The History of Anesthesiology

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Morphine: Part of the Anesthetic Regimen

The Papaver Somniferum

Plate 185, from William Woodville's *Medical Botany*, London, James Phillips, 1793. Courtesy of the Boston Medical Library in the Francis A. Countway Library of Medicine, Boston, MA

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Introduction

Beyond the references in this compilation of papers on Morphine and Anesthesia, a number of other writers from the earliest times onward have linked the two. For example, Pliny, Roman naturalist and author, observed that it was the custom to give such nostrums (mandragora, opium) to subjects, "before the cutting, cauterizing, pricking or lancing of any member, to take away the sense and feeling of such extreme cures". George Wolfgang Wedel in his monograph (Opiologia, 1682) stated that, "Opium in a moderate draught might be given to the patient on the night preceding the operation (amputation), for thus he bears the burning and cutting of the limb, with a readier spirit, and various (unpleasant) symptoms will be averted".

Nussbaum of Munich, before Claude Bernard's experimentation, accidentally discovered that an injection of morphine appeared to intensify and prolong chloroform anesthesia. William Thomas Green Morton who gave the first public demonstration of ether anesthesia on October 16, 1846, in Boston, had experimented with opium and ether before that historic occasion. Another of the pioneers, Walter Channing, Professor of Midwifery and Jurisprudence at the Medical Institution in Cambridge, (Harvard), and author of "On Etherization in Childbirth" (1848) often gave morphine to patients in the first stage of labor. Around the turn of the century, several physicians (Schneiderlin, von Steinbüchel) proposed a mixture of scopolamine and morphine (twilight sleep) for the relief of obstetric labor pains. "There is no new thing under the sun."

Finally, that morphine as an analgesic has survived to the present in anesthetic practice is somewhat surprising in view of its multifold, often adverse effects: respiratory depression, postural hypotension, bronchospasm, pruritus, wheal and flare at the injection site (the latter four owing to histamine release) nausea and vomiting, smooth muscle spasm (biliary tract), urinary retention, and intestinal stasis (smooth muscle relaxation).

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— 1 —

MORPHINE, A NEW SALT-FORMING BASE AND MECONIC ACID, AS THE CHIEF CONSTITUENTS OF OPIUM*

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*Translated from Sertuerner: Ueber das Morphiuim, eine neue salzfähige Grundlage, und die Mekonsäure, als Hauptbestandtheile des Opiums. *Annalen der Physik* 55:56–89, 1817. Reprinted from Keys, TE, Faulconer, A, FOUNDATIONS OF ANESTHESIOLOGY, II, Park Ridge, IL, Wood Library-Museum of Anesthesiology, 1993, pp 1078–1084.

Morphine, a New Salt-forming Base, and Meconic Acid, as the Chief Constituents of Opium*

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About 14 years ago, Mr. Derosne, a pharmacist in Paris, undertook an analysis of opium almost at the same time I did, and he published it in the *Annales de Chimie*, volume 45, 1803. But our results were so different and contradictory that the subject remained largely unsettled. My dissertation, in particular, has received little attention. It was written in a cursory manner; the amounts with which I had worked were small, and it was said that others had repeated my experiment with less fortunate results. Yet, convinced as to the accuracy of my findings in general, and in spite of having undertaken them at a very early age, I believed that it was errors in method which had brought about the failure of others.

Therefore, to resolve these controversies and to correct, if need be, my previous work on opium, I undertook a second analysis of this peculiar plant substance. I was pleased to find that almost all my former observations were confirmed in entirety, and the new data are sufficient to remove all doubts. The following will show that Derosne's method of analysis of opium, as well as his observations, were wrong, and that he did not actually ascertain the active ingredient of opium. What he took to be the active ingredient was a combination of this substance, *morphine,* with the *acid of opium.*

I shall here publish my experiences with the greatest possible conciseness, and I am convinced that the chemist and the physician will read them with benefit. They will throw new light on the main characteristics of these two substances and the mixture of opium. These observations, I believe, will contribute not only knowledge about a *new remarkable plant acid,* but also data on a *new alkaline, salt-forming base, morphine.* The latter is a most unusual substance which, it appears to me at present, is related to ammonia. It may even yield further clarification of the relationships of the other salt bases. It is true that my earlier views about opium and its constituent parts are now confirmed, yet I also found some discrepancies in what I had written previously. These may be excused by my youth at that time, and by the fact that I had done my researches with small quantities.

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* Translated from [excerpts from] Sertuerner: Ueber das Morphium, eine neue salzfähige Grundlage, und die Mekonsäure, als Hauptbestandtheile des Opiums. Annalen der Physik. 55:56-89, 1817.

1. Morphine

1. Eight ounces of dried opium were extracted repeatedly with small amounts of hot distilled water until the latter no longer was colored by the process. After evaporation, a clear extract was obtained from the various samples of fluid which became very turbid when diluted with water; only with the help of heat or by the addition of a larger quantity of water did it regain its transparency.

The extract, diluted with warm water, was then oversaturated with ammonia, whereupon a grayish-white substance precipitated which soon, however, assumed the shape of crystals, displaying transparent granules. These were repeatedly washed with water until they were no longer colored. They represent *morphine,* as will be demonstrated in the following investigations, the true active principle of opium, but still combined with some extractive matter and meconic acid.

2. The dried substance, consisting of nothing but small granules, weighed 16 drams. It was treated with dilute sulphuric acid to a slight oversaturation, and again precipitated from this solution by ammonia. It was then repeatedly extracted with dilute ammonia in an attempt to separate it from other extracted material. Since separation could not quite be achieved in this way, I ground the precipitate down to a fine powder, and extracted this powder several times with very little alcohol, which stained very dark. In that way I obtained about 8 drams of almost colorless morphine.

3. That portion of the morphine which had been dissolved in alcohol was recovered from it by crystallization, but the amount was not of consequence. The extractlike substance which was found with it, in the alcohol, as well as in the extracts containing ammonia, was not a pure extractive matter but an alkaline mixture of extractive matter and morphine, easily soluble in acids. This mixture was only slightly soluble in water, but readily soluble in alcohol. The extractive matter stained iron salts greenish, but also decomposed them at the same time, because of the morphine present. It also separated part of the oxide. Since the pure morphine is separated from its acid solutions in the form of a fine, glimmering powder, and its crystalline form proper is the parallelepipedon, with oblique side planes, it appeared to be the extractive matter, combined with the morphine, which changed the peculiar form of the crystals to this granular, almost cubical, form. This presumption was confirmed when this substance was treated with ammonia. Ammonia dissolved that part of the extractive matter (combined with morphine) which has an acid nature, but ammonia cannot separate it completely from morphine. Alcohol completes the separation and dissolves the remaining extractive matter in combination with morphine. There is a striking difference between the two materials: the one is taken up by ammonia, the other one by alcohol. The former is more readily soluble in water because

it contains less morphine than the brown substance obtained by the treatment with alcohol. In the latter morphine is predominant; therefore, it can be transformed into a resinlike substance in which morphine predominates, forming a basic compound. The concentrated aqueous extract of opium is always broken down into these two compounds by ammonia.

4. In order to make certain that the morphine thus treated was absolutely pure, I dissolved it repeatedly in alcohol and recrystallized it, thus obtaining it in completely colorless and regular, nicely joined, horizontally lying parallelepipedons with oblique side planes. The crystalline substance which Derosne obtained by extracting opium with alcohol, however, has a prismatic form ascending with an angle of 30 to 40°, and stains iron solutions red.

5. *Pure morphine* has the following *characteristics.* It is colorless. Only a small amount is dissolved in boiling water, but it dissolves easily in alcohol and ether, particularly when heated. These solutions taste very bitter, and morphine crystallizes from them in the form already mentioned. The sensitive rhubarb pigment becomes brown in alcoholic as well as in aqueous solutions, and litmus paper, reddened by acids, turns blue again. The ammonia used plays no part in this, since pure morphine does not contain any trace of it, as will be demonstrated sufficiently, in the following, on the basis of treatment of this substance with potassium.* Morphine dissolves very easily in some acids with which I brought it into contact, forming with them specific and entirely neutral compounds which represent a series of peculiar salts. Of these I shall mention the following.

Morphium subcarbonicum is formed when morphine is brought into contact with carbonic acid and when its solution is broken down with potassium bicarbonate; it is more readily soluble in water than is morphine. I could not examine the form of its crystals.

Morphine carbonate crystallizes in short prisms.

Morphine acetate crystallizes in fine rays, and is very soluble.

Morphine sulfate (Morphium sulphuricum) crystallizes in branching rays, and is also soluble.

Morphine hydrochloride (Morphium muriaticum) forms featherlike crystals which often show a radiant formation; it is considerably less soluble than the other morphine salts and precipitates suddenly, when cooled, to a shiny, silvery white, featherlike salt substance, if evaporation proceeds too far.

Morphine nitrate (Morphium nitricum) forms rays which radiate from a common center in all directions.

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* The special property of morphine and of the acidic extractive substances to produce multiple compounds with acid and basic substances includes Derosne's precipitate, sometimes ammonium, sometimes potassium.

I have not examined *morphine meconate (Morphium meconicum);* but *Morphium sub-meconicum* crystallizes in prisms as it is obtained through alcohol from the aqueous extract of opium; it is only slightly soluble and much water is needed to free the residue of opium from it.

Morphine tartrate (Morphium tartaricum) crystallizes in branching prisms, and has much morphologic similarity to the preceding types.

The various *salts* of morphine seem to be very harmful, since I experienced headache each time after I had tasted one of them. They are rather easily soluble in water. Almost all of them have a glimmerlike glare, and they apparently tend to disintegrate.

In the series of salt-forming bases morphine would have to be placed immediately behind ammonia, being separated by the latter from all its compounds. It fits into a series of alkalies, and is distinguished from the potent bases, such as potassium, sodium and ammonia, only by its lesser potency; otherwise it would combine, like the former, with oxidized oil to form soaps. Its affinity to acids is less than that of ammonia, and even less than that of magnesia. But it separates most of the metal oxides from their compounds with acids, such as iron from its compounds with sulphuric acid, hydrochloric acid and acetic acid. It breaks down some of the salts of mercury, lead and copper. Copper acetate thereby loses its green color and probably forms with it a threefold compound like ammonia. It attracts carbon dioxide from the atmosphere, combines with the extractive matter like the other salt-forming bases and forms with it various compounds.

Morphine *melts* easily at a comparatively low temperature, and in this state looks very similar to melted sulphur; when cooled it crystallizes again. It *burns* readily, yielding in heated, closed vessels a firm, dark, resinlike substance with a peculiar odor. In the heat it combines with sulphur, but is broken down instantaneously, forming hydrosulphuric acid. Due to lack of time I have been unable to determine the components of morphine; they probably are oxygen, carbon and hydrogen, perhaps also nitrogen.* A galvanic column combined with a little drop of mercury did not produce any noticeable changes in the morphine; but the circulating drop of mercury appeared to increase in size and its consistency seemed to have changed.

2. Effects of Morphine on the Human Body

The most peculiar feature of morphine is the effect it produces in animals after they have eaten it. To establish its effect with certainty (because animal experiments do not give infallible results), I made experiments on

* I have asked a young man with experience in chemistry, Mr. Lange, to follow up the further reactions of this strange substance to acids, etc., and I hope that he will obtain results which may throw some light on the other salt-forming bases, especially since morphine contains carbon, which we cannot expect in any other salt base. At the same time, he will also describe in more detail some meconic acid salts.

myself and also persuaded several other persons to undergo some trials.

I think it is my duty to draw special attention to the untoward effects of this new drug so that possible accidents may be prevented. It has been asserted, even publicly, that several persons have taken rather large amounts of this agent without any apparent ill effects. If it actually was morphine that was taken in those cases, it must be assumed that the substance is not dissolved in gastric juice. My earlier experience, news of which apparently had not gotten about, had caused me to ask explicitly that the agent be given only when dissolved in alcohol, because it is not readily soluble in water. Hence, it presumably is not dissolved in the stomach without the alcohol.

To test my earlier experiments rigidly, I asked three persons, none of them older than seventeen years, to take morphine with me. Warned by the effects of earlier experiences, I gave each one only half a grain dissolved in half a dram of alcohol, and diluted with several ounces of distilled water. A redness, even visible in the eyes, appeared all over the face, particularly in the cheeks, and the vitality seemed to be increased in general. When another half-grain was taken, half an hour later, this condition became more marked, and was associated with a transient tendency toward vomiting. A dull headache, with stupefaction, was felt. Without waiting to see if other effects, perhaps bad ones, would appear, 15 minutes later we swallowed another half-grain of morphine, undissolved, in the form of a coarse powder, together with ten drops of alcohol and half an ounce of water. The result became obvious quickly in the three young men, and was very drastic. The effect manifested itself in stomach-ache, weakness and marked stupefaction bordering on unconsciousness. I had the same experience; reclining, I fell into a dreamlike state and felt a slight jerking in the extremities, particularly in my arms, which seemed to accompany the pulse stroke.

I became so alarmed by these obvious symptoms of true intoxication and particularly by the weak condition of the three young men that I, only half-conscious, drank a quarter of a bottle (6 to 8 ounces) of strong vinegar and made the others do the same. This was followed by vomiting of such vigor that one of us, whose constitution was rather frail, remained in a critical state of very painful, continuous retching for several hours after the stomach had been completely emptied. It seemed to me that the vinegar gave to the morphine this attribute of causing vigorous and continuous vomiting. With this in mind I gave the subject carbonated magnesia, and the vomiting soon ceased. During the night we slept very soundly. Toward morning the vomiting began again, but ceased soon after a considerable amount of carbonated magnesia had been taken. Constipation and lack of appetite, stupor, headaches and stomach-aches did not disappear until several days had passed.

Even in small doses morphine is a potent poison, as can be judged by our own very unpleasant experience. Its salts may possess an even stronger ac-

tion. The violent reaction to the last half-grain of morphine probably was due to the concentrated state in which it acted upon the stomach, since it arrived there in the form of a coarse powder and was dissolved only in the stomach. Therefore, when morphine is to be used, I recommend that the foregoing data be kept in mind, and that similarly caution be exercised in the use of morphine salts; it is particularly important not to take too little water as a diluent.

Since none of the other components of opium possesses properties like those described herein, it is probable that the therapeutic effects of opium are due to the pure morphine. I must leave it to the physicians to test this. Until now they were using only the salt of the meconic acid and morphine. Possibly we might also expect different therapeutic effects from the various morphine salts. On the basis of my own experience I can report that a very bad toothache, which had not responded to opium, was relieved soon by morphine dissolved in alcohol, even though the concentration of the agent in this solution was low.

My opinion that the effects of the various salts of morphine are different stems from the sensation which they seemed to cause when I merely tasted them. Since morphine meconate, which is the active principle of opium, is not easily soluble in water, pure alcohol must always be used in the tincture of opium. In addition, the tincture should never be allowed to become too cold, for if it does, the morphine will precipitate, together with some fluid resin, extractive matter and meconic acid, and the drug will be found to be weaker in the cold state than when it is moderately warm.

It would be desirable for competent physicians to investigate this subject thoroughly, since opium is one of our most important drugs.

— 2 —

NEW METHOD OF TREATING NEURALGIA BY THE DIRECT APPLICATION OF OPIATES TO THE PAINFUL POINT*

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Art. IV. New Method of Treating Neuralgia by the Direct Application of Opiates to the Painful Points*

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An immense improvement was effected in our treatment of neuralgic affections, when M. Valleix directed attention to the fact, that while, on the one hand, the superficial nerves of the body are of all others the ones most commonly affected with this disease, there are some points of their course in which it is much more liable to be seated than in others, although, in these, no structural alterations can be discovered to account for this liability. These points are usually more or less morbidly sensible to pressure, even in the intervals between the attacks of the sharp lancinating intermittent pain. A very slight touch in these situations is often sufficient to excite acute suffering; in other cases, however, even firm pressure is borne without any complaint. The points in the course of any nerve which are thus liable to be the seat of tenderness are, according to Valleix:

1. The place of emergence of the nervous trunk.
2. The point where a nervous twig transverses the muscles to ramify on the integuments.
3. The point where the terminal branches of a nerve expand in the integuments.
4. The point where nervous trunks become superficial during their course.

It is perhaps scarcely necessary to remark that all these points are precisely those where the nerve tends towards the surface, and therefore where, of course, it is the most amenable to local treatment.

Acting on the result of this observation, M. Valleix introduced a plan of treatment, which, as an external remedy, I have largely employed ever since my attention was first directed to his work in 1842.

It consists in the application of a succession of small blisters *over the points* in the course of the nerves which are painful on pressure. Valleix does not recommend, as a general rule, the application of morphia endermically, but suggests that it may be attempted with advantage in some cases. I have almost invariably employed an ointment containing morphia to dress the blistered surface, and have been accustomed to ascribe much of the benefit of the treatment to this. In some cases, I have seen relief follow the application of an ointment containing strychnine to the blistered surface, but this must be used with great caution, as very disagreeable results often ensue from its use.

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* Edinburgh *Medical and Surgical Journal*, 82:265-267 [265-281] (Apr.) 1855.

It has frequently occurred to me, however, that a more direct application of the narcotic to the affected nerve, or to its immediate neighbourhood, would be attended with corresponding advantage, and as the painful points so frequently correspond with those in which the nerve becomes superficial, I thought this might perhaps be accomplished. In pursuit of this object, I have made several attempts to introduce morphia directly by means of acupuncture needles and otherwise, but without success.

Having occasion, however, about the end of 1853, to endeavour to remove a naevus by injection with the acid solution of perchloride of iron, I procured one of the elegant little syringes, constructed for this purpose by Mr. Ferguson of Giltspur Street, London. While using this instrument for the naevus, it occurred to me that it might supply the means of bringing some narcotic to bear more directly than I had hitherto been able to accomplish on the affected nerve in neuralgia. I resolved to make the attempt, and did not long lack opportunity.

