AN EXPERIMENTAL INVESTIGATION OF THE PHARMACOLOGICAL ACTION OF NITROUS OXIDE

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In the years 1844 and 1846 a peculiar and immortal glory fell upon the dental profession. For in the first of these years Horace Wells, a dentist of Hartford, Connecticut, first used nitrous oxide as an anesthetic in the extraction of teeth. In 1846 William T. G. Morton, a former pupil and partner of Wells, first made known to the world and publicly demonstrated the anesthetic properties of ether. Thus the earliest practical beginnings of modern analgesia and anesthesia must be credited to the dental profession. It has accordingly seemed especially appropriate that this article, the major portion of which has already appeared elsewhere,[1] might also be published here, for the great majority of American dentists will scarcely have access to the former publication.

Since this article deals almost entirely with the oldest of the modern anesthetics, nitrous oxide, it may be of further interest to add that many of the modern nitrous oxide machines have been devised either by dentists or by others who have had in mind especially the needs of the dental profession while developing these forms of apparatus.

In the early days nitrous oxide was administered pure or almost pure, air being very generally excluded. This led to the production of asphyxia after a very brief period and thus the duration of the anesthesia was necessarily short. At a later period it was appreciated that a certain admixture of air with the gas was feasible and even often improved the character and extended the duration of the anesthesia. In 1868 E. Andrews of Chicago first used pure oxygen with nitrous oxide. This was a great advancement, which, although not generally appreciated at that time, has now come to be fully recognized as indispensable in the scientific administration of nitrous oxide.

Some months ago I devised a closed method for the administration of nitrous oxide and other anesthetics in conjunction with oxygen. I have used a number of different types of apparatus in connection with this method one of which has been described in a former publication.[2] My chief object in the present article is to discuss certain features of the pharmacological action of nitrous oxide as studied by this method. No morphine, scopolamine or other hypnotic has been used in any of the experiments herein reported.

I may refer briefly to an improved form of apparatus which I have used in these experiments (Fig. 1). A rotary pump of less capacity than that used in the device previously described is attached to a very much smaller and more compact frame. The chief object in this has been to simplify the apparatus and to reduce its size and weight. A number of valves, tubes, etc., shown in the illustration have been found by experience to be unnecessary, but in the experimental development of the device they were included as precautionary measures. The apparatus carries only two tanks, one for oxygen and one for nitrous oxide, for experience has shown that since tanks need to be renewed only at con-

siderable intervals, and, if the breathing bag be filled moderately full at the moment when either tank becomes exhausted there will be ample time to remove the empty tank and replace it by a new one before a fresh supply of the gas (generally oxygen, of course) is required. Realizing the great value of simplicity and lightness in any form of apparatus intended for constant use, I have spent much time and energy in trying to produce as simple a device as possible. It is perfectly evident that the apparatus here shown is much more complicated than it need be, but for the benefit of others who may be interested in the sub-

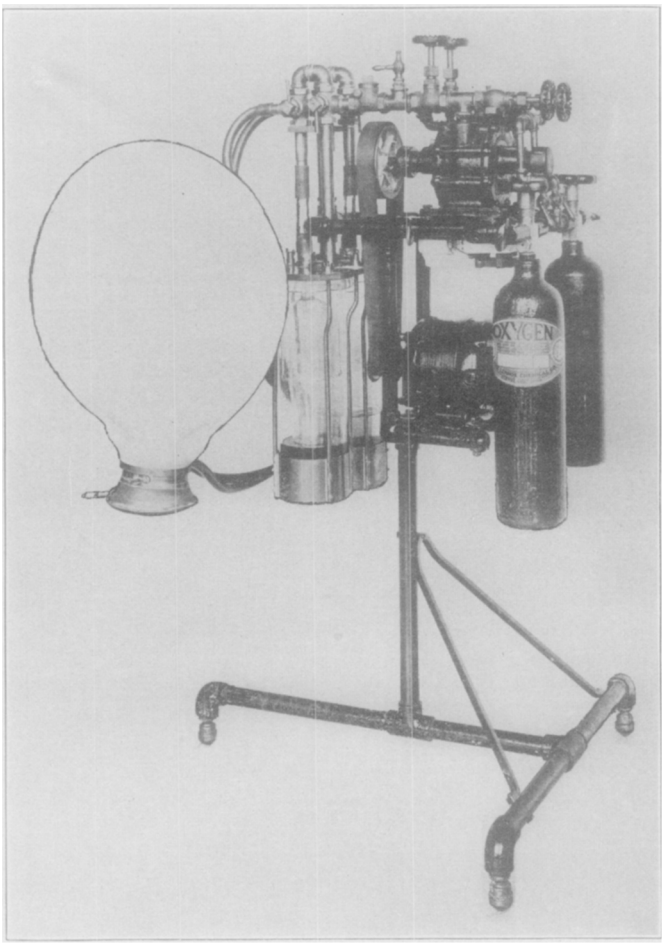

Fig. 1.—Nitrous oxide apparatus with large bag as used for experimental purposes. (For discussion, see text.)

ject of nitrous oxide anesthesia, I have thought it worth while to include here an illustration of the apparatus with which much of the work discussed below has been carried out. For a detailed description of the general principles on which the device is operated I must refer the reader to the article indicated above. By further reference to the diagram shown in Fig. 2 it will be seen that by means of a motor and a rotary air pump, air or other gaseous or volatile substances (chiefly nitrous oxide and oxygen so far as the present article is con-

cerned) are kept circulating within a closed system of tubes and vessels, and through a breathing bag into and out of which the animal breathes.

The vessels are two in number and consist of glass jars, the one containing sulphuric acid which serves to sterilize, dry and warm the air (or gases) which are washed through the acid, while the other jar contains sodium hydrate solution through which the air or gases, including the exhaled CO_2 from the patient are washed. The CO_2 is immediately absorbed by the sodium hydrate forming sodium carbonate and water according to the following equation:

$$2\ Na\ OH + CO_2 = Na_2\ CO_3 + H_2O.$$

The sodium carbonate being a soluble salt of course remains in solution (to-

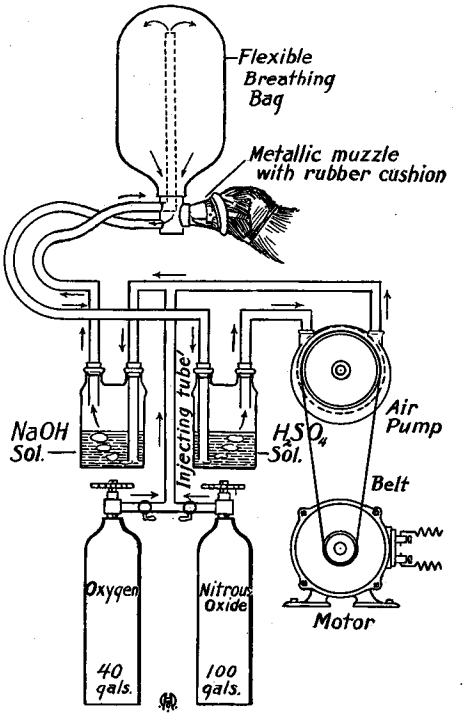

Fig. 2.—Schematic diagram to explain the plan of construction of the apparatus shown in Fig. 1. The motor turns the rotary air pump which keeps the air (or gas and oxygen) circulating. (For discussion, see text.)

