

from our tables as regards the percentage of positive reactions according to days of the disease, obtained with the Flexner strain and by the three methods:

TABLE 3.—PERCENTAGE OF POSITIVE RESULTS TO FLEXNER ORGANISM OBTAINED IN RELATION TO DAY OF DISEASE

Days	Agglutination		Fixation		Conglutination	
	% Pos.	Number	% Pos.	Number	% Pos.	Number
1-4	9	11	27	11	50	6
5-8	56	16	28.5	14	60	10
9-12	59	17	53.3	15	72.7	11
13-16	75	6	60	5	66.6	3
17+	54	11	44.4	9	100	6

In respect to early diagnosis the conglutination is thus markedly superior to the other two methods. The apparent superior value of fixation over agglutination (27 per cent. to 9 per cent.) in the first four days is fictitious, as a positive reaction was obtained in 28.5 per cent. of the negative cases. The results with the Shiga organism show a similar course, except that they are lower in percentages, with the exception of the fixation reactions. The conglutination with Shiga is relatively and absolutely (with the exception of the initial days) lower than with the other reactions.

TABLE 4.—PERCENTAGE OF POSITIVE RESULTS TO SHIGA ORGANISM OBTAINED IN RELATION TO DAY OF DISEASE

Days	Agglutination		Fixation		Conglutination	
	% Pos.	Number	% Pos.	Number	% Pos.	Number
1-4	8	11	0	9	11.1	9
5-8	19	16	21.4	14	9.9	11
9-12	27	15	45.4	11	18.1	11
13-16	50	6	60	5	0	3
17+	27	11	62.5	8	42.8	7

CONCLUSIONS

Of 45 cases of infantile dysentery ("infectious diarrhea") dysentery bacilli were isolated in 38 cases (84.4 per cent.). In 35 of these bacteriologically positive cases mannit-fermenting strains only were isolated. The mannit-non-fermenting variety (Shiga) was isolated in 3 cases, in one of which it was found in conjunction with fermenting strains. Dysentery bacilli (acid mannit) were found in one of 15 control cases.

Evidence of reaction on the part of each patient to either mannit-fermenting or mannit-non-fermenting types of dysentery bacilli was sought in the blood serum. In every case, so far as practicable, three methods of serum diagnosis were employed, the well-known reactions of agglutination and of fixation, and one novel reaction, the reaction of conglutination (Bordet and Gay, Streng). The serum in many cases was tested at intervals in order to determine the time of occurrence in the disease of a positive reaction by each method.

Reactions with the Flexner strain were much more frequent than those with the Shiga strain; this is owing not only to a direct relation to the organisms producing the infections under consideration, but also, in all probability, to a greater agglutinability of the Flexner organism.

In the doses employed, fixation reactions were obtained with the Flexner, but not with the Shiga strain in over a quarter of the control cases (28.5 per cent.). It was found with both Flexner and Shiga much more frequently (50 to 60 per cent.) in the positive cases subsequent to the first week.

A positive agglutination reaction was obtained in one control case to Flexner; it occurred in 55.5 per cent. of the positive cases with Flexner ranging from 9 per cent. during the first four days to 75 per cent. at the third week (thirteen to sixteen days). In about half as many cases a reaction was obtained with Shiga.

No positive conglutination reaction was obtained in control cases. The reaction was present more frequently than either agglutination or fixation during the disease (63.1 per cent. to Flexner). In addition, conglutination was obtained with this organism in 50 per cent. of the cases during the first four days of the disease. Reactions with the Shiga type as given by conglutination were absolutely and relatively fewer than by the other methods. This would seem to indicate a more absolute specificity for this reaction.

It would seem, then, that in the conglutination reaction we have a means of serum diagnosis in infections by the dysentery bacillus which is far superior to any other as yet devised. The further investigation of this new reaction as applied to diagnosis of other bacterial infections is of immediate interest.

In conclusion, we wish to express our thanks to Dr. F. P. Gay for suggesting this investigation and for advice during its pursuit.

SCOPOLAMIN AND MORPHIN IN NARCOSIS AND IN CHILDBIRTH

Report to the Council on Pharmacy and Chemistry

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[The following report was submitted to the Council on Pharmacy and Chemistry of the American Medical Association, which authorized its publication.