Miss ——, an old lady, who had long laboured under gastric and nervous symptoms, had suffered severely for four days from cervico-brachial neuralgia. This lady had the idiosyncrasy of not being able to take opium. Of this she had warned me many years before, when she first came under my care, and I consequently never prescribed it for her; however, once, when she was seen with me by the late Dr. J. H. Davidson, he, disbelieving her former experience, prescribed opium, with the effect of bringing on a severe fainting fit.

The narration of her case may date from November 26th. She had not been able to sleep for the three previous nights from the violence of the neuralgic pain, and was quite exhausted with severe suffering. The usual internal remedies, with the exception of opium, had been tried, but without the least alleviation of her agony. Under these circumstances, I resolved to put in practice the plan which I had so long revolved in my mind.

Accordingly, on November 28th, I visited her at 10 P.M. to give the opiate the benefit of the night. Having ascertained that the most tender spot was the post clavicular point of Valleix, I inserted the syringe within the angle formed by the clavicle and acromion, and injected twenty drops of a solution of muriate of morphia, of a strength about double that of the officinal preparation.

In about ten minutes after the withdrawal of the syringe the patient began to complain of giddiness and confusion of ideas; in half an hour the pain had subsided, and I left her in the anticipation of a refreshing sleep.

I visited her again about 11 A.M. on the 29th; was a little annoyed to find that she had never wakened; the breathing also was somewhat deep, and she was roused with difficulty. Under the use of somewhat energetic stimuli, however, these symptoms disappeared, and from that time to this the neuralgia has not returned.

— 3 —

ANESTHETICS AND ASPHYXIA BY THE COMBINATION OF CHLOROFORM AND MORPHINE*

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*Translated from Bernard, Claude, *Leçons sur les Anesthésiques et sur l'Asphyxie.* Paris, J.-B. Baillière et fils, 1875, pp 225–241. Reprinted from Keys, TE, Faulconer, A, *FOUNDATIONS OF ANESTHESIOLOGY, II,* Park Ridge, IL, Wood Library-Museum of Anesthesiology, 1993, pp 1098–1107.

Anesthetics and Asphyxia by the Combination of Chloroform and Morphine*

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Gentlemen:

Today we shall study the combined actions of chloroform and morphine. By such a combination an anesthesia is obtained which presents some particular phenomena, and it will bring to light some interesting considerations on the general physiology of anesthetics. We shall see, finally, that this combination offers some invaluable advantages to the practice of experimental physiology and to that of surgery.

Here is how I was led to the discovery of this succession of facts.

Five years ago, in 1864, I was carrying out experiments here on the properties of the alkaloids of opium. A dog was regaining consciousness after it had been subjected to the action of chloroform. The cornea had regained sensitivity, and I injected 5 centigrams of morphine chlorhydrate under the axillary skin. The dog very soon fell into a state of narcosis, which was natural, since it had received the dose of morphine necessary to produce this effect. But, curiously enough, the unconsciousness produced by chloroform returned at the same time. It was not astonishing that both effects should be present, since both substances had been given; but it was more surprising to see the unconsciousness produced by chloroform returning after it had vanished, since no new dose of chloroform had been given that could explain such a return of anesthesia.

The same phenomenon also was observed in a human being by Dr. Nusbaüm,*[1] of Munich, the same week in which I was led by chance to make this experiment. This surgeon was removing a tumor from the neck of a woman. Chloroform anesthesia had been maintained for about one hour and the operation was not completed. Not daring to prolong the action of the chloroform, in fear of a fatal accident, Dr. Nusbaüm had the idea of substituting morphine. Morphine had been used in surgical operations before the discovery of the anesthetic properties of chloroform. However, instead of obtaining only the effects of morphine, he observed that anesthesia caused by chloroform did not disappear, but persisted for a prolonged period.

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* Translated from Bernard, Claude: *Leçons sur les Anesthésiques et sur l'Asphyxie.* Paris, J.-B. Baillière et fils, 1875, pp. 225-241.

* This surname in the original text was erroneously given as "Nusbaüm." The correct surname is "von Nussbaum." He practiced in Munich, Germany. [A. F. and T. E. K.]

These experiments were repeated thereafter on human beings and animals.[2] I proceeded with them from a physiologic standpoint, and I am going to repeat them now in an attempt to explain them, and to see if an understanding of the physiologic mechanism involved can be gained.

First, we must realize that if the experiment we made at first is done in a reverse manner, the results will not be the same. That is, if chloroform is given to an animal already under the influence of morphine, you will perceive that the effects will not be the same, although other very interesting phenomena will be manifested under such circumstances. Here is a dog which has received morphine for some time. The animal is in the state usually produced by the influence of this alkaloid at the beginning of its action: its sensitivity or rather its excitability is greatly enhanced. We now cause the dog to inhale chloroform in a dose much smaller than that which would be necessary to anesthetize the animal in a normal state, and although the sensitivity or excitability of the animal becomes greater than normal, this rapidly disappears. The animal is now under the influence of both morphine and chloroform. To maintain the animal completely under this double influence of the two agents all that is needed is to continue the inhalation of chloroform in very small doses.

You can see how remarkable the action of chloroform is when it is added to that of morphine. I do not know of any other means of immobilizing animals so completely. This enables us to obviate one of the greatest difficulties encountered in physiology when surgical procedures are carried out on living organisms: we now have a means of keeping them inert without abolishing the phenomena of life. The animals, as you can see, fall into a state of absolute relaxation; their limbs become flaccid and can be put into any position; they are like warm cadavers and can be kept in that state for a long time, half a day, if one wishes, which is sufficient for the longest operations.

In physiologic experiments, then, we shall combine chloroform with morphine, but instead of doing what we observed at first—that is, giving chloroform first and then morphine—we shall proceed in a reverse manner, giving morphine and then chloroform, as we have just done in your presence. If chloroform is given first the unconsciousness thus produced lasts a long time because of the influence of morphine, whereas if morphine is given first, consciousness is recovered very soon after the inhalation of chloroform has been discontinued. We thus have a way of surpressing and re-establishing consciousness alternately and rapidly, a very important factor in certain cases. After immobilizing an animal by this means, one can immediately experiment on the state of its consciousness by allowing consciousness to be regained. For example, one can take advantage of the combined effect of chloroform and morphine to open the spinal canal, and then regulate the action of the chloroform in such a manner that the sensitivity of the various

roots, and particularly the return of sensation, can be studied.

We shall now bring to your attention a certain number of experiments carried out under different conditions on animals, by the combination of the effects of chloroform and opium and its alkaloids. After this we shall comment on the applications of the results of these experiments to medicine and surgery.

1st Experiment. A big greyhound dog is caused to inhale chloroform; when the animal is anesthetized we inject subcutaneously 10 centigrams of chloroform. The mask is then removed, and the animal regains consciousness within 3 or 4 minutes. This proves that the subcutaneous injection of chloroform does not prolong anesthesia. When the animal has completely regained consciousness, we inject opium into the jugular, discontinuing the injection at the first cry. The animal first becomes agitated, then quiets down, and *becomes unconscious and not excited.* The intravenous injection of opium has caused the phenomena of chloroform to reappear. In addition, the opium has produced its customary effects: defecation and redness of the skin. Nevertheless, this return to unconsciousness does not last very long; after fifteen minutes the animal becomes excitable again, and consciousness returns within twenty-six minutes. Still, we observe that the corneal reflex of the animal was never absent at any time. The pulse remained at 150.

2nd Experiment. We inject a solution of opium into the jugular vein of a terrier weighing 7 kg., until the animal begins to cry out and to take deep inspirations. Soon the animal is stuporous, although still excitable. We then inject some chloroform under the skin, and notice that the animal does not become unconscious or unexcitable. This proves again that the subcutaneous injection of chloroform does not have much effect. After a few minutes we allow the animal to breathe some chloroform, and it then becomes unconscious and unexcitable. After the chloroform mask has been removed, the animal remains unconscious for a longer period than would have been the case under normal circumstances (about half an hour).

3rd Experiment. A small dog is rendered unconscious with chloroform, and when the corneal reflex is abolished 1 cc. of a saturated solution of morphine chlorhydrate (5 centigrams) is injected into the jugular vein. Neither agitation nor redness of the skin appears. Unconsciousness is deep, complete and dangerous to life. When the chloroform mask is removed consciousness soon comes back. The mask now contains very little chloroform, since none has been added since the beginning of the experiment. The mask is repeatedly applied. It is observed that unconsciousness is then very easily produced each time, after only a few inspirations through the muzzle.

4th Experiment. We now inject 2 cc. of a physiologic solution (N/1) of morphine (1 decigram) into the pleural space of a dog. After eighteen minutes the animal still howls, and is not yet in complete stupor. We then be-

gin to produce ether anesthesia. The dog first becomes agitated and shows no degree of loss of consciousness. If we continue to administer ether the animal still moves, although the hind legs finally become inert, while the forelegs and eyes still remain sensitive. (Ether thus does not seem to exert more effect on dogs that have received morphine previously than it does on animals not so treated.) We then give the animal some chloroform, and almost immediately it becomes inert and unconscious.

5th Experiment. Fifteen cubic centimeters of a saturated solution of morphine chlorhydrate (0.75 gm.) is injected into the jugular vein of a medium-sized dog that previously has received several injections of morphine. The animal first howls, becomes agitated, and when let loose runs away and lies down in a corner of the room as though under stupor. An hour later the animal is put into a retention cradle, on its back. But it does not want to stay there, and jumps down, away from the table. Two days later we inject 2 cc. of the same solution (0.10 gm.) into the trachea of this refractory dog in order to find out whether morphine given by this route has any particular local action, and whether it will produce unconsciousness more pronounced than that which follows intravenous administration. We again obtain very slight anesthesia, the reason for this being without doubt that the animal has become accustomed to morphine. (I shall note in this respect that it has been stated occasionally that the same animal should be used in order to obtain comparable results in different experiments. This principle, however, does not seem to be true, so far as experiments with opium and its alkaloids are concerned. The results of the second experiment are never similar to the results of the first when morphine is used, because toleration of the agent is rapidly developed.) We then give chloroform to the animal in order to find out whether its resistance to morphine will change in any way the effects of anesthesia. This proves not to be the case: the animal is readily anesthetized with chloroform, perhaps even sooner than normally. We carry the action too far, and the animal finally dies of the chloroform. Respiration stopped first, and the heart slowed down and then stopped. We immediately remove the chloroform mask, to find that the heart is still beating, although weakly and irregularly, and that the pulse has become almost unobtainable. Respiration stops for three to five minutes; the heart is beating very weakly when we see that the animal suddenly seems to come back to life. There are about fifteen rapid and noisy inspirations, then the animal collapses and remains unconscious; its heart stops almost immediately. Once the heart has stopped, we endeavor to see whether a spray of cold water directed into the nostrils and ears will revive the animal, but it will not; it is too late. We see, by this experiment, that although chloroform is active in smaller doses when it is used in combination with morphine, it nevertheless can become lethal if sufficient precautions are not taken.

6th Experiment. We already know that rabbits are less sensitive than dogs

to the action of morphine: they sleep with their eyes open and bulging out of the orbit. On the other hand, they are much more sensitive to the action of chloroform, and it is difficult to chloroform them without killing them. Ether generally will suffice to put them to sleep; it is therefore interesting to study the effects of mixed anesthesia.

Into two adult rabbits we inject subcutaneously 2 or 3 cc. of a physiologic solution of morphine (10 to 15 centigrams). After a while the animals finally become quiescent; that is, they remain quietly on the table with their eyes open. But if they are put on their backs they become agitated, and will not remain in that position. While under the influence of a very slight amount of opium one of the rabbits is given ether, and the other chloroform. Both go into a stage of excitement when anesthesia is started, and subsequently both lose consciousness. But the rabbit that was given chloroform dies, whereas the rabbit that was given ether recovers from the anesthesia thus produced.

Hence, although dogs cannot be anesthetized with ether, even when they previously have been given opiates, rabbits can be anesthetized perfectly well under such circumstances.

7th Experiment. A dog is chloroformed to the point at which the corneal reflex is abolished. Then 1 cc. of a physiologic solution of morphine (0.05 gm.) is injected subcutaneously. As soon as the chloroform mask is removed, consciousness returns almost as rapidly as if the animal had not received morphine. Three quarters of an hour later chloroform again is administered to the animal, and at the same time 1 cc. of the solution of morphine is injected. As soon as the animal becomes unconscious the mask is removed. This time the dog remains unconscious for a longer period (approximately 20 minutes), because of a heavier saturation. Yet we perceive that anesthesia is not complete; we find that when the animal is pinched repeatedly it finally cries out. It does not respond to burns in the groins or the snout, although tickling of the flanks brings on reflex movements of the hind limbs. The jaws are completely relaxed; the back of the mouth is not sensitive. These examples show clearly that conditions of combined anesthesia can be as varied as those of ordinary anesthesia, if a strict procedure is not followed and if well-based physiologic conditions are not present. We shall see later how accuracy can be obtained by control of the technic of anesthesia in such a manner that the respiratory phenomenon and loss of the anesthetic agent in turn are controlled. To maintain prolonged anesthesia with safety, it is necessary that the concentration of the anesthetic agent in the blood be maintained at a definite constant.

It was to be supposed that this combination of the effects of chloroform with those of morphine would be useful in surgery, especially when these agents are used as we used them. That is, morphine would be given first, subcutaneously or otherwise, and then chloroform would be administered,

chloroform being active in much smaller doses. By this method anesthesia is produced without occasioning a too-intense stage of excitement, and, above all, without incurring the risk of accidents involved in the use of large and repeated doses of chloroform.

Today we have passed beyond the stage of suppositions: trials have been made by several physicians and surgeons and have been rewarded with success. The results originally obtained by Nusbaüm led him to repeat his trials in three surgical cases, and each time he achieved the same success. In a case of resection of the maxilla the patient was unconscious for eight hours.[3]

Since our first publications[4] in which we demonstrated the advantages of combined anesthesia for surgical procedures on animals, some French surgeons have applied our method in surgical operations and deliveries. A few of these surgeons had witnessed our experiments during our lectures on experimental medicine given at the College of France. These trials, however, have been few and are not well known. That is why we shall report herein the most important documents thus far known to science on the subject.

Mr. Guibert, of Saint-Brieuc, who told me about his first trials as early as 1869, presented the details of them to the Academy of Sciences[5] in 1872.

". . . I have attempted in the past two years," he said, "to use this combination of morphine and chloroform in man.

"I have obtained thereby two distinct states, which are only different levels of the action of chloroform in a person already under the influence of morphine. The first is analgesia and the second is anesthesia.

"1. *Analgesia.* The first effect of chloroform used according to the usual technic, and inhaled by a person who previously has received a hypodermic injection of 1 to 2 centigrams of morphine chlorhydrate, is the production of a state of analgesia. Mental activity, senses and voluntary movements remain intact. This state usually is sufficient to diminish very markedly sensitivity to pain when deliveries and minor surgical operations are carried out.

"2. *Anesthesia.* When the inhalation of chloroform is maintained without interruption for a sufficient period of time, unconsciousness is obtained with anesthesia and muscular relaxation, a state which is invaluable in the conduct of major operations (combined anesthesia).

"Most of the facts that I have gathered concern the first of these stages, analgesia, which as yet has neither been described nor applied to therapy. My observations in at least thirty cases, of which fifteen were deliveries, seem to me to indicate that a state of analgesia can be of great value in the conduct of difficult deliveries, operations in the absence of lesions of the nerve trunks, and in the treatment of very painful conditions such as lead colic and hepatic and renal colic. The dose of morphine used varied from 1 to 2 centigrams. It is more difficult to evaluate the amount of chloroform used because of its evaporation. The following example, however,

shows that the amount of chloroform required is relatively small. A patient suffering from lead colic had only to breathe chloroform from an open bottle and at intervals in order to maintain himself for many hours in a state of analgesia.

"It is especially in difficult deliveries that analgesia seems likely to find routine use. It relieves pain very notably, and can be used for many hours without any danger to the mother; it has no adverse effect upon the child's health, and it does not greatly modify the regular uterine contractions. It does not predispose to the occurrence of hemorrhage in the postpartum period.

"This is how I proceed in deliveries. I inject subcutaneously approximately 1 centigram of morphine chlorhydrate in the forearm when the woman finds it difficult to tolerate the pains of uterine contractions, and when I see the signs of agitation, anxiety and discouragement appear. About a quarter of an hour after this injection I have the patient begin to inhale chloroform in the usual manner whenever she senses the onset of a uterine contraction. After about twenty inspirations of air mixed with chloroform vapor the pain of the contractions subsides, instead of increasing, even though the contractions continue. I have the patient discontinue the inhalation of chloroform as soon as the particular contraction stops. I follow this technic during the entire length of the labor by having the woman breathe chloroform only at the time of the contractions.

"Thus, a state of agitation, anxiety and discouragement is superseded by a contrasting state of quietness, well-being and calm, and the woman is most grateful for it. When the head of the infant bulges in the perineum, when the physician can see that the next pains will be severe, and when analgesia is wearing off, there is no need for reluctance to give another hypodermic injection of 0.5 centigram of morphine. Such a dose, added to the effect of the first one, will suffice to enable the woman to tolerate the excruciating pains associated with passage of the head of the infant, and sometimes it will even abolish these pains.

"Analgesia materially alleviates the state of extreme fatigue that follows difficult deliveries.

"I have received a report of a pelvic version which was effected with the greatest of ease with the aid of this analgesic state for a trunk presentation, and more than 16 hours after the membranes had ruptured. During the version itself the mother was able to answer questions, and yet did not cry out or complain. The combined action of chloroform and morphine completely dissipated the contraction or retraction of the uterus which, under these circumstances renders the version so difficult for the obstetrician and so painful for the mother.

"To the present, at least, this state of analgesia has seemed to me to be rather easy to maintain without reaching the stage of anesthesia, provided

that the inhalation of chloroform is frequently interrupted.

