CHAPTER 2

ABSORPTION AS A SITE OF INTERACTION

The absorption of foreign chemicals involves transfer of these molecules across various barrier membranes of the body, such as the gastrointestinal epithelium, pulmonary epithelium, renal tubular epithelium, hepatic parenchyma, the skin, and placental membranes. Transfer in one direction produces absorption; in the opposite direction, it results in excretion.

The substances are transferred across biological membranes by four mechanisms: simple diffusion through the membrane and down a concentration gradient; filtration through aqueous pores in the membrane; pinocytosis through microscopic invaginations of the cell wall that engulfs droplets of extracellular fluid; and active transport by which compounds are transported across membranes against a concentration gradient by processes involving carriers and requiring energy. Simple diffusion is generally considered to be the principal mechanism by which foreign compounds are transferred across cell membranes. Active transport occurs with certain compounds, but the roles of filtration and pinocytosis are largely unknown. In the transfer of foreign compounds by simple diffusion, only lipid-soluble un-ionized molecules readily pass through the membranes. Nonelectrolytes are transferred according to their lipid-solubility, and electrolytes move according to their degree of ionization and lipid-solubility of the un-ionized molecules. The degree of ionization of an organic electrolyte is a function of the dissociation constant of the compound and the pH of the medium.

When humans are exposed to a chemical, a biological or toxicological effect can occur only after the substance has been absorbed. As a rule, only that part of a substance that is present in a dissolved, dispersed molecular form can be absorbed. The uptake by an organism of an environmental or applied substance is highly dependent upon the degree and the rate at which the absorbable form of the substance contacts the surfaces of the organism that are capable of absorption. When a person is exposed to toxic substances in industrial or other environments, the form of the substance markedly influences absorption and, therefore, toxicity. The properties of the substance, such as fineness of distribution, lipid or water solubility, the size of the droplets in a fog, or the size of dust particles in an aerosol, will all determine the depth of penetration into the lungs. Absorption of gases and vapors from the lung is also a function of their solubility in blood, lung ventilation, and pulmonary circulation rates. The presence of a certain concentration of a toxin in the air does not always provide the same degree of risk.

In occupational poisoning, absorption occurs primarily through the respiratory tract, although the skin may also be important. Both organ systems are in direct and continuous contact with the environment. Absorption of gases through the respiratory system is directly dependent on the concentration of gases in the inhaled air.

ABSORPTION FROM THE LUNG

Despite extensive toxicological studies of volatile or volatilizable halogenated aliphatic hydrocarbons and aromatic hydrocarbons,

the routes of administration most frequently used have been either oral or intraperitoneal, the agent having been dissolved in a suitable vehicle beforehand. Only in the past 5 to 7 years have scientists become concerned about the respiratory tract as a significant route of absorption.

Pulmonary Dynamics

There is surprisingly little quantitative information concerning the absorption of substances from the lung although most texts infer that it is a rapid process (Fingl and Woodbury, 1975). The lung possesses all of the attributes that are essential for an excellent absorptive organ. The alveoli, of which there are from 300 to 400 million in one adult human, are lined with a single layer of flattened epithelial cells that form an extremely thin barrier (0.5 -1.0 μm thick) between the alveolar air and an interstitium richly supplied with capillaries (Levine, 1973). The total surface area of the lung is approximately 70 m^2, and the surface area of the pulmonary capillaries is estimated to be 90 m^2. The lung exchanges air at a rate of approximately 12-15 liters/min. It receives all of the blood supply from the right side of the heart in a volume equivalent to that received by the entire body from the left ventricle during the same time (Levine, 1973). The organ is functionally structured so that it rapidly removes the material present in the alveolar air.

The respiratory rate is much higher (20-30 liters/min) for individuals who work at an active rather than a sedentary job. Physical activity also increases the blood flow through the lungs, which may

increase the rate of absorption of a volatile chemical with low water solubility.

Absorption Characteristics

The rate of absorption in the lung is dependent upon particle size and solubility of the chemical on the alveolar surface. As a rule, gases (and volatile liquids) are small molecules that readily cross the alveolar epithelium. Inhaled aerosols (suspended liquid droplets or solid particles) will deposit along various segments of the bronchial tree, primarily at points where the airstream changes course and velocity, e.g., in the bronchioles. The point of impaction (or deposition) depends on particle size; particles with a diameter >10 μm are deposited in the nasal passage, those with a 2 μm diameter will reach the alveolar sacs. Particles of pollen, dusts, fumes, and volatilized solvents are smaller than 10 μm. Particles of cigarette smoke are less than 1.0 μm. As a general rule of thumb, the smaller the particle, the deeper into the respiratory tract it will penetrate (Levine, 1973).

Most gases readily cross the alveolar epithelium to enter the bloodstream. As a result of this and the fact that the alveolar epithelium has a large surface, gases are absorbed very rapidly. On the other hand, this also means that gases are excreted rapidly through the lungs if they are not bound to tissue components. For chemical substances in the form of mists (droplets suspended in air), dust (particles suspended in air), and aerosols, the particle size is the decisive factor for determining the degree of penetration of the inhaled substance into the lung.

Retention does not necessarily mean absorption. For instance, in pneumoconiosis the substance is retained locally. Retention can be due to deposition of inhaled particles in different levels of the respiratory system. Large particles deposit in the nose, the trachea, and the bronchi. From there they are transported toward the throat by ciliary epithelia and are usually swallowed. Absorption may then take place from the gastrointestinal tract and not from the respiratory system. Smaller particles penetrate deeper into the respiratory system and deposit in the smaller bronchi and on the alveolar epithelium. Particles of less than 10 μm in diameter are deposited on the surfaces of the respiratory tract. The percentage of deposition decreases as particle size decreases below 1 μm, being minimal at approximately 0.2 μm. But often, the absolute numbers of these fine particles are much greater than for larger particles. Hence, the mass deposited may actually be greater than that for fewer large particles. In addition to particle size, the specific gravity, the charge on the particles, and the hygroscopicity of the particles help determine the tendency of the particles to aggregate into larger particles. The frequency and depth of an individual's respiration, which often depend on age, occupation, working conditions, and environmental temperature and humidity, play a role in determining the amount of substance retained in the lungs.

