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SOME FACTORS INFLUENCING DISTRIBUTION, METABOLISM AND ACTION OF BARBITURATES: A REVIEW

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SINCE the introduction of the diethyl barbituric acid, now called barbital, by Fischer and von Mering (1) in 1904, an enormous literature has appeared on the chemistry, pharmacology and clinical uses of this drug and its numerous derivatives.The pharmacologic research of the first quarter century has been reviewed by Kochman (2). In 1939, Tatum (3) summarized important contributions up to that time. The rapid progress in biochemistry, analytical chemistry and other basic sciences in the last two decades has greatly intensified and expanded our knowledge of the pharmacologic action of these drugs. Their extensive clinical use, particularly the introduction of certain members as intravenous anesthetics, has led to numerous clinical investigations.

The authors of this review have made no attempt to present a survey of all, or even the greater part, of this immense field. Instead they have confined themselves to a selected and limited area. The aim was to summarize and critically review, where possible, certain factors which govern and modify the distribution, metabolism and action of barbiturates. While by necessity the majority, but by no means all, of the publications contributing to this field are based on animal experimentation, the authors have tried to emphasize their obvious or possible importance for the clinical use of these drugs under a variety of circumstances. It is hoped that in this way the data assembled and reviewed will also contribute to a better understanding of clinical observations and perhaps serve as a guide in specific situations where clinical experience may still be meager or absent.

In view of the outstanding importance which analytical chemical procedures play or should play in many studies of this type, a survey of these methods forms the first part of this review. This is followed by presentation and analysis of the publications concerning themselves particularly with the chemical aspects of distribution and metabolism of the barbiturates.

Certain biological conditions which cause variations in response are taken up next, followed by a discussion of a selected number of papers which deal with the modification of barbiturate action by other drugs. The experimentally and clinically important question of the role of the liver and kidneys in the action and metabolism of barbiturates forms the last part.

Read in part before the Biennial Western Conference on Anesthesiology, San Francisco, California, March 21, 1955, and accepted for publication January 26, 1956. The authors are in the Department of Pharmacology of the Abbott Laboratories in North Chicago.

The authors wish to emphasize that they have not tried to present a complete bibliography or to discuss all papers bearing on the subjects of this review. On the other hand, the reader will find it understandable that certain reports are repeatedly discussed at several places in this review. Such repetition appeared to be occasionally necessary in the interest of clarity of some topics and to illustrate the interrelation of various factors.

Generic names of drugs have been used throughout this paper where possible. Table 1 lists these generic names in alphabetical order and permits reference to trade names and chemical composition.

TABLE 1
CHEMICAL NAMES

Generic Name	Trade Name®	Chemical Name
Allobarbital	Dial	5,5-diallylbarbituric acid
Amobarbital	Amytal	5-ethyl-5-isopentylbarbituric acid
Aprobarbital	Alurate	5-allyl-5-isopropylbarbituric acid
Barbital	Veronal	5,5-diethylbarbituric acid
Butallylonal	Pernoston	5-(2-bromoallyl)-5-sec. butylbarbituric acid
Carinamide	Staticin	p-α-toluenesulfonamido-benzoic acid
Chlorpromazine	Thorazine	2-chloro-10-(3-dimethylaminopropyl)-phenothiazine
Cyclobarbital	Phanodorn	5-(1-cyclohexen-1-yl)-5-ethylbarbituric acid
Dimercaprol	BAL	2,3-dimercapto-1-propanol
Diphenhydramine	Benadryl	2-diphenyl-methoxy-N,N-dimethyl-ethylamine
Disulfiram	Antabuse	Tetraethylthiuram disulfide
Hexethal	Ortal	5-ethyl-5-hexylbarbituric acid
Hexobarbital	Evipal	5-(1-cyclohexen-1-yl)-1,5-dimethylbarbituric acid
Kallikrein	Padutin	pancreatic extract, free from insulin, histamine, and choline
—	Megimide	β,β-methyl ethylglutarimide (NP13)
Mephobarbital	Mebaral (or Prominal)	5-ethyl-1-methyl-5-phenylbarbituric acid
Metharbital	Gemonil	5,5-diethyl-1-methylbarbituric acid
N-methyl thiopental	—	5-ethyl-1-methyl-5-(1-methylbutyl)-2-thiobarbituric acid
Pentobarbital	Nembutal	5-ethyl-5-(1-methylbutyl)-barbituric acid
Phenobarbital	Luminal	5-ethyl-5-phenyl-barbituric acid
Physostigmine	Eserine	an alkaloid from *Physostigma venenosum*
Promethazine	Phenergan	10-(2-dimethylaminopropyl)-phenothiazine
Pyrilamine	Neo-Antergan	2-((2-dimethylaminoethyl)(p-methoxybenzyl) amino) pyridine
Secobarbital	Seconal	5-allyl-5-(1-methylbutyl)barbituric acid
Serotonin (Enteramine)	—	3-(2-aminoethyl)-5-indolol
Thialbarbitone	Kemithal	5-allyl-5-(2-cyclohexen-1-yl)-2-thiobarbituric acid
Thiamylal	Surital	5-allyl-5-(1-methylbutyl)-2-thiobarbituric acid
Thioethamyl	Thioamytal	5-ethyl-5-isopentyl-2-thiobarbituric acid
Thiopental	Pentothal	5-ethyl-5-(1-methylbutyl)-thiobarbituric acid
Trihexyphenidyl	Artane	2-cyclohexyl-2-phenyl-1-piperidine-propanol
Tripelennamine	Pyribenzamine	2-(benzyl(2-dimethylaminoethyl)amino)-pyridine
—	Eunarcon	5-(2-bromoallyl)-5-isopropyl-1-methyl barbituric acid
—	Hydergin	hydrogenated ergot alkaloids: dihydroergocornine methane sulfonate dihydroergocristine methane sulfonate and dihydroergocryptine methane sulfonate
—	LSD	N,N-diethyl-lysergamide

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METHODS

It has been said that the history of a science lies in the history of its methods. This is also true for the field of drug metabolism because only since the development of accurate and specific methods have we begun to understand some of the phenomena associated with the actions of barbiturates. Because most barbiturates have many properties in common, they will be discussed as a group rather than as individuals compounds.

There have been two modern reviews, by Maynert and Van Dyke, (4) and by Raventos (5), in which the work on methods has been summarized. We have surveyed the most widely used techniques in table 2, with some indication of their limits and specificity.

TABLE 2
SUMMARY OF GENERAL METHODS

Method	Estimated Limit of Determination (mg.)	Specificity
Gravimetric	10	fair
Colorimetric	.05	metabolites may interfere
Paper Chromatographic	.05	good
Ultraviolet	.01	metabolites may interfere
Infrared	1–0.1	good
Radioactive	.001	metabolites may interfere

The method of choice should (1) be specific for the unchanged drug but not the metabolites; (2) require only small amounts of biological material; (3) be accurate, and (4) be simple. To be useful in clinical work it should be capable of determining at least 10 micrograms of barbiturate in 1 to 5 grams of blood or tissue with an accuracy of ± 5 per cent.

The gravimetric method is the oldest and was used by Fischer and von Mering (1) in the study of barbital. It has the disadvantage of requiring a high order of purification, large amounts of barbiturate (about 10 mg.), and consequently large samples of biological material. Today its use is largely limited to autopsy material.

The best known colorimetric method was described by Koppanyi *et al.* (6) by which a blue color was formed with cobaltous chloride in alkaline solution. The method needs special precautions to insure specificity because many of the barbiturate metabolites contain the barbiturate ring intact and also give a color. The values obtained are usually high. It has a limited degree of sensitivity.

Hellman, Shettles and Stran (11) were the first to apply the exceedingly useful ultraviolet absorption method to the determination of thiopental in blood. Since then this method has been refined by Jailer and Goldbaum (12) and has been widely used. These early procedures had the disadvantage of lack of specificity, because it was later found that some barbiturate metabolites in which the ring was

intact had absorption characteristics similar to the parent drug. In most tissues the unchanged drug is responsible for the major part of the absorption but, in urine, the ultraviolet absorption is mostly caused by metabolites.

Brodie *et al.* (13) increased the specificity of the method by use of hexane: iso-amylalcohol mixtures and rigorously controlling the pH of the extraction. They were able to extract the unchanged thiopental from tissues and urine, leaving the metabolites behind in the water phase. A similar method for pentobarbital and secobarbital has also been described (14). These methods will measure about 10 micrograms of barbiturate in 2 to 5 Gm. of tissue or blood. While the principle of ultraviolet absorption is mostly used for quantitative work, Goldbaum (15) has described an adaptation which qualitatively differentiates between the spectra of different barbiturates by their characteristic shift in absorption spectra when measured at two different pH's. Maher and Puckett (16) have summarized their results with this method on nineteen commercially available barbiturates. Their data cover three years experience with this procedure in routine toxicological analyses in man.

Infrared spectroscopy has been little applied to date for quantitative work, but is becoming more widely used for identification. This method can be applied to samples as small as 1 mg. with existing commercial equipment. With special adaptation, using the KBr pellet technique, about 100 microgram is the present limit (Anderson and Woodall, 17).

The radioactive isotope method is a useful technique particularly in the study of metabolites. In our hands (Taylor *et al.* 8) we were able to measure as little as 1 microgram of sulfur labeled thiopental. The sensitivity of the method is largely dependent on the ability of the chemist to synthesize a product having a high degree of radioactivity. In fact, getting the compound synthesized with the desired isotope in the proper position, the special counting equipment and the time needed are some of the deterrents to working in this field. To date only C^{14}-pentobarbital and thiopental and S^{35}-thiopental have been studied by this method. As with the ultraviolet procedure, special precautions are necessary in measuring the unchanged drug because most of the metabolites are also radioactive.

Paper chromatography has proven to be a simple method useful for detecting and identifying mixtures of barbiturates. The lower limit of sensitivity is about 50 micrograms and is largely dependent on the reagent used to identify the band. Several references to this method are given by Raventos (5). For more recent work see Deininger (7) who gives the Rf values for thirteen barbiturates. This method is particularly useful in the study of metabolites of radioactively tagged thiopental (8) and pentobarbital (9, 10).

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The methods used for the isolation and identification of metabolites are variants of those applied to the parent drug, with the addition of classical chemical procedures to determine structure. One technique that has not received the attention it deserves is the use of ion exchange resins. This will undoubtedly be explored in the near future.

Pentobarbital and amobarbital have been labeled with N^{15} in the barbiturate ring (Van Dyke *et al.* 18) and their metabolism studied in dogs (Maynert and Van Dyke, 19, 20). The results are summarized by Maynert (21). As a general tool, N^{15} labeling has not been used by other investigators of barbiturate metabolism. As a method, N^{15} determinations are time consuming, require a mass spectrograph, specialized synthesis and lack the sensitivity obtainable with radioactive isotopes.

There is a remote possibility that someone may develop a more sensitive fluorescent method, using the spectrophotofluophotometer which has recently come into existence (Bowman *et al.*, 22), but for the next few years most investigators will probably use the ultraviolet method of Brodie and his collaborators for measuring barbiturates in biological tissues and fluids.

DISTRIBUTION IN THE BODY

After administration, barbiturates are soon found in practically all tissues, the amount depending on the dose and type of the barbiturate and time after administration.