"In a case of amputation of a breast done with the aid of combined anesthesia I observed a marked and progressive slowing of the pulse from 100 to fifty-four beats. Obviously, the patient's life never was in any serious danger. This case demonstrates that a very marked effect is exerted on the circulation, and one which should cause the physician to use caution. Half an hour after inhalation was discontinued the pulse gradually increased to eighty beats."

Labbé and Goujon[6] have presented similar observations to the Academy. On January 27, 1872, on his service at La Pitié, Dr. Labbé did a submalleolar amputation on a young man. Twenty-five minutes prior to the operation 0.02 gm. of morphine chlorhydrate was injected into the medial aspect of the thigh. The administration of chloroform was then begun. A short period of excitation was manifested; seven minutes later the patient was completely unconscious and remained so for a long time after the operation, which lasted seventeen minutes. The amount of chloroform used was 28 gm. This patient, even though complete sensation had not yet returned, answered all questions perfectly well and was fully awake.

On the same day, Drs. Labbé and Goujon proceeded similarly with another patient who underwent a rather prolonged operation (curettage of the greater trochanter). Chloroform was given twenty-five minutes after the injection of morphine. Anesthesia was complete within six minutes. The operation lasted thirty-two minutes, and 25 gm. of chloroform was used. The patient had a rather prolonged period of excitation, but finally became fully relaxed, and did not feel any pain during the entire procedure.

Drs. Labbé and Goujon continue their observations as follows:

"3rd patient. Tuesday, January 30, We proceeded with a patient who was to be operated upon for anal fistula. As did the other two patients, he received an injection of 0.02 gm. of morphine chlorhydrate a quarter of an hour before the operation. The stage of excitement lasted five minutes, and was followed by complete anesthesia. The amount of chloroform used was 18 gm.

"4th patient. A twenty-year-old girl received 0.02 gm. of morphine chlorhydrate by injection before an operation for ovariotomy. Chloroform was administered twenty minutes after this injection. The short stage of excitement was followed in six minutes by complete anesthesia. The operation lasted one hour and forty-five minutes, and 48 gm. of chloroform was used to maintain anesthesia during that time. During the procedure the patient was in a state of complete relaxation. She was very calm when she recovered consciousness after the operation, and said she had not felt any pain during the procedure and was not feeling pain at the moment.

"In summary, despite the fact that these trials are still incomplete, we can make the following statements.

"1. It is possible to obtain anesthesia in man, as shown in animals by Claude Bernard, much more rapidly by combining the action of chloroform with that of morphine.

"2. This form of anesthesia lasts longer, and can be maintained for a long period with small doses of chloroform, thus diminishing considerably the risk of fatal accidents.

"We also believe that the preliminary dose of morphine chlorhydrate could be increased slightly without risk, and that it would be somewhat advantageous to give this injection a somewhat longer time before the operation than we did."

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A STUDY OF MORPHINE, SCOPOLAMINE AND ATROPINE AND THEIR RELATION TO PREOPERATIVE MEDICATION AND PAIN RELIEF*

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A STUDY OF MORPHINE, SCOPOLAMINE AND ATROPINE AND THEIR RELATION TO PREOPERATIVE MEDICATION AND PAIN RELIEF*

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Differing opinions of the pharmacological action of morphine and the atropine group are frequently expressed by our clinical associates. We have therefore studied effects of the hypodermic administration of these drugs to ten normal men, in the following doses:

Morphine Sulphate	gr. 1/4
Scopolamine Hydrobromide	gr. 1/100
Atropine Sulphate	gr. 1/50
Morphine and Scopolamine	gr. 1/4 and 1/100
Morphine and Atropine	gr. 1/4 and 1/50

One one-hundredth of a grain of atropine (0.00064 grams) was found to be almost devoid of effect, either subjective or objective, in three individuals. The dose was therefore increased in the experiments to one-fiftieth of a grain (0.0013 grams). Although clinical experience has taught that morphine is stable for long periods in tablet form, this has not been the case with scopolamine. Only ampules of scopolamine were used. The supply must be from a reliable manufacturer and must not be stored for long periods. Whether the same is true of atropine is not known. Since no ampules were available, tablets of atropine sulphate were used in these experiments.

Respiratory changes and the consumption of oxygen per minute were recorded at one-half hourly intervals before and after administration of the drugs by the use of a Sanborn apparatus ordinarily employed in the determination of oxygen consumption from which the basal metabolic rate is calculated. All readings were taken personally and not by the laboratory technicians. Blood pressures and pulse rate were observed immediately following each record of respiration.

In order to determine the possible variable between normal readings taken during a period of one hour's rest and at the end of a much longer rest period, seven subjects were studied by administration of the drugs at the end of one hour in the dorsal position without movement while three individuals were observed under completely basal conditions; that is, they were required to sleep in the laboratory not taking food or being otherwise disturbed in the morning. One and one-half hours before readings were begun they carefully assumed a comfortable position in bed convenient for the taking of records and maintained it for the period of observation (7 hours).

We have recorded one-half hourly readings before and after drug administration of: (1) systolic and diastolic blood pressure; (2) pulse rate; (3) oxygen consumption; (4) respiratory rate; (5) tidal exchange; (6) minute-volume respiration, and (7) subjective effects. A complete analysis of these data will be published later. Generalizations can be drawn as follows:

1. The most marked changes in both respiration and circulation occur within one and one-half to two hours of administration of all five drugs and combinations.
2. No marked changes in blood pressures occurred in any individual with any drug or combination.
3. The pulse rate increased following morphine, atropine and their combination; whereas the increase in rate was slight or absent following scopolamine alone or in combination with morphine.
4. The respiratory rate was slightly decreased by morphine and slightly increased by scopolamine and by atropine. With the combinations, little change in rate occurred.
5. Tidal exchange was slightly increased with morphine and decreased with scopolamine.
6. Minute-volume exchange showed a definite decrease with morphine in nine of the ten individuals. With scopolamine and atropine, there was a definite increase in a majority of individuals. Morphine and scopolamine showed a moderate decrease early, followed by normal exchange or above. Exchange with morphine and atropine was less than that with morphine and scopolamine.
7. Changes in oxygen consumption were not marked. In the three individuals who were completely basal, a possible 10 per cent decrease or increase in metabolic rate was noted. This change could be explained by variations in depression of activity. Careful mathematical analysis of the figures may shed more light on these data.
8. An outstanding feature of the subjective effects is the predominance of nausea and vomiting in a majority of subjects following experiments in which morphine alone had been given. Nausea persisted in several individuals for six to ten hours after readings had been terminated. It was always relieved in the recumbent position and recurred on resumption of activity. Morphine and atropine was followed by less of this effect and morphine and scopolamine very rarely caused nausea on arising.

Some amnesia was noted in several of the subjects following scopolamine alone or in combination. No amnesia followed morphine

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or atropine. Scopolamine caused definite psychic sedation in all but one subject. He was hyperactive mentally and somewhat disoriented. Psychic or mental effects of atropine were absent.

These experiments seem to us to confirm our clinical belief that morphine when combined with scopolamine in individualized doses serves the purpose of pain relief and preanesthetic medication more satisfactorily than either drug alone or combined with any other agent with which we are familiar. The ratio of morphine to scopolamine found ideal for a majority of individuals is 25:1. The optimum time of administration for premedication before induction with an inhalation agent is at least one and one-half hours since the maximum respiratory changes are found to occur within that period, and desirable sedation and analgesia is maximum at that time while persisting for three to five hours after administration.

It is well known that in a few scattered clinics a combination of morphine and scopolamine has been used as the sole means of producing surgical anesthesia. Since a careful study of the changes in respiration and circulation, accompanying the heavy dosage necessary to produce such a result, has not appeared in the literature, the accompanying

TABLE 1. *Morphine and Scopolamine Anesthesia*

TIME	B.P.	PULSE	O_2	RESPIRATORY RATE	RESPIRATORY EXCH	RESPIRATORY M.V.	
7.15	124/70	88	300	17	350	5950	7.20 MS. 1/4 SCOP. 1/200 7.50 MS. 1/4 SCOP. 1/150
8.20	130/70	100	307	21	290	6090	8.15 MS. 1/4 SCOP. 1/75
9.50	142/80	124	300	15	292	4256	8.50 M.S. 1/4 SCOP. 1/100 9.20 M.S. 1/2 SCOP. 1/50 9.50 M.S. 1/4 SCOP. 1/75
10.10	138/84	124	307	16	360	5760	TOTAL M.S. GRS. 2 SCOP GRS. 1/15 (APPROX) 10.07 OPERATION COMMENCED (VENTRAL HERNIORRHAPHY)
11.15	130/70	132	277	22	260	5720	
12.10	130/80	128	306	21	320	6720	12.27 OPERATION COMPLETED
1.40	120/60	116	280	18	330	5940	

table may be of interest. The readings were made in the same manner as that already described.

It will be noted that a total of two grains of morphine sulphate (0.12 grams) and one-fifteenth of a grain of scopolamine hydrobromide (0.004 grams) were administered hypodermically to this female patient in divided doses over a period of two and one-half hours. Seventeen minutes after the last hypodermic, operation was begun for the repair of a large postoperative hernia of the anterior abdominal wall, an operation requiring as profound anesthesia as is usually encountered. Operation lasted two hours and twenty minutes. The surgeon was not embarrassed by poor relaxation or in any other manner.

The condition of the patient at various periods is represented in the several columns in the table. It will be noted (1) that the changes in blood pressure were not greater than might have been expected to occur during anesthesia and operation, if, for instance, ether by inhalation had been administered. (2) The pulse was definitely increased in rate although not excessively so. (3) Consumption of oxygen, expressed in cubic centimeters per minute, was slightly decreased but certainly not more than might be expected from the decrease in muscular activity accompanying complete bodily relaxation. (4) The rate of respirations, tidal air, and minute-volume exchange were certainly not more variable than might be expected with other methods of anesthesia for such an operation.

Obviously this result could not be obtained with the use of morphine alone nor with scopolamine alone. In other words, we believe it is evident that in certain respects, particularly regarding respiration, there is a balancing effect of one drug against the other, whereas there is an actual additive effect in the direction of satisfactory anesthesia. Atropine, in our experience, has not been a useful substitute for scopolamine.

Anything that has been said is distinctly not to be taken as approval of morphine-scopolamine anesthesia for routine clinical surgery. The method is too time-consuming and exacting for other than experimental use. Exceptionally intelligent and alert management by the anesthetist is necessary to prevent development of dangerous respiratory depression or obstruction in some individuals.

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CLINICAL STUDIES ON MORPHINE I. THE IMMEDIATE EFFECT OF MORPHINE ADMINISTERED INTRAVENOUSLY AND INTRAMUSCULARLY UPON THE RESPIRATION OF NORMAL MAN*

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CLINICAL STUDIES ON MORPHINE. I. THE IMMEDIATE EFFECT OF MORPHINE ADMINISTERED INTRAVENOUSLY AND INTRAMUSCULARLY UPON THE RESPIRATION OF NORMAL MAN *

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IT IS well known that morphine is a respiratory depressant. Because of the increasing use of intravenous morphine in civilian and military medicine (1), it seemed pertinent to measure its effect upon the respiration of normal individuals of varying ages. To complement these data, similar evidence was obtained upon subjects given morphine intramuscularly. Previous quantitative studies of the action of morphine on human respiration have been limited almost entirely to small groups of subjects who have received the drug subcutaneously (2, 3, 4).

Methods.—Twenty-six subjects (3 female, 23 male) received morphine sulfate intravenously; their ages ranged from 19 to 88 and their weights from 42.2 to 87.4 kilos. The six subjects over the age of 70 received 10 mg. (gr. ⅙); the others received 15 mg. (gr. ¼). The drug was dissolved in 2 cc. of physiological salt solution and injected over a period of time ranging from fifteen seconds (4 subjects) to two minutes (22 subjects). Twenty-three subjects (7 female and 16 male) received morphine intramuscularly into the deltoid muscle; their ages varied from 20–88 years and their weights from 47.7 to 99.5 kilos. Eleven of these were given 20 mg. (gr. ⅓), 2 received 15 mg. (gr. ¼), 1 received 12 mg. (gr. ⅕) and 9 received 10 mg. (gr. ⅙).

Each subject lay supine for twenty to forty minutes to obtain semibasal conditions and to become accustomed to the face mask employed. Respiratory minute volume was measured by strapping tightly a half mask (35 subjects) or full face mask (14 subjects) on the subject's face; the subject was then required to breathe through Sadd valves, the expiratory side being connected to a Bohr gas meter. Respiratory rate was recorded by a pneumograph placed on the abdomen or chest. Subjects breathed room air throughout and not 100 per cent oxygen as in other studies (3). While the mask-valve system provided an increase in dead space there was not sufficient accumulation of carbon dioxide to increase respiration. In a control series of 25 subjects breathing through the same masks and valves, the average change in respiratory minute volume was actually —1.3 per cent over a thirty minute period.

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Results.—A. Intravenous injections: The complete data are presented in table 1. The figures are grouped according to (1) control values for respiratory rate, depth and minute volume (average of three to ten minutes before injection of morphine) and (2) post-injection measurements. The latter are divided into (a) "maximal depression" (b) measurements from the third to seventh minute inclusive (average), (c) sixteenth to twentieth minute inclusive (average) and (d) thirty-first to thirty-fifth minutes inclusive (average). The "maximal depression" represents the lowest volume or rate of respiration in any minute in the post-injection period; as such it is not strictly comparable to the control pre-injection figures since the latter represent the average of at least three minutes. Since the "maximal depression" of minute volume occurred between the third and seventh minute in 17 of the 26 subjects and the maximal depression of the rate occurred between the third and seventh minutes in 16 of 26 subjects, average values for these five minutes are presented; they probably represent a truer value of the degree of respiratory depression than do the values for the single minute listed under maximal depression. During the actual injection, subjects often breathed more rapidly and deeply. We could detect no fall in blood pressure at this time (Riva-Rocci method); it is possible that anxiety and nervous tension may have contributed to the hyperpnea.

Minute volume of respiration was depressed 13.6 per cent during the third to seventh minutes post-injection, 13.1 per cent during the sixteen to twenty minute period and 11.6 per cent at the thirty-one to thirty-five minute period. The maximum decrease in minute volume was 40 per cent in subject M. D. Since we were interested particularly in the immediate effects of intravenous morphine, we made no attempt to prolong the measurements over a period of hours. However 17 of the 26 subjects were followed for forty-five minutes, 13 for fifty minutes, 6 for sixty minutes, 5 for seventy minutes and 2 for eighty minutes. In no instance did respiratory minute volumes at these longer intervals differ significantly from the volumes recorded at thirty-one to thirty-five minutes. The maximal depression of minute volume occurred in the three to seven minute period in 17 instances; only rarely did the minute volume decrease progressively throughout the thirty-five minute experimental period.

The decrease in respiratory minute volume was achieved by a decrease in both rate and depth in most instances. Following intravenous morphine the rate was depressed in 18 of the 26 subjects, and increased in 6; there was no change in 2. The depth was decreased in 22 of the 26 subjects, unchanged in one and increased in only 3.

The "maximal depression" figures (showing a 29.7 per cent average decrease in minute volume) are included only to illustrate the gravest situations that were encountered following intravenous morphine in these subjects. It must be emphasized again that these figures are deliberately exaggerated; low single minute volumes are often encoun-

tered during measurements upon normal subjects. However, it was apparent from inspection of the continuous respiratory record that morphine administered rapidly by vein produced more marked respiratory depression for a one to two minute period soon after injection than at any other time during the period of observation. The duration of "maximal depression" was surprisingly transient.

B. Intramuscular injections: The complete data are presented in table 2. The onset of respiratory depression following intramuscular injection was slower and the maximum depression may not have been observed during the thirty minute post-injection experimental period. Maximal depression of minute volume occurred in the three to seven minute period in only 2 of the 23 subjects given morphine intramuscularly (as compared with 17 of 26 given morphine intravenously). Minute volume was depressed on the average 2.7 per cent at three to seven minutes, 11 per cent at sixteen to twenty minutes and 12.4 per cent at twenty-six to thirty minutes.

The decrease in minute volume following intramuscular morphine was achieved mainly by a decrease in rate. Rate decreased in 19 of the 23 subjects. Depth increased in 9 subjects, decreased in 8 and remained essentially unchanged in 6; the average figures show no significant change in depth over the thirty minute period.

Discussion.—The prime purpose of this investigation was to determine whether morphine given intravenously is a dangerous respiratory depressant. The data presented indicate that the maximal respiratory depression following morphine is approximately the same whether the morphine be administered intravenously or intramuscularly. These figures are similar to those obtained by Wangeman and Hawk (3) following the subcutaneous injection of morphine. The depression noted in our studies was probably greater than would occur clinically if morphine were administered to patients with severe pain; our subjects were free from pain and all outside distracting influences. On the other hand, greater depression might be observed if respiratory damage were present at the start, as in cases with cranial injury.

While these studies confirm with quantitative data the respiratory depressant action of morphine in man, they do not contraindicate its use by the intravenous route. Respiratory depression appears to be no greater when morphine is so given. Indeed in one respect morphine appears to be safer when given intravenously, since the full degree of respiratory depression becomes apparent within three to seven minutes in most instances. Following intramuscular or subcutaneous morphine, the depression may gradually deepen over a period of thirty to ninety or more minutes. If the patient given intravenous morphine is watched carefully over a ten minute period post-injection, the maximal depression will usually be noted. The time course of this respiratory depression is also important when morphine is injected intravenously as preoperative medication before general anesthesia; induction of general

TABLE 1

EFFECT OF MORPHINE ADMINISTERED INTRAVENOUSLY ON RESPIRATORY MINUTE VOLUME, RATE AND TIDAL AIR

M.V. = minute volume in cc./minute, R.R. = respiratory rate/minute, T.A. = tidal air in cc. Subjects' age and weight are listed in first column. The last 6 subjects received 10 mg. morphine sulfate; the remainder 15 mg.

