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## A practical discussion of intravenous anesthesia

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A PRACTICAL DISCUSSION OF INTRAVENOUS  
ANESTHESIA

SENIOR THESIS

by

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## PREFACE

In this monograph I have attempted a survey of the literature pertaining to all of the drugs which have been used by the intravenous route, for the production of anesthesia. Some of the drugs represent old and outmoded methods, while others represent the newest and the most recent discoveries resulting from the endless search for a perfect anesthetic agent. However, for the sake of completeness, each drug will be discussed as fully as the time permits, with as few as possible remarks concerning the efficacy or inefficacy of that particular method as compared to methods of administration other than intravenous administration.



## INTRODUCTION

The field of intravenous anesthesia has been, from the beginning, and still is, one of the most bitterly contested points in medical literature. It presents renowned scientists championing its cause, and hosts of equally brilliant men who denounce it with sincerity. It is the purpose of this paper to only give the opinions, both pro and con, upon this controversial subject, and not to endeavor to decide the issue. The bitter fight between those advocating the inhalation route, and those upholding the intravenous methods, will be given in a fair and impartial attitude by the writer, and if a verdict is to be rendered in favor of either, it is left to the reader's discretion to do so.

I am including a brief chapter on the history, describing the evolution of anesthesia, in general, in order to more clearly and logically show the reader the preliminary step by step progress that science has undergone in its search for the perfect anesthesia,- the utopia of anesthetists. Intravenous anesthesia, as other anesthesia, has its good and bad points, and a definite place in anesthesia. Perhaps it is best to place its choice with the surgeon. That evidence which gives the surgeon the most peace of mind, knowing his patient's condition as he should, will decide its applicability in each instance.

## HISTORY

"And the Lord God caused a deep sleep to fall upon Adam, and he slept; and He took one of his ribs and closed up the flesh instead thereof". It has been claimed that in the "deep sleep" which the Creator "caused to fall upon Adam", is the germ of the idea of anesthesia that has come down to us from the dim ages of the past. It is probable that primitive man used digital compression of the carotid arteries to produce anesthesia, as the inhabitants of some countries do today. This method was practiced by the race of Assyrians before performing the operation of circumcision. Curiously too, the literal translation of the Greek and Russian terms for the carotid is "the artery of sleep".  
(108)

The ancient Egyptians are believed to have used Indian hemp and the juice of the poppy to cause a patient to become drowsy before a surgical operation. Pliny (108) relates, that they applied to painful wounds a species of rock brought from Memphis, which was powdered and moistened with sour wine. This is the first record of local anesthesia with carbonic gas. It is probable that the "wine mingled with myrrh", which, according to St. Mark, was offered to Christ before he was nailed upon the cross, was indeed a narcotic draught, given with the object of lessening his sensibility to the agony that was forth-coming from his persecutors.

The earliest reference to anesthesia by inhalation is contained in the works of Herodatus, who states that the Scythians were accustomed to produce intoxication by inhaling the vapor of a certain kind of hemp which they threw upon the fire. This was probably *cannabis indicus*, or Indian hemp.

During the fifteenth century, several new drugs had been introduced and used as an inhalation, in mixed form. The following is the composition of the sleeping sponge, and the method used. "Take of opium, of the juice of the forest mulberry, of the seeds of lettuce, of the seeds of dock, which has large round apples, and of the water-hemlock, each an ounce. Mix all these in a vessel, and then place it in a new sponge; let the whole boil until the sponge consumes it all. Place the sponge in hot water for an hour and let it be applied to the nostrils of him who is to fall asleep". The sleep produced was so profound it often continued for several days. (108)

Local anesthesia was not unknown during the middle ages, and Cardow recommends the inunction of a mixture consisting of opium, celandini, together with oils. Now crushed seeds of poppy and henbane were applied as a plaster to parts about to be cauterized. Local anesthesia was also produced by freezing. During the seventeenth and eighteenth centuries the interest in anesthesia began to wane and few allusions are made to it until late in the eighteenth century. Thus, from the dawn of creation, an

anesthesia for surgical operations had been practiced to some extent, but, owing to the uncertainty of the potency and action of the powerful narcotics and palliatives administered and the danger attending their use when exact science was unknown, the practice seemed likely to fall into oblivion. At last a series of brilliant discoveries in chemistry created a new epoch in the history of anesthesia.

The chemical era of anesthesia brought about the discoveries of Priestley about 1767. These led up to the plan of administering gases and vapors of definite composition through the lungs. In course of time, nitrous oxide, which had been discovered by Priestley in 1776, was introduced by Humphery Davy as an inhalant, and he discovered to his great delight that it relieved pain. About this time, Professor Thompson of Glasgow was accustomed to amuse his students annually by allowing them to inhale ether and nitrous oxide until they were intoxicated. It is an extraordinary fact that, even in the face of such experiments, no one among the investigators who stood at this time on the brink of so great a discovery ventured over the threshold. The things that are the most apparent may be the longest buried, and so with the discovery of efficient anesthesia. (109)

In 1844, however, Dr. Colton, a pupil under Turner of London, delivered a lecture at Hartford, Connecticut. Some demonstrations for the amusement of the audience were done. Dr. Wells who was in the audience induced a Dr. Riggs to be

the operator and extract a tooth while under the influence of the nitrous oxide. This was done and, as Wells stated, without pain. Wells then demonstrated its use several succeeding times. He was asked to address a class at the Massachusetts General Hospital, at which time his experiment was not successful, and the whole thing was denounced as humbug. He became disappointed, his death occurring due to this, at thirty-two. To Wells, however, belongs the credit for having first shown the practicability of producing insensibility by the use of nitrous oxide and establishing the principle of anesthesia.

In 1828, Faraday had called attention to the anesthetic properties of ether. In 1839, Clarke and Morton began amusing their friends by the use of ether, just as nitrous oxide was first used. Morton began studying the more serious side of the unconsciousness brought on by ether, and finding his conclusions similar to those of Wells, he had the opportunity to use ether on several extractions. These proved to be very successful and he obtained permission to test his new anesthetic on a surgical patient at the Massachusetts General Hospital. The operation was a big success and soon after (1846) a meeting was held in Boston to decide on a name for the "sleep producing" substance. Morton himself chose the name "letheon", but subsequently Dr. Oliver Wendell Holmes suggested "anesthesia" for the condition, and the word "anesthetic" for the agent. These were immediately taken up by the profession and laity.

Chloroform as a substance had been known for some time. It also passed through a series of more or less amusing experiments, before Waldie and Simpson became aware of its practical uses. In 1847, Simpson first used chloroform anesthesia with success and reported the same to the Medico-Chirurgical Society of Edinburgh. The advent of chloroform gave an impetus to other investigators, and during the last fifty years such agents as ethyl chloride, ethyl bromide, ethylene, amylene, all of the barbiturates, and others have been produced, many of which have been abandoned because of some defect or the other.

The induction of general anesthesia by the intravenous injection of drugs was first effected in man in 1872 by Ore; the drug employed was chloral, fifty-three cases were reported, in fifty-one of which satisfactory results were obtained.(77) Further experience however, proved that the procedure was not without danger and the method does not seem to have been further developed until 1909. In that year Burkhardt published his application of the principle, using solutions of chloroform first, and then later, solutions of ether.

In 1910, Professor Federoff, of St. Petersburg, suggested the intravenous administration of hedonal. (77) Then, one by one, ether, hedonal, paraldehyde, and the so numerous barbiturates sprung into prominence, each in turn occupying the attention of those inflamed with the idea of finding a perfect intravenous anesthetic. The

literature concerning the history of this search is far too vast to consider at this time, and will be taken up under each individual discussion of the separate drugs.

## INTRAVENOUS ROUTE IN GENERAL

Five to ten years ago, some men felt that most of the old, time honored anesthetic agents were to be discarded, and to be replaced by certain widely proclaimed new anesthetics and that the long established inhalation route for general anesthesia was to be but little used and that the intravenous route would supplant the pulmonary way. A review of the literature on anesthesia, a consideration of the reports of anesthetists and their evaluation of the experiences with some of the recently introduced anesthetics and methods, compels one to feel that there is no ideal anesthetic nor perfect method, that there is no possibility at present of discarding either old anesthetics nor old methods, and that each anesthetic and method, whether old or new, has its definite indications as well as its equally definite contra-indications. According to M. Babcock, (81) the wrangle over intravenous anesthesia versus inhalation anesthesia is a most unnecessary thing, because there is a definite time and place for both in the field of anesthesia.

Felix Rood, (76) is one of the more pronounced champions of the intravenous cause, and states that excellent though administration of anesthetics by inhalation are, there are certain inherent defects in any method of administration through the respiratory tract. Although in most cases the results obtained by inhalation are good, cases very frequently do arise in which the objections to this



method are of very great importance. An attempt may, perhaps, be made here to enumerate some of the more commonly stated difficulties suggested by those opposed to the inhalation route. In the first place, one is limited to the use of highly volatile substances, and it is probable that if solubility rather than volatility is the physical factor required, the number of available drugs may be greatly increased. Rood, (76) contends that the respiratory method must always in essence, be indirect. The anesthetic is absorbed from the vapor introduced into the air passages, so that the dose actually entering the blood is rendered variable by the variability with which it enters the chest, being subject to all of the accidents of laryngeal spasm, respiratory spasm, and of variations in the depth and energy of respiration. Another argument common among the supporters of the intravenous route is that the exposure of a very large surface of the respiratory tract to an irritating gas must be regarded as a disadvantage and danger. This seems quite logical, because most of us have at some time inhaled a strong breath of ether, and found it quite irritating, and it seems reasonable that such a vapor used in a long anesthesia might at times lead to serious complications. In operations upon the mouth, jaws, or pharynx, the difficulties of the surgeon are much increased by his having to share the field of operation with the anesthetist. It is clear, I believe, from the various articles, that if the direct administration of the anesthetic by the blood can be safely

effected, it does dispose of all of these difficulties in the use of inhalation drugs, and leaves the way very open for the intravenous route.

It is sometimes a little difficult to see the relative uses and disadvantages of a new medical or surgical method in their true perspective; and it seems that one of the most important questions connected with the subject is a careful consideration of the indications for the employment of the intravenous method of anesthesia. Perhaps it would be well to enumerate the collective advantages promulgated by the advocates of the intravenous route. (1) Absences of deleterious after-effects both gastric and pulmonary. (2) Introduction of a quantity of saline fluid by means of which shock may either be combatted or prevented. (3) Absence of pulmonary irritation. (4) In certain cases the separation of the spheres of activity of the surgeon and anesthetist. Points two and four, to me are quite plausible arguments, but the others are not as baldly convincing, and need more proof to back them up.

Infusion anesthesia is by far the more complicated of the two methods, (77) This says Page, accounts for its more limited use.

Bernhard Friedlaender, (67) attacks the problem of the deleterious effects of anesthetics from a little different angle. He believes that there are two distinct injuries done, namely, injury to the vital functions, and injury to the psychic element. He states that the former naturally is

more threatening to the life of the organism than the latter, and therefore, all attention is directed by the physician and anesthetist toward the objective injuries of the vital functions, and very little thought is given to the matter of the psychic element. From the standpoint of vital function, Friedlaender, (67) says that he considers the inhalation anesthetic "ether" to be the least harmful, and the most adaptable anesthetic in that respect. But, his contention is that any inhalation anesthetic, presents definite possibilities of injuring the psychic element.

Friedlaender does not stand alone on this point, as a review of the literature will show. Many men register that definite complaint against inhalation anesthesia without pre-medication or basal anesthesia. The induction of an inhalation anesthetic may produce a severe and often lasting psychic trauma upon the patient. In turn the psychic trauma will cause shock and will undoubtedly reduce the resistance of the organism. (67) From personal experience, one knows that the fear instilled in one immediately upon placing the anesthetic mask over his face, is often greater than the fear of the operation or procedure.

We speak of intravenous anesthesia as the direct method of anesthesia because by this method we do not require the assistance of an intermediary system, such as the respiratory or the G.I. tract to assist us in our anesthetization. The anesthetizing agent is placed directly into the bloodstream, through which medium it presumably acts upon

the C.N.S. From the point of view of the anesthetic, then, the method is direct. Flagg, (79) has summed up the most complete, and wholly impartial views on the subject of intravenous anesthesia, and lists the advantages and disadvantages as follows: 1. The general anesthetic must be preceded by an operation under local anesthesia, (meaning the insertion of the cannula). 2. The preliminaries to the administration of the anesthetic involve a loss of much time and, from this point of view, the method is impractical as a routine in the large hospital. 3. The proper administration implies familiarity with the surgical technique required. 4. The blood pressure is raised, the bleeding is increased and the fluid has a tendency to collect in the abdomen. 5. It is an open question as to the harm done by the injection of a normal saline solution in the bloodstream of a healthy patient. 6. The possibility of septic thrombosis must be considered, and the tendency to pulmonary edema. The fore-going were all disadvantages and the following is a list of the compilation of advantages. 1. Ideal control of the administration. 2. Not dependent upon the rate or the depth of the respiration. 3. The minimum amount of the anesthetic is employed. 4. There is little or no cumulative action. 5. The technique is sufficiently complicated to exclude thoughtless experimentation.

The above are only a few of the pro and con cumulative thoughts concerning a very argumentative subject, and further more scrutinizing consideration will be dealt with in the following consideration of the drugs administered intravenously.

