Review Article

The Metabolism of Drugs Employed in Anesthesia

Part II

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Metabolism of Specific Drugs

Agents Acting on the Autonomic Nervous System

These agents affect the sympathetic nervous system (vasopressors and vasodilators) or the parasympathetic system (parasympatholytics). Some are endogenous in man and some exogenous. The biologic disposition of endogenous parasympathetic agents, rarely used in anesthesia, will not be reviewed, but the inactivation of exogenous parasympathetic agents will be described. On the other hand, the biologic disposition and means of inactivation of catecholamines, often used during anesthesia, will be reviewed.

Catecholamines

Epinephrine and norepinephrine, both catecholamines, dihydroxybenzene derivatives with a side-chain including an amine group, with their metabolic precursors and metabolites, are the only endogenous catecholamines of importance. The only important synthetic catecholamine is isoproterenol (Isuprel).

Norepinephrine. The disposition of norepinephrine depends upon its intracellular or extracellular locus. When released from postganglionic sympathetic nerve endings, it is inactivated by diffusion, uptake, or metabolism.[59, 213] When diffused from the synaptic cleft, it may enter the vascular system, with resultant increase in circulating levels; this effect is seen with cyclopropane and diethyl ether. It is the result, not the cause, of increased sympathetic nerve activity.

More important than diffusion in limiting the response to neurogenically-released norepinephrine is uptake by the nerve endings of norepinephrine previously released by it, followed by storage within cytoplasmic granules for subsequent release. Uptake of norepinephrine is inhibited by compounds such as cocaine.[338] The ability of cocaine to compete for uptake results in potentiation of adrenergic responses, including the vasoconstriction characteristic of cocaine.

Norepinephrine is metabolized by catechol O-methyltransferase (COMT), which transfers the methyl group of S-adenosylmethionine to the 3-hydroxy group of the catecholamine to form normetanephrine.[25, 31] Extracellular norepinephrine may also be methylated to epinephrine by phenylethanolamine N-methyl transferase,[25] quantitatively a less important conversion (fig. 1). Normetanephrine is further metabolized by oxidative deamination, a reaction catalyzed by monoamine oxidase (MAO), to form 3-methoxy-4-hydroxymandelic acid (vanillylmandelic acid, VMA), which is the main urinary metabolite.

Norepinephrine released intracellularly, either spontaneously or by reserpine compounds, is inactivated principally by oxidation to dihydroxymandelic acid, a reaction catalyzed by MAO. Dihydroxymandelic acid is methylated to VMA, a reaction catalyzed by COMT (fig. 1). The methylation or deamination resulting in the formation of VMA take place within the nervous system, but presumably also in the liver and kidney.

Epinephrine. Epinephrine is subject to disposition by the same routes as norepinephrine: diffusion (more accurately, redistribution: epinephrine is released directly into the circulation from the adrenal medulla); uptake by tissues; and metabolism. Metabolism of epinephrine apparently differs little in route of degradation whether endogenously released,

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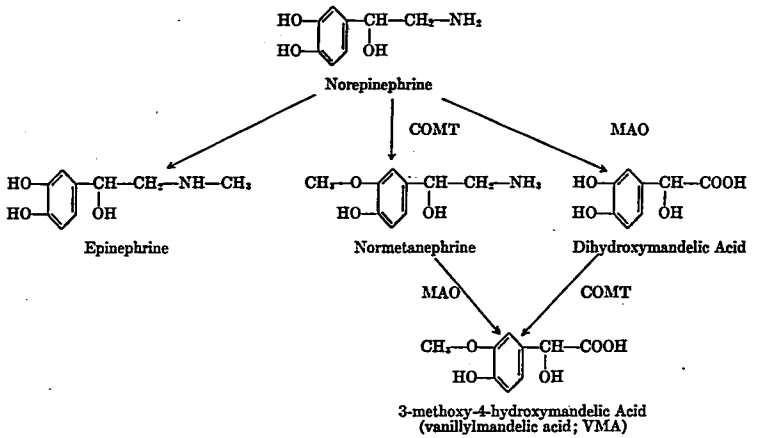


FIG. 1. Major routes of metabolic inactivation of norepinephrine.

exogenously administered, or endogenously produced secondary to methylation of norepinephrine. The three pathways of metabolism (fig. 2) are similar to those of norepinephrine (fig. 1). Methylation to methylepinephrine with phenylethanolamine N-methyl transferase serving as the enzyme is least important; or O-methylation is catalyzed by COMT to produce metanephrine; or, finally, oxidation is catalyzed by MAO to produce dihydroxymandelic acid. Metanephrine and dihydroxymandelic acid are metabolized principally to VMA and excreted. Most exogenous epinephrine undergoes metabolism and is excreted as the free or conjugated form of its products.[219] Within 24 hours of infusion of epinephrine in normal subjects, over 80 per cent is recovered from urine as O-methylated metabolic products, 40 per cent as VMA and 40 per cent as free and conjugated metanephrine. Most of the remaining 20 per cent is excreted as dihydroxymandelic acid and conjugated VMA.[25]

Whereas norepinephrine is released into tissues, epinephrine is released into the circulation so there are quantitative differences in the pathways by which the two are metabolized. Inactivation of circulating epinephrine by COMT-catalyzed O-methylation is more important in inactivation than oxidation by MAO or N-methylation.[160] On the other hand, oxidation of norepinephrine by MAO is quantitatively more important than O-methylation by COMT or N-methylation. Marked variations from species to species and from tissue to tissue make it difficult to determine sites and routes of metabolism. The liver in most mammals, however, contains large amounts of both COMT and MAO; hence it is an active site of metabolism of catecholamines released within the liver and also those delivered to it after release into the circulation at peripheral sites.[166, 174] Decreases in MAO and COMT activity have been observed with cirrhosis.[161]

Blood levels of catecholamines during anesthesia are determined by rates of entry into, and removal from, the vascular system. The ability of tissues to extract norepinephrine depends not only upon delivery of the catecholamine to metabolic sites by blood flow but upon the number of sites available. This in turn is a function of the density of sympathetic nerves. The heart, with a high blood flow and a high concentration of sympathetic nerve endings, accumulates intravenously-administered norepinephrine rapidly, whereas the seminal vesicle, with a high density of sympathetic

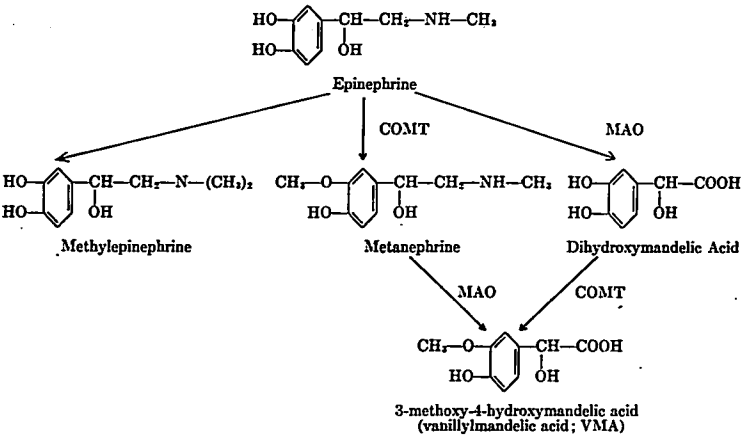


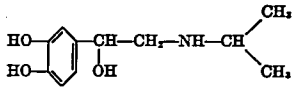
FIG. 2. Metabolic inactivation of epinephrine.

nerve endings but with low blood flow, accumulates less norepinephrine as does the intestine, with high blood flow but low sympathetic nerve content.[214]

Although enzymes are important in defining the metabolic fates of catecholamines, duration of action is influenced primarily by distribution and uptake, not enzymes. Both MAO and COMT, concerned with initial biotransformation, are also active at subsequent stages of metabolism. Metabolites initially formed with MAO as catalyst are further metabolized by COMT, while those formed by the action of COMT are broken down by MAO, with the result that both catecholamines appear in the urine as essentially the same metabolite. Finally, whereas MAO is principally responsible for the initial conversion of catecholamines within tissue,[160] particularly within the central nervous system,[323] COMT is principally responsible for the initial biotransformation of circulating catecholamines.

In clinical concentrations, diethyl ether, cyclopropane, methoxyflurane, and halothane have no effect either on uptake of norepinephrine by nerve endings or on COMT metabolism as judged by their effects on chronotropic response to postganglionic nerve stimulation.[276]

A third catecholamine, isoproterenol (Isuprel), like epinephrine and norepinephrine, is demethylated followed by oxidation, the major



Isoproterenol

urinary metabolites being 3,4-dihydroxymandelic acid and the glucuronide and (probably) sulfate conjugates.[172] However, there is essentially no tissue binding of isoproterenol.[172] The short plasma half-life (about 1.4 minutes) of intravenously-administered isoproterenol is due to rapid tissue distribution, followed by a slower disappearance from plasma owing to metabolism; 20 minutes after injection of labelled drug, less than half of the radioactivity is accounted for as unchanged drug.[244]

Vasoactive synthetic compounds which are not catecholamines include amphetamine, ephedrine, mephentermine (Wyamine), metaraminol (Aramine), phenylephrine (Neo-synephrine), and methoxamine (Vasoxyl).

