THE METABOLISM OF BARBITURATES*

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This review is an attempt to examine critically a limited part of the large volume of literature which has appeared on the metabolism of barbiturates. A more general treatment of the pharmacology and therapeutic use of this group of drugs may be found in several other reviews (50, 51, 91, 120, 121). The following discussion is restricted to absorption, distribution in tissues, sites of degradation, excretion and metabolic fate of the drugs. Also, the methods, both chemical and pharmacological, which have been used in studies of the barbiturates are examined. Consideration of excretion and metabolic fate is limited to those drugs which have received clinical use or are closely related to such drugs. Studies of the effect of stimulants, diuretics and possible metabolic inhibitors on the metabolism of the barbiturates are beyond the scope of this paper.

Inasmuch as trade names or U.S.P. names are used for convenience, a glossary and index appear at the end of this review. There the reader will find synonyms, chemical structures and page references. Strict chemical terminology is not followed in the discussion to the extent that "barbituric acid" and "barbiturate" are used interchangeably.

METHODS

The relative value of all information concerning the distribution and excretion of barbituric acid derivatives depends upon the reliability of the quantitative methods used to obtain this information. For the purpose of discussion the methods may be divided into five types: (1) gravimetric, (2) colorimetric, (3) ultraviolet spectrophotometric, (4) isotopic and (5) pharmacological.

(1) Gravimetric Methods

This method has probably been used more than any other for the determination of unchanged barbiturate in the urine. It was first used by Fischer and von Mering (33) at the time of the introduction of barbital into medicine. Many modifications have been described, but a common feature of all is the extraction of the barbituric acid from the urine with an organic solvent, usually ether or ethyl acetate (48, 105). After evaporation of the solvent the barbiturate is purified and weighed.

The problem of obtaining the barbituric acid in as pure form as possible without the losses which accompany recrystallization has been attacked in many different ways. Pucher (105) employed a preliminary extraction of the urine with petroleum ether in which the barbiturates are insoluble. Klingenfuss and Reinert (68) made the urine alkaline and carried out a preliminary extraction with ether.

* This review was made possible by a grant from the United States Public Health Service for investigative work in this field.

Other investigators have chosen to use only one extraction and purify the crude barbiturate after evaporation of the solvent. If the barbituric acid contains only saturated groups, some of the impurities may be removed by oxidation with potassium permanganate (49, 105) or potassium dichromate (113). The barbiturate may be purified by precipitation with mercuric sulfate (36) or as a copper sulfate-pyridine complex (132). These procedures yield pure products, but the loss of barbiturate may be high (68). The crude barbiturate may be treated with charcoal (4) which removes color and often yields a pure product; however, there is always at least a small loss of barbiturate due to adsorption on the charcoal (48, 113). The crude product may also be purified by sublimation. This technic has been successful in many cases (55, 118), especially when the amount of product was small.

The results obtained by the gravimetric method are of doubtful value unless the product is pure enough to allow its identification by melting point and mixed melting point determinations. If the amount of product is large enough, a crystalline derivative of the barbituric acid such as the di-*p*-nitrobenzyl derivative (49) or the dixanthyl derivative (31, 32) may be prepared for additional proof of identity. The numerous qualitative color and precipitation tests which have been proposed are all of questionable value.

The gravimetric method has been used with considerable success for the determination of barbital in the urine. It is probable that the method can be adapted to yield results of comparable significance for many of the other barbiturates, even though they are administered in much smaller doses and are largely degraded in the body. However, adequate control experiments must be run with each new drug to determine completeness of extraction, loss during purification, and the limits of the method. With drugs which are degraded *in vivo* it becomes even more important than with barbital to determine the identity of the product by the determination of the melting point. Unfortunately, many studies which have appeared on the excretion of barbiturates in the urine contain no data on the adequacy of extraction or the purity of the final product. With drugs which may yield closely related metabolites in the urine it obviously is not desirable to circumvent the final isolation by running Kjeldahl nitrogens (115) or determining barbituric acid derivatives by an argentimetric method (116).

The greatest limitation of the gravimetric method is that a relatively large amount of barbiturate (ca. 5 to 10 mgm.) must be present in the sample for an adequate determination. This consideration has made the technic very difficult for studies of the concentration of barbiturates in various tissues under the conditions of usual dosage. Large samples of tissue (100 to 1000 gm.) must be employed. Furthermore, the isolation of barbiturates from tissue is much more difficult than from urine, although Herwick (55) and Kozelka (84) have designed good procedures for quantitative recovery. Nevertheless, examination of tissues has usually been limited to cases of fatal poisoning (2, 105).

(2) *Colorimetric Methods*

The colorimetric method for barbiturates which has received most study depends upon the interaction of the barbiturates with a cobaltous salt in an alkaline

medium. It was used as a qualitative test by Parri, Zwikker (132) and Bodendorf and was adopted for quantitative purposes by Koppanyi (79, 80). The first method described by Koppanyi was a visual comparison procedure in which a blue color was generated in a barbiturate-containing chloroform solution by the addition of anhydrous methanolic solutions of cobaltous acetate and barium or lithium hydroxide. The chromophore was unstable and quickly precipitated or faded. Later (73, 81) it was discovered that the use of isopropyl amine in place of the inorganic hydroxide yielded a stable color which could be measured in a standard colorimeter.

There have been several investigations of the specificity of the cobalt color. The test can apparently be used for all the disubstituted barbituric acids and thiobarbituric acids, although no linear relationship exists between the intensity of color and the molecular weight of the barbiturate (8, 21, 27). Koppanyi found that acetic acid and other chloroform-soluble acids give color in the test. This has been confirmed by Riley (112) who found that aldehydes also introduce errors. Koppanyi noted that theophylline and theobromine give a color similar to the barbituric acids, but he stated that these compounds can never be present in body tissues or fluids in concentrations sufficiently high to give a positive test. Thymine, biuret, guanidine, oxamide, hippuric acid and creatinine also yield color, but most of these compounds apparently do not enter chloroform extracts in detectable amounts. Lecithin and other phospholipids interfere with the color test, apparently by holding the lipophilic barbiturates in loose combination and preventing them from reacting with the cobalt (72). The phospholipids from tissue are removed by treatment with copper sulfate and sodium hydroxide, or they may be precipitated from the chloroform extracts with acetone (90). Sulfonamides give color in the cobaltous acetate—isopropyl amine test, but 100 mgm. of sulfonamide give less color than 2 mgm. of phenobarbital (82). Riley showed that the substituted acetyl ureas and acetamides which are *in vitro* hydrolytic products of the barbiturates do not yield any color. The cobalt color test is sometimes carried out in alcoholic solution rather than in chloroform, and various alkaline reagents are used. Studies of the specificity of the reaction under these conditions have been reported by Herwick (55), Mohrschulz (97) and Kozelka (85).

A considerable amount of criticism has been directed against the use of the cobalt color for the quantitative determination of barbiturates. Sack (113) reported that the color is very unstable and fades with the appearance of turbidity. Furthermore, he stated that the difference between the "blue" solutions of various barbiturate concentrations is neither large nor constant. Iversen (58) reported that the color of the complex compound is not suitable for colorimetry, since photoelectric tests showed that the color intensity for a given barbiturate concentration is not reproducible and not constant. He felt that an additional drawback was the fact that an approximate proportionality between the color intensity and the concentration was present only within the very narrow range of 20 to 100 mgm. per cent barbiturate in chloroform. Kozelka (84) studied the cobalt color in absolute alcohol solution, using sodium ethoxide as the alkaline reagent. He found that the cobalt and sodium must be present in a definite ratio

to each other as well as to the barbiturate present, if quantitative results are to be obtained. On the basis of this observation he felt that the reaction should be used only as a qualitative test or for semiquantitative purposes.