Figure 1 is a generalized diagram showing the major pathways of distribution and fate of a barbiturate. Entrance into the body may be

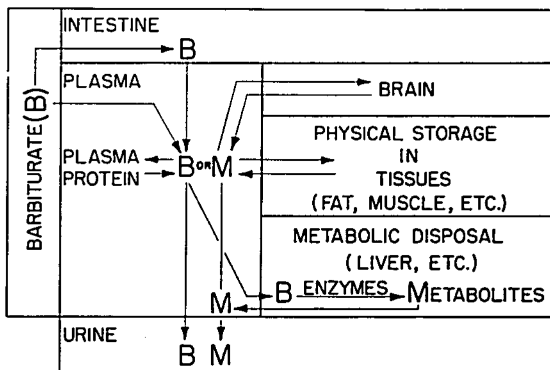

FIG. 1. A generalized, schematic diagram of the major pathways of the distribution and excretion of a barbiturate and its metabolites: B = barbiturate; M = metabolites. Arrows indicate direction of movement (adapted from Toman and Taylor, 64).

either by way of intestine or parenterally. In the latter case the blood stream contains most of the dose immediately or soon after the injection and the drug is then rapidly taken up by all tissues. When the brain concentration reaches a certain critical level, the animal falls asleep. The liver, muscles, and so forth, remove the bulk of the barbiturate from the blood. In the case of thiopental, 60 to 70 per cent of the drug in the blood may be adsorbed to the plasma proteins. During the period when the blood concentration is dropping rapidly the tissues may build up a concentration higher than the blood. After a time, depending on barbiturate and dose, the blood and the tissues come into equilibrium. From this point on, the decline in blood concentration is slow. The rate of decline beyond this point is often taken as a measure of the rate of metabolism of the drug. The blood and brain content decline with time until a concentration is reached below which the animal awakes. Metabolic degradation continues, however, until the drug is removed—a process that may take hours or even days after the hypnotic effect has disappeared. It is the rapid removal from the blood by the tissues that is responsible for the short action of the so-called "ultra-short" acting barbiturates.

With compounds such as N-methylphenobarbital, demethylation occurs in the liver, forming phenobarbital as the metabolite. This in turn is distributed throughout the body so that the hypnotic effect is the result of a combination of the unchanged drug and its metabolite (Butler, 23). It should be mentioned that metabolites are often further metabolized in turn before they can be excreted, so that the urine may contain several metabolites from a single barbiturate.

Table 3 lists tissue plasma ratios of some barbiturates in the tissues of the dog three hours after injection. As can be seen, the ratios all fall within a range that is usually no greater than threefold, except for fat which will be discussed separately. Data on tissue distribution of barbital, phenobarbital, pentobarbital, and secobarbital can be found in the paper by Goldbaum and Smith (24). These drugs do not show

TABLE 3

DISTRIBUTION OF SOME ULTRA-SHORT AND SHORT-ACTING BARBITURATES IN THE TISSUES OF THE DOG

Dose—40 mg./kg. (intravenously). Time: 3 hours

Barbiturate	Tissue/plasma Ratio							Ref.
	Fat	Brain	Liver	Kidney	Muscle	Lung	Spleen	
N-methylthiopental	24.5	1.7	2.5	2.5	3.1	—	—	25
Thialbarbitone	8.0	—	1.3	0.8	0.8	0.5	—	36
Thiamylal	8.0	0.7	1.6	0.9	1.3	0.9	0.7	36
Thiopental	6.0	1.2	1.6	1.2	1.3	0.8	0.8	36
Hexobarbital	3.2	—	1.3	1.1	0.9	—	—	36
Pentobarbital	1.1	1.2	1.9	1.4	0.8	0.6	1.2	14

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a preferential affinity for brain. Because of their particular importance in the pharmacodynamics of barbiturates, plasma, plasma proteins, brain and fat will be discussed in detail.

Plasma

As mentioned previously, the concentration of a barbiturate in plasma declines rapidly until an equilibrium point is reached, then declines more slowly. The time required for this equilibrium point or steady state to be reached varies both with species and barbiturate used. With a small dose in small animals (for example, rats and rabbits) up to thirty minutes may elapse before this is accomplished. For man, a large dose may take up to eight hours. With very small doses and short sleeping time, animals frequently awake before equilibrium is reached. Because awakening occurs on a rapidly falling concentration curve, anything that will slow down the exchange of the drug between plasma and tissues will result in a changed sleeping time —usually longer. It is this phenomenon, particularly with short-acting barbiturates, that has caused many conflicting reports on chemical agents prolonging sleeping time of barbiturates.

If one plots the logarithm of the plasma concentration against time after this "equilibrium" has been reached, one usually obtains a straight line. This straight portion of the curve is used to calculate the rate of disappearance of barbiturate from the body. In certain instances (pentobarbital in man) it represents the rate of metabolic degradation; with barbital, it represents the rate of excretion; with phenobarbital, it is a combination of both.

Table 4 summarizes the recent literature on the rate of disappearance of individual barbiturates in various species. Many of the values have been calculated from the straight line portion of published data and graphs and are considered to be approximations. In some instances the rate expressed as per cent per hour metabolized is the average of several values. This is not mathematically correct but gives a close approximation. The "long-acting" barbiturates are slowly excreted, which accounts for their prolonged action, but the rate of removal from the body of "short" and "ultra-short" acting ones is not very different. As explained previously, their short action is dependent more on distribution phenomena than on the rate of metabolic degradation. Mice, with their rapid basal metabolism, destroy all barbiturates faster than other species listed here. Man usually shows the slowest rate of destruction.

Thiopental and N-methylthiopental (Papper *et al.* 25) give slightly anomalous results. In some human patients the thiopental curves never actually flatten out to give a straight line, so that values calculated at longer times after injection give slightly lower values. For example, Brodie's early work on thiopental suggested 15 per cent per

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TABLE 4

RATE OF REMOVAL OF BARBITURATES FROM BODIES OF DIFFERENT SPECIES

Barbiturate	Species	No. of Subjects	Dose	Rate		Remarks	Ref.
				% hour	% day		
Barbital	Dog	1	55 mg./kg.	3.5			52
	Man	4	1.5 Gm./each		23(19-25)[5]		80
Phenobarbital	Rat	10	47 mg./kg.	6.4		calcd. from data[1]	208
	Dog	1	46 mg./kg.	1.2	24	calcd. from graph[1]	23
	Rabbit	1	137 mg./kg.	1.5	30	calcd. from data[1]	209
	Man	3	0.75 Gm./each		17(14-27)		80
	Man	9	2-4 Gm./each	0.8	17		66
	Man	5	2.4 mg./kg./day		19(14-23)	after discontinuance	210
Aprobarbital	Man	3	0.75 Gm./each		48(35-70)		80
Pentobarbital	Mouse	40	50 mg./kg.	80		calcd. from graph	123
	Mouse	30	80 mg./kg.	78		whole body analyzed	211
	Rat	24	30 mg./kg.	31		calcd. from data	220
	Rat	16	60 mg./kg.	22		calcd. from data[1]	212
	Rabbit	5	25 mg./kg.	35			211
	Rabbit	10?	24 mg./kg.	39			213
	Rabbit	1	33 mg./kg.	32			209
	Dog	6	25 mg./kg.	15			211
	Dog	2	30 mg./kg.	31.5(30-33)			214
	Dog	4	? mg./kg.	15			14
	Man	6	0.75-1.0 Gm./each	4(0.5-6)			14
	Man	6	0.8-1.0 Gm./each	1.5			66
Secobarbital	Mouse	30	80 mg./kg.	50		whole body analyzed	211
	Rabbit	5	25 mg./kg.	44			211
	Dog	6	25 mg./kg.	14			211
	Man	6	1.3-1.4 Gm./each	2			66
Amobarbital	Rabbit	1	50 mg./kg.	40		calcd. from data[1]	209
Thiopental	Mouse	20	70 mg./kg.	40		whole body analyzed	215
	Mouse	10	70 mg./kg.	15		(plasma) (approximate)	216
	Rat	17	30 mg./kg.	7.5		0-6 hours 10%/hour[4] 6-12 hours 5%/hour whole body analyzed	26
	Dog	22	20 mg./kg.	6			26
	Dog	6	20 mg./kg.	15		(approximate)	216
	Dog	4	40 mg./kg.	5			14
	Man	3	12 mg./kg.	15			14
	Man	?	1-2 Gm./each	15			13
	Man	1	3 Gm./each	10[4]		(approximate)	36
Thiamylal	Dog	6	21 mg./kg.	15		(approximate)	216
	Man	1	3 Gm./each	10[4]		(approximate)	36
Thialbarbitone	Man	1	4 Gm./each	10[4]		(approximate)	36
Thiorthamyl	Dog	6	20 mg./kg.	15		(approximate)	216
5-isopropyl-5-(2-methylpentenyl)-2-thiobarbiturate sodium	Dog	6	21 mg./kg.	15		(approximate)	216
Methabarbital	Rat	10	50 mg./kg.	14		calcd. from data[1]	208
	Dog	1	50 mg./kg.		ca. 50	demethylated to barbital non-logarithmic	52
	Dog	1	49 mg./kg.	5		demethylated to phenobarbital	23
Hexobarbital	Mouse	5	100 mg./kg.	99 ± 6[3]		whole body analyzed	153
	Mouse	3	100 mg./kg.	99 ± 6[3]		whole body analyzed	153
	Mouse	6	200 mg./kg.	87.5 ± 5		whole body analyzed	132
	Rat	5	100 mg./kg.	160			214
	Dog	3	30 mg./kg.	35(23-46)			214
	Man	1	3 Gm./each	10[4]		(approximate)	36
N-methylthiopental	Dog	3	40 mg./kg.	15		(approximate)	25
	Man	6	2-3.5 Gm./each	10		(approximate)	25

[1] Logarithmic relationship assumed.
[2] Non-logarithmic-(proportional with time).
[3] Mean ± standard deviation.
[4] Same individual.
[5] Average and range.

hour for the degradation rate in man. As he studied longer time periods this value dropped to an average of 10 per cent per hour. Between sixteen to twenty-four hours after injection, the value actually may be 5 per cent per hour. The data of Papper *et al.* (25) for N-methylthiopental in man show a break in the plasma concentration curve at about ten hours after injection. Similar results were obtained by Shideman *et al.* (26), who measured total body destruction in the rat.

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Up to six hours after injection the rate of destruction is a straight line function with time and appears to be about 10 per cent per hour, but from six to twelve hours it is closer to 5 per cent. The investigators calculated the average and report it as 7.5 per cent per hour. This behavior seems to be characteristic for thiobarbiturates, but additional work on other barbiturates may show that it is a more general phenomenon. This is of importance because it means that one cannot assume the degradation of a drug to be a first order reaction and the rate of destruction always proportional to its concentration. The plasma constitutes about 10 per cent of the total body weight and the level of barbiturate at any time represents the sum total of several unknown factors acting simultaneously.