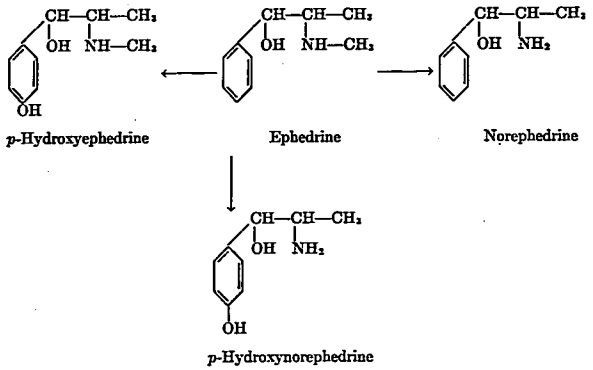
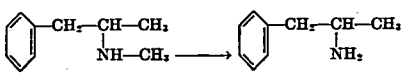
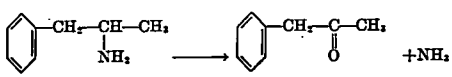


FIG. 3. Metabolic pathways involving L-ephedrine.

Synthetic Vasopressors. Their disposition is primarily metabolic, via N-demethylation, deamination, *p*-hydroxylation, or conjugation.

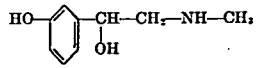
About 60 per cent of L-ephedrine is excreted unchanged in the urine, whereas the remainder (fig. 3) is demethylated to norephedrine, hydroxylated in the *para-* position to hydroxyephedrine, or both hydroxylated and demethylated to hydroxynorephedrine.[13] Demethylation of ephedrine is not catalyzed by MAO. Although the relative importance of demethylation and of hydroxylation varies in metabolic inactivation of vasoactive compounds, demethylation occurs more frequently. In fact, hydroxylation of D-methamphetamine does not occur but instead D-methamphetamine is demethylated to D-amphetamine.[15] Demethylation of ephedrine is catalyzed by hepatic microsomal enzymes which require as cofactors oxygen and NADPH. These enzymes are also responsible for catalyzing the oxidative deamination of amphetamine[14] as well as the demethylation of codeine and side-chain oxidation of barbiturates.[16] The enzyme which deaminates L-amphetamine has, however, no effect upon either D-amphetamine or upon D-ephedrine.[17] About half of a dose of amphetamine is excreted unchanged in the urine.





Phenylephrine can be metabolized in part by hydroxylation to epinephrine, and thence

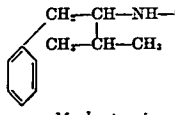
to metanephrine,[29] in a series or reactions un-



Phenylephrine

affected by COMT,[31] though the extent to which this occurs *in vivo* is undetermined.

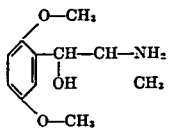
Mephentermine is almost completely metabolized by N-demethylation (nor-mephentermine) and subsequent hydroxylation (*p*-hy-



Mephentermine

droxynormephentermine) [349] in reactions comparable to those in the metabolic conversion of D-methamphetamine.

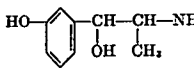
The reviewer has been unable to find data regarding the disposition of methoxamine. On the basis of metabolic conversions involving



Methoxamine

other vasopressors and the longer duration of action of methoxamine, it may be anticipated that its duration of action is governed more by distribution and renal excretion than by metabolism.

Metaraminol, an exception to the general rule that vasopressors are extensively metabolized, resists biotransformation by hepatic en-



Metaraminol

zymes that metabolize comparable substances, including deamination.[166] Distribution and urinary excretion of drug are the principal pathways to disposal. Although it is taken up by tissues and rapidly disappears from liver, metaraminol remains for days in the heart and central nervous system.[321] Unlike many other vasopressors, metaraminol exchanges with norepinephrine on a mole-for-mole basis at nerve endings and is inhibited by and released by compounds which inhibit or release norepinephrine.

Sympatholytics

Little information is available on the metabolic fate of compounds that interfere with sympathetic nervous system activity. The ganglionic blocker hexamethonium, like decamethonium (v.i.), undergoes no biotransformation but in man is excreted unchanged in the urine;[229, 266] duration of action is correspondingly long. The duration of action of the ganglionic blocker trimethapan (Arfonad) is, on the other hand, brief, for undetermined reasons. Approximately 30 per cent of the drug has been recovered within three hours in the urine of patients to whom trimethapan was administered for controlled hypotension.[145] The metabolic fate of the remaining 70 per cent is unknown.

Parasympatholytics

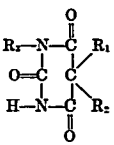
Chief among agents acting upon the parasympathetic nervous system are atropine and scopolamine. Atropine appears to undergo inactivation by a combination of urinary excretion and metabolic transformations which include hydrolysis and glucuronide conjugation, but the details of disposition remain unclear, in part because of pronounced species differences. The serum and liver of the rabbit readily and rapidly hydrolyzes the ester linkage in atropine,[39, 120, 159] which may account for the high tolerance of rabbits to atropine. But while the guinea pig also hydrolyzes atropine,[199] the mouse does not, instead conjugating atropine with glucuronic acid or oxidizing it in an undefined manner.[146] Data concerning disposition of atropine in man are chiefly derived from information obtained in two individuals.[163] In these men about half of the original dose appeared unaltered in the urine and approximately a third as unidentified metabolites, neither glucuronides nor metabolites previously found in rat and mouse. Although the metabolic products of atropine are undefined, in man and experimental animals the kidney eliminates the majority of both altered and unaltered products.[124, 162, 163, 199, 327]

The same uncertainty applies to the fate of scopolamine. Rabbits, though able to hydrolyze atropine, are unable to hydrolyze scopolamine.[39] In man, however, scopolamine probably undergoes extensive biotransformation since it cannot be recovered from the urine in unaltered form.[257]

Barbiturates

In view of a number of excellent reviews of barbiturate metabolism,[239, 247, 252, 296, 316, 359] the present review will be limited to a consideration of pharmacologic principles and chemical reactions, and how they relate to the biologic disposition of a representative selection of barbiturates used in this country.

The effects of barbiturates are significantly affected by their chemical structures, by whether they are oxybarbiturates or thiobarbiturates. Oxybarbiturates have the configuration



where R_1 and R_2 are hydrocarbon side-chains of varying length and complexity, R_3 most often an —H but occasionally a methyl or an ethyl group. Thiobarbiturates have a sulfur substituted for the oxygen atom in the urea portion of the ring:

Metabolic transformation is the chief means of inactivation. Redistribution affects the time of onset and duration of peak effect when oxybarbiturates are administered intravenously, but it plays a minor role in disposition, especially when the drug is administered orally or parenterally. Metabolic alteration results in, first, a marked decrease in pharmacologic activity; and, second, conversion to a more polarized form in which the drug is no longer reabsorbed in the renal tubules: hence, biotransformation facilitates excretion.[247] Although urinary excretion of unaltered barbiturate is insignificant in inactivation, excretion of metabolic products of oxybarbiturates is the principal means for elimination of the products of biotransformation. Urinary excretory mechanisms leave little accumulation of metabolites within the body. Not only is metabolism of the parent compound not inhibited by increasing concentrations of breakdown products, but metabolic pathways are more readily determined by analysis of urinary products than by analysis of blood or tissue.

The only important oxybarbiturate *not* excreted unchanged is barbital (R_1 —CH_2CH_3; R_2 —CH_2CH_3) (Veronal). Although the urinary excretion of unaltered barbital is accepted, less well appreciated is that the ratio of urinary clearance to glomerular filtration rate, about 0.09 in dogs, is the same for all dose levels and is unaffected by changes in urine flow.[155]

The ring structure of barbituric acid derivatives is unaffected by *in vivo* metabolism. Instead, biotransformation involves alteration of side-chain structure by oxidation or by dealkylation. In oxidation, either R_1 or R_2 is involved; never R_3 and never both R_1 and R_2. Dealkylation, on the other hand, usually involves R_3 and not R_1 or R_2. Oxidation of R_1 or R_2 can be to an alcohol, a ketone, or an acid. Many oxybarbiturates used in clinical practice are dialkybarbiturates with R_1 containing four carbon atoms and with R_2 consisting of an ethyl group (e.g., pentobarbital, amobarbital). The —CH_2—CH_3 group in such compounds is stable and is never the primary site of oxidation. If oxidation is ω (terminal), the product is usually a carboxylic acid. Non-terminal oxidations of alkyl groups are, however, more common than ω oxidations with four-carbon-atom chains.[125] Most side-chain oxidations of dialkybarbiturates involve the penultimate ($\omega - 1$) carbon atom.[245, 246, 250, 252] The question arises whether the preferred site of oxidation is the third carbon atom from the barbituric acid ring or the carbon atom next to the end of the chain (the $\omega - 1$ carbon). In studies using hexethal (R_1 —CH_2—CH_3; R_2 —CH_2—CH_2—CH_2—CH_2—CH_2—CH_3) (Ortal), with a side-chain longer than four carbon atoms, Maynert[249] found that 11 metabolites accounted for 48–58 per cent of

the drug administered. The metabolites consisted of $\omega - 1$ alcohol (15 per cent), a $\omega - 1$ ketone (9 per cent), three other alcohols (4.5 per cent), one other ketone (2 per cent), an unidentified barbituric acid with a carboxyl acid group (0.6 per cent), three carboxylic acid metabolites (22 per cent, 4 per cent as ω-carboxy acid, 2 per cent as hydroxy acid, 16 per cent as a β-oxidation product), and a glucuronic acid conjugate (1 per cent). The presence of the four alcoholic and two ketone metabolites indicated that nonterminal oxidation was restricted neither to the third nor to the carbon atom next to the end of the chain, but since the $\omega - 1$ alcohol and ketone made up 24 per cent of the hexethal administered while other alcohols and ketones made up less than 7 per cent, the data suggest that the penultimate ($\omega - 1$) carbon atom is the predominant site of oxidation of barbiturates with a four-carbon-atom side-chain.[53, 249] The formation of a hydroxy acid suggested that alcohols may be intermediates in the β-oxidation of barbiturate carboxylic acids. Furthermore, the formation of ketones during hexethal but not pentobarbital metabolism suggests that barbituric acids are oxidized in this manner only when a hydroxyl group is formed on a carbon atom more than three carbon atoms removed from the barbituric acid ring.

