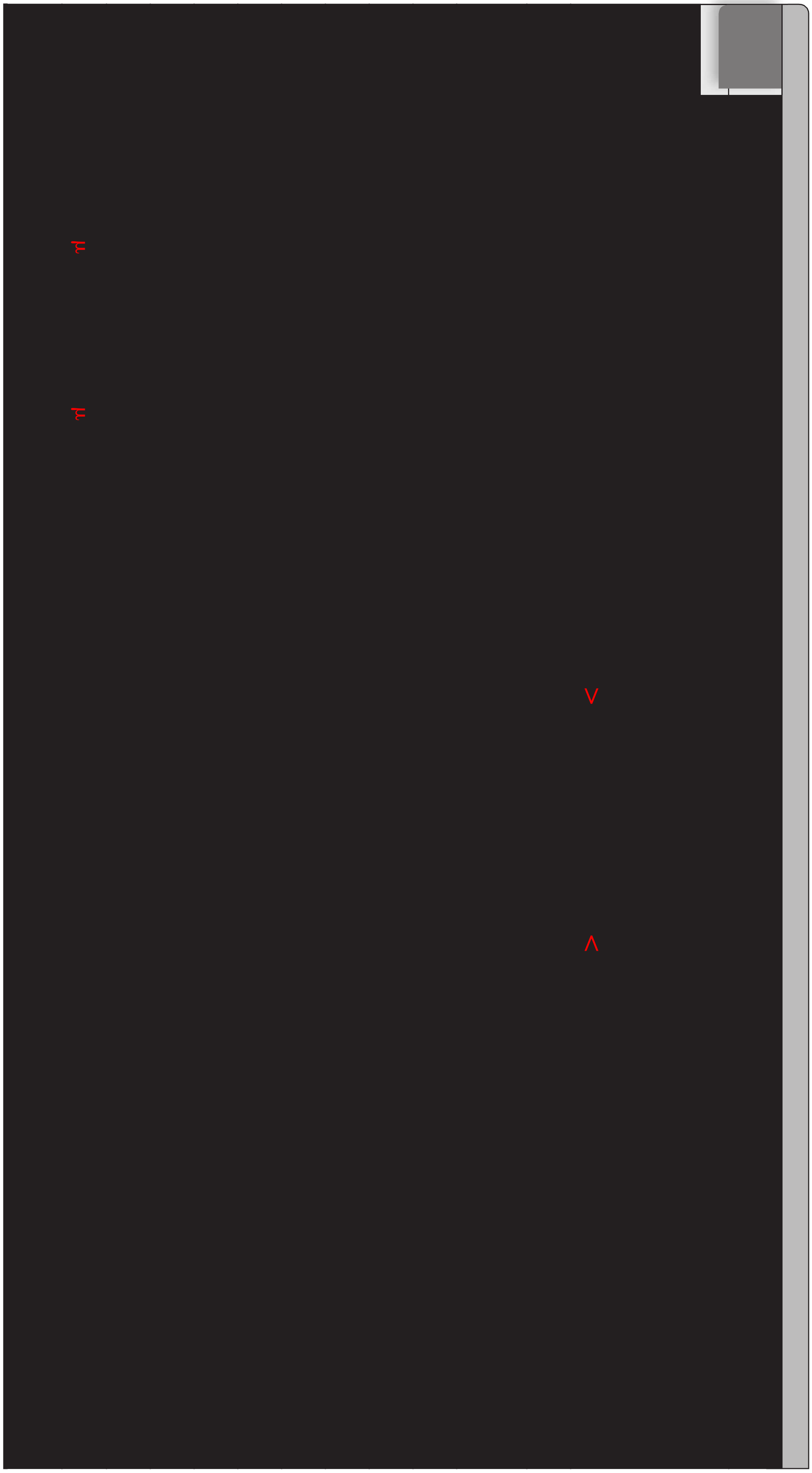
Patients with gout and renal insufficiency require reductions in allopurinol dosing because accumulation of its metabolite may underlie the complication of exfoliative dermatitis.[87] Similarly, renal failure increases the risk of myopathy and polyneuropathy associated with colchicine use. Use of intravenous (IV) colchicines should be avoided in all patients with renal impairment.[88]

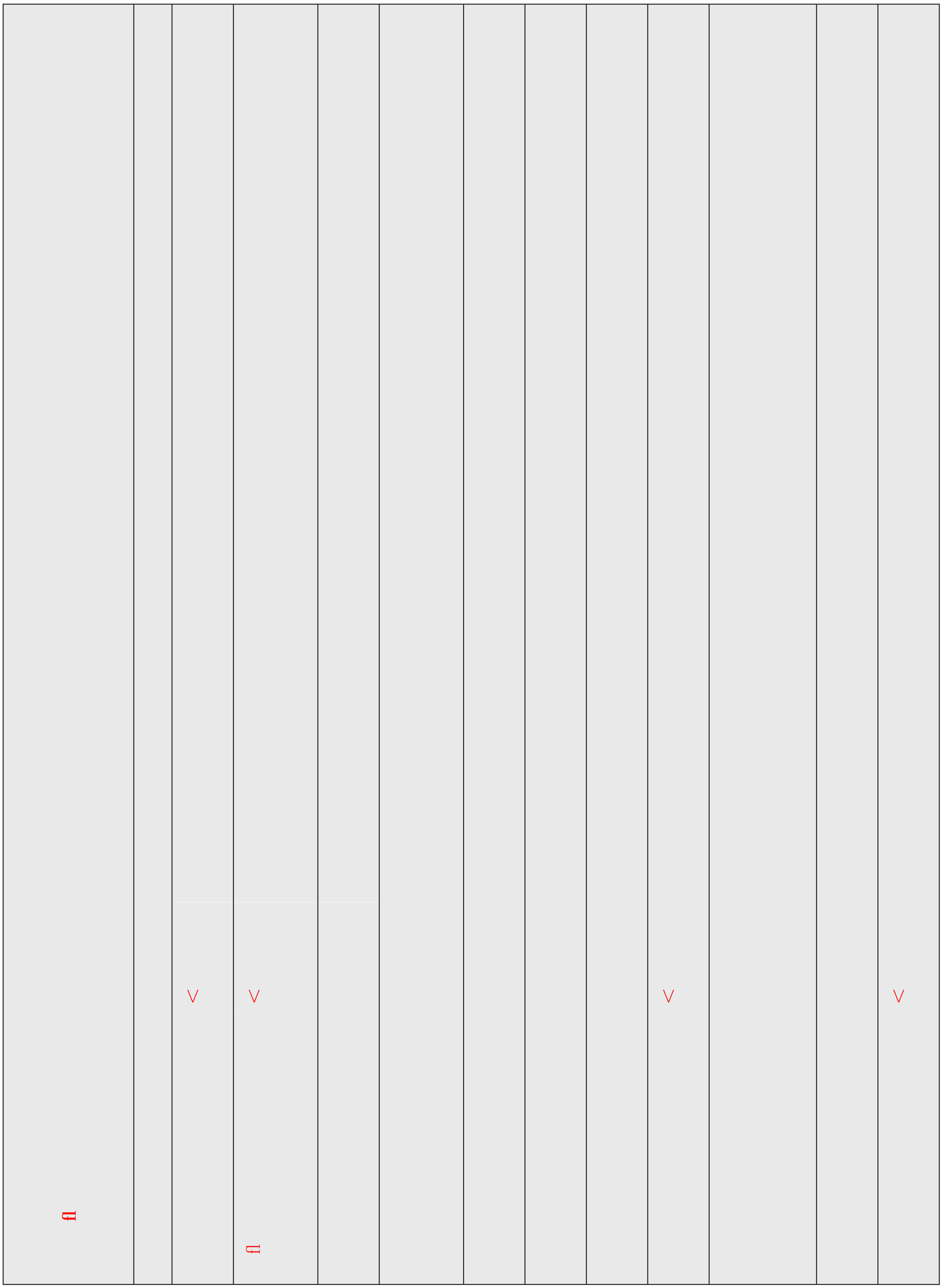
Sedatives, Hypnotics, and Psychiatric Agents

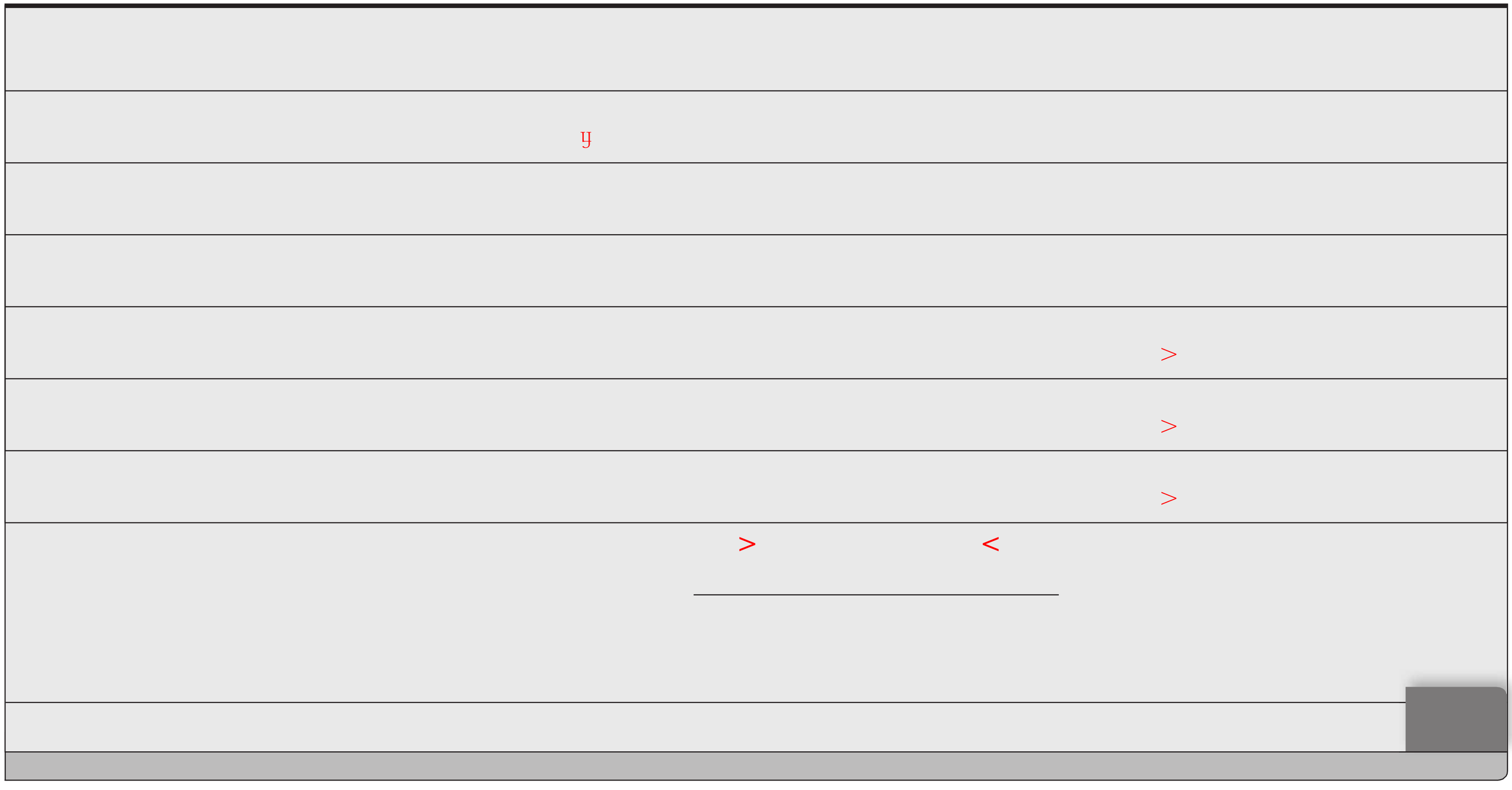
Tables 86.12, 86.13, and 86.14 provide dosage recommendations for sedatives, hypnotics, and psychiatric agents. The majority of drugs in this category are lipid-soluble, highly protein bound, and excreted primarily by hepatic transformation to inactive metabolites, but increased sensitivity to the sedative side effects occurs in patients with renal impairment. Additionally, though dosage reduction generally is not required, increased sensitivity to the side effects of tricyclic antidepressants mandates a cautious approach in their use. Similarly, renal failure may exacerbate extrapyramidal side effects associated with phenothiazine therapy. In contrast, lithium is water-soluble and undergoes renal elimination. Renal syndromes induced by lithium therapy include nephrogenic diabetes insipidus as well as acute and chronic renal failure. Lithium toxicity can be minimized by avoidance of volume depletion and concurrent diuretic therapy. Regular monitoring ensures adequate serum levels and minimizes the risk of toxicity.[89,90]

