The Pharmacology of Anesthetic Drugs

FIFTH EDITION

THIRD PRINTING

A SYLLABUS FOR STUDENTS AND CLINICIANS

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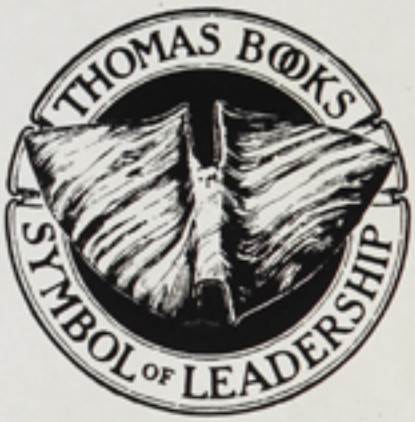
This classic was first written in 1939 when the specialty of anesthesia was in its incipient stages. Now completely updated and enlarged, it is entering its 5th Edition and has seen numerous printings. The format remains the same as in the original edition, with succinct statements describing the effect of a particular anesthetic or combination of anesthetics on a particular organ system. As before, the introductory pages give a general summary of the chemistry of anesthetic drugs.



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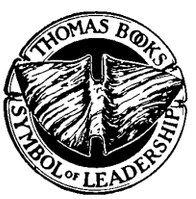

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To

E. A. ROVENSTINE, M.D.

who, with his emphasis upon the basic sciences
in the teaching of anesthesiology,
prompted the preparation
of this syllabus.

PREFACE TO FIFTH EDITION

During the past decade much data using sophisticated methods of study have been accumulated concerning anesthetic and adjunctive drugs. Much of these data has been accumulated from studies in man and are therefore clinically applicable. Furthermore, the introduction of the fluorinated compounds as anesthetic agents has prompted comparative studies of these agents with the older conventional drugs. In view of the foregoing, the entire volume has been drastically revised. Portions have been rewritten and new material has been added to update the volume. Even though the changes have been extensive, the same format and telegraphic style used in previous editions have been retained in this edition.

The problem concerning drug interactions has been assuming more and more importance. A table of interactions between adjunctive and drugs used for therapy prior to anesthesia has been added in which their effects are described, their avoidance and management should they occur.

John Adriani, M.D.

PREFACE TO FOURTH EDITION

Since World War II, chemists and pharmacologists have intensified their interest in the relationship of chemical structure of drugs to pharmacologic activity. This has led to the synthesis, laboratory investigation, and clinical trial of numerous new compounds. Families of drugs having similar pharmacologic responses have been developed from single parent derivatives by varying side chains and chemical groupings. As a result, anesthesiologists have been besieged with numerous depressants, stimulants, antagonists, and adjunctive drugs. Many of these have enjoyed only a brief span of existence and have already been discarded or supplanted by apparently more effective substitutes. Others appear to have earned a more permanent position and are enjoying widespread use.

In addition to research on new products during the past decade, the older conventional drugs have been studied in more detail with more precise methods and refined apparatus. In many cases, data heretofore available only from animal studies have been obtained in man. In this edition, therefore, it was necessary both to add data on new drugs and to bring up-to-date material on the well-established drugs used in clinical anesthesiology as, heretofore, the emphasis has been placed upon the anesthesiologist's use and interest in these compounds.

New Orleans, Louisiana John Adriani, M.D.

PREFACE TO THIRD EDITION

Nearly a decade has passed since the first edition of this book was prepared. During this period, anesthesiology has grown into a well-defined medical specialty. At the time of preparation of the original test, knowledge of certain aspects of anesthesiology was meager.

Although much still remains to be learned concerning basic principles and fundamentals, considerable data have been added to our fund of knowledge over the ten-year period. These advances in our knowledge have been in all aspects of anesthesiology. The greatest advances, however, have been in the pharmacologic aspects of the science. Most of the recently acquired pharmacologic data have been obtained in the operating room on surgical patients. Information not available from patients has been supplied by the laboratory. This newer clinical experience, coupled with the recently added laboratory investigations, has made possible a re-evaluation of earlier reported subject matter. In many instances, modification of the existing subject matter has been necessary; in others, the previous observations are still acceptable. As a result, certain gaps have appeared in the text which need to be filled if the book is to continue to serve the purposes for which it was intended and which it seems to have filled, as evidenced by five printings of the second edition. The author feels that, before any further publication is made, the original text should be completely rewritten and brought as nearly up-to-date as possible.

The purpose and general plan remains the same. Likewise, there has been no departure from the original form save for the inclusion of tables of the less common drugs used only occasionally by the anesthesiologist. Some of the more pertinent subjects of clinical importance have been elaborated upon and presented in greater detail. This has resulted in a larger volume. The properties and actions of non-narcotic drugs used in conjunction with anesthesia (e.g., curare, the central nervous system stimulants, and drugs acting upon the autonomic nervous system) have also been summarized. In describing these substances, emphasis has been placed upon their relationship to anesthesiology.

The writer is indebted to Mr. William Branks Stewart of the Department of Visual Education, Louisiana State University, School of Medicine, for the preparation of the diagrams used throughout the text.

New Orleans, Louisiana John Adriani, M.D.

PREFACE TO FIRST AND SECOND EDITIONS

This outline is limited to fundamentals. It was presented originally to acquaint the student anesthetist at New York University College of Medicine and Bellevue Hospital with pharmacologic facts relating to drugs in current use. The subject matter has been arranged in diagrammatic fashion to focus attention on physiological and pathological changes occurring in various organs and systems so that further study and interest in the fundamental sciences associated with anesthesiology may be stimulated. It is hoped that this outline will be helpful to the clinician who, although his major interest may be in another field, frequently employs the drugs reviewed.

The material presented is a compilation of data from periodicals, testbooks, and other sources in medical and scientific literature. The data will, of necessity, appear dogmatic in this type of arrangement. The reader should not be misled by the undeserved air of finality the syllabus assumes. There are many highly controversial issues. In these controversial matters, the data selected are those which have fallen in line with the clinical experiences of the writer. The reader should realize that the accumulated data are those of numerous observers who have utilized a variety of experimental methods and subjects and that interpretations may vary with the individual observer. Furthermore, in completing studies in anesthesia, variations in techniques of drug administration may alter experimental results, even though the studies were made under identical experimental conditions. Much of the included data is taken from observations on subjects other than man. Unfortunately, many results cannot be applied unreservedly to man since variations in species do occur. In many instances, the facts presented are the only ones available and must serve as a guide until human investigations are obtained.

Data on newer drugs, particularly the barbiturates and local anesthetics, are incomplete. These drugs are too numerous for individual treatment. Facts pertaining to the group as a whole have, therefore, been selected and a few important individual variations have been mentioned. Items of importance and interest to the clinician, with a direct bearing on clinical anesthesia or surgery, have been selected from less relevant material which are of major interest to the pharmacologist. A brief bibliography is provided. References to older experiments, frequently quoted in standard textbooks, are omitted. More recent periodicals are listed. Manuscripts describing several drugs are listed with the group of general articles. For the sake of brevity, the subject of the report is mentioned rather than its complete title.

The writer wishes to express his appreciation of the numerous suggestions and criticisms offered by Dr. E. A. Rovenstine, Director of the Division of Anesthesia at Bellevue Hospital, and to Dr. Bert B. Hershenson, a colleague and former member of the Division of Anesthesia.

New York, New York John Adriani, M.D.

CONTENTS

THE PHARMACOLOGY OF ANESTHETIC DRUGS

SECTION I. EFFECTS OF PHYSICAL AND CHEMICAL PROPERTIES ON PHARMACOLOGIC ACTIVITY

Central Nervous System Depressant Drugs

Drugs acting upon the central nervous system either stimulate or depress the various cells and structures. Depressant drugs are classed according to the type of action or responses they produce.

TYPES

ANALGESIC. Agent causing relief of pain. Usually accomplished without loss of consciousness or stupor. Acetylsalicylic acid, aminopyrine, and low concentrations of nitrous oxide are analgesics.
GENERAL ANESTHETIC. Agent causing loss of sensation accompanied by loss of consciousness. Ether, chloroform, cyclopropane are anesthetics.
NARCOTIC. Agent producing analgesia followed by, or accompanied by, sleep or stupor. Morphine, Dilaudid, codeine are narcotics.
SOPORIFIC, SOMNIFACIENT, HYPNOTIC. Agents causing deep sleep with little or no analgesia. Barbiturates, chloral, paraldehyde, Avertin, sulphonmethanes all come under this classification. Depth or intensity of hypnosis varies with dosage.
SEDATIVE. Agent causing mild depression. Quiets nervous excitement or calms without causing sleep. Bromides, barbital, phenobarbital, and small doses of hypnotics are sedatives. Psychosedatives (tranquilizers) have a selective action.
LOCAL ANESTHETIC. Agent capable of blocking nerve conduction when applied locally to any type of nerve tissue in any portion of the nervous system. Procaine, Pontocaine, benzyl alcohol are local anesthetics.
(No absolutely well-defined classification of nervous system depressant drugs can be made because some overlapping exists between the various types. Large doses of hypnotics may produce anesthesia. Minimal concentration of anesthetics (nitrous oxide, ethylene, ether, etc.) produces analgesia without loss of consciousness or reflexes.)