## ETHER

The method of introducing ether intravenously was first introduced by Burkhardt, and his immediate successes encouraged others to follow. (83) At the Berlin Surgical Congress, Kummel was able to report ninety cases. In no case of the ninety did post-anesthetic vomiting occur, although in a large number of the cases the operations were done for abdominal diseases of the gravest kind. Burkhardt used an ordinary infusing apparatus containing a 5 % solution of ether in normal saline. He allowed enough of the solution to run in to produce anesthesia, then interrupted the stream until the patient showed signs of coming round, when the dose was repeated. (83)

It was soon realized that the interruption of the stream brought with it a tendency to thrombosis in and about the cannula. To counteract this disadvantage two vessels were arranged, either of which could be connected with the cannula separately; one contained ether solution and the other held normal saline. In this case, the continuity of the stream was maintained with the saline in the intervals between the administration of ether. The great objection to methods of administration by periodic doses is that it is necessary to produce a greater concentration of the anesthetic in the blood after each dose than is essential for adequate anesthesia. (83)

This principle was fully emphasized by those to whom is

owed the introduction of the Vernon Harcourt apparatus. The chief modification introduced into this apparatus by Felix Rood, (83) was an indicator rendering possible a minute graduation of the in-flowing stream. The apparatus consists of an upper reservoir to contain a supply of the solution. This reservoir is connected by a rubber tube to a regulating chamber. This chamber besides acting as a regulator also acts as an indicator. And, although the stream of fluid is interrupted so that its rate of flow can be seen, the pressure at the same time is not interrupted, but is transmitted continuously to the top cushion of air contained above the fluid in the regulating chamber. The fluid then passes from the regulating chamber to the warming chamber and so on to the cannula.

Ether is soluble in normal saline to the extent of 10.8 per cent by volume. It was found that with a 10% solution of ether, a transient hemoglobinuria occurred. (83) On account of this, Rood used a 5% solution, and found that no hemoglobinuria followed. In order to be still more certain that there was no blood destruction, a number of specimens of the blood were taken at intervals throughout several administrations. These were examined microscopically, and showed no hemolysis. These should be sufficient grounds to say that there is no blood destruction by this method of anesthesia.

The usual preparation of the arm takes place, and a little local anesthetic is injected and the vein exposed and the cannula tied in. Strict asepsis must be used. When the

cannula is fixed into the vein the solution is at first allowed to flow in rapidly, the regulating tap being turned full on. Induction of anesthesia is usually quite smooth and rapid, three or four minutes being the average time. (83) According to Rood, struggling during induction is rare. The ordinary signs of anesthesia, of course occur-- automatic respiration, muscular relaxation, and abolition of reflexes. As soon as the smooth anesthesia is established, a little experiment will enable one to arrive at the minimum amount required, and the apparatus can be set to deliver this amount. (71) The noticeable features of this anesthesia, according to Felix Rood (83), who seems to have been an authority on this type of anesthesia, were the regularity and smoothness, and the ease with which the anesthetic could be administered, and the great rapidity with which the patients responded to slight alterations in the dosage.

The striking advantages of the method are seen in those cases where the patient is in a condition of extreme inanition. These patients often leave the table in a much better state than they were in before. So that in any case in which the patient is likely to be benefited by a saline infusion either as a means of relieving shock or hemorrhage, or if shock is expected, this method has given excellent results.

The relaxation obtained by this method, states Rood (83) of the abdominal wall, is quite equal to that produced by any other anesthetic, excepting stovaine, and for any type of case in which ether as an anesthetic is not contraindicated, this method has the one great advantage of absence of un-

pleasant after-effects. Some of the records of the German surgical clinics show that this is a marked feature of infusion anesthesia. Kummel reported ninety cases, and in no case did post-anesthetic vomiting occur. Rood (83) was not quite as fortunate in his cases, but out of 136 cases only 6 vomited at all, and of these, three were cases in which blood had been swallowed during the operation.

Of course, in reading any of the literature on this subject, one must remember that when this method was used it was far before anyone had even dreamed of the discovery of the efficacy of the barbiturates intravenously, and so it did seem quite marvelous to them that they had found a new route and method of administering anesthesia without the old bug-bear of post-anesthetic nausea and vomiting.

As a general criticism of the method, it was suggested by many that it was too complicated a procedure. Rood (83) admits this, but states that any great simplification of the technique or apparatus might lead to the adoption of an impromptu method with possible disastrous results. It must indeed, have been a huge and clumsy piece of apparatus, but from the records it must have also been a fairly efficient mode of administration.

Schlesinger, (71) in his discussion of this mode of administration, stated that intravenous methods of giving ether had a very definite but limited application. At this time the battle was waging over the superiority of ether over hedonal when given by infusion, and he claims that the advantages of ether over hedonal were that the patient came



round more rapidly; that ether was excreted by the lungs and caused much less bleeding, and that no vomiting occurred with this method. He also stated that thrombosis, if it occurred, was due to faulty technique.

One of the questions that immediately comes to the reader's mind, is how much was the total amount of ether introduced by this method in attaining anesthesia? Schlesinger (71) makes the following statement concerning this point. "The ether solution is allowed to flow rapidly until the patient is anesthetized, which requires about 10 minutes of time, and 8 ounces of the solution. After anesthesia is established the rate of administration is much slower, about 16 ounces of the solution per hour being ordinarily sufficient." Felix Rood, (76) reports one case of  $3\frac{1}{2}$  hours administration, in which  $4\frac{1}{2}$  ounces of ether and  $4\frac{1}{2}$  pints of saline solution were used, and several cases of over two hours duration. Flagg, (79), states that the amount of the solution administered depends upon the duration of the anesthesia, and that this amount varies from 500.-3500. c.c., with 1000. c.c. per hour being the average.

H. Kuttner, (74) one of the first to use the method in surgery, cautioned against the danger of air embolus and thrombosis, but these dangers were greatly diminished by the continuous flow system. Goyane's advocacy, (74) of the plan of introducing the ether and saline into an artery was not well responded to; indeed, the advantages claimed for the method hardly counter-balanced its obvious dangers. This

much had been demonstrated in the very early days of ether anesthesia, by Flourens and Claude Bernard. Professor August Bier, Dr. J.L. Ranschoff, and others sought to avoid these perils by localized intravascular injections of various drugs cut off from the general circulation by tightly fitting bands, but this procedure was of limited application. (74) At this time, intravenous infusion was confined to the use of ether, hedonal, and less frequently with that of paraldehyde. (72) At this time also, Chloroform was employed in this way, but it was found to be so highly dangerous, that it was soon cast aside by those in search of new intravenous anesthetics. The infusion apparatus used for all of these drugs was the same, and the apparatus was such a unique and complicated mechanism, that I think that it would be of interest to take it up here, in a more detailed manner.

As stated before, F.S. Rood (76) elaborated the apparatus. It consisted of a glass reservoir capable of holding about 3 pints of saline containing ether, this reservoir was controlled by a stopcock and connected by a rubber tube with a regulating chamber. This chamber had three openings, one uniting it with the reservoir, one connecting it by a rubber tube with the warming chamber controlled by the stopcock, and one that admitted air, and yet was capable of air tight occlusion by means of a rubber stopper. When the reservoir tap was opened and the regulating chamber tap was closed, the saline ether solution entered the regulating chamber and as

soon as this was half full, the air inlet was closed by inserting the stopper. As a result the air in the chamber became compressed by the fluid in the chamber, so that the fluid, as it escaped from the regulating chamber into the warming chamber was under pressure, and so passed in a continuous flow into the tube connected with the cannula. The warming chamber was immersed in warm water, the object being to warm the saline to a temperature below that at which ether escapes in bubbles. This chamber had its egress tube nearly half-way below its summit so that any air or volatilized ether would rise to the top of the chamber while only fluid went through the egress tube.

In administering ether thusly, full flow was permitted at first and in a minute or so the patient's breath would smell of ether, and anesthesia would rapidly follow. The ether supply was then lessened, but cessation of flow was not allowed because of danger of clotting in the cannula and subsequent danger of embolism. It need hardly be pointed out that the utmost vigilance was necessary in watching the signs of anesthesia, lest the flow be too great and ultimate death occur. Koenig, (74) and others asserted that fatal accidents often resulted from excessive quantities of saline-ether entering the circulation by over-sight. It has been shown that saline solution rapidly leaves the blood vessels, and Professor Bayliss, (74) proved that the addition of gum acacia prevented this, so bringing up the change by many, and substitution of the Bayliss gum saline as the vehicle

for ether.

This method while now frowned on, and laughed at, at one time was thought to have the ultimate of desirable qualities and may have had as enthusiastic following as some of our present day drugs have. Many thought that the possibilities of this new anesthesia would be unlimited. By this method anesthesia was induced without struggling or discomfort, it was light in character, and the patient resumed consciousness within a few moments after cutting off the ether solution, and so little wonder that it was thought to be a new and wonderful discovery and a boon to future anesthesia.

Buxton, in his book "Anesthetics", (74) states, "the type of patient that suggests saline infusion to stave off shock is peculiarly appropriate for intravenous etherization. Abdominal sections, especially in acute cases, are quite suitable. The young and the aged lend themselves equally to it if due care is taken to limit the amount infused to the capacity of the patient". He evidently was a firm believer in the efficacy of intravenous ether, but to me, the joker in the above quotation lies in the last 16 words, for that is exactly where intravenous ether fell down, and most of the products that supplanted or succeeded it, as someone's idea of the ultimate of desirable qualities in producing anesthesia, also lost face and failed in that respect of dosage and its determination in individual cases. There are many men who even staunchly hold to the principle that one of the basic requirements of an anesthetic is that it does not conform to

the title, "a fixed dose drug", and as will be shown later, their reasons for adherence to this principle are quite sound.

Flagg, (79) sums up the question of intravenous etherization with the following points in reference to the relative advantages and disadvantages of its use. The advantages are as follows: 1. Ideal control of the administration; 2. It is not dependent upon the rate or the depth of the respiration; 3. The minimum amount of the anesthetic is employed; 4. There is little or no cumulative action; 5. The technique is sufficiently complicated to exclude thoughtless experimentation. The disadvantages of the method are: 1. The general anesthetic must be preceded by an operation under local anesthesia; 2. The preliminaries to the administration of the anesthetic involve a loss of much time and, from this point of view, the method is impractical as a routine in the large hospital; 3. The proper administration implies familiarity with the surgical technique required; 4. The blood pressure is raised, the bleeding is increased and the fluid has a tendency to collect in the abdomen; 5. It is an open question as to the harm done by the injection of a normal saline solution in the bloodstream of a normal healthy patient; 6. The possibility of septic thrombosis must be considered; 7. This author believes that there is a tendency towards pulmonary edema.

## HEDONAL

In the extensive search for new derivatives of the known drugs, the discovery of Hedonal was made. Hedonal was made from the secondary methyl-propyl-carbinol by heating it with urea nitrate under pressure. Thus, it was a derivative of urethane, and possessed the chemical formula  $C_6H_{13}O_2N$ . It was used quite extensively for the production of anesthesia by intravenous infusion, but unlike its cousin, urethane, it was soon discarded, and fell into disfavor a few years after its discovery. (70)

Hedonal is a white crystalline solid, stable at the ordinary temperatures. Its solubility in water at 100. degrees F. is 1 in 100., and it readily crystallizes out of a saturated solution in long, fine needles. This solution can be boiled without the properties of the drug being affected. However, prolonged heating diminishes the concentration owing to the volatilization of a certain amount of the compound.

In 1910, Professor Federoff, of St. Petersburg, suggested the intravenous administration of hedonal. (77) However, since 1900 this drug had had some vogue as a hypnotic; it had also been given by mouth (in several Russian clinics) as a precursor of chloroform and ether with satisfactory results. Reports of its use as a general anesthetic first appeared in Russian journals, a preliminary note was published in German in 1910, and in the following year the

technique employed, was described by Jeremitsch, with the details of sixty-five cases. (77) Later, at the Congress of the German Surgical Association, Federoff contributed a brief account of 530 cases collected from three Russian clinics. The high-light of the report was that there was no death directly attributable to the anes+hetic in the series.

Experiments on animals by Dreser (77), showed that hedonal had 10 times the hypnotic effect of urethane and twice that of chloral; he found that the respiration was no materially affected in conditions of deep narcosis, although it did cause a slight fall in the blood pressure. Dreser noted that the drug had a diuretic action, which was attributed to the theory that in the body the substance was broken down into urea, carbon dioxide, and water. Lamposakow (77) carried out further experiments, and found that in dogs and rabbits, a dose of 0.4 to 0.5 grams to the kilo of body weight produced general anesthesia, and that the respiratory and cardiac rhythm remained regular under this dose. When he gave toxic doses, the heart continued beating, after paralysis of the vasomotor center. He considered that the presence of the amino radical antagonized the paralytic action of the drug.