Pentobarbital (R_1 —CH_2—CH_3; R_2 —CH(CH_3)—CH_2—CH_2—CH_3) (Nembutal) is also metabolized by oxidation of the longer of the side-chains, the methylbutyl chain.[52, 240, 250, 253, 254, 335] Essentially all pentobarbital is metabolized, less than one per cent being excreted unchanged in the urine. The principal urinary metabolite in man, the alcohol —CH(CH_3)—CH_2—CH(OH)—CH_3, accounts for 50 per cent of the urinary metabolic products, but a portion of pentobarbital is also metabolized to the corresponding acid[93, 362]: —CH(CH_3)—CH_2—CH_2—COOH. Like many oxybarbiturates, pentobarbital is metabolized in the liver by microsomal enzymes which require NADPH and oxygen as cofactors.[93] It is metabolized more slowly in man than its thio-analogue, thiopental, but in the dog the reverse is true.[52] Despite classification as a "short-acting" barbiturate, pentobarbital is relatively slowly inactivated in man. Metabolites are excreted in urine for five days following the administration of 500 mg.[248]; alterations in mental function persist for 14 hours following administration of 100 mg.[346] Metabolism of pentobarbital is significantly slower in the presence of diethyl ether.[33]

Two other oxybarbiturates with alkyl side chains are secobarbital (R_1 —CH_2—CH=CH_2; R_2 —CH(CH_3)—CH_2—CH_2—CH_3) (Seconal) and amobarbital (R_1 —CH_2—CH_3; R_2 —CH_2—CH_2—CH(CH_3)$_2$) (Amytal). Both undergo penultimate oxidation to an alcohol. Over half of amobarbital administered to man can be recovered from the urine as the alcohol —CH_2—CH_2—COH(CH_3)$_2$.[245, 246] The allyl group of secobarbital is characteristically stable, although double hydroxylation of the allyl group has been reported[347] as one of two metabolites found in the urine, the only reported instance of this type of reaction.

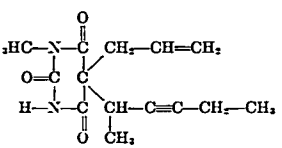
Butethal (R_1 —CH_2—CH_3; R_2 —CH_2—CH_2—CH_2—CH_3) (Neonal) also undergoes penultimate oxidation to an alcohol.[246] On the other hand, butabarbital (R_1 —CH_2—CH_3; R_2 —CH(CH_3)—CH_2—CH_3) (Butisol) is oxidized to the corresponding carboxylic acid,[231] indicating different metabolic pathways for three-carbon-atom and four-carbon-atom side-chains.

The phenyl side-chain of phenobarbital (R_1 —CH_2—CH_3; R_2 —C$_6$H$_5$) (Luminal) is more resistant to transformation than the alkyl chains of pentobarbital, with the result that phenobarbital is more slowly metabolized. Since it is more slowly converted to a polarized form not reabsorbed by renal tubules, a greater proportion is excreted unchanged. Approximately 27 per cent of the radioactivity found in the urine of animals following administration of labelled drug represents unaltered phenobarbital.[156] Most phenobarbital, however, is metabolized and excreted as free *p*-hydroxyphenobarbital (19 per cent) or *p*-hydroxyphenobarbital conjugated with glucuronic

acid (27 per cent).[69, 156] The pK of phenobarbital is such that the amount of drug unionized is significantly altered by changes in *p*H from 7.40, with consequent changes in tissue:plasma distribution coefficients, rate of tubular reabsorption and duration of action.[348] Phenobarbital is normally metabolized and excreted at a rate of approximately 30 per cent per day,[329] so slowly that it is one of the few barbiturates in which a cumulative effect can be observed with chronic administration.[72]

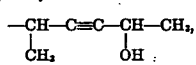
N-methyl-substituted oxybarbiturates (R_3 usually $—CH_3$, less frequently $—CH_2CH_3$) may be inactivated by N-demethylation (or de-ethylation) rather than oxidation of the R_1 or R_2 side-chains, depending upon the specific side-chain. Mephobarbital (N-methyl phenobarbital, Mebaral), is N-demethylated almost completely to phenobarbital, blood levels decreasing as the levels of phenobarbital rise.[67] Similarly, N-ethyl barbital is converted to barbital, N,N'-dimethyl barbital to barbital,[68] and N-methyl butabarbital to butabarbital,[139] but N-propyl barbital in only small amounts to barbital.[68] The enzymes responsible for N-demethylation of barbiturates and other N-substituted compounds[262] are found in the microsomal fraction of liver homogenates with NADPH and oxygen as cofactors.[73, 261, 322] The removal of a $—CH_3$ group by these enzymes probably entails initial hydroxylation of the $—CH_3$ group.[53, 261]

N-demethylation does not occur with the N-substituted barbiturate methohexital (Brevital).[261, 356] Instead, the acetylinic link un-



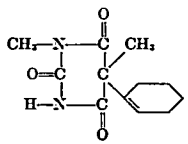
Methohexital

dergoes hydroxylation with formation of



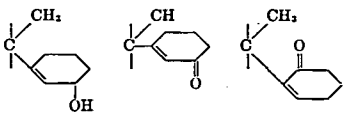
the allyl group remaining unreactive, not undergoing the hydroxylation observed for secobarbital.[347] Subsequent to side-chain oxidation of methohexital, a very small portion of the breakdown product may undergo N-demethylation.[356] The short duration of action of methohexital following intravenous administration is not related to rapid biotransformation but to rapid redistribution.[356] Per hour, 15–19 per cent of methohexital is metabolized, compared to approximately 20 per cent for methitural and 15 per cent for thiopental.[47]

With the N-methylated barbiturate hexobarbital (Evipal), some demethylation occurs,



Hexobarbital

but the susceptibility of the cyclohexenyl side-chain (R_2) to oxidation is greater than the susceptibility of the methyl group (R_3) to demethylation.[84, 261] Hexobarbital is converted *in vivo* primarily to hydrohexobarbital and to one of two keto-hexobarbitals by hepatic enzyme systems.[92] The conversion to hydrohexobarbital is by an NADPH-dependent hepatic



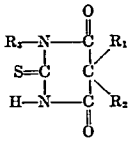
Hydrohexobarbital Keto-hexobarbital Keto-hexobarbital Side-chain Oxidations (R_2) of Hexobarbital

microsomal system requiring oxygen. The derivation of keto-derivatives is not directly from hexobarbital, but is from hydrohexobarbital,[359] a reaction catalyzed by an NAD- or NADP-dependent enzyme in the soluble portion of liver homogenates.[236] The presence of two metabolic products, one derived from the other, and two separate enzyme systems illustrate the complexities encountered in defining metabolic pathways of barbiturates. The relationships between the breakdown products of hexobarbital are further complicated in that the keto-form derived from hydrohexobarbital may be converted to hydrohexobarbital in a reversible

reaction catalyzed by a reduced NAD- or an NADP-enzyme-dependent system.[336] Pretreatment with phenobarbital stimulates to varying degrees all enzymes involved in hexobarbital metabolism. The rate of formation of hydrohexobarbital from hexobarbital is increased 50 per cent by pretreatment, but the rate at which hydrohexobarbital is formed from keto-hexobarbital is increased 150 per cent.[359] Demethylation of the nitrogen atom does not involve unchanged hexobarbital, so that small amounts of keto-norhexobarbital are also excreted.

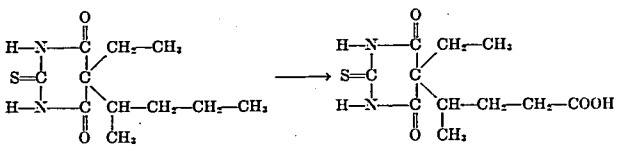
The rate of inactivation of hexobarbital is more rapid than with clinically important barbiturates. Its short action is due primarily to rapid metabolism. This, combined with its oral and parenteral efficacy, makes it an especially useful barbiturate not as widely appreciated in this country as in Europe.