W. A. PUCKNER, Secretary.]

E. Schmidt isolated scopolamin from several solanaceous plants and described it about ten years after Ladenburg had obtained hyoscin from the mother liquors in the manufacture of hyoscyamin. Schmidt's studies were more complete and exact than those of Ladenburg, and the name scopolamin is now applied correctly to the substance for which Schmidt first gave the true formula, $C_{17}H_{21}NO_4$, Ladenburg having given the formula for hyoscin, incorrectly, as $C_{17}H_{23}NO_3$. The term scopolamin was at first applied to levo-rotary hyoscin by Schmidt, while Hesse called the racemic form atroscin, and this term is still used commercially by Merck.

The scopolamin, or hyoscin, sold was often impure, and, since different individuals showed marked differences in reaction even to the pure substance, dependent on a variety of conditions which will be discussed later, certain investigators maintained for a time that scopolamin and hyoscin were not identical, at least in physiologic action, but this question may be considered as definitely settled now, and chemists and pharmacologists agree that scopolamin and hyoscin are identical, and it may be taken that whatever is said here concerning scopolamin is intended to apply equally to hyoscin.¹

The abuse of scopolamin in anesthesia has arisen largely through a misunderstanding of its pharmacologic action, and, since an understanding of these actions is essential to a comprehension of the question at issue, they will be summarized briefly before the general question of the use of scopolamin and morphin in anesthesia is considered.

PHARMACOLOGIC ACTIONS

Kobert² states that scopolamin exists in the optically active and inactive forms. Large doses act like atropin

1. For a discussion of this point, see THE JOURNAL, Dec. 21, 1907, p. 2103.

2. *Pharmakotherapie*, Second ed., p. 481.

on the pupil, accommodation, skin, heart, lungs, intestines and on all glands, but quite small (therapeutic) doses have a different action; thus the vagus is slightly stimulated, not depressed, and the pulse rate is therefore slowed, and only after large doses is there vagus paralysis. Small doses abolish cerebral excitement, this narcotic action being so strong that the maximal dose at first was placed at 0.5 milligram (1/130 grain) in all countries, but now, unfortunately, and without sufficient reason, this amount has been doubled. Kobert believes this larger dose to be applicable to the optically inactive form alone.

Kochmann states that small doses stimulate the vasomotor center, with a rise of blood-pressure and little change in the pulse rate; large doses cause a fall of blood-pressure from injury to the excitomotor apparatus in the heart. Moderate doses cause vagus paralysis in the rabbit, but this does not follow the use of even large doses in the dog. He states that scopolamin has no sedative action on the rabbit, while in man and the dog it induces sleep without analgesia.

Normal dogs survived enormous doses of scopolamin, and only those which had been previously injured succumbed. Normal frogs could not be killed by the largest doses.³ The rabbit exhibits primary paralysis of respiration, as man does, but man suffers no injury from therapeutic doses. Scopolamin is excreted by the kidneys.

These results of Kochmann's are confirmed for the greater part by Kionka (1908), but his results with dogs were slightly different, in that Kionka observed some analgesia and two distinct types of action, some becoming somnolent at once, while others exhibited restlessness, incoordination, hallucinations and sank to sleep gradually.

Kionka also tested the solutions which Kochmann had used two years previously and found no quantitative or qualitative differences in physiologic action, though the optically active had become optically inactive. Kionka also compared the physiologic actions of optically active and inactive scopolamin in freshly prepared solutions and could detect no essential difference between them, but differences were seen in the actions of the same specimen of scopolamin on different individuals of the same species. These differences in individuals were perceptible in the frog, and, becoming more pronounced with the cerebral development of the species, were more marked in the dog than in the rabbit, and, of course, attained their maximum in man.

Ernst perfused the spleen and kidney with solutions of scopolamin of various concentrations, but there were no constant effects on the blood vessels in the series of twenty-two perfusions. Cushny found that levo-rotary hyoscin acts twice as energetically as the racemic form on the terminations of the secretory fibers in the salivary glands and on the inhibitory fibers in the heart, but that they act alike on the central nervous system in man and other mammals, and on the terminations of the motor nerves in the frog, but that they do not act on the central nervous system of the frog even with the largest doses.

The physiologic actions of morphin are so well known that they do not require exhaustive discussion here.