gether with the H_2O formed) in the jar, the CO_2 being thus removed from the air (or nitrous oxide and oxygen) which the animal breathes. During this process the oxygen is consumed (250 to 300 c.c. per minute for an adult man at rest) by the animal or patient. More oxygen is injected into the system from time to time in just such quantities as the animal actually consumes. The nitrous oxide, being a stable gas, is not broken down at all either by the animal or by the acid or sodium hydrate. Consequently there need be but little waste of the N_2O and only a small amount (experimentally I have estimated that from 1½ to 3 gallons will be necessary for a man weighing 160 pounds) is required to saturate the blood sufficiently to produce anesthesia. When a given amount of

N_2O is injected into the closed system and breathing bag, the animal, whose lungs virtually form a part of the closed system, will at once begin to absorb N_2O into its blood from the pulmonary alveolar walls. This absorption goes on until an equilibrium in the quantity of N_2O contained in the animal's blood and tissues on the one side and that contained in the breathing bag and tubes on the other is established. It is important, however, to remember in this connection that the affinity of the blood and presumably of the central nervous system is greater for N_2O than is the affinity of water for N_2O. So far as is known at present N_2O does not form any special chemical combination with the blood or other tissues of the body. It is apparently held in solution in the blood and tissues in the same way as any other indifferent gas dissolves in a liquid, i.e., in direct proportion to the partial pressure exerted by the gas on the liquid. The lipoid content of the blood and central nervous system is generally considered to account for the increased solubility of the gas in these tissues over that in water.

The breathing bag and face-piece shown in Fig. 1 are also modified considerably from that which I first used. The bag shown here I have found well adapted for experimental observations. It is chiefly from this standpoint that I want to discuss the action of nitrous oxide in this article. This bag holds three gallons, but the sides of the bag are flat and when not in use fall together as the air or gas passes out. When in use only about one or two gallons of air or gas need be injected into the bag and this permits the subject to have a full and free opportunity to breathe in any way he pleases. It is desirable that no excess pressure, as from an overfilled bag, be introduced to embarrass the breathing of the subject. The excess amount of work which may thus be easily thrown on the respiratory apparatus in the course of an hour may be astounding, as a brief mathematical calculation will readily show. And the problem is still further complicated both directly and indirectly by the embarrassment to the heart and lung circulation which the amount and peculiar application of this excess work involves. A further feature to be noted in the face-piece is the large opening, about three and one-half inches in diameter, which connects the bag to the air cushion resting on the face. Thus the subject breathes almost directly into the large flexible bag and obstruction of the respiration is reduced to a minimum. While this bag and face-piece serve very well for experimental observations, there are certain objections which may be made to them from a practical standpoint. The first of these is the difficulty of making an air-tight contact between the subject's face and the rubber cushion on the face-piece. The second is the inconvenience of having the large bag near the patient's head. At present, however, I wish to avoid any extensive discussion of the clinical side of this subject.

THE GASES INVOLVED IN NITROUS OXIDE ANESTHESIA.

The pharmacological relations of at least four gases must always be considered in nitrous oxide anesthesia. These are N_2O, oxygen, CO_2, and nitrogen. And it may be worth while to remember that a small amount of argon, neon, crypton, xenon, etc., are also present. Ordinarily these gases are supposed to be inactive in the animal organism, but under the peculiar conditions established in the gaseous content of the body under nitrous oxide anesthesia, I am inclined to

believe that the presence of these substances, at least at the beginning of the anesthesia, should not be entirely forgotten.

It should be emphasized that the method which I have here used permits investigation of peculiar gaseous relationships which no other device heretofore employed for this purpose could well reveal. For by this method the supply of the four gases (N_2O, CO_2, N, and O) concerned in the animal's respiration may be separately and independently controlled. The CO_2, of course, is eliminated by the animal, but it may be allowed to accumulate in the breathing bag for experimental purposes and its relative action in combination with the other gases thus studied. The relative effects of CO_2 and O in ordinary forms of breathing and in asphyxia have been thoroughly studied by numerous investigators.[3] When, however, nitrous oxide is introduced, the conditions are very materially changed and only a small amount of work has been done on this phase of the problem.

It was supposed by Sir Humphrey Davy that nitrous oxide was decomposed in the body which thus became flooded with an excess of oxygen which was promptly changed to carbon dioxide. This carbon dioxide then acted as a depressant and caused the anesthesia. It was later shown that nitrous oxide was not thus broken down but was excreted by the lungs in the same form as that in which it had been absorbed. The theory then became prevalent that nitrous oxide acted solely by excluding oxygen from the tissues and that its action was chiefly a matter of asphyxia. That asphyxia may, and in practice certainly does often play a considerable part during the production of the anesthesia, no one at present doubts. But it has been thoroughly established that nitrous oxide possesses distinct specific depressant powers of its own on the central nervous system. In 1897 Kemp[4] published a series of observations on the gaseous content of the blood during nitrous oxide anesthesia. He drew off blood from the femoral artery of dogs anesthetized with various mixtures of N_2O and air and of N_2O and O, and found that complete anesthesia could be produced by the gas when the blood contained quantities of oxygen fully capable of maintaining consciousness and of carrying on the ordinary process of metabolism. When nitrogen was substituted for the N_2O, the percentage of oxygen breathed remaining the same, the anesthesia gradually passed off and the animal regained consciousness. And it has been found by the late Sir Frederic W. Hewitt[5] that a mixture of nitrous oxide 80 per cent and oxygen 20 per cent (the amount present in air) is fully capable of producing anesthesia in suitable subjects. These observations prove beyond doubt that N_2O possesses specific depressant powers on the central nervous system. It has also been shown by Kemp as well as by others that under N_2O anesthesia the CO_2 content of the blood is greatly reduced below the normal. But in most cases, however, it has been found that the oxygen content of the blood is reduced in even still greater degree below the normal than is the carbon dioxide. As ordinarily administered N_2O causes the nitrogen (and presumably the argon, etc.) contained normally in solution in the blood and tissues to be rapidly washed out of the system. Kemp's blood analyses for the dog show in several experiments a complete absence of nitrogen from the gases drawn off by the vacuum pump. It is to be noted that in all other forms of anesthesia the nitrogen (about 1.7 vol. per cent) remains dissolved in the blood.