CHEMICAL NATURE

All available agents fall into two chemical groups: inorganic and organic.

INORGANIC. With the exception of nitrous oxide (N_2O) and carbon dioxide (CO_2), and salts of bromine and magnesium, inorganic compounds play little if any part in depression of the central nervous system.

ORGANIC. The majority of anesthetic, analgesic, hypnotic, and narcotic drugs are organic compounds containing carbon, hydrogen, oxygen, and in some cases halogens, nitrogen, and sulphur. Some are gases or highly volatile liquids; others are nonvolatile or solid. The volatile and gaseous agents are administered by inhalation; the nonvolatile by other routes. The chemical nature of central nervous system depressants is best understood by studying the various classes of organic compounds from which they are derived.

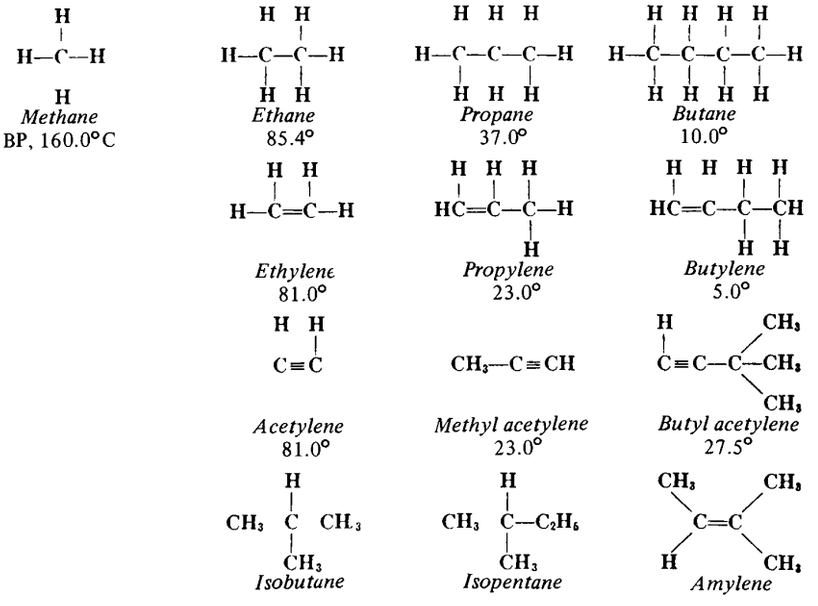
Hydrocarbons. These compounds are composed entirely of carbon and hydrogen. Three major groups exist: the aliphatic or open chain, the alicyclic or closed ring structures, and the aromatic. The aliphatic and alicyclic groups contribute important inhalation agents; the aromatic does not. Aliphatic hydrocarbons are subdivided into saturated and unsaturated derivatives.

SATURATED HYDROCARBONS. Saturated straight chain hydrocarbons possess feeble anesthetic properties. They are of no clinical value because the effective concentration is high and the margin of safety is narrow. Potency increases as molecular weight increases. Methane has been tried but is not potent. Others likewise are not suitable.

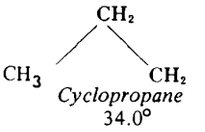
UNSATURATED HYDROCARBONS (DOUBLE BONDED). Ethylene is the most widely employed derivative in this group. Propylene has been tried but possesses undesirable effects on the circulation. Higher members of the series are unsatisfactory.

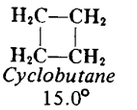
UNSATURATED HYDROCARBONS (TRIPLE BONDED). Acetylene is the only satisfactory compound in this group. Methyl acetylene and higher molecular weight derivatives are toxic and unsatisfactory.

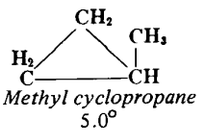
BRANCHED CHAIN DERIVATIVES. Both saturated and unsaturated derivatives have been tried and found to be limited in usefulness. *Amylene* has been used intravenously but possesses undesirable side actions.



CYCLIC HYDROCARBONS. Lower members of this series are useful. Methyl-substituted derivatives have been tried and found toxic. *Cyclopropane* and *cyclobutane* have been used clinically.


Cyclopropane
34.0°

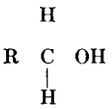

Cyclobutane
15.0°


Methyl cyclopropane
5.0°

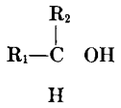
Lower molecular weight members are gases or volatile liquids which are poorly soluble in water but soluble in lipoids. Specific gravity is less than that of water. Narcotic potency increases as molecular weight increases. Narcotic potency increases as unsaturation increases (acetylene-ethylene-ethane). Hydrocarbons are chemically inert *in vivo*. Margin of safety varies but as a rule decreases as molecular weight increases. Some hydrocarbons cause deleterious effects upon cardiac tissues or induce undesirable neuromuscular responses such as convulsions or twitchings. Volatility and water solubility decrease as molecular weight increases.

Alcohols. Substitution of one hydrogen atom of a hydrocarbon by a hydroxyl (OH) group yields an alcohol. Alcohols containing one hydroxyl group are known as monohydric alcohols, two as dihydric, three as trihydric, and so on. Alcohols are either aliphatic, alicyclic, aromatic, or heterocyclic. Aliphatic alcohols produce hypnosis and general anesthesia; aromatic and heterocyclic alcohols are important in local anesthesia (see Local Anesthetics). Alcohols are classed as primary, secondary, or tertiary, depending on the position of the hydroxyl group.

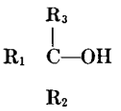
PRIMARY ALCOHOLS. Primary alcohols have two hydrogen atoms on the hydroxyl bearing carbon. *Ethyl alcohol* is the most important primary aliphatic alcohol with anesthetic activity.

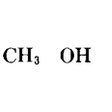


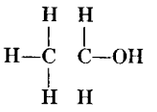
SECONDARY ALCOHOLS. Secondary alcohols have one hydrogen and two radicals on the hydroxyl bearing carbon. No important secondary aliphatic alcohol is used for anesthesia or hypnosis.

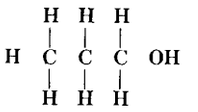


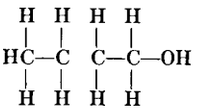
TERTIARY ALCOHOLS. Tertiary alcohols have three radicals on the hydroxyl bearing atom. *Amylene hydrate* is the only currently employed drug in this group.

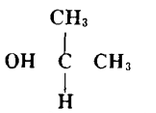


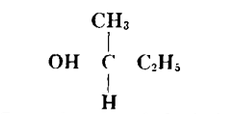

Methyl
BP, 66.0°

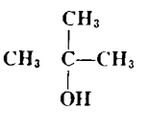

Ethyl
78.5°

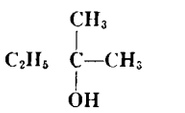

Propyl
97.0°


Butyl
117.0°


Secondary propyl


Secondary butyl alcohol


Teriary butyl


Tertiary amyl
(amylene hydrate)
BP, 102.0°

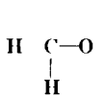
Substitution of the hydroxyl group for a hydrogen atom in an aliphatic hydrocarbon decreases its narcotic potency. Likewise, water solubility increases; lipoid solubility decreases. The compound loses its inertness *in vivo* and becomes more reactive. Narcotic potency is decreased and decreases still more with additional hydroxylation. Volatility and flammability are also decreased. Potency increases as molecular weight increases up to eight carbon atoms. Branching of the chain increases potency. Alcohols are polar substances and are metabolized in the body. Tertiary alcohols are more potent than secondary, and secondary more potent than primary. Halogenation with cholorine or bromine increases potency and effectiveness. Unsaturation with triple bond gives rise to acetylenic alcohols (methylparafynol).

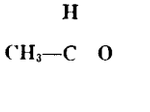
Aldehydes. Oxidation of primary alcohols yields compounds containing aldehyde (CHO) group. Substitution of a hydrogen atom of an alicyclic, aromatic, and heterocyclic compound converts it to an aldehyde. Aldehydes polymerize to form metaldehydes and paraldehydes. Alcohol and aldehydes condense to form acetals. Paraldehydes and acetals depress the central nervous system.

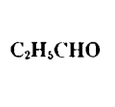
ALIPHATIC ALDEHYDES. No important aliphatic compounds are nervous system depressants. Acetaldehyde is least toxic of this group but is irritating and feeble in its action.

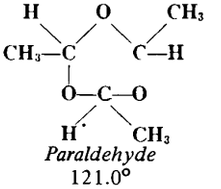
ALICYCLIC AROMATIC AND HETEROCYCLIC ALDEHYDES. No important nervous system depressants exist in these groups.