The mechanisms of absorption from the lung surface are poorly understood. Studies with a number of lipid-insoluble drugs (e.g., urea, mannitol, sucrose, insulin, ouabain, and dextran) in aqueous solution have demonstrated that absorption is mediated by a nonsaturable process of diffusion, which is extremely rapid. The absorption rates are related

to the molecular size: the higher the molecular weight, the slower the rate of absorption (Schanker, 1978). Analysis of absorption rates of known compounds suggests that the pulmonary epithelium contains at least three different types of pores, which allow molecules of a certain size to pass while excluding larger molecules (Enna and Schanker, 1972). The absorption rates of chemicals with low lipid-solubility are similar to those of chemicals absorbed through membrane pores. Highly lipid-soluble chemicals of low molecular weight diffuse very rapidly through the lipoid barrier. Some of them (e.g., salicylic acid, procaine, and digoxin) have absorption half-times of 1 min or less (Burton and Schanker, 1974; Enna and Schanker, 1972; Lanman et al., 1973). There also appears to be a specific carrier-type transport process that is saturable and appears to be shared competitively by a number of organic anions (e.g., phenol red and disodium chromoglycate) (Schanker, 1978).

Anesthetic agents are probably the closest chemical analogs to which marine personnel might be exposed. Therefore, an examination of pulmonary absorption of these agents should be useful. A constant rate of absorption of anesthetics across the alveolar membrane is established by maintaining a constant concentration (particle pressure) of agent in the inhaled air (Goldstein et al., 1974). Thus, inhalation by workers in an "empty" contaminated tank would result in a rapid equilibrium between blood and air concentrations. At a constant rate of absorption, the rate at which a plateau concentration of a material in the blood is approached is dependent upon the rate of elimination and the solubility of the agent. One

does not take into account the quantity of the agent that must be transferred and distributed before equilibrium is attained (Goldstein et al., 1974).

Astrand (1975) and Astrand and Gamberale (1978) have demonstrated that the evaluation of the TLV for water-immiscible solvents, such as methylene chloride, trichloroethylene, styrene, toluene, and white spirit, should be based on actual measurements of uptake into blood rather than on ambient air concentrations. They showed that the percentage of uptake by volunteers (determined by blood levels) varied with the quotient between the alveolar air concentration and the inspiratory air concentration. A linear relationship with a negative slope demonstrated that the percentage of uptake decreased when the alveolar air concentration approached that in the inspiratory air and that the uptake increased when the alveolar concentration was lower than that measured in the inspiratory air. For all solvents studied, the concentrations in alveolar air rose sharply during the first 5-10 min of each exposure period, rising only slightly during the remainder of the test. The concentration of the solvent in arterial blood was found to be a very close linear function of the alveolar air concentration. Therefore, the acute toxicity to such solvents should be related to uptake rather than to ambient air concentration, and a factor estimating pulmonary ventilation should be taken into account.

ABSORPTION FROM THE SKIN

Although exposure to chemical substances via the skin has been studied very little, it is probably a more significant occurrence than is usually suspected. This is especially true for maritime workers

exposed to common cargo chemicals. The skin is an important route by which foreign substances are absorbed into the body. The intact skin with its lipid sebaceous layer is not very permeable to hydrophilic substances. In contrast, lipophilic substances generally penetrate the skin readily by diffusion through the sebaceous layer. The degree to which chemicals are absorbed through the skin is influenced appreciably by the base in which they are applied, e.g., an ointment base (an emulsion of water in oil) or a cream base (an emulsion of oil in water). Local conditions, such as humidity of the skin, temperature, and contact between clothing and skin, also influence absorption, e.g., the higher the temperature of the environment, the greater the absorption through the skin. A damaged skin can be penetrated by hydrophilic as well as by lipophilic substances. Therefore, washing the hands with abrasives, which damage the skin, or with organic solvents such as gasoline and turpentine, which remove the sebaceous layer, increases the chance for penetration by toxic substances. Chemical substances that act as allergens can also penetrate the damaged skin, thereby increasing the risk of developing allergies. In contrast to highly hydrophilic substances, highly lipophilic substances are normally well absorbed through the skin. Phenols, such as phenol and salicylic acid, have special properties. These substances penetrate the skin and cause keratolysis. Concentrated solutions of strong bases, such as sodium hydroxide, and strong acids, such as nitric acid (which colors the skin yellow) and sulfuric acid, also damage the skin.

Dynamics of Skin Absorption

The classic principles of absorption through a lipid-protein series of membranes to the circulatory system, distribution of biotransformation, and eventual excretion via normal biological channels continue to operate in the maritime situations (Goldstein et al., 1974; La Du et al., 1971).

Results of numerous studies have indicated that chemicals penetrate the skin predominantly by passing through a lipidlike barrier. This conclusion is based on many isolated observations that lipid-soluble molecules are absorbed much more rapidly than lipid-insoluble molecules and ions (Calvery et al., 1946; Gemmell and Morrison, 1957; Malkinson, 1956; Rothman, 1954; Wilson, 1961) and on a study of the passage of nonelectrolytes across the excised rabbit skin (Treherne, 1956). Treherne showed that various alcohols and urea derivatives diffuse across whole skin at rates that are roughly proportional to the ether-to-water partition coefficients of the compounds. He concluded that the lipoid barrier of the skin is located within the epidermal layer since the dermis is freely permeable to many solutes and displays the characteristics of a highly porous membrane.

For some time, there was no general agreement among investigators as to the main pathway by which compounds traverse mammalian skin. Some authors stressed the importance of the epidermal route, while others contended that the route through hair follicles, sweat glands, and sebaceous glands was predominant. In later work, Tregear (1961) developed a technique whereby chemical penetration could be assessed using small areas of skin that contained either a desired number of hair follicles or none at all. Studying in this way the absorption of

tri-n-butyl phosphate from the skin of living pigs, he showed that the hair follicle is no more penetrable than an equivalent area of epidermis. In fact, regions of the skin devoid of hair follicles were penetrated slightly more rapidly than regions containing these structures.

Because of the relatively great thickness of the skin, chemicals penetrate this boundary much more slowly than they do most other body membranes. However, the percutaneous absorption of ionized compounds is enhanced by ionophoresis, a method in which a chemical solution in contact with an electrode is placed against the skin and a galvanic current is applied to both the chemical electrode and another electrode placed elsewhere on the body. Absorption through the skin can also be enhanced by dissolving a compound in oil, an ointment base, or other organic solvent and then rubbing it into the skin. Dimethyl sulfoxide (DMSO), an unusual solvent that is miscible with water as well as with many organic solvents, also enhances the percutaneous absorption of certain chemicals (Stoughton and Fritsch, 1964; Weyer, 1967).