Federoff and Jeremitsch, after having satisfied themselves by experiment on animals, adopted the use of hedonal as an anesthetic for man. They employed an interrupted infusion method, a 0.75% solution in normal saline was injected under air pressure. The needle was inserted into

a superficial vein, and sufficient of the hedonal solution was injected to produce anesthesia; the needle was then withdrawn and reinserted if a prolonged anesthesia was necessary. The results obtained were, on the whole, satisfactory, but less so when leg veins were injected. C.M. Page, (77) whose apparatus for intravenous infusion was later modified by Z. Mennell, used this means of obtaining anesthesia in a number of cases, and regarded it as a valuable method. However, he did caution against its employment in what he chooses to call "unsuitable cases". Page found that the average amount of hedonal solution required to produce anesthesia was 500. c.c., and that the induction period ranged from 2. to 13. minutes. He found that the narcotic effect of the hedonal persisted for a long time after the infusion had ceased, and remarked that this was a very undesirable feature of the method. Another undesirable feature was the fall in blood pressure and the appearance in a great many cases of cyanosis, Page points out as a possible danger the onset of cyanosis, and Federoff recorded some instances of temporary cessation of respiration. (77)

Hedonal, as supplied by Bayer, is dissolved in normal saline at a temperature of 70. degrees F., to make a 0.75% solution; the resultant fluid is filtered once, boiled for five minutes, and stored in sterile flasks. The contents of the flask are warmed up to about 140. degrees F., and poured in a tank, which is furnished with a thermometer



gauge and tapped exit tube. From the latter runs a yard of pressure tubing; in the course of this a dropper is inserted; it terminates in an ordinary fine infusion cannula. Before infusing, the temperature of the fluid in the tank is reduced to about 115. degrees F. The usual exposure of vein is done, and the cannula tied in. The fluid is run in at a rate of 50. to 150. c.c. per minute. The rapidity of flow can be accurately controlled by regulating the tap of the tank and watching the flow through the dropper.

Within a minute or so of the commencement of the infusion, the patient becomes drowsy, and often yawns; he has a subjective feeling of warmth and well-being, the face flushes, and if the infusion is too rapid a certain degree of cyanosis arises. (77) Then follows a period in which the patient appears to be in a state of deep natural sleep, and this state quickly merges into one of deep anesthesia.

The amount of fluid necessary to induce anesthesia varied considerably-- e.g., 40. c.c. sufficed in a child aged 10 months; 1,000. c.c. were necessary in a heavily built man, aged 25; the average dose necessary in an adult was found to be 500. c.c. As stated before, the period of induction varied from 2. to 13. minutes.

The rate of return of complete consciousness is slow and variable, and to most of the experimenters this was recognized as a serious draw-back to the use of the drug. Usually the patient slept for six to twelve hours after the

cessation of the anesthetic and then awakens. Drowsiness often persisted for twenty-four hours. In some articles, I noticed cases where numerous times emotional disturbances occurred, and a period of excitement came on an hour or so after the operation. This too, is certainly a quite undesirable feature. On further reading, I found numerous cases where vomiting and headache were common occurrences.

Some of the dangers of hedonal anesthesia are cyanosis, postoperative excitement, and respiratory failure from overdosage. Federoff, (77) reported that temporary stoppage of respiration occurred in eight of 530 cases, but that after the use of artificial respiration, normal breathing started again. Some of the other undesirable features noticed were the prolongation of narcosis after the operation, especially with reference to the possibilities of inhalation of vomitus.

The sponsors and champions of hedonal administration claim the following advantages in its use. The technique is simple, the solution is readily handled and sterilized, and the active part is not volatile. Here arises the question as to the relative advantage or disadvantage the volatility of the drug offers. To me it seems as though volatile drugs should be safer, because of the more prompt and efficient elimination attained by way of the lungs. As one can see by looking over the advantages listed above, any and all of them, are certainly open for argument, and far from convincing. The rest of the advantages given by

those championing this drug, I will merely state, without comment, and the reader can take them for what they are worth in his consideration. Page, (77) concludes with the statement that, "the anesthesia attained is of a steady and complete type, the relaxation of the muscles is remarkable being often as good as that given by spinal anesthesia. The respiratory movements are steady and quiet. The removal of the anesthetist from the scene of the operation in head and neck cases is a distinct advantage. The quiet sleep, insensitiveness to pain, and absence of straining are other advantages." There are other statements, too numerous to list, but one of them that I found listed as an advantage, seems to back-fire and act as conclusive evidence as to the drug's undesirability. The statement is as follows, "owing to the comparatively slow rate at which the drug is excreted, very small quantities of the solution suffice to maintain anesthesia when once it is completely established." (77) The fact that it is slowly excreted seems to me a distinct disadvantage, because I believe, at the present time, the general consensus of opinion is that the faster the rate of elimination, the less toxic the drug becomes, and the more desirable it is as an anesthetic.

It was found that hedonal infusion was unsuitable for cases in which pulmonary engorgement or a gross cardiac lesion existed, for operations upon the air-passages, and for patients with high blood pressure. The experiences of the greater share of those working

with this type of anesthesia, confirmed Burkhardt's views of the danger of intravenous hedonal. (75) Not only have great complications arisen from its administration, but deaths have resulted from its use. (74) A discussion on the use of hedonal, held before the Medical Society of London, provoked somewhat diverse views, but the consensus of opinion was against the use of intravenous hedonal. (78)

## SOMNIFAINE

The men who have done considerable work in the field of anesthesia with this drug, and those who have been its chief advocates, are, in the vast majority, workers on the European continent. Comparatively little literature on this subject has been written by clinicians of England or the United States, and the use of this drug has never been accepted, in these countries, with much enthusiasm. This drug is really a combination of two hypnotics which are derivatives of the malonyl-urea group. The two substances are diethyl-barbituric acid and allyl-isopropyl-barbituric acid. This combination received considerable attention in Europe since 1921, but seems not to have interested the profession in this country to any great extent.

Its origin, in 1920, is credited to Redonnet, and Cerne was the first to use it in relieving the pains of labor. (19) During 1921-1923, Bardet and v. Cleisz developed its clinical use in obstetrics, and Fredet and Perlis used it in minor surgery, later extending its use to major surgery. Since then, there have been in the foreign literature quite a number of articles by various authors. The results reported have been variable. In 1925, H.M.F. Behneman after seeing an article on its use interested O.H. Schwarz of Washington University in the drug. Before trying it clinically however, Schwarz

wanted to have some experimental data available, and Behneman and Woodmansee undertook an investigation of the substance at Washington University, St. Louis, under the direction of the Department of Pharmacology. Their results were not published and clinical use of the drug was not attempted. However, I. Macdonald, (60) states that in 1926, in France, the experimental and clinical researches of Fredet and his associates on the use of somnifaine, or somnifene, as the drug was known in France, seemed to show that in intravenous injection for surgical anesthesia, the general anesthesia was reduced to an extreme minimum, and in some cases it was eliminated entirely. Hewer, (58) in his general discussion of anesthetics, states that since the Great War, the intravenous injection of somnifaine has been practiced in France, to a certain extent, but the excitement seen was regarded as too detrimental for its common use.

The drug, as said above, is a combination of diethylbarbiturate and allyl-isopropyl-barbiturate, in 2. c.c. ampoules, containing 0.10 gram of each drug in the form of a diethylamine salt. The solution is rendered stable by the addition of small amounts of alcohol and glycerine. Recently, a new form has come into use in ampoule form, in which the allyl-isopropyl-barbiturate is the only constituent. This form was advocated by Fredet, (19) and I. Macdonald. (60) According to the foremost worker on this drug in the United States, J.H. Fjelde (19)

the reason for the preference of this new drug, over the use of the old combination, is that the diethylbarbiturate in the old drug, was eliminated rather slowly, and had, therefore, a delayed and prolonged effect which, in the opinion of most, was undesirable.

Allyl-isopropyl-barbiturate has the highest lipid solubility of all the barbiturates so far known, a feature which according to the most up to date conceptions, (19) is of prime importance as regards the hypnotic action. Due to this high degree of lipid solubility, it acts very quickly, so that sleep arises within a few minutes. According to the literature, allyl-isopropyl-barbiturate, is about five times as hypnotic as, for instance, diethylbarbiturate, while its toxicity is not increased in the same ratio as its hypnotic influence. According to J.H. Fjelde, (19) on the other hand, this hypnotic influence does not last longer than desirable in the ordinary cases, because the elimination of the drug, from the system proceeds rapidly. This drug should, therefore, leave the patient free from prolonged after-effects, a feature which is of great importance in general medicine, and also, owing to the rapid elimination even of large doses, the chances of cumulative effects should be likewise greatly reduced, when the drug is used over long periods of time. Later on, in the clinical consideration of the drug, we will see if this holds true for this drug.

Macdonald, (60) states that the interesting research

done by Fredet, demonstrates that the seat of action of Somnifaine is chiefly in the nerve centers, while J.H. Fjelde, (19) is even more specific, and claims that the action seems to be exerted directly on the sleep center. The drug is carried by the red cells, for which it shows a special affinity. It is fixed with predominance in the nerve centers, but is retained to only a very slight degree by the liver, kidney, and other tissues. When introduced into the blood, it is eliminated unchanged by the kidneys, and elimination commences very soon after injection. (19)

Somnifaine, in non-toxic doses, but of sufficient strength to produce anesthesia, exert only a slight effect on the respiratory and cardiac centers, and the blood pressure also shows very little alteration. Fjelde says that there is a slight lowering of the pressure after injection, but that this quickly recovers. The liver function likewise is not altered. That the glyco-regulatory mechanism is not affected, was demonstrated by spontaneous glycosuria after injection of sugar.

Fjelde's interest in the intravenous form of obstetrical anesthesia led him to obtain the drug, and in October, 1926, with Kent E. Darrow, he started to use it in various surgical conditions. He also used it in about 100. obstetrical cases, and states that the results were generally good. In surgery, he usually combined it with local or caudal anesthesia, or ethylene, the latter



combination was the most frequently used.

In using somnifaine in surgery, there are two distinctly different phases of its use: first, the preoperative preparation for ethylene anesthesia; and, secondly, actual anesthesia for abdominal operations, or in combination with a local anesthetic. To Fjelde, (19) the first one is the more important method, because by its use, he has practically eliminated the use of ether, and does every type of abdominal operation with ethylene alone. He claims this to be a distinct advantage because of the occasional difficulty in obtaining good relaxation with ethylene alone. He states also, that the use of this combination of somnifaine and ethylene cuts down the ethylene necessary to one to two gallons per minute, instead of the usual two to three, and the percentage flow is cut to one half the maximum, supposedly, when fifteen to eighteen per cent oxygen is used.

The technique of Fredet's method, as stated by I. Macdonald, (60) is as follows: 1. A hypodermic injection of morphine is given, varying from a minimum of 1. cg. up to 2. cg. as a maximum. It is advantageous to associate scopolamine with the morphine in doses varying from two-thirds mg. up to three-quarters of a mg., according to the weight of the patient, and whether his general state is cachectic or satisfactory. 2. From 20 minutes to 40 minutes later, after the morphine-scopolamine injection, the intravenous injection of allyl-isopropyl-malonyl urea

is made very slowly; 3 minutes, at least, should be spent in the injection. The dose is calculated according to weight, age, and the general state of the patient. Generally, in fairly robust adults, 1. cc. per kilogram of body weight is used, never passing 0.07 gram; In the aged or cachectic patients, 0.04 or 0.03 gram should be enough. Ampoules of the drug were obtainable containing 0.01 gm. in each cubic centimeter of water. 3. Five minutes after the intravenous injection a small amount of chloroform or ether was given to permit the incision being made about 10 minutes after the intravenous injection. During the operation the general anesthetic could often be dispensed with, to be resumed should the patient move and at the end, to facilitate the suturing of the wound.

According to Macdonald, (60) postoperative vomiting was very rare, and the patient awoke four to five hours after operation to fall asleep quietly again. He does admit that excitement was frequently observed, and this seems to be also the point that most clinicians found to be unfavorable to its use. Macdonald used this anesthesia in 33 cases during a period of 2 years, and, although it did not replace routine methods, it was his choice in 2 types of cases,--when the patient was a bad risk from pulmonary complications or from probable hepatic and renal insufficiency, and again when he was certain that the operation must be prolonged.

In the Cardiff City Mental Hospital about 50 cases

were treated with Somnifaine during a two year interval. The results, according to Quastel, (103) were definitely encouraging except in so far as toxic symptoms, including the production of ketosis, were demonstrated in a large percentage of the cases. The toxic by-effects were often so alarming that it became necessary to discontinue the treatment. It was felt, however, that the success obtained in the prolonged narcosis treatment of many cases of mental disorder warranted a search either for new drugs, which would produce sufficiently deep narcosis without the demonstration of toxic by-effects or for a modification of the then present methods of obtaining narcosis, which would diminish or eliminate the toxic action.

The toxic effects of narcotic treatment with the use of somnifaine, have been described by A.M. Meerloo, and M. Muller (103). These include bulbar symptoms, such as derangements of swallowing mechanism, indistinct speech, ataxia, tremor of the lips, and vasomotor paralysis. A frequent accompaniment of prolonged narcosis is the development of ketonuria, which becomes more marked as the narcosis proceeds. Doubtless, the effect has much to do with the actual dosage of the narcotic, certain patients responding more vigorously than others. In the past, it has always been considered advisable, according to Quastel, (103) to cut short treatment with somnifaine as soon as a definite ketosis has been produced, and considering the drug as a whole, he states that he believes

it is very advisable to entirely dismiss it from clinical use, until some change has been made whereby the present dangerous toxicity has been decreased to a very considerable degree, or better yet, eliminated entirely.

## PARALDEHYDE

From the formation of the word, we would expect to find that aldehyde had been named by the Arabian alchemists. On the contrary, the drug is of comparatively new discovery and was named by Liebig, (110) who contracted the name alcohol-de-hydrogenatum, to aldehyde. Aldehyde is prepared from alcohol by the action of manganese dioxide and sulphuric acid gently heated together. Paraldehyde is formed by polymerization or linking together of three molecules of aldehyde and is prepared by adding a small proportion of pure sulphuric acid to acetaldehyde.