TABLE 5

BARBITURATE PLASMA LEVELS AT AWAKING—SINGLE DOSE

Barbiturate	Species	Dose mg./kg.	Route	No. of Subjects	Plasma Level at Awaking	Remarks	Ref.
					microgm./ml.		
Barbital	Man	200	Oral	1	15	approximate	217
	Man	0.6 gm./each	Oral	1	8	approximate	217
	Man	?	Oral	1	8	approximate	217
Phenobarbital	Man	?	Oral	1	12		217
Pentobarbital	Mouse	50	IP(?)	40	26		123
	Rat	30	IP	12	29		220
	Rat	60	IP	16	20		212
	Rabbit	15	IV	10	10 ± 1[1]		211
	Rabbit	25	IV	5	11 ± 2		211
	Rabbit	25	IV	15	10 ± 2		211
	Rabbit	30	IV	6	12 ± 2		218
	Rabbit	35	IP	6	12 ± 0.4		218
	Dog	20	IV	6	15 ± 2		211
	Dog	25	IV	6	17 ± 2		211
	Man	0.75–1.0 Gm./each	IV	1	8	approximate	14
	Man	0.8 Gm./each	Oral	1	8	approximate	217
	Man	2.0 Gm./each	Oral	1	10	approximate	217
Secobarbital	Rabbit	15	IV	5	10 ± 1		211
	Rabbit	25	IV	15	8 ± 2		211
	Rabbit	25	IV	5	9 ± 1		211
	Dog	20	IV	6	11 ± 1		211
	Dog	25	IV	6	12 ± 1		211
	Man	0.6 Gm./each	Oral	1	8		217
Hexobarbital	Rat	100	IP	5	41		214
Thiopental	Mouse	30	IV	3	32	(serum)	90
	Mouse	45	IV	3	49	(serum)	90
	Mouse	70	IP	20	27 ± 2		215
	Mouse	70	IV	10	22	estimated from graph	216
	Rabbit	25	IV	6	20 ± 4[2]		221
	Rabbit	25	IV	6	23 ± 3		33
	Rabbit	27	IV	6	19 ± 4		162
	Dog	10	IV	6	9	estimated from graph	216
	Dog	20	IV	6	12 ± 0.5		216
	Dog	30	IV	6	15	estimated from graph	216
	Dog	35	IV	6	18	estimated from graph	216
	Dog	25	IV	?	17	(serum)	90
	Dog	40	IV	?	24	(serum)	90
	Man	59	IV	1	33	same subject	219
	Man	36	IV	1	23		
	Man	67	IV	1	28	same subject	219
	Man	40	IV	1	19		
	Man	43	IV	1	20	same subject	219
	Man	22	IV	1	13		
	Man	50	IV	1	26	same subject	219
	Man	54	IV	1	25		219
	Man	65	IV	1	27		219
	Man	33	IV	1	17		219
Thioethamyl	Dog	20	IV	6	23 ± 8		216
Thioamylal	Dog	21	IV	6	9.5 ± 0.6		216
5-isopropyl-5(2-methylpentenyl)-2-thiobarbiturate sodium	Dog	21	IV	6	6.4 ± 1.3		216

[1] Mean ± standard deviation.
[2] Average deviation.

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Data on the relationship between plasma levels of different barbiturates and awaking have been previously summarized by Maynert and Van Dyke (4). Values obtained by the ultraviolet spectrophotometric method have been incorporated in table 5. There would be more data except for the unhappy tendency on the part of some workers not to indicate awaking time. As a result, many fine analytical reports in the literature are useless for correlation studies. With the exception of the mouse and the rat, all species studied awoke within the surprisingly narrow range of 8 to 17 micrograms per milliliter when given barbital, phenobarbital, pentobarbital or secobarbital. Also, the plasma level at awaking was not dependent on the size of the dose. The data on thiopental showed that species of animals other than mice and rats awake at levels between 13 to 49 micrograms per milliliter. Unlike the oxygen analogues, plasma levels at awaking in man were dependent on size of dose—those receiving high doses awoke at high plasma levels. It is these data on which Brodie *et al.* (219) based their contention that an acute tolerance is developed with thiopental. The reasons for this are at present unknown.

It is perhaps surprising that there was not a greater range in plasma values considering the many factors that have been shown to influence plasma values, such as: (1) the concentration of barbiturate in arterial blood is slightly higher than in venous blood [Peterson *et al.* (27)]; (2) the relative amount of water in the subject [Taylor *et al.* (28)]; (3) hemodilution as with thiopental [Tureman *et al.* (29)]; (4) loss in plasma volume as with pentobarbital [Simpson *et al.* (30)]; (5) carbon dioxide tension [Dundee (31), Rayburn *et al.* (32)]; and (6) the degree of binding of plasma proteins [Goldbaum and Smith (24), Taylor *et al.* (33)], just to mention a few.

PLASMA BINDING

Plasma values are usually determined on the whole plasma, as a matter of convenience. However, all barbiturates investigated to date are bound to a varying extent by the albumin fraction of the proteins. Of seventeen barbiturates studied *in vitro* by Goldbaum and Smith (24), binding to bovine serum albumin was shown to be the least for barbital (5 per cent) and the greatest with thiopental and hexethal (65 per cent). The binding is reversible and is dependent on both the concentration of the albumin and of the drug in the ultrafiltrate. The chemical structure of the side chain was important with compounds having longer chains, being bound more strongly than those with short chains. The sulfur analogues were more strongly bound than the oxygen members. As a rule short-acting barbiturates are more strongly bound than long acting ones.

The concentration of the unbound drug in the plasma water or ultrafiltrate is the physiologically active concentration in the blood.

This was shown by Taylor *et al.* (33) using thiopental in rabbits. Twenty-four hours after bilateral nephrectomy, rabbits slept longer and awoke at a higher *total* plasma level than the controls. However, an analysis of both groups showed that the concentration of thiopental in the plasma ultrafiltrate was not significantly different. It should be mentioned that brain tissue has a greater affinity for secobarbital, pentobarbital and thiopental (but not barbital and phenobarbital) than the plasma in the rabbit (Goldbaum and Smith, 24). The significance of binding by the tissues is not known.

BRAIN

With the exception of barbital and phenobarbital the equilibrium between brain and plasma is rapidly established and remains relatively constant thereafter. In one report (26) the brain plasma ratio in a rat given thiopental was 0.7 at one minute after injection and 0.5, twenty-four hours later. The data from the literature is summarized in table 6.

It is a well known phenomenon that the short-acting barbiturates, such as the thiobarbiturates and the N-methyl barbiturates, have a rapid onset of anesthesia. Butler (34) showed that within one minute after the injection of hexobarbital into mice, the drug had reached its maximum concentration in the brain. Thiopental behaves in a similar manner in rats [Bollman *et al.* (35), Shideman *et al.* (26)]. Brodie (36) found thiopental in the cerebrospinal fluid of a dog within a few minutes after injection into the blood stream [Mark *et al.* (37)]. This indicates that thiopental passes into the brain with great rapidity. Probably most of the barbiturates having rapid onset of action penetrate the brain rapidly.

Phenobarbital and barbital are known for the delay or lag in the onset of anesthesia even by intravenous administration. Butler (34) analyzed the brains of mice injected with barbital. He found that brain concentration increased gradually and was accompanied by increasing neurological effects until sleep occurred at a concentration of about 0.30 mg. per kg. of brain. Greig and Mayberry (38) also showed that, after the injection of barbital in mice, an average of sixteen minutes elapsed before sleep occurred. When physostigmine was injected with barbital, the lag was reduced by one-half. Analyses of the brains showed that sleep occurred at the same concentration and that the barbital penetrated the brain faster in the presence of physostigmine. Thus it would seem that the lag of onset of sleep with barbital is caused by the slowness with which it penetrates the brain.

The distribution of barbiturates in the different anatomical regions of the central nervous system has been investigated by several workers: (1) barbital in dog brain [Maynert and Van Dyke (39)]; (2) thiopental in dog brain [Brodie (36)]; (3) thiopental in cat brain [Taylor *et al.* (40)]. These investigators concluded that brain as a whole did

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not preferentially concentrate barbiturates when compared to other tissues of the body and that there was no significant difference in the different regions of the brain. The work of Hubbard and Goldbaum (41) is partly opposed to this view. Working with thiopental in the dog, they found that with an average plasma level of 1.7 mg. per 100 ml. there was no significant difference in the various regions. However, when larger doses were given, so that the plasma level was higher than this figure, then a significant difference could be demonstrated.

TABLE 6

BARBITURATE BRAIN/PLASMA RATIOS IN ANIMALS AT VARIOUS TIMES

Barbiturate	Species	Dose IV mg./kg.	Time													Ref.
			Minutes							Hours						
			1	5	10	20	30	36	40	1	2	2.5	3	4	24	
Barbital	Rabbit	50		0.4						0.7						24
Phenobarbital	Rabbit	33			0.5											209
	Rabbit	50		0.6						0.7						24
	Rabbit	140					0.8									209
Pentobarbital	Rat	60[1]								1.0		1.0		0.8		212
	Rabbit	15							1.7							211
	Rabbit	33[1]			1.1											209
	Rabbit	50		1.7						1.4						24
	Dog	40											1.2			14
Amobarbital	Rabbit	33[1]		1.5												209
Secobarbital	Rabbit	15						1.6								211
	Rabbit	33[1]												1.4		209
	Rabbit	50		1.7						1.5						24
Thiopental	Mouse	70[1]								0.5						215
	Rat	15		0.6	0.6											73
	Rat	30	0.7		0.5		0.6			0.6	0.7				0.5	26
	Rat	40	0.7		0.7		0.6			0.7	0.7					35
	Rabbit	20			1.0											40
	Rabbit	50		1.8						0.9						24
	Dog	25				1.4										42
	Dog	40											1.2[2]			36
	Dog	65													1.0	42
	Dog	77										1.6				13
Thiamylal	Dog	40											0.7[2]			36
N-Methylthiopental	Dog	40											1.7			25

[1] I.P.
[2] Same animal.

Furthermore, the possibility exists that the sensitivity of various areas of the brain to a given barbiturate level may be different. There is, though, at the present time no adequate experimental evidence in support of such an assumption.

FAT

One of the discoveries resulting from the study of tissue distribution of barbiturates is the dynamic inter-relationship between fat

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depots and duration of action. Brodie *et al.* (13) showed that the fat of thiopental dogs contained 75 per cent of the dose two and a half hours after injection. This occurs in the rat also [Shideman *et al.* (26)]. Other barbiturates also display this phenomenon. Table 4 shows some data taken from Brodie *et al.* (14, 42) in which several barbiturates were given in equal amounts to dogs. At the end of three hours, the tissues were analyzed for the unchanged barbiturates. The ratio of fat and brain to plasma are listed. The first five compounds are thiobarbiturates. It can be seen that they have a great affinity for fat. Hexobarbital, an N-methyl barbiturate, also shows this tendency, while pentobarbital had little affinity for fat.

In recent work with several N-methyl thiobarbiturates Swanson and Chen (43), and Papper *et al.* (25) have shown them to be ultra-short acting in single doses. Their short effect was explained by their remarkable affinity for the fat depots. At the end of twenty-four hours, the fat to plasma ratio was 100. Anderson and Magee (44) found that feeding corn oil before administering thiopental decreased the sleeping time. Stavinoha and Davis (45) showed that oil feeding of rats two hours prior to thiamylal (but not pentobarbital) significantly shortened sleeping time. Hermann and Wood (46) demonstrated that lean rats slept longer on thiopental than fat rats. We have shown in rabbits of the same weight and sex, that length of sleeping time was correlated with the relative amount of body water—the greater the amount of water (the less the amount of fat) the longer the sleeping time [Taylor *et al.* (28)].