In thiobarbiturates, the results of the substitution of a sulfur atom for the oxygen in the urea portion of the barbituric acid ring of oxybarbiturates are a marked increase in lipid



solubility and a decrease in ionization at *p*H 7.40. Thiobarbiturates cross the blood-brain barrier more rapidly than oxybarbiturates, and blood levels are more affected by redistribution. Metabolism of a thiobarbiturate such as thiopental commences immediately upon intravenous injection and continues as blood levels are altered by redistribution and tissue uptake; although hepatic metabolism has a demonstrable effect on plasma levels immediately after injection,[305] the degree and duration of response to thiopental are functions of tissue uptake and vascular distribution.[294]

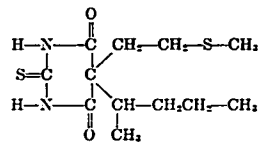
Metabolic inactivation of thiopental is achieved by oxidation to the corresponding carboxylic acid: [49, 57, 240, 362]



Thiopental is metabolized primarily in the liver[241, 317] by microsomal enzymes requiring NADPH and oxygen as cofactors,[93] at the rate of 10 per cent per hour for the first six hours following injection in animals.[317] Since 90 per cent of the drug is metabolized 12 hours after administration,[317] the implication is that the rate of metabolism expressed as per cent of initial dose oxidized increases with time after administration. The rate of metabolism in man is approximately 15 per cent per hour.[57]

It has been suggested that thiopental undergoes some metabolic desulfuration to the oxy-analogue, pentobarbital.[82, 140, 325, 332, 361] While some desulfuration occurs, as in the conversion of thiobarbital to barbital,[65] thiamylal to secobarbital,[325] and thiobutabarbital to butabarbital,[140] so little thiopental is converted to pentobarbital in man that pentobarbital cannot be detected in plasma when thiopental is exerting its maximal therapeutic effect.[144] Even if desulfuration of thiopental occurs, isolation of pentobarbital during thiopental anesthesia is mainly the result of *in vitro* extraction procedures rather than biotransformation.[138, 144] Response to thiopental is determined by redistribution, tissue uptake, and metabolism, and also by a reaction best described as acute tolerance. In this reaction, consciousness is regained following administration of large doses of thiopental at blood levels significantly higher than the blood levels when consciousness is regained following smaller doses.[56, 111, 179]

Methitural (Neraval), also a thiobarbiturate,



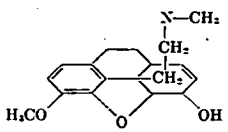
contains a sulfur atom in the R_1 side-chain in addition to the sulfur atom in the barbituric acid ring. Methitural is highly lipid—soluble and is almost completely metabolized in the liver before excretion.[42] Metabolism of methitural is more rapid than that of thiopental.[42, 184] Approximately 20 per cent per hour is metabolized in man.[47] The methyl-butyl side-chain is not the primary site of metabolic degradation: inactivation of methitural is by means of a ketone-like oxidation of the sulfur atom in the R_1 side-chain, to a sulfoxide (—S—).[104] Whether oxidation to a carboxylic

acid also takes place has not been determined.

Narcotics

Studies of the metabolism of narcotics have been characterized by attempts to relate *in vivo* biotransformation to mode of action.[333] Although such studies have failed to establish a relationship between action and metabolic conversion, the attempts have served as a potent stimulus for the development of a great deal of information regarding the biotransformations involved in narcotic disposition.

Codeine is extensively metabolized and excreted in urine, small amounts appearing unaltered. After administration of codeine-N-methyl-C^{14} in man, approximately 76 per cent of the radioactivity appears within 24–30 hours, about 11 per cent unchanged, the rest in the form of metabolites; an additional 7 per cent appears in expired air; only 0.5 per cent appears in feces.[3] Comparable recovery rates follow administration of codeine-3-methoxy-C^{14}.[3] Codeine is metabolized rapidly. Within 15 minutes of intravenous injection of 30 mg. of C^{14}-labelled codeine phosphate, $C^{14}O_2$ can be recovered in exhaled air.[6]



Three pathways are involved in codeine metabolism: N-demethylation to norcodeine, O-demethylation to morphine, and glucuronide formation. Although species differences exist in the amounts metabolized by each route,[6-8, 116, 222, 237, 365, 367] N-demethylation to norcodeine occurs to a greater extent than O-demethylation to morphine. Within 24 hours of administration of 30 mg. of codeine in man, 1.2–4.0 mg. of morphine, 2.2–2.8 mg. of norcodeine, 10.7–11.7 mg. of conjugated codeine, and 1.5–3.7 mg. of unchanged codeine are recovered in the urine.[6]

The demethylation takes place in part in the liver,[8] where two enzyme systems exist for the two types of demethylation reactions.[18, 116] The N-demethylating enzyme is microsomal, requires NADPH and oxygen, converts the methyl group primarily to aldehydes, and is the enzyme responsible for deamination of amphetamine and ephedrine as well as side-chain oxidation of barbiturates. The O-demethylating enzyme has a different cellular localization, different co-factor requirements, and is not involved in barbiturate metabolism. The enzymes responsible for conjugation of codeine with glucuronic acid are also present in hepatic microsomes[28]; the same enzymes are involved in conjugation reactions by which other narcotics (*v.i.*) are inactivated.

Demethylation of codeine also occurs in the central nervous system,[4, 185] where codeine has its principal pharmacologic effect. This has led to the suggestion that codeine exerts its analgesic effect through conversion to metabolic products, particularly morphine. In support of this hypothesis is the observation that analgesia does not begin until O-demethylation to morphine has occurred; furthermore, the concentration of morphine within the central nervous system (of rats) is the same when analgesia is produced by morphine as when equal analgesia is produced by codeine.[185] However, it has also been reported that at peak analgesic effect following administration

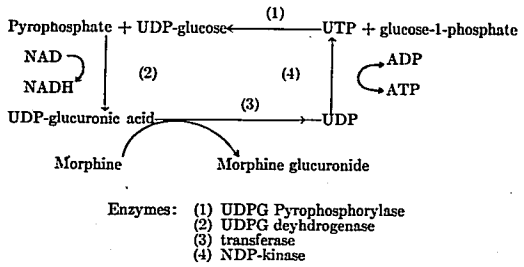
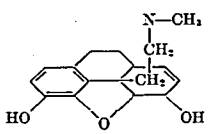


FIG. 4. Morphine glucuronide synthesis. (Adapted with permission from Takemori: J. Pharmacol. Exp. Ther. 130: 370, 1960.)

of codeine-N-C^{14} to rats, no C^{14} present in the cerebral cortex and in the midbrain is in the form of morphine even though within this period (30 minutes) the rat converts codeine to morphine in the liver.[7] Furthermore, if the analgesic effect of codeine were the result of conversion to morphine, nalorphine would be expected to antagonize codeine analgesia to the same extent that it antagonizes that produced by morphine, but nalorphine does not antagonize this effect[4]; therefore, the consensus is that metabolism to morphine is not responsible for the analgesic effect of codeine. The alternative possibility, that the analgesia of codeine is related to conversion to norcodeine, has not undergone comparable investigations, but in mice the intraventricular injection of norcodeine produces analgesia similar to that produced by codeine, also indifferent to antagonism by nalorphine.[4]

Morphine, like codeine, is inactivated largely



in vivo and is excreted in the urine in inactive forms, only small amounts of free drug being recovered. The two major pathways by which morphine is metabolized are N-demethylation and conjugation. The main urinary form of morphine is a glucuronide conjugate. Conjugation of morphine with glucuronic acid[28, 40, 143, 168, 33, 363, 369] takes place within the liver. The glucuronide is then excreted in bile or urine by glomerular filtration, not by tubular excretion.[34] Depending upon the species, 80–90 per cent of morphine administered is excreted in the urine, approximately 10–15 per cent as unaltered drug, 15–30 per cent as the glucuronic acid conjugate, the remainder as complex, poorly-defined metabolites.[5, 119, 264, 272] Up to 6 per cent is excreted as carbon dioxide in exhaled air and up to 10 per cent in feces.[119] Fecal excretion probably represents morphine originally conjugated in the liver and excreted in bile, with later hydrolysis of the conjugate within the gastrointestinal tract, some of the drug hydrolyzed then excreted in the feces and some reabsorbed into the enterohepatic circulation.[238]

Although more than one form of morphine conjugation is possible, present evidence indicates only one form that occurs to any extent, the monoglucuronides.[5, 143, 191, 272, 312, 363] The synthesis of glucuronides (fig. 4) takes place in the liver, involving UDP-glucuronic acid formation from UDP-glucose, the glucuronic moiety then transferred to form morphine glucuronide and free UDP, the former excreted and the latter available to combine with more glucose to form UDP-glucose.[330]

A portion of morphine is N-demethylated[19, 20, 119, 238, 267–272] to normorphine and formaldehyde in a reaction catalyzed by the hepatic microsomal enzyme concerned in the N-demethylation of other narcotics in the presence

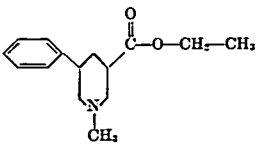
of NADPH and oxygen as co-factors.[19] The formation of normorphine from morphine is a reversible reaction. Morphine can be synthesized *in vivo* and *in vitro* from normorphine in both brain and liver.[23, 76, 77, 80] Similar methylation involving nor-derivatives of meperidine, codeine, and nicotine also occurs, representing the general reaction involving N-methyl transferase, which catalyzes transfer of methyl groups from S-adenosylmethionine to nor-compounds.[80]

It was hypothesized that demethylation (or dealkylation) of narcotics to nor-derivatives is the first step whereby narcotics produce their analgesic effect, analgesia resulting from the cellular actions of the nor-compounds rather than the parent drug.[37] This theory received support from the observation that N-demethylation occurs not only in the liver but also in the central nervous system where morphine exerts its main pharmacologic effects.[115, 267–269] In addition, narcotic antagonists such as nalorphine[26, 117] and levallorphan[331] inhibit N-demethylation of morphine and antagonize analgesia. However, this theory has been abandoned.[353] The ease with which the product of demethylation, the nor-derivative, is remethylated to the parent narcotic compound indicates that the analgesic role of nor-compounds is unlikely. Furthermore, in animals analgesia cannot be related to central nervous system concentrations of nor-derivatives. The concentration of nor-morphine in the brain of an animal to whom nor-morphine has been administered is four to five times higher than the concentration in an animal made equally analgesic by morphine.[185] In addition, no parallel exists between narcotic potency and extent of demethylation.[117, 118] Both meperidine and codeine are demethylated to a greater extent than morphine, yet the latter is a more potent analgesic. Finally, though nalorphine inhibits N-demethylation of morphine, its ability to do so is not related to antagonism of morphine-induced respiratory depression.