The skin efficiently retards the diffusion and evaporation of water except at the sweat glands. The epidermis, although only approximately 0.2-mm thick, is largely responsible. The outer, horny layer (stratum corneum) consists of a continuous sheet of flattened cells that are densely packed with keratin, which constitutes a barrier to the penetration of water-soluble substances. Thus, the intact epidermis behaves qualitatively like cellular membranes in general. Chemicals penetrate at rates determined largely by their lipid/water partition coefficients, except for the very smallest molecules (Griesemer, 1959; Katz and Poulsen, 1971; Scheuplein and Blank, 1971).

Even very soluble substances penetrate slowly in comparison with their rates of penetration of other, thinner cell membranes. The underlying dermis, which consists of loosely arranged connective tissue and is vascularized, is freely permeable.

Toxic effects are often produced by accidental absorption through the skin of highly lipid-soluble substances that are used for various industrial purposes. General experience leads people to suppose that the skin is a reliable protection against the environment, but little thought is given to the possibility of poisoning by this route. Carbon tetrachloride, other organic solvents, and phenolics penetrate the body in this way and can cause serious toxic effects. Organic phosphates, such as diisopropyl fluorophosphate (DFP), parathion, and malathion, and nicotine insecticides have caused deaths in agricultural workers as a result of percutaneous absorption. Chlorovinylarsine dichloride (lewisite), a mustard gas, is readily absorbed through the intact skin.

Some chemical groups are characterized by their property of conferring water solubility on the molecules to which they belong. These hydrophilic, lipophobic, or polar groups are: $-OSO_2ONa$, $-COONa$, $-SO_2Na$, $-OSO_2H$, and $-SO_2H$. The following groups are less efficient: $-OH$, $-SH$, $-O-$, $-CO$, $-CHO$, $-NO_2$, $-NH_2$, $-NHR$, $-NR_2$, $-CN$, $-CNS$, $-COOH$, $-COOR$, $-OPO_3H_2$, $-OS_2O_2H$, $-Cl$, $-Br$, and $-I$. The presence of unsaturated bonds, such as those in $-CH=CH-$ and $-C\equiv C-$, helps to promote hydrophilicity (Hummel, 1962). Other groups (lipophilic, hydrophobic, or nonpolar) increase the liposolubility of the compounds of which they are part. Examples of these groups are aliphatic hydrocarbon

chains, aryl alkyl groups, and polycyclic hydrocarbon groups. Compounds carrying hydrophilic and lipophilic groups in proper equilibrium can modify the characteristics of the boundary surface between two lipids, a lipid and a solid, or a liquid and a gas. Such compounds, called surfactants, are used mainly as detergent, wetting, dispersing, foaming, and emulsifying agents (Moilliet et al., 1961).

Surfactants deeply affect the permeability of cellular membranes by disintegrating or lysing those of high activity through denaturation of the proteins of which the membrane is part or simply by enwrapping it with a layer, which interferes with the absorption of compounds of low activity. Because they disorganize cellular membranes, cause hemolysis, and are easily absorbed by proteins, surfactants are generally not applied to body tissue intentionally.

The sweating of maritime personnel working in a poorly ventilated area may favor absorption of chemicals through the skin. The increased moisture on the skin from perspiration may solublize chemicals that previously could not readily pass through the skin. Sweat is usually acid and provides the opportunity for acid-salts to exist in the lipid-soluble state, thus favoring absorption. Finally, the sweating and associated increased body temperature will cause dilation of the blood vessels in the skin, providing abundant circulatory exposure to any chemical that is capable of moving through the skin barrier.

DERMAL REACTIONS TO TOPICAL CHEMICAL EXPOSURES

Hypersensitivity Reactions

Sensitivity can develop from repeated contact with or repeated ingestion of a certain chemical, even after long intervals. The hyper-

sensitivity reaction is not specific for a particular substance, but it is closely related to the nature of the sensitization process. This process is based upon the formation of specific antibodies for substances that are foreign to the body. Increased sensitivity may be based on increased concentration of an active substance in the plasma or tissues, as a result of a certain dose or degree of exposure. It may also result from enhanced bioactivation caused by inducing agents or decreased elimination or detoxification, e.g., by combining with an enzyme inhibitor that may be involved in a substance's metabolism or with an inhibitor of renal excretion.

Allergic Reactions

Allergic reactions are often observed on the skin. To induce such a reaction, the allergen must enter the organism. Allergic hypersensitivity to a group of chemically related substances is called cross-allergy. Under certain circumstances, practically any substance can cause an allergic reaction. This tendency is dependent partly on the constitution of the individual and partly on the properties of the substance. Some compounds, such as dinitrochlorobenzene, produce hypersensitivity reactions in practically everyone exposed to them. Quinine induces a hypersensitivity reaction in a relatively high percentage of individuals, while other substances, such as carbohydrates, produce hypersensitivity only in exceptional cases.

Photoallergic Reactions

Certain substances, when present in the skin, may undergo photochemical alterations to products that are allergens. Once an allergic sensitization of this nature takes place in an organism, exposure to

sunlight will produce a reaction whenever there is exposure to the substance. This skin reaction has the same characteristics as any allergic reaction, but may be limited to those parts of the skin that were exposed to sunlight. There must be repeated exposure to the causative substance before the photoallergic reaction will occur. These reactions have been seen after exposure to substances such as tetrachlorosalicylanilide, hexachlorophene, and bithionol.

Photosensitization

Photosensitization results from a combined exposure to certain substances and sunlight. The ensuing skin reaction exhibits the characteristics of sunburn erythema, but it is independent of the specific properties of the substance in question. A genuine photosensitization can occur even upon the first contact with a substance and exposure to sunlight. Photosensitization often remains long after exposure to the causative substance. This may be due to binding of the sensitizing substance in the skin.

Phototoxic Reactions

A phototoxic reaction occurs when a substance in the skin is changed into a toxic substance by a photochemical reaction influenced by sunlight. The nature of the symptoms depends on the kind of toxic substance formed and, therefore, on the nature of the substance to which the individual is exposed. Although repeated exposure is usually necessary to produce a photoallergic reaction, photosensitization and phototoxic reactions will occur upon first exposure to the substance if there is simultaneous exposure to sunlight.