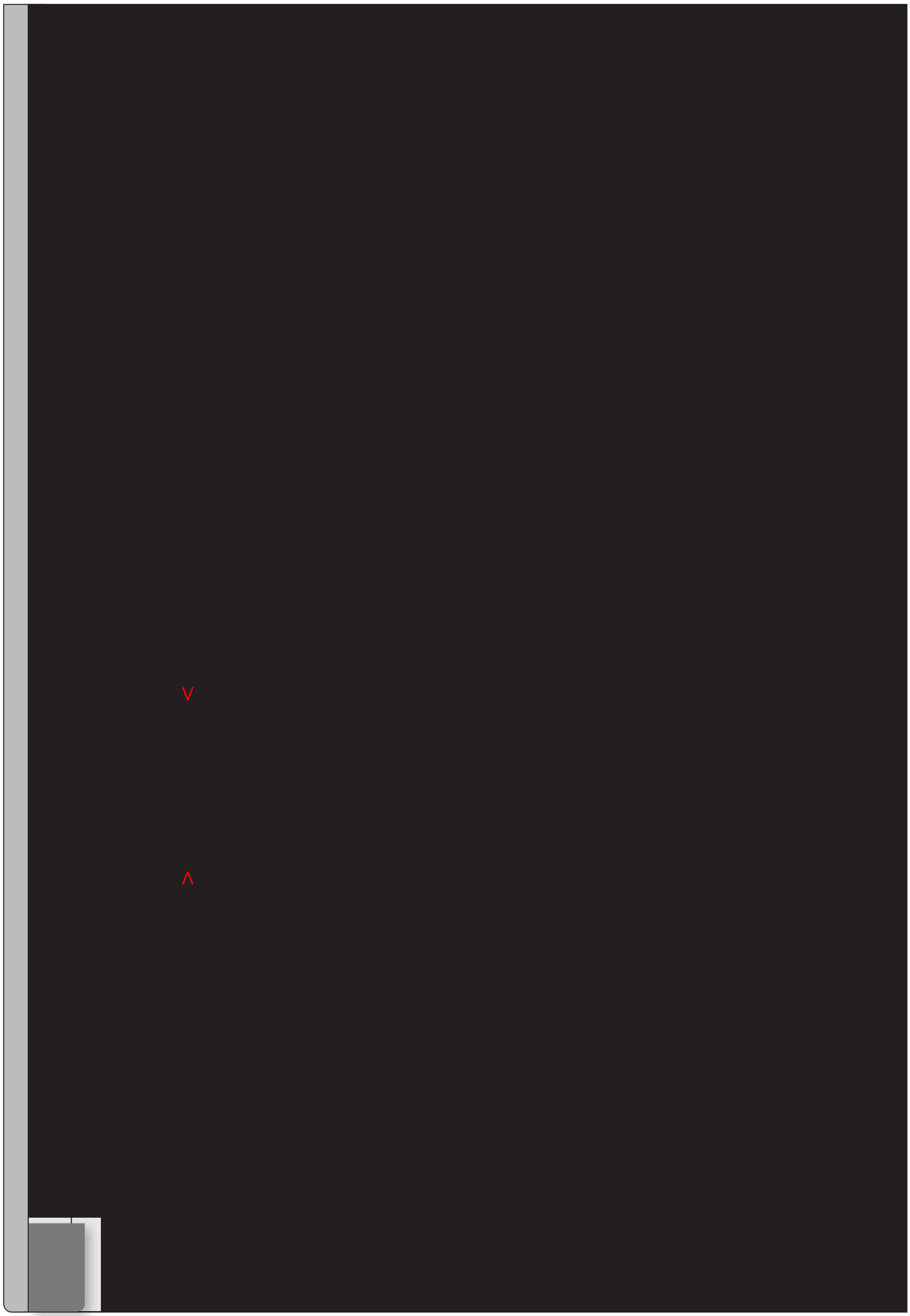
Miscellaneous Agents

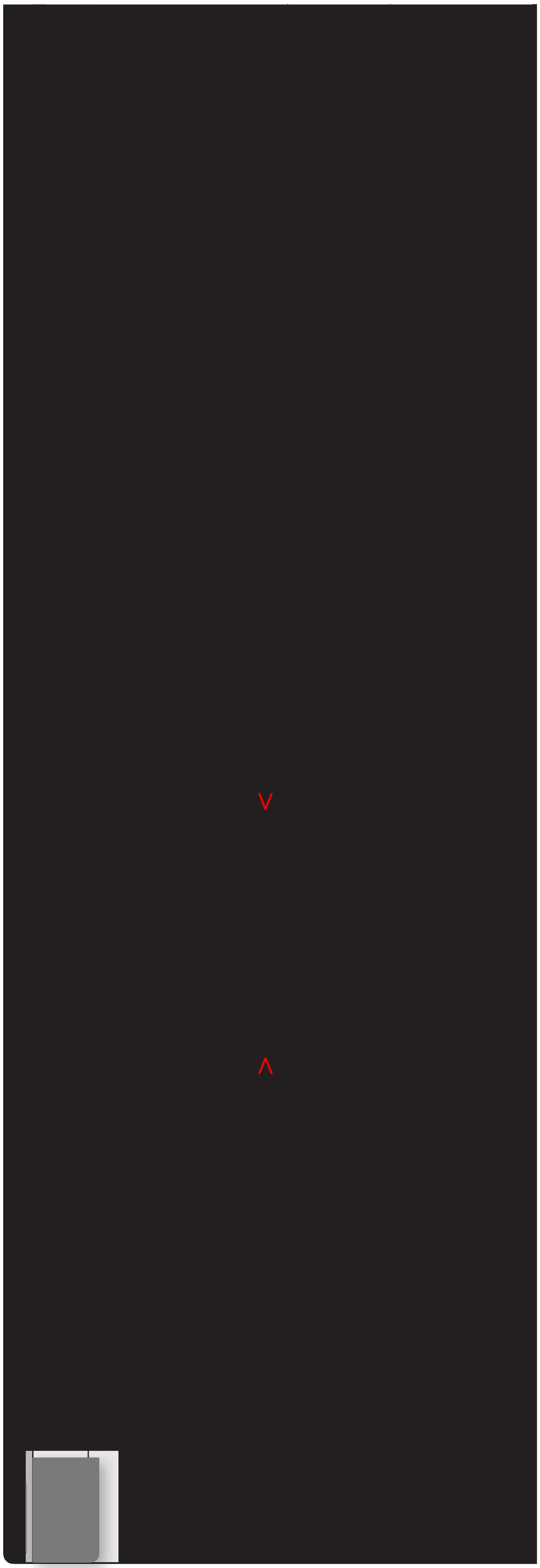
In Tables 86.15 and 86.16 are provided dosage recommendations for a wide variety of miscellaneous agents.

