DURATION OF ANAESTHESIA WITH THIOPENTAL WHEN COMBINED WITH EACH OF MANNITOL, UREA, SODIUM BICARBONATE, OR TROMETHAMINE ("THAM," "TRIS")*

ALLEN B DOBKIN, M D , JACOB S ISRAEL, M D , AND PETER H BYLES, M B

DURING THE PAST FOUR YEARS, some relatively simple compounds have been under trial for the treatment of serious metabolic disturbances which have long troubled the clinician. Mannitol and urea have been used primarily as osmotic diuretics, sodium bicarbonate has been used to reverse metabolic acidosis, and tromethamine has been used to treat both respiratory and metabolic acidosis, but it is an osmotic diuretic as well.

This report deals with a study to determine whether these compounds affect the duration of thiopental anaesthesia. The experiments were done because the compounds are being used more and more during or immediately following the administration of anaesthesia, and the authors felt that it was important to know particularly whether they alter the duration of anaesthesia.

METHOD

Crossover experiments were carried out four times, at weekly intervals, with each drug, using 10 mongrel dogs of comparable size (initial weight 13.5 to 19.8 kg, mean 17.6 kg), using a technique previously employed in such studies^{1 2 3}. Prior to each experiment, the dogs were weighed in the fasting state (12 hr). All but one dog increased in weight during the four months (Nov 1962 to Feb 1963) that these experiments were in progress. In every experiment, each dog received 25 mg/kg of thiopental intravenously in a 2.5 per cent solution, injected at the approximate rate of 200 mg/minute, and this was followed in alternate experiments by the injection of the test drug. The dose selected for each of the four drugs was within the therapeutic range of its primary use. In fixing the dose, consideration was given also to the matter that these data might be applied to evaluating the combination with thiopental in man.

Sodium bicarbonate was injected rapidly, in a 7.5 per cent solution (75 mg/kg body weight), the total dose being administered in less than 30 seconds in each case. Tromethamine was injected in a 3 per cent solution (300 mg/kg) in 5 per cent dextrose/water by drip infusion regulated so that the total dose was administered in 15 minutes. The latter method was used also with the mannitol (20 per cent solution in water, 1000 mg/kg body weight) and the urea (30 per cent solution, 1000 mg/kg body weight).

After each injection, the dog was placed on the floor of the laboratory and allowed to recover without being disturbed or stimulated. The recovery time of each animal was recorded as the time which had elapsed from the beginning of

*From the Department of Anesthesiology, State University of New York, Upstate Medical Center, Syracuse, New York

the injections until the dog lifted its head and, then, until it attempted and was able to stand on all four paws without collapsing. As soon as the dog recovered, it was removed from the room so that it would not stimulate its "sleeping" companions.

RESULTS

The data from the four crossover experiments are summarized in Tables I and II, together with a statistical analysis of each. No untoward effects were observed during the injection of thiopental or during recovery in the control experiments. Of the four drugs tested, two caused apparent side-effects: with tromethamine, one dog retched during the injection, three dogs vomited fluid after the injection, and one dog stopped breathing abruptly some minutes after the injection and expired. Three dogs vomited while the urea was being administered. During the recovery period, most of the animals that received mannitol and urea urinated.

Sodium bicarbonate was the only agent of the four which caused an appreciable reduction in the recovery time from thiopental sleep. Mannitol was the only

TABLE I

Drugs	Concentration used (%)	Chemical structure
Mannitol Osmotril®, Travenol®	20	$\begin{array}{ccccccc} & & \text{H} & \text{H} & \text{OH} & \text{OH} & \\ & & & & & & \\ \text{HO} & \text{CH}_2 & -\text{C} & -\text{C} & -\text{C} & -\text{C} & -\text{CH}_2\text{OH} \\ & & & & & & \\ & & \text{OH} & \text{OH} & \text{H} & \text{H} & \end{array}$
Urea Urevert®, Ureaphil®	30	$\text{H}_2\text{N}-\text{CO}-\text{NH}_2$
Sodium bicarbonate	7.5	NaHCO_3
Tromethamine Talatrol®, "THAM," "Tms"	3.0	$\begin{array}{c} \text{NH}_2-\text{C} \begin{array}{l} \nearrow \text{CH}_2\text{OH} \\ \text{CH}_2\text{OH} \\ \searrow \text{CH}_2\text{OH} \end{array} \end{array}$