	Control			Post-Injection												
				Maximal Depression				3–7 min.			16–20 min.			31–35 min.		
	M.V.	R.R.	T.A.	M.V.	Time (Min.)	R.R.	Time (Min.)	M.V.	R.R.	T.A.	M.V.	R.R.	T.A.	M.V.	R.R.	T.A.
S. M. 22–177 lbs.	7900	15.5	510	4100	16	4	13	6900	10	690	5100	8.4	607	4900	7	700
H. M. 24–135 lbs.	5650	12.8	441	4400	2	12	2	4800	12.2	309	5600	12.4	451	5920	13	455
I. C. 35–185 lbs.	9700	22.4	433	7500	34	18	35	9360	22.4	418	8640	21.2	407	8000	19.2	416
P. R. 19–195 lbs.	10400	25.4	410	8400	9	24	6	9360	26.2	357	9820	26.4	307	10400	27.2	368
A. K. 23–139 lbs.	8250	20.3	405	6000	26	18	22	10500	29.5	356	7400	20.5	360	8200	24.3	335
M. D. 30–115 lbs.	7870	18.4	427	3400	3	10	3	4700	14.6	322	7100	17.2	412	7420	19.2	372
M. N. 24–148 lbs.	8540	7.4	1150	5600	3	6	4	5880	6.6	891	6760	8	845	6480	8.6	741
R. L. 26–180 lbs.	7580	15	506	5200	3	12	4	5800	11.2	518	6680	15.4	433	6640	13.4	480
C. G. 29–120 lbs.	6700	10.2	657	5000	5	9	5	5480	10.4	527	6880	10.8	637	6500	12	541
J. McS. 25–155 lbs.	8150	16	510	4400	7	8	6	6200	11.8	525	7400	15	493	8000	15	533
J. K. 21–136 lbs.	7200	9.4	745	4600	10	9	7	7720	11.4	677	5840	11.4	512	6320	12.6	501
J. H. 23–152 lbs.	5570	6	920	3600	3	4	4	4360	5.2	838	5000	7.8	641	5100	9	566
R. N. 24–140 lbs.	7100	13	546	6000	4	11	3	6320	13	486	6640	13.8	481	6600	13.6	485
E. S. 25–120 lbs.	5760	13	443	4000	11	9	10	5560	10	556	4360	10.8	404	5400	13.2	409
W. C. 26–146 lbs.	8600	12	716	6200	6	14	2	7120	15.6	457	7240	16.6	436	8100	18.6	424
E. H. 30– 93 lbs.	5560	10.3	540	3600	4	8	4	4160	9.2	452	4080	9.2	443	4100	9.8	418
E. J. 30–145 lbs.	7720	9	857	5600	4	7	5	6360	8.2	776	6800	9.8	694	7040	11.2	628
C. H. 23–192 lbs.	9600	15.3	627	7000	3	13	2	8000	14	571	8240	14.4	572	8400	16	525
T. N. 25–152 lbs.	7400	7.3	1000	5400	2	7	2	7000	8.6	814	6760	8.2	824	6800	8	850
J. M. 24–173 lbs.	7420	13	570	4600	3	8	3	5520	10.2	541	6000	11	545	6600	11.4	578
P. C. 74–155 lbs.	9680	15	645	7800	6	12	6	9100	16.6	548	8480	12.6	689	8100	11.4	710
A. P. 75–150 lbs.	10840	12.8	846	8600	5	12	5	9480	13	729	9160	14	654			
H. F. 88–105 lbs.	7744	17.6	440	4800	6	13	5	5720	19	301	6950	15.6	445	6960	13.8	504
H. H. 80–123 lbs.	6876	14.2	484	4200	8	10	12	6240	13.4	466	6400	12.2	524	6400	11.8	542
L. G. 79–150 lbs.	7466	20.8	358	6400	3	16	7	6560	17.8	369	6680	17.2	382	6560	16.8	390
C. M. 76–140 lbs.	8880	15	582	7000	6	14	2	8520	15.2	561	7680	14.4	533	8520	15.6	546
Average	7850	14.2	605	5520	7.4	11.1	6.9	6780	13.6	541	6825	13.6	530	6940	14.1	520
Per Cent Change				−29.7%		−21.8%		−13.6%	−4.2%	−10.6%	−13.1%	−4.2%	−12.4%	−11.6%	−0.7%	−14%
Control 25 subjects	7500	12.9	581											7400 −1.3%	13.1 +1.5%	565 −2.7%

TABLE 2

EFFECT OF MORPHINE ADMINISTERED INTRAMUSCULARLY ON RESPIRATORY MINUTE VOLUME, RATE AND TIDAL AIR

Legends as in table 1. Dose of morphine indicated for each subject in the first column.

		Control			Post-Injection								
					3–7 min.			16–20 min.			26–30 min.		
		M.V.	R.R.	T.A.	M.V.	R.R.	T.A.	M.V.	R.R.	T.A.	M.V.	R.R.	T.A.
B. G.	20–121 lbs. 20 mg.	6300	20.5	367	4700	15.4	305	5300	19	278	4200	16.6	253
M. D.	44–163 lbs. 20 mg.	10900	16.5	660	11600	17.4	666	10600	16.8	630	10750	16.2	663
B. F.	56–162 lbs. 20 mg.	10200	18.5	550	9400	18.2	516	8240	17.8	463	7750	17	455
F. K.	49–175 lbs. 20 mg.	7100	21.5	330	6520	19	343	6620	17.6	375	6720	17.6	381
C. E.	59–219 lbs. 20 mg.	10000	16.1	621	10200	16.8	606	8860	14.8	600	8500	13.2	644
W. P.	61–110 lbs. 20 mg.	7400	17	435	6920	16.8	412	6000	16.2	370	5875	15.7	374
A. B.	58–187 lbs. 20 mg.	9650	22.8	423	7740	15	516	7400	16.8	440	6860	16	428
L. R.	47–170 lbs. 20 mg.	7870	18.7	415	7200	13.6	529	6200	14.5	426	4875	12.5	390
G. B.	54–134 lbs. 20 mg.	10950	18.8	582	10000	16.6	602	8460	15	564	9060	15.4	590
C. C.	61–140 lbs. 20 mg.	8550	16.2	527	7180	17.2	417	6880	17	404	6780	15.6	434
B. R.	56–163 lbs. 20 mg.	7100	22.3	315	7240	21.8	332	6400	18.4	353	6380	17.6	357
M. P.	63–128 lbs. 15 mg.	6370	15	424	6680	16.4	407	5380	14.8	363	5870	15.2	386
W. S.	49–137 lbs. 15 mg.	7970	14.2	563	7100	15.4	461	7400	14.2	521	7600	15.2	500
W. M.	57–130 lbs. 12 mg.	6580	23.7	278	6900	23.8	300	6160	22.2	277	5500	20	275
P. C.	74–155 lbs. 10 mg.	9900	14.1	707	9440	13.8	684	9360	13.2	709	8640	13.6	635
A. P.	75–150 lbs. 10 mg.	8600	14.5	595	10000	15	666	9000	12.5	720	9600	13.2	727
H. F.	88–105 lbs. 10 mg.	5340	18.7	285	5620	19	294	5240	17.5	299	5480	17.5	313
H. H.	80–123 lbs. 10 mg.	10000	24	418	10200	23.8	428	7200	16	450	7900	18	432
L. G.	79–150 lbs. 10 mg.	9140	22.9	400	9160	23	395	8680	21.4	405	8960	21	426
C. M.	76–140 lbs. 10 mg.	11180	17.5	638	11300	18	627	10560	15.2	694	9600	15.2	631
C. R.	68–145 lbs. 10 mg.	7680	20.7	371	8100	21.2	382	7680	20.2	380	7760	19.6	396
L. R.	68–160 lbs. 10 mg.	5110	17	301	6000	17	352	5500	15.8	348	5600	15.8	357
L. C.	68–116 lbs. 10 mg.	6100	18.4	331	6250	18.5	337	6200	17	364	6200	16.6	373
Average		8270	18.6	460	8060	18.0	461	7360	16.7	456	7240	16.3	455
Per Cent Change					−2.7%	−3.2%	0	−11%	−10.2%	−1.0%	−12.4%	−12.3%	−1.0%

anesthesia should be delayed ten minutes post-injection until the maximal depression has been noted. If this precaution is observed, the intravenous route is a useful one prior to general anesthesia, since it enables the anesthetist to avoid the annoying combination of increasing respiratory depression from morphine and the anesthetic agent.

Morphine was given intravenously to 6 subjects over 74 years of age and intramuscularly to 9 subjects over 68 years. The average amount of respiratory depression was less in these patients than the average for the whole series. The dose of morphine was smaller in the aged group; nevertheless they do not appear to possess the great sensitivity to morphine often attributed to them. Cheyne-Stokes respiration, however, did occur in 3 of the 9 subjects given morphine intramuscularly and in 2 of 6 receiving it intravenously. Two of this group breathed periodically before morphine and one of the younger group showed this phenomenon during the light sleep induced in her by the morphine given intravenously. Cheyne-Stokes respiration may occasionally be detected in normal sleeping individuals and does not necessarily indicate severe respiratory damage unless fully developed and prolonged.

The data obtained contradict the statement frequently made that morphine increases the depth of respiration. Depth was decreased in 7 of our 23 subjects given morphine intramuscularly, in 3 of 5 subjects (3) given morphine subcutaneously and in 22 of our 26 subjects given morphine intravenously. Davis (5) noted increased depth of breathing in only 3 of 19 cases of pneumonia following the administration of morphine. In these patients arterial oxygen saturation fell 3.1 per cent. The supposed increased respiratory efficiency brought about by morphine is open to doubt. Increased depth of breathing is often observed in patients receiving an overdose of morphine, particularly when the respiratory rate is depressed to 2–4 per minute. In subject S. M. (see table 1) the rate decreased from 15.5 to a minimum of 4.0 and at this time his depth had increased from 510 cc. to 1025 cc.; the overall effect however was a decrease in minute volume. It appears from the above data that the differential action of morphine upon rate and depth of respiration is dependent upon the type of respiration present, the dose of the drug and the route of administration. It is probably safest to regard morphine as a drug capable of depressing all phases of respiration.

An interesting finding was the statement made by 4 subjects that respiratory effort diminished following administration of morphine. One subject stated that she felt she had stopped breathing, but that she did not care. Another volunteered that "breathing became easy and unimportant." Another felt that he could have held his breath as long as he wanted. These subjective sensations regarding respiration suggest the possibility that the beneficial effects of morphine in the treatment of clinical dyspnea may be related to a sensation that respiration

was easier rather than to any measurable improvement in respiratory function.

Conclusions.—Morphine was administered intravenously to 26 subjects and intramuscularly to 23. The respiratory responses of these normal individuals was measured.

Following intravenous injection morphine produced maximal depressant effects within three to seven minutes in the majority of instances. Respiratory minute volume, rate and tidal exchange were diminished.

The intensity of action of morphine on respiration is not significantly increased by intravenous administration.

The clinical significance of these observations is discussed.

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CLINICAL STUDIES ON MORPHINE II. THE EFFECT OF MORPHINE UPON THE CIRCULATION OF MAN AND UPON THE CIRCULATORY AND RESPIRATORY RESPONSES TO TILTING*

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DESPITE the fact that morphine administered intravenously to dogs produces a marked fall in blood pressure (1), it is generally believed that in man "therapeutic amounts of morphine . . . have little if any effect upon the blood pressure, heart rate or rhythm" (2).

During a study of the effect upon human respiration of intravenously administered morphine (3) certain reactions suggestive of a circulatory origin were reported by our subjects. These included fullness in the head, a sensation of warmth spreading throughout the body, a feeling of faintness, palpitation, vertigo, nausea, and vomiting. Some of these symptoms became evident only when the subject stood up at the end of the study.

Consequently, we decided to investigate the circulatory effects produced in man by the intravenous and intramuscular injection of morphine together with the effect of morphine upon the normal circulatory adjustments to change of position.

Methods.—Each subject lay supine on an operating table, ballistocardiograph or tilt table for twenty to thirty minutes before the control observations were begun. Blood pressure was measured by the Riva-Rocci method with the stethoscope placed over the brachial artery, the arm being maintained at the level of the heart. Pulse rate was counted at the radial artery. Respiratory minute volume was measured by attaching Sadd valves to a full face mask and conducting the expired air through a Bohr gas meter or a delicately balanced spirometer. Respiratory rate was recorded by a pneumograph placed around the chest or abdomen. Cardiac output was calculated by the area method (4) from tracings obtained on the horizontal (5) ballistocardiograph. Morphine sulfate was administered in doses of 10 to 30 mg. When given intravenously, the drug was dissolved in 2 cc. of physiologic saline solution and injected during a fifteen second to two minute period. Intramuscular injections were made into a deltoid muscle.

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The responses to changes in position were observed by placing the subject on a tilt table. This was equipped with a footboard rather than the hip suspension device of Mayerson (6). After a control period, each subject was tilted abruptly to an angle of 75 degrees (head up) for a ten or fifteen minute period (or less if consciousness was lost). The subject was then tilted back abruptly to the horizontal position and after about five minutes morphine was injected intramuscularly. Thirty minutes later, a second tilt was performed. After return to the horizontal position, some subjects were wrapped with elastic bandages from toe to groin and a third tilt was performed.

The subjects ranged in age from 19 to 89 years. All had essentially normal cardiovascular and respiratory systems. They were either normal medical students or patients being studied preoperatively for elective operations. None had been confined to bed for any unusual period of time before the experiment.

RESULTS

I. Circulatory Effects of Morphine Administered Intravenously to Subjects in the Supine Position.

During the intravenous injection of morphine, the pulse was counted frequently in 19 subjects. In 18, the rate increased by 8 to 42 beats per minute; in one (an 89 year old man) there was no change. The average maximal immediate increase for the 19 subjects was 19 beats per minute. Blood pressure was measured in 11 of these subjects during the injection. The systolic pressure increased in 6 (2 to 12 mm. of mercury), decreased in 2 (4 mm. of mercury) and was unchanged in 3; the average change was an increase of 3 mm. of mercury. The diastolic pressure increased in 4 (2 to 4 mm. of mercury) and was unchanged in 7; the average change was an increase of 1 mm. of mercury.*

Cardiac output was measured on the ballistocardiograph during the intravenous injection of morphine in 7 subjects (table 1). It was increased in 6 and essentially unchanged in one. The increase in cardiac output per minute was effected chiefly by the increase in heart rate, for there was no consistent change in stroke volume.

The immediate circulatory changes described were brief. The time required for the pulse rate to return to approximately normal levels was ten minutes or less in 16 subjects, ten to twenty minutes in 2, twenty to thirty minutes in 2 and forty minutes in 1. The cardiac output per minute had returned to control values by the end of the two minute injection period in 2 subjects; when the next reading was taken (at forty minutes after injection) 6 of the 7 had deturned to approximately normal figures.

* Control injections of saline solution intravenously produce no measurable circulatory changes.

TABLE 1

THE EFFECT OF 15 MG. OF MORPHINE SULFATE ADMINISTERED INTRAVENOUSLY ON THE CIRCULATION

		Control	During Injection, seconds			After Injection, minutes					
			60	90	120	5	10	20	30	40	60
H.M.	B.P.	112/64			120/80	120/80	118/80	108/76		110/62	
M—24	P.	62	85	78	72	68	66			60	
5'6"	S.V.	0.34	0.30		0.36						
135 lbs.	C.O.	21	26		26					22	
A.K.	B.P.	102/60		110/64	116/58	116/58	106/68	106/70	106/68	106/68	104/70
M—23	P.	74	102	104	98	86	86	86	82	80	76
5'11"	S.V.	0.27		0.27	0.35						
139 lbs.	C.O.	21		28	34					27	
S.M.	B.P.	98/74		102/72		116/90			108/78	108/78	
M—22	P.	78	108	124	108	96			90	76	
5'9"	S.V.	0.26		0.21	0.21						
177 lbs.	C.O.	20		26	23					18	
M.D.	B.P.	102/60			104/60	104/60	104/64	104/60	110/66	106/66	108/60
F—30	P.	76	88	92	86	88	84	88	88	78	84
5'8"	S.V.	0.36			0.36						
115 lbs.	C.O.	27			31					26	
P.R.	B.P.	98/60	110/64		100/60	98/58		98/60	96/60	96/60	100/66
M—19	P.	78	92	90	90	76		84	72	78	80
6'3"	S.V.	0.26	0.27		0.22						
195 lbs.	C.O.	20	25		20					21	
R.L.	B.P.	108/76			104/76				104/68	104/68	
M—26	P.	70	78	82	82				70	70	
6'2"	S.V.	0.31		0.27	0.28						
180 lbs.	C.O.	22		22	23					24	
M.N.	B.P.	112/70			116/74			112/80		104/74	
M—25	P.	92	108	112	104			80		76	
5'8"	S.V.	0.33		0.37	0.35						
148 lbs.	C.O.	30		42	36					28	

B.P.—blood pressure; P.—pulse rate; S.V.—stroke volume, expressed as cc./lb./min.; C.O.—cardiac output, expressed as cc./lb./min. Sex, age, height and weight of subjects are listed in the first column.

These data confirm the observations of Papper and Bradley (7), and indicate that after the intravenous administration of morphine the only circulatory changes which are significant are the immediate increase in pulse rate and in cardiac output.

II. Circulatory Effects of Morphine Administered Intramuscularly to Subjects in the Supine Position.

Morphine was also injected intramuscularly in 30 individuals; blood pressure and pulse were measured at thirty, sixty and ninety minutes after injection (table 2). There was no significant change in systolic pressure in 23 of these subjects; in 4 the systolic pressure increased

(12 to 20 mm. of mercury) and in 3 it decreased (10 to 20 mm. of mercury). There was no significant change in diastolic pressure in 16, an increase in 11 (8 to 25 mm. of mercury) and a decrease in 3 (8 to 12 mm. of mercury). Pulse increases were noted in only 9 of the 30 subjects. None of the above changes is statistically significant.