Other investigators do not appear to be in complete agreement with these observations. Using a photoelectric colorimeter, Krause (88) found that the method of Koppanyi gave an average variation in color intensity of 7 per cent in duplicate determinations on standard Amytal solutions in the concentration range of 18 to 300 mgm. per cent. However, by a suitable choice of amounts and concentrations of the reagents, he was able to reduce the average error of duplicate determinations to 1.5 per cent for the same range of concentrations. Krause believed that the results obtained by Kozelka were due largely to the use of suboptimal amounts of reagents. Cohen (21) has also studied the optimal conditions for the cobalt color. He found that the stability of the color was satisfactory and that by observing certain precautions the method could be used for the quantitative determination of barbiturates.

Koppanyi's procedure for the determination of barbiturates in urine consisted of treatment of the urine with sodium hydroxide and copper sulfate, removal of the copper hydroxide precipitate by filtration and subsequent extraction of the filtrate with ten volumes of chloroform. Tissues containing barbiturate were liquefied with sodium hydroxide, then treated with copper sulfate and filtered; the filtrate was then acidified and extracted with chloroform. Some criticism has been directed toward these methods. Iversen (58) contended that purification through the formation of a voluminous copper hydroxide precipitate in urine involves a loss of barbiturate. Kozelka (84) has reported that the Koppanyi procedure for tissues gives low recovery of added barbiturates. Moreover, the above authors and others have objected to the large amount of chloroform which is needed. Riley (112) and Krause (88) have shown that chloroform extracts of urine that contain no barbiturates give a certain amount of color due to urinary pigments and chromogenic substances. However, the copper hydroxide purification was not employed by these workers. Koppanyi maintains that the copper hydroxide procedure, when properly executed, gives satisfactory results, but he has also described alternative methods (46, 90). A few workers (8, 97, 108) have tried to use chromatographic adsorption in connection with the cobalt color method, but their studies have not been exhaustive enough to contribute much to an improved quantitative method. Cohen (21) has recently described a rather laborious method for the extraction of barbiturates on the basis of experiments in which barbiturates were added to tissues and body fluids and subsequently analyzed by the cobalt color method. He reported a recovery of 93 per cent or more, but the amount of added barbiturate was large (5 to 40 mgm.) and he does not mention the quantity of tissues or fluids employed.

It would appear from the information available at present that with proper technic the cobalt color method is suitable for the study of the concentration of *barbital* in body tissues and fluids under the conditions of usual dosage. On the other hand, the method has been shown to yield erroneous results when used to study barbiturates which are degraded *in vivo*. For example, using the colorimetric

method, Koppanyi (74) found that 5 to 41 per cent of doses of Neonal and about 8 per cent of doses of Amytal are excreted in the urine. In contrast, Herwick (55) and Shonle (118) using chemical isolation and pharmacological methods showed that these substances are excreted only in traces. Likewise, Krause (88) showed that dogs fed Amytal excrete in the urine in 48 hours color-producing substances equivalent to about 16 per cent of the dose. However, the substances gave no precipitate with copper sulfate and pyridine. Using a procedure involving adsorption on charcoal and elution Brundage and Gruber (8) found that Ortal and pentobarbital yield substances which give color with cobalt but do not have appreciable pharmacological activity. Koppany (46, 77) has also shown that metabolites of the barbiturates yield color with cobalt.

Certain other colorimetric methods not employing cobalt have been used for the quantitative determination of barbiturates. In her studies on the distribution of Dial and Phanodorn in the central nervous system, Vogt (126) used a method involving titration with potassium permanganate. The method was not stoichiometric, and calibration curves were required. Owing to the extensive purification procedure employed, her recovery of the barbiturates added to tissue was only about 50 per cent. Raventós (108) has used a green color produced by the addition of anhydrous methanolic solutions of copper sulfate and diethyl amine to a chloroform solution of a thiobarbiturate. He demonstrated good recoveries of Kemithal added to blood, liver and brain. The procedures of Vogt and Raventós are subject to the criticism that it has not been proved that some metabolites of the drugs do not react in the same manner as unchanged drug.

(3) *Ultraviolet Spectrophotometric Methods*

It has been recognized for a number of years that 5,5-dialkylbarbiturates in aqueous alkaline solution have a characterisitic absorption in the ultraviolet region of the spectrum. Hellmann (52) was the first to describe a spectrophotometric method for the estimation of thiopental in blood. His procedure utilized a characteristic absorption band at 288 mμ in ether solution. Jailer and Goldbaum (59) modified the method for thiopental by employing chloroform for the extraction and by making the measurement of the ultraviolet absorption in chloroform or preferably in sodium hydroxide solution. Subsequently Walker (127) and Goldbaum (44) described fairly similar procedures for the determination of 5,5-disubstituted barbituric acids. More recently Gould and coworkers (45) have reported the use of continuous extraction with ether instead of multiple extraction with chloroform, but further details of their procedure are lacking.

The factor limiting the sensitivity of the ultraviolet spectrophotometric procedures is the ratio of the amount of barbiturates to the amount of other tissue "chromogens" concomitantly extracted. With the methods of Walker and of Goldbaum the minimal concentration of barbiturates in blood to yield satisfactory results is about 0.4 mgm. per 100 ml. Samples of blood from 0.5 to 5 ml. depending on the concentration of barbiturates are sufficient. The method of Goldbaum is sensitive to 1.0 mgm. of barbiturate per 100 gm. of tissue. Samples of tissue of 0.5 to 5 gm. are employed. In the absence of other drugs with absorp-

tion in the ultraviolet, these procedures are perhaps 4 times as sensitive as the cobalt color method (127).

The ultraviolet absorption methods measure the total amount of barbiturates in the extracts, and hence are subject to the same criticism as the cobalt color methods. Their use can give much valuable information about the metabolism of the barbiturates, but until the intermediary metabolism of these drugs is more thoroughly understood one cannot be certain to what extent metabolites containing the barbituric acid ring are being measured as unchanged drug.

(4) *Isotopic Methods*

Only two short papers have appeared on the use of isotopes for the study of the metabolism of the barbiturates. (112a, 125). Isotopic methods have the advantage that they can yield information about the extent to which at least a portion of the drug is degraded to compounds which enter the metabolic pool. For example, van Dyke and coworkers (125) examined the excess N^{15} in the urinary ammonia and urea after the oral administration of pentobarbital labeled with N^{15} and found that less than 8 per cent of the isotope was contained in these fractions. Furthermore, the amount of unchanged drug and of the metabolites can be determined with precision by the method of isotope dilution. The disadvantages of the isotope methods are the expense of the isotopes, the organic synthesis required and the special equipment necessary for the quantitative determination of the isotopes.

(5) *Pharmacological Methods*

Several investigators have tested extracts of urine for hypnotic activity in mice or rats after the administration of barbiturates. This method has been used principally for the study of barbiturates which are largely degraded *in vivo* and yield only very small amounts of unchanged drug in the urine (55, 118), or to confirm or disprove data obtained with the cobalt color method (8, 74). The results of pharmacological testing are at best very crude. Furthermore, there is always the possibility that certain of the metabolites of the barbiturates possess some hypnotic activity.

Other pharmacological methods have been used in elucidating specific features of barbiturate metabolism which are discussed below.