3. Githens reported a case in which 4/5 of a grain (52 mg.) of scopolamin had been taken at one dose without injury. The results in this case have been widely quoted, but the evidence concerning the actual dose is circumstantial, the patient having taken all that was left after previously using some of the solution. The solution was not sterile and it had been kept standing for some time. Finally, the precise quantity originally present in the bottle is not vouched for by Githens.

Schneiderlin, Korff and Blos were the earliest advocates of the use of scopolamin and morphin in narcosis, and their statements of the physiologic actions and antagonisms of these two alkaloids have been summarized by Kochmann about as follows:

1. Morphin slows the pulse; scopolamin increases the rate.

2. Morphin slows the respiration and renders it shallow; scopolamin causes it to become deeper and quicker.

3. Morphin paralyzes sensory nerves; scopolamin paralyzes the motor.

4. Morphin induces miosis; scopolamin, mydriasis.

5. Morphin is a vasodilator; scopolamin, a vasoconstrictor.

6. Morphin leaves the secretions unchanged; scopolamin paralyzes them.

The synergistic action in narcosis and the wide-spread antagonisms of side actions have been the chief arguments used by Schneiderlin and Blos in support of their claims concerning the value of the combination, but it is hardly necessary to say that the antagonisms are more apparent than real, or that they are in part purely imaginary. Thus, while morphin is, indeed, a miotic and scopolamin a mydriatic, the action of morphin is purely a central one, while the mydriatic action of scopolamin is purely peripheral. As to the paralysis of the sensory endings, it may be said that there is no evidence in the literature of any such action from morphin, and, on the contrary, it is well known that its analgesic action is purely central, while the paralysis of motor endings by available doses of scopolamin occurs only to a very limited extent, and then to the detriment of the heart.

There is no antagonism between scopolamin and morphin on the respiration in the doses often used by Schneiderlin, Korff and Blos. The effects of morphin on the circulation, according to Sollmann,⁴ are complicated and variable and of but little importance, as they are pronounced only with very large doses. The effects of scopolamin and morphin on the pulse rate are alike quite as often as they are unlike.

Since the recommendation of scopolamin with morphin was based on such a complete misconception of true conditions, it is not surprising that, after the sacrifice of perhaps thirty lives (and just how many no one can say positively), we are back to almost the identical position in which we should have been but for the unfortunate enthusiasm of the early advocates of this combination; i. e., its use preliminary to inhalation anesthesia—precisely the object which Schneiderlin had in view when he administered the very first dose.

Those who wish to pursue this phase of the question are referred to the papers of Kochmann, Kionka, H. C. Wood, Jr., Cushny, de Stella and others who have studied the pharmacologic actions of these two drugs.

Schneiderlin was led by his observations of the effects of scopolamin on the insane to use scopolamin and morphin for the purpose of reducing to the minimum the amount of chloroform required for anesthesia in the case of a patient suffering from carcinoma of the breast. The results so far exceeded his expectations that he experimented further and found that scopolamin and morphin alone sufficed in some cases for light anesthesia. He gave amounts up to 2.5 milligrams (1/25 grain) of scopolamin and 7 centigrams (1 1/6 grains) of morphin in the space of an hour and fifteen minutes.

4. Text-book of Pharmacology, Second ed., p. 186.

Although he found the effects of scopolamin variable and his observations extended only to some ten cases, he drew rather broad deductions, concluding that scopolamin and morphin are not dangerous; that the unforeseen accidents of chloroform inhalation were thereby avoidable; that the constant attendance of the physician is unnecessary, merely an attendant to be at hand in case the tongue should fall back into the throat and the respiration cease; the condition of the pupils was urged as a guide to the administration of the two drugs, than which, as we have seen, nothing could be more fallacious.

This paper of Schneiderlin's is not readily accessible to the general reader, in this country at least, and it is remarkable how considerably the average critic has dealt with Schneiderlin's reasoning and deductions.

I believe that we should be inclined to consider as little less than reckless one who would pronounce a new anesthetic harmless, because ten patients had survived its administration. Apparently Schneiderlin had no idea of its possibilities for degenerative changes on the internal organs. He even went so far as to advise initial doses of 1 milligram of scopolamin and 3 centigrams of morphin if in haste to operate. It must be said, in justice to Schneiderlin, that he did not pretend to have perfected the technic of scopolamin-morphin anesthesia.