Paraldehyde is a clear, volatile, inflammable liquid having an unpleasant penetrating odor and a disagreeable taste. It is soluble in cold water to a greater degree, than in hot water. It mixes freely with vegetable or mineral oil. It freezes at a comparatively high temperature with formation of a white solid. According to Cushny, (72) paraldehyde is a polymer of ethyl-aldehyde, resembles alcohol in its effects, though it is a much more powerful narcotic, and rarely induces any symptoms of excitement. It does not effect the heart directly, even in large doses, and has no such effects on the protein metabolism as has been observed under the prolonged use of chloral. The pulse is slightly slower and the carbonic acid exhaled is less than normal. These changes, however, are due to the muscular movements being lessened and are

hardly greater in extent than the changes that occur in natural sleep. (72) According to Noel, (72) very large quantities have been taken without fatal results and in fact without any more serious consequences than prolonged unconsciousness.

Paraldehyde has been extensively used as a hypnotic and sedative, especially in the treatment of acute alcoholics and for controlling the violently insane. It is commonly stated to be the safest hypnotic known. (110) It acts first on the cerebral centers and later on the lower parts of the nervous system. It has no deleterious effects on the circulation, respiration, blood pressure, or metabolism. It is excreted unchanged, largely through the lungs but partly by the skin and kidneys. The renal effect is a mild diuresis. There are no known subsidiary effects on the functions of other organs.

Dr. George A. Elliott, (110) formerly of Butler Hospital, now at the Connecticut State Hospital at Middletown, has made an intensive study of blood chemistry following the intravenous injection of paraldehyde. He injects from six to nine c.c. of pure paraldehyde as an anesthetic for minor operations. Paraldehyde is itself a powerful antiseptic and need not be sterilized. The anesthesia appeared almost immediately and lasted for several minutes, long enough for dental extractions and various minor operations. There was complete relaxation, some fall in blood pressure and some respiratory depress-

ion. The blood was taken for chemical examination a half minute after the injection and at intervals during the next twenty-four hours. Blood sugar was undisturbed, Non-protein nitrogen was unaffected. Creatinine was also unchanged. The coagulation time was reduced from an average of three minutes to ninety seconds. There was no bleeding after dental extractions, a pulmonary hemorrhage frequently could be checked, and hemorrhage from a wound of the hand ceased after oral administration of paraldehyde.

The hypnotics vary in efficiency and in safety. They vary in effect on conscious perception, on reflex activity, and in their relief of pain. Pure hypnotics, as barbital, produce sleep. Sedatives, as paraldehyde, in addition to their hypnotic action, have a powerful an effect on relief of pain that their analgesic action overshadows their hypnotic effect. The immediate result of the administration of a narcotic is often stimulation rather than sedation of reflex activity. In some subjects, therapeutic dosage of narcotic relieves pain but has no hypnotic nor sedative action. On the other hand, administration of a pure hypnotic in the presence of severe pain will usually not result in hypnosis, but in a state of active delirium. These considerations indicate that narcotics are not ideal pre-anesthetic hypnotics and that the pure hypnotics are not suitable for relief of postoperative pain and discomfort.

Noel, (72) has the following method of administering paraldehyde intravenously. Starting at first with small doses, 4. c.c. of the pure drug were injected into a vein. Almost before the syringe was empty the patient was unconscious. He slept naturally for about two hours. Subsequently 8. c.c. were injected with satisfactory results. It was found, however, that the pure drug caused a certain amount of local discomfort and coughing, and it was therefore diluted with saline to form a 10% solution. One hundred c.c. of this solution produced in about 40 seconds an anesthesia lasting about twenty minutes, and suitable for minor surgical procedures. Paraldehyde, while acting temporarily as an anesthetic, had a prolonged hypnotic effect, considerably reducing the amount of ether subsequently required. Being volatile, it was rapidly excreted by the lungs, and this, says Noel, (72) is an important element in the safety of the drug, and an advantage which could never be claimed for the use of hedonal.

In comparison with avertin, paraldehyde has less effect on conscious perception and memory, less effect in relief of pain but a greater depression of reflex activity. (110) The paraldehyde patient may come to the operation apparently conscious and responsive to painful stimuli but will develop muscular relaxation in the presence of severe operative stimulation under a very small dosage of the anesthetic. Paraldehyde does not depress the respiration, does not affect the blood pressure or metabolism. It is



generally conceded that it is without effect on the liver and kidneys, and does not influence blood chemistry. It has a marked hemostatic effect. In comparison with avertin the margin of safety is very great, and the expense is almost negligible. (110)

In comparison with morphine, paraldehyde is a powerful sedative but is inefficient in analgesic action. It does not depress the respiratory center and does not stimulate the vomiting center. It does not abolish the protective coughing reflex, and it does not check secretions nor diminish the flow of urine, on the contrary, it is a mild diuretic. In comparison with morphine, paraldehyde has a very great margin of safety.

Paraldehyde is an efficient pre-anesthetic hypnotic, showing a minimum of deleterious effects upon the organs of the body and their functions. Its margin of safety is several times as great as that of morphine or avertin, but less than that of the barbiturates, and for that reason, with the introduction of the barbiturates, it was soon dropped from clinical use, in favor of the more beneficial advantages found in the use of the barbiturates.

## BARBITURATES IN GENERAL

For years the medical profession has looked forward to the possibility of a drug that would numb the sensorium and make the patient oblivious to his surroundings and yet not act in a deleterious way on any of the vital organs. Thierfelder and von Mehring, (99) in 1880 made the observation, which was later confirmed by others, that the sleep producing action of alcohol was related to the number of ethyl groups present. A few years later, Schmiedeberg conceived the idea of producing a nitrogen containing hypnotic, knowing that intravenous injections of ammonia preparations raised the blood pressure. Then Schmiedeberg succeeded in preparing urethane; and, following in the order named, paraldehyde, amylen hydrate, sulphonal, trional and chloroformamide were produced.

It was then observed that the intensity of the hypnotic action of sulphonal depended upon the number of ethyl radicals linked to a central carbon atom, and for this reason Fisher and von Mehring, (99) in 1903 successfully completed the synthesis of a nitrogen-containing compound. This substance was prepared by treating diethylmalonic acid ester with urea and sodium ethylate. The preparation was placed on the market under the name of "veronal", the generic name of which is "barbital". Since that time a large number of barbital derivatives have been prepared, differing one from the other largely

in the substitution of one or both hydrogen atoms by other radicals. It is possible to develop a great number of these substances.

In 1924, Fredet and Perlais, (99) two Frenchmen, succeeded in inducing general anesthesia with the barbituric acid series. They used a mixture of di-ethyl allyl-barbiturate (trade name "sommifene"). This was administered intravenously. In 1927, Bumm, following the lead of Fredet and Perlais, used a barbituric acid derivative intravenously. This compound he believed decomposed more readily than somnifene. He utilized sodium sec-butyl bromopropenyl barbiturate, (trade name is "pernokton"). He believed that the elimination of the pernokton was more rapid in the body and would permit a more rapid recovery from the anesthetic than would be possible with the other preparation.

In 1926, Page and Coryllos, (63) used sodium amytal, sodium iso-amyl-ethyl-barbiturate, to produce general anesthesia in animals.

All derivatives of barbituric acid have certain characteristics in common which have long been recognized:

1. They are primarily hypnotics; only occasionally will amounts ordinarily producing hypnosis produce analgesia or anesthesia. Sufficiently large amounts will induce analgesia and anesthesia in both animals and man. However the dosage of such amounts precludes their routine use in man. (64)
2. There may be a marked variation in the

effects observed with a given amount in the same or different patient. This variability of action has made it difficult to select the proper dosage. 3. The amount required to produce a given therapeutic effect bears approximately the same relationship to the fatal dose in each of these various compounds, in their clinical application. 4. All members of the barbituric acid series may depress the respiratory and circulatory systems when amounts large enough to produce deep hypnosis are administered. 5. Comparatively large amounts of any of the derivatives of barbituric acid may produce hallucinations, and so forth, when the amount excreted or destroyed reaches a certain level.

Zerfas, (64) points out that derivatives of barbituric acid have many characteristics in common, but differ largely in toxicity, and rate and manner of elimination. Lundy, (87) has recently made an exhaustive review of the literature on this subject. The therapeutic margin of safety, based on experimental animal work, has been determined for a great many of these compounds. In clinical medicine we are interested to know the proportion of the fatal dose that will be required to produce a given effect. For all practical purposes that relationship is about the same for all the commonly employed derivatives of barbituric acid. Diethyl-barbituric acid, (barbital) is frequently cited as being the least toxic of these compounds, mainly because the amount required to produce death in animals is relatively

large. Should one desire to produce a given effect short of the fatal dose, the amount of barbital required would bear about the same relation to the fatal dose as that of a compound considered two or three times as toxic. Should subsequent sub-lethal amounts of barbituric acid be given before the entire amount was eliminated each time, barbital would ultimately prove decidedly more toxic than those compounds eliminated or destroyed at a faster rate.

Fitch, and his associates, (95) state that there seems to be little advantage that can be claimed clinically for the intravenous use of one barbiturate over another, except in so far as the advantage lies in differences in duration of depression and in the total quantity of the drug that the organism must destroy or eliminate.

According to Friedlaender, (67) most of the barbituric acid derivatives such as veronal, amytal, allonal, ipral, luminal, noctal and pernocton have been tried out experimentally and clinically and their action has been similar in the human being and in animals; namely, as sedatives, analgesics, or hypnotics, depending upon the amount administered. The toxic reactions of individuals to the various barbituric acid derivatives are essentially the same, with the exception of pernocton and noctal.

The use of the derivatives of barbituric acid as anesthetics and hypnotics has been closely studied in the last few years, especially in the United States, and

the literature is now extensive. (66) Lundy, (85) quotes no fewer than 466 references. As regards the use of the barbiturates in human surgery, one may draw the following conclusions: (95) 1. The employment of a barbiturate as the sole anesthetic is inadvisable. 2. As basal hypnotics the barbiturates are among the most valuable drugs available. 3. The suitability of a barbiturate as a basal hypnotic depends largely upon toxicity, and shortness of action. The greater the toxicity the smaller is the dose required, and the smaller the amount of the drug to be detoxicated or eliminated.

The barbiturates can be administered in one of two ways, either by mouth or intravenously. The former route has the advantage of simplicity, but accurate dosage, which is essential for successful anesthesia and which varies with each individual patient, is difficult to obtain. The intravenous method is commonly employed, because it allows the minimal effective dose to be determined accurately. (69) With this, a solution of the chosen drug is injected at a predetermined rate, ceasing when consciousness is lost. The duration of administration varies according to the toxicity of the drug employed; it is shortest with Pernocton and longest with Amytal. (69) A warning, however, was issued by the Council of Pharmacy and Chemistry of the American Medical Association, regarding the intravenous administration of barbiturates. It is stated that these compounds require large amounts of alkali for solution;

amytal, for example, requires a degree of alkalinity the equivalent of a buffer solution with a pH of 9.5, and therefore this drug, and for that matter any other barbiturate, will not remain in solution with the chemical reaction of the blood. (69) The compound is precipitated and then there is a foreign body, in the colloidal state, within a sensitive colloidal system,--namely, the blood, whose physio-chemical properties and physiological functions are unintentionally and undesirably affected. R.C. Garry, (69) states that this action, which is not peculiar to the barbiturates, is probably responsible for certain reflex effects arising either from the disturbed colloidal equilibrium of the blood or from marked alkalinity of the injected solution, or both. These intravenous reflexes which may be invoked by irritation of the depressor nerve endings or of the vagus nerve terminations in the viscera, and which result in sudden circulatory and respiratory disturbances, are unnecessary and undesirable; they complicate the ordinary hypnotic action of the barbiturates, and submit the patient to additional risk.

In view of these facts the Council of Pharmacy and Chemistry maintains that any advantages that can be procured by giving Barbiturates can be procured by giving them by the mouth; and that, in the present state of knowledge, the intravenous route should be reserved for only emergencies and for those cases in which oral administration is physically impossible. The wisdom of this attitude

is generally recognized, for, although it is not in harmony with the favorable opinions, based upon clinical investigation rather than upon pharmacological experiment, originally entertained regarding the intravenous administration of these compounds, it is in the best interests of the patient. (69)



## AMYTAL

One of the most recent derivatives of veronal is amytal (iso-amyl ethyl barbituric acid). This drug was first described by Shonle and Moment (62) in 1923, and was promptly used by Page, (63) in pharmacological experimentation. At first the difficulty of preparing the soluble sodium salt of amytal delayed the use of this drug as an anesthetic for human beings. Very recently however, the presence on the market of the sodium salt of amytal in stable form has permitted its wide application as an anesthetic in man. (64) A full description of the clinical use of the barbituric acid group of drugs, both in surgical and in non-surgical cases, may be found in the Proceedings of the Staff Meetings of the Mayo Clinic. (85)

Intravenous administration of a 10% solution causes a very rapid onset of anesthesia, but the injection must be carried out very slowly, because of severe circulatory disturbances. In man, 20-25. mgm. per kilogram of body weight is sufficient for complete surgical anesthesia, and 12.-20. mgm. per kilogram of body weight is adequate to lower the dose of such volatile anesthetics as ether, or nitrous oxide and oxygen, to  $\frac{1}{4}$  of the usual amount required. (85) Stormont, Lampe, and Barlow, (86) working on rats, showed that premedication with amytal or other barbiturates permitted the production of full anesthesia

with a lower percentage of nitrous oxide and a higher percentage of oxygen than is usually necessary.