ABSORPTION AND DISTRIBUTION IN BODY FLUIDS

The absorption of barbiturates occurs readily from the gastro-intestinal tract. According to Weese (128), a considerable part of a dose can be absorbed from the stomach, and narcosis can follow intragastric administration to guinea pigs with a ligature around the pylorus. Most authors agree that rectal administration is much more efficient than the oral route; this avoids immediate passage through the liver which is the most important organ in degrading all but a few of the barbiturates. For example, Werner, Pratt and Tatum (130) using rabbits found that the ratio of the oral to the intravenous LD_{50} was 15:1 or more for the sodium

salts of thiopental, Thioethamyl and Evipal, whereas the corresponding ratio of rectal to intravenous doses was 2.2 to 3.1:1. The oral:intravenous LD_{50} ratio of a longer-acting barbiturate, sodium pentobarbital, was 6:1, and the rectal:intravenous LD_{50} was 1.4:1. It would be expected that sodium barbital, which undergoes virtually no destruction in the liver or other tissues, would be found to differ little in potency by all three routes.

Barbital, unlike all barbiturates with shorter duration of action, has a slow onset of action (15 minutes or more) following the intravenous injection of an anesthetizing dose. Bush (9) estimated the ratio of free acid to sodium salt of several representative barbiturates. This ratio for both barbital and Amytal was 2.5:1 at pH 7.5. Since with intravenous administration there is a long latent period for barbital and a short one for Amytal, Bush's determinations gave no support to the view of Klimesch (67) and Starkenstein and Klimesch (119) that after barbiturates which cause immediate narcosis, the lipid-soluble free acid is relatively more abundant in the plasma. However, it does appear likely that delayed equilibrium between plasma and nervous tissue accounts for the long latent period of action of barbital (*cf.*, the serial blood determinations of Dille *et al.* (28)).

The briefly summarized *in vitro* experiments of Bennhold with Evipal (6) led him to the conclusion that both plasma albumins and globulins bind the drug when it is transported intravascularly.

Except for barbital, which probably undergoes no degradation in the body, the relationship of estimated blood level to pharmacological effect has to be accepted with caution since most methods do not convincingly distinguish between the administered barbiturate and metabolically altered derivatives which, at present, appear also to be barbiturates. (An exception is the gravimetric method used by Tatum, Nelson and Kozelka [122].) Even if levels in the blood are accurately determined, their correlation with pharmacological response is best for short and very short acting drugs and poorest for a long acting barbiturate such as barbital. Dille, Linegar and Koppanyi (28) reported that, after the intravenous injection of 225 mgm. per kgm. of sodium barbital into a dog, the blood level of the drug fell from 39 to 25 mgm. per cent during the first 10 minutes at which time it can be assumed that the dog was not yet anesthetized. It is probable that the dog was anesthetized during the succeeding 1 to 5 hours when the blood level was 12 to 15 mgm. per cent (similar to a dog receiving 300 mgm. per kgm.). Also, after recovery of consciousness in a human with barbital poisoning, the blood level may be only slightly below that of a similarly poisoned patient in coma (7.6 compared with 8.4 mgm. per cent [35]), a fact which again suggests that the blood level of barbital does not always accurately reflect the level in the central nervous system. On the other hand, using Amytal, a short-acting barbiturate, Tatum, Nelson and Kozelka (122) observed that rabbits regain their righting reflexes at about the same blood level (2.9 mgm. per cent), although there were wide differences in the duration of anesthesia. Data from the single case of Jailer and Goldbaum (59) suggests that it may be possible to relate

depth of anesthesia with the blood level of thiopental. The apparent relationship between the blood levels of barbiturates and pharmacological effect is listed in Table 1.

Anderson and Essex (1) confirmed the work reported in the unpublished thesis of Delmonico who found cyclic fluctuations in the blood level of barbiturate in dogs. Anderson and Essex injected either Amytal or pentobarbital and determined barbiturate colorimetrically by Levvy's method (89) after having concluded that Delmonico's method was unreliable. Even more unusual was their finding that cyclic disappearance and reappearance of pentobarbital occurs in the

TABLE 1

Apparent Relationship between Blood Levels of Barbiturates and Pharmacological Effect

BARBITURATE	METHOD*	ANIMAL	PHARMACOLOGICAL EFFECT		REFERENCE
			Coma or surgical anesthesia	Respiratory arrest	
			mgm. per cent	*mgm. per cent*	
Barbital	C	Dog	12–15†		28
Barbital	U	Dog	15–18		35
Barbital	U	Man‡	9–21		35
Phenobarbital	U	Rabbit	7–17		44
Phenobarbital	U	Man	5–10		44
Phenobarbital	U	Man	10–13		35
Amytal	U	Rabbit	7		44
Amytal	G	Rabbit	3		122
Pentobarbital	U	Rabbit	4.5–7		44
Seconal	U	Rabbit	6.5		44
Thiopental	C	Rabbit	4.8	7.4	19
Thiopental	U	Man	2.0–3.0		59
Kemithal	C	Rabbit	8.8	19	19
Kemithal	C	Man	2.3–4.5		19

* C = colorimetric, G = gravimetric, and U = ultraviolet spectrophotometric.

† One to 5 hours after anesthetic dose.

‡ After a therapeutic dose of barbital, the blood level was 5.0–5.5 mgm. per cent by a colorimetric method (89).

heart-lung preparation with or without kidneys or extremities or both in the circulation. No other investigator has observed "cyclic disappearance from and reappearance in the blood" of intravenously injected barbiturate.

According to Goldbaum (44) the level of various barbiturates is slightly if at all higher in the plasma than in the whole blood of rabbits. Yet Fretwurst and Voss (42), investigating human blood in cases of poisoning by barbital and phenobarbital (drugs used by Goldbaum), asserted that erythrocytes contain virtually no barbiturate.

There are serious discrepancies in the reports on the concentration of barbiturates in cerebrospinal fluid. The differences appear in part to depend upon variations in dose and in interval between administration and sampling. The

gravimetric method used by Kozelka and Tatum (86) revealed 0.20 mgm. per cent of phenobarbital in human cerebrospinal fluid 30 to 45 minutes after the oral administration of 585 mgm. of the drug. Even larger doses of various barbiturates, particularly barbital (up to 10 gm.) and phenobarbital (up to 6 to 7 gm.) had been ingested by the patients or subjects of Purves-Stewart and Willcox (107) and Fretwurst and Voss (42). Samples of cerebrospinal fluid were investigated 3 to 35 hours after the drug was taken. For example, Purves-Stewart and Willcox, using an undisclosed method, observed 7.7 to 9.0 mgm. per cent of phenobarbital in the cisternal fluid with little change from the sixteenth to the thirty-fifth hour. Fretwurst and Voss found little difference in the concentration of barbital or phenobarbital in the plasma as compared with the cerebrospinal fluid. One patient is reported to have taken 800 mgm. of phenobarbital (compared with 585 mgm. for the patients of Kozelka and Tatum). Nineteen hours later the plasma and cerebrospinal fluid contained, respectively, 4.2 and 3.1 mgm. per cent of the drug. If it be assumed that the patient had an extracellular fluid volume of about 12 l., this fluid would have contained about 60 per cent of the dose despite excretion, destruction and tissue localization or binding. This seems very unlikely. Vogt injected barbital or Dial into dogs and consistently found less drug in the cerebrospinal fluid than in various parts of the central nervous system (126).