All of this indicates that body fat plays a definite role in the duration of thiobarbiturate anesthesia by extracting the drug out of the blood stream, and thus causing the blood concentration to fall below the level needed to maintain unconsciousness. However, the rate at which thiopental moves into the fat from plasma is relatively slow as compared with the speed at which other tissues of the body take it out of the blood stream. For small doses of thiopental, causing short sleeping times, the tissue affinity is probably more important than fat. Therefore, the tissue binding is important for the short sleeping time, but with large or repeated doses the fat plays an increasingly important role in terminating anesthesia.

EXCRETION

The barbiturates of moderate duration of action owe this property mostly to their slow rate of metabolism. Because excretion by the kidney is slower yet, the "long-acting" barbital remains in the body for a long time. It is excreted to the extent of 90 per cent in the urine over a period of days. Phenobarbital, diallylbarbituric acid, aprobarbital, and methyl phenylbarbituric acid are excreted unchanged up to 25 per cent of the dose. Maynert and Van Dyke (4) point out that

barbiturates with less than three carbon atoms in the alkyl side chain are apt to be excreted unchanged. Barbiturates having longer alkyl side chains are largely metabolized with only a small per cent of the unchanged drug excreted in the urine, unless given in very large amounts.

METABOLISM

As previously mentioned, the physiological distribution largely determines the duration of effect of low doses of barbiturates. However, with high doses the duration of effect may be determined by their metabolic degradation. Even after the effect has disappeared, removal of the drug proceeds for hours or even days. From the point of view of the body, barbiturates are treated as a foreign substance. Their degradation is largely determined by their chemical structure and physicochemical properties. Primary metabolites (1) are usually of the same order of magnitude in molecular weight as the parent drug, (2) do not accumulate to any extent in the body [Giotti and Maynert (47)], (3) are more water soluble, (4) may be conjugated with glucuronic acid, and (5) are generally excreted rapidly by the kidney.

The general mechanisms of barbiturate metabolism have been well classified by Raventos (5). For our purpose, we will discuss only the three major mechanisms: (1) side chain oxidation, (2) nitrogen dealkylation, and (3) desulfuration of thiobarbiturates. Hydrolysis of the barbiturate ring has been shown to take place *in vivo* [Van Dyke *et al.* (18)], but it is not considered a major pathway. A single compound may react to one, two or to all three of these mechanisms. For example, N-methyl thiopental is demethylated to thiopental, which is in turn partly desulfurated and in part oxidized on the side chain to thiopental carboxylic acid.

The most important and most studied pathway is side chain oxidation. Most barbiturates having more than three carbon atoms in the side chain have yielded metabolites with —OH, —COOH, or —CO groups in the side chain. These metabolites have shown no anesthetic action quantitatively comparable to their parent drugs. Some of the metabolites recently studied have been those derived from thiopental [Brodie *et al.* (13)], pentobarbital [Maynert and Van Dyke (48)] hexobarbital [Bush *et al.* (49)], and phenobarbital [Butler (50)]. Recently there have been attempts to find a short acting barbiturate utilizing the principle of incorporating an easily oxidizable group on the alkyl side chain. At present there is not sufficient clinical evidence to indicate their success.

Dealkylation of barbiturates having N-alkyl groups in either the one or three position has been shown to be an important mechanism for hexobarbital in animals [Bush and Butler (51)], mephobarbital [Butler (23)], and metharbital [Butler (52)]. Of the alkyl groups

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studied, the methyl group is removed at a faster rate than the ethyl [Butler (53)]; larger groups are scarcely touched. Unlike the oxidation of side chains, dealkylation produces a compound that still has hypnotic properties. For example, the removal of the N-methyl group from mephobarbital produces phenobarbital. Because this reaction is more rapid than the elimination of phenobarbital, considerable amounts of phenobarbital accumulate in the animal. This makes it difficult to assess the hypnotic potency of the original compound. It is of interest that barbiturates may be methylated, since it has been reported by Deininger (54), that nor-hexobarbital can be methylated in the mouse to hexobarbital.

Desulfuration of thiobarbiturates has been demonstrated for thiobarbital (Gad, (55), [Bush and Butler (56), Raventos (57)] and thiopental [Taylor *et al.* (40)]. The sulfur atom of thiopental was oxidized in part to inorganic sulfate in the rat [Taylor *et al.* (8), Spector *et al.* (58)]. Some thiourea was found, indicating that ring opening occurred as a minor pathway. The intermediates between thiopental and inorganic sulfate were not investigated beyond the observation that the sulfur in them is still bound and is not inorganic [Taylor *et al.* (8)]. In instances where the corresponding oxygen analogues have been isolated they have made up only a small portion of the metabolites. Recently Winters *et al.* (59) have shown that rat liver mince *in vitro* can desulfurate thiopental to produce pentobarbital. Thioethamyl can be converted by the same preparation to secobarbital [Spector and Shideman (60)]. It will be of interest to see if this mechanism takes place to any extent in man, or whether it is confined to rat liver only.

ENZYMATIC DESTRUCTION

It is beyond the scope of this paper to discuss the inhibition of tissue enzyme action by barbiturates. Such work has been recently reviewed by Bain (61) and by Brody (65). However, we wish to mention briefly the metabolism of barbiturates by enzyme systems at the cellular level. The literature up to 1952 has been reviewed by Shideman (62). Shideman showed that thiopental was destroyed *in vitro* by fortified cellular homogenate of rat liver. The destruction was enhanced by oxygen and was connected in some way with the oxidative phosphorylation system. Liver was the chief organ of destruction, but other tissues, such as kidney, brain, and muscle, were also capable of destroying the drug.

Brodie and his co-workers (63) explored the enzyme systems in rabbit liver that destroy a large class of drugs. Side chain oxidation and N-dealkylation are among the reactions covered by these systems. They found that these enzyme systems were located in the microsomes of the liver. Microsomes from other tissues were examined but, in

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general, the activity was found only in the liver. The system consists of more than one enzyme and was unusual in requiring both reduced triphosphopyridine nucleotide and oxygen. Brodie concluded that it was likely that the number of the drug metabolizing enzymes was relatively small and that they were unusually specific.

DYNAMIC VARIATIONS IN RESPONSE

The lack of consistency in the response of experimental animals, and even more so of humans, towards hypnotic drugs is one of the most complicating and disturbing factors in critical studies in the field. The general problem of variation of response to drugs has been reviewed by Clark (67). We have tried to attack this problem by determining, in groups of rabbits by means of slow intravenous infusion, the individual dose in mg./kg. which is necessary to produce respiratory paralysis with several barbiturates (68). When this stage was reached, the animals were revived by artificial respiration and picrotoxin injections. The experiments were then repeated several times, allowing rest periods of one week between them. These results permitted us to obtain a good estimate of the range of response, as well as the calculation of an average dose for respiratory paralysis from individual graded rather than quantal responses. Furthermore, the variation of response of each animal on several occasions could be determined. The results confirmed the suspected large variations in sensitivity to these drugs, amounting to a spread of about 50 per cent above and below the calculated average dose in unselected animals. It was also demonstrated that a considerable variation in response existed in the same animals to the same drug on different occasions. However, these variations were significantly smaller than those between animals. DeBeer *et al.* (69) have made an analysis of the influence of various factors upon the duration of action of hypnotics in the albino mouse. Over eighteen months, he found periods lasting for months at a time where a series of similar sleeping time responses were observed. He thought to note correlations with temperature, barometric pressure and humidity. Nevertheless, the author warns not to confuse the mere presence of a correlation with a causal relationship. It may be of interest that we noticed on one occasion a sudden failure of rabbits to respond to doses of thiopental which had always proved to produce a definite hypnotic effect in numerous experiments. A check of atmospheric conditions showed that, on this particular day, the barometric reading was close to the lowest value ever recorded in this area. A further attempt to measure experimentally and statistically the variability of response was made by Clark and Raventos (70). Carefully designed and executed experiments in mice with cyclobarbital and hexobarbital were used to test the "intensity" of response (that is, the occurrence or absence of sleep) with a given

dose as well as the duration of action. This was done both in selected and unselected groups of animals. The intensity of response of individual animals showed a fair consistency. This is in agreement with the clinical experience that the person who once has had an abnormal response to a drug is more likely to show a similar reaction at another occasion than a person taken at random from an unselected group. However, duration of responses of individual animals failed to show significant correlation on repeated tests unless the animals were previously separated into sensitive and insensitive groups. This variation may be due to actual changes in efficiency of the body to detoxify or excrete the drug on different occasions. This view is further supported by the work of Krautwald (71), and Krautwald and Oettel (72), who found considerable daily variation in the amount of several barbiturates excreted in the urine by dogs, and by Mirsky and Giarman (73) using spectrophotometric methods for the determination of thiopental degradation in mice.

TEMPERATURE EFFECTS

It is not surprising to find changes in environmental and/or body temperature an additional complicating factor in determining the action of barbiturates. Indeed, there can be little doubt that differences in environmental temperature are certainly involved in the discrepancy of data regarding toxicity and duration of action. The importance of temperature for drug action has been ably reviewed by Fuhrman (74). From this survey, as well as from later studies, it is obvious that no general agreement exists on the subject. It is fairly clear, however, that in mice and rats lowering of body temperature usually results in a prolongation of sleep following barbiturate administration. However, the dose-effect relations under different temperatures seems to be subjected to a number of complicating factors leading to unpredictable results. For instance, Shaw and Shankly (75), using a series of different dose levels of pentobarbital, showed that the duration of action of this drug is greater at high body temperatures with low doses and at low temperatures with high doses. However, it is not clear from their paper whether or not the animals which did not sleep at the low doses were included for the calculation of average sleeping times. Raventos (76) found that the sensitivity of mice decreased with lower body temperature towards hexobarbital and increased towards phenobarbital. It is interesting to speculate to what degree here the great difference in speed of detoxification between the two drugs and the tendency of hexobarbital to accumulate in fat depots may account for the opposite behavior of the two barbiturates. According to Fuhrman (77) the duration of action of phenobarbital, but not of barbital, is affected by temperature changes. This author explains this difference by the fact that the former, but not the latter, is subjected to temperature sensitive metabolic degradation in the body.

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There is no parallelism beween the influence of temperature upon the minimal hypnotic dose or duration of action on one hand, and modification of the LD_{50} on the other. Thus Raventos (76) noted no change of the LD_{50} of hexobarbital in mice between 20 and 30 C. of environmental temperature, while phenobarbital was more toxic at 20 C. In contrast, Richards (78) found a progressive lowering of the toxicity of thiopental in mice when the temperature was decreased from 38 to 35, to 30 and further to 22 C., though the differences became small towards the lower temperatures. Using frogs, Richards (78) found the lowest toxicity in a temperature range from 10 and 38 C. to lie at a 20 degree environmental temperature, while an increased toxicity was noticed at higher and lower temperatures. This phenomenon does not seem to be necessarily confined to poikilothermic animals, because Shaw and Shankly (75) found in rats the lowest mortality to a given dose was at 38.5 C., with an increase of toxicity at both higher and lower body temperatures. It should be noted that Richards measured environmental, and Shaw and Shankly body temperatures. It can hardly be considered surprising that the optimal, that is, the lowest, toxicity temperature is considerably higher in the warm blooded animal as compared with the poikilotherms.