Direct Chemical Irritation

Direct chemical irritation is caused by substances that readily react chemically with various tissue components. As a rule, such substances do not reach the general circulation since they have already reacted with tissue at the site of contact with the organism. Direct chemical irritation is sometimes labeled a local irritant action, an etching action, a caustic action, or a necrotic action, depending on the reactivity of the substance. The intact skin offers a certain resistance to the substances, although the resistance is often inadequate.

Chemical Dermatitis

Direct damage to the skin can be caused by contact with chemically reactive substances. These substances include nitrogen mustards and related biological alkylating agents called vesicants (blistering agents) and keratolytic agents, especially phenols, such as salicylic acid. Compounds known for their etching action on the skin are strong alkaline solutions such as sodium hydroxide and potassium hydroxide solutions. Concentrated nitric acid causes not only a strong local alteration of the pH, but it also oxidizes and causes nitration of various components of the skin. Organic solvents remove protective lipid sebaceous layers in the skin, thereby paving the way for the development of allergic dermatoses and chemical dermatitis. Various substances then penetrate the skin through the pores and along the roots of the hair, especially by way of the sebaceous glands. Thus, these are the places where chemical dermatitis is initially manifested.

ABSORPTION FROM THE DIGESTIVE TRACT

Foreign compounds may be absorbed from the mouth or from other areas of the gastrointestinal tract, mainly by simple diffusion. Active transport mechanisms are unlikely to be involved since absorption is proportional to concentration and is unaffected by the simultaneous absorption of compounds of similar structure. When active transport is involved, the transport mechanism has a limited capacity and can be saturated as concentration increases or when similar compounds compete for the same mechanism (Parke, 1968).

In general, absorption takes place along the entire length of the gastrointestinal tract, but the chemical properties of each substance determine whether that material will be absorbed in the strongly acid stomach or in the nearly neutral intestine. Gastric absorption is facilitated by an empty stomach in which the compound will have good access to the mucosal wall. The absorption of some chemicals is aided by the consumption of a fatty meal. Intestinal absorption is favored by the large surface area of the intestinal villi, the presence of bile, and a rich blood supply.

The principles governing the absorption of chemicals from the gastrointestinal lumen are the same as those for passage of chemicals across biological membranes elsewhere. A low degree of ionization, a high lipid/water partition coefficient of the un-ionized form, and a small atomic or molecular radius of water-soluble substances all favor rapid absorption. Water passes readily through the wall of the gastrointestinal lumen in both directions. Magnesium ion is poorly absorbed and acts as a cathartic, retaining an osmotic equivalent

of water as it passes down the intestinal tract. Ionic iron is absorbed as an amino acid complex at a rate usually determined by the body's need for iron. Glucose and amino acids are transported across the intestinal wall by specific carrier systems. Some compounds of high molecular weight, e.g., polysaccharides, neutral fats, cannot be absorbed because they are destroyed by gastrointestinal enzymes, e.g., insulin, epinephrine, and histamine. Substances that form insoluble precipitates in the gastrointestinal lumen or that are not soluble either in water or in lipid obviously cannot be absorbed (Goldstein et al., 1974).

Absorption from the Mouth

Foreign compounds are absorbed from the mouth by diffusing into the mucous membrane of the oral sulci and thence into the bloodstream. They are not exposed to the gastrointestinal digestive juices nor are they transported directly to the liver, as are chemicals absorbed in the stomach and intestines. Since foreign compounds are metabolized principally in the liver, absorption from the mouth delays metabolism and may prolong the activity of a chemical.

Absorption from the Stomach

It has long been believed that absorption of compounds from the stomach is negligible, except for ethanol. This is largely true for nutrient substances, especially macromolecules that require digestion, but it is now known that many foreign compounds, e.g., acidic compounds such as salicylic acid, aspirin, and barbiturates, are readily absorbed from the stomach by simple diffusion of the un-ionized molecules across the gastric mucosa.

Absorption from the Small Intestine

The intestinal epithelium, like the gastric mucosa, allows the passage of undissociated foreign molecules by the process of simple diffusion. Weak acids and bases are absorbed through this route. Alteration of the pH of the intestinal content changes the degree of ionization of the foreign compound and, hence, the extent of absorption.

Certain foreign monosaccharides, amino acids, and pyrimidines are sufficiently similar to natural compounds to be absorbed by the active transport mechanisms that are involved in the absorption of nutrients. Various foreign macromolecules, such as bacterial toxins, are slightly absorbed from the intestine, probably by pinocytosis.

Absorption from the Colon

The pattern of absorption from the colon is similar to that for the small intestine. Weak acids and bases are absorbed readily, whereas highly ionized compounds are absorbed slowly.

Factors Affecting Gastrointestinal Absorption

The absorption of foreign compounds from the gastrointestinal tract may be affected by a number of factors. Accelerated emptying of the stomach's contents into the intestinal tract reduces gastric absorption but may increase intestinal absorption. Increased intestinal peristalsis results in more efficient mixing of the intestinal contents, allowing increased absorption, but it also expedites the emptying process, consequently reducing intestinal absorption. Increased blood flow through the intestines and greater cardiac

output, both of which are associated with digestion and absorption of food, accelerate the absorption of foreign compounds. Gastrointestinal secretions lead to pH changes that alter the degree of ionization and absorption of foreign compounds. Secretion of mucus affects absorption, and enzymes lead to hydrolysis of esters and amides. Calcium, iron, and other metals may form insoluble chelates with certain compounds (e.g., tetracycline) and impair their absorption. The particle size of foreign compounds affects their rate of solubility, especially for those with low solubility. Consequently, it also affects absorption, which occurs only from solution.

SITES OF CHEMICAL INTERACTION WITH ABSORPTION

Chemicals may interact at any phase of their passage through the body. Many interactions occur during absorption, distribution, metabolism, or excretion or at the receptor sites, and can alter the effects of respiratory, topical, or gastrointestinal exposure of maritime workers to chemicals. Specifically, one or more of the following mechanisms are involved: direct effect on the chemical; modification of gastrointestinal absorption; modification of dermatomucosal absorption; alteration of distribution; modification of action at receptor sites; modification of biotransformation; and alteration of excretion (Martin et al., 1971). These mechanisms involve an enormous number of biological, chemical, and physical factors.