DISTRIBUTION IN TISSUES

After absorption or intravenous injection, barbiturates probably enter all cells and are actually concentrated or localized in some tissues such as the liver and kidneys. This distribution throughout all tissues is illustrated by the appearance of barbital in the gastric juice and pancreatic secretion (20) and in the fetal tissues (25, 26). Phenobarbital can be detected in human milk after a single dose of 100 mgm. (124). It is likely that equilibrium, however unstable, is achieved more quickly for short-acting barbiturates than for long-acting drugs, especially barbital with its long latent period of action. Only barbital undergoes no metabolic change, and since the principal degradation products of the other drugs are probably pharmacologically inactive barbiturates, colorimetric or ultraviolet spectrophotometric determinations of drugs other than barbital in tissues yield little reliable information concerning the actual concentration of injected drug, especially after intervals of an hour or more. This objection does not hold for the gravimetric method of Kozelka and his colleagues who actually identified the barbiturate after isolation (84, 86, 87). Apparently little degradation of phenobarbital, Amytal, Neonal, or pentobarbital occurs within 15 minutes after intraperitoneal injection of large doses into rats, since practically all the injected barbiturate can be recovered and identified (84). On the other hand, within three hours after the oral administration of pentobarbital to dogs, the urine contains considerable amounts of degraded pentobarbital, probably in the form of barbiturate, and almost no unaltered drug (96, 125).

The concentration of barbital in tissues after the administration of doses ranging from innocuous to fatal has been investigated. Among the first careful toxico-

logical reports in man is that of Pucher (105) who found the following concentrations of barbital in the tissues after fatal poisoning from a dose of 6 gm.: kidneys 19.4, brain 14.0, liver 12.8 and spleen 12.1 (all expressed as mgm. per 100 gm.). Similar observations were made by Zwikker and Steenhauer (133). Experimental studies have largely been performed in mammals. Dille, Linegar and Koppanyi (28) concluded that the uptake of barbital by the tissues is relatively faster at low than at high blood concentrations, a finding which is not surprising. Tissue concentrations in comparison with blood concentrations varied with the dose and with the interval between injection and sampling. An example is the authors' dog number 3, from which samples were taken 22 hours after the injection of 300 mgm. per kgm. of sodium barbital: blood 8.0, various divisions of brain 2.0 to 7.0, liver 14.0 and kidney 17.5 (all expressed as mgm. per 100 cc. or 100 gm.). Other examples of tissue analyses will be found in several reports (2, 71, 72, 77, 79, 126).

Experiments with barbital alone should be considered in any attempt to decide whether there is significant localization of barbiturate either in the central nervous system or specifically in the diencephalon where "centers" regulating the degree of wakefulness or sleepiness are believed to reside. During the period 1927–1937, E. and I. Keeser contended that after small doses of barbital (*e.g.*, 25 mgm. per kgm.), intravenously administered to rabbits or dogs, specific localization of the drug occurred in the diencephalon, as revealed by the presence of easily sublimed drug in crystalline form (60–65). Similar sublimation of extracts of other cerebral structures (cortex, pons and medulla, cerebellum) revealed no barbital or only a much smaller quantity (mesencephalon). No quantitative data were offered. M. Vogt (126) made a careful attempt to secure quantitative evidence of such specific localization. Her methods permitted recovery of about 50 per cent of large doses of drug, but were only qualitative with doses of 10 to 100 mgm. per kgm. She found no evidence of localization of barbital in a specific division of the brain.

Work which might be cited as favoring localization in the brain in comparison with other tissues (*e.g.*, 31 and 32) contains no adequate description of methods. In fact, Fabre in 1925 reported relatively enormous *total amounts* of barbital in the brain in comparison with other tissues such as the liver (31, 32); yet in 1934 in another study (30) he stated that the *concentration* of barbital in the liver was higher than in the brain. All other work supports the contention of Vogt and of Koppanyi and his colleagues that barbital is not specifically localized in the brain and, more often than not, is there in lower concentration than in such tissues as the liver, kidney and spleen (2, 71, 72, 77, 105, 128, 129, 133).

The cross-circulation experiments of Koppanyi and Linegar (76) indicated that as the blood level of barbital fell, the drug diffused from the central nervous system and rapid recovery could follow. It would seem that barbital is loosely bound to nervous tissue and probably to other tissues as well.

There are reports of tissue distribution of other barbiturates by methods, either colorimetric or ultraviolet spectrophotometric, which probably cannot distinguish the drugs from closely related degradation products. The drugs studied were phenobarbital (44, 72, 77), Amytal (25, 44), Dial (72, 126), Sandoptal (72),

Phanodorn (126), pentobarbital (28, 44, 72, 77), Seconal (44) and thiopental (59). A careful gravimetric method has also been used for Amytal (87, 122).

DETOXIFICATION

The detoxification of barbiturates depends upon renal excretion or destruction in the tissues or both. Barbital is the only barbiturate which appears to leave the body without alteration, and its detoxification depends, in a practical sense, entirely on renal excretion; this may extend over days (4, 33, 95). Excretion of barbital may be markedly reduced by renal disease (3) and may be so impaired in animals with experimental nephritis (potassium chromate, tartaric acid or uranium acetate) that anesthetic doses lead to death (100). The period of survival after total nephrectomy is greatly shortened if barbital has been administered (56, 94). Although phenobarbital is in a large part degraded in the body in some unknown fashion, experimental studies indicate that functioning kidneys are necessary for its detoxification (56, 94). It has not been demonstrated that the kidneys play an *essential* part in the detoxification of the other barbiturates.

The most important other single organ for detoxification, as would be expected, is the liver. Liver damage by chloroform, carbon tetrachloride or phosphorus markedly increases the toxicity of barbiturates such as Amytal, pentobarbital and Evipal (18, 66, 93, 103, 104, 122), whereas this increase is not observed after nephrectomy (56, 128). In the experiments of Tatum, Nelson and Kozelka (122), in which the liver was damaged with carbon tetrachloride, unusual amounts of Amytal persisted in the liver until delayed detoxification finally permitted recovery. Partial hepatectomy, with proper precautions, has the same effect on all the common short-acting barbiturates used orally (94, 114).

The extent to which other tissues participate in the degradation of barbiturates appears to be less important. Assaying Evipal biologically, Martin, Herrlich and Clark (93) observed that destruction of the drug, especially by liver and less strikingly by skeletal muscle and spleen, occurred *in vitro*, but that no such destruction by kidney, brain and oxygenated blood could be demonstrated. Likewise from *in vitro* experiments, Dorfman and Goldbaum (29) concluded that kidney, skeletal muscle and brain do not destroy a number of barbiturates which are degraded to a varying extent by liver. However, they relied upon an ultraviolet spectrophotometric method which perhaps yields more significant results concerning disappearance than persistence of drug. Masson and Beland (94) believed that the kidney participates as much as the liver in the detoxification of Dial, Neonal, Phanodorn and Delvinal; however, Hirschfelder and Haury (56) who also performed experiments with the first three drugs of this group observed no change in potency after nephrectomy.

Apparently the liver inactivates a thiobarbiturate like thiopental so efficiently that extensive reduction of functional hepatic tissue is necessary before the liver's importance in this regard can be revealed. Masson and Beland (94) denied that hepatic degradation of thiopental occurs; however, accumulating data reveal that this is an erroneous interpretation and suggest that a sufficiently large

proportion of the liver had not been removed from their rats. Shideman, Kelly and Adams (117) made Eck fistulas in rats and damaged the livers of mice with carbon tetrachloride. They had no difficulty in demonstrating a marked increase in the potency of thiobarbiturates (thiopental, Surital and Thioethamyl) and of pentobarbital in such animals. The potency of barbital was not changed. Hepatic tissue *in vitro* will likewise degrade thiobarbiturates (29, 117). Lastly, patients with extensive hepatic disease may be anesthetized for remarkably long periods by thiopental (99, 117). Experiments in dogs with Eck fistulas and experiments with the heart-lung preparation with or without liver or kidney continue to support the view that the principal degradation of thiopental occurs in the liver. Some destruction occurred in the heart-lung preparation and more destruction was found when the kidney was in the circulatory circuit, in agreement with findings *in vitro* (29, 66).