The development of tolerance to narcotics has been thought related to metabolic transformation. Specifically, it was proposed that tolerance is due to impaired ability of the organism to N-demethylate morphine.[20] Although early data supported such a possibility, recent experiments indicate that the theory is untenable. For example, no correlation exists[117, 353] between susceptibility of narcotics to enzymatic action and analgesic potency, a relationship which would be expected if the decrease in potency in tolerant organisms were due to impaired metabolism. Livers obtained from tolerant animals are less able to N-demethylate narcotics *in vitro* than those from non-tolerant animals; this is not true of central nervous system tissue. The ability of brain slices to N-demethylate morphine is the same in tolerant animals as it is in non-tolerant controls.[115] The impaired ability of livers from tolerant animals to demethylate morphine is better ascribed to a decreased hepatic concentration of the enzymes than to altered enzymatic specificity.[117] Although the hepatic enzymes involved in demethylation of morphine are decreased in the tolerant state, the result is alteration in rate of demethylation and not alteration of the ultimate fate of morphine which is unchanged in tolerant animals.[363]

Some O-methylation of morphine to form codeine also takes place in animals both *in vivo* and *in vitro*.[116] The reaction is reversible; morphine is synthesized by biologic O-methylation of codeine.[6]

Meperidine (Demerol), like morphine, is largely excreted in inactive forms. Only about 5 per cent of meperidine administered to man

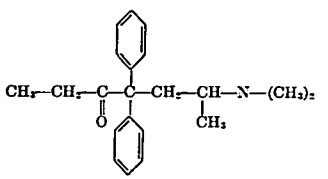


Meperidine

is excreted unchanged, the remainder undergoing H-demethylation to nor-meperidine, de-esterification to meperidinic or nor-meperidinic acid, or conjugation, presumably with glucuronic acid.[61, 230, 288–290] Inactivation of meperidine by demethylation is not as important as is de-esterification, whereas conjugation involves both meperidine and the demethylated product. Thus of 60 per cent of the meperidine administered to man which may be recovered, about 5 per cent is unchanged, 5 per cent nor-

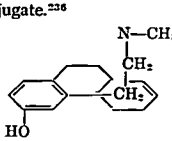
meperidine, 20 per cent meperidinic acid, 7 per cent nor-meperidinic acid, 12 per cent bound meperidine, and 12 per cent bound normeperidine.[290] The fate of the remaining 40 per cent is undetermined. The rate of biotransformation in man ranges from 10 to 20 per cent per hour and is the same in tolerant as in non-tolerant subjects.[61] N-demethylation occurs in the liver and requires microsomal enzymes together with NADPH and oxygen.[19, 117] De-esterification also takes place in the liver, and to some extent in blood and renal tissue.[288] Only the intact meperidine molecule can be metabolized by the liver, subsequent demethylation of the de-esterified molecule or subsequent de-esterification of the demethylated molecule occurring to come extent in extrahepatic tissues.[288]

Methadone (Dolophine, Amidone) is almost completely metabolized, little drug being excreted unaltered.[355] Methadone is primarily N-demethylated by hepatic microsomal enzymes.[19, 117, 308]



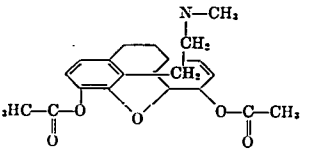
Methadone

Levo-dromoran (Levorphanol) has a plasma half-life of about 75–90 minutes.[364] Only 2 to 5 per cent of the drug is excreted in the free form, approximately 40 per cent as a urinary conjugate.[236]



Dihydromorphinone (Dilaudid) has the same molecular structure as morphine except for an added —OH group, and undergoes essentially the same fate.[180] The metabolic fate of *methyldihydromorphinone* (Metopon) has not been elucidated, but, based upon metabolic pathways affecting other narcotics, demethylation may be involved.

Diacetylmorphine (heroin; Heroine) is rapidly and completely metabolized.[280] Plasma half-life is 2.5 minutes.[354] Metabolism is by

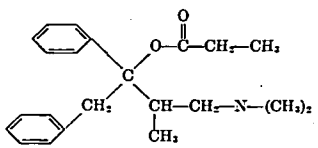


Diacetylmorphine

deacetylation to 6-monoacetylmorphine and morphine, and, except for a brief period following administration, it is to these two metabolites that heroin owes its effects.[354]

Anileridine (Leritine) is a congener of meperidine which undergoes conversion to normeperidine either directly by dealkylation or indirectly following initial acetylation,[232] though small amounts may be oxidized and excreted as anileridinic acid.[291] *Alphapropidine* (Nisentil), also a meperidine congener, probably undergoes similar metabolism.

The analgesic compound *propoxyphene* (Darvon) is an instance in which N-demethylation is prominent in inactivation, although only one methyl group is removed.[223] Only approximately 10 per cent of the drug is recovered unaltered from the urine.



Propoxyphene

It has been suggested that *phenazocine* (Prinadol) is biotransformed by conversion to a catechol, which in turn is O-methylated.[29]

The narcotic antagonist *nalorphine* (Nalline) is inactivated almost entirely by conjugation with glucuronic acid in the liver,[28, 182, 366] although a small amount is dealkylated to normorphine by hepatic microsomal enzymes.[27, 267–269] The rate of conjugation is such that *in vivo* most is in the bound form, although, like other narcotics undergoing conjugation, it enters and leaves the central nervous system as the free drug.[182] The rate of inactivation

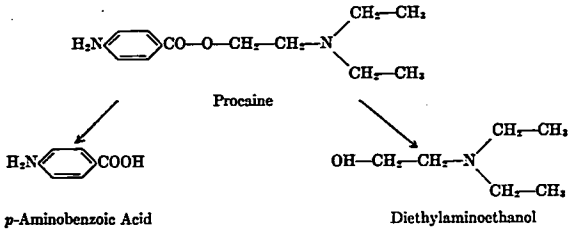
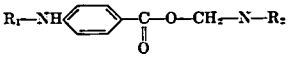


FIG. 5. Procaine hydrolysis, an example of metabolism of ester-type local anesthetics.

of nalorphine is greater than that of morphine. About 75 per cent added to liver slices is conjugated within 2.5 hours [312]; thus, the antagonism produced by nalorphine may wear off before the narcotic which it has antagonized has been inactivated metabolically. Nalorphine inhibits enzymatic demethylation of morphine, methadone, meperidine, heroin, and codeine, but this effect is not related to its ability to antagonize narcotics. Nalorphine has no effect on the rate of inactivation of narcotics by conjugation.

LOCAL ANESTHETICS

Local anesthetic agents can be divided on the basis of molecular configuration into two groups. The metabolic means by which they are inactivated are determined to a large extent by structure. One category carries an ester linkage in the intermediate chain between the amino group and the aromatic ring:



Examples of this type are cocaine, procaine (Novocaine), tetracaine (Pontocaine), piperocaine (Metycaine), chloroprocaine (Nesacaine), and hexylcaine (Cyclaine). The second group includes amides with a variety of different linkages between the amino group and the aromatic residue. Examples include lidocaine (Xylocaine), dibucaine (Nupercaine), and mepivacaine (Carbocaine).