In man there is a post-anesthetic sleep, and drowsiness, governed by dosage, for 12.-72. hours. This considerably increases the necessary nursing attention. Neither in animals nor in man are there signs of post-operative distress. (87) The statement by early workers that carbohydrate metabolism is unaffected by amytal, made this drug the anesthetic of choice during the wave of experimental investigation into carbohydrate metabolism which followed on the discovery of insulin. This sweeping claim for amytal as a true "physiological" anesthetic has not stood the test of time. Glucose injected intravenously is not removed from the blood at the usual rate, presumably due to inhibition of the storage of glycogen in the liver. (88) However this may be, there seems to be a general consensus of opinion that amytal anesthesia has a less disturbing effect on carbohydrate metabolism than the majority of other anesthetics in general use. This may be not without significance in anesthesia in man if damage to the liver is feared.

As is to be expected, amytal lowers the body temperature, certainly by enforced inactivity and possibly by a direct depressor action on metabolism. All barbituric acid derivatives are respiratory sedatives. Amytal, however, in anesthetic dosage, does not greatly diminish the minute-volume of respiration, and the respiratory center

remains sensitive to carbon dioxide. (89) Amytal has a definite toxic action on the heart, and this is more marked the more rapid the administration. (90) For this reason rapid intravenous exhibition of the drug is fraught with danger. The blood pressure falls rapidly, and one hour or more may elapse before it regains its previous level. This fall in blood pressure is due both to dilatation of the heart, with reduction in minute-output, and also to vaso-dilatation. (91) Large doses administered rapidly may cause heart block, ventricular fibrillation, and death. In clinical use, amytal lowers the systolic and diastolic pressure, and this fall in blood pressure may be alarming if the administration be rapid. (85)

Because of the great controversy over the use of amytal in Obstetrics, the following information may throw some light on the subject: in vitro, amytal, even in high concentration, has no effect on the movements of the guinea pig uterus, and the response to "pitocin", is unaffected. (92) Amytal has found great favor and has been used successfully in many obstetrical clinics.

Barbituric acid derivatives do not all react in the same way; they are excreted in variable amounts and with variable speed. Amytal does not appear as such in the urine of dogs, whatever the route of administration. (93) There seems to be no detrimental effect on the kidneys, and like other anesthetics, amytal inhibits water diuresis. (94) The known effects of amytal on laboratory

52.

animals are correlated with the more recent experiences of amytal as an anesthetic in human beings. Although amytal has been definitely disappointing as an anesthetic in physiological research work, yet, when properly used, its pharmacological actions may be of no hinderance to its use as an anesthetic in man. (84)

The effects of sodium amytal on the circulatory system are somewhat dependent on the amount, rate, and manner of administration of the drug. It is possible by the rapid intravenous injection of sub-lethal doses of sodium amytal in animals to produce death or an immediate fall in blood pressure to alarming levels. Lieb and Mulinos, (97) state that sodium amytal when given intravenously to laboratory animals, depressed the circulation and produced a prolonged temporary paralysis of the vagus to the heart, which lasted from one to one and a half hours. Shafer, Underwood, and Gaynor, (98) have confirmed these findings reported by Mulinos. They also found the greatest slowing from stimulation of the vagus in decerebrate animals and the least in those just under amytal, while intermediate slowing was observed in dogs under ether. The blood pressure increased following stimulation of the vagus under amytal, if the vagus carried a greater number of pressor impulses. Lundy, (87) and others have observed an increase in blood pressure in two cases following the intravenous administration of sodium amytal to their surgical patients.

As a rule, following the intravenous injection of sodium amytal in man at a comparatively slow rate, one c.c. per minute, a decrease in both the systolic and the diastolic blood pressure occurs, usually during the time the drug is being injected, and becomes most marked when the patient loses consciousness. Mason, Baker, and Pilcher, (99) reported that the systolic pressure in all but a few instances fell to an average of 30. mm. of mercury, and the diastolic to an average of 15. mm. during the induction of anesthesia, but returned to normal levels early in the operation. Patients with hypertension, those who are markedly sclerotic, and patients who are debilitated from chronic illness, may show much greater decreases in blood pressure, even to alarming levels and subsequent death.

James Poe, (57) states that because of the possibility of a great fall in blood pressure, elderly patients with general arteriosclerosis and hypertension are considered unsatisfactory subjects, as the fall in blood pressure may have serious consequences, and hence the dose should be very much limited, if used at all, in these cases.

Animals given fatal doses of sodium amytal died of respiratory failure, which usually precedes that of the circulatory system, though failure of both sometimes occurs simultaneously, particularly if the drug is injected rapidly. Isenberger, (89) in a series of experiments on animals designed to show the effect of narcotics

on the function of respiration, found that moderate doses of sodium amytal resulted in a slight decline in the rate of respiration accompanied by a compensatory increase in depth. Small doses of morphine given preliminary to sodium amytal seemed to render the action of sodium amytal more uniform as well as more intense, and thus reduced the amount of both sodium amytal and morphine required. Isenberger, (89) also calls attention to the fact, however, that morphine may be chiefly responsible for the changes in the respiration observed after morphine and sodium amytal have been given in sequence in therapeutic doses; also, that basal narcosis, as a result of the proper administration of sodium amytal in combination and sequence with morphine preceding the administration of a general anesthetic, such as ether, and full surgical anesthesia with relaxation, were safely and easily established and adjusted. At the same time, there appeared to be retained a definitely higher degree of respiratory reserve than when ether alone, or ether preceded by morphine alone, was used to a state of similar degree of anesthesia and relaxation.

Clinical observation of the administration of comparatively small amounts of sodium amytal for pre-anesthetic preparation of patients has been described, and follows closely that defined for animals. The respirations are usually regular in rate, but are frequently reduced in amplitude. There was little change in the color of the

skin, although a slight degree of cyanosis has been noted. Mason, Baker and Pilcher, (99) call attention to the development of a flush of the skin, sometimes resembling a febrile reaction.

When the drug is injected intravenously the induction of sleep is rapid and quiet. Drowsiness, noted by drooping of the eyelids, yawning, and slurring of words, comes on after the administration of 3.-9. grains. These same authors also noted that as the dose was increased the patient became reflexly hypersensitive, and finally entered a profound state of narcosis. The pupils became contracted and in some cases fixed, so that they would not react to light. The corneal reflex was diminished and the gag reflex remained intact. The knee jerks were often exaggerated during the period of hyperesthesia. In this state, patients sometimes became restless, if stimulated.

The period of unconsciousness may last anywhere from 3.-6. hours, depending upon the amount of the drug given. When a sufficient amount of the drug was eliminated or destroyed, the patients passed through a mildly restless period of comparatively short duration, in which they were disoriented, moved aimlessly about, and uttered incoherent statements. During the following hours they continued to be drowsy, and slept at intervals.

L.G. Zerfas, (64) states, "in our earlier work, we used sodium amytal in approximately 100. cases as the sole anesthetic. It was soon apparent that the marked

depression upon the circulatory and respiratory systems carried with it certain dangers which would not warrant its general use. The greater proportion of the patients were restless and delirious for a period of time, which added further to the difficulties of its employment as an anesthetic agent. Also there were no clean-cut criteria for judging the dosage when administered in such amounts". This drug and other barbituric acid derivatives have been employed in smaller doses to a definite advantage in the pre-anesthetic preparation of the patient.

Holman and Palmer, (100) state that the occasional restlessness and the mild delirium after operation are a definite disadvantage, but are usually absent when amytal is administered in smaller doses, ranging from 7.-12. grains. In their experience with the intravenous administration of the drug the drop in blood pressure is a distinct disadvantage. Even with small doses this drop may be alarming, and may be sufficient to warrant postponement of the operation. They think it may be an evidence of an individual idiosyncrasy to the drug, and its possible appearance makes frequent observations on the blood pressure during the administration of the drug imperative. They conclude from their experiences with its use in 150. cases of general surgery, that sodium amytal provides the normal induction of a natural sleep without the apprehensive struggling of a conscious patient. There was noted a marked reduction in the postoperative



nausea, struggling, and pain. In operations upon patients with exophthalmic goiter, and upon very apprehensive, excitable patients, sodium amytal has, they believe, a very definite place in anesthesia, and may be used in doses of 7.-12. grains with definite advantage to the patient.

Mason and his associates, (99) using sodium amytal intravenously, called attention to the variation in individual susceptibility to the drug. They found that the minimum dosage required barely to erase consciousness varied frequently from 3.-9. grains, illustrating the impracticability of estimating the proper dosage. From their experience with its use in 305. cases, they concluded that when the drug was used for the pre-anesthetic preparation of the patient, with a dose just large enough to make the patient lose consciousness, it gave more satisfaction than any other drug used. In patients with hyperthyroidism, and in those who were nervous, it gave the most satisfying results. When the drug was given slowly and the administration stopped as soon as the patient lost consciousness, they considered that no serious or untoward effects would be experienced. They suggest the following surgical indications for its use: hyperthyroidism, and laparotomies in which it is desirable to have relaxation with ethylene; kidney operations, using sodium amytal supplemented by ethylene; to produce unconsciousness wherever there is an emotional element of any degree before

any type of operation; for the control of postoperative delirium or excitement; and as a pre-operative measure to promote rest in highly toxic goiter cases.

The uses of this drug for purposes other than pre-anesthetic preparation of the patient, include the control of convulsions as observed in tetanus, eclampsia, status epilepticus, strychnine poisoning, and cocaine and pre-caine poisoning. It has also been used in controlling patients with delirium tremens, unmanageable mental cases and various postoperative psychoses.

In the field of anesthesia, patients who are poor anesthetic risks may be considered poor risks when sodium amytal is used for pre-anesthetic preparation. Patients with hypertension, hypotension, generalized arteriosclerosis and those who are emaciated are poor subjects for the use of sodium amytal. Patients with pulmonary infections, lung abscesses, and bronchiectasis should not receive enough of the drug to interfere with the gag reflex, and it is better on the whole to use very small amounts, 3.-6. grains, preferably without producing a total loss of consciousness. The drug should also be given cautiously or not at all, following very large doses of morphine, or in those patients particularly sensitive to morphine and similar drugs. The intravenous administration of the drug should be stopped at once if an acute drop in blood pressure or a marked decrease in the amplitude of the respiration occurs. The intravenous method carries with it certain

disadvantages, such as the dangers from too rapid administration, more acute respiratory and circulatory depression, and the technical difficulties and dangers inherent in intravenous administration of drugs. However, the effects are obtained almost immediately; the minimum amount required for the individual patient may be judged more accurately; and the rate of elimination or destruction proceeds at a faster rate. As is well known, no fixed rule can be used for calculating the dosage, and individual variations exist in man. This one point alone is sufficient to contraindicate the use of barbituric acid derivatives in large doses. It is considered, however, that doses of 3.-9. grains, not exceeding 15. grains, are comparatively safe limits for the clinical use of sodium amytal. (84)

## PERNOCTON

The desired qualities in obstetrical anesthesia are those of general anesthesia with important additions. These additions are: 1. The anesthetic should not interfere with uterine contractions; 2. If possible, it should permit reflex abdominal muscle contractions; 3. It must not effect the foetus. It was the search for a drug that would fill the above prerequisites that led to the discovery of the barbiturate called pernocton, and until the advent of pernocton, it could not be said that such an anesthetic, with the partial exception of nitrous oxide, existed.

The extent of anesthesia is determined by the concentration of the anesthetic in the blood and tissues, and the appropriate concentration is such that the cortical cells are depressed, but the medulla, with its respiratory and cardiac centers, is not so affected. (68) Pernocton is a 10% solution of the sodium salt of secondary butyl-B-bromallyl barbituric acid. It is a white crystalline substance soluble with difficulty in water, but readily in alcohol.

Animal experiment has shown that acetonyl barbituric acid is the fragment of the pernocton molecule which is excreted in the urine, and this represents only one-fifth of the amount administered, that is, the remainder is destroyed in the body. Moreover, an animal can be fed

with acetyl acetonyl barbituric acid with the result that only a small portion can be recovered from the urine, pointing to the fact that the molecule can be oxidized by the organism. (68)

The chemical formula of pernocton is  $C_{11}H_{14}O_3N_2BrNa$ . It was introduced in Europe and has been extensively used there during the last ten years. It has also been used recently in this country in both surgery and obstetrics with good results. It appears to have an advantage over the other barbiturates because of its early detoxication within the body, and hence is without the prolonged sleep and depression that so often follows the use of the other hypnotic drugs of this type. Pernocton has also the advantage of stability when in solution and hence is prepared in a sterile solution, ready for immediate use. (57) Pernocton has been in use in Germany since 1927. (58) Its advantage over sodium amytal and nembutal is that it is stable in solution so that no mixing or dilution is necessary.

Pernocton, by the introduction of the  $-CH_2-CBr=CH_2$  group, acquires one of the most desirable attributes of a good hypnotic, the property of rapid decomposition or alteration to non-toxic substances within the tissues. According to R.F. Matters, (68) one of the most significant structural advantages is the presence of the secondary butyl radicle which by its asymmetric carbon atom

simulates naturally occurring molecules. The toxic margin with pernocton is very high; intravenous administration to rabbits gives a ratio of 1:10 for average narcosis dose.