TABLE II
THE EFFECT OF SOME DIURETICS ON THIOPENTAL NARCOSIS IN DOGS

Drugs	Dose (mg/kg)	Recovery time (minutes)							
		Head up			Signif P	Legs up			Signif P
		Mean*	S.D.	% Diff		Mean*	S.D.	% Diff	
Thiopental alone	25	43	±10			54	±11		
+mannitol	1000	52	±17	+23	<0.01	68	±18	+26	<0.001
Thiopental alone	25	48	±22			60	±20		
+urea	1000	54	±18	+13	<0.02	65	±18	+12	>0.05
Thiopental alone	25	66	±15			84	±36		
+NaHCO ₃	75	42	±11	-27	<0.05	66	±17	-24	<0.001
Thiopental alone	25	53	±11			64	±31		
+THAM	300	48	±14	-11	<0.05	62	±15	-2	>0.05

*Each mean time represents 20 administrations of thiopental alone and 20 with the test drug, except in the "THAM" experiments in which each mean time represents 18 administrations.

one which caused an appreciable lengthening of the duration of recovery. Urea appeared to produce a trend to lengthening while tromethamine appeared to produce a shortening of the duration of recovery, but these effects were not very significant statistically.

DISCUSSION

Mannitol, a hexahydroxy alcohol (the reduced form of Mannose), is prepared either as a sterile 25 per cent aqueous solution or as a sterile 20 per cent aqueous solution which is buffered at a pH of 6.4 to 6.8 with sodium hydroxide. Although mannitol has been used to measure glomerular filtration rate for many years,⁴ it has now been found to be of value as a therapeutic agent to reduce elevated cerebral spinal fluid pressure⁵ and intraocular pressure.⁶ After intravenous infusion, it is restricted to the extracellular fluid compartment and is freely filtered by the kidney glomeruli, creating a high osmotic pressure in the lumen of the renal tubular system, causing inhibition of resorption of water and aiding the irrigation of the tubules and the excretion of urine. Mannitol has been shown to increase renal blood flow, decrease renal vascular resistance, and reduce the haematocrit, associated with marked alteration in the shape and diminution in the size of red blood cells.⁷ It promotes the excretion of sodium and chloride, along with water, without appreciably increasing potassium excretion. Mannitol also appears to be an effective prophylactic agent against functional renal failure in surgical procedures in which serious renal effects are prevalent, particularly those incidental to vascular (aneurysmectomy) and cardiac surgery.⁸⁻¹³ It is also used to promote diuresis in exogenous and endogenous intoxications as seen with overdoses of sedatives, uric acid nephropathy, and transfusion reactions.¹⁴⁻¹⁸ The recommended initial test dose in man is 200 mg/kg administered in 3 to 5 minutes. If there is an adequate response by passage of at least 40 ml urine per hour, then larger doses may be given. In our clinical use of mannitol, no obvious side-effect has been observed during the period of anaesthesia for vascular surgery, aside perhaps from an expected increase in urinary output, nor did it appear to prolong the duration of anaesthesia, as occurred in the experiments reported above.

Considering its action in the body, one might expect that mannitol would reduce the effect of a single large dose of thiopental by increasing the rate of excretion in the urine. On the other hand, this action may, in the acute experiment, cause a persistently higher blood level by its osmotic effect and so explain why thiopental sleep may instead be prolonged. Nahas and associates have suggested that the depressant action of mannitol might be due, in part, to the osmotically induced shift of water from intracellular to extracellular compartments and a resulting increase in the alkalinity of the chemosensitive cells. However, they state further that the alterations in acid-base balance between intracellular and extracellular compartments produced by mannitol result in respiratory changes which cannot be accounted for by the classical theories relating pulmonary ventilation to hydrogen ion or $p\text{CO}_2$ changes in arterial blood.¹⁹

Urea is a powerful osmotic diuretic which has been used clinically for more than 100 years. In a 30 per cent solution with 10 per cent invert sugar in water, it is now used primarily to lower intracranial pressure, as recently recommended by Javid and Settlege,²⁰ although it is also recommended for the treatment of

oliguria following burns, surgery, and trauma,²¹ but its use in these conditions is still being evaluated. Rosomoff²² has shown that urea causes water to shift from brain tissue to the cerebrospinal fluid and the blood, doubling the volume of the latter fluid compartments and reducing the brain water to the same extent as can be accomplished by inducing hypothermia.