Does the absence of this supposedly inactive gas in any way affect the anesthesia? In many instances I have observed dogs going under the influence of N_2O in which it appeared to me very probable that the elimination of this nitrogen was essential to the production of successful nitrous oxide anesthesia. It is, unfortunately, extremely difficult to prove this point. For one must, as a general rule, empty out most of the air (nitrogen) from the apparatus (and lungs and tissues of the animal) in order to fill this space with nitrous oxide so as to be able to obtain a sufficiently high percentage of the gas to produce the anesthesia. This makes difficult the solution of the question as to whether or not the absence of the nitrogen in any way influences the nature of the anesthesia.

In most forms of nitrous oxide apparatus used heretofore breathing had to be carried on under a greater or less degree of pressure. It is interesting to consider what influence, if any, this may have in tending to dam back the CO_2 produced in the tissues. While this gas did not apparently accumulate in large quantities in the blood in the analyses made by Kemp, still one is inclined to suspect that the tissues may have been trying to form the ordinary amounts of the gas but were either unable to do so or else they could not pass it over to the blood. And any such accumulation of CO_2 in the tissues may very well influence the nature of the anesthesia produced. And similarly any of the immediate precursors of CO_2, if allowed to accumulate in the tissues or blood, may affect the character of the anesthesia produced.

THE SYMPTOMS PRODUCED BY NITROUS OXIDE.

I have studied this topic both from the standpoint of animals and from that of man.

A frog placed in an atmosphere containing a high percentage (90% to 98%) of N_2O becomes well anesthetized in from three to four minutes. When again placed in fresh air the animal fully recovers in about one minute. Profound anesthesia is readily obtained.

The symptoms in dogs vary greatly with the animal and the method of administration. Fig. 3 shows a record of the respiratory movements in a dog just beginning to inhale N_2O. The animal was lying quietly on the table and made no resistance in any way. The record was obtained by tying a stethograph around the chest wall and connecting it by rubber tubing to a recording tambour. The first part of the tracing shows the normal respiratory movements when the animal was breathing a sufficient percentage of oxygen and the CO_2 was not allowed to accumulate to excess. At the point indicated N_2O was run into the breathing bag and shortly thereafter the depth of the respiration began to increase. This is mainly due to the action of N_2O. It is the typical effect of this gas on the respiration. There is one other point to be considered in the experiment, however, and that is the fact that in this case when the N_2O was run into the bag then the oxygen which the bag contained was considerably diluted. This would also cause the animal to breathe more deeply. But independently of this dilution of the oxygen, the first effects of nitrous oxide in sufficient concentration appear to be to stimulate the respiratory center. After a time, as the animal passes more fully under the influence of the gas, the depth of the respiration decreases while the rate varies somewhat, but on the whole is accelerated beyond

the normal. This does not seem to be due to any accumulation of CO_2 in the breathing bag or apparatus, for it is very easy to wash out the CO_2 as fast as it is formed. The animal usually does better, however, if a certain amount of rebreathing and CO_2 accumulation is permitted.

These same phenomena occur in the human subject. It is very interesting to experience the beginning action of the gas. If one fills the bag partly full of oxygen and breathes this for a while (washing out the CO_2), he may at first note a very slight sense of fullness in the head and possibly there may be a feeble flushing of the skin especially of the face and neck. Whether this is due to a slight CO_2 accumulation in the lungs (dead space, etc.), caused by the small amount of obstruction to the normal respiration, or is due entirely to excitement or the mere feeling that one "expects something" I have not been able to determine. It is of but little consequence, however, and soon passes off as one ad-

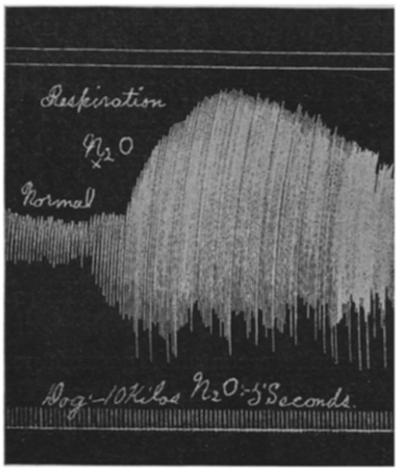

Fig. 3.—This tracing shows the respiratory movements of a dog to which (at X) nitrous oxide (plus oxygen) was administered. There is a slight mechanical exaggeration of the respiration record because the animal had been breathing mainly with its diaphragm before the gas was given, but after this the chest movements became much increased. The stethograph recorded more of the thoracic movements than it did of the abdominal.

justs himself to breathing into and out of the bag. Slight odors, as from a new rubber bag, or of oil from the pump, etc., sometimes cause one to be a little apprehensive. And the mere act of fixing the attention on the respiration is sufficient to cause certain minor variations in most subjects. When the N_2O is turned on, however, there is an immediate feeling of ease in breathing. The sensation can best be compared to the effect of oiling a new machine. One is somewhat surprised how readily he can breathe deeply and fully and without special exertion. This sensation does not occur if one instead of running nitrous oxide into the bag, should fill it to a corresponding degree with oxygen. I have been inclined to believe, therefore, that it is due to a direct stimulation of the respiratory center by the N_2O. I have considered the question of whether or not the processes of diffusion of the gases in the lungs, or the rate or ease of absorption or excretion of the oxygen or CO_2 through the alveolar epithelium might be influenced in any way by the presence of N_2O rather than of nitrogen. I have

not been able to reach any conclusion on these matters. It seems probable that certain obscure changes are produced in the metabolism of the tissues on account of the subnormal CO_2 and oxygen content of the blood, as shown by Kemp. It would be interesting to know whether or not these low percentages of CO_2 and oxygen persist in the blood in those cases in which anesthesia is produced by approximately 80 per cent N_2O and 20 per cent oxygen as in Hewitt's experiments. I have occasionally believed that in rare instances in dogs which were fully anesthetized I could raise the percentage of oxygen in the bag to perhaps 30 per cent without allowing the animal to revive. In this case, of course, while I might markedly increase the percentage of oxygen in the bag, I did not correspondingly lessen the amount of N_2O in the animal and in the apparatus. In this feature there is a great difference between the apparatus which I have here used and most other forms of nitrous oxide machines, for in these if the amount of oxygen administered is increased, this generally means a *corresponding diminution of the amount of N_2O given with correspondingly increased chances for variations in the character of the anesthesia.*

I have noted only occasionally, as have a number of my students, that just as one begins to breathe a fairly concentrated mixture of N_2O, there may be detected a faint metallic sweetish taste on the tip of the tongue. The sensation reminds one of the taste of saccharine. In my own case this taste has never lasted for more than a second or two, but one student was able to detect it over a prolonged period. It is probably due to N_2O carried in the blood from the lungs to the taste organs.