Schneiderlin's truly remarkable announcement was soon followed by observations by other surgeons. Bloss took up the investigation within a month of the appearance of Schneiderlin's paper and about two years later he published his results in 105 cases. Bloss repeats the fallacious statements made by Schneiderlin concerning the antagonistic actions of the two alkaloids, and, despite one death in his series, which he attributed to an accident that could be avoided thereafter, he commended the method warmly. Bloss gave even more morphin than Schneiderlin had done—up to 12 centigrams (2 grains) in two portions—and was more enthusiastic in his praise of the combination. In this connection it is interesting to note that about three years later Bloss wrote to de Maurans, stating that he rarely used the method after leaving the hospital.

Korff reported on 80 cases in which he used scopolamin and morphin, employing doses of 1.2 milligrams (1/50 grain) of scopolamin and 3 centigrams (1/2 grain) of morphin in three portions of 0.4 milligram (1/150 grain) scopolamin and 1 centigram (1/6 grain) morphin each. Korff modified this dose somewhat after about a year, but still adhered to doses that have been abandoned by conservative surgeons. The use of such a dangerous combination could hardly fail to cause a number of deaths, and there was the inevitable reaction, many abandoned the method altogether, while others continued to use it in a modified form.

Disregarding the early methods, which no longer obtain among well-informed surgeons, but which are considered in order to gain a better understanding of the question, we will discuss the use of scopolamin and morphin preliminary to general anesthesia and to induce the so-called twilight sleep in obstetrics.

SURGICAL USES

The principal advantages and disadvantages have been observed by numerous investigators, and it is useless to enumerate these observations in each case. Therefore the opinions of the majority are considered collectively, except when it may be necessary to call attention to opposing views.

ADVANTAGES

The advantages which can be claimed conservatively for scopolamin and morphin in anesthesia may be briefly summarized as follows:

1. It permits economy of chloroform or ether, with the attendant advantages; it reinforces spinal anesthesia.

2. There is lessened postoperative nausea and emesis, with the decreased danger of pneumonia and other side-actions.

3. The stage of excitement is lessened or abolished, and the fear of anesthesia is eliminated largely.

4. The course of anesthesia is rendered smoother and more uniform.

5. There is decreased salivation after ether and a diminution of pneumonia.

6. There is sleep of some hours following operation, with the avoidance of pain which commonly follows operations with chloroform or ether.

7. In addition to those mentioned, there are minor advantages which will be mentioned later.

1. *Economy of Chloroform and Ether.*—It is claimed by a very large majority of observers that scopolamin and morphin effect an economy of chloroform and ether. While this is a matter of prime importance, it is so purely a surgical question that it cannot be considered exhaustively here, but the following citations illustrate the point: Zadro (1909) states that 60 grams (2 ounces) of Billroth's mixture and 100 grams of ether suffice for an operation of an hour, but with 0.5 milligram (1/130 grain) of scopolamin and 1 centigram (1/6 grain) of morphin, 25 grams (5/6 ounce) of Billroth's mixture and 80 grams (2 2/3 ounces) of ether, or 120 grams (4 ounces) of ether, suffice. Among others who report economy of ether is Flatau, who states that this economy is not attended with lessened emesis. Schoemaker (1909) reports that he found no marked economy of chloroform or ether, but he admits that these act less injuriously after scopolamin and morphin. If the latter statement is correct, we must conclude that less than usual of chloroform and ether were actually used.

2. *Lessened Nausea and Emesis.*—Bloss states that patients take food almost immediately after an operation following the use of scopolamin and morphin, and that recovery is rapid in consequence. Several observers state that patients look fresher and better than after chloroform or ether alone. Hartog (93 cases) states that nearly all patients show an extraordinary good condition after operation following the use of scopolamin and morphin, and Klein remarks that such patients recover quicker and better than after long chloroform narcosis alone. A great majority of observers report that there is less emesis immediately following operations, with scopolamin and morphin, than with chloroform or ether alone.

The disadvantages and dangers of this postoperative emesis do not require detailed discussion here, but, in addition to the fatal pneumonia, which it causes so often, there are many minor disadvantages resulting from it. Flatau says that postoperative emesis is often the cause of hernia as well as hemorrhage. Bloss calls attention to the increased viscosity of the blood commonly resulting from emesis and the inability to take water. Korff claims that the ability to take food soon after an operation greatly lessens the danger of hemorrhage, and that many stitches are pulled out during emesis. The ability to take food soon after an opera-

tion certainly hastens repair and increases the resistance to infection.