PARALDEHYDES. Higher molecular weight paraldehydes have been studied but are toxic. Paraldehyde, the simplest member of the series, is useful as a sedative and hypnotic. Paraldehyde is derived from acetaldehyde.


Formaldehyde
BP 21.0°


Acetaldehyde
21.0°


Propionaldehyde
49.0°

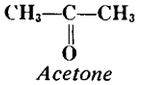

Paraldehyde
121.0°

The conversion of an alcohol into an aldehyde causes an increase in irritating properties and a weakening of narcotic potency (ethyl alcohol is more useful and less irritating than acetaldehyde, its corresponding aldehyde). Potency increases as molecular weight increases. Water solubility and volatility decrease as molecular weight increases.

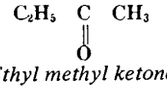
Polymerization to paraldehydes forms an entirely new series of compounds distinctly unlike aldehydes. Paraldehydes are more potent than the aldehydes from which they are derived. They are also less soluble, less volatile, and less irritating. Potency and toxicity increase as molecular weight increases. Volatility decreases as molecular weight increases. Halogenation of aldehydes enhances their potency (see next page under Halogenated Derivatives).

Acetals. The interaction of alcohols with aldehydes produces acetals. Acetal is the most useful member of this group.

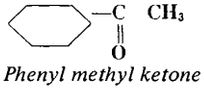
Ketones. Oxidation of secondary alcohols yields ketones – compounds containing the carbonyl (C=O) group. Ketones are of relatively little importance as central nervous system depressants. Halogenated ketones, unlike the aldehydes, are not useful as nervous system depressants. Phenyl methyl ketone or *hypnone* has been used as a hypnotic and sedative. Potency of ketones increases as molecular weight increases.



Acetone
BP, 61.0°



Ethyl methyl ketone



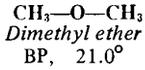
Phenyl methyl ketone

Acids. Organic acids are compounds containing the carboxyl (COOH) group. The replacement of a hydrogen atom of a hydrocarbon by a carboxyl group nullifies its action as a nervous system depressant. The carboxylic acids, therefore, are of no importance as anesthetic agents.

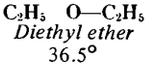
Esters. The interaction of an organic acid with an alcohol results in an ester. Esters may be derived from aliphatic, alicyclic, aromatic, and heterocyclic acids and alcohols. Esters derived from aliphatic alcohols and carboxyl acids are mild hypnotic and sedative substances. None are clinically important. Such esters are less potent than the alcohols from which they are derived. The majority of local anesthetic drugs are complex esters of aromatic or heterocyclic acids and complex alcohols (see Local Anesthetics).

Ethers. Compounds formed by attaching two organic radicals to an oxygen atom are known as ethers. They may also be termed organic oxides. Ethers may be classed as aliphatic, alicyclic, aromatic, or heterocyclic. Aliphatic and alicyclic ethers are potent and useful for general anesthesia. Aromatic and heterocyclic ethers play no role in general anesthesia but appear in local anesthetics. Ethers may be symmetrical if both radicals attached to the carbon atom are similar or they may be unsymmetrical if the radicals are dissimilar. Unsaturated linkages may appear on one or both radicals of ethers.

SATURATED ALIPHATIC ETHERS. *Diethyl ether* is the most useful and potent of this group. Ethyl propyl ether has been used clinically also but is not generally accepted. Dimethyl ether has been used clinically but is not satisfactory.

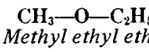


Dimethyl ether
BP, 21.0°

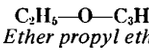


Diethyl ether
36.5°
Ether

UNSATURATED ALIPHATIC ETHERS. *Divinyl oxide* is the most important compound of this group. Higher molecular weight compounds are not satisfactory.

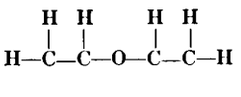


Methyl ethyl ether

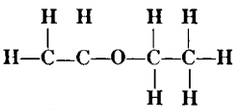


Ether propyl ether

MIXED ETHERS. Various alicylic and aliphatic ethers have been prepared and tried clinically. None has yet attained any widespread clinical use. Cyclopropyl methyl ether, or Cyprome, cyclopropyl ethyl ether or Cypreth have been tried but discarded.



Divinyl ether
BP, 28.0°



Ethyl vinyl ether

Aliphatic and alicyclic ethers are more volatile than the alcohols to which they are related or from which they are derived. They are miscible with lipoids and hydrocarbons, highly flammable, and slightly soluble in water. The presence of unsaturated linkages and the presence of the alicyclic radicals increase their potency. Low molecular weight ethers are very volatile, pungent, and require low concentrations for surgical anesthesia. Toxicity increases with increase in molecular weight. Unsaturation may cause an increase in secretory activity of ethers.

Halogenated Derivatives. Compounds derived from chlorine, flourine, and bromine are useful central nervous system depressants. Iodine yields toxic or nonanesthetic derivatives. The most useful compounds are aliphatic hydrocarbons, alcohols, and aldehydes. Alicyclic compounds are of no importance; aromatic derivatives are toxic. The aliphatic halogenated compounds discussed below are important.

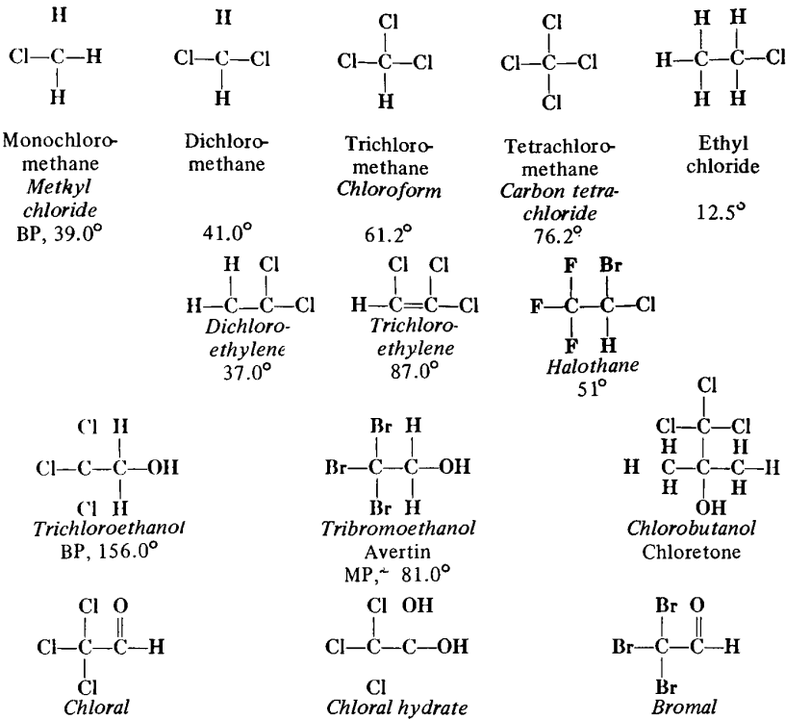
HALOGENATED HYDROCARBONS. (SATURATED). Many derivatives of bromine and chlorine possess a depressant action on the nervous system. *Chloroform, halothane,* and *ethyl chloride* are currently used. The majority of derivatives in this group are administered by inhalation.

HALOGENATED HYDROCARBONS (UNSATURATED). *Trichloroethylene* is the only member of this group employed clinically for inhalation; other derivatives are irritating, toxic, or not easily volatilized.

HALOGENATED ETHERS. Halogenated ethers containing bromine and chlorine have not been suitable clinically. The introduction of flurone has resulted in suitable ethers. Methoxyflurane (Penthrane) and fluroxene (Fluothane) are useful compounds.

HALOGENATED ALCOHOLS. *Trichloroethanol* and *tribromoethanol* are potent hypnotics used for basal anesthesia. Drugs in this group are nonvolatile and cannot be administered by inhalation. They are formed by reduction of aldehydes. Halogenation increases the potency of aliphatic alcohols.

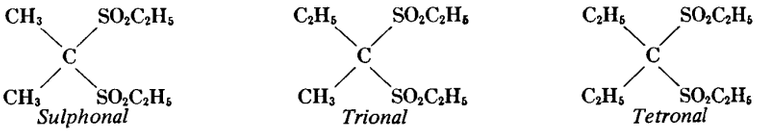
HALOGENATED ALDEHYDES. *Chloral* and *bromal* are used clinically. These derivatives are more volatile than the corresponding halogenated alcohols. Halogenation diminishes irritating qualities and improves potency of aliphatic aldehydes. Hydrates form when they interact with water. Halogenated aldehydes, like the alcohols, are not sufficiently volatile to be used for inhalation.



Halogenation enhances narcotic potency and causes a decrease in volatility of aliphatic substances. Flammability decreases as the number of halogen atoms increases. Chlorinated derivatives are more volatile and less potent than brominated compounds. Many halogenated hydrocarbons are of limited usefulness because they are toxic to the heart and liver.