It will be noted from Fig. 3 that the animal did not struggle as the gas was administered. In some cases I have seen dogs go quietly to sleep and apparently never be conscious at all that they were being anesthetized. In a gentle animal which is especially susceptible to the gas, this may frequently occur. It is by no means the rule, however, and there is often struggling especially if the animal was excited before the anesthesia was started. It is well known that certain human subjects are especially resistant to the gas and I have frequently found this to be true for dogs. In some cases I have been entirely unable to obtain any true anesthesia at all. In these cases cardiac slowing and other complications nearly always come on as one attempts to crowd the gas. This appears to be partly due to stimulation of the vagus center in the medulla for section of the vagi usually accelerates the heart and this is generally even more marked after atropine. I have seen three or four especially striking cases of this kind. An animal which is excited or struggles is much more liable to manifest these cardiac symptoms. After atropine the animal usually takes the gas considerably better, indicating better aeration of the blood in the lungs from the improved circulation. The slowing of the heart may be very marked and apparently may be the cause of death in some cases. I have not taken string galvanometer tracings of the hearts of these animals, but this would be instructive. It has seemed to me in one or two instances that peculiar arrhythmical contractions were set up in the heart and that this finally ended suddenly either with complete stoppage of the heart, or with the establishment of a condition resembling heart block. The cause of these reactions is not at all clear. One would suspect a lack of oxygen, or CO_2 poisoning, but when the CO_2 is well washed

out of the gases breathed and the conditions are the same as those under which other animals have been well anesthetized, then one is inclined to look for a difference in the animals. I suspect that very nearly, if not quite this same thing, may have occurred in a few instances in man." For that reason I wish to refer briefly to Fig. 4 which is a tracing of the apex beat of a dog which was given nitrous oxide. The animal was not a good subject, but was finally apparently well anesthetized. After the anesthesia had continued for perhaps half an hour, the pulse in the femoral artery became irregular and finally stopped rather suddenly. With considerable difficulty the animal was revived by means of intermittent compression of the chest. But when the respiration was restored, the animal did not promptly regain consciousness and remained in a semicomatose or somnolent condition for two or three hours. It was noticed about five hours after the animal revived that the heart was irregular and the tracing here shown was made. The animal improved and in about a week the heart had apparently returned to normal. The animal was kept for forty days thereafter, but no further cardiac disturbance was observed.

It seems evident to me that the human subject must be very much more susceptible to nitrous oxide than is the average dog. The anesthesia in all cases is

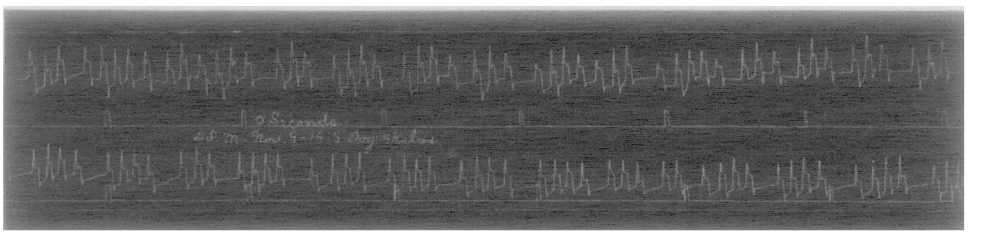

Fig. 4.--Tracings of the apex of the heart in a dog in which under nitrous oxide anesthesia cardiac irregularities developed. For a full description, see text. This tracing was taken about five hours after the animal had been anesthetized. At this time it was observed by Mr. John A. Higgins that the animal was in a dazed or semicomatose condition, and that the heart beat was very abnormal. The record here shown was then made.

of a much lighter form than that produced by ether. In dogs it is as a rule impossible to destroy the corneal reflex, for in the deepest anesthesia in these animals the slightest touch of the cornea or eye lid or even eye lashes causes immediate winking. The eyes remain open and keep up peculiar rolling or staring movements so that one often wonders whether or not the animal is fully anesthetized. If the gas be removed suddenly, however, the animal wakes up and stares about in a way which shows that it had been completely unconscious. During the anesthesia the pupils are dilated but the light reflex is preserved.

THE ACTION OF NITROUS OXIDE UNDER VARYING CONDITIONS.

If pure N_2O be inhaled, unconsciousness results in a period of from thirty to sixty seconds. But if oxygen be added to the inhaled gas, the time required to produce unconsciousness rapidly increases as the oxygen rises from zero up to five, ten or more per cent. With more than ten or twelve per cent oxygen content mixtures of nitrous oxide and oxygen usually produce unconsciousness only after considerable periods or not at all, depending on the patient. There seem to be great variations in this respect, however, in the human subject, and

I have noted a similar reaction in animals. I should like to emphasize this point in particular since it has a direct bearing on the administration of nitrous oxide by the method which I have here used.