DIRECT EFFECT ON THE CHEMICAL

Chemicals may interact directly with each other, either chemically or physically, after they have been administered. Protein

hydrolysates bind barbiturates, digitoxin, digoxin, tetracyclines, and many other drugs. Amino acids, e.g., cysteine, as well as tetracyclines and other potent chelators can interact with calcium-containing medications and, if rapidly infused intravenously, may cause hypocalcemic tetany. Components of a mixture other than the primary chemical may also interact directly with another chemical. Thus, bisulfite and sulfur dioxide, which are used as preservatives for sympathomimetic amines such as epinephrine and phenylephrine, inactivate penicillin G if injected at the same time. A drug may also be affected by chemical interactions when it is topically applied strictly for its local dermal, mucosal, or gastrointestinal effects. It may be adversely affected if some substance hinders its contact with the surface, prevents it from exerting its effects, or destroys or inhibits its activity through some chemical or physical reaction. Thus, soap may inhibit the antifungal activity of acrisorcin on the skin.

PULMONARY ABSORPTION INTERACTIONS

There have been many studies of commonly used industrial solvents, but many were conducted in different laboratories with different inhalation chambers and techniques, most used only single acute administrations, and a number of them had no accurate control over dosage. Very few studies used combinations of agents, and few extensive studies have been conducted in one laboratory.

In one extensive inhalation study, Gage (1970) of Imperial Chemical Industries, Ltd. (ICI) examined the subacute toxicity of 109 volatilizable industrial chemicals in rats for 6 hr/day up to 4 weeks.

He established provisional optimal exposure limits, which he derived from safety factors applied to the highest concentrations producing no adverse effects in the animals. Unfortunately, the coadministration of other chemicals was not investigated. A study of single and repeated exposures to inhaled chloroform (85, 50, and 25 ppm) revealed, not unexpectedly, that repeated exposure (7 hr/day, 5 days/week for 6 months) resulted in more adverse effects than did the single exposures (Torkelson et al., 1976). Rats exposed to 25 ppm of chloroform for 4, 2, or 1 hr/day for 6 months were not adversely affected. The exposure of rats, rabbits, and monkeys to inhaled 1,2,4-trichlorobenzene (25, 50, and 100 ppm) for 26 weeks resulted in pathological changes in the livers and kidneys at 4 and 13 weeks of exposure, but no exposure-related abnormalities were observed after 26 weeks of exposure, suggesting possible physiological adaptation to the chemical insult (Coate et al., 1977).

Few inhalation studies have been conducted with combinations of volatile chemicals. Considerable difficulty is encountered with such research since many industrial solvents have different and quite specific target organs (Hayden et al., 1976). Acute neurotoxic effects of organic solvents may be caused by direct action on the nerve cell membrane or on energy metabolism, whereas chronic neurotoxic effects may be explained by the formation of chemically and biologically reactive intermediates, the development of the neuropathy being dependent upon the stability of the toxic metabolite (Savolainen, 1977). Specific interactions involving biotransformation may involve combinations of organic chemicals. These phenomena are dose-dependent. A recent

inhalation study with animals involving methylene chloride and ethanol demonstrated the complexity of such interactions (Balmer et al., 1976). An antagonism between these two chemicals was suggested by hepatic damage that followed a single 6-hr exposure of rats. However, results of a 5-day, 6-hr/day exposure suggested that ethanol potentiated the effects of methylene chloride.

MODIFICATION OF GASTROINTESTINAL ABSORPTION

Two substances may complex in the gastrointestinal tract, so that both are poorly absorbed. Tetracycline tablets that are formulated with calcium carbonate lead to insoluble calcium salts of the antibiotic, which result in erratic blood levels. Neomycin interferes with the absorption of fats and lipid-soluble drugs from the small intestine. A surprising example of drug interaction operating on absorption is that the presence of phenobarbital reduces the plasma level of the antifungal agent griseofulvin.

Gastrointestinal absorption may be hindered by mechanisms other than direct complexing. For example, intestinal flora can alter many chemicals through hydroxylation, decarboxylation, and ester hydrolysis. Consequently, antibiotics that act upon the flora, abolishing some, can alter the ultimate levels of the chemical in the plasma. Enzymes involved in the transport of essential nutrients across the intestinal wall may also be inhibited by drugs. This, in turn, may result in rather complex interactions.

Alteration of the Functions of the Gastrointestinal Tract

Two major functions of the gastrointestinal tract that affect absorption are the rate at which its contents are transported from the stomach to the rectum and the metabolism that occurs within its bacterial flora. Accordingly, any chemical interaction that markedly influences motility or bacterial balance and growth can have important impacts on rates of absorption. The time required for the stomach to empty varies with the intensity of the gastric motility. Therefore, the length of time a chemical remains in the intestinal tract before it is excreted varies with the intensity of the intestinal peristalsis. The absorption rate of a drug that is absorbed readily from the stomach can be increased by slowing the emptying time, thereby increasing gastric retention. For a drug that is absorbed more readily from the intestines, the absorption rate can be increased by accelerating passage from the stomach into the intestines, i.e., decreasing gastric retention.

Cathartics tend to reduce the absorption of any given medication and, if abused, may also precipitate or aggravate the toxic effects of some drugs by inducing excessive potassium loss. Drugs may also alter gastric motility and emptying time by modifying the contractility of the smooth muscle. Codeine, morphine, and other opiate analgesics decrease motility and depress absorption of drugs that are absorbed more readily from the intestines and increase absorption of those that are absorbed more readily from the stomach. Anticholinergic agents inhibit absorption by decreasing gastrointestinal motility. Cholinergic stimulants accelerate gastric emptying time, thereby

depressing absorption of drugs that are more readily absorbed from the stomach and enhancing absorption of those that are more readily absorbed from the intestine. The gastric emptying time is also modified by exercise, temperature, volume, the nature of the solid and fluid contents, emotional problems, and other factors.

Modifying or eliminating the intestinal flora with antimicrobial agents may alter the susceptibility of patients to a drug. Because antimicrobial action may diminish bacterial synthesis or metabolism of some drugs in the tract, gastrointestinal absorption and systemic toxicity may be either decreased or increased.