Sulphonated Compounds. Sulphur-containing compounds are of little clinical importance with the exception of the thiobarbiturates (see Barbiturates) and the sulphonated aliphatic compounds derived from sulphonic acid. The sulphone methanes, derived from ethyl sulphonic acid, possess hypnotic properties. Aromatic sulphonic acid derivatives do not.

SULPHONE METHANES. Three important compounds exist in this group; *Sulphonal, trional,* and *tetronal.*

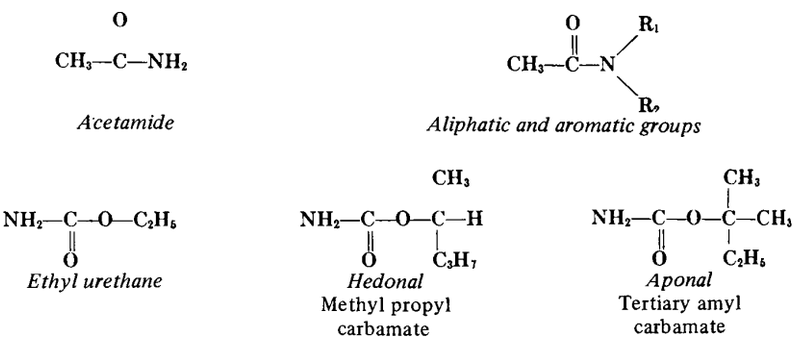


The sulphone methanes are little used clinically because they are feeble hypnotics. They dissolve in water with difficulty and possess cumulative properties.

Amides. Amides may be considered as ammonia with one of its hydrogen atoms replaced by an acyl radical. They may also be considered as carboxylic acids with the hydroxyl group replaced by an animo group. Certain amides possess hypnotic and sedative actions. Amides are nonvolatile drugs.

SUBSTITUTED ALIPHATIC AMIDES. Amides have no depressant effects unless the hydrogen atoms are substituted by aliphatic, aromatic, and other groups. No member of this group is employed clinically.

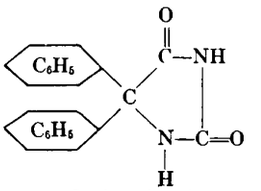
URETHANES. Carbamic acid, the monamide of carbonic acid, forms esters with various aliphatic alcohols. This group of esters is known as *urethanes.* Ethyl carbamate (or *ethyl urethane), hedonal,* and *aponal* have been used clinically. Potency of urethanes increases as molecular weight increases. Urethanes formed from primary alcohols are less potent than those formed from secondary; those from secondary less potent than those from tertiary. Ethyl urethane, hedonal, and aponal are important urethanes.



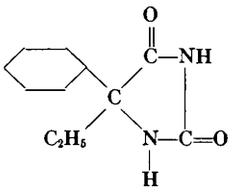
Substituted Ureas. Urea, the diamide of carbonic acid, possesses no depressant action. Substitution of the hydrogens of the amino groups by alkyl, aromatic, aryl, and other radicals produces a large series of hypnotic derivatives.

Ureides. Urea reacts with carboxylic acids to form compounds known as ureides and water. Monocarboxylic acids form open chain ureides; dicarboxylic and other acids with two acidic groups form cyclic ureides. Two groups of cyclic ureides are important as central nervous system depressants: the hydantoins and the barbiturates.

HYDANTOINS. These are derived by condensation of glycocollic acid with urea. The five-membered glycocollyl urea gives rise to two important anti convulsants, *dilantin* and *nirvanol*, by substitution of the two hydrogens on the 5 position with aromatic and alkyl groups.

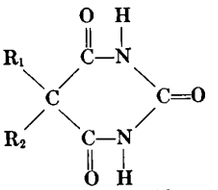


Diphenyl hydantoin
Dilantin



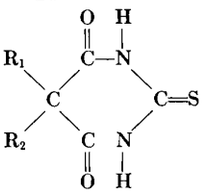
Phenyl-ethyl-hydantoin
Nirvanol

BARBITURATES. These are derived by condensation of urea and malonic acid. The malonyl urea which forms is a six-membered cyclic structure which gives rise to many hundred compounds if substitutions are made on the various atoms of the ring. Substitution of the two hydrogen atoms on the 5 position by alkyl, aromatic, alicyclic, and other radicals yields some of the most useful sedative and hypnotic drugs utilized in clinical medicine.

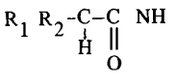


Barbituric acid

THIOBARBITURATES. Condensation of thiourea with malonic acid gives rise to a series of derivatives known as thiobarbiturates. These are similar to barbiturates except that the oxygen atom is replaced by sulphur. Thiopental is the most important member of this group.



NONBARBITURATE HYPNOTICS. A series of cyclic compounds containing the structural segment



which endows hypnotic activity to barbiturates, ureas, and related compounds has been prepared. Among these are dioxypyridines: methyprylon (Noludar), pyrithyldione (Presidone) and glutethimide (Doriden).

Miscellaneous Synthetic Heterocyclic and Aromatic Analgesics. Derivatives of piperidine (meperidine), heptanone (methadone), ethylene diamine (antihistamine drugs), aromatic amines (ephedrine), complex basic esters (atropine, Syntropan, etc.), derivatives of cyclopentoperhydrophenanthrene (various hormones) possess either general or local anesthetic action. Many nonhypnotic substances in this category are used as adjuncts to anesthesia.

Alkaloids. Alkaloids are nitrogen-containing substances elaborated by plants. Nitrogen, usually in the form of a primary, secondary, or tertiary amine, confers basic properties to the compounds. Alkaloids are usually aromatic, alicyclic, or heterocyclic. They are unique because minute amounts produce physiologic activity. They form salts with inorganic and organic acids. Alkaloids possess optical activity. Alkaloids derived from opium are the only central nervous system depressants of clinical importance. Alkaloids of the coca plant are useful local anesthetics (cocaine). Numerous synthetic substances similar in properties and reactions to alkaloids have been prepared. Many alkaloids formerly obtained from plants are now prepared synthetically.

Alkaloids are poorly ionized at the pH of the body fluids, which makes them lipophilic and causes them to penetrate the lipoid barrier of the cell membrane readily.

Relation of Physical and Chemical Behavior to Depressant Effects on the Cell

Depressant drugs exhibit a variety of chemical and physical properties in artificially prepared systems of oil-water, oil-protein, or protein-water interphases *in vitro* designed to simulate protoplasm and cell membranes. Similar behavior is believed to occur in the living cell.

WATER SOLUBILITY. Volatile inert agents, as a rule, are nonpolar, poorly soluble, and poorly ionized. Useful nonvolatile agents are polar and are both lipid-and water-soluble. All drugs must possess some degree of water solubility to be carried to the cell. The majority of drugs are more soluble in blood than in water, but a parallelism exists between solubility in the two. Water solubility may be an index of blood solubility.

LIPOID SOLUBILITY. Most drugs with narcotic activity are highly soluble or miscible in oils and lipoids (lipophilic). A parallelism exists between oil-water solubility coefficients and the quantity absorbed by nerve tissues since nerve cells are rich in lipoid substances. A good correlation exists between potency and the coefficient of partition of the drug between equal volumes of oil and water at 37.5°C. Drugs possessing ratios of high magnitude are known as *lipophilic* agents. For the most part, potency of anesthetics parallels an increase in magnitude of this coefficient. Ionized drugs are polar and insoluble in lipoids and penetrate cell barriers poorly.

EFFECTS OF COLLOIDS. Protoplasm is colloidal in nature. Colloidal properties are due to lipids and proteins. Proteins believed to be "coagulated" are altered reversibly by depressant agents. Colloid particles, because of their size and the fine division, present a large surface to the dispersion medium (solvent) and a large area for adsorption.

EFFECTS OF ADSORPTION. Many depressant drugs are readily adsorbed on surfaces of activated substances such as charcoal or silica. The large surface possessed by particles in a colloidal solution favors adsorption to these particles. This type of phenomenon may occur on the cell membrane.

EFFECTS OF SURFACE TENSION. Some drugs decrease surface tension of water. Similar decrease or a decrease in interfacial tension may occur in protoplasm, altering cellular permeability and ability of substances and ions to migrate.

EFFECT ON VISCOSITY. Viscosity of colloidal films is usually increased by many anesthetic drugs. Changes in viscosity may decrease permeability of the cell membrane.

EFFECTS ON ENZYME ACTIVITY. Some drugs decrease enzyme activity, particularly enzymes which facilitate oxygen utilization (oxidases, dehydrogenases, phosphorylases), and interfere with liberation of energy and biochemical processes. Activity of energy-releasing enzymes and those which aid in detoxification may also be suppressed.

EFFECTS ON ELECTRICAL CHARGE. Potential difference develops at liquid-liquid interphase of two immiscible liquids containing ions. Charge may be altered by an anesthetic drug.