The testimony is conflicting in regard to the actual frequency of emesis after operations following scopolamin and chloroform or ether, but the real benefits of scopolamin and morphin in this respect cannot be shown by tables giving merely the frequency of emesis; the interval before its occurrence is of even greater importance. This is illustrated strikingly in Ries' report. Ries states that emesis occurred in about 60 per cent. of his cases in which chloroform was used after scopolamin and morphin, and in about 36 per cent. of those where ether followed, but only once in the series of 185 major operations did emesis occur within twenty-four hours, and he did not have a single case of pneumonia in the entire series.

As to the actual frequency of emesis after scopolamin and morphin and chloroform or ether, there is little doubt that it is materially decreased in the first twenty-four hours following operation, and, indeed, in the whole period concerned. Schoemaker (1909) states that there was emesis in about 10 per cent. of his 3,000 cases in which scopolamin and morphin were used, which was a marked reduction from that seen when he used chloroform or ether alone.

Platau claims that emesis is not lessened by small doses of scopolamin and morphin, but the effective doses used by Grimm and by Schoemaker were quite small, 0.5 milligrams of scopolamin, and 1 and 1.5 centigrams of morphin, respectively, and the results obtained by Ries, previously mentioned, were obtained from the use of 0.65 milligram of scopolamin and 1.0 centigram of morphin (1/100 grain scopolamin, 1/6 grain morphin).

The lessened tendency to postoperative pneumonia after scopolamin and morphin with chloroform and ether, owing to lessened emesis and lessened salivary secretion after ether, is shown by the following figures: Boesch states that there were only 0.7 per cent. of cases of postoperative pneumonia following 2,000 operations with scopolamin and morphin and inhalation anesthesia since 1905, and even less than that of late. Zadro gives 0.9 per cent. (it should be 1 per cent.) in 770 cases against 4.8 per cent. with chloroform alone in 1908. He cites the results in Kümmel's clinic, where there were 0.7 per cent. of postoperative pneumonia when scopolamin and morphin were used, against 2.5 per cent. without them. In other clinics as high as 5 per cent. of postoperative pneumonia is reported where scopolamin and morphin are not used.

Grimm reports that there were 43 cases of pneumonia with 18 deaths following 1,754 laparotomies between 1895 and 1905 when scopolamin and morphin were not used, but there were only 6 cases of pneumonia and none fatal in 839 laparotomies where scopolamin and morphin were used before inhalation anesthesia.

If the averages just given are sustained by the observations of other surgeons, there can be little doubt of the beneficial action of scopolamin and morphin in preventing postoperative pneumonia, and in that event we must consider them indispensable, despite a higher immediate mortality than with ether or chloroform alone. The foregoing does not take account of the possibility of fatty degeneration of different organs resulting from scopolamin and morphin, but that probably does not occur with small doses.

3. *Lessened Excitement.*—It is so nearly universally admitted that there is lessened excitement in the early stage of anesthesia following the use of scopolamin and

morphin, that the subject may be dismissed with a few words. Sieber states that morphin alone is preferable for the purpose, and Zadro claims that there is no influence on the stage of excitement in the case of alcoholic patients, but this is denied by Grimm. Hartog reports the case of an hysterical patient in whom tonic and clonic convulsions followed the injection of scopolamin and morphin, but these subsided when anesthesia was induced by inhalation.

4. *Anesthesia Smoother.*—Zeller states that no other anesthetic produces such smooth narcosis in severe operations as scopolamin and morphin. Several observers refer to his effect of scopolamin and morphin, and those who work with dogs in laboratory experiments have noted this effect of morphin.

5. *Decreased Saliva.*—The profuse flow of saliva during the inhalation of ether is said to be a prolific source of pneumonia following its aspiration, and of emesis, from the effects of the ether in the saliva swallowed. Scopolamin checks this secretion very effectively, and it may indeed lead to extreme dryness of the mouth and throat difficulty in swallowing, intense thirst and diminished expectoration, which may prove a serious disadvantage.