One can at least speculate in an attempt to reconcile some of these diverging observations. Obviously the mechanism of acute death is different from conditions which govern the duration of action of these drugs. The rate of detoxification is of only limited importance in experiments designed to determine acute toxicity when large doses of the drug enter the circulation rapidly. Especially under extreme conditions of temperature it becomes quite important if the drug suddenly depresses the respiration in an organism which has an increased need for oxygen at high temperature, or if the depressant action of large drug doses adds itself to the already critically slowed metabolism at very low temperatures. It should not be forgotten that barbiturates, especially in higher doses, lower the temperature and make particularly small animals more nearly poikilothermic.

On the other hand, increased temperature tends to speed destruction of the drug if given in non-fatal amounts and decreased temperature diminishes the need for oxygen. Furthermore, extreme temperature changes may affect the absorption speed of drugs given by a route other than intravenous, or perhaps intraperitoneal, injection. It is easy to see how, dependent on circumstances, these various factors may lead to apparently contradictory results.

Assuming then that the duration of action of most barbiturates is governed largely by enzymatic destruction, Q_{10} should lie between 2 and 4, which figure is also realized according to Fuhrman (77). On the other hand, for the LD_{50} Richards (78) found a Q_{10} of 1.4 to 1.7 for frogs for the 22 to 35 C. interval, and 1.3 and 3.09 for the 22 to 35 C. and the 35 to 38 C. interval, respectively, for mice with thio-

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pental. This in a way also supports the assumption that the temperature factors controlling duration are not identical with those determining acute toxicity.

Reflecting for a moment on certain modern clinical trends, especially the use of so-called "hibernation" procedures involving both physical cooling, and the use of drugs which affect body temperature, the problem of analyzing the mutual effects of temperature and drug actions appears a formidable one. This realization points clearly to the need for more critical research in this field.

TOLERANCE

The possibility of tolerance to repeated administration of various barbiturates has been studied repeatedly. Tatum (3) in 1940 reviewed earlier work on this problem. Because of the great differences in technique, route of administration, criteria and species of animals used, it is difficult to reconcile some of the divergent results. However, a review of published data indicates clearly that tolerance, though to a variable degree dependent on the above factors, can be demonstrated in experimental animals. For example, Kinsey has shown that in rabbits (79), rats (80), and guinea pigs (81) tolerance to pentobarbital develops rapidly, resulting in a marked reduction of sleeping time after the first few daily injections. From then on, a lower relatively stable response develops which is subject to some irregular variation. Other authors have obtained comparable results. Ettinger (82) noted that the sleeping time in dogs dropped to about one half of the initial value on repeated injections of allobarbital or pentobarbital, but remained stable on further repetitions. Masuda *et al.* (83) reported the development of tolerance in rabbits with pentobarbital, butallylonal and amobarbital, but not with hexethal or hexobarbital. Newer study and review of this phenomenon was undertaken by Gruber and Keyser (84). Their paper includes also a discussion of previous reports on this subject. They could produce tolerance, as evidenced by marked decrease of sleeping time, in dogs, rats and rabbits to various barbiturates, but no increased resistance to the fatal dose resulted. To obtain tolerance to hexobarbital, it was necessary to give two injections daily, which may explain Masuda's negative results with this drug. Cross tolerance could be developed (84, 85). Krautwald and Oettel (72) found a reduction of depth and duration of anesthesia with barbital and phenobarbital in dogs, and noticed an increased reflex activity during tolerance formation to barbital. Of interest was the absence of exaggeration of these symptoms on withdrawal. It is evident from most studies that tolerance, once established, disappears in a number of days. Kinsey (79) noticed in his experiments that rabbits once made tolerant reacted with increased sleeping times (that is, decreased tolerance) when only one injection was given every four days, and then with shorter ones as soon as more frequent injections were made. How-

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ever, depending on species, drug and circumstances, tolerance may persist for longer or shorter periods.

There have been few studies into the mechanism of tolerance, and the theories offered are not very satisfactory (Dundee, 86). Masuda *et al.* (83) claimed that amobarbital disappeared at a somewhat faster rate in tolerant rabbits. Krautwald and Oettel (72) studied several barbiturates in this respect and found increased excretion during the tolerance period only with barbital. Hubbard and Goldbaum (87) produced tolerance to thiopental in mice by daily intraperitoneal injection of 50 mg./kg., which resulted in a 50 per cent decrease of sleeping time within a few days. No faster destruction of the drug was noted in this state and the authors conclude that an adaptation to higher tissue levels may be the cause of the lessened susceptibility. Dundee (86) agrees with this interpretation. The reviewers have the impression that no convincing evidence exists at the present time for a faster destruction of barbiturates in the tolerant state.

The possibility of rather acute tolerance formation to thiopental in man is presented in a brief report by Davies (88) who observed the need for increased amounts of this drug for induction, though not maintenance, in a patient subjected to seven thiopental anesthesias in about three weeks.

Brodie *et al.* (219) determined the plasma level of thiopental at the time of awaking and found this level to be higher when large doses of the drug were given than with small ones, which the authors also interpret as evidence for an acute tolerance formation. In a certain contrast to this stands the report of Lous (89), who studied serum levels of patients with severe barbiturate poisoning and noticed no difference in the values on awaking between individuals who had taken very large amounts as compared with smaller ones. Giarman *et al.* (90) likewise feel that, in mice, a critical level exists for thiopental in the brain which determines sleep or wakefulness.

Fraser and Isbell (91) treated dogs for 180 to 195 days with various barbiturates. On withdrawal, mild abstinence symptoms developed after the short-acting drugs. When barbital was withdrawn after 211–239 days, severe weakness, delirium and convulsions developed in these animals. Some prior studies on this subject which failed to produce definite abstinence symptoms can probably be explained by a too short treatment period.

The excellent studies of Isbell *et al.* (92) in volunteers gave fairly conclusive evidence that a considerable tolerance to short-acting barbiturates can be developed by chronic administration, though to a lesser degree than to the opiates. One of us (RKR) came to the same conclusion in observing a patient's behavior while taking 0.5 to 1.5 Gm. of pentobarbital daily. The dangerous delirium tremens resembling symptoms and occurrence of convulsions following acute withdrawal can here only be mentioned.

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AGE, WEIGHT AND SEX

The effect of age upon the susceptibility to pentobarbital in rats has been investigated by several authors. Homburger *et al.* (93) have reviewed this subject and showed that, while the newborn is more susceptible than the adult, the older heavier group becomes again somewhat more susceptible. These authors again draw attention to the reciprocal relationship between metabolic rate and narcotic effect and suggest that the metabolic rate of the brain is the determining factor. While the brain metabolism of the young rat is much lower than that of the adult, this is not the case for internal organs like liver or kidney. DeBoer (94) found both very young and very old dogs more sensitive to thiopental. According to Carmichael (95), thiopental is slightly less toxic in old than in young guinea pigs, while the difference was probably not significant in rats. This paper also contains references to similar studies with pentobarbital.

Dundee (96) tried to correlate weight and dose for thiopental in man. Except with the extremes the correlation was poor, perhaps due to the great variation of body fat, which is of great importance as a depot for this barbiturate. He could show, however, that males were more resistant to this drug than females; furthermore, persons below 25 years of age needed larger doses and those above 46 years, less.

Another observation of basic interest is the greater resistance of male rats, apparently confined to this species, to several short-acting barbiturates, though not towards the long acting group or thiopental —but note the just mentioned observation by Dundee. This was first described by Holck and Kanan (97) and confirmed and elaborated on by other authors, as for example by Moir (98) and by Streicher and Garbus (99). Castration, and the injection of estrone or testosterone propionate have been shown to modifiy this response (Holck *et al.*, 100). Crevier *et al.* (101) claim that the former hormone slows, and the latter accelerates, the destruction of pentobarbital in the liver of rats. Further support for this has been brought forward by Quinn and coworkers (102) who showed that testosterone administration to female rats decreased their sensitivity to hexobarbital and increased the enzyme activity of liver microsomes.

DRUGS ENHANCING THE ACTION OF BARBITURATES

Theoretical interest in the possibility of retarding or accelerating the normal rate of metabolism of barbiturates, as well as the practical desire to control the duration of clinical barbiturate effects by pharmacologic means, has led to numerous studies of this problem. A wide variety of substances and procedures has been employed in these attempts. Since it is impossible to mention or discuss all of them in detail, we shall confine ourselves in this review to representative investigations involving various drug groups.

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The terms "prolongation," "potentiation," "restoration of sleep," "enhancement," and the like have been used rather loosely, and sometimes promiscuously, for various phenomena. Essentially the papers referred to below report experiments describing the following observations:

1. Prolongation of barbiturate sleep beyond the control value by use of a second drug.
2. Lowering of the minimal effective (MED) and/or minimal lethal dose (MLD) by a second drug.

In 1 or 2 above the additional drug may have been given prior to, with, or after the injection of the barbiturate.

3. Restoration of sleep by the injection of a second drug when the animals awoke from the sleep caused by the barbiturate.

In principle such effects can be brought about by one or more of the following modes of actions:

A. Slowing of the metabolic degradation or excretion of the barbiturate. Drugs acting in this manner will prolong sleep, but will not necessarily change the MED and MLD of the barbiturate. In order to meet this definition, such actions should be specific and not secondary to a general toxic effect resulting in a decrease of total metabolic rate and temperature of the animal.

B. "Potentiators," in the strict sense, act by decreasing the brain threshold of the barbiturate necessary to induce or maintain sleep. Given at the end of the barbiturate action they may restore the hypnotic effect. Potentiatory actions will often result in a lowering of the MED and/or MLD of the barbiturate. Here, too, results obtained by giving the modifying drug in doses causing severe toxic effects of their own must be excluded.

C. Changing the distribution of the barbiturate in the body or increasing the permeability of the blood-brain barrier. Without blood and tissue level determination of the barbiturate, these actions may be indistinguishable from B.

The possibility for other mechanisms exists. It is obvious that a combination of pharmacologic and biochemical procedures is necessary to determine the mode of action involved in modifying barbiturate effects. These include the determination of barbiturate levels in plasma, brain and other tissues as required by the specific investigation. In certain instances *in vitro* studies or the isolation and identification of excretion products may be helpful. The conditons of the experiments, criteria for "sleep" and its duration, should be well defined and adequate control experiments performed. Since only a minority of the papers reviewed satisfy these requirements, it was not possible to group the experimental results according to "modes of action." This forces the present reviewers to confine themselves often to report-

ing the observations only, and at best to speculate regarding the interpretations.

With few exceptions we have omitted reference to synergistic effects caused by the combined use of a barbiturate with other drugs producing marked depression or sleep in experimental animals, such as alcohols, opiates, bromides and other hypnotic agents.

SULFONAMIDES AND CHEMICALLY RELATED COMPOUNDS

Shortly after the introduction of sulfanilamide and its congeners it was observed by Adriani (103) and Butler *et al.* (104) that animals pretreated with large doses of these drugs became much more susceptible to barbiturates, resulting in longer sleep and decreased tolerance. This was especially the case with thiobarbiturates. However, further experimental investigation within more therapeutic levels of these chemotherapeutic agents [Lorhan *et al.* (105), Richards (106)] as well as clinical experience proved that this phenomenon appears to be outside of practical range [Papper (107), Wainwright (108)] unless sulfonamides were given to the point of clinical cyanosis [Lundy and Adams (109)]. A more recent experimental paper by Koerner (110) showed that animals given daily doses of barbiturates, and especially thiobarbiturates, became more sensitive to sulfa drugs and penicillin. The reviewers doubt that Koerner's data are relevant outside the range of extreme dosage.