The urea preparation is usually given in a dose of 1 to 15 gm per kg body weight, by intravenous infusion in one to two hours. Maximum effect on the brain is said to occur in one to two hours and persists for 3 to 10 hours. This solution is contraindicated in patients with poor renal function and serious tissue damage occurs if it is allowed to leak from the vein.

The explanation for the trend to longer duration of anaesthetic "sleep" rather than its abbreviation is probably the same as with mannitol. A reason why more prolonged sleep was not evident is perhaps that urea, when administered relatively quickly, appears to cause medullary irritation as manifested by the incidence of retching and vomiting. Limitations inherent in the experimental design made it unfeasible to administer the urea preparation more slowly without using a longer-acting intravenous anaesthetic.

Sodium bicarbonate administered intravenously causes the excretion of an increased volume of an alkaline urine. The initiating event is an increase in the concentration of bicarbonate in the extracellular fluid and glomerular filtrate, consequently, there is a rise in the bicarbonate load delivered to the renal tubule. Bicarbonate reabsorption results indirectly from hydrogen ion-sodium ion exchange between the tubular cell and tubular urine. With high bicarbonate loads, the amount of hydrogen ion which reaches the tubular urine is not sufficient to convert all of the filtered bicarbonate to carbonic acid and CO₂. Thus, bicarbonate ion with equivalent amounts of cation and an isosmotic quantity of water will escape absorption and augment the urine volume. Sodium bicarbonate is not used as a diuretic clinically because it does not mobilize oedema fluid and it may cause chronic alkalosis which reduces the effectiveness of mercurial diuretics.^{23 24}

The use of sodium bicarbonate has recently come into prominence for the treatment of metabolic acidosis which follows induced hypothermia or prolonged severe cardiorespiratory depression, as well as that following circulatory arrest, poisoning with methyl alcohol, phenol, polymeric phosphates, formalin, and salicylate intoxication in children.²⁵

Huckabee has shown that metabolic acidosis develops rapidly during severe hypoxia on account of anaerobic glycolysis²⁶ and Clowes and his associates have shown that postoperative patients do poorly when they have metabolic acidosis as well as hypoxia.²⁷ Ebert and his associates have shown that ventricular efficiency is greater during metabolic alkalosis than during metabolic acidosis,²⁸ and Thrower and his associates have attempted to show that the cardiovascular response to vasopressors is augmented or restored when metabolic acidosis is reduced by sodium bicarbonate.²⁹ Ledingham and Norman have demonstrated that following circulatory arrest neither a high arterial pCO₂ nor variation of the arterial pH seems responsible for inadequate myocardial function, but when the metabolic acidosis is present and is treated by administration of sodium bicarbonate, the response to vasopressors is augmented and recovery is more likely.³⁰

More reliable data are still required on this subject, but circumstantial evidence points to some benefit with alkalizing drugs as a part of acute resuscitative treatment. In man, the recommended initial dose of sodium bicarbonate is 60 mg/kg body weight, using a 3.75 per cent solution. This dose is said to raise the carbon dioxide content of the blood approximately 1 mEq/L (or 2 vol % CO₂). However, alkalization should be attempted slowly, as the patient's condition permits, and the effect of each injection should be followed by determination of the arterial blood pH and pCO₂. In the starved, dehydrated patient, it must be realized that treatment of metabolic acidosis in this way may aggravate a potassium deficiency and cause sodium intoxication.

The dog appears to require a somewhat higher dose of sodium bicarbonate than that recommended in man to accomplish a similar reduction in fixed acids.³⁰ Therefore, in this study, a 7.5 per cent solution was used and a total dose of 75 mg/kg body weight was administered. Although there is no reason to believe that the animals became hypoxic because of respiratory depression, and developed a metabolic acidosis, perhaps the finding that thiopental "sleep" was shortened by the administration of sodium bicarbonate points to yet another mechanism by which this substance is useful in the treatment of severe cardiorespiratory depression.