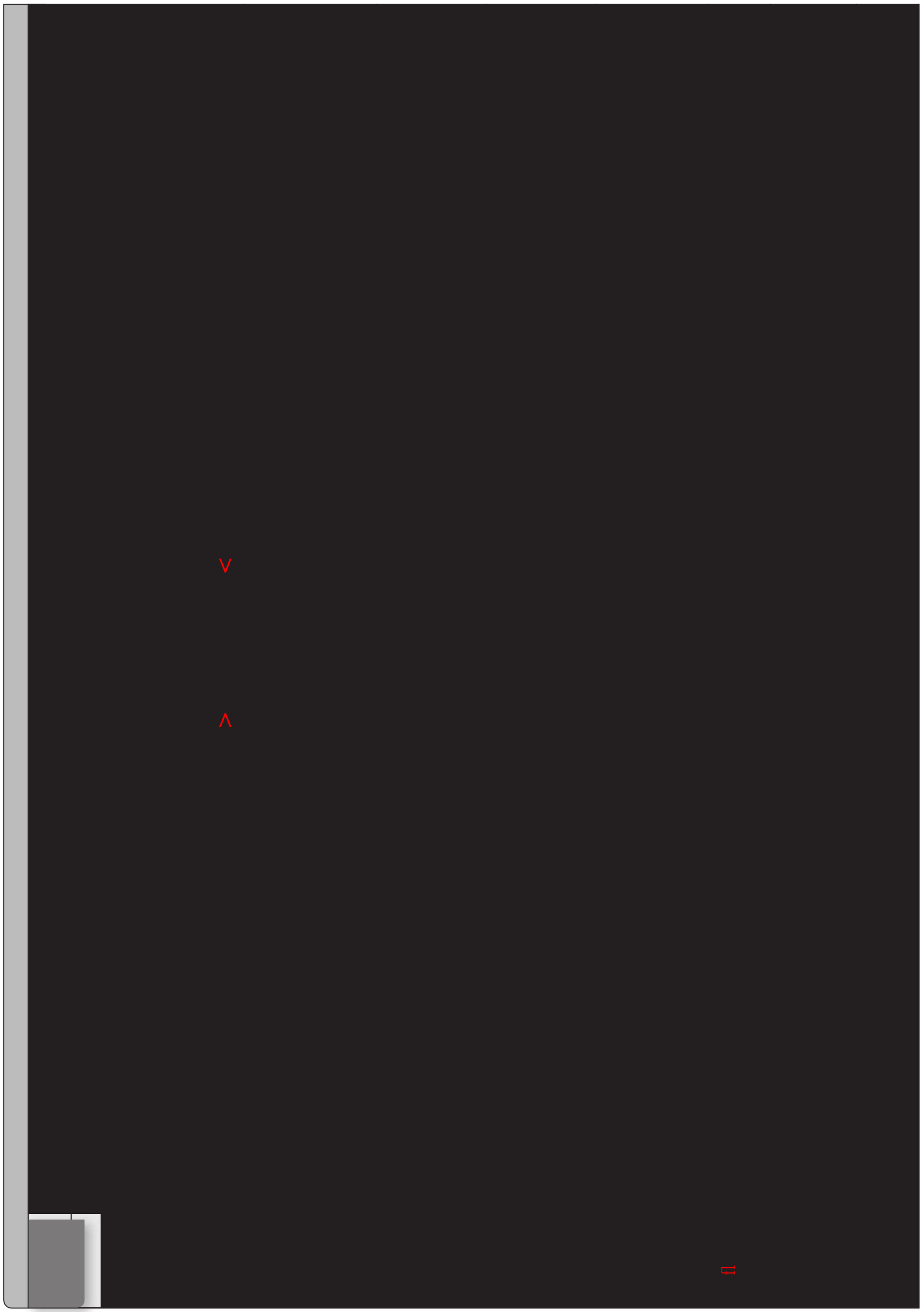


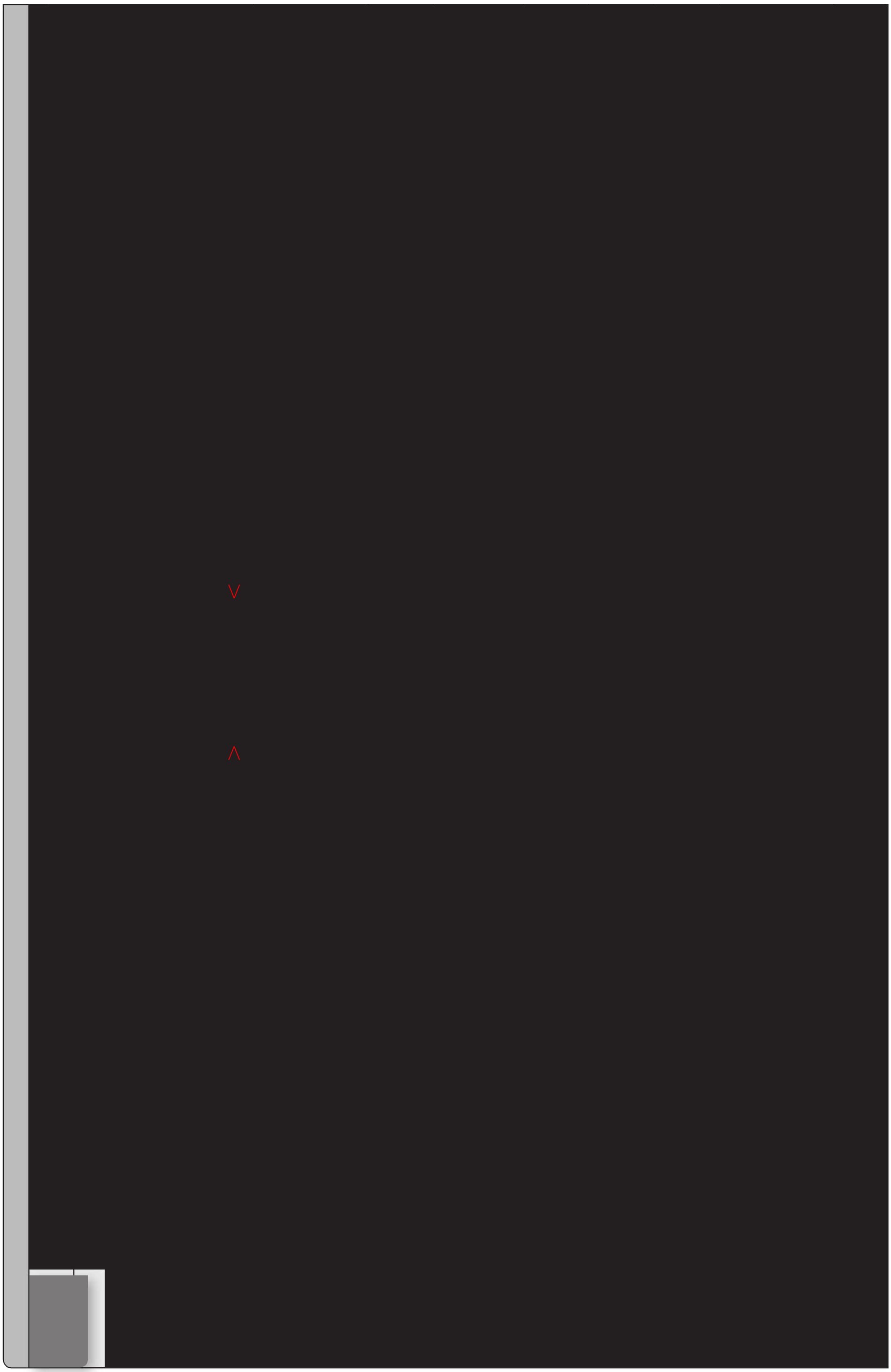


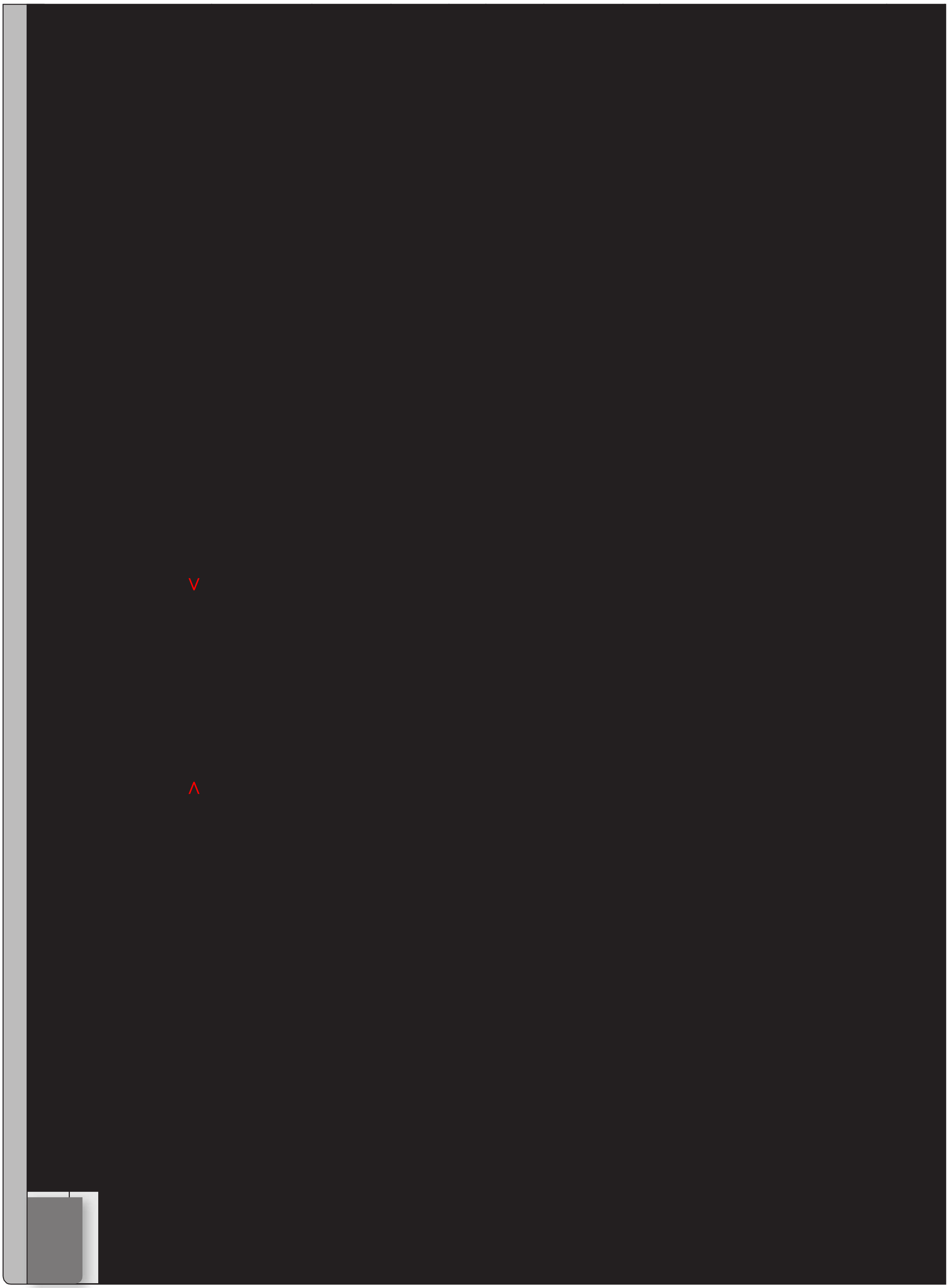












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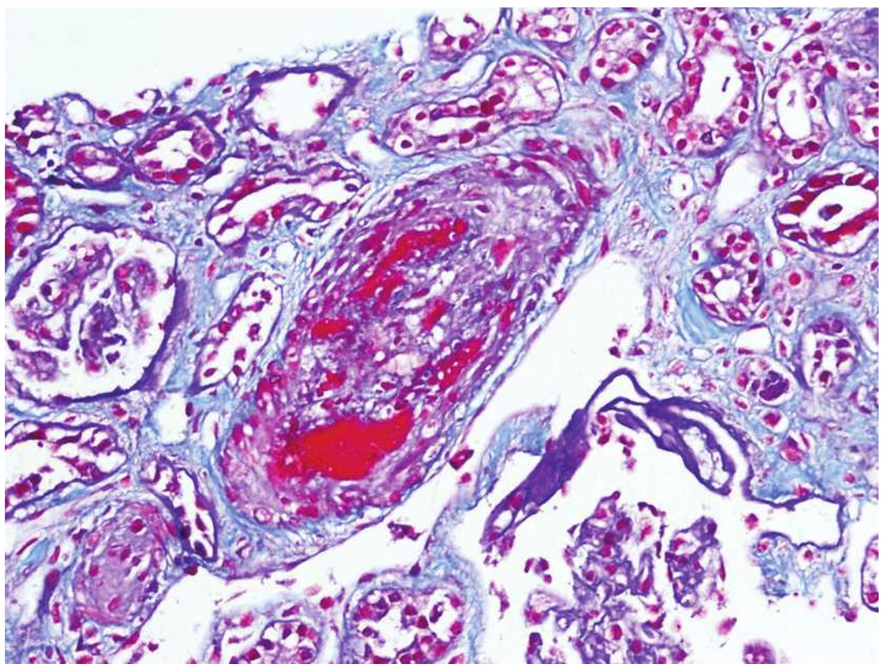