A compound bearing some chemical relationship to the sulfonamides, namely carinamide, was reported by Goldbaum and Hubbard (111) to prolong the action of secobarbital, pentobarbital and thiopental in mice in proportion to the dose of this drug given. Urine and total body analysis of mice showed that the disappearance of pentobarbital was retarded under the influence of carinamide; this was a metabolic action rather than an effect upon excretion. The prolonging effect of sulfonamide type drugs which we have reviewed above has not been studied from this viewpoint, probably because the interest in sulfonamides had already decreased before improved analytical methods for the study of the barbiturates were developed.

DISULFIRAM

Recently the question of affecting the action of barbiturates was raised with respect to disulfiram (Antabuse®). Graham and his coworkers (112) reasoned that this compound, because of its inhibiting effect upon aldehydedehydrogenase, may prolong the duration of barbiturates since depression of acetaldehyde breakdown is thought to be an important phase of the action of pentobarbital (Persky *et al.* 113). Greig (114) contests the validity of Persky's data. Graham and his co-workers found that rats and guinea pigs given disulfiram orally twice prior to the injection of cyclural or phenobarbital slept con-

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siderably longer. Giarman and his associates (115) subjected mice to repeated administration of disulfiram and reported a 600 per cent prolongation of the effect of thiopental. However, these investigators tried to explain this observation by the inhibition of xanthine-oxidase by disulfiram, which they believe to be of importance in the destruction of thiopental. No analytical proof for this assumption was given. Winters *et al.* (116), in cooperation with the reviewers, failed to confirm these findings in mice and dogs but saw some effect in rats; however, no significant influences on plasma thiopental levels were noted. Gruber *et al.* (117) were able to produce this phenomenon, though to a lesser degree, in rabbits and mice and pointed out that the time interval between the administration of disulfiram and the injection of the barbiturate is rather critical and this may have been responsible for some of the discrepancies. They failed to demonstrate an effort of disulfiram upon urethane, ether or chloral hydrate. However, Winters and Shideman (118) as well as von Proosdij-Hortzema and de Jongh (119) saw also prolongation of barbital, urethan, chloroform or ether anesthesia. Winters and Shideman explain the effect of disulfiram chiefly on the basis of its own depressant effect upon the central nervous system. This view is supported by the finding of Johnston *et al.* (120) who could prolong hexobarbital anesthesia by administration of carbon disulfide, which is known to be set free in the body from disulfiram. In the opinion of the reviewers the effect of disulfiram is probably largely explainable by such mechanisms. In a recent paper, Mirsky and Giarman (73) have been unable to reproduce their earlier data in mice in spite of varying the time intervals between disulfiram administration and thiopental injection. A moderate effect was seen in rats. While inhibition of thiopental degradation by rat liver slices *in vitro* was noted, the authors now seem also inclined to attribute the main action to the depressant effect of disulfiram itself. Of practical interest is the report of Jepson and Korner (121) who saw no difference in the effect of thiopental in patients who were under the influence of disulfiram as compared with untreated persons.

Other Metabolic Inhibitors

Stimulated by the work of Bain (60) who showed that barbiturates may exhibit an uncoupling effect on the oxidative and phosphorylating processes in the liver similar to dinitrophenol, Edson and Carey (122) studied the effect of the related dinitro-orthocresol upon the action of six barbiturates in rats. Only with toxic doses of dinitro-orthocresol occurred a significant degree of intensification and prolongation of barbiturate action. This was most evident with thiobarbiturates and least with hexobarbital. Brody (65) has recently again discussed the "uncoupling" effect of barbiturates.

Kahn (123) explains his observation that dimercaprol prolongs pentobarbital anesthesia in mice on the basis of the antagonism of

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the active sulfhydryl groups of this compound against the oxidative destruction of this barbiturate. He could confirm by blood level studies significant retardation of the disappearance of the barbiturate in dimercaprol treated animals. Giarman and Flick (124) use essentially the same theory to explain the prolongation of thiopental action by the administration of large doses of dehydroascorbic acid (which forms ascorbic acid in the body), and to a lesser degree by cysteine-cystine. However, no actual blood level studies to support this presumptive mechanism of action were submitted.

ANTIHISTAMINICS

Drowsiness or even sleep is known to be a frequent clinical side action of many antihistaminic drugs, in fact this "side effect" is now used for therapeutic purposes. However, pharmacologists have found it very difficult to produce sleep by antihistaminics in experimental animals, although ataxia and a moderate depression of reflexes has been observed. The present writers were unsuccessful in causing sleep even in the monkey, by gradually increasing to toxic levels the dose of diphenhydramine—a drug having clinically rather potent sedative effects. However, that the depressing effects are only masked by the more overt stimulating action of these drugs in animals has been shown by Winter (125). This author demonstrated that premedication with tripelennamine, pyrilamine, or diphenhydramine, and the like greatly prolonged the effect of hexobarbital anesthesia in mice. This has been confirmed by most investigators under variously modified conditions. Such work has been reviewed by Lightstone and Nelson (126) who failed to find a relationship between the degree of clinically observed depressing action of the antihistaminics and their prolonging effect upon pentobarbital anesthesia in rats. They noticed that the level of the barbiturate in the brain was always higher when antihistaminics were administered. We would appear to be dealing, then, with an effect upon permeability of the blood-brain barrier. This observation seems well worthy of confirmation. Apparently the success of such potentiation experiments depends not only on the drugs used (van Neer and Zwaan, (127), but also on the sequence and time intervals between administration. However, in the experience of the reviewers in somewhat similar experiments, some relationship between prolongation of barbiturate action in animals and the occurrence of depression in humans seems to exist, at least as far as the centrally more potent antihistaminics are concerned.

Among the phenothiazines typified by promethazine, an antihistaminic with a potent depressing action, there have recently been developed agents such as chlorpromazine in which the depressant effects upon the central nervous system have become of primary interest. Although these drugs were originally introduced for the purpose of

so-called "potentiated anesthesia," their action appears to be in part additive and will not be further discussed here (see Dundee, 128). For the same reason, the synergistic action of the muscle relaxant, mephenesin, with barbiturates need only be mentioned (Berger and Lynes, 129).

ATROPINE-LIKE SUBSTANCES

Among the drugs having some distant relationship to atropine, a prolonging effect upon barbiturate anesthesia has been described by Maxwell *et al.* (130) with SKF–525A (α-diethyl aminoethyl diphenylpropylacetate), by Everett (131) with the related P–19 (Abbott) (diethylaminoethyl α,α diphenyl-propionate), and by Fouts and Brodie (132) with compound 18947 (Lilly) (2,4-dichloro 6-phenyl-phenoxyethyl diethylamine). These drugs have no significant central nervous system action if given alone, even in fairly high doses. However, it was found that in mice they greatly prolonged the effect of many barbiturates which are known to undergo *in vivo* metabolic degradation. Curiously, according to Cook *et al.* hexobarbital (133), but not thiethamyl and thiopental (134), were affected by SKF–525A, whereas Achor and Geiling (135) noticed definite prolongation of sleep and retardation of thiopental degradation in mice with SKF–525A, as did Everett with P–19 (131). Mirsky and Giarman (73) found SKF–525A effective in prolonging thiopental action in mice and rats and explain their disagreement with Cook on the basis of the difference in the time permitted to elapse between the administration of the potentiator and the barbiturate. Neubert and Herrken (136) produced prolongation of hexobarbital action by a similar compound, namely the phenyldiallylacetic acid ester of diethylaminoethanol and related esters and amides. They believe that this drug affects chiefly those barbiturates which are degraded by oxidation of the side-chain. While these "inhibitors" thus seem somehow to interfere with the normal metabolism of these drugs (Axelrod *et al.* 214), the exact mode of action has not yet been determined. In the meantime our own group and others have observed similar, though less marked, effects with certain drugs possessing clinical anti-Parkinson activity, such as trihexyphenidyl and atropine. French authors (137, 138) have recently reported prolongation of the hypnotic action of several barbiturates in rats by a series of new smooth-muscle antispasmodics, some of them being chemically related to the above mentioned drugs. However, since this effect was also observed with barbital, the mechanism of action is not clear and the authors do not offer an explanation. SKF–525A and Lilly 82947 do not reinduce sleep when injected in mice recovering from barbiturate anesthesia (132). Thus their effect could be explained entirely on the basis of their inhibitory action on the rate of barbiturate degradation. In contrast, P–19 (Abbott) will restore sleep under similar conditions (131). Unfortunately, here, as in many other

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experiments of this type, plasma level determinations of the barbiturate are not given. Consequently, an exact differentiation regarding the mode of action as "potentiation" or "metabolic inhibition" (or both) —cannot be undertaken for P–19.

MISCELLANEOUS DRUGS

Substances closely related to barbiturates have also been studied. Wenzel and Keplinger have recently reported (139) some prolongation of hexobarbital sleep in mice by pretreatment with uracil and related oxypyrimidines. They propose the occurrence of a competition of these compounds for the same enzymes which also destroy barbiturates.

Of clinical interest is the peculiar barbiturate hypersensitivity of persons suffering from porphyrinuria. Severe toxic effects, such as paralysis, may result from the use of barbiturates, especially intravenous thiopental, in such individuals (Dundee and Riding, 140).

Goldin *et al.* (141) found that isonicotinic acid hydrazide (INA) and some related compounds prolonged the action of pentobarbital in mice. This barbiturate antagonized the central nervous system stimulating actions of INA.

Prolongation of barbiturate sleep in experimental animals has also been produced by calcium and strontium (Cole, 142), iodides, glycerine, sucrose and sorbitol (Krantz and Farrel, 143), phenylboric acid (Caumolle *et al.*, 144), and nitrates and nitrites, the latter two possibly due to vasodilating action (Wooster and Sunderman, 145). Werle and Lentzen (146) found that various vasoactive drugs, including Kallikrein, acetylcholine, adenylic acid, vasopressin and epinephrine, affected the duration of Eunarcon® and hexobarbital anesthesia in a manner which could not be related to their vascular effects.

According to Brooks and associates (147), small non-adrenolytic doses of hydergine did not affect significantly the depressant action of barbiturates, including secobarbital or pentobarbital, upon oxygen consumption unless these barbiturates were given in hypnotic amounts. Starkenstein and Weden (148) have shown that cholesterol prolongs barbital sleep, presumably by promoting the entrance of the drug into the brain. Their experiments were confirmed by de Farsouche *et al.* (149) for thiopental. It appears possible that the quicker onset of barbital anesthesia following the injection of certain surface active agents (Cole *et al.*, 150) is likewise due to increased permeability of the blood-brain barrier. The same chemical prolonged thiopental sleep in mice somewhat, which was due at least in part to slowing of its degradation. There occurred, likewise, a moderate prolongation of pentobarbital sleep. Giarman *et al.* (90) at one time suggested that prolongation of thiopental action by the administration of α-tocopherol phosphate is due to a change of the diffusion rate in and from the brain. However, in a later paper, Mirsky and Giarman (73) de-empha-

size this view in favor of a metabolic inhibition of thiopental degradation and a slight direct depressing action of α-tocopherol phosphate. Konzett (151) sees changes of brain permeability as the cause for the ability of certain dyes, such as methylene blue and neutral red, to make subthreshold doses of hexobarbital and phenobarbital effective. Prolongation as well as re-induction of pentobarbital and thiopental sleep by procaine in guinea pigs has recently been described by Maynert and Kalow (152), apparently without affecting the metabolism of the barbiturates. The reviewers must again point out that direct measurement of cerebral concentrations of barbiturates is the obvious procedure for testing such hypotheses.