Effects of Depressant Drugs at the Cellular Level

EFFECTS ON LIPOIDS. Lipophilic anesthetics are absorbed by cells rich in lipoid (nerve and adipose) tissue. Lipid solubility is important because it either limits or facilitates penetration into cells. Lipid-soluble substances are poorly ionized. Depressant effects on cell activity are more pronounced with drugs having high oil-water coefficients. Most anesthetic drugs are neutral substances or weak organic acids with high or moderate degree of lipid partition capabilities. Not ionized at physiologic pH. Highly ionized substances do not penetrate the lipid barrier of the cell membrane since they are highly polar.

BIOTRANSFORMATION. Most volatile agents are inert or are destroyed slowly in the cell. Ether, cyclopropane, ethylene, etc., are not altered even slightly by intracellular biochemical processes. Most nonvolatile drugs are metabolized in the microsomes.

EFFECTS ON INTRACELLULAR FLUIDS. Water content of cells is decreased during depression induced by drugs. Fluids transude outward. The reaction is reversible. Viscosity is increased. Intracellular pH is less than that of the interstitial fluid. A significant difference in pH on one side of a membrane may cause significant differences in proportion of ionized and un-ionized molecules on one side as compared to the other.

PHYSICAL PHENOMENA. The cell membrane is polarized with a positive charge on outside and a negative charge inside. Anesthetics may depolarize the membrane or stabilize it by preventing ionic migration (local anesthetics). Ionized substances may pass through membranes with large pores but are unable to diffuse through a lipid barrier.

EFFECT ON INTRACELLULAR BODIES. Mitochondria and microsomes are surrounded by lipid membranes. Nonpolar substances enter these bodies and interfere with energy release (mitochondria) or biotransformation (microsomes). Detoxification occurs in liver microsomes. Energy release occurs in mitochondria.

PASSAGE THROUGH THE CELL MEMBRANE. Cell membrane consists of protein film overlaid on both sides with lipid material, with pores through which substances pass. Substances pass in or out of a cell by passive diffusion or active transport in which energy is utilized. Nonpolar substances dissolve in the lipids of the membrane and readily pass inward.

Ionized substances readily pass through cellular membrane if they spontaneously revert to the un-ionized form. Rate of passage of a drug is proportional to the partition coefficient and to the differences of the concentration on the two sides of the membrane. In some membranes, pores may have electrostatic charges which may influence passive migration of ions.

BONDING WITH RECEPTORS. Bonding of a drug on the cell surface or in the cytoplasm with receptors occurs by (1) weak covalent bonding, (2) van der Waal's forces of electronic attraction (adhesion or cohesion), (3) hydrogen bonding, (4) ionic bonding, (5) coordinate bonding.

EFFECTS ON CELL METABOLISM. Metabolism of nervous tissues is depressed by anesthetics. Some enzymes in the mitochondria are inhibited by depressant drugs. Energy production, oxygen consumption, and CO_2 output are reduced.

TOLERANCE AND PHYSICAL DEPENDENCE. Tolerance develops to depressant drugs at the cellular level. Repeated use causes habituation or psychic craving in an intact organism. Addiction (physical dependence) manifests by physiological disturbances when a drug is withdrawn. This is due to inability of the cell to function without a drug. Withdrawal symptoms do not occur if physical dependence has not developed.

Depressant (anesthetic) drugs possess three characteristics: (1) they depress all types of cells; (2) they have predilection for nervous tissue; (3) their action is reversible cells return to normal when the drug is removed from the cell. *Narcosis,* in the biological sense, refers to decrease in cellular activity; in the clinical sense, it indicates stupor, sleep, or loss of consciousness.

Theories of Narcosis

Narcosis is a reversible decrease in cell activity produced by physical or chemical agents. Physical agents such as cold, electricity, or pressure may also reduce cellular activity. Chemical substances, both inorganic and organic, known as anesthetics, hypnotics, and sedatives, likewise reduce cellular activity. The concept is unitarian. Different chemical agents produce the same type of response. Many theories have been proposed, but none satisfactorily explains the basic mechanism involved. The following theories which have been propounded are based on chemical, physicochemical, or physical changes such as solubility in different media, effect on proteins, changes in permeability of cell membrane, adsorbability, ability to form hydrates.

Basis of Theory	*Year*	*Proposition*	*Proposer*	*Evidence*	*Objection*
Lipoid solubility. Lipophilic qualities of anesthetics facilitate uptake by high-lipid-containing cells.	1847	All fat solvents are narcotics. They cause narcosis by washing lipoids out of cells.	Bibra & Harless	Blood lipoid increases during anesthesia. Lipoid content of certain cells reduced.	Recovery occurs too rapidly to account for return of lipoid into the cell.
Lipoid solubility.	1866 1895	Narcotic substances exert a direct reaction on cellular lipoids.	Hermann Richet	Aliphatic hypnotics dissolve in red blood cells because they are highly soluble in lipoids and lipoids are abundant in these cells.	Solubility in water not same as blood and lymph. Work done on olive oil and oils not similar to body fats. Applies to inert nonreactive nonpolar substances only; does not include or explain action of heterocyclic substances, alkaloids, and inorganic substances. Explains mode of transport to nerve tissues but not its action in cell. Oil-water ratio not a true index of amount adsorbed by tissues.
Lipoid solubility.	1899 1901	Narcotic efficiency parallels coefficient of partition between oil and water. Lipoids in cell and on cell membrane absorb drug because of this great affinity.	Meyer Overton	Narcotic potency of aliphatic compound increases as coefficient of partition between oil and water increases. Effect is most marked in cells in which lipoid predominates and plays a role in cell function. Relative efficiency depends on affinity for lipoid-containing neurons and remaining (water) constituents.	
Lipoid solubility.		Same as above.	K. Meyer	Concentration of a drug which causes narcosis is constant and averages 0.06 moles per liter, irrespective of potency.	Same as above.
Surface tension lowering effects.	1904	Substances which lower surface tension of water pass more readily into the cell and cause narcosis by decreasing metabolism.	Traube & Czapek	Parallelism exists between ability of drugs to lower surface tension of water and their narcotic potency.	Experiments were done on air-water interfaces at room temperature. Should be done on two liquid interfaces at body temperature. Many exceptions (chloroform and ethyl alcohol).
Adsorption to activated surfaces alters cell functions.	1931	Drug becomes concentrated at the surface of the cell due to adsorption. Drug may thus alter permeability and metabolism.	King Also data by Lillie, Warburg, & Hiller	Narcotic activity of certain drugs parallels amount of substance adsorbed at paraffin water interfaces. Certain drugs applied to surface of amebae cause depression of activity. None if injected directly into cell.	Most experiments have been done on artificial systems or *in vitro*. Duplication of results in higher forms of life is not successful. Many substances which are adsorbable are nonnarcotic.
Changes in permeability of cell membrane by interaction of drugs with cell-membrane constituents.	1912	Permeability of cell membranes decreased by narcotic concentrations of aliphatic and other central nervous system depressants. Toxic concentrations increase permeability.	Lillie Höber	Low concentrations of aliphatic substances added to aqueous media prevent swelling of nerve and muscle cells in hypertonic solutions.	Most of the data are from *in vitro* studies or from studies on structures of lower forms of life. Some substances which increase permeability are nonnarcotic, and some narcotic substances increase permeability.
Change in permeability of cell membrane.	1915	Lipids are concentrated at the cell membrane. Anesthetics enter lipids and change configuration of the membrane.	Winterstein	Lipoids concentrate at cell membrane because they lower surface tension. Drugs pass into lipoid in cell membrane, cytoplasm, and decrease permeability and reduce metabolic activity.	Same as above.
Formation of hydrates by the anesthetic and water in the cell.	1961	Anesthetics form hydrates which are clathrates. These form an ice cover at membranes of neuronal tissues and plug up the pores in the membrane, thereby reducing transmission of impulses at synapses of neurons.	Miller	Inert anesthetics form hydrates *in vitro* and form ice cover at membrane surface.	Has not been demonstrated *in vivo*. A correlation exists between partial pressure required for anesthesia and dissociation pressure of the hydrate of the anesthetic.
Formation of hydrates.	1961	Micro-ice crystal.	Pauling	An interaction of a nonhydrogen-bonding anesthetic with water molecules occurs, forming microhydrate ice crystals. Ions are trapped on electrically charged side chains of protein molecules and decrease energy of electrical oscillation in the brain, causing narcosis.	Has not been demonstrated *in vivo*, but *in vitro*. A correlation exists between partial pressure of the anesthetic and partial pressure required to form ice crystals.