Local anesthetics of the ester group are inactivated by hydrolysis. Typical of this is the fate of procaine (fig. 5).[55, 212] Depending upon species and the local anesthetic, hydrolysis may occur primarily in the liver or in plasma, although some hydrolysis takes place in both areas. The enzyme catalyzing the hydrolysis is a cholinesterase which in plasma is the pseudocholinesterase involved in metabolism of succinylcholine. In man procaine is metabolized mainly in plasma, only slightly in the liver, whereas cocaine is metabolized primarily in the liver, only slightly in plasma. In other species, however, the rate of hydrolysis of procaine by plasma cholinesterase may be lower than in man [12]; in the dog, the majority of procaine is metabolized in the liver.[357] In addition to species-dependence, the rate of metabolism is affected by *p*H and temperature.[334] Ester-type local anesthetics other than procaine may also be hydrolyzed by plasma cholinesterase, but at slower rates (*e.g.*, teracaine [121, 190]; still other ester-types are metabolized only slightly by plasma enzymes in man. The majority of piperocaine, for example, is inactivated in man in the liver. As a rule, esters of *p*-aminobenzoic acid (procaine, tetracaine) are more susceptible to metabolism in plasma in man than to metabolism by hepatic tissue, whereas esters of other acids (cocaine, piperocaine) have a greater tendency to be metabolized by the liver. Halogenation of local anesthetics also alters the rate of hydrolysis, though it rarely affects the site. Halogenation on the 2 position of the benzene ring of esters of *p*-aminobenzoic acid increases the rate of metabolism, substitution with chlorine increasing the rate more than substitution with fluorine, though fluorine has a greater effect than bromine.[129] However, because of

species differences in sites, and rates, attempts to make generalizations based upon studies of a limited number of local anesthetics are usually of limited value. Furthermore, although the rate of removal of local anesthetics from the vascular system is a major determinant of systemic toxicity, the rate of metabolism is but one, and not the only, determinant of the rate of removal from blood. Ninety per cent of the lidocaine administered intravenously to animals is removed from the circulation within an hour.[328] This is comparable to the rate at which procaine is removed following intravenous injection, even though lidocaine is not significantly metabolized in blood. Lidocaine is removed rapidly from blood because of high lipid solubility and entry into tissue at rates which do not apply to procaine. A half hour after intravenous administration of lidocaine, 33–36 per cent can be recovered from tissues, but only 18–20 per cent of procaine administered can be recovered at the same time.[328]

Since plasma pseudocholinesterase metabolizes certain local anesthetic agents as well as succinylcholine, the individual who has an atypical form of pseudocholinesterase not only will be unable to metabolize the neuromuscular blocks, leading to prolonged apnea, but will also be unable to metabolize local anesthetics at normal rates, and may show unexpected systemic toxicity.[102] In all 16 patients examined by Foldes, *et al.*,[130] who had atypical forms of pseudocholinesterase, the rate of hydrolysis was prolonged for all substrates tested (acetylcholine, butyrylcholine, benzoylcholine, succinylcholine, and procaine), but the impairment of procaine hydrolysis was greatest, and there were five patients whose plasma did not hydrolyze procaine at all. In such a patient, the potential toxic effects of procaine can be avoided by the use of lidocaine, which is not metabolized by pseudocholinesterase.

Lidocaine, an amide, is primarily metabolized in the liver by microsomal enzymes with reduced NADP and oxygen.[176, 177, 259, 328] The first step in the inactivation of diethyl glycine-2,6-xylidine (lidocaine) is either oxidation to monoethylglycinexylidine with subsequent hydrolysis to xylidine and monoethylglycine,[176 177] or hydrolysis followed by oxidation prior to sulfate conjugation.[328]

Drugs Affecting Neuromuscular Function

Neuromuscular blocking agents can be divided into three categories according to mechanism of inactivation: compounds excreted in the urine entirely unchanged; neuromuscular blockers entirely metabolized; and muscle relaxants partially metabolized and partially excreted.

Gallamine (Flaxedil) and decamethonium (Syncurine) are muscle relaxants which undergo no metabolism and are excreted in the urine.[275, 284] Although serial determinations of plasma levels of these compounds have not been done following intravenous administration, a rapid initial decrease in plasma concentration would be expected, owing to redistribution followed by a more gradual decline as the compounds undergo excretion.

d-tubocurarine, the most widely employed of the curare group of neuromuscular blockers, is inactivated by a combination of renal excretion and metabolism. The amount of *d*-tubocurarine inactivated by biotransformation depends upon the species, not taking place in the dog [93] or cat.[352] In man, however, metabolism of *d*-tubocurarine [83, 225] may involve as much as two-thirds of the amount administered,[191] though the site of detoxification and the biochemical reactions involved are unknown.

Metabolism of *d*-tubocurarine is, however, of negligible significance in determining the degree and duration of response to intravenously administered drug, as compared to redistribution.[83, 84, 93, 193] As Cohen, *et al.*,[83] emphasized in their analysis based upon a nine-compartment analog model, the distribution of intravenously administered *d*-tubocurarine consists of three phases. The first is a rapid decrease in plasma concentration owing to redistribution within extracellular fluid and establishment of an equilibrium between drug in solution and drug bound to plasma protein. The initial decrease is so great that the plasma half-life is only 7 minutes. The protein binding involves albumin, gamma-globulin, and other protein fractions including fibrinogen. The degree of binding may vary from patient to patient.[9, 83] The second phase of distribution has a half-life of about 45 minutes, representing disappearance of drug from extracellular

fluid as urinary excretion and further distribution to tissues with low blood flows. The third and final phase is more prolonged and more gradual than the second. Lasting approximately two hours, it represents destruction and excretion of the drug, recent experiments with labelled drug indicating that excretion is the more important.[82a] The duration of action therefore is determined initially by protein binding and redistribution, with excretion important thereafter. The rate of excretion is such that one hour after intravenous injection approximately 30 per cent can be recovered in urine, 50 per cent is recoverable after two hours, 65 per cent after three, and 75 per cent after four hours.[98] The importance of renal excretion in limiting duration of action is shown in a nephrectomized animal where the drug disappears at a normal rate from the plasma during phases one and three, but phase two may be eliminated.[83] Determinants of response to *d*-tubucurarine may be altered further by alterations in *p*H influencing not only degree of ionization but also response at the neuromyal junction.[192, 209, 287]

The significance of the mechanisms for disposition of *d*-tubocurarine is twofold. First, phases two and three are so long, detectable plasma levels being present for as long as 15 hours following intravenous injection of the drug,[98] that a cumulative effect may occur following repeated injection. Second, with inadequate urinary flow owing to dehydration, renal disease, shock, etc., plasma levels of *d*-tubocurarine may be maintained at effective concentrations for periods well in excess of the normal duration. Prolongation of plasma levels may result in no gross ventilatory change but with enough neuromuscular blockage so that alveolar gas exchange is inadequate and the patient is unable to overcome otherwise trivial airway obstruction. One hour following intravenous administration to a normal man of 0.1 mg. *d*-tubocurarine per pound of body weight, respiratory activity apparently has returned to normal, yet 25 per cent of the original dose of *d*-tubocurarine still may be present in the plasma.[84]

Succinyldicholine is metabolized readily and completely. The enzyme responsible, plasma pseudocholinesterase, hydrolyzes succinyldicholine to succinylmonocholine and choline, the succinylmonocholine subsequently being broken down further to succinic acid and choline in a reaction also catalyzed by pseudocholinesterase.[158, 339, 358] Hydrolysis to succinic acid is slower than hydrolysis of succinyldicholine to succinylmonocholine. Accumulation of succinylmonocholine, therefore, may occur if succinyldicholine is administered by intravenous infusion for prolonged periods. Since succinylmonocholine possesses neuromuscular blocking properties approximately one-twentieth those of succinyldicholine on a mg/kg body weight basis, prolonged impairment of neuromuscular function can result.

The rate of hydrolysis of succinyldicholine depends upon the amount of pseudocholinesterase in plasma and its activity. In the presence of liver disease synthesis of pseudocholinesterase may be impaired to the extent that plasma levels can no longer hydrolyze succinyldicholine at normal rates, resulting in prolonged apnea. The considerable hepatic damage necessary to decrease plasma pseudocholinesterase to the point where clinically significant prolongation of paralysis occurred would be associated with obvious derangement of other functions of the liver. Attempts to correlate low pseudocholinesterase levels with duration of neuromuscular blockade have not been successful; there is doubt that hepatic damage causes prolonged apnea for this reason. On the other hand, precise quantitation of the relationship between abnormal forms of pseudocholinesterase and prolonged apnea has been achieved.[196] Approximately one of 2500–3000 persons has atypical pseudocholinesterase, present in normal amounts but incapable of hydrolyzing succinyldicholine and other esters. Atypical pseudocholinesterase is identified by measuring the extent to which dibucaine (Nupercaine) inhibits the enzymatic hydrolysis of benzoylcholine by the subject's plasma cholinesterase. The dibucaine number calculated is approximately 80 per cent in normal individuals and 16 per cent in persons with atypical pseudocholinesterase.[102, 123, 195, 197] The atypical form is transferred genetically.[123, 194, 273] Prolonged apnea more often results from succinylcholine administration with atypical cholinesterase than from inadequate circulating

levels of the enzyme, but prolonged apnea resulting from either is rare indeed. Prolonged apnea following succinylcholine administration usually results from nonenzymatic causes.

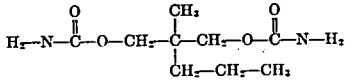
The fate of neuromuscular blockers other than succinyldicholine and *d*-tubocurarine has not been investigated thoroughly. No information is available regarding the fate of laudexium methylsulfate (Laudolissin). Dimethyl tubocurarine (Metubine) in man undergoes the same disposition as *d*-tubocurarine except that it is excreted faster, 55 per cent appearing in the urine within two hours.[242] Mephenesin, acting upon the central nervous system rather than the neuromyal junction, is metabolized completely following oral administration in man, about 28 per cent appearing in the urine in an oxidized form as a lactate.[300] Zoxazolamine (Flexin), another centrally-acting muscle relaxant, is chiefly hydroxylated on the benzene ring by hepatic microsomal enzymes requiring NADP, with excretion of resulting hydroxyzoxazolamine in conjugation with glucuronic acid. A second pathway is hydroxylation of the amino group.[91]

Drugs employed in anesthesia to antagonize nondepolarizing neuromuscular blockers include anticholinesterases such as neostigmine (Prostigmin). The majority of parenterally-administered neostigmine is excreted rapidly in urine. Approximately 40–60 per cent appears unaltered within an hour,[41, 279] another 12 per cent appearing as a metabolite of the product of hepatic disruption of the ester linkage. The metabolic fate of edrophonium (Tensilon) has not been reported.