Tromethamine was first used *in vivo* by Nahas, in 1959, to show that this organic buffer might be useful in the treatment of acidosis due to either renal (metabolic) or respiratory impairment, and would be eminently useful because it distributes widely through body fluids, does not contain sodium, and acts also as an osmotic diuretic.³¹ This work was confirmed by Miller, Brindle, and Gilbert.³² The fact that tromethamine is a non-sodium-containing buffer is of particular importance for the patient with cardiac disease, since the only other agents used to combat acidosis are sodium bicarbonate and sodium lactate—which in a 45 mEq dose contain 2.5 gm of sodium.

When administered intravenously, this compound acts as a weak base which reacts, as follows, with acid metabolites

In the body, A⁻ may be bicarbonate, chloride, or lactate. The more acid that is present, the more the reaction moves to the right. The acid-neutralizing effect of tromethamine is thus quite similar to that of sodium bicarbonate. At pH 7.40, it is 70 per cent ionized and at pH 6.0, it is virtually completely ionized. Tromethamine is very soluble in water and is isosmolar with blood in a 0.3 molar solution. To reverse respiratory acidosis, it buffers carbonic acid, thus lowering the arterial pCO₂. In the kidney, it acts as an osmotic diuretic, there is a fall in haematocrit, indicating that a redistribution of body water takes place from intracellular to extracellular space, increasing the excretion of sodium, potassium, bicarbonate, and chloride, and increasing the pH of the urine. Cardiac effects of tromethamine have been described as indirectly due to reversal of metabolic and respiratory acidosis, thereby increasing the contractile force and inotropic response to sympathomimetic amines.³³ One report states that tromethamine (as well as urea) significantly shortens the sleeping time in rats after pentobarbital administration, but no actual data were published.³⁴

Nahas and associates¹⁹ have postulated that tromethamine alters the ratio of free to combined carbon dioxide and acts on the respiratory centre either indirectly by a lowering of the $p\text{CO}_2$ in extracellular fluid or directly by intracellular buffering. They attribute an early depression of ventilation to the lowering of $p\text{CO}_2$ in the extracellular fluid and a subsequent depression (which occurs in the presence of an elevation of $p\text{CO}_2$ in extracellular fluid) by the penetration of tromethamine into the cells of the respiratory centres where it will accept hydrogen ions and increase buffering capacity. However, there is still no clear explanation for the neurophysiological mechanism which brings about the decrease in pulmonary ventilation with tromethamine or mannitol.

In clinical use, this compound can restore buffer base to normal levels and may be useful in restoring the response to resuscitative measures. In adults, the buffer may be used in 0.3 molar solution and 500 mg/kg given in one hour, or 36 grams may be given in 500 ml 5 per cent dextrose in water (0.6 molar). In children, it is best to dilute 9 grams in 150 ml 5 per cent dextrose in water and to give 50 ml in the first hour for treatment of salicylate poisoning. However, indiscriminate use of this buffer is inadvisable and it should not be used unless conventional methods of therapy are ineffective.^{35 36}

Unfortunately, its administration intravenously carries with it two serious dangers. By reducing the responsiveness of the respiratory centre to carbon dioxide, it causes respiratory depression and even apnoea, therefore, it is essential to provide automatic intermittent positive pressure breathing during its administration. Since this is true, it is probably unwise to use it for the treatment of respiratory acidosis, since intermittent positive pressure breathing accomplishes the same thing. The other drawback is one that is similar to mannitol and urea—they cause tissue damage when they leak around a vein. A further drawback to use of tromethamine is that large doses cause severe hypoglycaemia, so that it is necessary to administer dextrose in water along with it.^{37 38}

Although Nahas has stated that tromethamine stimulates respiration in the dog anaesthetized with thiopental sodium until 1.25 gm/kg is exceeded whereas respiratory depression occurs when 1.50 gm/kg is administered, it was obvious to us that as little as 300 mg/kg can cause persistent apnoea (and death) in the dog. In any case, our experiment did not show any significant effect which would lead to a more rapid recovery from thiopental "sleep," although there was a slight trend in this direction.