Basis of Theory	*Year*	*Proposition*	*Proposer*	*Evidence*	*Objection*
Changes in colloid of cell: (a) Coagulation or flocculation of protein.	1867	Coagulation or flocculation of protein causes dehydration and reduction of metabolism.	Ranke	Noted clouding of muscle cells by chloroform, which he thought was coagulation of protein.	Concentrations necessary to cause coagulation experimentally are greater than those encountered clinically. Experiments done on unnatural systems *in vitro* or on cells of lower forms of life.
			Binz	Noted changes in transparency of cytoplasm of nerve cells after exposure to chloral and morphine.	
	1875		Claude Bernard	Said narcosis due to reversible semicoagulation of protein of cytoplasm of cell.	
	1931		Bancroft	Ultramicroscopic reversible coagulation occurs which is visible with ultramicroscope.	
	1882		Dubois	Noted shrinkage of cells due to loss of fluid following exposure to depressants.	Narcosis does not always follow dehydration and fluid loss in cell.
	1907		Hober	Noted shrinkage of cells due to water loss from cell following exposure to depressants.	
(b) Increase in viscosity.	1930		Ebbecke	Drugs alter protein and increase viscosity of cytoplasm.	
(c) Combination with protein of cell.	1907	Narcotic combines with protein and other constituents of protoplasm. Drug becomes loosely adsorbed on colloids.	Moore & Roaf	Amount of chloroform in blood greater than physical laws of solubility or lipid content allow.	Amount of chloroform required to produce effect is greater than is necessary for narcosis.
Decrease in cellular oxidation:	1860	Bivalent carbon atom which was thought to play role in cellular oxidation inhibited by narcotics.	Mathews-Brown	None. Based on conjecture.	No experimental data which support the theory. All based on conjecture.
		Depressant drugs interfere with tissue oxidation.	Baglioni	None. Surmised that the drug decreased oxidation.	Anoxia and narcosis are not similar.
(a) Oxygen deprivation.	1909	Narcotics cause oxygen deprivation which causes cell to be narcotized.	Verworn	Narcosis is accompanied by diminished oxidation, manifested by decreased oxygen uptake.	Diminished oxidation is the result, not the cause, of narcosis. Narcotics do not interfere with accessibility of oxygen to the cell.
(b) Narcotics inhibit oxidation.		Anesthetics inhibit oxidation.	Warburg	Activated charcoal adsorbs oxalic acid which is in turn oxidized. Anesthetics inhibit this oxidation.	Data obtained from *in vitro* experiments on a purely physical system.
(c) Inhibition of respiratory enzymes. (d) Suppression of formation of high energy phosphate bonds.	1934	Oxidative processes inhibited by anesthetics.	Quastel, Wheatly & Janet	Oxygen consumption of brain slices in microspirometer reduced because of decreased oxidation of glucose, lactate, and pyruvate.	Data are from *in vitro* studies on excised fissues. Anesthetics mobilize carbohydrates in tissues, reducing availability and thereby decreasing oxidation. Suppression of oxidation could be the result of narcosis and not the cause. Describes the phenomenon of narcosis rather than explaining it.
Electrical potentials of nervous tissue altered by narcotic drugs. Polarity reversed.	1936	Action potentials on brain tissue observed under narcotic drugs similar to those of normal sleep.	Burge, Derbyshire, Bremer *et al.*	Reversal of polarity of cortex in relation to sciatic nerve occurs during narcosis.	
Molecular volume.	1957	Relates molecular volume determined by van der Waal's constants.	Wulf Featherstone	Narcotic potency increases with increase of molecular size.	Many exceptions. Chloroform should be weaker than ether because molecule is smaller.
Thermodynamic activity.	1939	Interposition of narcotics molecules in nonaqueous cellular phase causes changes which interfere with facilitation and ionic exchange.	Ferguson	Narcotic activity of a drug is propostional to its thermodynamic activity. Partial Pressure required for narcosis.	Data are mathematical and physicochemical. Obtained in the laboratory.
Protein (solubility). Uptake of anesthetics.	1965	Anesthetic molecules "adsorbed" to proteins.	Featherstone	More of an inert drug dissolves in body fluids than can be accounted for by water and lipid solubility. The anesthetic is entrapped in coils of protein molecule. It is not combined with the protein.	Does not explain the mechanism whereby narcosis occurs as a result of this phenomenon.

Basis of Theory	*Year*	*Evidence*	*Proposer*	*Proposition*	*Objection*
Interference with phos phorylation and release of energy in the cell.	1962	Drugs such as ether interfere with oxidation by causing uncoupling.	Clements & Wilson	Drugs interact with lipoprotein in membranes and change the dielectric constant and permeability of a membrane, thereby interfering with ion transport. The drugs affect mitochondrial membranes and suppress oxidative phosphorylation in the mitochondria.	Derived from *in vivo* data. Experimental proof *in vivo* is lacking.
	1951	Same as above.	Brodie & Bain	Certain drugs in anesthetic concentration uncouple oxidation from phosphorylation in mitochondria.	Data are from *in vitro* studies of rat brain. Not all anesthetics are capable of doing this. Nonanesthetics also may cause uncoupling.
	1955	Same as above.	Hulme & Krantz	Ether uncouples phosphorylation from oxidation. High-energy bonds are necessary for synthesis of acetylcholine, which is necessary for neuronal transmission. Their absence interferes with acetylcholine synthesis, which interferes with nervous activity.	Supporting data are derived from *in vitro* studies. Exceptions are known. Does not occur with xenon and N_2O.
Thermodynamic activity.	1948	The work required per mole to transfer an anesthetic from the pure liquid to the narcotized cell is the same for all substances which produce equal degrees of narcosis at equal thermodynamic activities.	Brink & Pasternack	Anesthetics produce their effects by fitting their molecules into regions of a cell in the same manner as they fit into their own liquids.	Experimental verification *in vivo* is lacking.
	1954	Thermodynamic activity of the narcotic multiplied by its molal volume equals a constant. This constant is nearly of the same numerical value for all potent drugs.	Mullen	Narcosis is caused by inert molecules. A fraction of the total occupy a nonaqueous phase.	This is actually an extension of Ferguson's theory and resembles the Meyer-Overton theory without considering solvents.

Routes of Administration

SUBCUTANEOUS ROUTE. Useful for nonvolatile water-or oil-soluble hypnotic and narcotic drugs. Not satisfactory for administration of irritating drugs which may cause sloughs. Rate of absorption varies with blood supply to the tissue. Slow absorption occurs from subcutaneous fat due to poor blood supply to this tissue. Oily solutions used for continuous slow absorption.

INTRAMUSCULAR ROUTE. Useful for irritating drugs, drugs dissolved in oil or aqueous solutions to be rapidly absorbed. Excellent blood supply to muscle tissue favors rapid absorption. Absorption slow in shock or hypotension from other causes.

INTRAVENOUS ROUTE. Useful for water-soluble anesthetics, hypnotic, and narcotic drugs. Factors which modify absorption by other routes are not present in this method. Desired blood concentration is promptly obtained. Has disadvantage of being noncontrollable (i.e. blood concentration cannot be varied or reduced in the event of overdosage). Also, the drug may pass from blood and be stored in tissues, causing cumulative action.

INTRAMEDULLARY ROUTE. Useful when veins are not accessible. Sternum is used for adults; long bones for infants. Drug passes into venous circulation with almost the same speed as if directly injected into the veins.

INTRA-ARTERIAL ROUTE. Not suitable. Spasm of artery and its tributaries may result in gangrene-or other damage characteristic of ischemia.

TOPICAL ROUTE. No appreciable absorption occurs through the skin. Local anesthetic drugs pass through and anesthetize the mucous membranes of the nose, throat, trachea, bronchi, uretha, vagina, rectum, bladder, esophagus, and stomach.

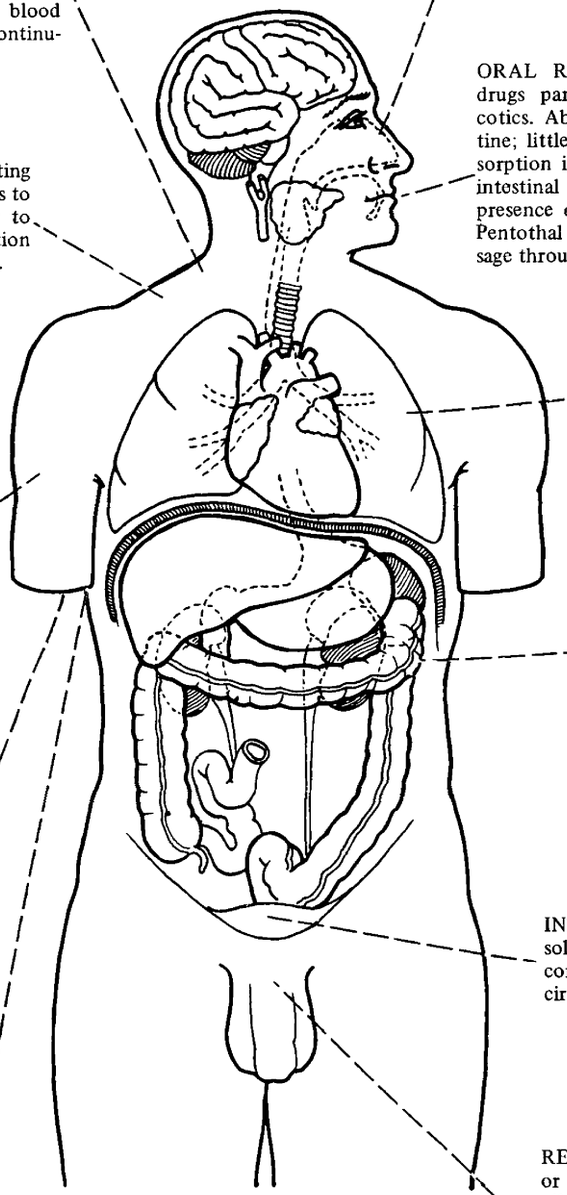
ORAL ROUTE. Useful for nonvolatile soluble drugs particularly analgesics, hypnotics, and narcotics. Absorption is mostly from the small intestine; little, if any, occurs from the stomach. Absorption is influenced by variable factors such as intestinal motility, pH of intestinal contents, and presence of other substances. Some drugs such as Pentothal and Evipal are rapidly destroyed on passage through the gastrointestinal tract.