6. *Long Sleep.*—Many observers mention the prolonged sleep following operations after the use of scopolamin and morphin with chloroform or ether, and state that the patient is thereby spared much suffering, which is otherwise experienced so often. Zeller states that patients often sleep from four to six hours, and Terrier and Desjardins say they may sleep as long as eight or ten hours. While this sleep is usually an advantage, there are conditions under which it may prove distinctly detrimental. Routier denies that postoperative pain is materially lessened by the use of scopolamin and morphin.

7. *Miscellaneous Advantages.*—Various individual observers mention minor advantages in addition to those already discussed, including the following: There is no mask to interfere with asepsis of the face when scopolamin and morphin are used alone for anesthesia (Blos); scopolamin and morphin anesthesia is suitable in cases in which chloroform and ether are unavailable (Dirk and others); but this is hardly borne out by what has been said of the physiologic actions of the two alkaloids and by the experience of Ely, Sexton and others. Penkert says that scopolamin and morphin "twilight sleep" and spinal anesthesia constitute the most humane method of narcosis at our disposal. Grimm is one of the few who advocates the use of scopolamin and morphin for use in general practice. Roith states that the method is more reliable than that with other anesthetics, and not more troublesome.

DISADVANTAGES

The disadvantages of scopolamin and morphin preliminary to chloroform or ether anesthesia may be summarized as follows:

1. They frequently fail to produce the desired effect.
2. They often act injuriously on the respiration and circulation.
3. There are numerous contraindications, of which many are not sufficiently defined.
4. The action is variable with different individuals.
5. They are not suited for general practice.
6. They have caused a number of fatalities.
7. There are several minor disadvantages that will be discussed later.

1. *Failure to Produce Effect.*—Nearly all observers agree that in a fairly large percentage of cases the objects sought are not attained by the use of scopolamin and morphin, whether these objects are limited to the avoidance of the stage of excitement with small doses, such as Kochmann and most observers advise, or the effort is made to economize chloroform or ether greatly, as Korff (1908) still attempts by somewhat larger doses. Twenty-five per cent of failures is probably a fair estimate, but this does not apply to the prevention of post-operative pneumonia, in which, as stated, the results appear to be far better.

2. *Effects on Respiration and Circulation.*—It is well known that morphin depresses the respiration in all doses that produce any perceptible systemic action. The effects of scopolamin are, unfortunately, not so well known, and the effects of the two when combined are even less understood, though there is considerable evidence that their synergistic action in narcosis is sometimes extraordinary, in that their combined action is then much greater than the sum of their separate actions would be.

This is not a wholly anomalous condition, though it is one which is frequently overlooked. Gottlieb and Eeckhout's results with opium furnish us with an example of this peculiar synergistic action. They found that tincture of opium acts with more energy than can be accounted for by the potency of the separate alkaloids which it contains. Honigmann states that the action of a mixture of chloroform and ether is sometimes far greater than the sum of the action of the two acting separately. Wholly analogous to this is the action of atropin in antagonizing pilocarpin. Magnus states that 250 times as much atropin is required to produce stimulation when it acts alone as that required to overcome the depression from pilocarpin.

This remarkable synergy of actions has been observed on precisely those structures, i. e., those of the nervous system, in which we would expect the greater variation in reaction because of their highly specialized character, and it is with narcotics—even the identical narcotic that we have under consideration—that these peculiarities have been observed.

We are familiar with wide variations of actions, or idiosyncrasies, toward morphin, and it is possible that we are to become equally familiar with idiosyncrasies toward scopolamin. Scopolamin in large doses paralyzes the respiration, and it is apparent from the testimony of many clinical observers in cases in which death followed the use of the mixture, that the synergistic action of scopolamin and morphin is occasionally exerted on the respiratory center in a very remarkable way. Unfortunately, we do not know the precise conditions which call forth this unusual synergistic action, but we do know that whatever tends to depress the respiratory center favors this unfortunate reaction. The respiratory depression may be direct, or it may be caused indirectly through anemia, general weakness or extremes of life.

The evidence is irrefutable that scopolamin and morphin may cause death from paralysis of respiration—a paralysis against which artificial respiration and all means of stimulation are ineffective.