Alteration of Physiochemical Characteristics

A chemical interaction may modify gastrointestinal absorption if it alters the physiochemical characteristics of the chemical or the contents of the tract. It can do this by altering the pH, forming a nonabsorbable complex like those formed by certain ions (Al, Ba, Ca, Mg, Sr) with tetracyclines, and modifying rates of deaggregation or dissolution of the drug in the ambient fluid. Moreover, it may modify the diffusion rate of the compound by altering miscibility, viscosity, and other factors exerting an osmotic force, such as magnesium sulfate, a cathartic whose slightly absorbable ions retain water in the intestinal tract. The interaction may also result in the formation of a salt that is either more or less soluble, stable, or absorbable than the original chemical, e.g., soluble iron salts form insoluble carbonates on contact with antacids and other drugs containing the carbonate radical. Furthermore, absorption may be

modified when a chemical is sequestered in a lipoid. Mineral oil does this when given as a cathartic dosed with oil-soluble vitamins A, D, and K, thereby preventing the vitamins from making adequate contact with the intestinal epithelium. Perhaps the most significant of these physiochemical mechanisms are alteration of pH and complexation.

Alteration of Mucosa

The condition of the gastrointestinal mucosa may affect absorption in the tract. The rate at which drugs are transported into the body is usually highest where surface areas are large and vascularization is profuse as in the peritoneal membrane, pulmonary endothelium, and intestinal villi. If the intestinal mucosa is destroyed by toxic doses of an agent such as tannic acid, absorption of a chemical may be as rapid as it is when administered intramuscularly or subcutaneously.

Alteration of Transport Mechanisms

Alteration of active and passive transport from the gastrointestinal tract through its lining into the body fluids may strongly influence chemical absorption by this route. The size of the pores in the absorbing membrane, lipoid solubility, electrochemical, hydrostatic, osmotic, and pH gradients, and many other factors can modify active or passive mechanisms that are involved in gastrointestinal absorption. Chemical interactions may interfere with an active mechanism by competing in the transport cycle.

Amino acids like methyldopa are absorbed slowly from the intestinal tract in the presence of certain natural amino acids that are ingested in the food because primary phenolic amino acids compete

for the same transport sites. The presence of food itself markedly affects the rate of absorption. Either more or very little of a chemical is absorbed if it is rapidly transported through the tract; highly ionized at the ambient pH and its ions are poorly absorbed or nonabsorbable; rendered insoluble or poorly diffusible in gastrointestinal fluid at the absorption site; converted into an insoluble salt, chelate, or other insoluble complex; rendered unstable by the ambient pH; converted into its un-ionized form, which is lipid-insoluble; or sequestered from the absorbing tissues by a nonabsorbable lipoid. The opposite conditions enhance absorbability.

DRUG INTERACTIONS

The likelihood of a drug interaction increases if one medical specialist prescribes a topical drug for the eye while another administers a systemic medication. An adverse drug reaction may occur when a potent, long-acting anticholinesterase agent is applied topically to the eye and, while the drug is actively inhibiting cholinesterase in the body, a muscle relaxant like succinylcholine is adminstered prior to general anesthesia, since there would be continual uncontrolled stimulation of the afferent nerves. A topically applied drug that is absorbed through the skin to membranes of the ear, eye, mouth, nose, rectum, urethra, or vagina may interact with drugs administered perorally or parenterally. Drug interactions that influence rates and sites of dermatomucosal as well as gastrointestinal absorption and function must be avoided.

ALTERATION OF DISTRIBUTION

The most important aspects of distribution that can be modified by chemical interactions are transport, binding, and redistribution.

Alteration of Chemical Transport

The rates and routes of the distribution of a chemical from its site of intake to its sites of action, biotransformation, storage, and excretion may be profoundly influenced by another chemical. Onset, intensity, and duration of action may be affected by changes in fluid flow, physical factors, and transport across membranes. Any physiologically active chemical that alters the flow rate and volume of fluid in the cardiovascular or lymphatic system may also alter the rate at which a drug is moved from one area of the body to another. Therefore, cardiac stimulants, diuretics, hypertensive (pressor) and antihypertensive (hypotensive) agents, and other cardiovascular drugs may influence the distribution of other chemicals. The rate at which an absorbed chemical moves from its site of intake to other areas of the body is influenced appreciably by miscibility, solubility, surface tension, viscosity, and other characteristics of the ambient fluids. Therefore, modification of any of these characteristics may cause the chemical to remain at its site of entry for a prolonged period or diffuse more rapidly than normal. Since transmembranal transport is effected by active transport mechanisms, convective absorption, facilitated or passive diffusion, phagocytosis, and pinocytosis, a chemical interaction that modifies any of these factors also modifies chemical distribution in the body. The rate of transport also varies with the characteristics of the membrane and the forces that drive

the chemical across the membrane. The permeability of some membranes, notably walls of the lymph capillaries, may be increased by histamine and some other chemicals as well as by massage, sunlight, and warmth to such a degree that the walls present no real barrier between the lymph inside and the interstitial fluid outside the vessels.

Displacement from Binding Sites

Displacement of a drug from its binding sites in plasma and tissues may enhance its activity because it is then free to contact receptor sites, initiate its action, and produce physiological effects. The more tenaciously bound chemicals can displace those less firmly bound from binding sites, thereby causing shifts in plasma concentrations and, possibly, major redistribution of the released chemical in the body compartments. Displacement of a substance from its secondary binding sites may activate or potentiate its physiological activity, increase its toxicity, or produce a beneficial effect. Salicylates, sulfonamides, and certain other drugs may precipitate kernicterus in infants by displacing bilirubin from protein binding sites. Displacement of a chemical from its bound state also makes it available for urinary excretion, thereby increasing the rate of its excretion from the body.

MODIFICATION OF ACTION AT RECEPTOR SITES

Interferences with the mechanisms of chemical action at receptor sites may cause hazardous augmentation or reduction of drug effects through activitation or inhibition of mechanisms involving enzymes, neurohumors, and other components. A chemical interaction may enhance

activity at a receptor site if it displaces protein-bound, endogenous, physiologically active chemicals, increases synthesis of active endogenous chemicals, increases release of endogenous stored chemicals, prevents binding to secondary receptors, preserves the active agent at its receptor sites, sensitizes effectors to chemicals, or enhances the affinity between receptors and chemical compounds. An interaction may decrease or destroy activity at a receptor site if it promotes chemical binding to protein and chemical storage, decreases synthesis of active endogenous chemicals, prevents the release of endogenous stored chemicals, prevents drug binding at receptor sites, desensitizes effectors to chemicals, decreases the amount of chemical at receptor sites and its affinity for these sites, or depletes the stores of neurotransmitters and other active chemicals produced in the body.