FIGURE 53.31

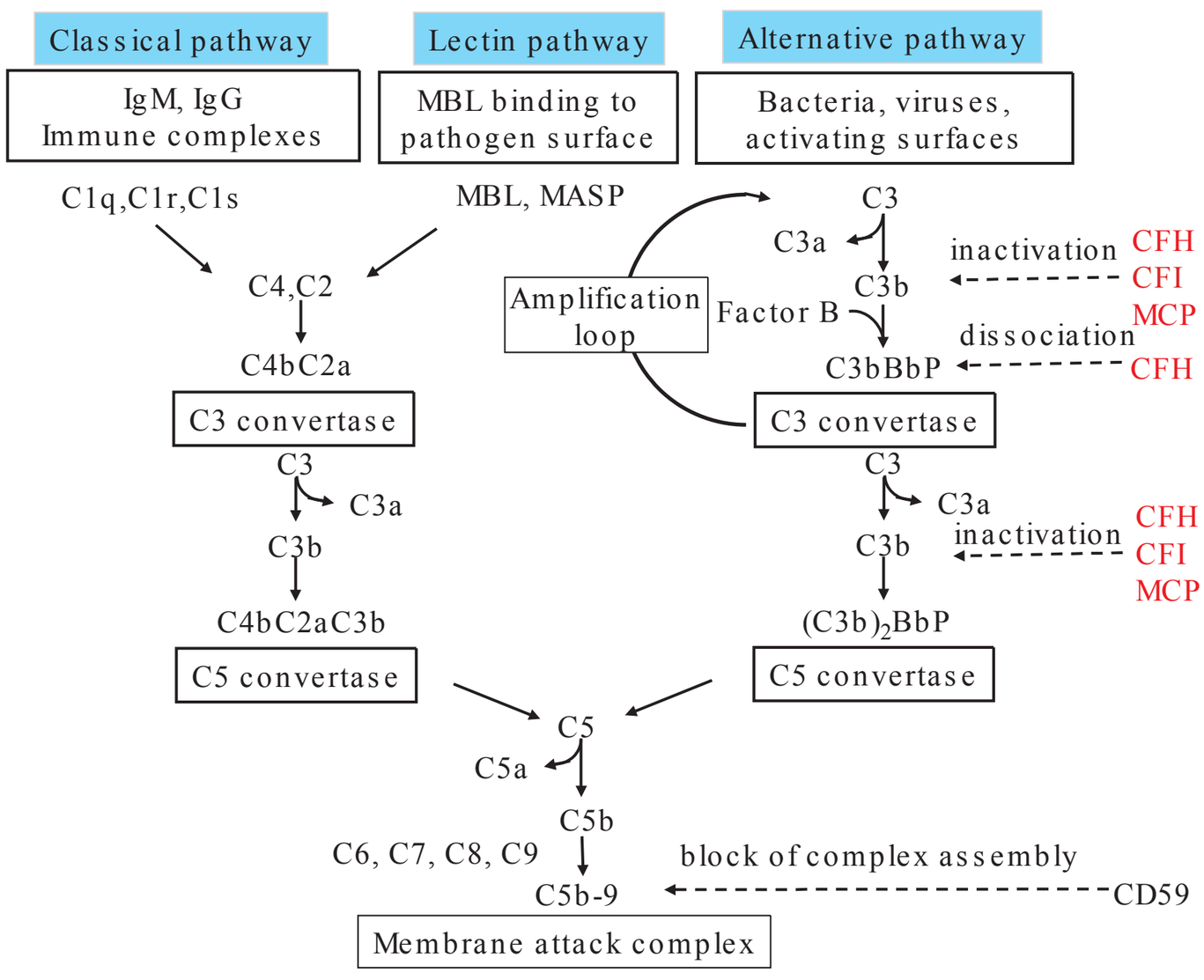


FIGURE 55.12

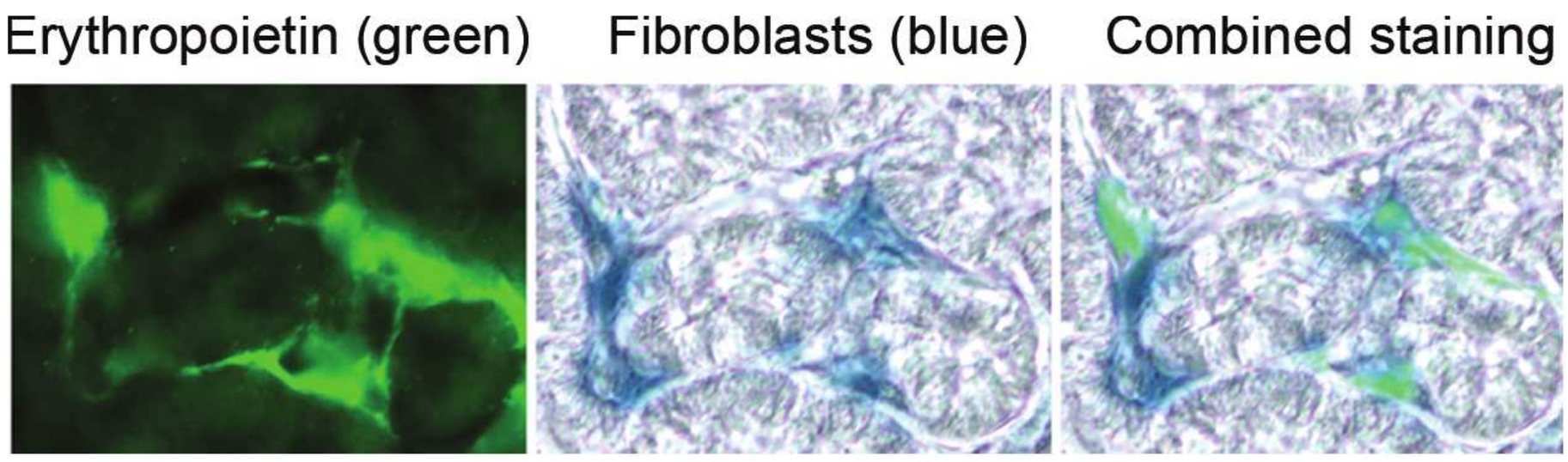
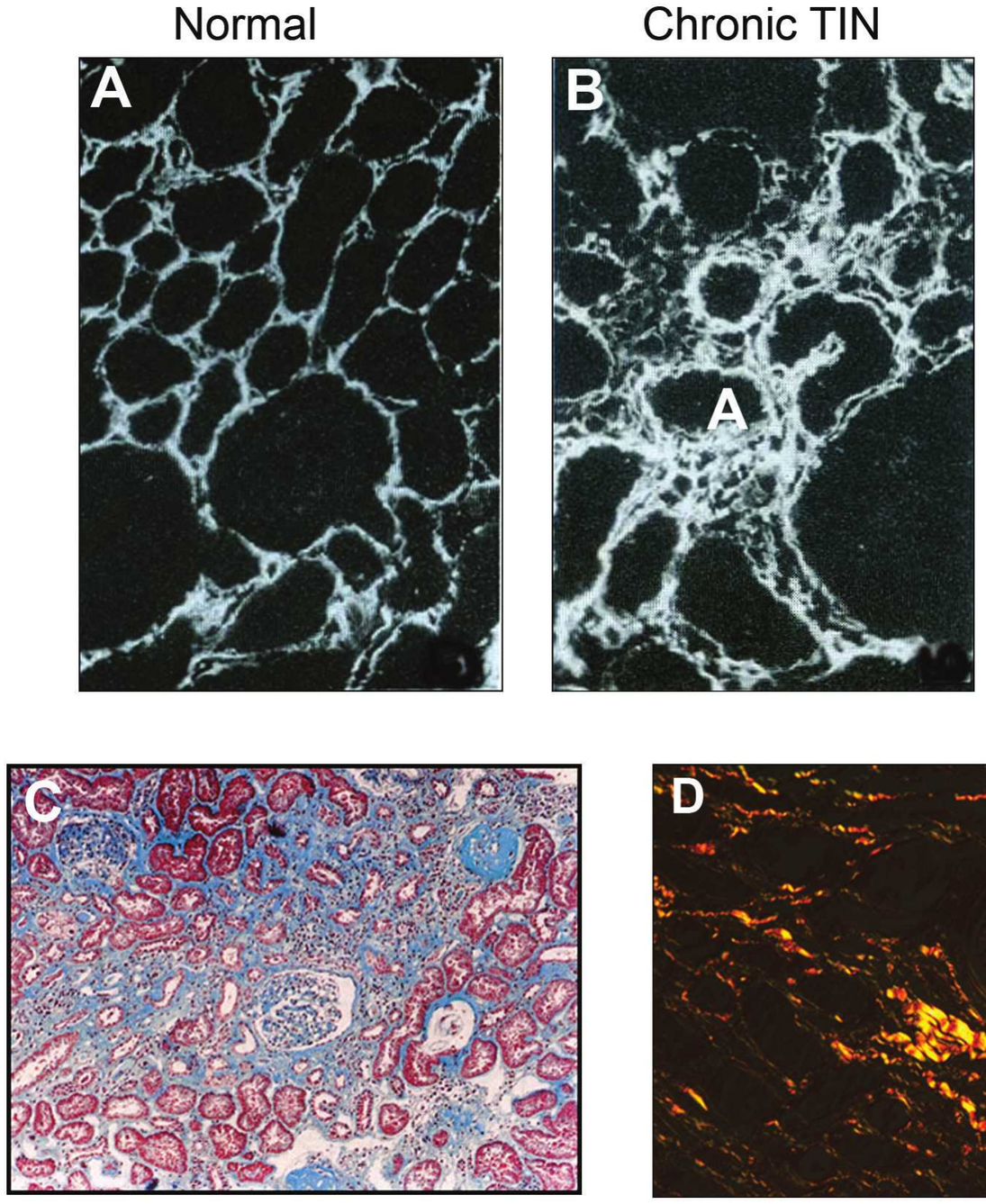
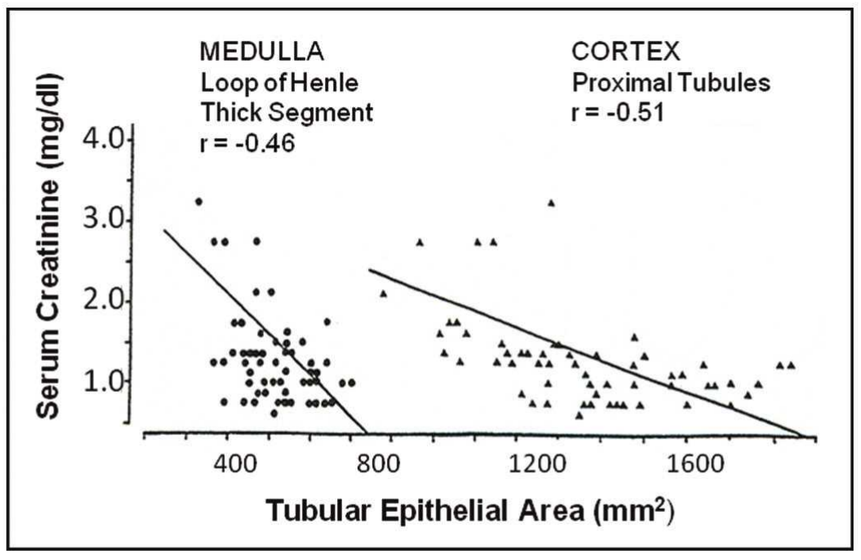