It will be noted by reference to Figs. 1 and 2 that there is a considerable "dead space" in the apparatus. The wash jars, tubes, pump, etc., and the breathing bag all represent space which in the beginning contains air. When the animal is connected to the apparatus then its lungs also add "dead space" to the system. This "dead space" contains oxygen and nitrogen. The oxygen can be readily used up by the animal, but the nitrogen must be gotten rid of. The amount of this nitrogen depends on the construction, size, etc., of the apparatus and on the size of the animal. The blood (and tissues) of the animal also contain about 1.7 per cent of nitrogen which presumably diffuses out into the lungs and is then breathed out when nitrous oxide and oxygen are administered. It is necessary to remove a large part of this nitrogen from the apparatus to secure the best success. This is done by filling the bag partly full of nitrous oxide and running the pump for a while. The animal breathes the mixture of air and N_2O and absorbs a portion of the gas, while at the same time some of the nitrogen in its blood is breathed out. The sodium solution and the sulphuric acid in the wash jars also absorb some nitrous oxide. In a little while the bag is emptied out into the air. This is accomplished by opening a valve on the right (positive) side of the machine while the pump is running. In one or two seconds the bag can be emptied as much as desired and then more N_2O is run in until the bag is about one-half or two-thirds full. This is repeated about three or four times as a rule with dogs. One should not hurry this process. It usually takes at least five minutes to anesthetize a dog deeply and any attempt to crowd the gas faster generally excites the animal and does not improve the anesthesia. It is better to proceed slowly and allow the animal's blood to become as nearly saturated as possible for each concentration of the N_2O. In this manner the action of the drug is brought on slowly and in a perfectly successful experiment the animal may be fully anesthetized apparently without being conscious that anything unusual is occurring. Often it is not necessary to give any oxygen until the animal is anesthetized, for the oxygen in the apparatus and in the lungs, etc. ("dead spaces") serves to keep the animal in good condition for some time. When needed, however, more oxygen should be injected.

It may seem that five minutes is an unreasonably long time to require for the production of nitrous oxide anesthesia. We should remember, however, that much more time than this may be required with ether, etc., and when we think of anesthetizing an animal in thirty to fifty seconds with nitrous oxide it is interesting to consider the possibility of doing this same thing with chloroform or ether vapor which are exceedingly well absorbed by the blood. And it is probable that in any rapidly produced nitrous oxide anesthesia there may be a considerable element of asphyxia which is undesirable.

In this connection I should like to refer to some physiological experiments[7] on respiration which involve certain features usually concerned in nitrous oxide anesthesia.

"1. *The Immediate Effects of Total Rebreathing (Due Chiefly to Excess Carbon Dioxide).*—The nostrils are compressed with a nose-clip and the sub-

ject breathes from and into a rubber bag containing 20 to 40 liters of air. The amplitude of respiration is soon augmented, and in the course of a few minutes the subject is panting heavily forty times a minute. He usually develops a typical carbon dioxide headache, but this wears off in fifteen or twenty minutes after the experiment is ended." These results are produced by breathing for a *"few minutes"* into a closed bag. If in addition to these effects, which are due chiefly to carbon dioxide accumulation, there be added the further effects of oxygen want which are usually present from the very beginning in the administration of nitrous oxide, what will be the results of these purely physiological phenomena when complicated by the addition of nitrous oxide in those forms of apparatus in which rebreathing into and out of a closed bag is carried on for considerable periods of time?

"2. *The Effects of Insufficient Oxygen Without Excess of Carbon Dioxide.* —The above mentioned bag is refilled with 20 to 40 liters of fresh air and the experiment performed again, but with this difference, that a vessel of 1 or 2 liters capacity filled with soda-lime or broken sticks of sodium hydrate is placed between the bag and the subject's mouth so that he breathes through it into and from the bag. The carbon dioxide exhaled by the subject is thus absorbed, and he gradually consumes the oxygen in the bag. As a rule there is *no noticeable deepening or quickening of the breathing,* and the subject will first become cyanosed and then unconscious without appreciable augmentation of breathing. This experiment should *always be carefully supervised,* as it is not free from danger. If continued for more than ten minutes, it is usually followed by a severe frontal headache, developing slowly for several hours thereafter, together with other ill effects and lasting from twenty-four to forty-eight hours." It is particularly interesting to consider this experiment in connection with those forms of nitrous oxide apparatus in which the patient inhales the gas (plus a varying but usually small amount of oxygen) from a tank or reservoir and then exhales out into the open air. In these machines the carbon dioxide is probably fairly completely removed as fast as it is exhaled from the lungs. The small percentage of oxygen usually given (e.g., from two to ten or twelve per cent) with the nitrous oxide may cause a rather close simulation of the conditions established in the above experiment in which *cyanosis* and *unconsciousness* may be produced *without any anesthetic.* I should like to give one further quotation bearing on this point from Haldane and Poulton.[8] * * * "Still more sudden exposures to anoxemia occur when air containing little or no oxygen is breathed; for in this case the oxygen previously present in the alveolar air, and even in the venous blood, is rapidly washed out; the result is that consciousness is suddenly lost *without evident preceding hyperpnea,* although abundance of CO_2 is present in the arterial blood. Haldane and Lorrain Smith observed sudden loss of consciousness after 50 seconds on breathing air which was afterwards found to contain 1.8 per cent of oxygen. During any exertion the loss of consciousness is still more sudden. Thus it is a common experience with miners going into an atmosphere of nearly pure fire damp (CH_4), or climbing up so that their heads are in the gas, that they drop suddenly as if they were shot."

I do not care to discuss this point further, but may state briefly that my own experiments, together with the results obtained by others, have led me to

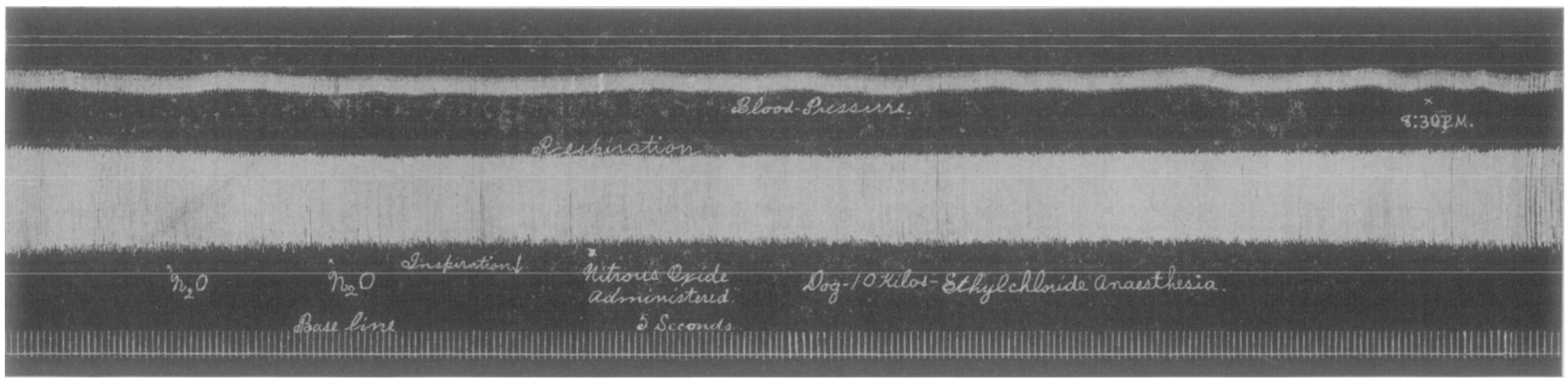

Fig 5.—Blood pressure and respiration in a dog anesthetized with ethyl chloride. At three places, as shown on the record, nitrous oxide was run into the breathing bag. This was done in order to observe the effects of the gas on the circulation and respiration. The results were practically nil so far as can be observed from the record.