Of considerable theoretical interest are a series of observations by Brodie and his associates. These authors have shown (153, 156) that reserpine produces its prolongation of barbiturate and ethyl alcohol sleep without any evident effect upon the metabolism of the hypnotics. This is also true for chlorpromazine. A similar effect can be obtained by combining serotonin (5-hydroxytryptamine) with such hypnotics. The administration of lysergic acid diethyl amide (LSD) resulted in a marked reduction of the potentiating action of reserpine, while LSD alone did not modify the barbiturate effect. This, together with evidence that reserpine depletes the serotonin content of the brain, has led to the claim that certain central effects of reserpine, such as the prolongation of barbiturate action, may be due to the release of serotonin.

THE "GLUCOSE EFFECT" AND RELATED PHENOMENA

A chance observation by Lamson and associates (157) has led to a series of investigations of another modification of barbiturate effects. These authors reported that the injection of glucose solutions in dogs which were just about to recover from barbiturate sleep caused immediate return to the hypnotic state; however, a "wide variation" in the response of the dogs was noted. Guinea pigs awaking from hexobarbital or pentobarbital anesthesia were put to sleep again by small amounts of glucose or certain of its metabolites, such as lactate and fumarate, but not by sodium chloride or sucrose. The authors believed that they had excluded osmotic effects. In their hands subcutaneous injection of glucose or sodium lactate (2 cc. of a 50 per cent solution) greatly reduced the effective dose of hexobarbital. In later papers (158, 159) this group reported an increased rate of penetration into the brain by barbiturates in the presence of glucose metabolites, but not glucose itself. The return to sleep induced by glucose metabolites could be blocked by acetylcholine or, in case of lactate, also by adrenergic blocking drugs. Acetylcholine also prevented the faster penetration rate of the barbiturate into the brain. Curiously, Greig and Mayberry presented evidence in another paper (38) that physostigmine actually increases the rate of penetration of barbital into

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the brain of mice and shortens the interval between injection and onset of anesthesia. Epinephrine re-induced sleep in awaking guinea pigs, mice or dogs. The hypnotic dose of barbiturates was lowered by epinephrine (159). Reinhard (160) had observed prolongation of hexobarbital sleep in mice pretreated with epinephrine or insulin, whereas Westfall (161) reported the opposite effect with these two agents in rabbits. Richards and his associates (162) had repeated and essentially confirmed the basic phenomenon reported by Lamson *et al.* with thiopental, hexobarbital and pentobarbital. However, they found that, in guinea pigs or rabbits, sleep was also often re-induced by the injection of sucrose, sodium acetate, sodium malonate, sodium butyrate, urea, sodium chloride, sodium sulfate, plain water and other materials. Even mere withdrawal of blood or its intracardiac injection restored sleep in guinea pigs. Not all drugs were effective in both species, and some were more effective when given intravenously or intracardially, others by the intraperitoneal route. In rabbits, no change in the plasma thiopental levels occurred upon successful restoration of sleep.

Stuhlfauth and Englhart-Golkel (163) actually shortened the effect of small doses of thiopental in rats by prompt injection of fructose or glucose. With higher amounts of the barbiturate, no effect upon the duration was observed.

Lasagna (164) succeeded in re-inducing sleep in guinea pigs awaking from hexobarbital anesthesia by the injection of potassium chloride. This salt lowered also the minimal effective dose of hexobarbital. Sodium chloride did not reproduce these effects. While the author drew attention to the known actions of barbiturates upon blood potassium and also certain interrelationships between glucose metabolism and potassium, he refrained from drawing too far reaching conclusions from his observations. Bester and Nelson (220) described prolonged action of pentobarbital or return to sleep by the injection of 50 per cent glucose I.P. but not by sodium citrate, lactate, succinate, pyruvate or acetate. The level of the barbiturates in the brain was higher following glucose injection. This seems to disagree with claims by Lamson that, not glucose, but its metabolites accelerate penetration into the brain. According to Bester and Nelson (22) an inverse relationship exists between liver glycogen formation and clearance of the barbiturates from the blood. These authors engage in a highly speculative explanation for the observed prolonged barbiturate effect which the reviewers find difficult to accept.

It is our opinion that, at the present time, the assumption of a specific action of glucose and its metabolites in producing such effects as described by Lamson and associates and others appears hardly warranted. Certainly, osmotic effects, permeability changes, and the like may play a role in these phenomenon, but it appears difficult to find a common denominator on the basis of available data.

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COMMENT

It is evident from these reports that prolongation of barbiturate anesthesia, restoration of sleep and lowering of the minimal effective dose can be produced by various procedures. In view of the great variations in technique, criteria of sleep, drugs and doses used, and the like, it is not surprising that controversy exists regarding the outcome and interpretation of experiments which in some aspects appear comparable. The difference in reaction to hypnotic agents, as well as to the drugs used together with them, among the various species used, is considerable. For similar reasons the possible clinical significance of many of these observations remains problematical. The state described as "sleep" in animal experiments is more often better termed "anesthesia" in the clinical sense. In this short review, space has not permitted us to present details of the experimental procedures and the reader is urged to consult the original papers whenever necessary.

As already indicated in the beginning of this chapter, a review and scrutiny of the papers discussed above makes it clear that the criteria necessary for analyzing the mode of action involved in these observations have been satisfactorily fulfilled only in a limited number of these studies. This is in part due to the fact that adequate analytical procedures for barbiturates have only relatively recently become available. However, satisfactory data on plasma and tissue concentrations are often lacking in some of the more recent publications. As a result, the reviewers must leave the reader with a certain feeling of dissatisfaction which they were unable to resolve for themselves by means of the data at hand.

PROCEDURES THAT SHORTEN BARBITURATE ACTION

Attempts have not failed to shorten barbiturate action and to counteract toxic overdosage. We shall not concern ourselves here with the pharmacologic antagonism between analeptic drugs and barbiturates, but confine ourselves to presumptive metabolic actions. Recently a new drug, β,β-methyl ethylglutarimide (NP13 or Megimide®) has been introduced as an allegedly specific antagonist to barbiturates on the basis of structural resemblance. However, the data published (225) do not give satisfactory evidence for a specific action. Experiments in this laboratory (226) in which the action of NP13 is being studied against hypnotics of various structure, strongly indicate that this drug is an unspecific central stimulant and convulsant rather than a "specific" barbiturate antagonist.

Cutting and Koppanyi (165) were able to shorten barbital anesthesia in dogs or rats by massive glucose or saline infusions. This barbiturate is excreted almost completely unchanged. The explanation offered by these investigators that faster excretion, and possible redistribution of the drug away from the central nervous system, are

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responsible for this effect is likely to be correct. However, in clinical barbiturate poisoning we agree with those who warn against excessive use of fluids, especially sodium chloride, in view of the ever present danger of pulmonary and cerebral edema. More recently, several attempts have been made in experimental animals and also clinically to remove barbiturates from the body by the use of the artificial kidney or by peritoneal lavage. The latter method did not seem to be successful in dogs, since it did not shorten recovery time (227). However, considerably more promising results were obtained experimentally and clinically by means of the "artificial kidney." Alwall *et al.* (228) could reduce the phenobarbital blood level in rabbits by exchange ultrafiltration procedures by 68.6 per cent in 6 to 7 hours. This was far superior to forced diuresis. In two patients a similar procedure reduced the blood level by 60–75 per cent in 6 to 7 hours. This work has been confirmed and extended by others (228). An interesting observation by Soskin and Taubenhaus (166), namely reduction of sleeping time in rats under pentobarbital or amobarbital anesthesia by large doses of sodium succinate, was explained by these authors by the ability of brain tissue *in vitro* to utilize succinate in the presence of barbiturate. Larson and his associates (167) could antagonize the depression of oxygen consumption caused *in vitro* by pentobarbital brain slices with sodium succinate. Unfortunately the great majority of the experimental investigators were unable to corroborate the *in vivo* results [Beyer and Latven (168), Corson *et al.* (169), Lardy *et al.* (170), Pinschmidt *et al.* (171), Larson *et al.* (172), Schack and Goldbaum (173), Giarman *et al.* (174)]. An antagonistic effect of this salt against the depressing action of large doses of barbiturates on gastric secretion and motility was reported by LaBarre and Hans (175). Westfall (161) studied also the effect of pyruvic acid and found it to shorten pentobarbital sleep in rabbits.

Clinically, sodium succinate has been tried as an antidote against barbiturate poisoning. Barrett (176) has reported favorable results. However, one of the reviewers (RKR) has been disappointed with its clinical value and no other advocates for its use seem to have come forward. Aside from its highly questionable effectiveness, one would doubt the advisability of infusing large doses (15 to 30 Gm.) of a sodium salt in patients already in the danger of pulmonary and cerebral edema.

Tucci (177) and his associates have reviewed the experimental data and conducted controlled studies of the effect of sodium succinate in humans in thiopental anesthesia. The authors emphasize the great variations in response to thiopental itself and the difficulty in evaluating the effects of drugs of the type of sodium succinate. They did not arrive at any definite conclusions regarding the possible merit of this drug. Brody (65) has drawn attention to the interesting fact that while oxidation of succinate is not inhibited by barbiturates, the un-

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coupling of phosphorylation (that is formation of high energy bonds) from oxidation, a characteristic action of the barbiturates (Bain, 61) is also present at the succinate step of the Krebs cycle. This may be one reason for the failure of succinate to affect materially the duration of barbiturate action *in vivo*.

A physical method for the treatment of prolonged barbiturate coma has been suggested by Robie (230, 231 232). He has treated such patients by prolonged electro-stimulation through the head with the Reiter stimulator. Sometimes using higher currents than necessary to cause convulsive seizures in normal individuals, he produced muscular contractions and increased respiratory movements in the comatose patient. This author believes that the duration of coma may be significantly shortened by this procedure, which can be used in combination with other suitable management.

Blachly and Brookhart (233) have conducted a careful study of this method in dogs. According to their results, the stimulation of respiration and circulation is of a reflex nature and can be obtained likewise if the electrodes are applied to extremities. While temporary arousal could be produced, no permanent awakening or protection against lethal effects could be achieved. These authors suggest that, clinically, electro-stimulation should be applied peripherally rather than centrally, since the beneficial effects would be equally good and obtained with lesser risk of damage.

