TOXICITY OF CHEMICAL AND PHYSICAL AGENTS Toxicology is defined as the science of poisons. It studies the distribution, effects, and mechanisms of action of toxic agents. More broadly, it also includes the study of the effects of physical agents such as radiation and heat. Approximately 4 billion pounds of toxic chemicals, including 72 million pounds of known carcinogens, are produced each year in the United States. In general, however, little is known about the potential health effects of chemicals. Of the approximately 100,000 chemicals in use in the United States, less than 1% have been tested experimentally for health effects. In Europe the number of available chemicals is less than one-half that in the United States, but many of these chemicals are released into the environment as indus trial products or discharged as human and animal wastes. We now consider some basic principles regarding the toxicity of exogenous chemicals and drugs. 0 The definition of a poison is not straightforward. It is basically a quantitative concept strictly dependent on dosage. The quote from Paracelsus in the 16th century that "all substances are poisons; the right dosage differentiates a poison from a remedy" is perhaps even more valid today, in view of the proliferation of therapeutic drugs with potentially harmful effects. 0 Xenobiotics are exogenous chemicals in the environment that may be absorbed by the body through inhalation, ingestion, or skin contact (Fig. 7-2). ' Chemicals may be excreted in urine or feces or eliminated in expired air, or they may accumulate in bone, fat, brain, or other tissues. ' Chemicals may act at the site of entry, or they may be transported to other sites. Some agents are not modified upon entry in the body, but most solvents and drugs are metabolized to form water-soluble products (detoxification) or are activated to form toxic metabolites. 0 Most solvents and drugs are lipophilic, which facilitates their transport in the blood by lipoproteins and penetration through lipid components of cell membranes. 0 The reactions that metabolize xenobiotics into nontoxic products, or activate xenobiotics to generate toxic compounds (Fig. 7-3; see also Fig. 7-2), occur in two phases. In phase I reactions, chemicals can undergo hydrolysis, oxidation, or reduction. Products of phase I reactions often are metabolized into water-soluble compounds through phase 11 reactions of glucuronidation, sulfation, methylation, and conjugation with glutathione (GSH). Water-soluble compounds are readily excreted. 0 The most important cellular enzyme system involved in phase I reactions is the cytochrome P-45() system, located primarily in the endoplasmic reticulum (ER) of the liver but also present in skin, lungs, and gastrointestinal (GI) mucosa and in practically every organ. The system catalyzes reactions that either detoxify xenobiotics or activate