Intravenous administration is desirable in that it admits of absolutely accurate dosage and rate of absorption by the nerve cells. Intramuscular or enteral administration is uncertain in this respect and, although necessary when more dangerous compounds are used, it is not important in pernocton anesthesia, except perhaps for additional amount which are given intramuscularly mainly because of the slower absorption. (68)

Its initial use was tried in asylum practice, and the first clinical knowledge of its value is due to Bumm, head of the Surgical Clinic at the Charite, Berlin, Germany. (Taken from R.F. Matter's report, (68)) Bumm's first review of 100. cases begins the literature upon this subject. Since then, 1927, until April, 1930, two hundred thousand cases of clinical administration have been reported. In giving pernocton, it is very necessary that one should induce by suggestion a satisfactory mental attitude in the patient. The dose of pernocton is 1. c.c. per 12.-15. kilograms of body weight, the rate of injection being 0.75 c.c. per minute.

The method of administration now most universally adopted was originally taken from a paper by Brammer, of the Universitats Frauenklinik, Freiburg im Baden, whose 1500. pernocton deliveries have been completed and of

these he has especially analyzed 225. cases to determine the best procedure. In the same paper is given a minute analysis of the results of pernocton anesthesia as used in other clinics, and he indicates especially the following: (taken from R.F. Matter's discussion of the original paper in German, #68) "Goldschmidt states that 3.5 c.c. is the lowest amount that suffices for a case. Vogt uses 8.8 c.c. as an initial intravenous injection, and after 45. minutes gives 4. c.c. intravenously, in addition. He says there are no ill effects. Mutz gives 3.5 c.c. intravenously and 1.5 c.c. intramuscularly. He says that anesthesia lasts for three hours." Brammer states that using 5. c.c. of pernocton, it was found that the intravenous route was many times more efficacious than the intramuscular route; he considers that the latter has a variable rate of absorption. He further advises that in primiparae the pernocton should be given when the os is "five shillings" dilated; the cervix in multiparae should be dilated only "three shillings". The average duration of the "twilight sleep" for the single dose in 72. women was found to be 2.5 hours, and the average duration in 28% was 1.45 hours. In 80% of Brammer's cases the anesthesia lasted for 3. hours and the amnesia was complete.

Matters (68) makes the following conclusions: 1. Pernocton is a suitable obstetrical anesthetic; 2. It has been abundantly tried and fulfills all the requirements of obstetrical anesthesia; 3. The results he

obtained corresponded closely with those published in Europe; 4. Quiet surroundings and careful suggestion are essential to the technique; 5. The intravenous route is the more exact and suitable method of injection, while the more slowly absorbed intramuscular injection is used for additional doses to maintain the concentration of the anesthetic in the blood.

Friedlaender, (67) states that the psychological explanation of sleep is the theory which best lends itself to an explanation of the action of pernocton. As will be shown later, the method of giving pernocton includes preparation for hours, even days before the advent of the operation. The patient is prepared by suggestion for what to expect and is told how pleasant and harmless pernocton is. This suggestion as a preliminary is very essential, for it induces a state of mind which is the first step to beneficial sleep. (67)

Pernocton directly paralyzes the receptive ability or rather the ability to synthesize ideas and impressions and thus produces narcosis. The narcosis induced by this drug is one step beyond natural sleep, for the individual cannot be roused by ordinary stimuli. Pernocton is described by some as a paralyzer of the ability to concentrate on limited number of stimuli. Pernocton belongs to the group of hydrocarbons, all of which possess the ability to produce narcosis in varying degrees of toxicity and effectiveness. As a general rule, "all other factors being



equal, the effectiveness of action of a hydrocarbon increases with the length of the chemical side-chain." (67) A limit to this rule is soon reached, for the longer the side-chain, the less volatile, soluble, and absorbable the drug becomes. It can readily be seen that an insoluble, non-volatile, and non-absorbable drug, no matter how powerful it is, is of no use.

Pernocton has an especially effective length to the side-chain; not too long as in amytal, where the variation in solubility of different lots is due to the excessive length of the side-chain. Another factor enhancing the value of pernocton is the halogen replacing one of the hydrogen atoms. (67) Bromine supplies all of the benefits of the halogen, at the same time lacking all the dangerous qualities of the other halogens. In short, pernocton, according to its advocates, contains all the factors making for therapeutic effectiveness and has no determinate qualities such as undue toxicity or difficulty of management.

This is really highly debateable and only the opinion rendered by those who champion the use of pernocton. The relatively slight toxicity of pernocton as compared with the other barbiturates is due to the rapid decomposition of the drug in the body. This same author, (67) who so strongly champions the use of pernocton, also made the following statements which have a bit of a contradictory air to his previous conclusions: "From the beginning of

our investigations we had in mind the two main factors, ease of control and harmlessness on one hand, and preservation of the patient's constitution on the other. Because these two factors were not found in any one of the anesthetics known today, we sought for and obtained the desired results by combining pernocton with an inhalation anesthetic, preferably ether." (67)

Pernocton's use, therefore, is principally that of basal anesthesia, or an induction medium, followed by ether. With this combined anesthetic, somatic sensibilities are to a great extent eliminated. Complete anesthesia with pernocton is never attempted by the wise, states one author. The determination of the proper dose depends upon the weight and the psychic condition of the patient. As a rule, 1. c.c. of the 10% solution of pernocton per 12.5 kgm. of body weight will be sufficient to put the patient into a deep sleep in from one to two minutes.

Examinations too painful to the patient to be carried out without anesthesia, and minor surgical operations can be made under the influence of pernocton. The drug has been used in cases of general surgery, in operations upon the thyroid gland, stomach, gall-bladder, appendix, kidney, prostate, etc. In 700. cases reported by Bernard Friedlaender, (67) there was not a single fatality, and in only 4. cases were there found an excessive amount of excitability which was believed to have been due to an improper technique, namely, too rapid injection of the drug.

The method for the intravenous injection of pernocton is as follows: 1. Pernocton is a hypnotic to be used intravenously. If used intravenously in the proper dose, instant sleep is produced with the elimination of all sensation; 2. Its principal use is for induction and the support of an inhalation anesthetic and it serves to avoid all psychical disturbances of the patient; 3. The average dose need not be more than 1. c.c. to 12.5 kilograms of body weight; 4. The intravenous injection should be stopped even if the full dose has not been given; 6. In fifteen to twenty minutes after the injection, a small amount of ether may be given to the patient by inhalation; 7. The normal sleep after operation may last from two to five hours, reducing postoperative pain to a minimum.

The conclusions that I reached, after reading most of the available data, which is enormous in amount, concerning pernocton and its use are as follows: 1. Pernocton, in chemical structure, combines the advantages necessary in anesthesia in the possession of a long side-chain and a halogen replacement of the hydrogen atom without suffering the disadvantages of similar compounds, namely, insolubility, toxicity, etc. 2. Pernocton produces a state closely related psychologically to natural sleep, with the added benefit of rendering the subject impervious to external stimuli. 3. Pernocton should be administered in a dosage relative to the body weight.

4. Pernocton should never be administered in doses great enough to abolish the reflexes. In major operations it should be used as an extreme hypnotic for induction, and combined with a small amount of ether. 5. Pernocton may be used effectively as the sole anesthetic for painful examinations, and minor surgical operations, but the danger in this sole use of pernocton is great. 6. The 700. cases with no fatalities and only 4. cases where extreme excitability was present are seemingly fair evidence of this drug's beneficent effectivity

## NEMBUTAL

Nembutal, sodium ethyl methyl butyl barbiturate, has the characteristics of the barbituric acid series more clearly developed than any other barbiturate. It is about twice as toxic as sodium amytal, (96) and its action is much shorter. Lundy, (96) states that it is more sedative than hypnotic and that it causes delirium and restless-ness less often than other barbiturates. Nembutal (Abbott) is supplied in ampoules (gr.  $7\frac{1}{2}$ ) for intravenous use after being dissolved in distilled water, 10. c.c.

For the injection a 10. c.c. syringe is used with a fine hypodermic needle, and the solution is injected at the rate of about 1. c.c. per minute. When administered intravenously the injection need not be begun until 10. minutes before the time of operation, for the effect is quickly and accurately obtained. No calculation of dose on a body weight basis is necessary, the amount being determined by the progressive effect during injection. The solution should be freshly prepared and quite clear. The injection should be carried out at the rate of about 1. c.c. per minute, a close watch being kept on the patient throughout. The patient's response to questioning becomes gradually more and more indistinct and without any period of excitement, the patient passes into a quiet sleep. The dose is the minimum amount necessary to

produce this effect after slow and careful injection. The minimal dose in Magill's series of clinical cases, (66) was grains 3. and the maximum was grains  $7\frac{1}{2}$ . When sleep ensues after intravenous injection respiration is quiet, diminished in amplitude, and normal in rate. It has been stated by some that a fall in blood pressure takes place during the injection of a barbiturate, (85) but other experimenters such as Magill, (66) find that with nembutal the fall in blood pressure is trivial or absent in all their cases.

During the course of the operation after intravenous injection the amount of the supplementary anesthetic required is less than with oral or rectal administration. This, says Magill, "is clearly the result of the more exact dosage by the intravenous route." And, perhaps it is due to this more accurate dosage that a survey of literature reveals that the post-operative effect following intravenous injection is more marked than with oral or rectal administration. Drowsiness or sleep from 1.-5. hours after operation is the usual course, with hazy memory for events during that period.

In order to compare the results obtained with other barbiturates, I.W. Magill, (66) administered sodium amytal intravenously to 23 cases, and pernocton to 15 patients. All of these patients were adults. Induction of pre-operative sleep with sodium amytal compared favorably with nembutal, but the recovery period was much longer.

Pernocton has been reckoned equal to nembutal in toxicity, and the recovery period was about equal. (95)

It is in the intravenous use of nembutal that the greatest advantage over other methods of administration, lies. By this method it is possible to determine the dose accurately during injection of the drug. Here, again, the reaction of the patient seems to bear little relation to age, body weight, or habits. Intravenous injection of a drug in connection with anesthesia is open to criticism as an unnecessary complication not unattended by danger. If injection is carried out carefully and slowly, with aseptic precautions, it need involve little more risk, and certainly no more discomfort, than a hypodermic injection. From the adult patient's point of view, a prick with a hypodermic needle is usually expected before an operation, and to many it is more acceptable than the retention of a rectal injection of any kind. Intravenous injection of nembutal is available, further, when rectal premedication is ruled out by the nature of the operation. It requires a minimum of apparatus and preparation. The following might serve to summarize the subject: 1. Intravenous injection of nembutal provides a pleasant method of bridging the gap between consciousness and unconsciousness, before general anesthesia. 2. The amount of anesthetic subsequently required is diminished. 3. Post-operative nausea and vomiting are diminished or absent. 4. The chief disadvantage is postoperative restlessness

in a small percentage of cases, about 10%. (95)

It has recently been well established that there is great variability in duration of the sedative and hypnotic actions of different members of the barbituric acid series. As regards hypnotic action they have thus been arbitrarily divided into "long-acting" and "short-acting" barbiturates. Sodium iso-amyl-ethyl barbiturate, (sodium amytal) is a good example of the first, and nembutal may be taken as typical of the short-acting barbiturate hypnotics.

In surgical cases experience of a good many has proved that a short acting barbiturate, having a brief hypnotic action, is safer and more satisfactory than long acting barbiturates. In general, Volwiler, (59) says, the long acting barbiturates are antispasmodic and hypnotic with a durable hypnotic action; the short acting barbiturates are antispasmodic and sedative with hypnotic action of short duration but of sufficient length to cover the period between administration and the induction of surgical anesthesia as well as of the operation itself. In medical cases, he points out, a short acting hypnotic is often preferable because the hypnotic effect is still long enough to assure hours of rest for the patient, yet the product is eliminated so rapidly that there is much less likelihood of "hangover", more commonly experienced after the long-acting barbiturates. Furthermore, the barbiturates of the short acting series are characterized by the fact



that a smaller dose produces a very intense if more fleeting action. This means a more rapid elimination and a decreased tendency to any possible toxic or other undesirable effects, with a wider margin of safety.

While in laboratory animals general surgical anesthesia has been induced successfully by the employment of barbiturates alone, a resume of the literature shows that clinical attempts have not been uniformly satisfactory for the human subject. The general opinion of clinicians is that the barbiturates find their field of usefulness as hypnotics and as pre-anesthetic sedatives.

A pharmacological report by Fitch, Waters, and Tatum, (95) covered an accurate laboratory and clinical comparison of sodium amytal and nembutal, as well as the German preparation, pernocton. These investigators, (95) found that to produce sleep in an ordinary previously morphinized individual, 0.6-1.4 grams of amytal, 0.4-0.8 grams of pernocton, and 0.2-0.5 grams of nembutal were required. They also found that both the period of postoperative sleep and the postoperative excitation were distinctly less with nembutal than with the other two barbiturates.

Dr. John S. Lundy, (87) reported clinical confirmation of the pharmacological observations of Fitch, Waters, and Tatum. (95) Based on his observations on several thousand cases in the Mayo Clinic in which sodium amytal or nembutal were employed he found that the latter is essentially an antispasmodic and sedative,

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with less delirium incident to its use than with the former. Moreover, it is twice as effective, thus permitting smaller dosage, and the period of recovery is only half as long. Dr. Lundy, (87) concluded that the nembutal is particularly advantageous in obtaining pre-operative sedation regardless of the final anesthetic used and in cases in which it is desired that the barbiturate effect should be of short duration. Barlow, (86) in experimental work on rats has found that pre-medication with 22.5% of the lethal dose of nembutal intensified the anesthetic properties of nitrous oxide. He, (86) concludes, "correlation of the premedication values of avertin and the nine barbituric acid derivatives indicate that the order of efficiency from high to low is as follows: nembutal, avertin, dial, allonal, neonal, phanodorn, pernocton, luminal, amytal, and barbital."