PULMONARY ROUTE. Useful for gases and liquids which volatilize below 60° C. Gases and vapors gain access to blood by diffusion into the pulmonary capillaries through the alveolar membrane. Drug is carried to the left heart and thence to the tissues.

INTRAPERITONEAL ROUTE. Useful for nonirritating nonvolatile hypnotic and narcotic drugs. Large serous surface favors almost immediate absorption. Drug passes into lymphatics. Absorption greater in area around diaphragm. Used in animals. Danger of adhesions and infection precludes use in man.

INTRATHECAL ROUTE. Useful for water-soluble local anesthetic drugs to block nerve conduction. Drug slowly passes into venous circulation from spinal fluid.

RECTAL ROUTE. Useful for either volatile or nonvolatile drugs. Vegetable or mineral oils are often used as vehicles for lipoid-soluble drugs. Absorption proceeds almost entirely from the colon unless ileocecal valve is patent. Absorbed drugs pass through the liver, which may cause modification or may temporarily store them before passing them into the systemic venous circulation.



Distribution and Elimination

Nervous system depressants may be eliminated unchanged through various excretory channels or may be rendered physiologically inert by chemical alteration by the body. The exact fate of the drug depends on its chemical nature and physical properties. Most volatile agents are inert and are eliminated unchanged. Nonvolatile agents are detoxified.

BRAIN. Lipophilic substances accumulate in nervous tissue because of its high lipoid content and excellent blood supply. Nerve, like other tissues, is mostly water. Amount of lipophilic drugs in nerve tissue is greater relatively but not absolutely than in other tissues.

SPINAL FLUID. Distribution of drugs in spinal fluid varies. It may equal plasma concentration or may follow some pattern as other constituents such as glucose.

LUNG. Inert drugs (volatile) are eliminated almost entirely in the exhaled air, regardless of route of administration. Ether administered by rectum or vein is eliminated by exhalation.

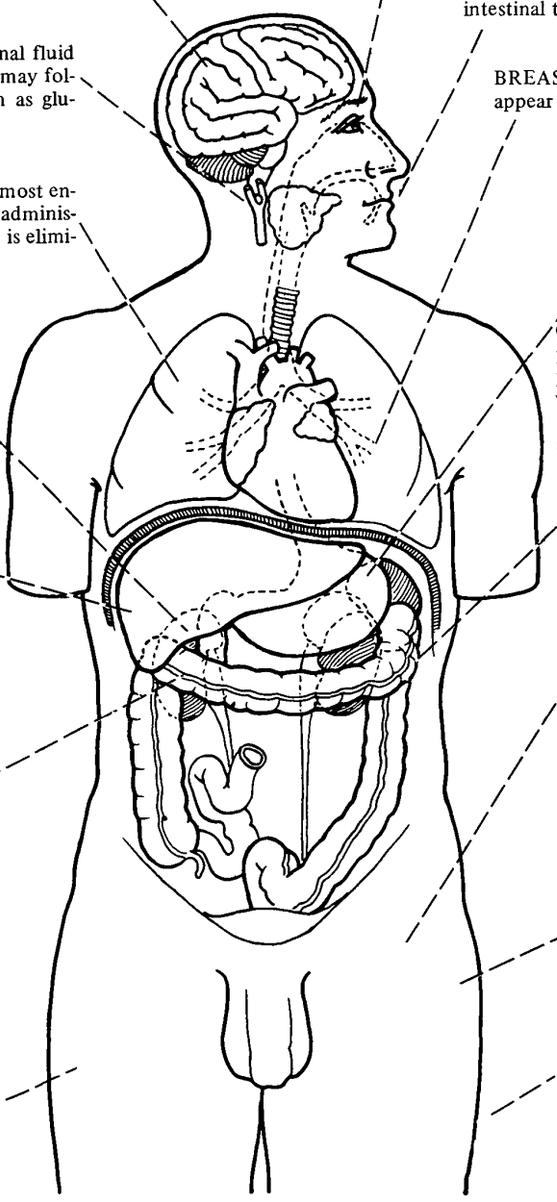
BILE. Drugs or their by-products may be excreted by the liver into the bile and then pass into intestine. May pass on into feces or may be reabsorbed over and over, giving prolonged action.

LIVER. Drugs may be temporarily stored, particularly when absorbed from the gastrointestinal tract. The majority of drugs are detoxified by the liver or, if several tissues inactivate the drug, the liver usually plays the dominant role.

KIDNEY. Drugs and by-products of detoxification appear in glomerular filtrate in proportion to plasma concentration. Some drugs are reabsorbed by the renal tubules; some are eliminated by excretion by the tubules. The kidney plays a minor role in actually detoxifying drugs.

PLACENTA. Depressant drugs, both volatile and nonvolatile, readily pass through to the fetus. The placenta presents no barrier.

BLOOD. Distribution between cells and plasma varies with many drugs. Certain drugs–particularly lipophilic agents such as cyclopropane, chloroform, or ethylene–exist in greater amount in cells than in plasma; others such as ether and alcohol are more equally distributed between cells and plasma.



EYE. Drug passes into tears in small amount.

SALIVA. Drug may appear in saliva, pass into gastrointestinal tract, and be reabsorbed.

BREAST. Both volatile and nonvolatile agents may appear in milk.

STOMACH. Volatile drugs may pass into gas contained in hollow viscera. An equilibrium is established between the agent contained in blood and that in gas.

COLON. Nonvolatile drugs or their by-products may be excreted into colon and pass outward with the feces. Gases in hollow viscera may contain volatile agents. Concentration is usually proportioned to the tension present in blood.

MUSCLE. Many drugs absorbed and stored by muscle, particularly water-soluble drugs or drugs with low oil-water ratio (ether). Muscle may detoxify some drugs.

SUBCUTANEOUS FAT. Great affinity is shown for lipophilic agents. Saturation and desaturation are slow because of poor blood supply of these tissues. Minute amounts of drugs are gradually passed back into systemic circulation after drugs are eliminated from other tissues, causing drug to be present in blood for many hours.

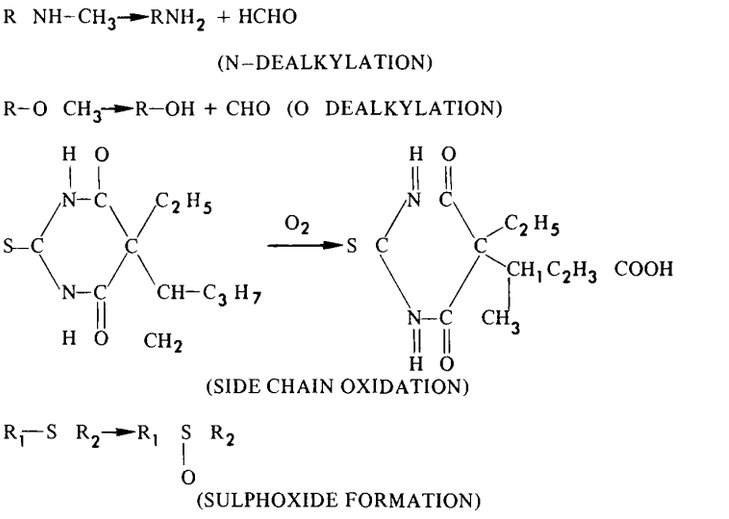
SKIN. Drug appears in sweat. Certain drugs or by-products of detoxification may cause skin rashes (bromides and barbiturates). Volatile drugs diffuse through skin (cyclopropane, ethylene, and N_2O). Rate of diffusion varies with drug.