FIGURE 57.1





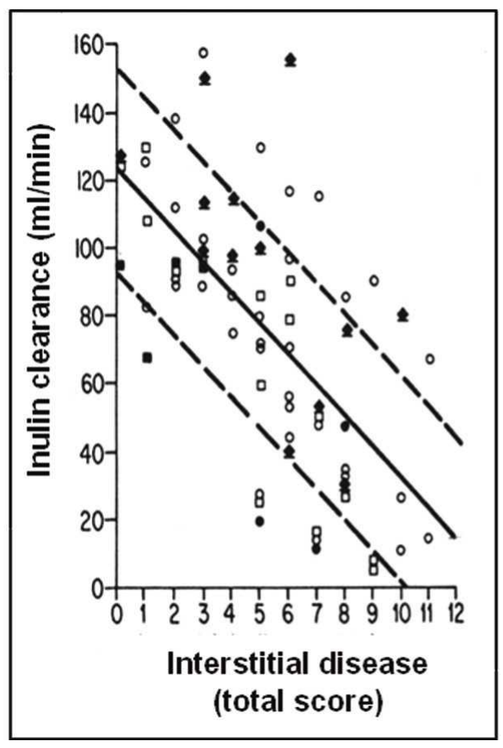


FIGURE 57.2

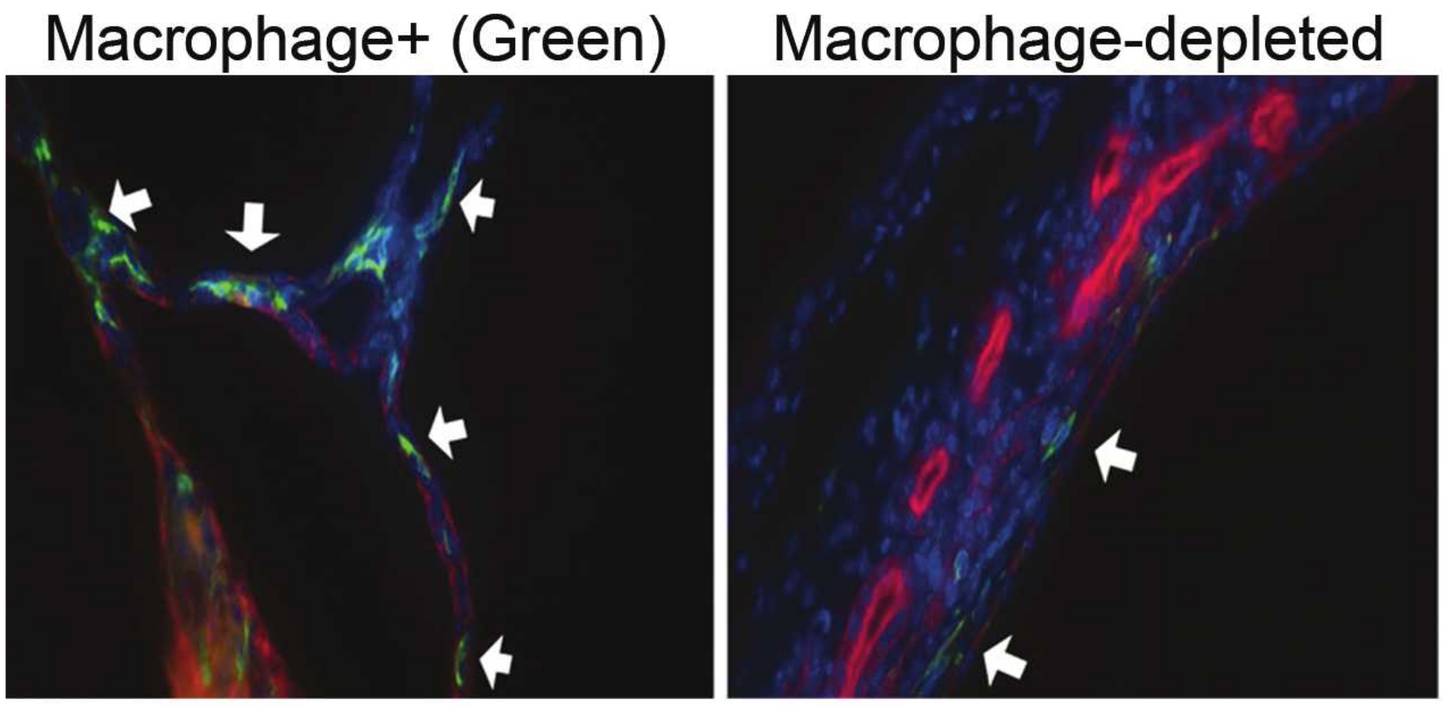
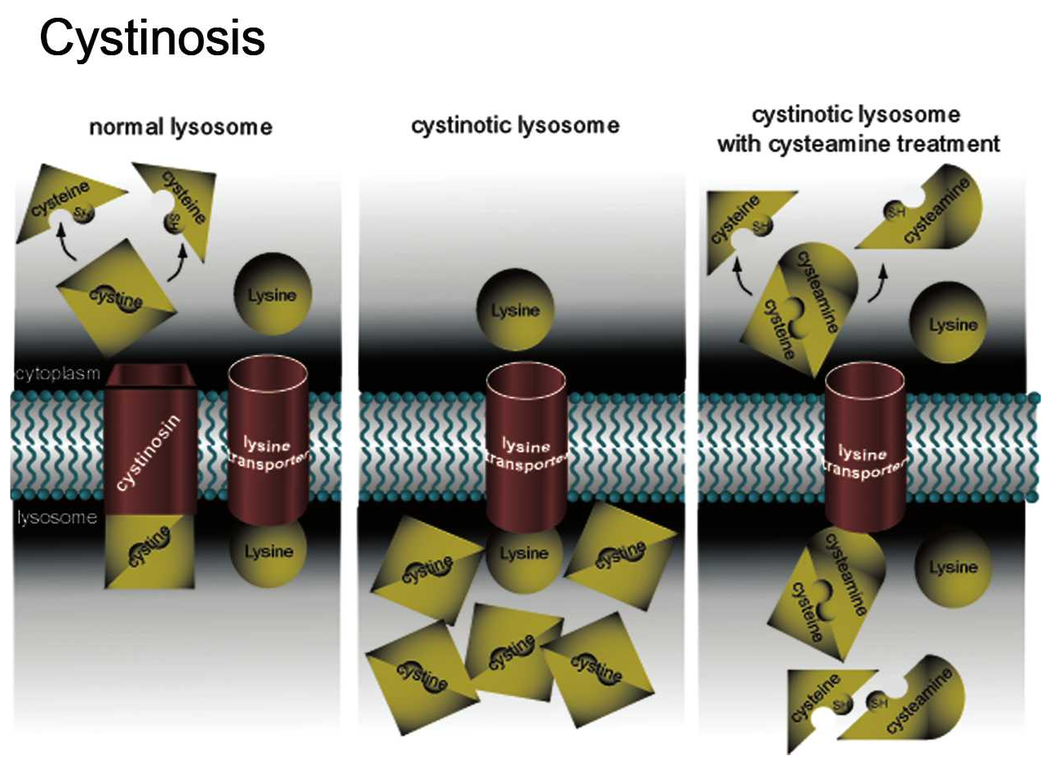