conclude that it is impossible to obtain a rapid (1 minute) production of anesthesia and unconsciousness in dogs with nitrous oxide and oxygen at atmospheric pressure unless the oxygen content of the mixture is so low that the loss of consciousness is due *almost entirely* to the lack of oxygen. Presumably, with certain modifications, this is true in the human subject also. On the other hand it seems probable that in all dogs which do not possess a special idiosyncrasy against the gas, mixtures of nitrous oxide and oxygen containing sufficient amounts of the latter to avoid most if not all asphyxial effects, may be used to produce anesthesia *provided sufficient time be allowed for the gas to act and the* CO_2 *be completely removed as fast as it is excreted by the lungs.* If a high per cent of oxygen is used, anesthesia cannot be quickly produced but asphyxia may be avoided. The time required may be considerable, perhaps from five to fifteen

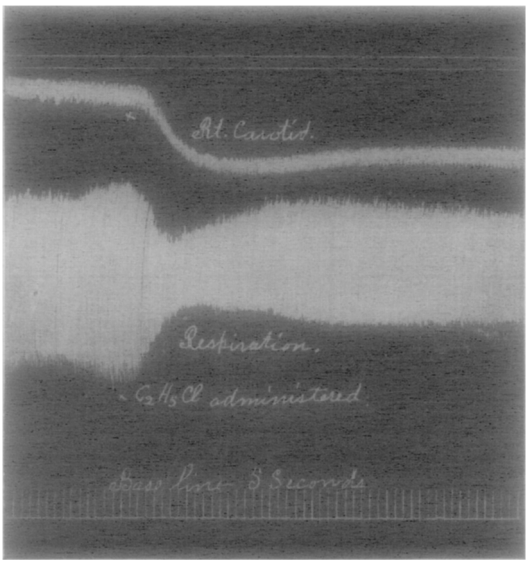

Fig. 6.—This animal was anesthetized with nitrous oxide. At the point indicated ethyl chloride was injected into the bag. There is an immediate fall in pressure and the respiration is much diminished.

minutes or longer. But as the tissues gradually become more and more saturated with the gas, there will be a gradual depression of the central nervous system which will finally result in unconsciousness.

It was long ago observed by Goldstein[9] that anesthesia appears more quickly and with a proportionately less degree of asphyxia, the higher the organization of the brain—namely, earlier in man than in laboratory animals. I have been able to confirm this observation many times. And in addition the anesthesia appears as a general rule to be deeper in man than in dogs, although in some animals a profound anesthesia may be readily obtained if all carbon dioxide effects be carefully avoided.

It seems probable that in average cases the heart and circulation are not much affected by the gas. Fig. 5 shows the result produced by injecting nitrous oxide into the breathing bag when the animal was already anesthetized by ethyl chloride. Three injections were made but the effects on both blood pressure and

respiration were practically nil. This corresponds very well to the injection of an ordinary drug solution into the femoral vein when an animal is anesthetized with ether. (Fig. 6 shows the reverse of this experiment and illustrates the action of ethyl chloride on an animal already anesthetized by nitrous oxide.) As a kind of check on these experiments another tracing (Fig. 7) is shown in which at two places a small amount of carbon dioxide was injected from a tank into the breathing bag. There is an immediate stimulation of the respiration and the blood pressure falls, probably from a direct action on the heart. The gas was quickly emptied out and the bag was again refilled with nitrous oxide plus a suitable amount of oxygen. This shows quite well the action of even small amounts of carbon dioxide. I strongly suspect that some such action as this, either by excess of carbon dioxide, or from lack of oxygen, or both, constitutes the real cause of the undesirable after effects which are liable to follow from pro-

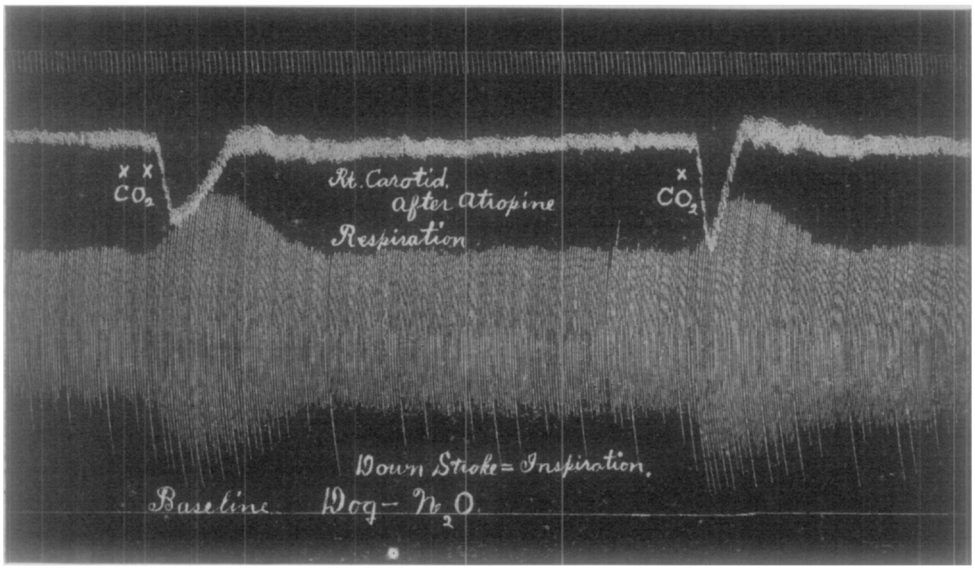

Fig. 7.—This tracing was made in a class experiment by Messrs. Mitchell, Day, Lueking and McKee. It shows the results produced on the respiration and blood pressure by injecting (twice) a small amount of carbon dioxide into the breathing bag while the dog was anesthetized by nitrous oxide. In each case the CO_2 was quickly emptied out of the bag after the animal began to show marked symptoms.

longed nitrous oxide anesthesia. And I am inclined to believe that these after effects may be very generally avoided by a correct and scientific administration of the nitrous oxide.