A sex difference in response to some barbiturates—adult females are more susceptible than adult males—has been reported by Holck as well as by previous investigators (57). Susceptibility to pentobarbital, measured by sleeping time, is increased after spaying or castration. The injection of testosterone into castrated male rats can reduce susceptibility to pentobarbital (16, 17, 98). Those interested in the rate of detoxification of barbiturate in intact mammals are referred to reports by Koppanyi and Liberson (75), Kohn and Grimes (69) and Das and Raventós (23). The drugs used were Amytal, barbital, Evipal, Kemithal, pentobarbital and thiopental. Das and Raventós (23) concluded that a very short-acting barbiturate like Evipal is detoxified in an exponential manner, *i.e.* a constant proportion (1/35 to 1/30) of the amount of the drug present in the body is inactivated per minute.

EXCRETION AND METABOLIC FATE

It is known that the body possesses two methods for removing the barbiturates: (1) destruction or chemical alteration principally in the liver, and (2) excretion through the kidneys. One barbiturate at least is largely excreted as such; others are destroyed in the body, and still others are partly excreted and partly destroyed. The fate of a particular barbiturate depends upon its chemical constitution, but at present one cannot predict from chemical structure precisely how the drug will be metabolized.

The metabolic fate of the barbiturates will be discussed with reference to a familiar classification based on the duration of hypnotic or anesthetic action (Table 2). This is a desirable approach, since there is some correlation between the *in vivo* stability of the individual barbiturates and their duration of action. As a matter of fact, the duration of action may be used as a biological test of stability. On this basis, the long-acting drugs, barbital, phenobarbital and Dial, appear to be relatively stable, and, indeed, they do appear in the urine in detectable and measurable quantities. On the other hand, those members of the series which, on the basis of a relatively short period of action, are more unstable appear in the urine only in very small amounts except under unusual conditions.

The barbiturate which has received most study is barbital. Fischer and von

TABLE 2

Metabolic Fate of Barbiturates

BARBITURATE	% UNCHANGED BARBITURATE EXCRETED	METHOD FOR DETECTION*	METABOLITE	% METABOLITE EXCRETED
Drugs with Long Duration of Effect				
Alurate	13–24	G (38, 68, 102, 111)	?	
Barbital	65–90	G (4, 33, 34, 47, 95, 111, 115) C (79)		
Dial	27–31	G (101, 110)	?	
Phenobarbital	11–25	G (47, 101, 111) C (79)	?	
Rutonal	25	G (101)	?	
Drugs with Moderate Duration of Effect				
Amytal	0	G (53, 55, 118) P (8, 55, 118)	?	
Butisol		Not adequately studied		
Delvinal		Not adequately studied		
Dormovit	2–3	G (41)	?	
Ipral		Not adequately studied		
Medomin	0	G (106)	5-cycloheptenonyl, 5-ethyl barbituric acid	1–5
Neonal	0	G (53, 55)	?	
Nostal	1–3	G (47) B (131)	5-acetonyl,5-isopropylbarbituric acid (47)	6–16
Ortal	0	P (8)		
Pentobarbital	0–3	G (54, 55, 118) P (8, 55, 118) I (125, 112A)	5-ethyl,5(3-hydroxy-1-methylbutyl) barbituric acid (96)	?
Pernoston	0.1–0.5	G (39)	5-acetonyl,5-*sec*-butylbarbituric acid	5–17
Phanodorn	2–7	G (40)	5-cyclohexenonyl,5-ethylbarbituric acid	12–19
Sandoptal	0	C (74)	?	
Drugs with Short Duration of Effect				
Eunarcon	0	C (43) B (43)	?	
Narconumal	0	G (10)	5-allyl,5-isopropyl barbituric acid	Trace
Prominal	0	G (15)	5-ethyl,5-phenylbarbituric acid	4
Seconal		Not adequately studied		

TABLE 2—*Continued*

BARBITURATE	% UNCHANGED BARBITURATE EXCRETED	METHOD FOR DETECTION*	METABOLITE	% METABOLITE EXCRETED
Drugs with "Ultrashort" Duration of Effect				
Evipal	0	P (12)	5-cyclohexenonyl,5-methylbarbituric acid	5
			isomeric 5-cyclohexenonyl, 1,5-dimethylbarbituric acids (13)	?
Kemithal	0.8–2	C (19)	?	
Thioethamyl		Not adequately studied		
Thiopental	Traces	U (59)	?	

* G = Gravimetric method (chemical isolation)
C = Colorimetric method
I = Isotopic method
U = Ultraviolet spectrophotometric method
P = Pharmacological method (bio-assay)
B = Determination of organic bromine
Figures in parentheses are references.

Mering (33) administered 4 gm. in 48 hours to a young man and found that about 70 per cent of the drug was excreted over a period of five days. Later studies (34, 47, 79, 111, 115) in which the gravimetric or cobalt color methods were used have shown that 65 to 90 per cent of a dose of barbital administered to man, dog, cat or rabbit is excreted in the urine. Only very small amounts are excreted in the feces. Normal humans eliminate about 8 per cent of the drug in the urine in the first 12 hours, 20 per cent in 24 hours, and 35 per cent in 48 hours (109). It has been demonstrated that traces of barbital are still detectable in the urine 8 to 12 days after the administration of a hypnotic dose (95). Bachem (4) reported that 90 per cent of small doses but only about 45 to 50 per cent of large doses is excreted. This work has been refuted by Mattisson (95) and Koppanyi (79).

Koppanyi and coworkers (78) studied the action of barbital in fowls and turtles. Fowls receiving anesthetic doses of the drug did not recover from the narcosis and eventually died of respiratory failure. The fowl could recover from anesthetic doses of those barbiturates which in the mammal depend only in part (phenobarbital) or not at all on renal excretion (pentobarbital, Neonal and Pernoston). With smaller doses, the amount of barbital excreted by the fowl was less than half of that excreted by the mammal. Furthermore, the period of excretion was greatly prolonged in the fowl. Turtles usually recovered from anesthetic doses of barbital, but did so very slowly. They excreted only a very small amount of barbital (10 to 25 per cent of the doses) over a period of weeks and appeared to show retention of the drug in the blood and organs 3 to 11 weeks after the administration of a single dose.

The other long-acting barbiturates appear to suffer some change in the animal body. The elimination of phenobarbital in the urine of man and dogs has been studied by different workers (47, 79, 101, 111) with good agreement in results. Dogs given single doses of 68 to 100 mgm. per kgm. and humans given 250 mgm. to 1.8 gm. daily over a period of several days excreted 11 to 25 per cent of the dose in the urine. The excretion may continue for as long as ten days after the administration of the drug (36). The closely related barbiturate, Rutonal (5-methyl, 5-phenylbarbituric acid) appears to be eliminated in a very similar way. Paget and Desodt (101) reported that the urine of a patient given 200 mgm. per day for 14 days contained 25 per cent of the drug.

The excretion of Dial has been studied less extensively than that of barbital and phenobarbital. Reiche and Halberkann (110) found that 3 patients given 100 to 300 mgm. daily for 4 to 11 days excreted 27 to 31 per cent of the drug in the urine. The Dial was excreted for 7 days after administration. was stopped. Paget and Desodt (101) studied the urine of a patient given 100 mgm. per day for 13 days and found 30 per cent of the administered drug. Koppanyi and coworkers (79) gave a dog a single dose of 80 mgm. per kgm. intravenously and with the cobalt color method found that 40 per cent of the drug was excreted in 2.5 days.