FIGURE 57.7



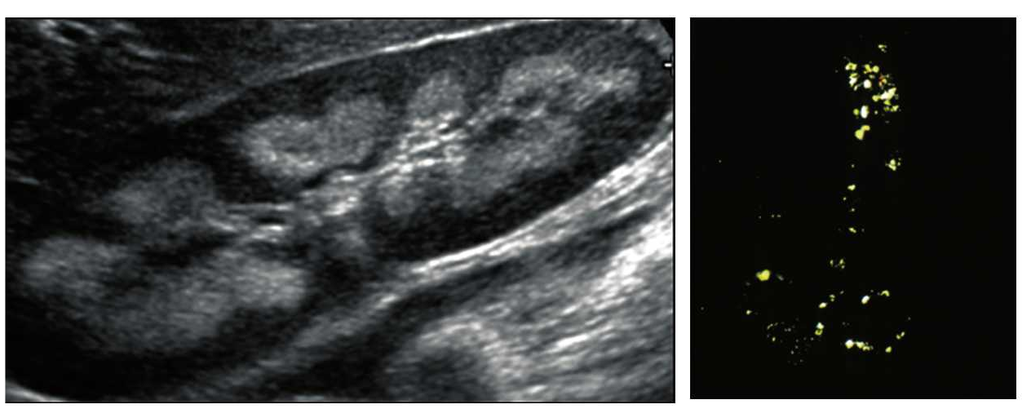


FIGURE 57.8

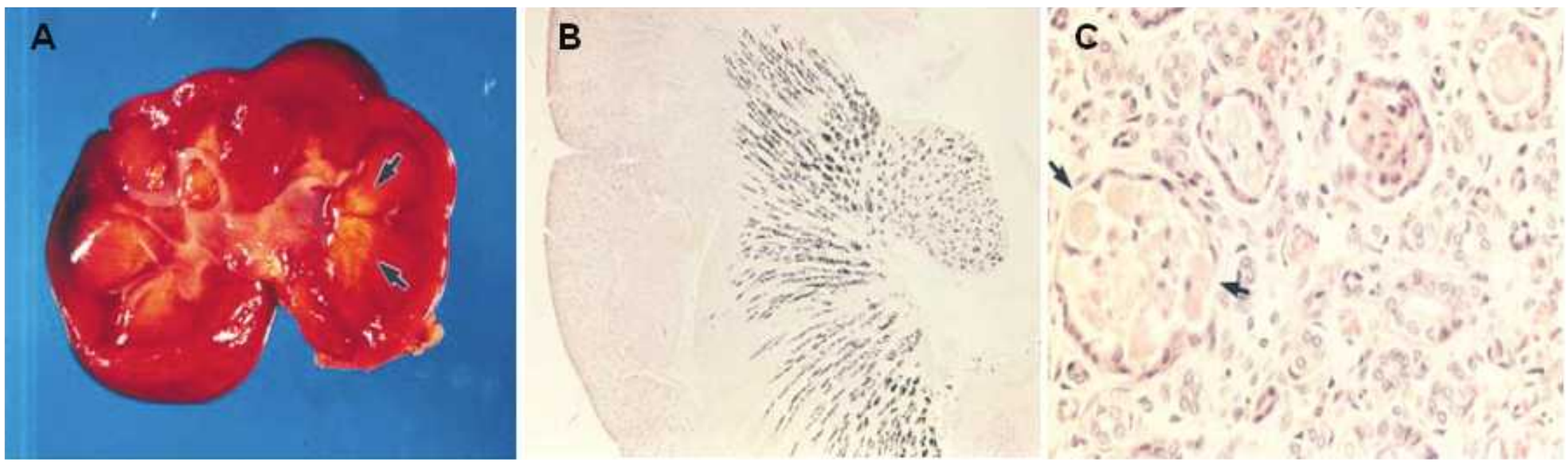
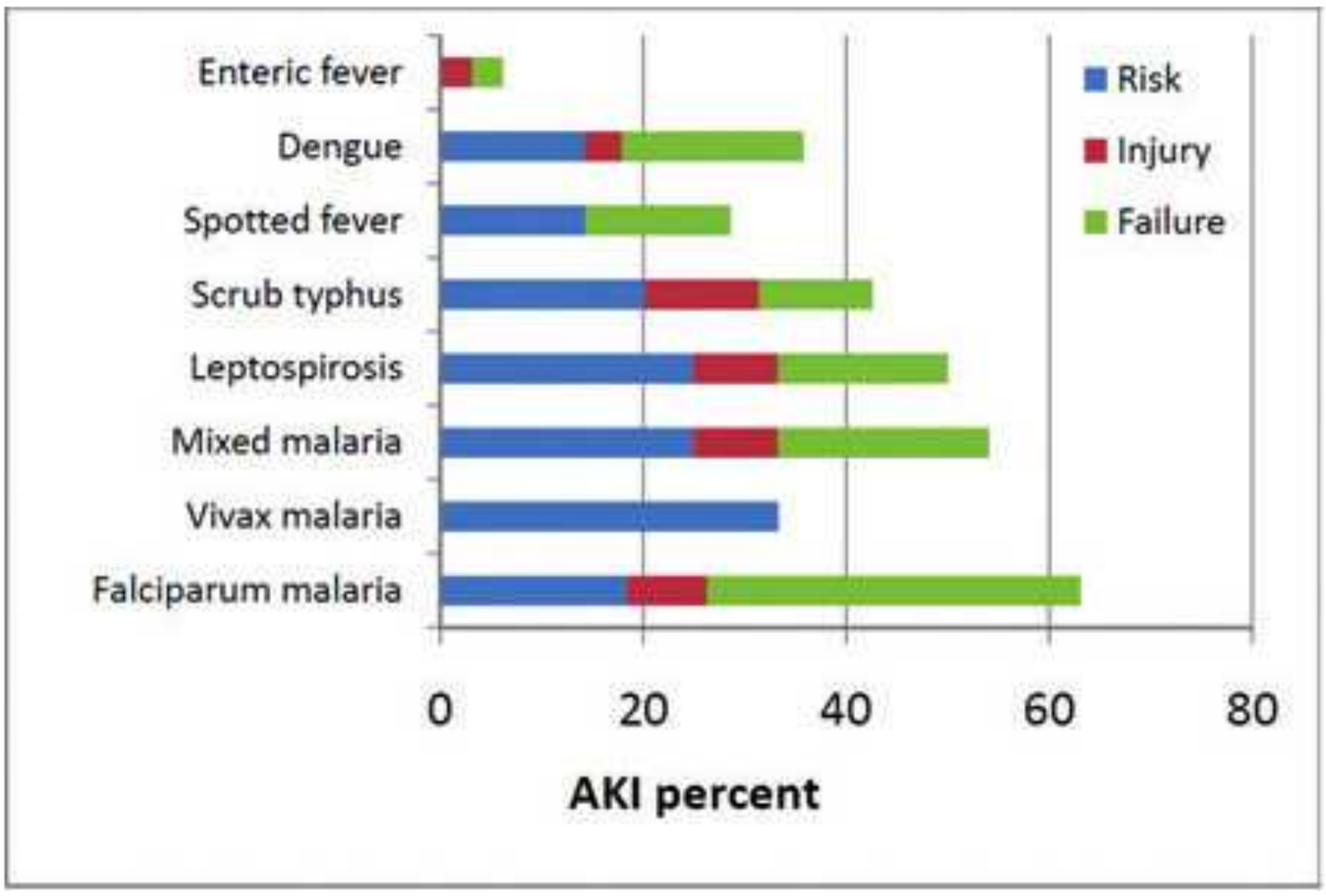
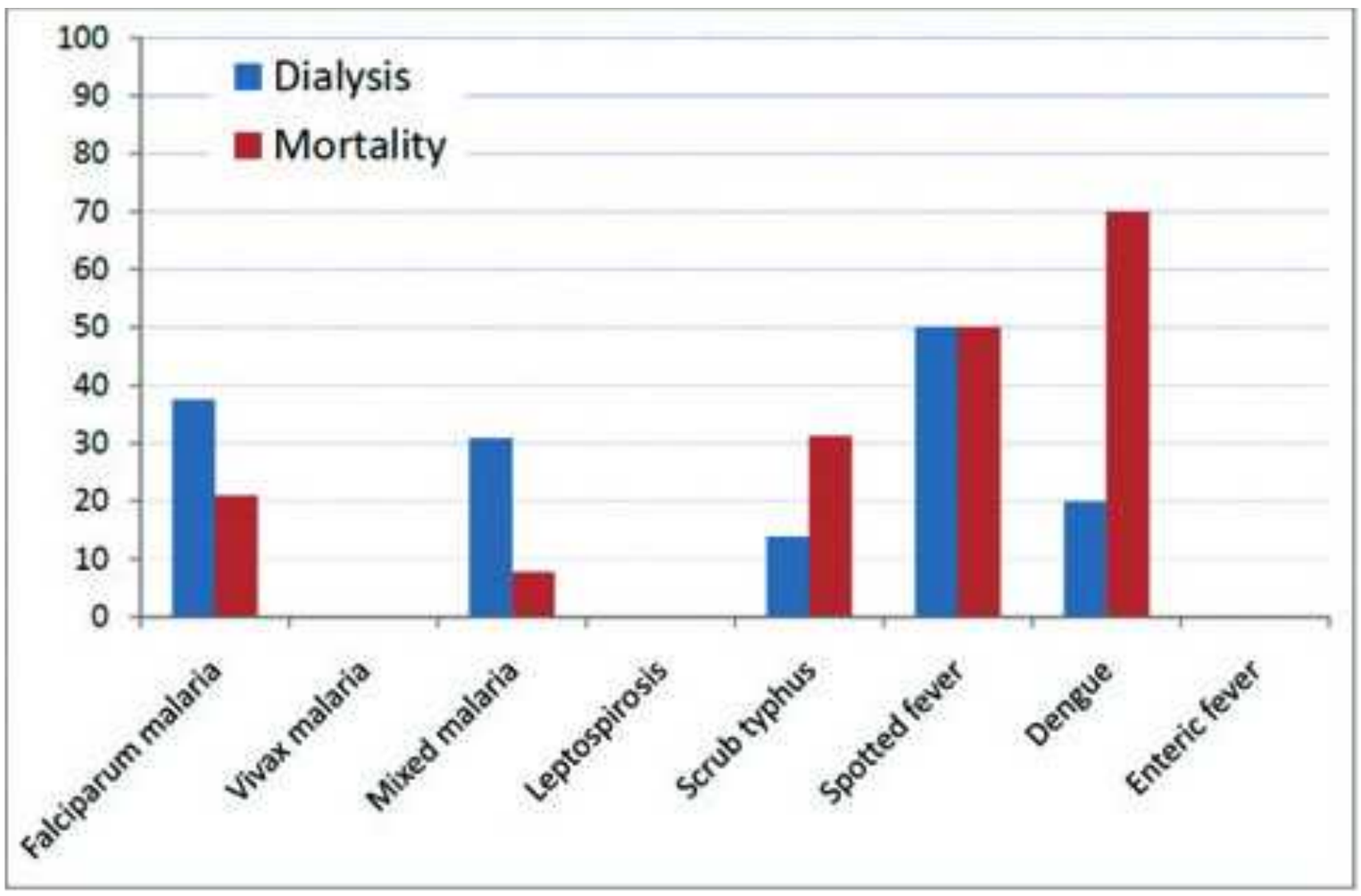