Sieber (1908) stated that Hartog alone had mentioned the lasting increased pulse rate after scopolamin and morphin, but the phenomenon is mentioned frequently thereafter, and its occurrence is in accordance with de Stella's statement that toxic doses of scopolamin increase the pulse rate, and furthermore, that toxic symp-

toms appear and disappear rapidly. Any considerable increase in the pulse rate after scopolamin and morphin must be considered an untoward symptom unless it can be accounted for satisfactorily.

Sieber mentions a case in which the pulse rate was 80 previous to the injection of a small dose of scopolamin and morphin, but in one hour the rate was 160. The heart, lungs and kidneys were apparently sound. This case of Sieber's must be considered as very unusual, and I am not aware of any case in which a dose not exceeding 0.5 milligram (1/130 grain) of scopolamin and 1 centigram (1/6 grain) of morphin has caused the death of a patient in fairly good condition and with sound organs, but the death reported by Ely very nearly fulfills these conditions. His patient was reported to have been in good general condition, but succumbed two hours after the administration of 1/100 grain scopolamin and 1/8 grain morphin (0.65 mg. scopolamin; 0.8 cg. morphin). There is no better authenticated cause of death from a narcotic than this one.

3 *Contraindications.*—Foremost, then, among the contraindications for the use of scopolamin and morphin are to be placed all conditions whereby the respiratory center is depressed, or is likely to be injured directly through prolonged anesthesia, or indirectly through the circulation by shock, hemorrhage or other cause. They are certainly contraindicated in all severe cardiac diseases and other conditions which interfere with the circulation. They are available for operations for simple goiter, but nearly all authorities agree that they are contraindicated in the presence of Graves' disease, which is to be inferred from what has been said. They are contraindicated in operations about the throat and mouth, since the prolonged sleep and interference with expectoration favor the aspiration of the blood. One death has been attributed partly to this, pneumonia, due to aspiration of blood, being the immediate cause of death.

The question of special indications and of contraindications for scopolamin and morphin has probably caused more disagreement than any other in connection with the subject of their use. Sick thinks there are no contraindications, while Sieber declares that there are no indications for their use. Sieber closes his article with the following exclamation: "*Also Weg bei der Narkose mit diesem unberechenbaren, meist nutzlosen, gefährlichen Gifte*" ("Away with narcosis by this uncertain, mostly useless dangerous poison").

Much of the controversy could have been avoided had greater attention been paid in the beginning to the physiologic actions of scopolamin and of morphin, and of the mixture acting as a unit.

4. *Variable Action.*—That the action of scopolamin and morphin is variable with different individuals follows naturally from what has been said, and it is impossible, of course, to foresee all of the conditions in man which will cause a greater or less deviation from the usual effects, and when a natural idiosyncrasy is intensified by disease or untoward conditions even small doses of scopolamin and morphin may prove fatal, as in the cases reported by Toth, Ely, Sexton and others.

These individual differences in reaction varying from no perceptible action in some cases to a fatal intoxication in others with precisely similar doses, constitute one of the greatest disadvantages of the use of scopolamin and morphin. Usually, however, the same patient reacts similarly at different times, but Hotz maintains that the same patient reacts differently at different times, and the possibility of this is precisely what is to

be expected in view of the disturbances of the respiration and circulation which may arise, and on which the untoward results depend.

5. *General Practice.*—The method is not usually considered as suited for general practice because of the constant attention required until the action has finally worn off, as the untoward symptoms may not arise until some time after the operation. It must be considered as unsafe to leave a patient without surgical care so long as sleep continues. There is probably little danger from small doses of scopolamin and morphin for patients whose general condition is good, and who show no serious effects from the operation, but the cautious surgeon will remain within call until the patient awakens.

6. *Fatalities.*—The ultimate fate of scopolamin and morphin in anesthesia must depend largely on their relative safety as compared with other agents, particularly chloroform and ether. While this is a surgical question for the most part, it must be considered with reference to the physiologic actions of these agents if we are to arrive at a correct estimate of the value of the method, for in fatal surgical operations there are so many factors involved that it is often impossible to determine the true cause of death. But when we see a series of deaths in which the clinical observations agree with what we know of the actions of the agents in question, the evidence is certainly very much stronger than it would be if the clinical observations did not agree with those actions.