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CHAPTER 3

ELIMINATION AS A SITE OF INTERACTION

The removal or clearance of volatile toxicants from the body may be facilitated by direct exhalation, which has been observed in studies of dimethylsulfoxide or paraldehyde; translocation from the alveolar air to the bloodstream and subsequent translocation into tissues where biotransformation may occur or the toxicant may be stored; and renal and/or fecal elimination. Despite the volatility of many of these toxicants, a number of them are extensively metabolized in the body rather than merely exhaled.

PULMONARY ELIMINATION

The removal or clearance of toxicants from the alveoli can be facilitated by exhalation, direct translocation from the alveolar air into the bloodstream, removal via bronchial ciliary action to the gastrointestinal tract, and phagocytosis and removal by the lymphatic system. Respiratory impairment or chronic exposure to vapors may markedly incapacitate pulmonary function by altering the pharmacokinetics of absorption and elimination. The inhalation by rats of acidic fumes, paraquat, aerosolized papain, and rock dust (in experiments to induce silicosis) all resulted in irritancy and damage, which appeared to increase the porosity of the pulmonary epithelium, thereby enhancing absorption (Gardiner and Schanker, 1975, 1976a,b,c). Partial collapse of the lung results in a narrowing of the bronchioles, which can easily be obstructed by fluid (Ebert, 1978). In chronic bronchitis, bronchiolar obstruction can result from fibrosis

and inflammation accompanied by marked alterations in secretions and loss of traction on the walls.

Pulmonary function can also be greatly affected by the particle size of a chemical and its concentration in the air. Inhaled agents strongly inhibit the ciliary action of the bronchial epithelium, resulting in reduced efficiency of particle removal and, consequently, an increase in the quantity of particles retained.

In a review of the absorption of drugs via the lung, Schanker (1978) maintained that many fundamental questions need to be answered. What actually happens to a droplet when it is deposited on the bronchiolar or alveolar epithelium? How does the coating of the alveolar surface influence the fate of inhaled agents? How rapidly do dry aerosols (dusts) of chemicals dissolve in the coating of the respiratory tract? Which factors determine the dissolution rates? What is the nature of membrane pores in the pulmonary epithelium? Which physiological and pathological factors influence the size, number, and distribution of pores in the respiratory tract? What are the effects of environmental variables (e.g., heavy smoking) and pulmonary disease on absorption rates of inhaled chemicals? These questions, as relevant for solvents as they are for drugs, are only a few of the many that must be answered. They do not begin to come to grips with the almost predictable, inherent covert toxicities, such as those observed for the aliphatic halogenated anesthetic halothane (2-bromo-2-chloro-1,1,1-trifluoroethane), which has been demonstrated to produce birth defects in children of operating room personnel (American Society of Anesthesiologists, 1974).

BILIARY ELIMINATION

Foreign compounds are absorbed from the blood of the hepatic sinusoids into the hepatic parenchymal cells. They are then transferred, as metabolites or conjugates, into the bile or are returned into the blood of the sinusoids, ultimately to be excreted in the urine or feces. Because hepatic parenchymal cells have highly permeable membranes, the boundary between the blood and the bile is extremely porous and permits the passage of most molecules and ions that are smaller than proteins. Therefore, many substances appear in the bile and in plasma in similar concentrations, but highly polar compounds such as the bile salts, bilirubin glucuronide, and conjugates of foreign compounds are excreted in the bile in much higher concentrations by a process of active transport. This active secretion appears to occur with compounds that are present in the blood as anions, have a molecular weight greater than 300, and are bound to plasma proteins. Biliary secretion may also be dependent on the binding of a foreign compound to the proteins of the hepatic cell. The rates of secretion of a number of azo dyes have been shown to be functions of the ratios of binding with liver proteins to the binding with the plasma proteins. Certain organic cations, e.g., the drugs procainamide, ethyl bromide, and mepiperphenidol, are similarly secreted into the bile by an active transport mechanism (Parke, 1968).

Foreign compounds are excreted in the bile mostly as conjugates, which may be hydrolyzed by hydrolytic enzymes (e.g., β-glucuronidase and sulfatase) in the bile or by enzymes of the intestinal secretion

and flora. Many glucuronides (such as those of phenol, estriol, and chloramphenicol) are hydrolyzed in the gut. Ethereal sulfates are more stable. Since conjugates are polar compounds, they are unlikely to be readily reabsorbed from the intestine, but their hydrolysis products, if nonpolar, may well be reabsorbed, transported to the liver, reconjugated, and excreted again in the bile. Such a cycle of biliary excretion, intestinal reabsorption, and reexcretion is known as enterohepatic circulation and occurs with chloramphenicol, stilbestrol, sulfonamides, and many other foreign compounds.

GASTROINTESTINAL ELIMINATION

From the pH-partition hypothesis, it may be predicted that organic bases, largely ionized at the pH of the gastric juice, will be secreted from the blood plasma into the stomach. This route of excretion was largely ignored until Parke (1968) showed that various parenterally administered drugs and other foreign compounds, such as aniline, aminopyrine, quinine, dromoran, and mecamylamine, may be secreted into the gastric juice. The excretion of nicotine into the stomach has been associated with its role in causing peptic ulcer.

Similarly, it may be predicted that weak organic acids and bases that are highly ionized at the pH of the intestinal lumen would be secreted by passive transfer from the blood plasma into the intestine when the concentration gradient is favorable. Likewise, one could expect organic acids to be secreted into the alkaline pancreatic juice.

SALIVARY ELIMINATION

To a minor extent, foreign compounds are excreted in body secretions by passive transfer of the un-ionized molecules. Sulfonamide drugs are excreted in the parotid saliva of humans at lower concentrations than those occurring unbound in the plasma. However, sulfonamides, phenobarbitone, and other acidic drugs are excreted in higher concentrations in the parotid saliva of ruminants, which is alkaline (pH 8.2-8.4). Penicillin is actively secreted by the salivary apparatus (Parke, 1968).