I have repeatedly observed, as have others, independently in my laboratory, that if one breathes a mixture of nitrous oxide and oxygen for a certain time, for example five minutes, and then passes under the influence of the gas to a given degree, he can then considerably increase the quantity of oxygen in the bag without lessening the influence of the nitrous oxide so far as the subject of the experiment himself can determine. The reason for this appears to be as follows: On breathing the N_2O at first the whole body of the subject after a time becomes saturated with the gas at the given partial pressure. (As the first portion of gas is absorbed, one can see the bag shrink fairly rapidly with ani-

mals.) More N_2O must be run into the bag to replace that absorbed. But after the anesthesia or analgesia has reached a given degree, then if no more gas, but only oxygen, is given, the effects of the N_2O on the subject should remain fairly constant. It will be noted that the gas is excreted only into the bag from which in a given time approximately the same quantity of N_2O will pass back again into the blood. Supposing the bag was filled to the amount of two gallons* with 90 per cent N_2O and 10 per cent oxygen. If then one adds a quart of oxygen to the bag the per cent of oxygen the patient would breathe should be increased by one-ninth of the total amount of mixed gases in the bag after the quart of oxygen is added. It would appear that this oxygen should be readily absorbed by the

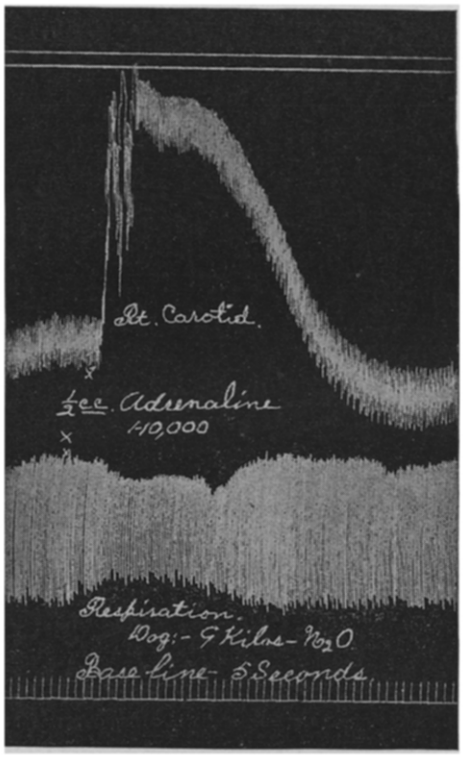

Fig. 8.—The animal was anesthetized with nitrous oxide. At the point indicated adrenaline (½ c.c., 1-10,000) was injected intravenously. The vagi were intact. (For discussion, see text.)

lungs in approximately the same proportion and quantity as oxygen is absorbed by the blood from the air (which contains oxygen in about the same proportion as the bag would now contain it, i.e., about 20 per cent). This would probably not be quite correct, for nitrous oxide has some power to displace oxygen from its solution in water (Sir Humphrey Davy[10]), and this probably holds good for the blood in the pulmonary capillaries also. On the other hand, when the quart of oxygen is run into the bag, the latter will be expanded by a volume equal to one quart and into this space the nitrous oxide already in the bag and also that dissolved in the blood and tissues of the subject, may diffuse. But if, for ex-

*For clearness of description I have assumed that the *volume* of one gallon of the gas may be considered equal to the volume of four quarts. We need not consider variations of temperature, pressure, etc.

ample, the blood and tissues of the subject had absorbed two gallons of N_2O and the bag contained two and one-fourth gallons of (mixed) gases after the quart of oxygen was added, then there would be a chance for the N_2O to be diluted by approximately one-seventeenth of the total volume of gases or 5.8 per cent. At that time the subject might be breathing almost 20 per cent of oxygen and this is readily absorbed by the hemoglobin of the blood. In other words, the relative increase in percentage of oxygen breathed when a given amount of oxygen is added to the bag, is greater than is the relative amount of dilution of the nitrous oxide with which the subject is saturated after the oxygen is added to the bag.

It was shown by Van Arsdale[11] in 1891 that the breathing of nitrous oxide

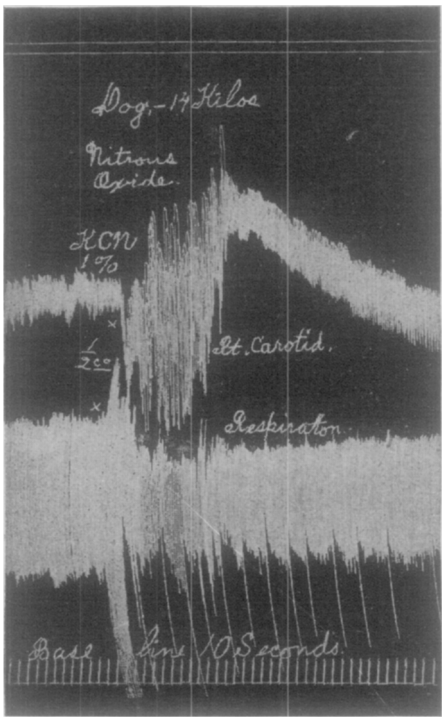

Fig. 9.—Dog anesthetized with nitrous oxide. At the point indicated ½ c.c. of 1% KCN was injected intravenously. The vagi were intact. (For discussion, see text.)

to and fro from a bag in which the gas (plus the desired amount of oxygen) was contained at an increased pressure above that of the atmosphere caused an increase in the depth of the narcosis produced. (This was an entirely different principle from that which Paul Bert[12] and later Claude Martin[13] used in which the patient or animal was placed in an air-tight room, the air pressure in which was raised one-fourth above that of the atmosphere after which 80% N_2O plus 20% oxygen was administered to the patient or animal.) I have tried to verify Van Arsdale's results many times. In some cases (with dogs) increasing the pressure of the gas in the bag does deepen the anesthesia, but in many other cases I have not been able to demonstrate any advantage from this increased pressure.

Perhaps the increased respiratory exertion, the marked hindrance to the pulmonary circulation and the attendant obstruction of gaseous exchange in the lungs were sufficient in many cases to overcome the advantages of the increase in absorption of the N_2O which the raised pressure might bring about.