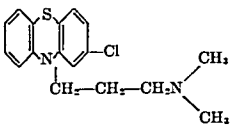
Tranquilizers

Most tranquilizers are carbamates or phenothiazine derivatives. Representative of the former is meprobamate, of the latter, chlorpromazine.

Meprobamate (Miltown) and meprobamate-like drugs differ from N-methyl carbamates such as neostigmine and certain insecticides in that the ester group is stable *in vivo*. Meprobamate metabolism involves, therefore, other portions of the molecule. These metabolic reactions are two [350]: oxidation to an alcohol and glucuronide formation. Approximately 60 per cent of meprobamate administered can be recovered in urine as the inactive 2-hydroxymethyl derivative.[121, 233, 350] The glucuronide, N-glucuronide, is unusual in that meprobamate does not have the molecular configuration usually associated with such conjugation.[233]



Meprobamate



Chlorpromazine

Chlorpromazine, like many other phenothiazines, is subject to many metabolic transformations; over 20 metabolites have been identified. The accuracy of defining pathways of breakdown and determining their significance is complicated in man by the fact that although urinary metabolites are obtained readily, there is evidence that the biliary system is the major excretory pathway.[359] Finally, the initial biochemical reactions often result in formation of compounds which in turn are further metabolized before excretion, confusing the interpretation of inactivation mechanisms based upon analysis of urinary metabolites.

Although details of chlorpromazine detoxification are subject to interpretation, it is agreed that in man metabolism includes eight different pathways [36, 126, 127, 154, 170, 186, 306]: *1*) Oxidation of the sulfur atom to a sulfoxide or, to a lesser extent, to a sulfone. The sulfoxide derivative is a weak, short-acting sedative, but it is doubtful that it contributes to the effect of the parent compound.[101] *2*) Dealkylation involving removal of the dimethylaminopropyl group. *3*) Dealkylation of one or both terminal methyl groups, the mono- or di-demethylated derivatives then being excreted as such or hydroxylated, the hydroxy compounds in turn conjugated with glucuronic acid or, to a lesser extent, with sulfate prior to excretion.[36] *4*) Demethylation plus sulfoxide formation. *5*) Conjugation of the unaltered chlorprom-

azine molecule with glucuronic acid. 6) Oxidation of the terminal dimethylamino group to an N-oxide. 7) Hydroxylation of the ring at one of the seven possible positions, followed by conjugation with glucuronic acid or sulfate. 8) Excretion of unchanged chlorpromazine. Metabolic cleavage of the central ring to diphenylamines does not occur. Although the percentage of chlorpromazine metabolized along each of the pathways varies from one report to another, the major metabolites are chlorpromazine-N-oxide, chlorpromazine sulfoxide, demethylated chlorpromazine, demethylated chlorpromazine sulfoxide, unchanged chlorpromazine, and glucuronides of these metabolites. The site of degradation and the enzymes concerned are incompletely defined, but sulfoxidation of chlorpromazine involves hepatic enzymes with NADPH and oxygen as cofactors[254]; presumably most of the other transformations also take place in liver.

The inactivation of other phenothiazines involves reactions comparable to those of chlorpromazine. Promazine, mepazine, and thioridazine (Mellaril) are oxidized to sulfoxides and, in the case of thioridazine, to a disulfone.[36, 126, 351, 370] Promazine also undergoes N-dealkylation with removal of the dimethylaminopropyl group to form phenothiazine, with excretion of phenothiazine or its breakdown product, phenothiazine sulfoxide.[126] Compounds such as promazine and thioridazine also undergo N-demethylation and glucuronide formation.[351, 370]

Inhalation Anesthetics

Until recently, inhalation anesthetics, with the notable exception of trichloroethylene, have been regarded as chemically stable compounds excreted unchanged by the lungs. Recent evidence obtained by Van Dyke, Chenoweth, and their associates indicates, however, that many inhalation anesthetics are unstable and do in fact undergo biotransformation. These involve only hydrocarbon anesthetics. Nitrous oxide, xenon and other inorganic compounds which exert a depressant effect upon the central nervous system have not been shown to undergo chemical alteration *in vivo*.

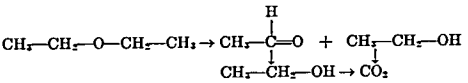
Those inhalation anesthetics reported to undergo the greatest degree of metabolism are the ethers and halogenated hydrocarbons. Cyclopropane and ethylene are said to be metabolized to some extent *in vivo*,[343] but the extent is not easily determined because of problems associated with administration and precise recovery of gaseous anesthetics. Similar methodological problems make for difficulty in accurate measurement of the amount of a volatile liquid which undergoes metabolism. Although the controlled administration of halothane can be accomplished with greater accuracy in experimental animals than administration of cyclopropane, because halothane can be injected or instillated in liquid form, precise determination of the percentage of halothane metabolized presents major problems. Even with data obtained from the experimental animal, their application to the clinical situation is complex, since the amount and duration of exposure to the anesthetic are so different following its single parenteral administration and following inhalation. For these reasons, data on the metabolism of inhalation anesthetics have primarily qualitative significance. It is easier to prove that halothane is metabolized than to determine the percentage of biotransformation following inhalation. In general, however, in animals approximately 1.5 to 12 per cent of the amount of anesthetic administered intraperitoneally or by intragastric instillation is metabolized, although recently it has been reported that as much as 20 per cent of the halothane clinically administered is metabolized.[296a]

One of two types of chemical reactions that affect inhalation anesthetics is dehalogenation. Most susceptible to removal is chlorine. The carbon-fluorine bond in halothane, for example, is not as easily broken as the carbon-chlorine bond, little or no cleavage of the carbon-fluorine bond occurring with fluroxene (trifluoroethylvinyl ether, Fluoromar).[343] That dechlorination occurs *in vivo* has been known for some time, as demonstrated by the recovery of small amounts of chloroform ($CHCl_3$) in expired air of dogs to whom carbon tetrachloride (CCl_4) has been administered. It is also known that *in vitro* CCl_4 can be converted to $CHCl_3$ by mouse liver, heart and kidney.[70] Similarly, 4 to 5 per cent of ^{14}C-labelled chloroform has been recovered as $^{14}CO_2$.[285, 345]

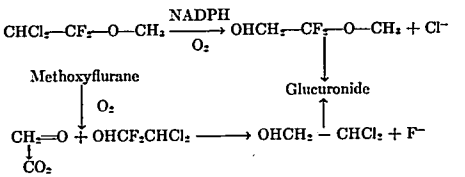
Only recently has it become evident that similar reactions affect chlorinated inhalation anesthetic agents. Thus, following the injection of ^{36}Cl-labelled halothane in animals, 2.9 per cent is recovered in the urine in the form of radioactive nonvolatile compounds[345] recently identified as principally the glucuronide conjugate of CF_3CH_2OH[341] resulting from dechlorination and hydrolysis of the parent molecule. Urinary excretion of ^{36}Cl continues for long periods, ^{36}Cl appearing in the urine for 14 days after two hours of administration of ^{36}Cl-labelled halothane.[345] *In vitro* studies show that halothane is enzymatically dechlorinated by hepatic microsomal enzyme systems[340, 342] which require reduced NADP and oxygen as cofactors.

In addition to dehalogenation, inhalation anesthetics may be metabolized by cleavage of ether linkages and splitting off of carbon atoms. The removal of carbon atoms from anesthetics which do not contain the ether linkage is exemplified by recovery as expired CO_2 of 0.84 per cent of the radioactivity when halothane-1-^{14}C is administered to animals, another 1.5 per cent being recovered in the urine in the form of nonvolatile compounds.[344] When diethyl ether is administered, 4 per cent of the radioactivity administered as the 1-^{14}C-labelled compound is recoverable as $^{14}CO_2$ over 24 hours, another 2 per cent in the urine as nonvolatile compounds.[345] Such findings do not prove that the ether linkage has been broken, but recovery as expired $^{14}CO_2$ of up to 2 per cent of the radioactivity following exposure to methoxyflurane labelled with ^{14}C in the methoxy position, together with another 5 per cent recovered in urine,[345] indicates that the ether bond of methoxyflurane is susceptible to cleavage.