Dr. I.W. Magill, (66) administered nembutal as a basal hypnotic to 262 surgical patients, the intravenous route being used. When nembutal is administered intravenously the effect is rapid, says Volwiler; (59) responses to questions gradually become more indistinct and, without any period of excitement, the patient passes into a quiet sleep. None but a trivial fall in blood pressure was observed by Dr. Magill, (66) in any case in which nembutal was administered intravenously. By the intravenous method the amount of supplementary anesthetic

required was less than with oral or rectal administration; also the postoperative sequelae were more marked following intravenous than following oral or rectal administration. Some degree of restlessness postoperatively was noted in only 13 cases. Dr. Magill, (66) regarded nembutal as the most outstanding anesthetic drug and one sure to be of great value in medical practice, i.e., in epilepsy, convulsions, eclampsia, delirium tremens, hysteria and any nausea.

In discussing Dr. Magill's paper, Sir Francis Shipway, (104) said that there seemed to be a great future for nembutal; he was using it constantly and saw no disadvantages from its use. Dr. Stanley Rowbotham, (105) unhesitatingly endorsed Dr. Magill's conclusions in regard to nembutal. He has administered it in 108 cases and states that compared with his experience with sodium amytal and pernocton there is no doubt that it is the best of the three drugs. In the majority of his cases there was a fall of 10.-15. mm. in the systolic blood pressure with nembutal whereas with amytal, the fall was usually double this amount, and postoperative restlessness was decidedly more marked. With pernocton, he reports that the results were even more unsatisfactory. Dr. Jas. Riddell, (106) states that as a preliminary sedative in nervous patients he found nembutal valuable and easier to employ than avertin per rectum. In his experience also it is preferable, in obstetric practice, to sodium amytal, intravenously or

orally.

John D. Graham, (107) states that the advantages possessed by nembutal are minimal dosage, more rapid elimination, greater freedom from after complications, and less tendency towards extreme restlessness or delirium. However, valuable as the drug is intravenously, in gynecological surgery, he states, it like other intravenous drugs has no place in obstetrics, but is very effective and efficient in this field when given intramuscularly.

John S. Lundy, (6) in his report on nembutal states that it is definitely sedative, antispasmodic and, of course, hypnotic. He reports a series of 2,300. cases in which nembutal was used intravenously to produce anesthesia. In this series 0.5 grams of nembutal was first dissolved in 7.5 c.c. of water so that the concentration was one grain per c.c. For adults the solution was injected at the rate of 1. or 2. c.c. per minute. The effect of the first grain was hardly apparent. After two grains were given the patient spoke of a definite effect; after three grains there was a general feeling of peace and well-being; after four grains, the patients usually fell asleep but were not anesthetized; after five grains the patients were more deeply asleep but not anesthetized; after six grains the patients were in beginning anesthesia; after seven grains anesthesia was usually apparent and after seven and **one-half** grains there were

few cases in which anesthesia was not complete.

George Carroll, (5) champions the use of nembutal as a sedative for preliminary medication to local, general and spinal anesthesia. He states that in preparing the patients for operation, as in emergencies, accidental and traumatic injuries, the rapid effect, small dosage and short duration of effect is advantageous. Also, while nembutal is not intended as a lone anesthetic, properly graduated dosage will produce a degree of anesthesia under which much can be done without additional use of other agents. He, (5) states that in properly selected cases under skillful manipulation, extensive surgery may be done with the employment of local infiltration or a very small amount of inhalation anesthesia. Its use in local and spinal anesthesia has been found to raise the tolerance to normal and reduce to a minimum the liability of disagreeable reactions and sequelae, and the recovery period is rapid, due to the small amount of anesthetic required, and is usually unaccompanied by nausea or vomiting, with a period of sedation lasting several hours.

Where time is an element of consideration, this intravenous method is most satisfactory. According to Carroll, (5) considerable latitude in dosage was found necessary due to the individual reaction, where effectiveness was observed to vary with age, and general physical condition and the dose required to produce sleep was best determined

by the rate at which the subject became unconscious. As regards the nembutal solution itself, he points out that the solution should be freshly prepared for each case as it hydrolyzes in aqueous solution, and only perfectly clear solutions should be used. In his cases, there has been no nausea or vomiting, the blood pressure frequently fell slightly at first, only to return to the previous level or above in a short time. The respirations became lessened in amplitude, the rate slowed, but no cyanosis was ever observed.

The contraindications are, as in general anesthesia, the aged, high or low blood pressure, arteriosclerosis and unstable cardio-vascular systems, pulmonary involvement or edema about the neck or throat. Carroll, (5) states that the chief dangers are broncho-pneumonia, and postoperative pulmonary edema, but that these are noted only after excessive doses, and that nembutal should not be given after large doses of morphine, nor should it be given except in smaller doses in the presence of known kidney impairment.

## EVIPAN

As the chemists of the firm Riedel did not succeed at the time, in spite of indefatigable efforts, in removing the exciting properties of the anesthetic pernocton injection, by modifying the nature of the solvent, it was, as a result, taken for granted that the excitation of reflexes was a property of all barbituric acid derivatives, so that we had practically given up the hope of finding an injectable anesthetic suitable for practical use.

Nevertheless, Weese (44) succeeded recently in discovering evipan-sodium, a derivative of barbituric acid, which does not possess the undesirable properties of all injectable anesthetics known up to now, particularly those of amytal and pernocton; on the contrary this new product shows a considerably greater solubility, as well as the property of a more complete splitting up and decomposition of its molecule within the organism.

Evipan-sodium is the sodium salt of evipan, i.e., of N-methylcyclo-hexenyl-methyl-barbituric acid, which latter substance was produced by Kropp and Taub, and was introduced at the time by Weese. Weese, (44) reports that in his experiments with evipan, he was impressed by the most striking fact that in comparison with other derivatives of barbituric acid, this particular one caused an extraordinary rapid and deep sleep without after-effects and without causing any symptoms of excitement. Weese also noticed at the time, that the margin between its minimum anesthetic

and toxic doses is very large and that only several anesthetic doses have a fatal effect. On the basis of these observations, efforts were made to create an injectable anesthetic for the purpose of short anesthesia, which resulted in the production of a sodium salt of evipan.

Evipan-sodium, also called endorm, is a whitish substance readily soluble in water. Organic solvents have also been found recently, in which evipan keeps permanently. (44) The manufacturers state for instance that the evipan concentrate represents a  $33\frac{1}{2}\%$  solution of the sodium salt in methyl-diglycol. Consequently, there was at first, for practical purposes, two different kinds of ampoules, i.e., 1. Ampoules containing a definite weight of the sodium salt, for the preparation of a 10% aqueous solution. 2. Ampoules containing a  $33\frac{1}{2}\%$  solution of evipan-sodium dissolved in methyl-diglycol, which had also to be diluted before use with 10. c.c. of sterile water, so as to obtain a 10% solution. The latter form is now the usual form, and the one that is used commercially.

Weese, (44) seems to have searched from the very beginning for a product for producing a short general anesthesia by injection. In fact, he directed his attention mainly to the rate of decomposition of the said substance. As a matter of fact during the last few years, both pharmacologists and clinicians have realized that the elimination of an anesthetic agent calls for very



careful consideration and represents a much more important factor when considering the applicability of a preparation than the factor of the difficulty of absorption by the circulation.

The curve of evipan-sodium anesthesia, is similar to that of all injection anesthetics, and as shown recently by Rehn and Killian, (45) for pernocton in their critical survey of our anesthesia processes, the rising is very steep and depends not only on the concentration and on the total dose of the product, but particularly on the rate of injection. If this is made with moderate speed, the anesthesia curve runs in such a manner that the action gives the measure both of the speed of the injection and of the dose injected. However, the culminating point of the depth of sleep and the anesthesia curve is always attained after the end of the injection, i.e., after from 5-10 minutes a point is reached which must be taken into consideration. On the other hand the downward curve of evipan-sodium anesthesia, when compared with that of other barbituric acid derivatives, is extraordinarily rapid, so that both experimentally and clinically, when using medium doses, one may reckon upon the awakening of the patient after 15-30 minutes.

The liver must be considered as the principal detoxicating organ, seeing that experiments have shown that hepatectomised animals, or animals which had been poisoned with phosphorus and whose liver was consequently very

damaged, awoke much more slowly. According to Weese, (44) evipan-sodium is hardly destroyed in the blood, the kidneys also do not participate in the process of detoxication of chemical decomposition. He found traces of unchanged evipan-sodium in the urine. Animals which had been submitted to repeated anesthesia over a period of several months exhibited no manifestations of tolerance, nor could any injury of the organism be observed.

The exceedingly good results obtained with animals, encouraged the experimental application of evipan anesthesia to human beings. Evipan-sodium anesthesia has been used by one author alone, H. Killian, (44) in over ten thousand cases without any certain case of death having become known. Generally speaking, everything that has been learned regarding evipan anesthesia when applied to animals, has been confirmed with human beings.

The packages intended for use in clinics contain each, two ampoules, i.e., a small ampoule with a quantity of dry evipan-sodium or with evipan-sodium dissolved in methyl-diglycol which is just sufficient, when mixed with the 10. c.c. of sterile water contained in the larger ampoule to make the solution ready for use. The technique of the injection is extremely simple and requires no special preliminary knowledge. The only important point is the difference as compared with injections of pernocton. Seeing that evipan-sodium is much more soluble and much more easily decomposed,

it is not necessary to maintain such a slow rate of injection as in the case with pernocton. On the contrary, experience has shown that, when inducing evipan-sodium anesthesia, it is possible to influence the duration of anesthesia and the depth of sleep by an adequate rate of injection. The indications of the various authors show that they have not all carried out the injections in the same way, but that there are slight differences. At the start, the firm that manufactured this product, set down a fixed rule for dosage on the kilogram per body weight scale. However, all those who have taken up the new method and have expressed an opinion, agree that it is neither desirable nor necessary to fix the dose in relation to the bodyweight of the patients.

H. Killian, (44) adopted the method of determining the dose according to the anesthetic effect. He gives a maximum dose for a single injection. Thus Ernst never exceeds 9. c.c. of evipan, whereas Baetzner mentioned 10. c.c. as the highest permissible dose per injection. Only Holtermann, (44) who likewise considers 10. c.c. as the normal maximum dose, has, at different times, injected, in individual cases, 15. c.c. of the 10% solution without ever having observed any visible damage. Other workers are said to have injected even from 30.-60. c.c. without any harm.

For an average evipan anesthesia, in which sleep must last from twenty to thirty minutes, in order to

adapt the rate of injection to the purpose, about 3.-4. c.c. are injected in the first minute during which the patient quickly falls asleep, and an additional 3.-4. c.c. are injected fractionally, in such a way that the respiration and color of the skin are not materially modified during the injection. The total dose required for every individual case is adjusted during the injection in accordance with the depth of sleep, i.e., the injection is simply stopped when the operator has the impression that the patient's sleep is deep enough. Naturally, the dose is regulated in accordance with the physical condition and the age of the patient.

Injections have been made in patients suffering from diabetes, from diseases of the heart, lungs, liver and kidneys without any undesirable effects so that one can conclude that evipan constitutes a preparation which is particularly suitable for patients who are seriously ill.

(44) In these cases, evipan anesthesia replaces especially the strong inhalation anesthetics, avertin, regional and spinal anesthesia; it also replaces gas anesthesia with ethylene or narcylene when dealing with arterio-sclerotic patients or hypnotic subjects.

If it is desired to use evipan only with a view to initiate anesthesia with other anesthetics, such as gas, ether, chloroform, remarkably small doses will render the patient unconscious. Three to four c.c. of the original solution are often sufficient even with patients of a

strong constitution. Furthermore if it is simply desired to perform to a short operation, such as can be carried out under ethyl chloride anesthesia, it is recommended to inject a small dose of evipan comparatively quickly i.e., 3.-5. c.c. within one minute, observing closely the patient's respiration. The above dose passing quickly into the blood stream, produces within a surprisingly short time a depth of sleep corresponding at least to the first section of the tolerance stage. (44)

The distribution of this comparatively small dose of evipan in the tissues and its decomposition take place so rapidly that after five minutes, already the quantity present in the blood is no longer sufficient for anesthesia. Consequently this mode of application of evipan makes it possible to obtain a light anesthesia of three to five minutes duration, which, in contradistinction with anesthetics of the same degree obtained with gas or ethyl chloride, causes no unpleasant subjective reaction whatever for the patient, with exception of the injection itself, and contrary to what happens with gas narcotics, the patient remains in a slightly drowsy condition for about an hour.