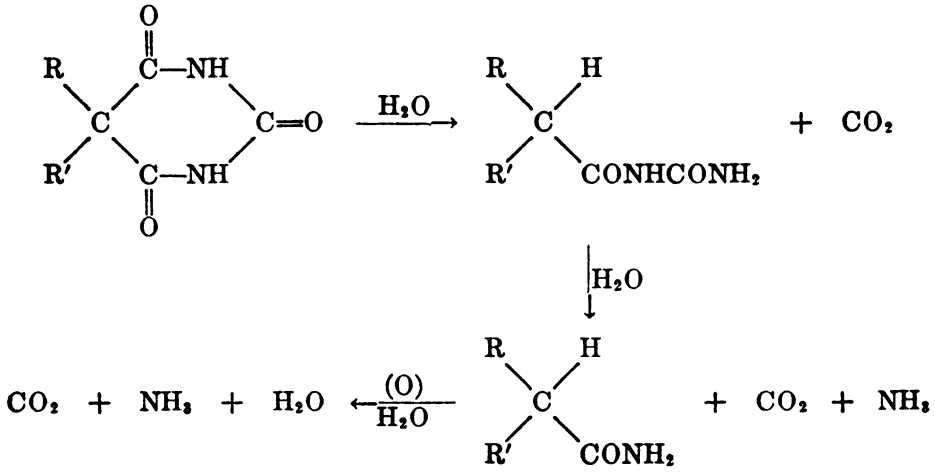
The elimination of Alurate in the urine has been studied after single doses in dogs and after repeated doses in humans. The results of most workers (38, 68, 102, 111) indicate an excretion of 13 to 24 per cent of the drug. With continued administration the unchanged barbiturate may be found in the urine 3 to 5 days after the drug is discontinued. In febrile patients the excretion of Alurate appears to be only 4 to 6 per cent (38). Fabre and Fredet (31, 32) have reported results which are in marked contrast with those of other investigators. They asserted that 46 to 90 per cent of doses of 0.55 to 1.0 gm. was eliminated by humans in 6 days. Furthermore, they stated that their product was identified by its melting point and by preparation of the dixanthyl derivative.

It will be noted that none of the barbiturates with persistent action contains an alkyl or alkenyl side-chain with more than three carbon atoms. It seems to be true that barbiturates with two short alkyl or alkenyl chains are relatively stable. Increasing the length of one of the chains increases the activity, but the molecule is then more susceptible to chemical change in the liver. In this way drugs of short or moderate duration of action are obtained. The addition of a methylene group to Alurate yields Sandoptal, a drug with moderate duration of effect. In contrast with Alurate, which is excreted to the extent of 20 per cent, Sandoptal is eliminated in the urine in negligible amounts (74). Likewise, the addition of two methylene groups to phenobarbital yields 5-*n*-butyl, 5-phenylbarbituric acid; whereas phenobarbital is excreted to the extent of 25 per cent, *n*-butylphenylbarbituric acid cannot be detected in urine (74). Nothing is known concerning the fate of Sandoptal or *n*-butyl phenylbarbituric acid.

There is some disagreement concerning the excretion of Neonal. Koppanyi and Krop (74), using the cobalt color method, concluded that dogs eliminate 5 to 41 per cent of the drug unchanged in the urine in 3 to 7 days. As was pointed out

previously, the use of the cobalt color method for the study of the excretion of drugs which are degraded *in vivo* might be expected to yield erroneous results. However, the above investigators stated that in every case the residues from the chloroform extracts of the urine had anesthetic activity in rats. Furthermore, the urine from the rats was chemically examined, and it was always possible to show the presence of barbiturates by means of the cobalt color test and to identify crystals of Neonal by microscopic examination of the dried chloroform extract. In contrast, Herwick (53, 55) was not able to isolate any unchanged Neonal from the urine of dogs given anesthetic doses, and all his extracts were inactive when injected into mice.

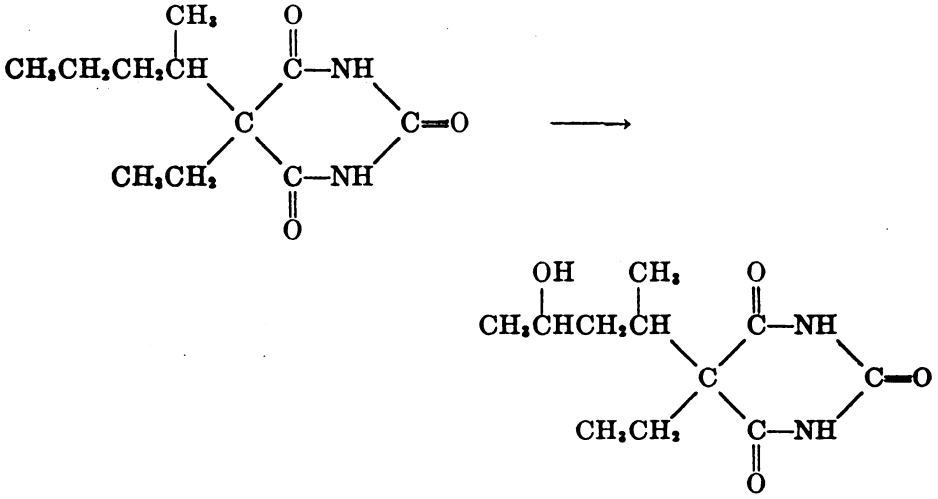
Amytal and Ortal appear to be eliminated in the urine in negligible amounts. The cobalt color method indicates an excretion of both of these substances in the urine (8, 74), but it is now pretty well established that the chromogenic substances are unidentified metabolites of the drugs rather than the unchanged drugs (8, 88). Herwick (53, 55) and Shonle and coworkers (118) carried out exhaustive attempts to isolate Amytal from the urine of dogs and patients given widely varying doses but obtained at most only traces of the drug. Koppanyi and Krop (74) reported that after the administration of Amytal extracts of urine possess anesthetic activity in rats. Other workers (8, 55, 118) have found no evidence for the presence of hypnotic compounds in the urine after administration of either Amytal or Ortal.



There is general agreement that only very small amounts of pentobarbital are eliminated in the urine (8, 54, 55, 118, 125). Shonle and coworkers (118) suggested that the destruction of pentobarbital and Amytal in the body involved hydrolytic cleavage of the barbituric acid ring. They explained the absence of the acetyl urea and acetamide derivatives in the urine by assuming that these compounds were completely metabolized to carbon dioxide, ammonia and water. Recently van Dyke and coworkers (125) demonstrated that such extensive degradation does not occur with pentobarbital. After the administration of pento-

barbital labeled with N^{15} they found that less than 8 per cent of the isotope was excreted as ammonia and urea.

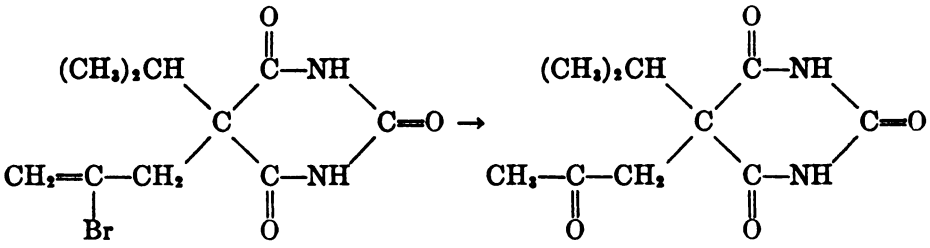
Only one metabolite of pentobarbital has been isolated in pure form and characterized. Maynert and van Dyke (96) described a new barbiturate which is apparently 5-ethyl,5(3-hydroxy-1-methyl-butyl) barbituric acid. Elementary analysis, ultraviolet absorption, the preparation of a crystalline acetate and the formation of iodoform with sodium hypoiodite were used to deduce the structure. The compound is optically active and, hence, must be derived from only one of the enantiomorphs of pentobarbital. It has no apparent pharmacological effect in mice. Herwick (54, 55) and Koppanyi and coworkers (77) have detected the presence in urine of metabolites with depressant or hypnotic activity, but no pure compounds were isolated. Also, Barris and Magoun (5) have reported the presence in urine of a reducing substance following injection of pentobarbital, but its identity is unknown. Using filter-paper chromatography, Roth and coworkers (112a) found evidence for five radioactive metabolites in the urine of mice after the administration of pentobarbital labeled with C^{14}. They stated that none of these compounds was urea or unchanged drug.