H. C. Wood, Jr., studied the cause of death in 23 cases in which scopolamin and morphin had been used, and he concluded that at least 9 of those deaths must be attributed to the scopolamin and morphin, the death rate being about 1 to 250 narcoses by this means. Roith collected statistics of 18 deaths in 4,000 cases of scopolamin and morphin narcosis, but he does not agree that scopolamin and morphin should be blamed for these deaths. De Maurans attributed 22 deaths to these agents up to November, 1905. Viron and Morel (1906) noted 25 deaths in 2,000 cases collected from the literature.

With the methods now in vogue with the more conservative surgeons, who use only small doses of scopolamin and morphin in connection with other anesthetics, the death rate is very much lower than the figures just given would indicate, but there is no reason to suppose that better results can be obtained when scopolamin and morphin alone are relied on to induce the anesthesia.

These figures are given by way of illustration of the question of scopolamin and morphin anesthesia, and are not intended as a complete statistical study of the subject, and when statistics are considered a sharp distinction should be made between those cases in which death follows large doses of scopolamin and morphin, intended to replace chloroform or ether wholly or chiefly, and those in which only small doses of scopolamin and morphin are used for the purpose of securing freedom from excitement, lessened emesis, smoother anesthesia and freedom from some of the more annoying minor symptoms. In the light of what has been said of the pharmacology of morphin and scopolamin, it is also necessary to distinguish between the results obtained by those who use the method for all cases and those in which there is careful selection of suitable cases.

The argument has been advanced, that certain deaths following the use of scopolamin and morphin, particularly those reported by Israels, were not due to scopolamin, because there was marked fatty cardiac degeneration, but de Stella concluded that scopolamin causes widespread fatty degeneration, and Israels said he had

never seen fatty degeneration from such small amounts of chloroform as had been used in those cases. Sexton's patient died within an hour and fifteen minutes of the injection of 1/6 grain of morphin (1 cg.) and 1/100 grain of scopolamin (0.65 mg.), with the usual symptoms of scopolamin intoxication, paralysis of respiration and rapid pulse. Rigidity of the muscles prevented artificial respiration in this case, but in the light of experience in other similar cases, it would, in all probability, have done no good.

7. *Minor Disadvantages.*—Among the minor disadvantages which have been mentioned by different investigators are the following: When the morphin and scopolamin are once injected they are wholly beyond control. One surgeon writes of his emotions at seeing his patient die while he and his assistants stood by helpless to counteract the effects of the drugs they had administered.

Every additional narcotic complicates the anesthesia.

Scopolamin does not cause muscular relaxation, a disadvantage, when used with spinal anesthesia particularly, and we have seen that muscular spasm interfered with artificial respiration in one fatal case at least.

The prolonged sleep may prove a disadvantage, as already mentioned. Hirsch mentions its interference with expectoration after operations about the mouth, and it is said that the prolonged sleep and the attendant respiratory depression may favor pulmonary edema.

Intense thirst, dryness of the mouth and throat and the difficulty in swallowing are sometimes complained of by patients.

Different investigators have attempted to explain many of the accidents which occurred early in the history of scopolamin and morphin anesthesia, on the ground that the drugs employed were impure or that the solutions underwent changes whereby toxic substances were formed.

Kionka maintains that apotropin is the only impurity which could be concerned in the increased toxicity of the scopolamin, but he had never been able to detect this impurity in any of the specimens of scopolamin examined, hence he thought it must be extremely seldom that this impurity could be present. Apotropin may be detected by Kessel's method. Potassium permanganate causes a brown precipitate when one part of apotropin is present in 20,000 parts of the solution. Morphin and many other alkaloids give this reaction, hence it is not applicable to the mixture of scopolamin and morphin. The Swiss Pharmacopoeia (1907) does not mention this substance as an impurity in scopolamin. Kobert attributed the death of a man who had scopolamin to apotropin, which was said to be present as an impurity.

While solutions of scopolamin do undergo some unimportant physical changes as previously mentioned, it is probable that sterile solutions do not undergo any essential change in the course of a few months. Ries was unable to observe any difference between the effects of those solutions which had been freshly prepared and those which had been kept for some weeks. This agrees with the results of Kionka's experiments with freshly prepared, and old, solutions of scopolamin. Hotz states that milk sugar is said to prevent the deterioration of scopolamin solutions. The physical changes observed are said to be probably due to the alkali of the glass.

(To be concluded in the next issue. The bibliography of this article will be found at the end of the concluding portion.)