III. The Effect of Morphine upon the Circulatory Response to Subjects in the Upright Position.

It is evident from the preceding data that morphine given intravenously or intramuscularly, even in dosage of 20 mg., produced no

TABLE 2

THE EFFECT OF MORPHINE SULFATE ADMINISTERED INTRAMUSCULARLY ON THE BLOOD PRESSURE AND PULSE RATE OF 30 SUBJECTS. DOSE OF MORPHINE INDICATED IN FIRST COLUMN

	Control	After Injection, minutes				Control	After Injection, minutes		
		30	60	90			30	60	90
N.S. M—21 146 lbs. 30 mg.	100/58 60	98/64 72	104/58 60		A.B. F—58 187 lbs. 20 mg.	140/100 88	148/96 84	145/104 76	
J. T. M—23 140 lbs. 20 mg.	122/72 68	114/74 68	124/74 60		G.B. M—57 134 lbs. 20 mg.	120/78 94	128/86 90	114/80 80	
T.B. M—22 170 lbs. 20 mg.	128/66 60	122/64 68	126/68 68		B.R. F—56 163 lbs. 20 mg.	138/95 78	138/92 88	148/100 88	
B.G. F—20 121 lbs. 20 mg.	110/68 68	95/62 66	105/60 66		B.F. M—56 162 lbs. 20 mg.	120/80 98	140/95 88	140/95 84	
J.V. M—21 146 lbs. 20 mg.	118/72 64	118/82 64	124/76 56		I.T. M—23 130 lbs. 15 mg.	118/75 84	112/78 86	108/80 82	
W.F. M—22 170 lbs. 20 mg.	94/66 54	96/66 54	94/66 50		W.S. M—49 137 lbs. 15 mg.	120/70 80	118/72 78	128/78 78	
R.R. M—22 157 lbs. 20 mg.	116/78 60	112/72 72	108/80 60	116/76 64	M.P. F—63 128 lbs. 15 mg.	100/55 64	112/65 70	110/60 68	
R.C. M—22 150 lbs. 20 mg.	120/80 82	116/78 80	112/70 68		C.E. M—59 217 lbs. 15 mg.	148/100 64	148/100 64	145/105 62	

TABLE 2—*Continued*

	Control	After Injection, minutes				Control	After Injection, minutes		
		30	60	90			30	60	90
R.G. M—20 160 lbs. 20 mg.	116/66 66	110/70 70	108/76 76		W.M. F—57 130 lbs. 12 mg.	138/90 84	132/82 88	118/78 88	
I.Z. M—62 168 lbs. 20 mg.	128/80 78	128/90 82	140/95 80		E.B. F—60 115 lbs. 12 mg.	140/80 92	138/80 78	130/75 76	130/75 76
F.K. M—49 175 lbs. 20 mg.	120/90 76	134/100 68	135/98 80		W.D. M—72 160 lbs. 10 mg.	158/72 80	158/70 76	148/72 74	
W.P. M—61 110 lbs. 20 mg.	102/85 92	100/78 80	105/78 84	105/78 84	F.C. M—81 161 lbs. 10 mg.	148/74 72	130/68 70	136/75 60	
C.C. F—61 140 lbs. 20 mg.	145/90 104	140/85 104	138/88 100	135/85 98	L.C. M—68 116 lbs. 10 mg.	124/72 92	118/82 80	118/82 82	120/80 88
M.D. M—44 163 lbs. 20 mg.	110/76 78	105/76 78	115/86 72		L.R. M—68 118 lbs. 10 mg.	100/65 92	105/70 90	105/72 88	110/80 88
L.R. F—47 170 lbs. 20 mg.	108/65 86	106/60 82	110/65 64	112/65 76	H.H. M—80 123 lbs. 10 mg.	180/90 88	180/90 88	170/90 76	

AVERAGE FOR ENTIRE GROUP

	Control	After Injection, minutes		
		30	60	90
Systolic	124.3	123.3	123.7	118.3
Diastolic	76.9	78.2	79.5	77
Pulse	78.2	77.5	73.5	82

important changes in blood pressure in normal supine subjects. So as not to overlook any tendency of morphine to affect the circulation, we decided to impose a strain upon the cardiovascular system by tilting each subject abruptly into the 75 degree head-up position. This produces a sudden displacement of blood from the upper to the lower parts of the body, with a consequent tendency toward cerebral anemia.

Lowering of the blood pressure in the aortic arch and carotid sinuses results and normally this initiates compensatory reflexes which accelerate and augment the heart beat and produce vasoconstriction to offset pooling of blood in the extremities. If morphine depresses the vasomotor center and produces direct vasodilatation in man (as found by Schmidt and Livingston (1) in dogs), these actions should interfere with the compensation to tilting after morphine, and thus reveal a circulatory action of the drug not apparent in the supine position.

Twenty-five subjects were tilted before and thirty minutes after the administration of morphine, each subject thus serving as his own control. All but four subjects were tilted for the same period before and after morphine; these four were tilted longer after morphine because of the presence of signs or symptoms suggesting imminent fainting.

A. Before Administration of Morphine.—The response of our group to tilting was essentially the same as that reported by others (8, 9, 10, 11). One minute after tilting to the head-up position, there was an average increase in pulse of 11.3 beats per minute, an average decrease in systolic blood pressure of 9.7 mm. and an average increase in diastolic pressure of 5.7 mm. of mercury. Two of the 25 (8 per cent) lost consciousness, one after nine minutes, the other after eleven minutes. Of the other 23, 14 were kept in the head-up position for ten minutes and 9 for fifteen minutes without any signs or symptoms suggestive of circulatory collapse.

B. After administration of Morphine.—When the same subjects were tilted thirty minutes after the intramuscular injection of morphine, 11 (44 per cent) either fainted or showed signs and symptoms indicative of imminent circulatory collapse. This occurred in 4, 4, 5, 5, 5, 6, 10, 12, 12, 14 and 14 minutes. It is obvious that morphine does produce circulatory changes in man, but as a rule these changes are revealed only when a strain is placed upon the cardiovascular system.

Certain data upon the 11 "fainters" and 14 "non-fainters" are presented in tables 3 and 4. Examination of data obtained during the pre-morphine tilts shows no important differences between the subsequent fainters and non-fainters that would enable one to predict susceptibility to fainting during the post-morphine tilt. The pre-morphine tilt in the group which subsequently fainted led to slightly less of an increase in pulse rate, a greater decrease in systolic pressure and less of an increase in diastolic pressure in the first minute of tilting, but these changes were not significant.

We were not able to determine from these experiments the predominant site of action of morphine upon the circulation. In 9 of the 11 fainters, the legs and thighs were bandaged from toes to groin with elastic bandages. These subjects were then tilted for a third time (within five minutes after the second tilt) and fainting occurred in

TABLE 3

BLOOD PRESSURE AND PULSE RATE DETERMINATIONS DURING TILT TO THE 75 DEGREE HEAD-UP POSITION BEFORE AND AFTER THE ADMINISTRATION OF MORPHINE SULFATE

Data presented are those obtained from the 14 "non-fainters."

Name, Sex, Age, Weight	Mg. M.S.	Systolic Blood Pressure									Diastolic Blood Pressure									Pulse Rate								
		0	1	3	5	7	9	11	13	15	0	1	3	5	7	9	11	13	15	0	1	3	5	7	9	11	13	15
J.T. M—23	0	116	102	104	98	104	104	108	108	104	70	72	78	80	84	86	88	90	86	76	88	88	92	92	92	92	88	88
140	20	114	104	106	108	106	104	105	102	102	74	80	80	84	84	84	85	84	85	68	88	84	84	84	84	80	80	84
T.B. M—22	0	124	124	122	112	116	110	120	112	116	66	88	90	80	80	88	86	85	80	64	80	76	68	76	72	80	72	88
170	20	122	120	120	128	116	116	114	124		64	82	84	84	78	76	84	84		68	76	76	80	92	92	92	92	
B.G. F—20	0	106	120	112	115	112	110	108			65	75	75	72	78	82	78			68	80	86	90	92	94	94		
121	20	95	105	105	108	108	106	105			62	75	75	80	80	76	75			66	92	96	94	94	96	96		
J.U. M—21	0	118	116	126	124	120	122	124	124	118	70	82	82	82	82	82	82	94	92	64	76	92	84	92	92	92	92	92
146	20	116	124	120	120	120	120	122			80	90	98	96	98	98	96			64	74	80	88	88	84	88		
I.T. M—23	0	112	118	120	120	120	122	122	112	118	75	90	95	86	78	80	82	78	84	82	104	88	88	90	86	92	94	100
130	16	112	110	122	124	120	122	118	115	112	78	75	90	88	85	85	88	88	88	88	126	100	98	100	106	108	86	92
N.S. M—21	0	98	94	98	96	92	94	94	92	86	60	80	70	72	76	70	70	76	76	68	88	100	96	100	96	100	100	96
146	30	98	90	94	98	88	100	100	100	100	64	78	78	82	78	78	74	74	78	72	88	96	92	92	88	100	96	92
W.F. M—22	0	86	76	90	88	90	92	92	90	90	60	62	72	78	68	76	72	76	74	58	82	90	94	90	90	96	96	96
170	20	96	90	92	94	98	98	98	98	98	66	70	72	74	76	82	80	80	80	54	80	90	90	88	86	90	90	88

TABLE 3—*Continued*

Name, Sex, Age, Weight	Mg. M.S.	Systolic Blood Pressure									Diastolic Blood Pressure									Pulse Rate								
		0	1	3	5	7	9	11	13	15	0	1	3	5	7	9	11	13	15	0	1	3	5	7	9	11	13	15
R.R. M—22	0	116	122	110	110	118	120	114	110	110	70	78	82	84	92	96	92	90	92	64	80	76	84	92	88	84	96	94
157	20	112	108	120	120	112	114	120	120	116	70	78	90	88	88	90	88	98	92	72	88	80	84	92	88	92	88	88
W.S. M—49	0	124	100	100	118	112	112				68	75	74	78	75	80				80	88	90	90	96	92			
137	16	118	105	112	118	120	122				72	76	78	80	78	80				78	84	86	88	88	88			
I.Z. M—62	0	130	104	100	110	110	100				80	78	76	76	74	76				88	90	80	76	78	88			
168	20	118	92	104	104	100	100				76	76	76	80	78	80				82	88	88	90	92	86			
F.K. M—49	0	120	115	116	120	115	118	122			80	90	90	90	96	104	110			78	84	84	82	82	78	80		
175	20	120	128	120	118	118	124				88	95	98	102	102	105				72	84	80	80	84	80			
M.P. F—63	0	104	70	95	98	95	86				50	50	55	62	60	55				64	76	82	86	86	86			
128	16	112	90	100	95	90	92				65	60	65	62	60	60				70	72	80	82	80	82			
C.E. M—59	0	146	138	148	150	148	150				102	100	108	105	104	105				66	72	84	70	72	78			
217	16	148	145	145	148	145	138				100	105	105	104	105	105				66	84	78	84	84	88			
W.P. M—61	0	108	105	95	88	92	100				85	90	86	78	80	88				92	100	96	100	100	96			
109	20	105	84	74	84	90	88				78	70	68	74	78	78				84	88	88	92	88	88			
Average		115	107	110							72	79	81							72	85	87						
		113	107	110							74	79	83							72	87	86						

TABLE 4—SAME AS TABLE 3

Data presented are those obtained from the 11 "fainters."

Name, Sex, Age, Weight	Mg. M.S.	Systolic Blood Pressure									Diastolic Blood Pressure									Pulse Rate								
		0	1	3	5	7	9	11	13	15	0	1	3	5	7	9	11	13	15	0	1	3	5	7	9	11	13	15
C.C. F—61	0	145	110	112	106	76	90	?			88	86	82	80	58	80	?			110	118	124	124	124	116	110		
140	20	140	88	95	98	86	70	80	84	68	85	72	80	86	68	60	72	65	62	104	118	118	120	120	116	116	114	114
W.M. F—57	0	138	140	150	152	140	150				90	90	98	100	90	105				82	96	120	104	104	118			
130	12	132	125	138	?						82	102	98	?						88	116	110	62					
M.D. M—44	0	110	110	110	112	112	112				76	80	85	88	88	90				78	86	102	94	90	90			
163	20	105	105	98	102	105	98	70	50		76	80	84	84	88	80	58	?		78	76	88	90	88	84	70	54	
L.R. F—47	0	108	100	100	112	112	112	110	110		65	70	68	70	72	70	74	75		86	90	88	92	90	90	90	90	
170	20	106	90	98	98	95	90	90			60	70	66	70	70	70	70			82	88	90	94	90	90	88		
E.B. F—60	0	146	128	120	130	120					80	90	80	85	84					80	96	96	100	102				
115	12	140	115	100	?						80	85	75	?						70	96	108	?					
A.B. F—58	0	155	125	130	140	136	132				105	100	118	120	118	116				92	100	120	112	114	104			
187	20	148	124	122	114	102	94	80	74		96	94	100	100	94	78	68	64		80	92	96	88	96	92	88	88	
G.B. M—57	0	120	100	100	104	106	100	100			78	80	76	78	82	80	80			94	106	104	106	110	108	110		
134	20	128	108	100	?						86	80	78	?						90	98	104	?					
B.R. F—56	0	138	120	124	128	116	116				95	90	94	90	85	85				78	80	90	88	84	86			
163	20	135	122	116	112	110	110	98	92	92	92	92	88	88	85	85	80	78	78	88	94	94	92	90	90	92	92	90
B.F. M—56	0	125	115	104	106	110	110	110			80	90	84	86	86	88	88			98	96	100	100	120	124	108		
162	20	140	132	108	92	80					95	100	90	78	65					88	92	92	96	64				
R.C. M—22	0	120	110	110	112	118	118	120	114	118	80	85	84	86	84	88	86	86	88	82	106	98	98	98	100	98	98	100
150	20	116	102	102	66						78	90	78	?						76	100	100	50					
R.G. M—20	0	112	120	114	106	103	96	98	80		68	76	70	80	80	76	74	?		66	78	94	96	92	100	92	68	
160	20	108	110	82	74						72	92	64	?						68	80	80	60					
Average		129	116	116							82	85	85							86	96	103						
		127	111	105							82	87	82							83	95	98						

only 2 of these.* While this suggests that peripheral vasodilatation is an important factor, it does not indicate whether this dilatation is due to depression of the vasomotor center or to a nitrite-like action directly upon peripheral vessels. The fact that the immediate pulse increase in response to tilting was greater after morphine than before suggests that the cardio-accelerator centers were not depressed by the drug. It is unlikely that the slight respiratory depression noted following morphine is responsible for the greater incidence of fainting (by a decrease in the thoracic pump mechanism); the decreases in respiratory minute volume, rate and depth were not marked and were equal in the fainter and non-fainter groups.

It is interesting to note that there was a greater tendency to faint in the older age group; 9 of 15 subjects (60 per cent) in the 44 to 63 year group fainted after morphine while only 2 of 10 (20 per cent) of the 20 to 23 year old group fainted. This difference may be attributed to the better muscular tone and consequent better support of the leg veins in the younger group, or to arteriolar sclerosis and decreased efficiency of compensatory reflexes in elderly individuals.

Even in those individuals who did not faint there was a decided difference in the circulatory reaction to tilting between the young and the old. The older subjects showed less of a compensatory response, i.e., a greater drop in systolic pressure and less of a rise in diastolic pressure and pulse rate (table 5).

TABLE 5

MAXIMUM CHANGES IN SYSTOLIC AND DIASTOLIC PRESSURE AND PULSE RATE DURING CHANGE FROM HORIZONTAL TO 75 DEGREE, VERTICAL POSITION. CHANGES EXPRESSED IN PER CENT OF PRETILT CONTROL VALUES

Only those subjects in table 3 (non-fainters) are included.

		Before Morphine, per cent	After Morphine, per cent
Systolic pressure	Young	− 6.0	− 3.7
	Old	−14.4	−14.3
Diastolic pressure	Young	+28.7	+24.5
	Old	+12.4	+ 6.5
Pulse rate	Young	+36.5	+41.7
	Old	+18.4	+22.5

A final observation of interest was the finding that blood pressures readily heard with the subject supine would often be difficult to obtain when the erect posture was assumed. This change in auscultatory findings was not related to a change in level of blood pressure. Oliver commented on this curiosity in 1895, citing evidence to suggest that the difference was due to constriction of the artery (12). The possibility

* It has been shown in other experiments that repeated tilting within the course of 1–2 hours does not change the subject's reaction to tilting. Therefore the improvement brought about by bandaging should be regarded as significant.

of increased muscle tone in the arm with consequent displacement of the vessel should also be considered.

IV. Effect of Posture on Respiration.

In the course of these experiments, considerable data were obtained upon the effect of posture on respiration. This is a subject of considerable theoretical and practical importance, especially in view of the current interest in resuscitation by tilting methods. Respiratory measurements were made during 42 tilts upon 16 subjects. In table 6 are shown respiratory minute volumes and respiratory rates in the control period in the horizontal position, in the first minute after tilting to the head up position, in the last minute in this position and in the first minute after return to the horizontal position. (No figures have been included in the latter 2 columns "vertical to horizontal tilts" for subjects who had fainted or were about to faint just before the return to horizontal position; these will be referred to later.) Three significant trends are shown by these data. (1) Upon tilting from the horizontal to the 75 degree head-up position, the respiratory rate *immediately* decreased in 28 of 39 measurements (average decrease from eighteen to sixteen per minute in the entire group) and the minute volume decreased slightly. These changes were most consistent and marked in the 16 subjects tilted before administration of morphine; in these the average decrease in rate was from 20.1 to 17.1 and in minute volume from 8.9 to 7.6 liters per minute. (2) As the tilt continued the respiratory rate and depth gradually returned to the control (horizontal) figures. By the end of the ten or fifteen minutes in the tilted positions no further changes had occurred in respiration such as those in heart rate. (3) Upon termination of the tilt, respiratory minute volume increased *immediately* in each subject. The average increase before administration of morphine was from 9.2 to 11.8 liters per minute, an increase of 28 per cent (maximal increase was 4.8 liters or 87 per cent); quantitatively, similar changes occurred when the tilt was performed after morphine. This increase in respiration was accomplished chiefly by an increase in the depth of breathing.