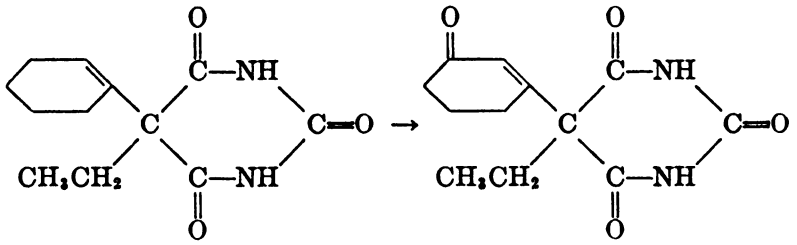
The isolation of 5-ethyl,5(3-hydroxy-1-methylbutyl) barbituric acid from urine provides the first positive clue to the metabolic fate of the dialkylbarbituric acids. It would appear that ethyl groups attached to the barbituric acid ring do not suffer change in the body. For example, diethylbarbituric acid is excreted unchanged. Increasing the length of one of the chains forms a molecule which is more susceptible to chemical change in the liver. Previously it was not known whether the change in such barbiturates was due to oxidation, hydrolysis, conjugation or a combination of these reactions. It now appears likely that direct oxidative attack of side chains containing four or more carbon atoms is an important phase of the chemical alteration of such compounds in the body.

Nostal and its homologue, Pernoston, provide other examples in which metabo-

lites of barbiturates have been isolated. Different investigators (47, 131) have reported that 1 to 3 per cent of single or repeated doses of Nostal is eliminated in the urine. Halberkann and Reiche (47) were able to isolate from the urine, in addition to the unchanged drug, 5-acetonyl,5-isopropylbarbituric acid in amounts which were sometimes as high as 12 to 16 per cent of the dose. Boedecker and Ludwig (7) gave the acetonyl derivative intravenously to rabbits and found that only 19 per cent of the compound was excreted unchanged. On the basis of this observation they postulated that the remainder of the compound was oxidized *in vivo* to 5-carboxymethyl,5-isopropylbarbituric acid. Although the latter compound has been prepared and shown to be without hypnotic activity, nevertheless it has never been isolated from urine. The metabolic fate of Pernoston is very similar. Although only traces of unchanged drug are excreted, 5 to 17 per cent of the dose may be accounted for as 5-acetonyl,5-*sec*-butylbarbituric acid (39).



The metabolic fate of Phanodorn was investigated by Fretwurst, Halberkann and Reiche (40). They found that 2 to 7 per cent of the drug is eliminated unchanged and that 12 to 19 per cent is excreted as a non-toxic compound which they isolated in pure form. On the basis of chemical analysis they believed that the substance was cyclohexenonylethylbarbituric acid, but a thorough-going investigation of its reactions and a proof of structure are still lacking.



A similar picture has evolved from work on two closely related drugs. After administration of 5-cyclohexenyl,5-methylbarbituric acid (*nor*-Evipal) to dogs, Bush and Butler (12) recovered 10 per cent of unchanged drug from the urine. Later (13) they were able to isolate a new compound in somewhat larger amounts. The elementary analysis corresponded to 5-cyclohexenonyl,5-methylbarbituric acid. The substance was relatively inactive as a hypnotic. Likewise, Pulver (106) found that 1 to 5 per cent of doses of Medomin is excreted as a non-hypnotic

compound with the elementary composition of cycloheptenonylethylbarbituric acid. A semicarbazone derivative was prepared, and the analytical values were in accord with theory. However, in neither case has there been a complete proof of structure.

Dormovit, 5-furfuryl, 5-isopropylbarbituric acid, has had some clinical use in Europe. Fretwurst and Never (41) found that a dog and 4 patients given the drug over a period of several days eliminated 2 to 3 per cent of the total dose administered. The excretion of unchanged barbiturate was complete 2 days after administration was stopped.

The short-acting and ultra-short-acting barbiturates are N-alkyl derivatives of disubstituted barbituric acids or disubstituted derivatives of 2-thiobarbituric acid. When these compounds are given intravenously they are much more active but for a much shorter period than any of the compounds mentioned thus far. It has been found, however, that long continued intravenous injection or repeated intravenous injection of these compounds may lead to a progressive prolongation of depression, indicating that the drugs are not being rapidly and completely destroyed as might be inferred from the short period of depression or anesthesia following the initial injection. Butler and Bush (15) suggested that these substances might be transformed *in vivo* not into inactive compounds, but into less active compounds of longer duration of action. They showed that this is definitely the case with N-methylbarbital (11, 15). Following the intravenous administration of anesthetic doses of this drug into dogs, they isolated barbital from the urine in as much as 69 per cent yield; only 2 to 3 per cent of unchanged N-methyl-barbital was recovered.

In similar experiments with N-methylphenobarbital (Mebaral or Prominal), Butler and Bush isolated phenobarbital with a yield of 4 per cent of the dose; no unchanged N-methylphenobarbital was recovered. They also studied the higher N-alkyl derivatives of barbital to see to what extent dealkylation was responsible for their short action. From the ethyl derivative 30 to 40 per cent of the dose was recovered as barbital. The *n*-propyl derivative in one case yielded a trace of barbital, but usually no barbital could be found. The isopropyl, allyl, *n*-butyl and phenyl derivatives yielded only very small amounts of hypnotic in the urine as determined by bio-assay in mice. Hence, although the inactivation of *n*-butyl and *n*-propylbarbital is even more rapid than that of the methyl and ethyl compounds, the inactivation cannot in any great measure be attributed to dealkylation.

The fact that little or no barbital is found in the urine after the administration of certain N-alkyl derivatives of barbital does not necessarily indicate that dealkylation does not occur, but rather that another reaction is much more rapid. The nature of this other reaction has not been determined. It is known, however, that the introduction of a methyl group on a nitrogen atom of a barbiturate alters the stability of the ring toward aqueous alkali to a degree dependent on the other groups present. It is possible that *in vivo* the rate of ring opening is in some cases more important than that of dealkylation.

Evipal is an N-methylbarbiturate of some clinical importance. Bush and Butler

(12) found that whereas *nor*-Evipal is excreted to the extent of 10 per cent, urine collected after the administration of Evipal contains such small amounts of narcotic material as to indicate that not more than 10 per cent of the drug is demethylated to *nor*-Evipal. Apparently the most important detoxification reaction is oxidation of the cyclohexenyl ring as occurs in Phanodorn and *nor*-Evipal. The same investigators (13) were able to isolate from urine 5-cyclohexenonyl, 5-methylbarbituric acid in an amount equivalent to about 5 per cent of the dose of Evipal. They also isolated two other substances; elementary analyses indicated that they were isomeric 5-cyclohexenonyl, 1,5-dimethylbarbituric acids.

No metabolites of Eunarcon, the N-methyl derivative of Nostal, have been isolated. The drug affords possibilities for demethylation and ring cleavage in addition to the formation of acetonyl compounds as in the case of Nostal and Pernoston. The only work reported on this compound is that of Glet (43). He found that urine collected after the administration of Eunarcon gave a negative reaction with the cobalt color test and contained no organic bromine.