FIGURE 61.3

FIGURE 62.1

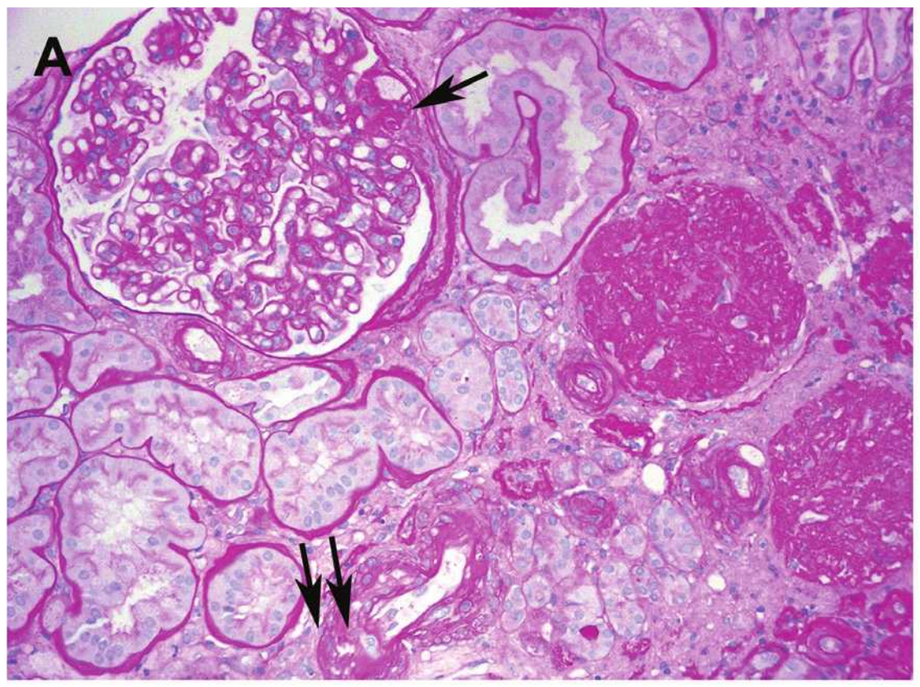


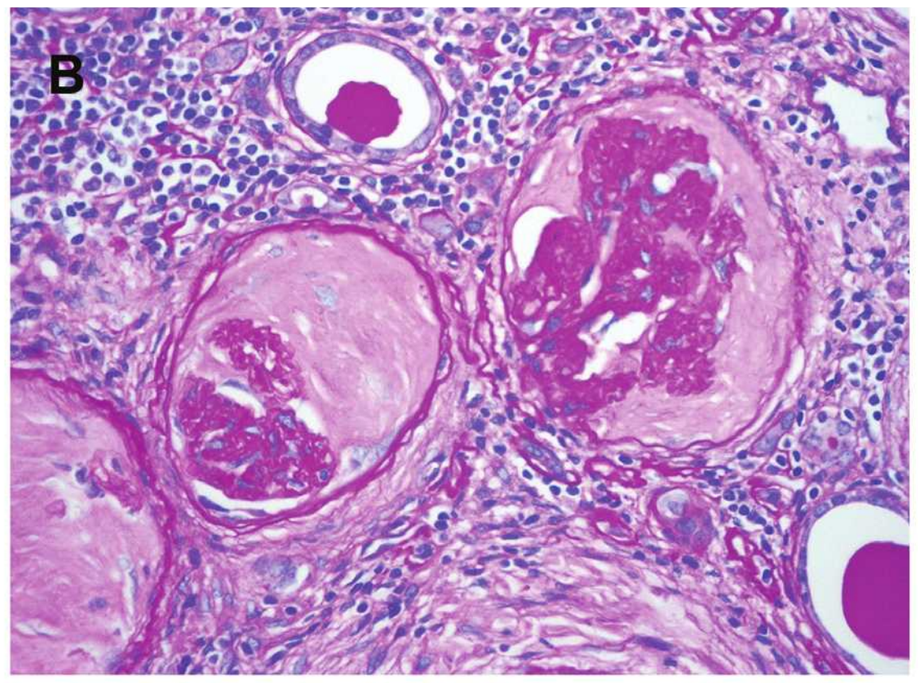
A

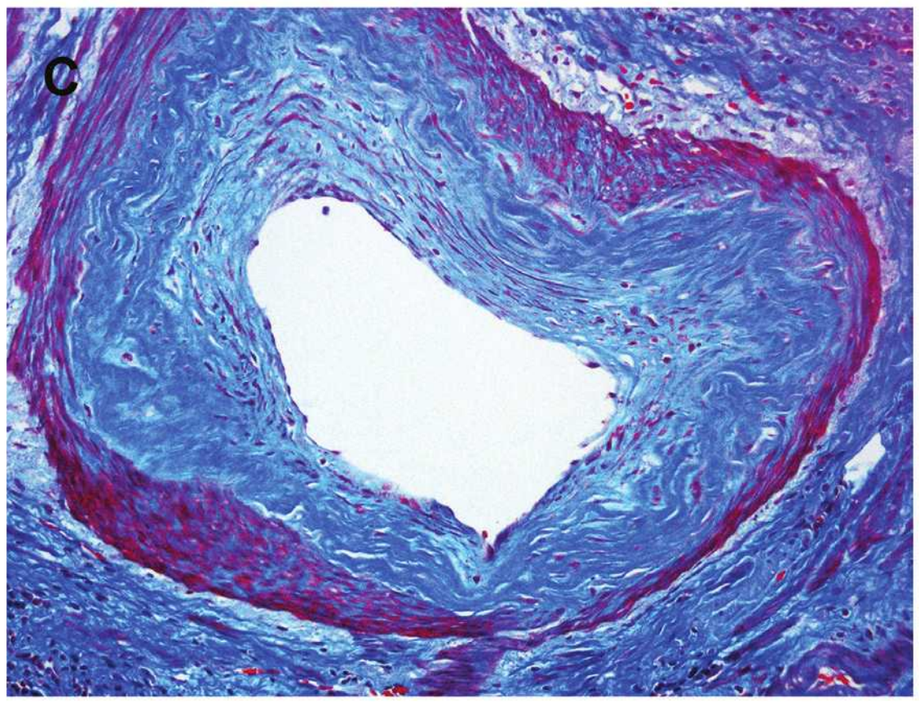


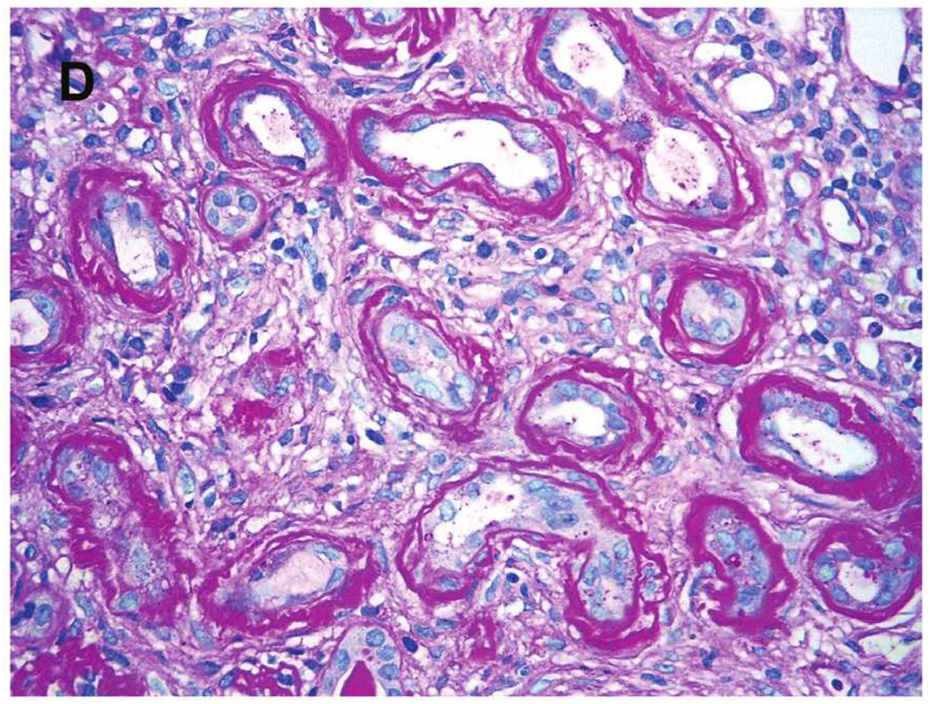
B

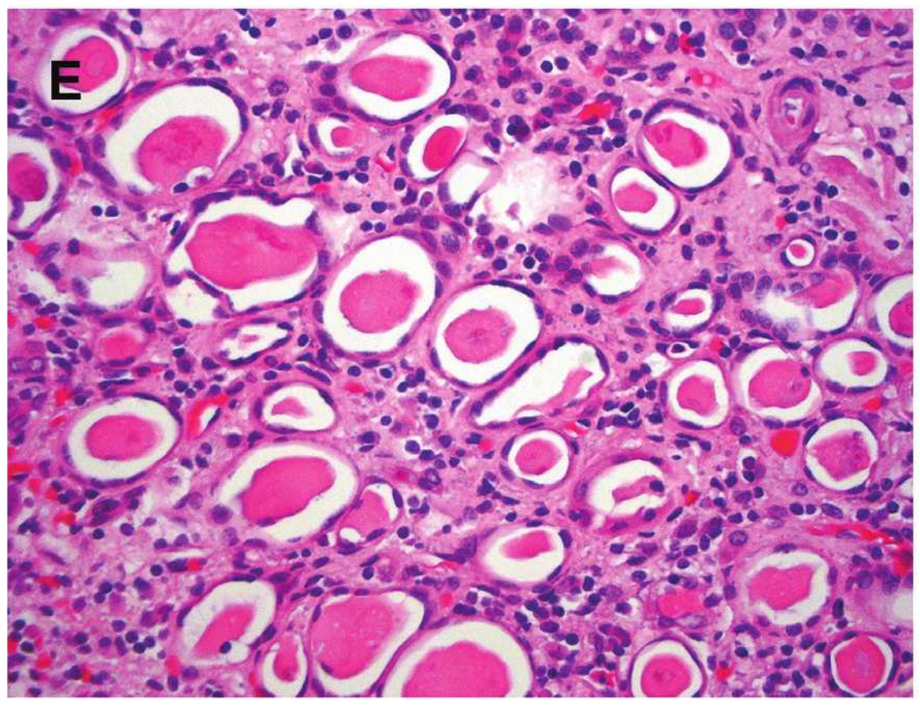
FIGURE 63.3 A,B