Alterations in respiration occurring during change in posture might be caused by several factors: (1) carotid sinus and aortic arch pressure reflexes, (2) changes in cerebral blood flow or (3) lung reflexes. The first may be discounted since tilting from the horizontal to the feet-down position would tend to decrease the pressure in the carotid sinus and aortic arch, decrease inhibitory reflexes to the respiratory center and so accelerate and augment respiration (13). The observed respiratory changes, both at the initiation and end of the tilt, are exactly the opposite of what would be expected on a pressure receptor reflex basis. The second possibility may also be dismissed since a decrease in cerebral blood flow should augment breathing, and vice versa (14); again the observed changes are exactly opposite. It is probable that the respiratory changes are the result of vagal Hering-Breuer re-

TABLE 6

RESPIRATORY RESPONSES TO TILTING. MINUTE VOLUMES OF EXPIRED AIR EXPRESSED AS LITER/MINUTE

Hor. = data obtained during control period in the horizontal position, and in the first minute after return to the horizontal.
Vert. = data obtained during first minute after tilting to the 75 degree head-up position, and during the last minute in this position.

Subject	Before Morphine								After Morphine								After Morphine and Bandages							
	Resp. Min. Vol.				Resp. Rate				Resp. Min. Vol.				Resp. Rate				Resp. Min. Vol.				Resp. Rate			
	Hor.	Vert.	Vert.	Hor.	Hor.	Vert.	Vert.	Hor.	Hor.	Vert.	Vert.	Hor.	Hor.	Vert.	Vert.	Hor.	Hor.	Vert.	Vert.	Hor.	Hor.	Vert.	Vert.	Hor.
B.G.	7.3	5.6	6.0	7.4	23	14	19	18	4.8	4.1	4.4	6.0	16	14	17	17	4.3	4.2	5.5	5.6	18	15	16	23
J.U.	8.9	8.9	9.5	12.5	16	15	14	15	5.7	5.8	8.0	10.8	11	9	16	16								
W.S.	8.1	6.2	8.1	11.7	15	13	16	17	7.9	7.4	7.8	11.6	17	14	15	17								
I.Z.	10.6	9.0	11.6	14.8	26	22	23	31	8.4	7.9	10.8	12.5	20	16	20	25	9.8	8.6	10.2	12.2	22	18	24	24
F.K.	7.2	5.8	9.6	12.4			20	21	6.7	5.6	8.5	13.1	20	13	16	17	8.4	7.1	6.8	10.8	17	17	15	19
M.P.	6.3	5.5	5.5	10.3	16	14	16	20	6.5	4.8	6.0	8.2	16	12	13	15								
C.E.	10.5	10.9	12.2	15.0	18	16	15	17	8.9	10.5	10.5	11.5	13	16	15	15								
W.P.	9.8	6.0	8.5	10.5	20	17	19	18	8.2	6.9	6.9	8.9	16	21	21	17								
C.C.	9.8	8.0	5.7	8.9	22	17	18	19	8.7	6.1			17	13			7.0	5.9	7.4	9.0	21	19	19	20
W.M.	7.0	5.4	7.1	8.2	25	18	24	23									5.2	7.0			21	23		
M.D.	11.0	10.7	13.6	14.8	17	14	19	20	10.1	8.5			16	14			8.4	7.2	9.8	12.2	17	18	18	18
L.R.			9.0	11.7			16	18	5.1	5.2			13	8			5.3	6.4			10	9		
A.B.	9.8	7.8	9.7	12.5	23	19	20	19	7.1	8.0			17	16			7.7	9.0	7.1	12.0			16	14
G.B.	10.0	10.2	12	14.1	16	19	19	19	8.3	9.7			14	15			8.9	8.3			15	17		
B.R.	7.4	7.6	8.5	10.5	24	24	24	24	6.0	5.9			16	18			7.3	5.0	5.4	8.3	18	16	17	16
B.F.	10.4	8.0	11.0	13.0	20	17	22	22	7.8	6.3			18	16			7.3	6.7	7.8	11.4	17	17	17	15
Average	8.9	7.6	9.2	11.8	20.1	17.1	18.8	20.1	7.3	6.9	7.8	10.3	16.1	14.4	16.7	17.4	7.3	6.9	7.5	10.2	17.6	16.9	17.8	18.6

flexes. In the feet-down position, the abdominal viscera slide down, pulling the diaphragm with them and thus causing the lungs to assume an inspiratory position. This leads to a slower respiratory rate. Upon return to the horizontal position the diaphragm moves upward and compresses the lungs, tending to augment respiration. However, the increase in minute volume at the termination of the tilt was much more marked and consistent than the decrease at the initiation of the tilt. Clearly, another factor must play a role at the termination; this is believed to be the result of sudden shift of a large volume of blood pooled in the lower parts of the body during the tilt (17, 29) to the lungs, with consequent pulmonary vascular congestion (15, 16, 30). The extent to which blood may be removed from the active circulation by tilting is indicated by the data of Asmussen (17) who measured leg volume with a plethysmograph and found that at a 60 degree head-up position, 550 cc. of blood could be immediately trapped in the legs alone.

V. Effect of Fainting upon Circulation and Respiration.

In these experiments, data were obtained upon 15 instances of fainting or imminent fainting (2 before morphine and 13 after morphine) in 11 subjects. The pulse at the moment of loss of consciousness was below 70 in 7 cases (68, 64, 62, 60, 58, 54 and 50), above 80 in 6 (82, 88, 88, 90, 110, 114): in 2 the pulse was imperceptible at the wrist at the moment of fainting but had been 108 and 104 a minute before syncope (table 7). The high incidence of pulse slowing at or near the moment of fainting has been described frequently (18, 19). Similar slowing occurs with the cerebral anemia attendant upon increase in intracranial pressure (20, 21) and upon hemorrhage in the supine position (22). The mechanism of this slowing is not known. One would expect that, as the blood pressure approaches shock levels, release of the inhibitory influences from the pressure receptors should lead to maximal pulse acceleration. Some new and more potent factors must supersede these reflexes in cases of cerebral anemia resulting from tilting, increased intracranial pressure and hemorrhage; why they do not slow the pulse in traumatic shock is unknown.

While fainting was often heralded by complaints of weakness, vertigo, anxiety and by pallor, sweating and coolness of the hands, in 6 instances the systolic blood pressure level fell very abruptly and there was little or no warning of imminent syncope. The diastolic blood pressure reading also fell abruptly in 8 subjects.

Respiration was measured in 11 tilts upon 8 subjects (1 before and 10 after morphine) at the moment of fainting or imminent syncope, with the subjects still in the feet-down position. The figures are shown in table 7 along with simultaneous arterial blood pressure measurements. The remarkable feature to be noted is the absence of marked hyperpnea. The maximal increase was from 10.1 to 15.1 liters and the average was from 7.7 to 9.2 liters per minute, an increase of only 20

per cent. At the same time the systolic pressure had decreased below 60 mm. of mercury in 4 instances and the average blood pressure fall was from 129 to 71 mm. systolic and 83 to 63 mm. diastolic. At least two mechanisms might be expected to augment respiration markedly in response to a falling blood pressure. Experiments on dogs indicate that the carotid sinus and aortic arch pressure receptors are capable of increasing respiration reflexly when arterial pressure decreases (13).

TABLE 7

BLOOD PRESSURE, RESPIRATORY MINUTE VOLUME AND PULSE RATE IMMEDIATELY BEFORE FAINTING

Subject	Blood Pressure		Pulse		Respiratory Min. Vol.	
	Control	Last Minute	Control	Last Minute	Control	Last Minute
CC*	145/88	82/70	110	110	9.7	7.3
CC	140/85	68/62	104	114	8.3	8.0
WM	132/82	<82/60	88	62	6.4	7.2
WM†	118/74	58/?	82	58	5.8	8.0
MD	105/76	50/?	78	54	10.1	15.1
LR	106/60	<90/70	82	88	5.1	11.0
AB	148/96	72/62	80	88	7.1	7.4
GB	128/86	<90/66	90	—	8.3	12.0
GB†	125/84	40/?	80	82	8.8	9.0
BR	138/92	92/78	88	90	6.0	8.1
BF	135/92	56/40	88	64	7.8	8.0
RG*	112/68	80/?	66	68	—	—
RG	108/72	74/?	68	60	—	—
EB	140/80	?/?	70	—	—	—
RC	116/78	66/?	76	50	—	—
Average	126/81	<71/63?	83	76	7.7	9.2

* Before morphine.

† After morphine and application of elastic bandages. All others—after morphine but before application of bandages.

Respiration has also been shown to increase under similar conditions even when the pressure receptors are completely denervated (23); this change was thought to be brought about by a decrease in cerebral blood flow which permits an accumulation locally of the metabolites constantly being formed within the respiratory center in the medulla (24). Regulation of respiration by alterations in cerebral blood flow is regarded by some (14, 24) to be of prime importance in the control of normal breathing. However, enough data are presented here to indicate that the peripheral pressure receptors and the central regulatory mechanism either do not respond well in unanesthetized man or are suppressed during cerebral anemia. It is significant that the anticipated increase in pulse rate is often lacking under these same conditions. It should be pointed out that the chemoreceptors of the carotid and aortic bodies are not concerned in this response to low blood pressure, since the arterial oxygen tension remains normal.

While we have insufficient information upon respiration during fainting in normal non-morphinized individuals, our 1 case suggests that the failure of respiration to respond more vigorously to cerebral anemia is not attributable to the action of morphine upon the respiratory center.

DISCUSSION

While it may be reassuring to clinicians to know that morphine given intravenously to normal supine patients does not produce the fall in blood pressure so characteristically seen in dogs, this does not mean that the drug has no effect upon the human circulation. During or immediately after an intravenous injection of morphine, both pulse rate and cardiac output per minute increased significantly. The cause of this circulatory effect is not clear. No drop in blood pressure could be detected at this time, using the Riva-Rocci technic.

It is possible that the compensatory mechanisms of unanesthetized man are more sensitive than the methods ordinarily used to measure blood pressure. Thus, reflexes from the pressure receptors of the carotid sinus and aortic arch areas may initiate reflexes for the stabilization of blood pressure even though little change in arterial pressure is noted by clinical measurements. On the other hand the increase in pulse rate and cardiac output which immediately followed the injection may have been caused by a cerebral action of morphine similar to that produced by other narcotics or anesthetics, i.e., the response being a reaction to the feeling of vertigo or imminent syncope. That it was not a result of anxiety about venipuncture is evident from the absence of changes in the pulse rate following the intravenous injection of physiologic saline solution.

Although the circulatory effects of morphine are unimportant in the normal supine individual, they assume much more significance when the circulation is put under a strain. A great increase in the incidence of fainting or circulatory collapse resulted from tilting head-up after the injection of morphine. This may be caused by a number of factors, such as decreased skeletal muscle tone, diminished respiration (3), depression of carotid sinus and aortic arch reflexes, depression of the vasomotor center, increased capillary permeability with loss of circulating fluid, or peripheral vasodilatation. Of all these factors, the last named is in our opinion the most important. The immediate response of pulse, systolic and diastolic blood pressure to tilting was not greatly different after morphine; this excludes marked depression of the pressure receptor zones and of the vasomotor center. While increased capillary permeability in the dependent areas may be an important factor when tilting is carried out for long periods (17), its effect cannot be great in a subject who fainted four minutes after tilting. If direct peripheral vasodilatation is the predominant factor, morphine consequently has a circulatory action similar to that of histamine (1) and the nitrites (25).

The influence of drugs upon the circulatory compensation in response to the erect position has not been studied extensively. The ability of various sympathetic amines to prevent orthostatic hypotension is well known (26). Weiss (25) has reported upon the action of sodium nitrite in inducing orthostatic collapse. Hill in 1895 (27) reported that chloroform rapidly paralyzed compensatory vasomotor mechanisms in dogs (the animals dying when the head was raised) and Gordh (28) has noted the effects of ether and short-acting barbiturates upon the response to tilting. It is particularly important that the effects of sedatives, analgesics and anesthetics upon the circulation be studied since these substances are often employed in individuals suffering from shock and hemorrhage.

Our results indicate that movement of a "morphinized" patient from the supine to the sitting or semi-erect position may be followed by vascular collapse. During operations performed with the patient in the sitting position, the surgeon or anesthetist must bear in mind the possibility of sudden vascular collapse if large amounts of morphine (and presumably other narcotics) have been used, particularly in elderly patients. In our clinical experience, vascular collapse occurs less often in such operations (such as section of the fifth cranial nerve for trigeminal neuralgia) if ether is used than if morphine and regional block are employed; this may be the result in part of the stimulating effect of ether upon the sympathetic nervous system (31, 32). Hill (27) also noted that ether paralyzed compensatory mechanisms very slowly and only when given in large amounts.

Our results also indicate that injured individuals given large doses of morphine should be transported by litter and not by "passive walking" between attendants. It is probable, in addition, that shock and hemorrhage impose strains upon the circulation analogous to those produced by our tilting experiments and if our interpretation is correct, morphine given in large amounts to patients with surgical shock or hemorrhage would be expected to aggravate the circulatory inadequacy. The same may be true of other conditions in which impairment of vascular regulatory mechanisms has been shown to occur, such as in certain types of heart disease, hypertension, thyrotoxicosis, neurocirculatory asthenia and following dorsolumbar sympathectomy (26). Finally, when a patient must be operated upon in the sitting position it might be of value to test preoperatively his response to tilting after morphine.

The data likewise demonstrate that prevention of pooling of blood in the extremities by bandaging of the legs (8, 33) is of real therapeutic value; 9 of 11 subjects (who fainted when tilted after morphine) did not faint when retilted after application of elastic bandages. Others have suggested that resistance to orthostatic circulatory collapse may be increased by "training," either by graduated periods in the head-up position (33) or by improvement of muscle tone through exercise (8,

11). Bandaging is obviously a more practical emergency or preoperative measure than these others.

Since warm environments predispose to circulatory collapse on tilting (16), it is likely that the hot humid environment of many operating rooms may be a factor in vasomotor collapse.

It appears, then, that bandaging of the legs, a temperate environment, and a supine or slight Trendelenburg position may prevent vascular collapse following strains upon the circulation imposed by morphine, hemorrhage, shock, the erect position or combinations of these. Sympathomimetic drugs may also be employed.

The respiratory responses to tilting from the vertical to the horizontal are of interest chiefly in that they supply an indication of the magnitude of the reflex respiratory response to sudden pulmonary congestion. In addition, it is noteworthy that the respiratory centers do not respond more vigorously to a marked fall in blood pressure level and presumably in cerebral blood flow.

CONCLUSIONS

1. The effect of morphine upon the circulation of man in the supine and erect position has been studied.

2. Morphine injected intravenously produces an immediate but transient increase in pulse rate and cardiac output.

3. Morphine administered intramuscularly or intravenously has no significant effect on blood pressure level while the subject remains supine. When the 75 degree head-up position is assumed, a circulatory action of the drug becomes apparent. This is manifest by an increased incidence of fainting in response to this postural change.

4. The clinical implications of these findings are discussed.

5. Data are presented on the circulatory and respiratory responses at the time of fainting.

6. The respiratory response to change in position has been measured.

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N-ALLYL NORMORPHINE: AN ANTAGONIST TO THE OPIATES*

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N-ALLYL NORMORPHINE: AN ANTAGONIST TO THE OPIATES * † ‡

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ANESTHESIOLOGISTS frequently plan treatment for a patient who has received an actual or relative overdose of an opiate. Similarly, they are often called upon to advise therapy for an infant with asphyxia neonatorum. In infants and adults in whom depression is not excessive, supportive therapy and mild stimulants such as caffeine or ephedrine have proved adequate. In more heavily narcotized individuals, the results of treatment have not been altogether satisfactory. Within the past year studies have indicated that a hitherto clinically untried drug, *n*-allyl normorphine, is an effective antagonist to opiate depressions and may prove to be a valuable adjunct to the list of drugs employed in the practice of anesthesiology. The present paper can be considered a progress report of investigations of *n*-allyl normorphine continuing at the University of Pennsylvania.

The ability of *n*-allyl normorphine to reverse the respiratory depression produced in animals by large doses of morphine was first described by McCawley, Hart and Marsh (1) in 1941. Since that time, however, little interest has been manifest in the drug except for two studies in animals (2, 3) and several abstracts (4, 5, 6). One abstract has reported an investigation of the drug in opiate addicts (7).

We became interested in *n*-allyl normorphine about nine months ago and have since administered it to about 400 patients. In a previous report (8) we described this agent as an effective antagonist to narcosis produced by large doses of morphine sulfate or meperidine hydrochloride but ineffective in counteracting the depression produced by cyclopropane, ethyl ether and thiopental. In patients given 20 to 90 mg. of morphine sulfate or 200 to 600 mg. of meperidine, intravenous administration of 5 or 10 mg. of *n*-allyl normorphine doubled or tripled the respiratory rate and increased respiratory minute volume as much as

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250 per cent. These effects reached a peak within one to two minutes, then declined gradually, but both values remained above the depressed levels for the sixty minute period of observation. In addition to respiratory stimulation, normorphine caused an elevation of blood pressure when it had been depressed by the narcosis. It was noted that, in the doses used, the antagonist seemed to have little awakening effect. An unexpected action was that when given in 5 or 10 mg. doses to normal volunteer subjects, the drug produced a depression of respiration and blood pressure.

Our subsequent studies have progressed along two general lines. The first was an attempt to determine which of the opiates can be antagonized by *n*-allyl normorphine. The second involved exploration of the drug in counteracting neonatal depression produced by the administration of sedative and analgesic drugs to the mother in the final stages of labor.