Narconumal is the N-methyl derivative of Alurate. Thalheimer (123) reported that in one human experiment more than 20 per cent of this compound could be recovered after an anesthetic dose of 2 gm. Also, Demole (24) stated that 4 per cent of an intravenous dose of 60 mgm. per kgm. given to a dog was excreted unchanged in the urine in the first 20 hours. If these results are reliable, the entire picture of the metabolism of the barbiturates is complicated further, because they would indicate that the N-methyl-barbituric acids can in certain cases be stable *in vivo*. Unfortunately, neither investigator mentioned his method of identification. Bush and Butler (10) have obtained results which are at variance with those of Thalheimer and of Demole. They found very small amounts of the demethylated compound but no unchanged drug in the urine of dogs anesthetized with Narconumal. In their opinion, the fact that the pharmacological activity in mice was much less than that of Alurate indicated that this compound is different from the other N-methyl compounds and is detoxified in a different manner.

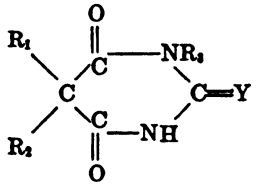
Two thiobarbituric acid derivatives which are of interest clinically are thiopental and Thioethamyl. Apparently these barbiturates are excreted in the urine only in traces (59), but the problem has not received much study. Recently Mark and coworkers (92) reported the isolation of two metabolites of thiopental from urine. They stated that one of these was purified and found to possess at most a mild sedative action. Further details are lacking.

There has been speculation that the sulfur of thiobarbiturates may be replaced by oxygen *in vivo*, which accounts for the prolonged duration of anesthetic effect following large doses. However, there is no chemical evidence to support this. Kozelka and Hine (83) were unable to demonstrate the presence of the sulfur-free analogs in the tissues after successive injections of thiopental and Thioethamyl into dogs and rabbits. Since they were also unable to detect the thiobarbituric acids by color reactions, it seemed probable that the residual depression is due to some metabolic product. Knowing that thiobarbital acts similarly to other thiobarbiturates, Bush and Butler (14) analyzed the urine of dogs treated with this

substance for unchanged thiobarbital and the easily detectable barbital. There was no evidence that either of these substances was present in the urine.

Kemithal, 5-allyl, 5-cyclohexenyl, 2-thiobarbituric acid, has had clinical use in England. Carrington and Raventós (19), using a copper sulfate-diethyl amine color method, found that rabbits given a total of 750 mgm. intravenously eliminated about 2 per cent of the dose in the urine. In addition they found substances giving a positive reaction in the cobalt color test equivalent to about 2.5 per cent of the dose. Nearly all these materials were excreted during the first 24 hours following administration. From the urine of a man receiving 6.0 gm. of Kemithal by intravenous injection, only 46 mgm. of thiobarbituric acid were recovered during the first 24 hours after anesthesia.

GLOSSARY AND INDEX[1]



COMMERCIAL NAME	N.N.R. OR U.S.P. NAME	R_1	R_3	R_3^2	Y[3]	PAGE REFERENCES
Allonal (see Alurate)						
Allurate	Aprobarbital	allyl	isopropyl			229, 231, 236
Amytal	Amobarbital	ethyl	isoamyl			220–221, 223–229, 232
Butisol	Butabarbital	ethyl	*sec*-butyl			229
Curral (see Dial)						
Delvinal	Vinbarbital	ethyl	1-methyl-1-butenyl			227, 229
Dial	Diallyl barbituric acid	allyl	allyl			221, 225–229, 231
Dormovit		furfuryl	isopropyl			229, 235
Evipal	Hexobarbital	cyclohexenyl	methyl	methyl		223, 227–228, 230, 234–236
Evipan (see Evipal)						
Eunarcon		2-bromallyl	isopropyl	methyl		229, 236
Ipral	Probarbital	ethyl	isopropyl			229
Kemithal		allyl	cyclohexenyl		S	221, 224, 228, 230, 237
Luminal	Phenobarbital	ethyl	phenyl			219, 224–231, 235
Mebaral (see Prominal)						
Medomin		cycloheptenyl	ethyl			229, 234
Narconumal		allyl	isopropyl	methyl		229, 236
Nembutal	Pentobarbital	ethyl	1-methylbutyl			221–225, 227–230, 232–233
Neonal	Butethal	*n*-butyl	ethyl			221, 225, 227, 229–232
Noctal (see Nostal)						
Nostal	Propallylonal	2-bromallyl	isopropyl			229, 233–234, 236
Numal (see Alurate)						

COMMERCIAL NAME	M.N.R. OR U.S.P. NAME	R_1	R_2	R_3^2	Y^3	PAGE REFERENCES
Ortal	Hexethal	ethyl	*n*-hexyl			221, 229, 232
Pentothal	Thiopental	ethyl	1-methylbutyl		S	221, 223-224, 227-228, 230, 236
Pernocton (see Pernoston)						
Pernoston	Butallylonal	2-bromallyl	*sec*-butyl			229-230, 233-234, 236
Phanodorm (see Phanodorn)						
Phanodorn	Cyclobarbital	cyclohexenyl	ethyl			221, 227, 229, 234
Phemitone (see Prominal)						
Prominal		ethyl	phenyl	methyl		229, 235
Rutonal		methyl	phenyl			229, 231
Sandoptal	Allyl barbituric turic acid	allyl	isobutyl			226, 229, 231
Seconal	Seconal	allyl	1-methylbutyl			224, 227, 229
Sigmodal		2-bromallyl	1-methylbutyl			
Soneryl (see Neonal)						
Surital		allyl	1-methylbutyl		S	228
Thioethamyl		ethyl	isoamyl		S	223, 228, 230, 236
Veronal	Barbital	ethyl	ethyl			217-218, 220, 223-230, 235, 237

[1] In this table no distinction is made between barbituric acid derivatives and their salts.
[2] R_3 = H unless otherwise designated.
[3] Y = O unless otherwise designated.

SUMMARY

Much published work on the metabolism of the barbiturates cannot be accepted as reliable because of the lack of specificity of the methods of determining the drugs. Colorimetric and ultraviolet spectrophotometric methods are sensitive, but they cannot distinguish the drugs from those metabolic products which also are barbiturates. (They are satisfactory only for barbital, which is not degraded *in vivo*.) The gravimetric method properly executed gives reliable results, but the sensitivity is not great. Isotope dilution procedures can be both sensitive and specific, but they require considerable special equipment. Pharmacological methods are neither sensitive nor specific.

The absorption, distribution, detoxification and excretion of barbiturates are discussed. It appears that the drugs are rapidly and completely absorbed. Perhaps they vary slightly in the rate at which they enter cells; barbital may be the slowest in this respect. Probably they leave cells readily, as the plasma level falls. The rates of excretion or degradation or both likewise vary and are the more rapid, the shorter the duration of action. Barbital is excreted without change in the urine, as also are appreciable fractions of doses of phenobarbital, Alurate, Dial and Rutonal. Only very small amounts of the other barbiturates escape metabolic alteration which occurs principally but not solely in the liver.

The identification of substances arising from the metabolic degradation of barbiturates is difficult and laborious. The products isolated result from the dealkylation of N-alkyl drugs (*e.g.*, Prominal) or partial oxidation of an alkenyl

or alkyl group in the 5-position (*e.g.*, Phanodorn, Evipal and pentobarbital) or both (*e.g.*, Evipal). Drugs containing the 2-bromallyl group (*e.g.*, Nostal and Pernoston) undergo hydrolysis of the bromine to yield acetonyl derivatives.

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