The intravenous injection of adrenaline in an animal under nitrous oxide anesthesia gives a practically normal reaction, i.e., the record is almost exactly like that produced by adrenaline in an animal under ether. The rise in pressure here probably supplies more oxygen to the brain and whatever asphyxia may have been present from the administration of the nitrous oxide is thereby reduced. (See Fig. 8.) On the other hand, the injection of cyanides (which are supposed to cause an internal asphyxia by lessening the tissue oxidations through inhibiting ferment action) causes a markedly increased reaction both as regards the respiration and the circulation. The animal also shows a more marked convulsive reaction than it does under ether. (See Fig. 9.) I have controlled this

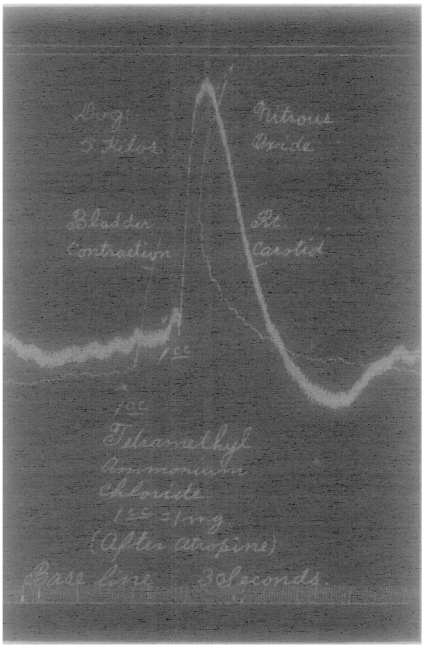

Fig. 10.—Dog anesthetized with nitrous oxide. The tracing shows the blood pressure (Rt. carotid) and the bladder contractions (up-stroke). At the point indicated 1 c.c. of tetramethylammoniumchloride was injected intravenously. The animal had previously received 1½ mgs. of atropine.

by anesthetizing the animal first with N_2O and obtaining records of the blood pressure and respiration from the cyanides and then giving the animal ether, after which more records were obtained.

The motor areas are much more sensitive under nitrous oxide than under ether. One can easily secure very extensive movements of the muscles of the opposite side and can readily pick out the areas for individual groups of muscles. I have observed that dogs under nitrous oxide anesthesia may not well withstand extensive operations, particularly if the abdomen is opened and the viscera manipulated in any way.

In several respects there is a striking similarity between the effects of nitrous

oxide and those of morphine in dogs. Among these may be mentioned the production of Cheyne-Stokes respiration. This is generally present in prolonged anesthesia in dogs. The irritability of the cord is also much less depressed than is the case with the methane series of anesthetics and this action also closely resembles that of morphine. As under morphine defecation also sometimes occurs, but I have generally been inclined to attribute this to asphyxia, although other factors may be involved. A peculiar feature is often noticed in the fact that the dogs, while lying quietly and apparently fairly well anesthetized, may be aroused and waked up by stimulation or shaking in a manner very similar to that possible under a moderate dose of morphine. When thus aroused there is also often observed a marked acceleration and increase in strength of the heart beat. If the animal be again left alone it will soon return into the somnolent, or perhaps analgesic state, very much as occurs after morphine. It is difficult to study the analgesic effect of nitrous oxide separately and apart from the pro-

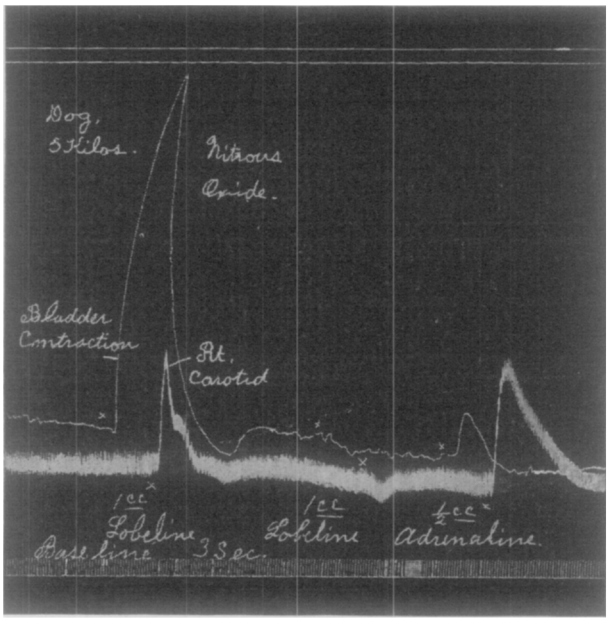

Fig. 11.—Dog under nitrous oxide anesthesia. Bladder contractions (up-stroke) and blood pressure. At the point indicated (on the left) 1 c.c. of lobeline was given intravenously. A marked contraction of the bladder and a small rise in blood pressure were produced. A little later a second dose of 1 c.c. of lobeline was given. Almost no results were produced by this, showing that the first dose of lobeline had produced ganglionic paralysis. Later a small dose (½ c.c.) of adrenaline was injected. This gave a slight bladder contraction and a small rise in blood pressure.

duction of total unconsciousness in dogs, for these animals, so long as they are conscious, are very likely to struggle and try to escape even though they feel no pain whatsoever.

The thought has occurred to me many times that nitrous oxide might be used as a hypnotic. By ordinary methods of administration this is obviously impractical. But by a slight modification of the apparatus which I have used I am inclined to believe this idea might be very well put into practice. I have tried repeatedly to compare the mild on-coming effects of the gas as breathed with a considerable proportion of oxygen with the physical and mental sensations pres-

ent as one begins to fall asleep. There is a very striking similarity, a marked feeling of tiredness and exhaustion, the limbs feel heavy and the eyelids tend to close. One's mentality gradually sinks and there is difficulty in maintaining connected thought. The natural inclination of the subject of the experiment is to lie down quietly and fall asleep. The sensations remind one of the feelings of a child worn out by a long day's play when it lies down at night to sleep. Sometimes I have noted slight muscular twitchings or feeble jumping or convulsive movements. These would probably not occur if the gas were administered very slowly with plenty of oxygen and a sufficiently long period of time were used to bring on the action of the drug. Suggestion appears to play a noticeable part in this action, for if one keeps perfectly quiet and at rest and tries to go to sleep, then the somnolent action of the gas is especially liable to be well marked. It would appear that this matter of suggestion extends even to dogs. For an animal which is petted and induced to lie down quietly and at complete rest may very often take the gas readily and peacefully fall asleep.

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THE HISTORY OF ORTHODONTIA

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(*Continued from page* 509.)

JOHN TOMES (1847) in *"Dental Physiology and Surgery"* illustrates "The Upper and Lower Jaws, with the *full complement* of finely developed teeth," and states:

"The reason for assuming that in these cases the permanent were kept back by the temporary teeth is, that the crown of the former is received between the fangs of the latter, and therefore cannot come through without the previous removal of the superimposed tooth. Again, irregularity in time seldom occurs to the same degree in any of the more anterior teeth, which, when the temporary teeth remain after the usual time for rejection, appear either anterior or posterior to them."

"Another cause of irregularity in the time of eruption of the adult teeth,