NUTRITIONAL FACTORS

Some nutritional conditions which modify barbiturate action should be briefly mentioned. That extreme inanition, anemia or other severe metabolic derangements lead in general to a greater sensitivity towards drug action is well known, for example, starving rats for 48 to 110 hours greatly prolonged sleeping time and decreased resistance to thiopental (DeBoer, 178). This was unaffected by the administration of thiamine. The same author reported also a marked increased effect of thiopental in dogs which had lost 10 to 20 per cent of their normal weight (179). Blackberg and Hrubetz (180) observed likewise prolonged sleep in starved rabbits injected with thiopental. Higgins and Mann (181) showed in well-controlled experiments that rats placed on diets deficient in vitamin B complex slept much longer after a standard dose of pentobarbital. Levy *et al.* (182) demonstrated, in mice, that thiamine deficiency alone did not cause increased sensitivity to thiopental and the most pronounced effect was obtained when niacin deficiency was produced by a low grade protein diet. This is in agreement with Burstein and Tui's (183) observations of a much lower resistance of hypoproteinic rats towards thiopental.

Richards *et al.* (184) demonstrated that guinea pigs placed on a vitamin C deficient diet became significantly more susceptible to pentobarbital, but not to thiopental or barbital. Inanition could be

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excluded as a cause. The failure of barbital to give similar results can probably be explained by the absence of metabolic degradation of this drug. Why the duration of thiopental effect was not influenced by vitamin C deficiency is not easily understood.

Green and Musulin (185) produced essentially the same effects using pentobarbital and phenobarbital in vitamin C deficient guinea pigs. Greig (186) has shown recently that ascorbic acid can counteract depressing action of pentobarbital on certain enzymes.

ROLE OF LIVER AND KIDNEY

The importance of the liver as the main place of inactivation and degradation of most of the short-acting barbiturates has been established for some time. The earlier literature on this phase and the effect of the barbiturates on the liver has been reviewed by several authors [Tatum (3), Richards and Appel (187), Hugill (188), Maynert and Van Dyke (4)]. For several years the role of the liver in the metabolism of thiopental remained unsettled. It was first assumed that this thiobarbital would be destroyed in the liver, like its oxygen analogue pentobarbital. However, Scheifly and Higgins (189) did not observe a prolongation of thiopental sleep in rats with partial hepatectomy, and Richards and Appel (187) failed to find an increased action of this drug in rats subjected to mild diffuse liver damage caused by carbon tetrachloride administration. Experiments by Masson and Beland (190) were in agreement with these findings.

Beginning in 1947, however, Shideman and his co-workers (191) reinvestigated this problem. They demonstrated that mice subjected to extensive liver damage by carbon tetrachloride and rats with subtotal hepatectomy or Eck fistulas slept seven to eleven times longer after a standard dose of thiopental and two other thiobarbiturates than untreated controls. A similar, though less extensive, prolongation of sleeping time with thiopental was found by Walker and Wynn Parry (192) in partially hepatectomized rats. These authors noticed a tendency of the return to normal sensitivity as the liver parenchyma regenerated with time. Meyers and Peoples (193) confirmed that serious interference with the normal blood supply of the liver greatly delayed recovery from thiopental anesthesia in animals. Richards and Kueter (unpublished data) compared the prolongation of sleeping time with hexobarbital and thiopental when groups of rats were treated with carbon tetrachloride for one, two, or three days, respectively. In spite of considerable variation of response it appeared that prolongation of hexobarbital sleep occurred earlier than with thiopental, that is, a more severe degree of liver damage was necessary to inhibit thiopental destruction than hexobarbital. Such factors may well have played a part in the negative results of the experiments of the earlier investigators.

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The clinical observations on the effect of thiopental in patients with liver damage are far from uniform. Lundy (194), Ruth *et al.* (195), as well as Anderson (196), did not notice a prolonged effect, whereas Miller and Tovell (197) and Shideman *et al.* (198) encountered a difference in such patients. This subject has been well reviewed by Dundee (199), who also studied the effect of this drug in patients with various degrees of liver impairment. He found that mild degrees of damage did not significantly change the response to thiopental; this was the case, though with more advanced damage. These clinical results are in good agreement with the just mentioned experimental finding of Richards and Kueter. Shideman (198) estimates that the active liver tissue must be reduced to about 30 per cent before impairment of thiopental detoxification becomes evident. In a later paper, Dundee (200) analyzes the effect of thiopental on the liver and warns against the use of very large doses of this drug in patients with liver dysfunction.

Walton *et al.* (201) noted the absence of liver damage in dogs after anesthetic doses of thiopental. In their experiments recovery of normal liver function in dogs treated with chloroform was not delayed by subsequent thiopental injections if oxygen was administered during anesthesia. This emphasizes again Hugill's (188) statement that anoxia plays an important part in liver damage caused by anesthetic agents. Present data do not always permit a satisfactory separation of anoxic liver damage from true hepatotoxic effects.

Earlier reports (Masson and Beland, 190) (Martin *et al.*, 202) described the kidney as of no importance in the destruction of thiopental. However, more recent studies by *in vitro* and *in vivo* methods indicate that this organ possesses the ability to degrade this barbiturate, though to a more limited degree than the liver (Dorfman and Goldbaum, 222) (Shideman and Gould, 203). A new aspect of the importance of the kidney for the action of barbiturates was evolved by Richards and associates (204, 205) who studied the effect of azotemia following removal of both kidneys or ligation of the ureters in experimental animals. Under these conditions an increased sensitivity to and prolongation of action of thiopental, but much less of hexobarbital, was noticed in nephrectomized rats and rabbits which paralleled the time elapsed after this operation and the concomitant rise of the NPN. Dundee and Annis (206) have confirmed the existence of a correlation between degrees of uremia and prolongation of sleeping time in dogs for some other barbiturates. Acute azotemia caused by injection of an artificial NPN solution in nephrectomized animals gave similar results (204). Nephrectomized animals were shown to degrade thiopental at a slower rate. Further studies revealed a decrease of the albumin-globulin coefficient in the plasma of nephrectomized rabbits, which resulted in a lower binding of thiopental in the plasma with a higher portion of the drug remaining unbound and physiologically active

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(33). This was not evident by determination of the total barbiturate plasma level. When a series of barbiturates were studied in nephrectomized animals, those strongly bound on plasma proteins were more prolonged in their action. Hexobarbital belongs to the group which is relatively little bound and is also little affected by the post-nephrectomy state. These factors play a part in the prolongation of the action of certain barbiturates under these conditions. They are, however, not the only ones. Changes in sensitivity and other factors are undoubtedly involved (Taylor *et al.*, 28).

One of us (RKR) had the occasion to observe a patient who had undergone a prostatectomy in an advanced state of prostate hypertrophy under thiopental anesthesia and remained in deep sleep for nearly twenty-four hours, but made afterwards an uneventful recovery. A more extensive study of the clinical aspects of this phenomênon was reported by Dundee and Richards (221). Carefully controlled observations showed that azotemia artificially induced in normal individuals by the ingestion of large doses of urea or occurring in patients due to urinary obstruction leads regularly to an increased sensitivity to thiopental, as evidenced by the amount needed for induction and especially maintenance of anesthesia. Thus, clinical experience substantiates the above reported studies in animals, drawing attention to the importance of metabolic disturbances subsequent to the removal or impairment of an organ.

With this thought in mind, one wonders how much of prolongation of barbiturate action observed after extensive liver damage in some experiments may have been due to the absence of the detoxifying organ and how much to a change of sensitivity or the like, caused by the general metabolic derangement subsequent to liver dysfunction. The work by Sandberg (207) is a case in point. This author studied the action of certain barbiturates in rats sixteen and twenty hours after hepatectomy or bilateral nephrectomy, respectively. However, he concludes without reservation that the changes in sleeping time must be due to the removal of the organs as the sites of drug detoxification. In the light of the above consideration this may be only a part of the story.

CONCLUSION

The authors would like to restate their hope that the information contained in this review will be of help to the experimental investigators as well as to the clinical anesthesiologists who may be looking for the experimental background for clinical observations or research.

Like all reviews, the present one will be overtaken in due time by new advances. We believe that, as previously, progress will be largely paced by further development of research methods. The recently accelerated progress in the study of the interaction between cellular enzymes and drugs is bound to contribute greatly to our basic

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understanding of drug action. Knowledge gained from such work and the diligent application of known and coming analytical methods will help to provide much needed clarification of the mechanism of action underlying observations of "prolongation" or "abbreviation" of barbiturate effects which we have discussed earlier. It would be surprising if after further evaluation some of the experimental findings would not prove of clinical usefulness. Simplifications and refinements of quantitative methods for the determination of barbiturates in plasma and tissues should greatly intensify their application to clinical anesthesiology. Physiological and neurophysiological techniques will likewise contribute to an increasing degree to the understanding of the pharmacology of barbiturates in man. The use of the electroencephalograph during clinical barbiturate anesthesia (223, 224) is cited just as an example. It is this mutual "feed-back" between experimental and clinical research which here, as in many other areas of medical science, will provide problems and answers in future research.

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ANNUAL MEETING OF THE AMERICAN MEDICAL ASSOCIATION

CHICAGO, ILLINOIS

The Section on Anesthesiology of the American Medical Association will meet at 2:00 p.m. on June 12, 13 and 14 in the Sheraton Hotel. The following program has been announced:

Tuesday, June 12

Surgeon-Anesthetist Teamwork in the Operating Room. Warren H. Cole.
The Misuse of Topically Applied Local Anesthetics. John Adriani and Donovan Campbell.
Transtracheal Resuscitation. Jay Jacoby.
A Clinician's Appraisal of Local Anesthetic Drugs. John J. Bonica.
Post-Operative Study of Anesthetic Complications. Marion G. Weitz and Bruce M. Anderson.
The Role of Hypnosis in Anesthesiology. Milton J. Marmer.

Wednesday, June 13

New Drugs and an Era of Analgesia and Amnesia. John S. Lundy.
The Automatic Maintenance of Anesthesia. M. Jack Frumin.
Hydroxydione (Viadril)—Observations Following One Thousand Administrations. F. P. Ansbro, Albert E. Blundell, Joseph C. Sweeney, Jr., and John W. Pillion.
The Use of Nisentil With or Without Antagonists for Supplementation or as Sole Agent of Anesthesia. Henry I. Lipson and Henry Rollie Bradford.
The Central Effect of Alphaprodine and of Chlorpromazine During Thiopental Narcosis. Valentino D. B. Mazzia, Joseph F. Artusio, Jr., and Alan Van Poznak.
Chlorpromazine: Mechanisms of Action. Erwin Lear, Albert E. Chiron, and Irving M. P. Pallin.
Hypothermia in the Management of the Poor Risk Patient Undergoing Major Surgery. S. N. Albert, J. Shibuya, M. Ajwani, W. A. Spencer, T. D. Armour, and J. R. Thistlewaite.

Thursday, June 14

Anesthetic Management of Patients With Respiratory Disease. Nicholas M. Greene.
Controlled Respiration During Caesarean Section. William K. Bannister.
Anti-Foam Agents in Pulmonary Edema. Max S. Sadove, Reuben C. Balagot, Rosauro Ma. Reyes.
Anesthesia for Splenectomy in Patients with Blood Dyscrasias. R. N. Reynolds and B. E. Etsten.
Hemodynamic Studies During Cyclopropane Anesthesia in Humans. Murray C. Thompson, Earl H. Wood, and Robert T. Patrick.
Changes in the Circulation Consequent to Intra-abdominal Manipulation. Angelo G. Rocco and LeRoy Vandam.
Anectine (Succinylcholine) and Inhalation Analgesia for Major Cardiac and Pulmonic Surgery. Seymour Schotz, Shirley S. Bloom, and Frederick W. Helmsworth.

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