Many examples can be cited in which an unpredictable and, often, a serious effect has been produced after administering two or more drugs in combination. This is particularly true in anaesthetic practice where we are dealing with potent hypnotic, analgesic, and relaxant drugs that are potentially intense cardiorespiratory depressants themselves. Yet, very little work has been done specifically to study the effect of drugs in combination. Loewe³⁹ has informed us of the imprecise concepts of synergism and antagonism, and we have been reminded that much more experimental work needs to be done on drug interactions, both in animals and in man. A leading article recently pointed out that such work requires many experimental subjects and is very laborious and time-consuming, particularly in man, but it can yield essential information which cannot be gained in other ways and is much less well-known than it should be.⁴⁰

Blood buffers and osmotic diuretics are now being used in treating patients who are seriously ill, and who, more often than not, are receiving anaesthetic agents, cardiotonic drugs, and other therapeutic agents which may facilitate recovery, but they may be instrumental in hastening death—as Calesnick and his associates found when other combinations of therapeutic agents were used ⁴¹

Therefore, it behooves the anaesthesiologist to learn not only the biochemical and physiological effects of each new therapeutic drug that he may be asked by a surgeon to administer during an anaesthetic, but he should ascertain also how the drug may change the response to general (or spinal) anaesthesia—otherwise, he will on occasion be left alone with a patient at the end of an operation, wondering why certain vital signs are so depressed or have failed to return in the expected time. Furthermore, the surgeon who studies new therapeutic agents should more often realize and consider the additional effects of the anaesthetics used on his patients, for these alone can greatly alter the over-all efficacy of a new treatment ⁴²

SUMMARY AND CONCLUSIONS

Crossover experiments were carried out on ten medium-sized mongrel dogs using intravenous injections of a therapeutic dose of mannitol, urea, sodium bicarbonate, and tromethamine (THAM), to determine whether any of these would alter significantly the duration of thiopental “sleep” induced with a single intravenous dose of 25 mg/kg body weight

Mannitol, in a dose of 1 gm/kg given over 15 minutes, prolonged recovery time by approximately 25 per cent, whereas sodium bicarbonate, in a dose of 75 mg/kg given within 30 seconds shortened recovery by about 25 per cent. Urea (1 gm/kg in 15 minutes) and tromethamine (300 mg/kg in 15 minutes) had no appreciable effect on recovery time although, with urea, there was a trend to delayed recovery, whereas with tromethamine, the trend was towards more rapid recovery. Urea and tromethamine caused retching and/or vomiting during administration in some of the animals, and tromethamine caused apnoea and death in one.

The biochemical effect of these drugs and the obscure mechanism of action on pulmonary ventilation were reviewed briefly along with their clinical applications. The prior unpredictability of their interaction with thiopental was evident from the results, and points to the importance of carrying out such studies before employing drug combinations clinically, particularly during the course of anaesthesia. Serious complications arising from the combination of therapeutic agents with anaesthetic drugs can only be prevented or managed effectively when one is aware of the specific responses that drug combinations can cause.

RÉSUMÉ

Chez 10 chiens bâtards de poids moyen, nous avons fait des expériences croisées en pratiquant des injections endoveineuses de doses thérapeutiques de mannitol, d'urée, de bicarbonate de soude et de trométhamine (THAM) pour préciser si l'une de ces substances pouvait modifier de façon marquée la durée

du sommeil produit par une seule dose de thiopental I V de 25 mg/kg de poids

Le Mannitol, à la dose de 1 gm/kg administrée au cours de 15 minutes, a prolongé d'environ 25 pour cent la durée du réveil, alors que le bicarbonate de soude, à la dose de 75 mg/kg donnée en 30 secondes, a abrégé cette durée de 25 pour cent. L'urée (1 g/kg en 15 minutes) et la trométhamine (300 mg/kg en 15 minutes) n'ont pas influencé de façon appréciable le moment du réveil bien que, avec l'urée, nous avons observé une tendance à un réveil tardif et, avec la trométhamine, la tendance était plutôt à un réveil hâtif. L'urée et la trométhamine ont provoqué chez certains animaux des nausées et/ou des vomissements au cours de leur administration et, chez un animal, la trométhamine a entraîné l'apnée et la mort.

Nous avons brièvement parlé de l'effet biochimique et du mécanisme d'action plutôt obscur de ces substances sur la ventilation pulmonaire ainsi que de leurs applications cliniques. D'après les résultats, il est évident que nous ne pouvons pas prévoir leur interaction avec le thiopental, et cela souligne l'importance de faire de semblables études avant d'employer de telles associations de substances en clinique, surtout au cours de l'anesthésie. Si l'on est bien averti des résultats spécifiques qui découlent des mélanges de médicaments, on peut alors éviter de sérieuses complications qui peuvent se produire après l'usage combiné d'agents thérapeutiques et d'agents anesthésiques et n'utiliser ces mêmes agents qu'à bon escient.

