example, tricyclic antidepressants (51) and neuroleptics. Antihistamines, alcohol, and analgesics, for example, acetaminophen and codeine, have also demonstrated varying effects among different ethnic and racial populations. Common genetic polymorphisms, that is, multiple forms of enzymes governing drug metabolism, affect the clearance from the blood of many therapeutically important drugs used in large patient populations. These polymorphisms are the rule rather than the exception, and genetic diversity is a major source of interindividual, interethnic, and racial differences in drug response. These genetic polymorphisms may influence a drug's action by altering its pharmacokinetic profile and/or pharmacodynamic properties. The result could be an increase or a decrease in the intensity of the patient's response and duration of the drug activity. Thus, dosage adjustments may be necessary for individuals from minority populations.

Body Weight

The usual doses for drugs are considered generally suitable for 70-kg (150 lb) individuals. The ratio between the amount of drug administered and the size of the body influences drug concentration in body fluids. Therefore, drug dosage may require adjustment from the usual adult dose for abnormally lean or heavy patients. The doses for certain drugs are based on body weight and are expressed on a milligram (drug) per kilogram (body weight) basis (e.g., 1 mg/kg).

As noted earlier, body weight is considered more dependable than age as determinant of drug dosage for youngsters, and for many drugs, the dose is based on milligrams per kilogram. In some instances, a pediatric dose may be based on a combination of age and weight (e.g., 6 months to 2 years of age: 3 mg/kg/day).

Body Surface Area

Because of the correlation between a number of physiologic processes and BSA, some drug doses are based on this relationship (e.g., 1 mg/M^2 BSA). The BSA for a child or adult may be determined using a nomogram (Fig. 2.10). The BSA is determined at the intersect of a straight line drawn to connect an individual's height and weight. For example, an adult measuring 67 in. in height and weighing 132 lb would have a BSA of approximately 1.7 m^2.

Sex

Because biochemical and physiologic factors produce different responses to certain drugs and drug dosages in men and women, both sexes should be included in clinical drug trials. Pharmacokinetic differences between women and men may be particularly important for drugs having a narrow therapeutic index, in which the smaller average size of women may necessitate modified dosing. Drugs with narrow therapeutic indices carry the inherent risk that drug blood levels may increase to toxic levels or decrease to ineffective levels with minimal dosing changes. Other important studies on women include the effects of the menstrual cycle and menopausal status on a drug's pharmacokinetics and the drug interaction potential of concomitant estrogen or oral contraceptive use (52).

Because virtually no clinical investigations have included pregnant women in their study protocols and thus drug effects are undetermined in these circumstances, great caution is advised for the use of most drugs during pregnancy and in women of childbearing age. Similar caution is applicable to drug use in nursing mothers because transfer from mother's milk to an infant is well documented for a variety of drugs (53,54).

Pathologic State

The effects of certain drugs may be modified by the pathologic condition of the patient. For example, if certain drugs are used in the presence of renal impairment, excessive systemic accumulation of the drug may occur, risking toxicity. In such conditions, lower than usual doses are indicated, and if therapy is prolonged, blood serum levels of the drug should be assessed and the patient monitored at regular intervals to ensure the maintenance of nontoxic levels of the drug. In these instances, pharmacokinetic dosing is an integral part of the clinical study protocol and of the approved product labeling.