DERMAL ELIMINATION

The elimination of foreign chemicals via the skin has not been studied extensively. There are only a few known cases of elimination of chemicals via this route. The antileprosy drug ditophal (diethyl dithiolisophthalate) is excreted in the sweat of human subjects in amounts that equal or exceed the total amount excreted in the urine and feces. To a minor extent, sulfonamides are also eliminated via the sweat glands and highly volatile liquids such as dimethyl sulfoxide are excreted via the sebaceous glands. Other highly liquid-soluble agents may also be eliminated via the sebaceous glands. With the exceptions noted above, it would be safe to claim that the skin is a relatively poor route for the elimination of exogenous chemicals that are absorbed by a different route.

RENAL ELIMINATION

Excretion by the kidney consists of three distinct processes: glomerular filtration, passive tubular transfer, and active tubular transport. Glomerular filtration produces an ultrafiltrate of the blood plasma, which contains foreign compounds and their metabolites in approximately the same concentration as that in the blood. Passively tubular transfer occurs in the kidney tubular epithelium. Like other biological membranes, the tubular epithelium, particularly in the distal tubule, behaves as a lipoprotein barrier allowing the transfer of lipid-soluble, un-ionized molecules. Therefore, the un-ionized forms of lipid-soluble compounds in the glomerular filtrate are reabsorbed into the bloodstream, whereas compounds of low lipid-solubility (such as barbital) are only partially reabsorbed. Moreover, compounds that are more highly ionized in the urine than in the blood plasma tend to diffuse across the tubular epithelium from the blood into the glomerular filtrate. Thus, when the tubular urine is more alkaline than the plasma, weak acids are readily transferred into the urine. Conversely, weak bases are transferred when the tubular urine is more acid. Therefore, the rate of renal excretion of weak organic electrolytes is largely dependent on the pH of the urine. For example, the rate at which amphetamine is excreted was 20 times greater in human subjects with urine of pH 5 than in others with urine of pH 8 (Parke, 1968).

The renal tubular epithelium also possesses at least two mechanisms of active transport--one for the secretion of strong organic acids and another for strong bases, both mechanisms being associated

with the proximal tubule. Compounds excreted by active transport are highly ionized and may be transferred into the tubular urine against high concentration gradients. It is unlikely that the active transport mechanisms can distinguish between strong and weak organic electrolytes. The lipid-insoluble, ionic forms of both are probably excreted by these mechanisms. Various drugs and metabolic conjugates, such as quinine, thiazide, acetazoleamide, glucuronides, and sulfate esters, are known to be secreted by active transport. Substances secreted by the same active transport mechanisms compete with each other for that mechanism. Consequently, the excretion rate of one compound can be reduced by administration of another. This competition has used pharmacological manipulations to inhibit excretion of a drug, thus preserving therapeutic blood levels. An example of this is the competitive effect of probenecid on the excretion of penicillin.

Endogenous amino acids and sugars are reabsorbed from the tubular urine by active transport, and similar mechanisms have been indicated for the active reabsorption of certain foreign compounds, such as p-aminohippuric acid. Administration of α-methyldopa produces a reversible aminoaciduria, which probably results from competition of the catechol for the kidney tubular reabsorption mechanism for neutral amino acids. In general, therefore, the relatively polar, lipid-insoluble metabolites and conjugates are less readily reabsorbed from the renal tubules and are more readily secreted by the active transport mechanisms than are the original nonpolar, lipid-soluble foreign compounds. This results in a high renal clearance of the polar

metabolites and, consequently, in a rapid elimination of the foreign compound from the body.

Interactions

As stated above, many volatile solvents are not exhaled but are extensively metabolized in vivo, and the products are eliminated via the urine. Following an inhalation exposure to benzene (110 ppm for 2-3 hr), from 30% to 50% was eliminated via the lungs, from 0.1% to 0.2% unchanged benzene was eliminated via the kidneys, and the balance was metabolized prior to excretion in the urine (29% as phenol, 2.9% as pyrocatechol, and 1% as hydroquinone) (Haley, 1977). Similar data can be provided for toluene, the bulk (50%) of which is excreted as hippuric or benzoylglucuronic acids (Dean, 1978; Hayden et al., 1977). Therefore, it is important to consider the factors that may influence the renal excretion of such metabolites. The excellent paper by Gillette and Mitchell (1975) has covered this in great detail. Their discussion is summarized below.

If a large proportion of a toxic agent is excreted via the kidney in a metabolized form (polar metabolites) using the active transport mechanisms available for acids (or bases) in the proximal portion of the tubule, then the biological half-life of this polar metabolite will be prolonged by inhibitors of drug-metabolizing enzymes; by severe morphological damage (necrosis) of the tissue at the site of detoxification and elimination (e.g., with toluene) (Hayden et al., 1977); by inhibitors of the renal transport system; and by the size of the dose, resulting in saturation of the renal transport system, the binding sites on plasma proteins, or the

detoxification processes that are essential for the formation of the metabolites or the depletion or exhaustion of essential cofactors.

One should ascertain what influence the above factors would exert on the ratio of metabolized to unchanged drug. Moreover, one should assess the relative importance of the drug-metabolizing enzymes in various tissues and their contributions toward the biotransformation of the agent. The influence of specific organ damage, such as hepatic necrosis, on the overall formation of polar metabolites and on the rerouting of a drug for excretion, either as a different metabolite or unchanged parent compound via the lungs or kidney, should also be examined.

Considering the biotransformation of the parent molecule by different tissues, is the rate of metabolism limited by the rate of blood flow through the tissues? The answer to this would also apply to renal elimination, during which any damage to blood vessels in the kidney markedly affects blood flow, urinary pH, and clearance of drugs and metabolites. These factors would also alter the toxicity of the parent chemical, perhaps by increasing the acute toxicity in relation to the chronic toxicity that is associated with the reactive metabolites.

FECAL ELIMINATION

The liver, which is responsible for the majority of phase I and II biotransformation reactions in the body, secretes large amounts of metabolites of exogenous and endogenous agents into the biliary tract, which empties into the duodenum. As stated above, most metabolites and many conjugated products are reabsorbed from the gastrointestinal tract

into the bloodstream, eventually to be eliminated via the kidneys. If the drug or metabolite entering the gastrointestinal tract is not readily reabsorbed or becomes incorporated into the food mass, it will be retained in the lumen and eliminated in the feces.

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