Metabolic Fate of Drugs

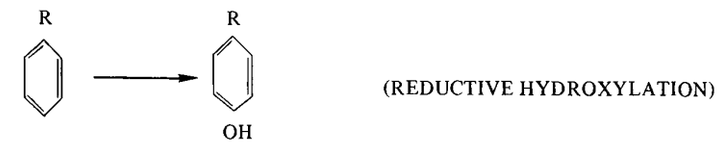
All drugs, both volatile and nonvolatile, are metabolized in varying degrees by the body. Volatile drugs, formerly classed as totally inert, undergo some change, though slight. The major portion of this type is eliminated unchanged via the lungs, intestinal tract, sweat, saliva, and kidney. Nonvolatile drugs are totally or partly metabolized. Urinary excretion is relatively unimportant in limiting the action of drugs since most drugs undergo chemical change before the kidney is able to excrete them. Most drugs, both volatile and nonvolatile, are metabolized in the liver within the microsomes by enzyme systems contained in these cytoplasmic bodies. Enzymes are involved in accelerating metabolic changes. A multitude of drugs, however, are metabolized along a surprisingly few chemical pathways. Unmetabolized portions are excreted by the kidney and to a lesser extent by other channels. The metabolic pathways are discussed below.

OXIDATION

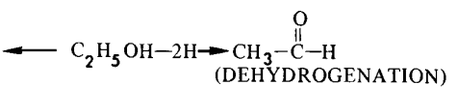
The enzyme systems involved in oxidation are triphospho-nucleo-dehydrogenases. The hydrogen acceptor is oxygen. Oxidation goes on by *N*-dealkylation, *O*-dealkylation, deamination, sulphoxide formation, aromatic hydroxylation, side chain oxidation, alcohol oxidation to aldehydes, and aldehyde oxidation to acids. In N-*dealkylation*, an alkyl group is removed from the nitrogen atoms of a compound and converted to a hydroxyl group, which is later converted to a carboxyl group. In O-*dealkylation*, the alkyl group is removed from an oxygen atom and hydroxylation occurs. This hydroxyl group may be oxidized to a carboxyl (acidic) group. In *deamination*, an amino group is removed from a compound and replaced by a hydroxyl group. In *sulphoxide formation*, a sulphur atom on the molecule is oxidized to an oxide. In *aromatic hydroxylation*, a side chain on a benzene ring is converted to a hydroxyl group and later metabolized by other mechanisms. In certain rings, heterocyclic compounds (the barbiturates), side chains undergo oxidation to a carboxyl group. For example, the methyl butyl group in thiopental is converted to a carboxyl group. Alcohols are oxidized to aldehydes by aldehyde dehydrogenase. Aldehydes may be oxidized, aided by various enzyme systems, to acetic acid and water (as occurs with alcohol). The reaction of greatest frequency is hydroxylation of side chains in an aromatic nucleus. The benzene rings may be hydroxylated in the *ortho* and *para* positions. Microsomes possess enzyme systems consisting of reduced triphosphopyridine nucleotide (TPNH) which, together with atmospheric oxygen, accomplishes hydroxylation of a side chain.



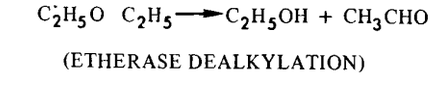
REDUCTIVE HYDROXYLATION. More than one hydroxylating system occurs during biologic oxidation. Benzene rings are oxidized to phenols. This is accomplished by microsomal hydroxylating systems. Oxidation may occur by *epoxidation*. An epoxide (-e-e-) forms which undergoes reduction to form a hydroxyl group. A hydroperoxide may form first which then undergoes reduction, or may form a peroxide which then is converted to two hydroxyl groups.



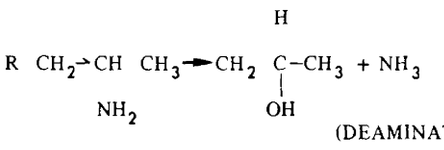
DEHYDROGENATION. Hydrogen is removed from the compound. Alcohol and aldehyde dehydrogenases requiring TPNH are located in the microsomes. Alcohols are oxidized to aldehydes and aldehydes to acids.



DEALKYLATION. Alkyl (methyl ethyl, etc.) groups are removed from nitrogen atoms by oxidative deamination, utilizing TPNH or DPN (diphosphopyridine nucleotide) and oxygen. Codeine, meperidine, diacetylmorphine are demethylated. *O*-dealkylation, mediated via enzymes which split ethers (etherases). Alkyl (methyl groups on oxygen atoms) and phenolic ethers (codeine, papaverine).

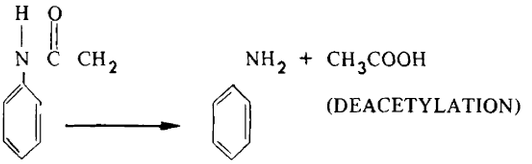


DEAMINATION. Amino group is removed and replaced by oxygen. Monamine oxidase deaminates compounds of the $RCH_2 - NH_2$ type and aromatic amines with the NH_2 groups on the ring. Demethylation is aided by microsomes in the presence of TPNH and oxygen. Amphetamine is detoxified in this manner.



(DEAMINATION)

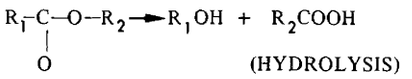
DEACETYLATION. An acetyl group is removed from a carbon atom by deacetylases. Deacetylation may occur in the kidney as well as liver.



(DEACETYLATION)

METABOLIC HYDROLYSIS

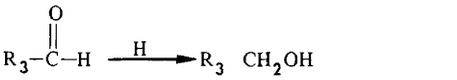
Esters (esterases) and amides split to corresponding acid and alcohol or amine (succinylcholine procainamide). Hydrolytics may release the active principle of a drug – procainamide (less active) converted to procaine (more active). The reverse also occurs. Esters form, aided by esterases which are more active than either component.



(HYDROLYSIS)

REDUCTION BY HYDROGENATION

Reductases add hydrogen to oxygen atoms. Ketones are converted to alcohols and nitro- to azo- groups. This is accomplished by hydrogen transfer from TPNH and DPNH in microsomes.

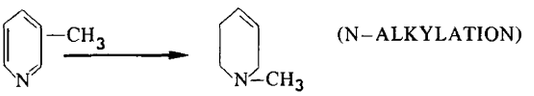


(HYDROGENATION)

METABOLIC CONJUGATIONS

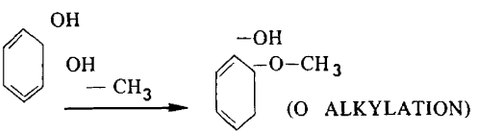
Conjugation adds a side chain to a molecule. Utilizes inorganic (sulphuric) or organic acids (glucuronic, acetic, etc.).

N-ALKYLATION. Mediated by transferases. Metabolic methylation of nitrogen in a ring. Types of conjugation are structures. This may occur from the transfer of methyl groups from methionine (*S*-adenosyl methionine).



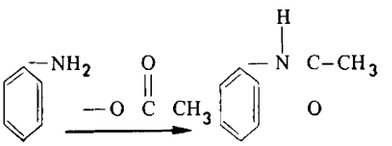
(N–ALKYLATION)

O-ALKYLATION. Alkyl group added to oxygen by transferases. This occurs in catecholamines. Catecholomethyl transferase converts epinephrine to metaepinephrine.



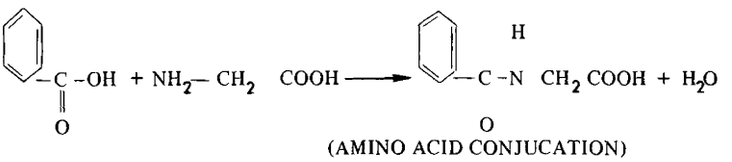
(O ALKYLATION)

ACETYLATION. Acetylation of primary amino groups is common with amino acids in many drugs. Acetate in the presence of ATP (adenosine triphosphate) is first activated by combining with coenzyme A to form "active acetate," which is a specific acetyl transfer enzyme which transports the acetyl group to the amine receptor. May occur in the liver and kidney mitachondria.



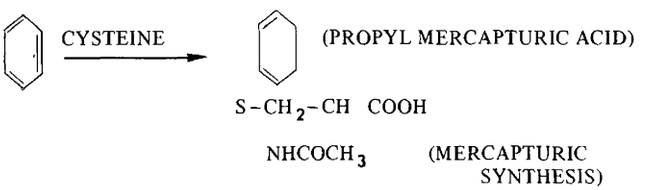
(ACETYLATION)

AMINO ACID CONJUGATION. Amino acid attaches to molecules with free carboxyl group (benzoic acid forms hippuric acid). Enzyme systems present in the kidney and liver microsomes. Serine, ornithine, glutamine, and lysine also are utilized in this form of conjugation.



(AMINO ACID CONJUCATION)

METCAPTURIC ACID SYNTHESIS. Mercapturic acid is produced from glutathione which supplies the cysteyl radical.



(PROPYL MERCAPTURIC ACID)
(MERCAPTURIC SYNTHESIS)