DRUG USE IN THE ELDERLY

In the elderly, multiple pathologies and medications used to treat them result in more drug interactions and adverse effects. Aging also results in changes in organ function, especially of the organs involved in drug disposition. Initial doses should be less than the usual adult dosage and should be increased slowly. The number of medications, and doses per day, should be kept as low as possible.

Even in the absence of kidney disease, renal clearance may be reduced by 35–50% in elderly patients. Dosages should be adjusted on the basis of creatinine clearance. Aging also results in a decrease in the size of, and blood flow to, the liver and possibly in the activity of hepatic drug-metabolizing enzymes; accordingly, the hepatic clearance of some drugs is impaired in the elderly. As with liver disease, these changes are not readily predicted.

Elderly patients may display altered drug sensitivity. Examples include increased analgesic effects of opioids, increased sedation from benzodiazepines and other CNS depressants, and increased risk of bleeding while receiving anticoagulant therapy, even when clotting parameters are well controlled. Exaggerated responses to cardiovascular drugs are also common because of the impaired responsiveness of normal homeostatic mechanisms. Conversely, the elderly display decreased sensitivity to β-adrenergic receptor blockers.

Adverse drug reactions are especially common in the elderly because of altered pharmacokinetics and pharmacodynamics, the frequent use of multidrug regimens, and concomitant disease. For example, use of long half-life benzodiazepines is linked to the occurrence of hip fractures in elderly patients, perhaps reflecting both a risk of falls from these drugs (due to increased sedation) and the increased incidence of osteoporosis in elderly patients. In population surveys of the noninstitutionalized elderly, as many as 10% had at least one adverse drug reaction in the previous year.

DRUG USE IN CHILDREN

While most drugs used to treat disease in children are the same are those in adults, there are few studies that provide solid data to guide dosing. Drug metabolism pathways mature at different rates after birth, and disease mechanisms may be different in children. In practice, doses are adjusted for size (weight or body surface area) as a first approximation unless age-specific data are available.

GENETIC DETERMINANTS OF THE RESPONSE TO DRUGS

PRINCIPLES OF GENETIC VARIATION AND HUMAN TRAITS

(SEE ALSO CHAPS. 82 AND 84)

The concept that genetically determined variations in drug metabolism might be associated with variable drug levels and hence, effect, was advanced at the end of the nineteenth century, and the examples of familial clustering of unusual drug responses were noted in the mid-twentieth century. A goal of traditional Mendelian genetics is to identify DNA variants associated with a distinct phenotype in multiple related family members (Chap. 84). However, it is unusual for a drug response phenotype to be accurately measured in more than one family member, let alone across a kindred. Thus, non-family-based approaches are generally used to identify and validate DNA variants contributing to variable drug actions.

Candidate Gene Studies in Pharmacogenetics Most studies to date have used an understanding of the molecular mechanisms modulating drug action to identify candidate genes in which variants could explain variable drug responses. One very common scenario is that variable drug actions can be attributed to variability in plasma drug concentrations. When plasma drug concentrations vary widely (e.g., more than an order of magnitude), especially if their distribution is non-unimodal as in Fig. 5-6, variants in single genes controlling drug concentrations often contribute. In this case, the most obvious candidate genes are those responsible for drug metabolism and elimination. Other candidate genes are those encoding the target molecules with which drugs interact to produce their effects or molecules modulating that response, including those involved in disease pathogenesis.

Genome-Wide Association Studies in Pharmacogenomics The field has also had some success with "unbiased" approaches such as genome-wide association (GWA) (Chap. 82), particularly in identifying single variants associated with high risk for certain forms of drug toxicity (Table 5-2). GWA studies have identified variants in the HLA-B locus that are associated with high risk for severe skin rashes during treatment with the anticonvulsant carbamazepine and the antiretroviral abacavir. A GWA study of simvastatin-associated myopathy identified a single noncoding single nucleotide polymorphism (SNP) in *SLCO1B1*, encoding OATP1B1, a drug transporter known to modulate simvastatin

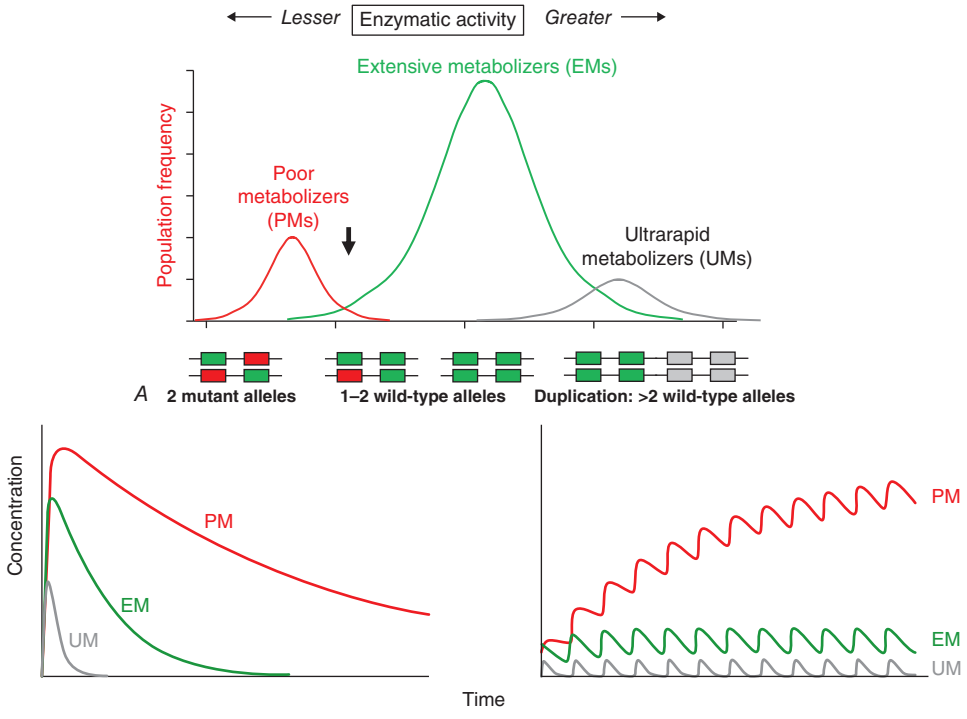

FIGURE 5-6 ***A.*** CYP2D6 metabolic activity was assessed in 290 subjects by administration of a test dose of a probe substrate and measurement of urinary formation of the CYP2D6-generated metabolite. The heavy arrow indicates a clear antimode, separating poor metabolizer subjects (PMs, red), with two loss-of-function CYP2D6 alleles, indicated by the intron-exon structures below the chart. Individuals with one or two functional alleles are grouped together as extensive metabolizers (EMs, green). Also shown are ultra-rapid metabolizers (UMs), with 2–12 functional copies of the gene (gray), displaying the greatest enzyme activity. *(Adapted from M-L Dahl et al: J Pharmacol Exp Ther 274:516, 1995.)* ***B.*** These simulations show the predicted effects of CYP2D6 genotype on disposition of a substrate drug. With a single dose (left), there is an inverse "gene-dose" relationship between the number of active alleles and the areas under the time-concentration curves (smallest in UM subjects; highest in PM subjects); this indicates that clearance is greatest in UM subjects. In addition, elimination half-life is longest in PM subjects. The right panel shows that these single dose differences are exaggerated during chronic therapy: steady-state concentration is much higher in PM subjects (decreased clearance), as is the time required to achieve steady state (longer elimination half-life).