ACKNOWLEDGMENT

The authors are indebted to Mr. Ronald Welgan for his devoted assistance in the laboratory. Drugs for testing were kindly supplied by Abbott Laboratories and Baxter Laboratories, Inc.

REFERENCES

- 1 VIRTUE, R. W. & KASTER, R. B. Effect of Megimide and Thiopental in Dogs. *Anesthesiology* 18: 686 (1957)
- 2 DOBKIN, A. B. & HARLAND, J. H. Drugs which Stimulate Affective Behaviour. 1. Action of LSD-25 against Thiopentone Anaesthesia in Dogs. *Anaesthesia* 15: 48 (1960)
- 3 DOBKIN, A. B. Potentiation of Thiopental Anaesthesia by Derivatives and Analogues of Phenothiazine. *Anesthesiology* 21: 292 (1960)
- 4 GOODMAN, L. S. & GILMAN, A. *The Pharmacological Basis of Therapeutics*, 2nd ed., pp 843-4. New York: Macmillan (1955)
- 5 SHENKIN, H. A., GOLUBOFF, B., & HAFT, H. The Use of Mannitol for the Reduction of Intracranial Pressure in Intracranial Surgery. *J. Neurosurg.* 19: 897 (1962)
- 6 SMITH, E. W. & DRANCE, S. M. Reduction of Human Intraocular Pressure with Intravenous Mannitol. *Arch. Ophthalmol.* 68: 734 (1962)
- 7 LILIEN, O. M., JONES, S. G., & MUELLER, C. B. The Mechanism of Mannitol Diuresis. *Surg., Gynec. & Obst.* 117: 221 (1963)
- 8 BARRY, K. G., COHEN, A., & LEBLANC, P. C., JR. Mannitolization. I. Prevention and Therapy of Oliguria Associated with Cross Clamping of Abdominal Aorta. *Surgery* 50: 335 (1961)
- 9 BARRY, K. B. & BERMAN, A. R. Mannitol Infusion. III. The Acute Effect of the Intravenous Infusion of Mannitol on Blood and Plasma Volumes. *New Engl. J. Med.* 264: 1085 (1961)
- 10 BOBA, A., GAINOR, J., & POWERS, S. R., JR. The Influence of Mannitol on Water and Electrolyte Excretion Following Trauma. *Surgery* 52: 188 (1962)
- 11 PARRY, W. L., SCHAEFER, J. A., & MUELLER, C. B. Experimental Studies of Acute Renal Failure. I. The Protective Effect of Mannitol. *J. Urol.* 89: 1 (1963)