Methods

The methods of study were as follows: In the first, large doses of various opiates were administered before and during nitrous oxide-oxygen anesthesia for minor operations. Following the completion of the surgical procedure, respiratory minute volume and rate were measured by means of a small spirometer. Blood pressure was recorded by ordinary ausculatory methods. *N*-allyl normorphine § was injected rapidly intravenously in 10 to 40 mg. doses after a suitable period of observation. The effect of the drug was observed for a period varying from one to twelve hours. The details of this method are described in our previous report (8).

In the second or obstetric study, *n*-allyl normorphine in 10 mg. doses (2 cc.) or 2 cc. of physiologic saline solution was injected intravenously into almost every patient admitted for delivery at the Hospital of the University of Pennsylvania. The nature of the injected solution was unknown to anyone in the delivery room, since all ampules were identical and were labeled by numbers only. The drug was administered as the patient was placed on the delivery table, usually about ten minutes before birth of the infant. Nitrous oxide-oxygen was administered to all but 19 of the 270 patients to be reported here. In 40 per cent of the cases ethyl ether was used as a supplement to the nitrous oxide. In the 19 patients not receiving the above agents, the mode of anesthesia was caudal, spinal, local or none. Observations of the labor and delivery were recorded by the anesthetist and obstetricians on a specially prepared form. The data comprise a preliminary report of this particular phase of the work.

Results

Study I.—*N*-allyl normorphine has been administered to 2 patients who had received 80 to 100 mg. of pantopon, 3 patients who received 6

§ Kindly supplied by Merck and Company.

to 8 mg. of dilaudid, 2 patients who were narcotized with 19 to 20 mg. of methadone, one patient given 60 mg. of morphine sulfate, and 2 patients narcotized with 150 and 200 mg. of seconal sodium. The antagonist was equally effective against all of these drugs (figs. 1, 2 and 3) except seconal sodium, where it was ineffective despite the largest doses of *n*-allyl normorphine used in the entire study (table 1). The character of the change was similar to that reported by us for morphine sulfate and meperidine (8).

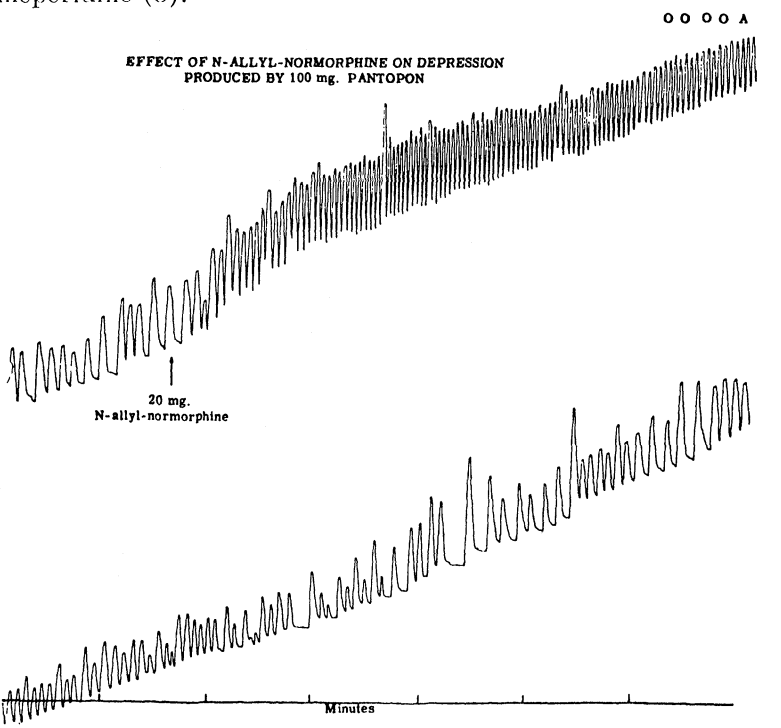

Fig. 1.

A number of observations made in this study supplement those reported previously (8). First, larger doses of *n*-allyl normorphine were more effective than the 10 mg. doses used in the first study. Second, in some patients the larger doses produced a rise in blood pressure even though the pressure had not been depressed by the narcosis. The rise was of the order of 30 to 40 mg. and was maintained above the control level for twenty to thirty minutes. In our earlier report, it was noted that a vasopressor effect was apparent only if hypotension pre-existed. Third, when an awakening action was evident, it was sometimes marked but was not sustained, for over the period of the following thirty minutes the patient would go back to sleep.

N-allyl normorphine was also administered to a patient suffering from an overdose of opiates as follows. The patient (B. C.), age 27 years, was 69 inches tall and weighed 152 pounds. For preanesthetic medication she had received 10 mg. of morphine sulfate and 0.4 mg. of scopolamine hydrobromide at 8:30 a.m. An uncomplicated hemorrhoidectomy was performed under low spinal anesthesia. Because of severe rectal pain, 8 mg. of morphine sulfate was injected intramuscularly at 12:00 noon and repeated at 12:30 p.m. Pain was relieved until 3:00 p.m. when 100 mg. of demerol was injected intramuscularly because of return of discomfort. Within ten minutes the patient became

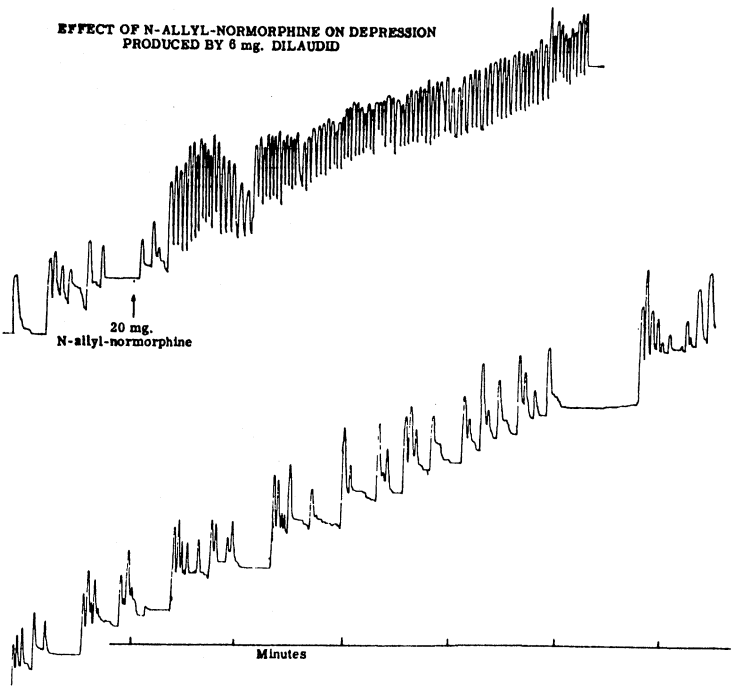

Fig. 2.

somnolent and began to perspire. Respiratory depression ensued and cyanosis was evident. During the next few minutes respiratory effort diminished to a gasp every thirty to forty seconds. The patient could not be aroused by painful stimuli. The pulse was strong and there was no apparent evidence of circulatory collapse although the blood pressure was not taken at that particular time. Artificial respiration was instituted and maintained by means of a bellows resuscitator. When the anesthesiologist arrived, respiratory efforts consisted of one or two gasps a minute, and cyanosis continued despite artificial respiration. Ten milligrams of *n*-allyl normorphine were injected intravenously

Within thirty seconds regular diaphragmatic breathing began and within another minute the respiratory rate was 24 per minute, with a satisfactory respiratory exchange. The color improved and the patient began to respond. Within several minutes the patient opened her eyes if spoken to. Her condition improved steadily after this episode.

Study II.—The preliminary results of the investigation of the use of the drug in obstetrics are summarized in tables 2, 3 and 4. We have excluded from these statistics all cases in the following categories: (1) Those in which we had reason to believe the drug had not been delivered into the infant's circulation. This included those instances in which

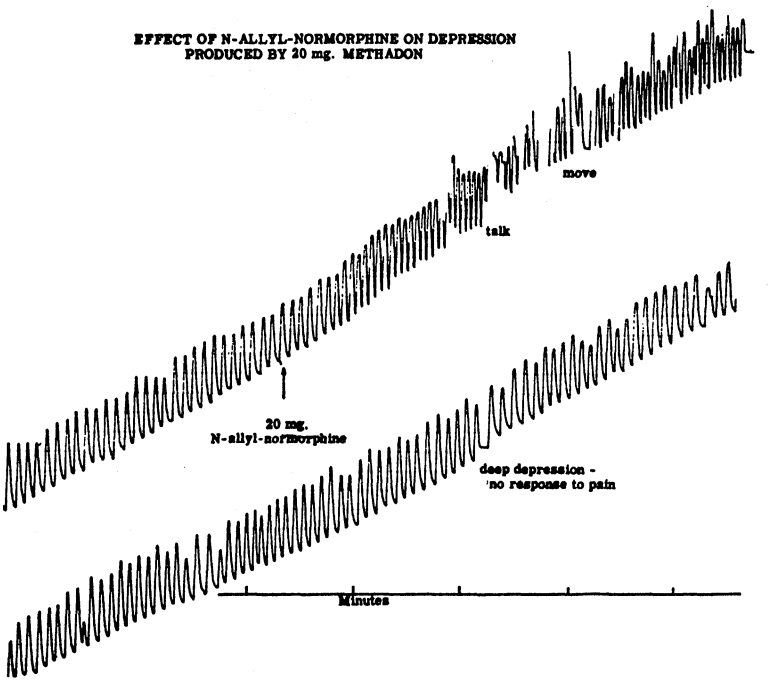

FIG. 3.

the drug was not completely injected intravenously, in which it had been injected less than four minutes or more than forty minutes before delivery. The figures of 4 and 40 are arbitrary and should not be interpreted as having been selected on the basis of evidence to indicate destruction of the drug or the time required to cross the placental barrier. (2) Those cases in which interpretation of the results was made difficult by the presence of unusual birth trauma or the delivery of twins.

The patients included in table 2 are those who were considered by the anesthesiologist to be (1) moderately depressed (no response to name or questions but response to pain stimuli), or (2) deeply depressed

TABLE 1

EFFECT OF *N*-ALLYL NORMORPHINE ADMINISTERED INTRAVENOUSLY ON RESPIRATORY MINUTE VOLUME AND RATE, PULSE RATE AND BLOOD PRESSURE OF SUBJECTS RECEIVING VARIOUS OPIATES

M.V. = minute volume in cc./minute
R.R. = respiratory rate/minute
P.R. = pulse rate/minute
B.P. = systolic and diastolic pressure in mm. Hg

Subject's age and weight are listed in first column, together with the total dose of the opiate administered and the dose or doses of *n*-allyl normorphine. Analeptic effect is graded from + = mild, to +++ = marked. J. M. is the only male.

	Control				After injection								Analeptic Effect
					1–2 min.				3–5 min.				
	R.R.	M.V.	P.R.	B.P.	R.R.	M.V.	P.R.	B.P.	R.R.	M.V.	P.R.	B.P.	
A. Pantopon													
K. R. 44–112 lbs. 80 mg. pantopon 10 mg. normorph.	8	4010	88	114/70	12	5310	—	—	17	7140	—	120/74	0
A. W. 49–129 lbs. 100 mg. pantopon 20 mg. normorph.	8	1380	72	106/70	20	4830	—	—	19	3820	—	150/96	+
B. Dilaudid													
L. T. 51–140 lbs. 6 mg. dilaudid	8	2730	64	94/60	15	6030	—	—	15	5125	48	110/70	+
20 mg. normorph. and in 40 min. another 15 mg.	14	4220	76	120/78	17	5810	80	140/70					+++
J. M. 16–107 lbs. 8 mg. dilaudid 20 mg. normorph.	12	4100	—	150/90	25	9000	—	—	25	7500	104	160/104	++
E. S. 33–135 lbs. 6 mg. dilaudid 20 mg. normorph.	6	1140	—	106/54	19	4900	—	—	23	4180	—	144/94	+
C. Methadon													
J. C. 54–161 lbs. 19 mg. methadon 15 mg. normorph.	20	6070	88	140/90	17	6840	—	—	20	7240	—	—	++
R. B. 35–115 lbs. 20 mg. methadon 20 mg. normorph.	9	1770	72	115/80	13	2570	—	—	18	3320	80	124/86	+++
D. Morphine													
E. W. 53–139 lbs. 60 mg. morphine 20 mg. normorph.	apnea 105 sec.		76	144/90	15	9050	84	154/94	would not tolerate mask				+++
E. Secobarbital Sodium													
D. J. 22–115 lbs. 150 mg. secobarb. 30 mg. normorph.	9	3330	56	100/60	10	4000	—	—	11	3520	60	105/70	0
E. S. 44–138 lbs. 200 mg. secobarb. 40 mg. normorph.	15	4340	—	—	15	3900	—	—	14	3640	—	—	0

(no response to pain). In these two groups the average sedative and analgesic medication consisted of 0.2 to 0.3 Gm. of secobarbital sodium, 200 mg. of meperidine and 0.7 mg. of scopolamine hydrobromide administered over an average of five hours before delivery. As can be seen from table 2, the time required for the infant to take his first gasp and to establish respiration was approximately twice as great in the control group. Statistically, these differences are highly significant.

In table 3 are listed those patients classified as being mildly depressed, that is, the patient would go to sleep if left undisturbed, but

TABLE 2

Moderately or Deeply Depressed

	N-allyl Normorphine	Control	t Value
Number of patients	33	30	
Time to gasp (sec.)	19.2±18.5	34.9± 33.7	2.28*
Time to establish cry (sec.)	51.2±55.4	104.4±102.7	2.57*

TABLE 3

Mildly Depressed

	N-allyl Normorphine	Control	t Value
Number of patients	56	48	
Time to gasp (sec.)	23.7±20.7	36.7±45.8	1.89
Time to establish cry (sec.)	72.3±79.7	90.1±94.3	1.02

TABLE 4

Not Depressed

	N-allyl Normorphine	Control	t Value
Number of patients	43	45	
Time to gasp (sec.)	32.4±30.7	27.5± 32.9	0.66
Time to establish cry (sec.)	72.2±70.1	86.1±151.6	0.48

* Indicates high statistical significance.

would awaken during uterine contractions. The average sedation consisted of 0.2 Gm. of secobarbital sodium in 50 per cent of this group of patients and no barbiturate in the remainder, 150 mg. of meperidine and 0.6 mg. of scopolamine hydrobromide administered during an average of four hours before delivery. The averages of the times required for the infant to gasp and to establish respiration are higher in the control groups but are not as statistically significant as in the more depressed group.

Table 4 contains the data from those patients considered to be not depressed and who were alert mentally. In this group the average

medication was 0.2 Gm. of secobarbital sodium in 20 per cent and no barbiturate in the remainder, 100 mg. of meperidine and 0.4 mg. of scopolamine hydrobromide administered in an average of two hours and forty minutes before delivery. The differences between the two groups were not statistically significant.

On several occasions *n*-allyl normorphine was injected directly into the umbilical vein of a depressed newborn infant. The dose used was 0.1 mg. in 2 cc. of solution. The indications for such therapy were failure of an infant to breathe, cyanosis or poor muscle tone. On each occasion the result was most satisfactory, with establishment of respiration within one minute and improvement in color and muscle tone.

It was notable that there was no stimulation of the mothers with the amounts of *n*-allyl normorphine used. Actually it was the consensus of the anesthesiologists that the depression of the patients was somewhat deeper than usually noted following completion of the delivery and repair of the episiotomy. This, however, was never of great concern and was not thought to be a deterrent to the use of the drug. There were no instances of undesirable effects or side reactions of the drug either in the mothers or infants. There were no antenatal or neonatal deaths in this series.

Comment

From the data presented it is apparent that *n*-allyl normorphine is an effective antagonist to depression produced by morphine, meperidine, pantopon, dilaudid and methadone. Although we have not as yet attempted to antagonize the depression that can be produced by metapon, we intend to do so in the near future. We have now had occasion to use the drug clinically four times in the treatment of opiate overdosage, with a satisfactory result each time. Frazer, Wikler, Eisenman and Isbell (9) have prepared a report for publication in which they describe the successful treatment of 2 patients with severe methadone poisoning. It will take time, however, to evaluate the real place the drug is to take as a therapeutic agent in the treatment of narcotic poisoning.

Our data do not yet enable us to state the optimal dose of this agent. We have seen no untoward reactions from any dose so far employed. It is probable that large doses can be used without danger in the presence of severe depression, thus following the experience common to all analeptic drugs.

Our data also indicate that *n*-allyl normorphine is a specific antagonist to depression produced by the opiates and is not effective against depression produced by other depressants of the central nervous system. In the doses we have employed it has been useless in depressions produced by cyclopropane, ethyl ether, thiopental and secobarbital sodium.

The figures presented in tables 2, 3 and 4 prove that the drug is valuable for the obstetrician and others concerned with the prevention

and treatment of neonatal asphyxia and depression. The ultimate role of the drug will depend upon the accumulation and careful analysis of a series of cases many times larger than the one here reported; this we are doing. These data will have to be analyzed from many additional aspects and not from the single viewpoint mentioned in this report. We are aware that the division of the cases on the basis of maternal depression may be improper and misleading, since it may not necessarily indicate the status of the infant.

It should be emphasized that *n*-allyl normorphine cannot be considered a panacea for all neonatal respiratory and circulatory difficulties. As mentioned previously, the drug is not an effective antagonist to barbiturates, and all of these moderately and deeply depressed obstetric patients had received barbiturates. Also, depression basically due to trauma of delivery, nuchal cord with resultant asphyxia, premature placental separation, intra-uterine pulmonary infection, or other similar conditions obviously cannot be affected by the drug. One of the infants born of a mother who had received *n*-allyl normorphine failed to breathe for five minutes after delivery. Not enough data are available as yet to analyze why this occurred. However, such instances are less common than in the control group, as is indicated by the statistics.

There are however, many intriguing aspects of the obstetric use of the drug which will bear investigating. A few are: (1) Can *n*-allyl normorphine be given simultaneously with meperidine to prevent fetal depression? (2) Will this drug enable medication to be given intravenously to mothers who are in rapidly progressing labor on admission? (3) Will a large series prove the antagonist satisfactory when administered into the cord vein of depressed infants?