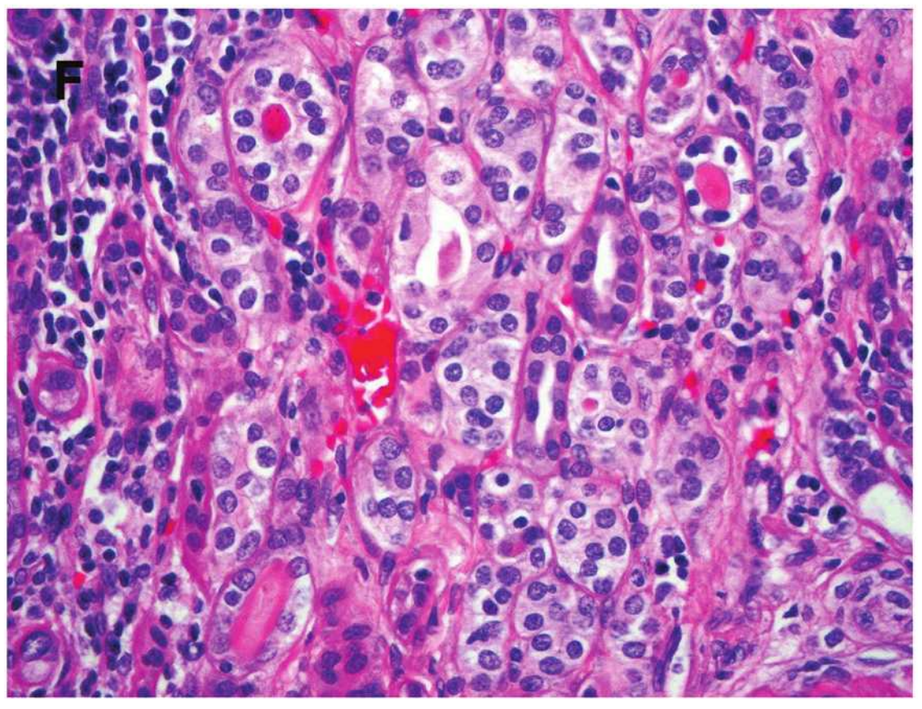


FIGURE 65.1

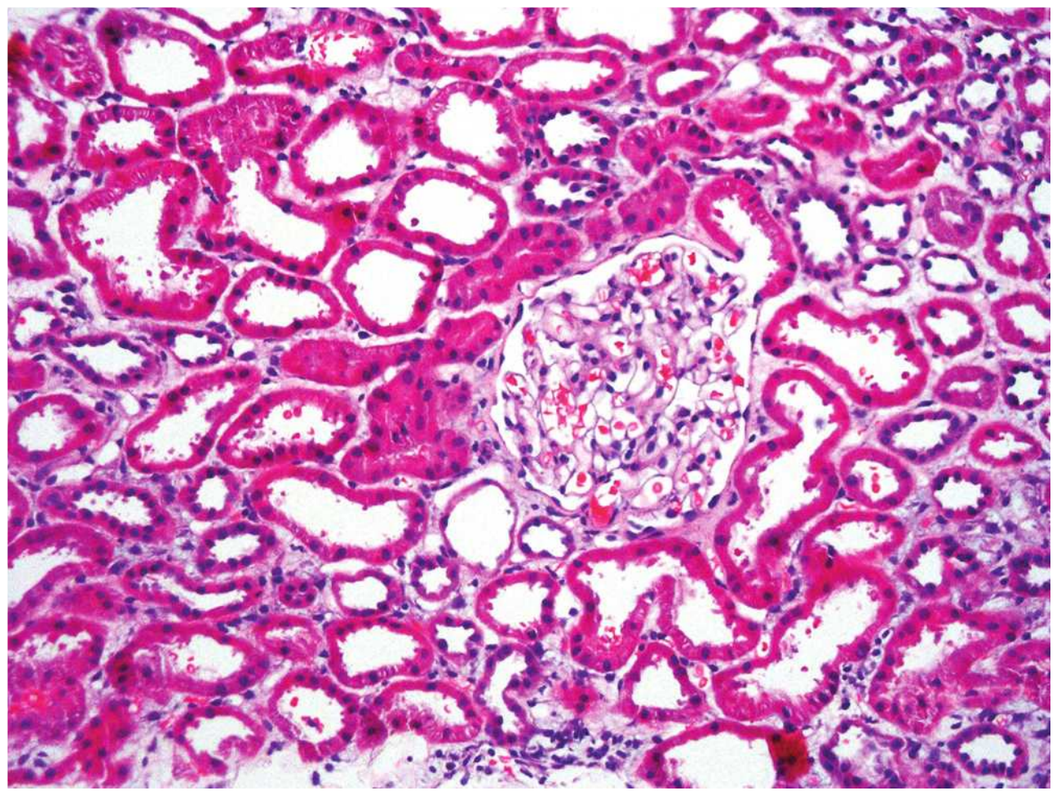


FIGURE 65.3

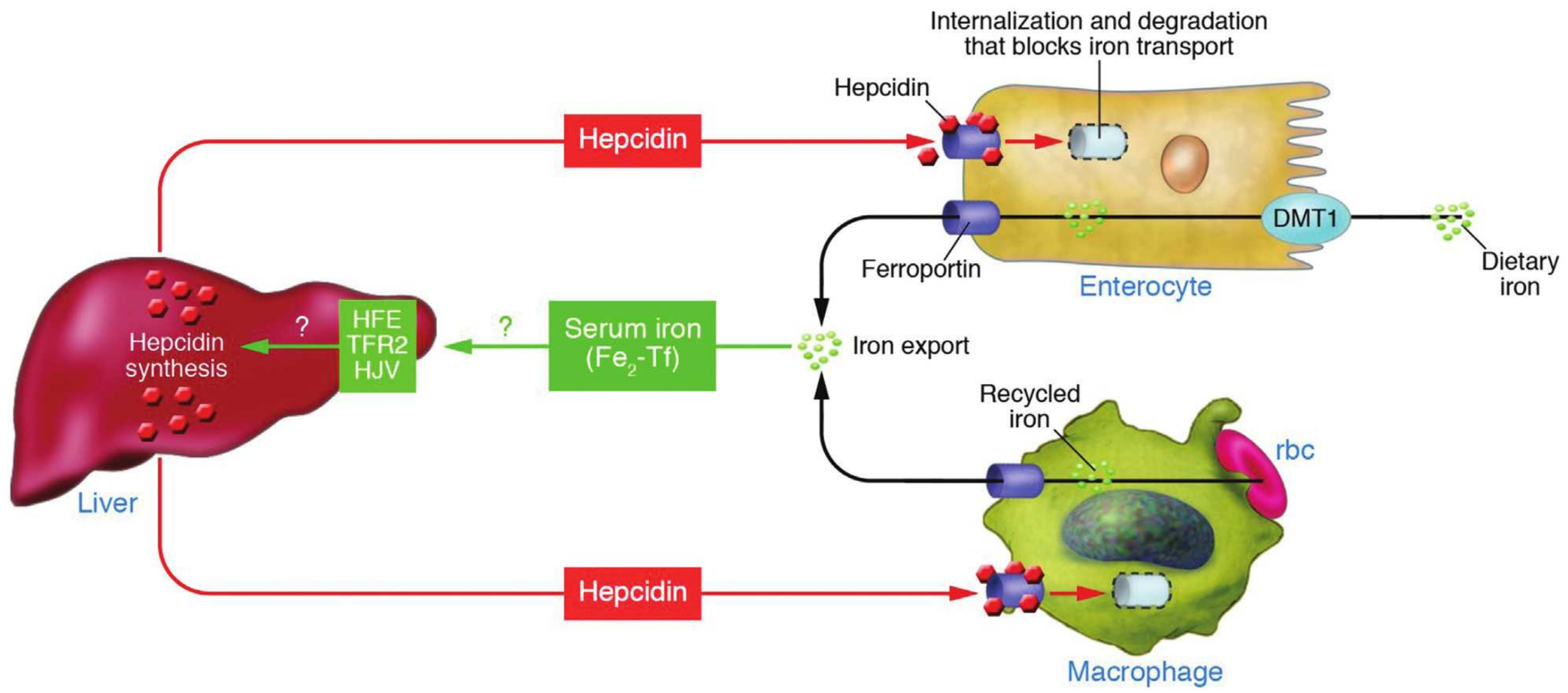


FIGURE 76.3

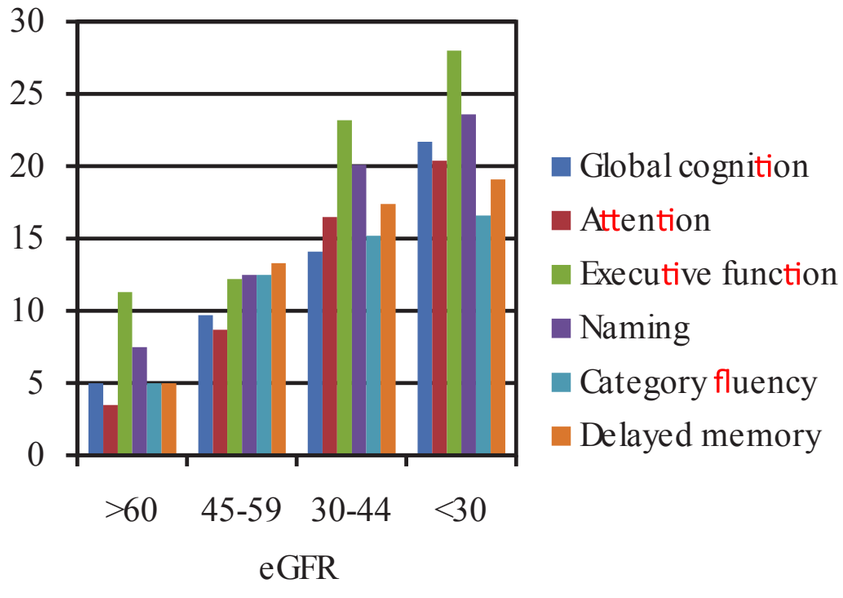


FIGURE 78.2

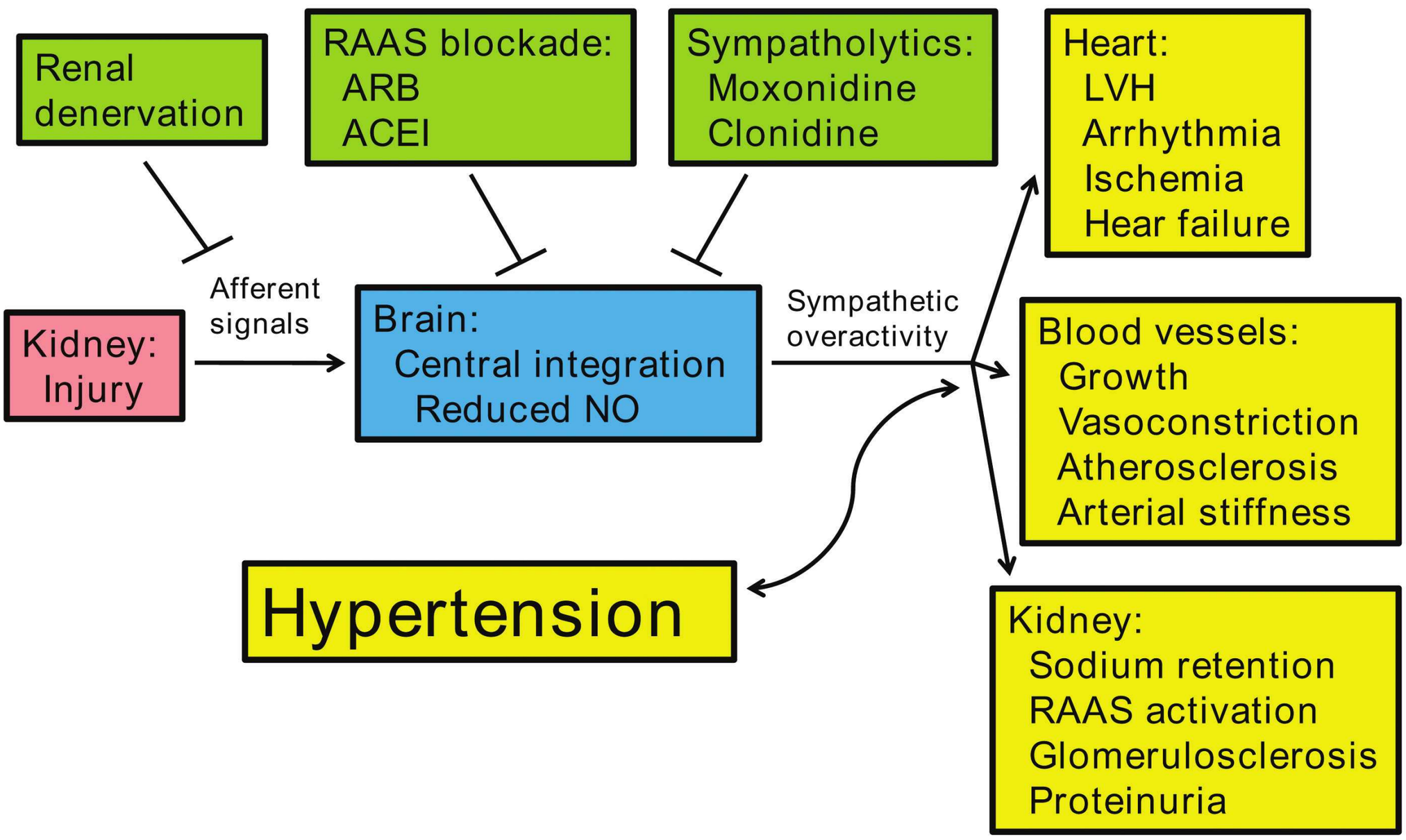


FIGURE 78.7