- 12 ATTAR, S, BORGES, F, CROWLEY, R A, ESMOND, W G, HOLLINGSWORTH, N, & BLAIR, E Use of Mannitol in Postperfusion Oliguria-Anuria *Circulation* 26 682 (1962)
- 13 BEALL, A C, JR, HOLMAN, M R, MORRIS, G C, JR, & DEBAKEY, M E Mannitol-Induced Osmotic Diuresis during Vascular Surgery *Arch. Surg* 86 34 (1963)
- 14 HARTHORNE, J W, MARCUS, A M, & KAYE, M Management of Massive Imipramine Overdosage with Mannitol and Artificial Dialysis *New Engl. J Med* 268 33 (1963)
- 15 GALAMBOS, J T, HERNDON, E G, JR, ACHORD, J L, & CHRISTY, J H The Effect of Osmotic (Mannitol) Diuresis on Electrolyte and Water Excretion in Ascitic, Cirrhotic Patients *Clin Res* 11 69 (1963)
- 16 GROSSMAN, A & BERNSTEIN, L M The Use of the Osmotic Diuretic Mannitol in the Management of Refractory Nephrotic Syndrome *Am J Dis Children* 102 616 (1961)
- 17 BARRY, K G & MALLORY, J P Oliguric Renal Failure Evaluation and Therapy by the Intravenous Infusion of Mannitol *J A M A* 179 510 (1962)
- 18 BARRY, K G & CROSBY, W H The Prevention and Treatment of Renal Failure Following Transfusion Reactions *Transfusion* 3 34 (1963)
- 19 NAHAS, G G, FINK, R B, PLOSKI, W S, & TENEIK, R E The Depressant Effect of Tris (Hydroxymethylaminomethane) and of Mannitol on Respiration *Ann NY Acad Sci* 109 783 (1963)
- 20 JAVID, M & SETTLAGE, P Effect of Urea on Cerebralspinal Fluid Pressure in Human Subjects *J A M A* 160 943 (1956)
- 21 JORGENSEN, H E & SCHLEGEL, J U Studies in Metabolism of Trauma III Postoperative Sodium Retention *Surg Gynec & Obst* 108 339 (1959)
- 22 ROSOMOFF, H L Effect of Hypothermia and Hypertonic Urea on Distribution of Intracranial Contents *J Neurosurg* 18 753 (1961)
- 23 GOODMAN, L S & GILMAN, A The Pharmacological Basis of Therapeutics, 2nd ed., pp 841-2 New York Macmillan (1955)
- 24 LICH, R, JR Kidneys, Fluids, and Electrolytes *J Kentucky M A* 53 219 (1955)
- 25 MODELL, W Drugs of Choice 1962-3, p 759 St Louis C V Mosby (1962)
- 26 HUCKABEE, W E Relationships of Pyruvate and Lactate during Anaerobic Metabolism III Effect of Breathing Low-Oxygen Gases *J Clin Investigation* 37 264 (1958)
- 27 CLOWES, G H A, ALICHNIEWIEZ, A, DELGUERIO, L R M, & GILLESPIE, D The Relationship of Postoperative Acidosis to Pulmonary and Cardiovascular Function *J Thorac Cardiovasc Surg* 39 1 (1960)
- 28 EBERT, P A, GREENFIELD, L J, AUSTEN, W G, & MORROW, A The Relationship of Blood pH during Profound Hypothermia to Subsequent Myocardial Function *Surg Gynec & Obst* 114 357 (1962)
- 29 THROWER, W B, DARBY, T D, & ALDINGER, E E Acid-Base Derangements and Myocardial Contractility Effects as a Complication of Shock *A M A Arch Surg* 82 56 (1961)
- 30 LEDINGHAM, I MCA & NORMAN, J N Acid-Base Studies in Experimental Circulatory Arrest *Lancet* ii 967 (1962)
- 31 NAHAS, G G Use of an Organic Carbon Dioxide Buffer in vivo *Science* 129 782 (1959)
- 32 MILLER, R A, BRINDLE, F, & GILBERT, R G B Studies with an Organic Buffer (THAM) during Apnoeic Oxygenation in Dogs *Brit J Anaesth* 323 248 (1960)
- 33 ALDINGER, E E, DARBY, T D, & THROWER, W B Effects of Tris (Hydroxymethyl) Aminomethane (THAM) on Acid-Base Derangements and Ventricular Contractile Force Elicited by Periods of Reduced Circulatory Volume *Fed Proc* 19 102 (1960)
- 34 BALAGOT, R C, TSUJI, H, & SADOVE, M S Use of an Osmotic Diuretic—THAM—in Treatment of Barbiturate Poisoning *J A M A* 178: 1000 (1961)
- 35 BRINKMAN, G L, REMP, D G, COATES, E O, & PRIEST, E M Treatment of Respiratory Acidosis with THAM *Am J Med Sci* 239 341 (1960)
- 36 KAPLAN, S, FOX, R P, & CLARK, L C, JR Amine Buffers in the Management of Acidosis *Am J Dis Children* 103 4 (1962)
- 37 BRINKMAN, G L The Use of THAM to Prevent Hyperventilation and Acidosis while Breathing Carbon Dioxide *Am J Med Sci* 239 728 (1960)
- 38 BENNETT, T E & TARRIL, R The Hypoglycemic Activity of 2-Amino-2 hydroxy-methyl-1,3-propanediol *Ann NY Acad Sci* 92 651 (1961)
- 39 LOEWE, S Antagonisms and Antagonists *Pharmacol Rev* 9 237 (1957)
- 40 Leading Article Interaction between Drugs *Lancet* ii 818 (1962)
- 41 CALESNICK, B, SMITH, N H, & BEUTNER, R Combined Action of Cardiotoxic Study on Acute Toxicity of Combined Quinidine, Meperidine, Pentobarbital, P and Procaine Amide *J Pharmacol & Exper Therap* 102 138 (1951)
- 42 SIMEONE, F A Surgery and Pharmacology *Clin Pharmacol & Therap* 4 149 (1963)