The cleavage of the ether linkage of methoxyflurane, like the cleavage observed in metabolism of analgesics (*v.s.*), is accomplished by hepatic enzymes.[340] Differences in rate of metabolism and sensitivity to substrate concentration indicate, however, that the pathway of metabolism involving ether-cleavage of methoxyflurane differs from that involving dechlorination.[342] Cleavage of the ether linkage of anesthetics probably is accomplished by addition of an hydroxyl group to form ethanol and acetaldehyde:

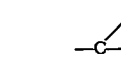


A halogenated ether such as methoxyflurane is susceptible to two types of biotransformation: dehalogenation and ether cleavage. Approximately 1.1 per cent of ^{36}C-labelled methoxyflurane administered to animals can be recovered from urine[345] as nonvolatile compounds, chiefly as the glucuronide of CH_2OH–$CHCl_2$[341] resulting from NADPH-O_2-stimulated microsomal defluorination of the parent compound. The two types of reactions may be summarized as follows:



Metabolism of trichloroethylene differs from that of other inhalation anesthetics in that it is significantly greater in extent and involves neither dehalogenation nor removal of carbon

atoms but rather relocation of chlorine atoms within the molecule and oxidation.[103] Approximately 20 per cent of trichloroethylene administered in the course of an anesthetic is metabolized, roughly 10 per cent to trichloroethanol and 10 per cent to trichloracetic acid.[25, 66, 85, 132, 149, 292, 315] The rate of conversion is extremely slow, metabolic products being found in the urine from 10 to 18 days following one period of trichloroethylene administration.[100, 256] The translocation of chlorine atoms, with the result that CCl_3CH_2OH and CCl_3COOH are formed from $CCl_2{=}CHCl$, is biochemically unusual. It is accomplished by a complex series of reactions including initial conversion of the ethylene linkage to a



linkage. Trichloroethanol and trichloracetic acid are derived in parallel from a common precursor, the alcohol not serving as a precursor for the acid.[100] It should be noted that trichloroethanol derived from metabolism of trichloroethylene is different structurally from trichloroethanol resulting from metabolism of chloral hydrate. In the former, all three Cl atoms are attached to a common carbon atom, whereas in the latter the Cl atoms are attached to both.

The clinical implications of the metabolism of inhalation anesthetics, with the exception of trichloroethylene, are more speculative than factual. The significance of the metabolism of trichloroethylene is twofold: first, it is metabolized in significant amounts to trichloroethanol, itself a central nervous system depressant; second, the rate of metabolism of trichloroethylene to trichloroethanol and the rate of excretion of trichloroethanol are measured in terms of days rather than hours. The result is that trichloroethylene anesthesia can be associated with a cumulative effect unlike that of any other anesthetic. This can result in depression of the central nervous system prolonged well beyond the period of administration especially if trichloroethylene is administered continuously for long periods to the same individual or administered repetitively at intervals of several days to the same patient.

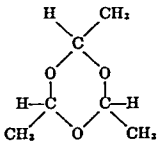
The significance of the metabolism of other inhalation anesthetics is less clear. There are three possibilities of clinical significance. First, the metabolic products may be toxic, of special concern in relation to the development of hepatic damage following halothane, particularly following repeated administration. Van Dyke[340] has stated, however, that the end products of metabolism of halogenated anesthetics mentioned above are nontoxic, although the lack of toxicity does not necessarily apply to the intermediate products of metabolism.[340] Second, although the degree to which inhalation anesthetics are metabolized is probably not enough to alter depth of anesthesia under clinical conditions, the rate of excretion of breakdown products is so much slower than the rate of elimination of the anesthetic via the lungs that the effects of the metabolites might extend far into the postanesthetic period. Third, enzymes responsible for metabolism of inhalation anesthetics are susceptible to induction not only by other compounds but also in themselves (self-induction). Pretreatment of rats with phenobarbital increases activity of the methoxyflurane ether-cleaving enzyme as well as activity of the enzymes involved in dechlorination of halothane and methoxyflurane.[340] Furthermore, exposure of rats to methoxyflurane increases activity of the methoxyflurane dechlorinating enzyme, with no effect on the ether-cleaving enzyme, so that upon subsequent exposure progressively larger amounts of the anesthetic are metabolized.[340] Enzyme self-induction becomes apparent only after animals have been exposed to methoxyflurane seven hours per day for ten days, but such observations raise the possibility of significant interactions between anesthetics and other drugs and interactions resulting from repeated administration of anesthesia to the same subject. In this connection, the increase in activity of certain hepatic enzymes following repeated exposure of animals to halothane[310] involves mitochondrial enzymes, a response different from that observed with enzyme induction as usually defined, which involves changes in endoplasmic reticulum and microsomal enzymes rather than in mitochondrial enzymes.

Miscellaneous Compounds

Chloral hydrate ($CCl_3CH(OH)_2$), like trichloroethylene, is metabolized to trichloro-

ethanol and trichloracetic acid.[157] Unlike trichloroethylene, however, metabolism of chloral hydrate does not entail intramolecular translocation of chlorine atoms. As with trichloroethylene, the formation of trichloroethanol and trichloracetic acid following administration of chloral hydrate is the results of metabolism of chloral hydrate, the trichloracetic acid not being the result of oxidation of trichloroethanol. The enzyme which catalyzes oxidation of chloral hydrate to trichoracetic acid is found in liver and is NAD-dependent,[94] whereas the hepatic enzyme involved in metabolism to trichloroethanol is catalyzed by an NADH-dependent alcohol dehydrogenase,[142] a portion of the resulting alcohol then being conjugated with glucuronic acid and excreted as the glucuronide. The relationship between the hypnotic effect of chloral hydrate and its metabolic conversion to metabolites, one a central nervous system depressant,[157, 243, 281] has been discussed earlier. This may be summarized by saying that while a considerable portion of the effect of chloral hydrate is ascribable to the action of its metabolite, trichloroethanol, the onset of action is due to chloral hydrate itself.[234]

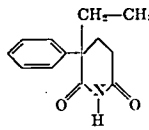
Paraldehyde is not an aldehyde in the strict



Paraldehyde

sense, but a heterocyclic compound formed by the polymerization of three molecules of acetaldehyde. A minority (11–28 per cent) of paraldehyde is excreted unchanged via the lungs,[225] the majority inactivated in the liver by depolymerization to acetaldehyde, in turn oxidized to acetic acid and eventually to carbon dioxide and water.[175, 225, 226] Failure to find significant tissue levels of acetaldehyde in animals following paraldehyde administration results from more rapid metabolism of acetaldehyde to acetic acid than conversion of paraldehyde to acetaldehyde.[175] Disulfiram (Antabuse), which inhibits the enzymes responsible for oxidation of acetaldehyde, results in toxic accumulation when administered in the presence of ethanol, another compound metabolized to acetaldehyde, but not when administered with paraldehyde. When disulfiram is administered with ethanol, the high blood levels of acetaldehyde do not alter the rate of metabolism of ethanol, and acetaldehyde levels progressively increase. When disulfiram is combined with paraldehyde, the increased blood levels of acetaldehyde inhibit further metabolism of paraldehyde and acetaldehyde levels remain below toxic levels although depressant blood levels of paraldehyde are prolonged.[211]

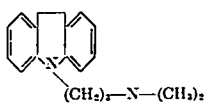
Glutethimide (Doriden), like thalidomide is a central nervous system depressant derived from glutarimide, but glutethimide is not tera-



Glutethimide

togenic. Glutethimide is completely inactivated by hydroxylation,[359] while thalidomide is metabolized by hydrolysis. Unchanged glutetimide is not found in urine. Approximately 95 per cent of the drug is recoverable as hydroxylated metabolites conjugated with glucuronic acid, and approximately 5 per cent appears as unconjugated metabolites. The molecular site of hydroxylation of glutethimide depends upon the form of the drug: dextrorotatory glutethimide is hydroxylated in the ring, while the levorotatory form is hydroxylated on the ethyl side-chain.[210] Since the hydroxyl group has a different position in the two metabolic products, and since the oxygen atom of the hydroxyl group serves for conjugation with glucuronic acid, two distinct glucuronides appear in the urine following administration of racemic glutethimide.

The anti-mental-depressant *imipramine* (To-



Impiramine

franil) is another compound which owes its effect to a metabolic product, desmethylimipramine, $-N-(CH_2)_3-NH-CH_3$, resulting from N-demethylation involving one of the two N-methyl groups.[38, 153, 171, 318]

Tribromethanol (CBr_3CH_2OH; Avertin), though infrequently employed, was one of the first central nervous system depressants about which metabolic information was available. It is inactivated in part by conjugation with glucuronic acid in the liver,[122] in part by oxidation to tribromacetic acid.[94]

Urethane (ethyl carbamate) is largely metabolized, only 4 per cent being excreted unchanged in urine of animals; the metabolites are unidentified.[46]

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Drugs

ANALGESIA The analgesic potencies of several antidepressant drugs were studied in mice using the phenylquinone writhing test. Imipramine was found to be as potent as codeine in doses of 1.7 to 9.2 mg. per kg. Other antidepressants such as amitryptiline and nortryptiline were even more active on a weight-for-weight basis. There was a definite dose-effect relationship between chemically-induced pain and relief by these substances. These drugs deserve a therapeutic trial in the treatment of chronic pain, particularly in cancer patients. (*Opitz, K., and Borchert, U.: Pain Relief with Antidepressant Substances, Klin. Wschr. 45: 887 (Sept.) 1967.*)

SCOPOLAMINE PSYCHOSIS Two cases of attempted suicide by ingestion of large doses of over-the-counter sleep medicine containing scopolamine (Sominex) are presented. In each instance there was a close similarity between the toxic effects of the drug and psychiatric disturbances of nontoxic origin. These and other documented case reports emphasize the importance of considering scopolamine intoxication in the differential diagnosis of coma, convulsions or disorientation. (*Bernstein, S., and Leff, R.: Toxic Psychosis from Sleeping Medicines Containing Scopolamine, New Engl. J. Med. 277: 638 (Sept.) 1967.*)