Summary

N-allyl normorphine has been shown to be an effective antagonist to depression produced in man by morphine, meperidine, pantopon, dilaudid and methadone.

In 255 obstetrical patients, *n*-allyl normorphine significantly shortened the interval between the delivery of the chin and the infant's first gasp or establishment of respiration when the child was born of a mother in a moderate or deep state of depression caused by analgesics and sedatives.

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VASCULAR RESPONSE TO LARGE DOSES OF INTRAVENOUS MORPHINE IN MAN*

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9/95

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CARDIOVASCULAR RESPONSE TO LARGE DOSES OF INTRAVENOUS MORPHINE IN MAN*

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Abstract Large doses of intravenous morphine (0.5 to 3.0 mg per kilogram of body weight) were used alone or in combination with inhalation anesthetic agents for anesthesia in over 1100 patients undergoing open-heart surgery.

Morphine, 1 mg per kilogram, was administered intravenously to seven subjects with aortic-valve disease and eight without major heart or lung disease. The cardiac subjects had higher control pulse rates and lower control stroke indexes than the normal subjects. In the cardiac but not in the normal subjects, significant increases in cardiac index, stroke index, central venous pressure, and pulmonary-artery pressure, and a significant decrease in systemic vascular resistance, were observed after morphine was administered, suggesting that large doses of morphine may be used with safety in patients with minimal circulatory reserve.

DURING treatment of patients requiring mechanical ventilation for respiratory failure, we observed that doses of morphine sufficient to suppress respiration usually did not have discernible hemodynamic effects in spite of the large doses frequently required. This observation and the fact that morphine has not been shown experimentally to cause cardiac depression led to a trial of the use of large doses of morphine as the sole anesthetic agent or as an adjunct to the induction and maintenance of anesthesia in patients with cardiac disease. Most of the patients receiving large doses of morphine were adults requiring open-heart surgery for acquired valvular disease. This group formerly presented many problems in anesthetic management because of the cardiac-depressant properties of the anesthetic agents employed.

Over 1100 patients in this hospital have now received from 0.5 to 3.0 mg per kilogram of morphine intravenously either alone or in combination with other agents. Morphine in doses of 1 mg per kilogram does not usually cause sleep in the presence of adequate oxygenation and carbon dioxide excretion; we have termed this dose "subanesthetic." The larger doses (up to 3.0 mg per kilogram) have been used for general anesthesia with only the addition of a muscle relaxant.

METHODS

Group A – "Normal"

Eight subjects, 24 to 71 years of age, without apparent heart or lung disease (seven requiring major abdominal operations, and one the removal of a post-traumatic thoracic aneurysm) were studied immediately before surgery.

Four pairs of control measurements were performed at 15-minute intervals, two during breathing of ambient air and two during breathing of oxygen from an anesthetic face mask. Morphine (10 mg per milliliter) was then administered intravenously at a rate of 10 mg per minute to a total dose of 1 mg per kilogram of body weight. Repeat measurements were performed five, 30 and 60 minutes after completion of injection. After the study, all patients were anesthetized for surgery with nitrous oxide and oxygen.

Group B – "Cardiac"

Seven subjects, 37 to 66 years of age, who had aortic stenosis, with or without aortic regurgitation, requiring open-heart surgery were studied. Pulmonary-artery catheters used for postoperative monitoring of pulmonary-artery pressure and venous admixture in the pulmonary circulation were positioned under fluoroscopic control. After insertion of a radial-artery cannula and central-venous-pressure catheter, a minimum of two series of control measurements was taken while the patients were breathing first ambient air and then oxygen via an anesthetic mask. The administered doses of morphine were as follows: one subject, 0.5 mg per kilogram; two subjects, 1.0 mg per kilogram; four subjects, 0.5 mg per kilogram followed by the studies, and then an additional 0.5 mg per kilogram and repeat studies.

Studies were performed 10 minutes to one hour after the administration of morphine. All patients were anesthetized with additional morphine or halothane after the study and operated upon for correction of their cardiac lesions.

In all subjects ventilation was monitored by recording end-tidal carbon dioxide tension (P_{CO_2}) from the anesthetic mask. The patients were encouraged to breathe deeply and regularly to maintain P_{CO_2} at control levels. Radial-artery blood samples were taken intermittently for direct measurement. No mechanical assistance of ventilation was given. All measurements of cardiac output were performed in duplicate by the dye-dilution technic.

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TABLE 1. *Hemodynamic Data* before and after 1 Mg per Kilogram of Intravenous Morphine in Eight Subjects without Demonstrable Heart or Lung Disease.*

INSPIRED GAS	CARDIAC INDEX (LITERS/MIN)	PULSE (BEATS/MIN)	STROKE INDEX† (ML/BEAT/M²)	MEAN SYSTEMIC ARTERIAL BLOOD PRESSURE (MM HG)	SYSTEMIC VASCULAR RESISTANCE (U)	CENTRAL VENOUS PRESSURE (MM HG)‡	ARTERIAL P_{CO_2} (MM HG)
Control:							
Ambient air	3.14 ± 0.86	70.6 ± 8.5	44.3 ± 9.8	77.0 ± 9.6	25.8 ± 5.7	4.3 ± 2.5	41.4 ± 2.9
Oxygen	2.93 ± 0.82	69.0 ± 7.7	43.3 ± 11.3	83.0 ± 8.0¶	30.2 ± 10.7**	4.4 ± 1.9	41.1 ± 3.3
After morphine:							
Oxygen for 5 min	3.07 ± 1.21	64.3 ± 10.0§	46.5 ± 14.1	78.8 ± 9.7	28.9 ± 9.7	4.6 ± 1.5	42.1 ± 5.3
Oxygen for 30 min	3.05 ± 1.43	67.4 ± 14.7	45.3 ± 15.8	77.4 ± 8.8	28.8 ± 9.0	4.7 ± 2.1	39.0 ± 9.0
Oxygen for 60 min	3.24 ± 1.60	65.9 ± 13.9	48.8 ± 18.7	76.3 ± 8.8‖	26.8 ± 8.2	4.9 ± 1.8	41.1 ± 8.6

*Mean ± 1SD.

†>control of "cardiac" group (0.10>p>0.05).

‡Pulmonary-artery pressure measured in 1 subject & found to be constant throughout study.

§Significantly < "air" control ($p < 0.05$); unchanged from "oxygen" control.

¶Significantly > "air" control ($p < 0.05$).

‖Significantly < "oxygen" control ($p < 0.05$); unchanged from "air" control.

**> "air" control ($0.10 > p > 0.05$).

All blood taken for sampling was replaced volumetrically with albumin in the "normal" group and with whole blood in the "cardiac" group.

The procedure and objectives of the study were explained in detail to each patient, and each gave informed consent.

RESULTS

Tables 1 and 2 and Figures 1 and 2 summarize the data obtained in the "normal" and "cardiac" groups, respectively.

Changes in pH were accounted for by respiratory changes in all cases. Except for these changes, there was no significant correlation between changes in $Paco_2$ and any other measurement. Changes in systemic vascular resistance and cardiac index were correlated significantly (rho = 0.78, p less than 0.01).

All subjects had arterial oxygen tensions (Pao_2)

TABLE 2. *Hemodynamic Data* before and after Intravenous Morphine in Seven Subjects with Aortic-Valve Disease.*

INSPIRED GAS	CARDIAC INDEX† (LITERS/MIN)	PULSE‡ (BEATS/MIN)	STROKE INDEX† (ML/BEAT/M²)	MEAN SYSTEMIC ARTERIAL BLOOD PRESSURE (MM HG)	SYSTEMIC VASCULAR RESISTANCE§ (U)	CENTRAL VENOUS PRESSURE† (MM HG)	MEAN PULMONARY-ARTERY PRESSURE† (MM HG)	ARTERIAL P_{CO_2}¶ (MM HG)
Control:								
Ambient air	2.92 ± 0.90	92.3 ± 10.7	31.0 ± 6.5	79.3 ± 8.3	29.6 ± 10.3	2.1 ± 1.1	19.9 ± 9.4	40.2 ± 4.3
Oxygen	2.88 ± 0.92	93.7 ± 10.0	33.4 ± 11.9	78.4 ± 6.6	29.5 ± 8.5	3.2 ± 1.0‖	17.7 ± 9.2	39.9 ± 3.1
After morphine:								
Oxygen, 0.5 mg/kg	3.66 ± 1.38	91.6 ± 12.9	37.8 ± 9.1	77.2 ± 8.2	24.7 ± 10.9	5.5 ± 2.0	21.9 ± 7.5	47.0 ± 10.0
Oxygen, 1.0 mg/kg	4.33 ± 1.22	94.1 ± 11.8	41.9 ± 13.3	80.0 ± 9.7	19.8 ± 5.4	6.1 ± 2.3	26.3 ± 10.9	48.7 ± 11.6

*Mean ± 1SD.

†Significantly increased after morphine administration ($p<0.05$).

‡Significantly > control of "normal" group ($p < 0.001$).

§Significantly decreased after morphine administration ($p<0.01$).

¶Increased after morphine administration ($0.10>p>0.05$).

‖>"air" control ($0.10>p>0.05$).

Cardiac index increased an average of 30 per cent after 0.5 mg per kilogram of intravenous morphine and 49 per cent after 1.0 mg per kilogram in the "cardiac" group, but did not change in the "normal" group.

Although blood pressure was unchanged in both groups, one subject in the "cardiac" group had a transient precipitous hypotension (Fig. 3), to a level of 50 per cent of control lasting for 40 seconds, after 60 mg of intravenous morphine administered within a period of three and a half minutes. No cardiac-output measurements were performed during this episode, and the blood pressure returned spontaneously to control levels.

In the cardiac group only, stroke index, central venous pressure, pulmonary-artery pressure, and $Paco_2$ were increased, and systemic vascular resistance was decreased after administration of morphine.

DISCUSSION

As shown in the present study, the intravenous administration of morphine, 1 mg per kilogram, has minimal effects on the cardiovascular system of supine intact man without clinically diagnosed heart disease. However, the presence of symptomatic aortic-valve disease alters the hemodynamic response to the drug. Patients in this "cardiac" group demonstrated a significant rise in cardiac index and stroke index, a decrease in systemic vascular resistance and a rise in pulmonary-artery and central venous pressures. Although there was an increase in above 400 mm of mercury while breathing oxygen.

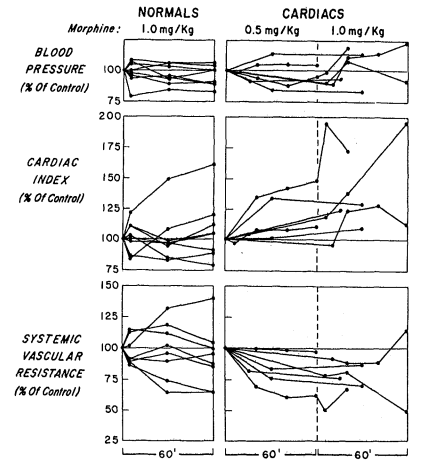

FIGURE 1. *Changes in Arterial Blood Pressure, Cardiac Index and Calculated Systemic Vascular Resistance from Mean Control after Intravenous Morphine (0.5 and 1.0 Mg per Kilogram) in Subjects with and without Acquired Heart-Valve Disease.*

the mean arterial P_{CO_2}, there appeared to be no correlation with the hemodynamic changes.

Except for the increase in central venous and pulmonary-artery pressures of the "cardiac" group, these findings are in line with the extensive experimental studies in animals on the cardiovascular responses to morphine, which have demonstrated that morphine causes relaxation of the peripheral vascular bed but has no direct cardiac effects. Circulatory receptor mechanisms remain intact, and compensatory sympathetic activity may be elicited by administration of the drug.[1-4]

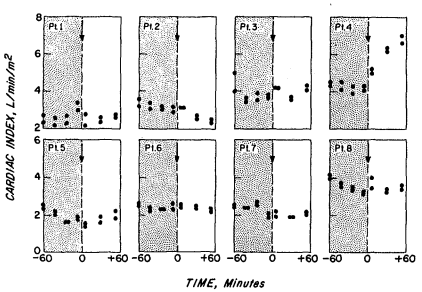

FIGURE 2. *Cardiac Indexes Measured in Eight Supine Subjects without Heart or Lung Disease before and after the Administration of 1 Mg per Kilogram of Morphine Intravenously.*

Subjects breathed ambient air for the first two control measurements and oxygen thereafter. The shaded area represents the control periods. Note the absence of a "characteristic" response to morphine in the intact subject.

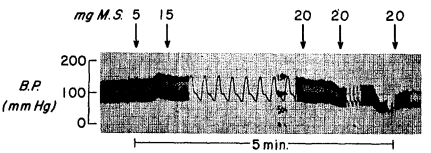

FIGURE 3. *Precipitous Hypotension in a 63-Year-Old 81-Kg Man with Aortic Stenosis after 60 Mg of Morphine Administered Intravenously over a Period of Three and a Half Minutes.*

This was the only hypotensive episode observed in the subjects of this study. The hypotension resolved spontaneously, and the blood pressure returned to normal within five minutes.

Several groups of investigators have demonstrated only minor transient hemodynamic changes after intravenous morphine administration to normal human beings.[5,6] Small doses (15 mg) had no significant effects on the circulation with the subject supine, but did abolish the compensatory response to changes in body position.[7]

In a study of patients with recent acute myocardial infarction, systemic arterial pressure was observed to fall transiently in half the patients after the administration of a maximum of 10 mg of intravenous morphine delivered at a rate of 1 mg per minute.[8] Precipitous hypotension followed the injection of 3 mg of morphine in one of these patients, but was reversed by elevation of the legs with improvement of venous return. A similar episode of acute but transient hypotension that resolved spontaneously in 40 seconds was seen to follow 60 mg of intravenous morphine in a patient from the present study with aortic-valve disease. Factors that predispose a patient to hypotension after intravenous morphine have not been identified by the present study; blood-volume replacement and vasoactive agents must be available to treat this occurrence when morphine is administered in the manner described.

We were unsuccessful in keeping the arterial P_{CO_2} as close to control levels in the "cardiac" as in the "normal" group. Nevertheless, there was no statistically significant change in the "cardiac" group, and the changes in P_{aCO_2} did not correlate with any of the observed hemodynamic changes. The difference in response is probably related to the presence of a larger respiratory physiologic dead space in patients with heart disease and congestive heart failure, or to the diminished ventilatory response of these patients to a carbon dioxide challenge because of extensive preoperative diuresis.[9]

Other factors concerning our findings in patients with aortic-valve disease are worthy of comment. Although stroke and cardiac indexes increased after intravenous morphine, heart rate did not decrease toward the level of the normal subjects. This obser-

vation may be related to augmented adrenergic activity in patients with heart disease.[10] Central venous pressure and pulmonary-artery pressure were elevated after morphine only in the "cardiac" group. Possible mechanisms for these changes may be increased flow through abnormal pulmonary vasculature, the constricting effect of carbon dioxide upon the pulmonary vasculature, acute right-sided heart failure, increased venous tone or changes in the pattern of ventilation. The return of central venous pressure to normal without change in $Paco_2$, frequently seen clinically after controlled ventilation is instituted, suggests that the rise is caused by the altered ventilatory pattern that follows the administration of large doses of intravenous morphine.

The correlation of calculated systemic vascular resistance and cardiac index after morphine administration is highly significant (p less than 0.01). On the basis of the present data, it is not possible to determine whether the changes in systemic vascular resistance were due to direct action of morphine upon the peripheral vasculature or were secondary to changes in cardiac output. The abnormally elevated vascular tone seen in patients with congestive heart failure may explain the consistent decreases in systemic vascular resistance seen in the "cardiac" group after morphine administration.[10]

The sensorium is known to have a profound effect on cardiac output.[11] Striking examples of this were observed during the control studies in our normal subjects. One subject had a marked increase in cardiac index after becoming uncomfortable before her last control measurement. Another demonstrated a marked decrease in cardiac index as he spontaneously fell asleep before the last control measurement. A decrease in cardiac output on the second determination has been described,[12] and was consistently observed in the present study. The role of apprehension in initial elevated measurements of cardiac output was demonstrated by its occurrence in a group of nonphysicians, but not in a group of physicians.[13]

Whether central-nervous-system factors are involved in the net effect of subanesthetic doses of morphine on the cardiovascular system of man is not known. Sixty milligrams of morphine has been shown to decrease cerebral oxygen consumption in human beings.[6] It is possible that these large doses of morphine do exert part of their effect on the vasomotor center.

The net hemodynamic effect of morphine on the circulation of supine human beings may be partially dependent upon the circulating blood volume. If the blood volume is below a threshold value, the increased capacitance and decreased resistance that follow morphine administration may cause stimulation of baroreceptors and result in catecholamine-mediated peripheral vasoconstriction and possible decreased cardiac output. Above this threshold for volume, the vasodilation that follows morphine may not lead to compensatory adrenergic stimulation, and the decrease in systemic vascular resistance may result in a higher cardiac output. The consistent increase in circulating blood volume found in patients with valvular heart disease[14] may account for the lack of a decrease in cardiac output in the "cardiac" group.

A consideration in the use of morphine in combination with other anesthetic agents is the possible depressant effect of the combination. Cardiac output, blood pressure and heart rate are consistently lower if morphine is given before administration of anesthetic agents in animals.[15] The rise in cardiac output normally seen during cyclopropane anesthesia in man is prevented by the preanesthetic administration of morphine.[16,17] We have not investigated the effects of interaction between morphine and other anesthetic agents.

The present data bear directly upon our clinical experience with large doses of morphine in severely ill patients with or without acquired heart-valve disease. Morphine stands in striking contrast to other anesthetic agents, which uniformly have a cardiac-depressant effect. When hypotension does occur, it may be readily reversed by blood-volume expansion or the administration of vasoactive agents. Consideration of the use of morphine as an anesthetic agent is indicated in patients with minimal circulatory reserve undergoing major surgery when the need for postoperative respiratory support is anticipated.

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