The cases of cessation of respiration observed occasionally with evipan anesthesia must probably be attributed to the preliminary administration of large doses of morphine or similar active products, a fact which has escaped the attention of some observers. (43) As evipan anesthesia is not only complete, but sets in within a

very short time without discomfort for the patient, there is not the slightest reason for influencing pure evipan anesthesia by the use of alkaloids. The administration of a preanesthetic agent has also been abandoned by most clinicians

Holtermann, (44) gives the most exact description of the symptoms of evipan anesthesia. After evipan injections the respiration as a rule does not remain at the normal level, but as the depth of sleep progresses, the breathing becomes simultaneously slower and somewhat deeper. According to the clinical measurements, during the period of increasing anesthesia a transitory depression of the respiratory activity takes place, which increases with the speed and volume of the injection. As with all preparations of that nature, it first manifests itself by a diminution of frequency which is compensated by a deepening of the successive respiration with a comparatively swift fall of the functional activity which in many cases caused slight cyanosis or even a temporary failure of the respiration of a non-dangerous character. The modifications of the respiration are therefore the best guide for correcting the speed of injection. After the respiratory depression which takes place during the first few minutes, that function is usually soon restored and a moderate hyperventilation may take place during the second half of the anesthesia.

The blood pressure falls during the injection and generally returns to a level which is 5.-15. mm. of mercury below the original figure, thus practically never causing any great anxiety. The falling blood pressure depends entirely on the rate of injection. The quicker and more carelessly the injections are made, the deeper is the initial fall. As in the case with all such anesthetics, the pulse rate increases somewhat, simultaneously with the modifications in the blood pressure; the average increase as given by Holtermann, (44) is from 10-30 beats per minute, but according to Killian, (43) the pulse rate generally falls again somewhat when the tolerance stage is reached and goes back to approximately the normal rate according to the nature of the intervention.

Generally speaking, only very seldom have complications been observed in the use of évipan. Only on a few occasions have disturbances of the respirations been observed at the end of the injection, these being probably due to a too rapid injection into oversensitive subjects. Baetzner, (44) reports that in isolated cases, after completion of the injection, the face of the patient became bluish and the respiration shallow, a condition however which quickly passed off.

Up to the present time, evipan anesthesia has mainly been used for light anesthesia or short anesthesia; and only to smaller extent for full anesthesia in cases of surgical interventions of average severity. In complete

agreement with the views of most clinicians, Ernst, (44) emphasized that its slight influence on the circulation and respiration, as well as its comparative harmlessness as regards liver and kidneys, permit of its use to the widest extent; that general anesthesia with evipan is now possible with old patients with damaged heart, in whose case surgeons hesitated up to now to use other methods of anesthesia. Disease of the excretory organs and of the liver have not disturbed up to now the favorable course of anesthesia, nor has the anesthesia had any prejudicial influence on the course of the disease, even when the same patients have been subjected repeatedly to evipan anesthesia at short intervals.

As no symptoms of habituation appeared, evipan anesthesia according to the experience of all authors, can be resorted to as often as desired and can consequently be repeated without danger on the same patient. Evipan anesthesia is used mainly for short anesthesia or for the inducement of full anesthesia with gas or a mixture of gas and ether. An exact specification of indications has not been possible up to now, seeing that no particular contraindications in the surgical field have come into the literature. However, the mode of action of the product, as shown in pharmacological experiments, we would anticipate with a fair degree of certainty that restrictions in the use of the preparation will be necessary with patients with diminished



respiratory surface or otherwise impaired ventilation; also, in the case of sub-uremic patients or subjects suffering from severe liver affections. The only influence on the field of indications is in regard to the duration of sleep, if, for the above mentioned reason, it is not desirable to make use of additional doses. It can at any rate be stated that, generally speaking, evipan anesthesia replaces light and protracted ethyl chloride anesthesia, also solesthin anesthesia, light ether anesthesia, short ether anesthesia, and to a certain degree also gas anesthesia.

If we now summarize all the data relating to the new preparation, we can assert that evipan takes a pre-eminent place in comparison with all the injection preparations of the barbituric acid class used up to now, on account of its being easily soluble and of its rapid decomposition, and that it will gain a predominant influence in the field of anesthesia. Whether it will supplant entirely pernocton which produces a considerably longer sleep of lesser depth, remains an open question for the time being.

The statistics which have been compiled up to now include over 15,000. cases in which evipan has been used mainly as a light or short anesthetic with only one certain case of death. These statistics are so extremely favorable that one cannot only recommend the method with conviction, but can predict a great future for it in all of the fields

in which short, or light types of anesthesia are desired.

In conclusion it may be said that evipan affords an excellent, quick acting anesthesia for short operations. Likewise, it is a reliable induction anesthesia for major operations. The smaller amounts of the added anesthetic then used to deepen the narcosis is an advantage. Evipan can be successfully combined with ether, nitrous oxide, local or lumbar anesthesia. The evipan affords a complete stage of tolerance, its action is short and certain, the post-anesthetic sleep is short, bad after effects are rare, its action is safe if the contraindications are observed, and the technique is simple. If evipan is properly used and with the caution advised by those clinicians acquainted most closely with it, one will only be able to recommend it. (44) M. Babcock, (81) does not seem to be of quite the same opinion as to the contraindications, and states that the contraindications for its use are so definite that he believes it will find but a limited field of usefulness. Hypotension, severe pulmonary infection, heart lesions, and patient's suffering from wasting diseases, he thinks should not be given evipan. Chas. F. Hadfield, (80) states that he has tested out evipan, and found it quite favorable and issued such a report. He also states that evipan has been well received after much thorough discussion by The Joint Anesthetics Committee of the Royal Society of Medicine. Lieber, (23) states that

the drug evipal, is new only in the sense that it has only recently become available in this country. He says that it has, however, been extensively used abroad, and in two years from the time of its isolation by Kraft and Taub, it had been administered well over 60,000 times. All of this work, seemed to him to show that this drug was indeed one of the most valuable anesthetic agents known.

## NEWER BARBITURATES

Increase in the use of intravenous anesthesia has been delayed because of lack of a suitable agent, but at times when a general anesthetic is needed the intravenous method is the best; (20) for example, if the cautery or diathermy is to be used, and thus an inflammable agent would be dangerous, or if portability is of importance. For intravenous anesthesia the barbiturates, particularly, have been employed. (87)

It was stressed by Lundy, (85) and others, that nembutal was different from the other barbiturates in common use, in that it was a relatively shorter acting drug. Then, still shorter acting barbiturates were sought, and most of what follows will deal with two of the newest barbiturates introduced quite recently by John S. Lundy and his co-workers.

In 1934, Lundy (20) began to use a still newer type of barbiturate, sodium ethyl 1-methyl butyl thiobarbituric acid, employment of which was attended by fair relaxation, short anesthesia, quick recovery, and absence of restlessness in almost all cases. (20) With the exception that oxygen is replaced by sulphur, this agent is the same as nembutal. This drug is approximately 33-50% stronger than evipan. It comes in an ampoule, together with a companion ampoule of sterile water. The solution used is 10%, and must be

clear.

Another barbiturate, sodium allyl secondary butyl thiobarbituric acid, referred to elsewhere as "barbiturate B", has been used in a few cases with results similar to those obtained with sodium ethyl 1-methyl butyl thiobarbituric acid. To avoid the long chemical names, I shall revert to terms used elsewhere and already mentioned in this paper; thus, sodium ethyl 1-methyl butyl thiobarbituric acid will be called barbiturate B. Although barbiturate B is less potent than barbiturate A, it is about as potent as evipan. Lundy, (20) prefers barbiturate A to barbiturate B in surgical cases for the same reason that he prefers nembutal to sodium amytal for surgical cases; because he wishes to use a minimal amount of drug to produce a given effect, anticipating that, at least in the average patient, the effect will be characteristic and that in the unusual case, fewer variations will be noted than if a larger quantity of another drug had been given.

The method of giving barbiturate A and barbiturate B, resembles that used in giving evipan. An empty stomach is desirable, if not essential, and if the patient has material in the stomach, it should be emptied. To administer barbiturate A safely, the dose is two-thirds to a half as much as the dose of evipan. In administration, the airway must be kept patent. Respiration may be depressed, and it is not sufficient to see the

respiratory movements; there must be evidence of respiratory exchange. Lundy, (20) puts a wisp of cotton over the nose and mouth and observes its motion.

The advantage of these short-acting barbiturates over other general anesthetics, and over certain local anesthetics, is in proportion to the brevity of the operation. Operations or painful procedures, especially minor ones, lasting up to ten or fifteen minutes, are satisfactory fields for these drugs. (20) For ambulatory patients undergoing distinctly minor operations, local anesthesia may be preferred. If the operation is of longer duration or is a major one, it is only in special cases that these short-acting agents are particularly useful. For example, barbiturate A has been used quite satisfactorily to produce anesthesia for three and a half hours, in a case of brain tumor complicated by pulmonary tuberculosis. Although, according to Lundy, (20) thirty four and one half grains were given, there were no ill effects. A Magill intratracheal tube provided an airway; it also furnished a means of artificial ventilation, and of administering an anesthetic by inhalation, if these had become necessary.

Barbiturate A is useful in small doses, to produce unconsciousness for induction of anesthesia by inhalation, particularly if patients have facial defects. Short acting barbiturates are indicated for intravenous administration to control convulsions induced by local anesthesia.

Lundy, (20) seems to differ from a great many other workers, in his opinion of the value of pre-medication. He states that he has found it advantageous to give morphine hypodermically, and nembutal by mouth, in small doses, to adults, preliminary to administration of the newer barbiturates, especially in the use of barbiturate B. With barbiturate A it is less important to give preliminary medication, because of the increased potency of the drug. He states, however, that less of either drug will be needed if preliminary medication has been given than if it has not been given. He cites the example of patients, who have had morphine, nembutal and atropine as medication before administration of barbiturate A, awakening in the course of the operation, giving no evidence of pain at the time, and answering questions readily, and then having no memory of either pain or the questions afterward. This maintenance of analgesia in the presence of return of consciousness was not noted in all cases in which preliminary medication had been given, but was never noted unless preliminary medication had been given. (20)

The patient does not perspire when these new agents are used and, in some cases, there has been noticeable absence of postoperative shock. The blood pressure falls when a large dose is administered. The patient, according to Tovell, (11) usually awakens quietly and there is seldom any nausea or vomiting. Also, he states that as the drug is given intermittently, the effect following

administration of each successive dose is increased. Unconsciousness produced by a large dose is of long duration.

These newer barbiturates, are of such comparatively recent origin, that extensive literature concerning its use, and efficiency are not obtainable. Not enough work has been done on them, at present, to warrant a logical decision as to their applicability to clinical medicine. For this reason, I am presenting them only as an example of some of the results obtained by those who are in a constant search for a new ideal drug, which when given by the intravenous route, will produce an anesthesia of the most desirable quality. The ideal agent for routine intravenous anesthesia has not been found, as yet, but the available agents have been found by most, to be satisfactory in certain types of cases.



## GENERAL CONCLUSIONS

Among clinicians, there is a great deal of interest in this question of intravenous anesthesia. Inhalation anesthesia has been brought to a high state of usefulness; local and regional anesthesia too, have been so perfected that they are useful and safe, and rectal anesthesia by the use of avertin, has advanced also. Intravenous anesthesia, using ether in saline solution, has remained undeveloped. The long-acting barbiturates were not safe because they produced restlessness that sometimes was difficult to control and tended to produce pulmonary edema and bronchopneumonia. Now, we have drugs that permit quick induction of anesthesia by the intravenous method which, in some cases, also produce analgesia.

Despite all of the improvements and progress that has been made in the last twenty years in the field of anesthesia, surgeons, chemists and pharmacologists are still seeking the ideal anesthetic. None of the previously discussed drugs quite fit the picture or measure up completely to the standards of this acme of anesthesia. No single standard can be held up as the requirements of the ideal drug, but after a perusal of various discussions of this subject, I have attempted to compile an arbitrary set of standards. In relieving the patient of pain and mental anguish during the operation, the ideal anesthetic will not bring added terrors of its own.

The patient will not remember the anesthetizing process as a hideous nightmare, and the worst part of his operative experience. The postoperative nausea of ether still remains one of the most revolting memories that the patient retains.

Secondly, the ideal anesthetic will induce anesthesia as gently, as quietly and as naturally as sleep itself. No longer will the patient be plunged into a seemingly endless eternity after a short period of consciousness, and therefore terrifying, struggle against suffocation.

Thirdly, it will be an anesthetic without irritation to organs of the body in its administration and elimination. It will not add to the hazards of the operation by inimical effects of its own such as ether produces in the air passages, chloroform upon the liver, and cocaine upon the nervous system.

After a thorough investigation of this problem of attempting anesthesia through the employment of the intravenous route, and after reading articles, pro and con, sponsored by enthusiasts of each side of the question, I have, myself, rather reached an "on the fence" attitude, and although I definitely am of the belief that anesthesia solely by this route, is not at present a plausible idea, I do think that there are certain indications, previously discussed, which definitely offer a field for intravenous anesthesia. The old theories and practices of employing ether, hedonal, somnifaine, paraldehyde and isopral, are

definitely outmoded, and although they once were used fairly extensively with success, I believe that we can dismiss them from the final analysis, as merely being of historical value, and useless in the light of practical present-day modes of producing anesthesia.

The next group of drugs of importance can be summarized under one heading; the use of barbiturates intravenously. My present belief is that the use of the barbituric acid derivatives administered intravenously promise to offer a worth-while addition to the armamentarium of the physician. I doubt the advantage to the surgeon of the use of those derivatives which result in many hours or days of depression. I believe that the use of the quickly detoxified barbiturates do slightly constitute, a very valuable background upon which to superimpose general anesthesia. None of the barbituric acid derivatives, at present available, appears to be a true anesthetic substance, and hence should not be considered for the replacement of the well established volatile and controllable anesthetic.

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