

4. Fascial repair is done in every case of recurrent incisional hernia.

5. Patients suffering from systemic disease should undergo careful preoperative rehabilitation.

6. The use of silk is preferred throughout in the closure of clean wounds.

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ABSTRACT OF DISCUSSION

DR. AMOS R. KOONTZ, Baltimore: I am especially interested in what Dr. Cave had to say about the use of silk in the closure of clean wounds. Silk has two advantages. First, it is not absorbed and therefore can be depended on to stay where it is placed until firm healing is secured. Second, there is very little reaction in the tissues around the silk sutures. The one big disadvantage of silk is that in the presence of infection it acts as a foreign body, and a sinus forms and persists, going down to the offending suture until the suture works its way out or is removed by the surgeon. This single disadvantage of silk is far outweighed by its advantages. Infections in clean wounds are now so rare as to be almost entirely negligible. On the other hand, what are some of the experiences with catgut? The chemicals with which catgut is treated in preparation cause a moist reaction in the tissues and a type of healing not nearly so firm as that obtained after suture with silk. Every one who has used much catgut has seen abdominal wounds break open two or three weeks after operation and the patient temporarily disemboweled. I have never seen that happen with silk. Another important point is the preoperative preparation of obese persons before attempting a cure for a postoperative hernia. Excessively obese persons should be put on a rigid diet and have their weight materially reduced. A great deal of the excess fat of obese persons is carried in the omentum. This increases intra-abdominal pressure. Besides, the fat in the abdominal wall weakens that structure, and both these factors militate against a cure of the hernia. Dr. Cave makes it a practice to soak ox fascia in physiologic solution of sodium chloride for two hours before operation. This is an excellent practice, as it is highly desirable to get all the alcohol removed before the fascia is implanted. One very important point in the operation for postoperative hernia, especially when fascia strips are used, is the question of drainage. Most of these patients are more or less obese, and a very extensive dissection is necessary in order to free the fascia in all directions from the large defect. If these wounds are not drained, a certain amount of serum almost invariably collects and tends to soften the tissues and delay healing. If the wounds are drained through an opening in the operative incision, secondary infection almost invariably ensues. My practice has been to use cigaret drains through stab wounds in the flank. These drains may be removed in from three days to a week and they keep the operative site absolutely dry, thus promoting firm and secure healing.

DR. ROBERT L. PAYNE, Norfolk, Va.: The ideal closure of an abdominal incision should include three factors: first, the approximation of every separate and distinct layer; second, total and complete obliteration of all dead spaces; third, the consummation of the first two points without tension on the blood and nerve supply of the tissues. I subscribe to the author's view that all ventral hernias begin from the inside out and that the most important structure of all those in the abdominal wall to coaptate properly is the transversalis fascia or the posterior sheath of the rectus. If this is properly approximated and held, the other structures will not separate. I believe that we are eventually going back to the procedures of our fathers and close all wounds with interrupted sutures. I believe that silkworm-gut through and through with careful separate coaptation of all the layers and with whatever material the individual operator prefers will give the best result. I cannot subscribe to the author's views regarding the use of silk. The first three years of my professional life I spent pulling out silk suture knots that were used in the hospitals where I worked. I never put in silk except in overlapping the full thickness of the abdominal wall and then only after boiling that silk on three consecutive days. One of the best procedures for the protection

of the patient against the occurrence of an incisional hernia is careful supervision after operation and providing for thorough and consistent postoperative narcosis. I mean by that that morphine or some other form of narcosis should be used freely enough to prevent those mechanical factors that contribute so much to incisional hernia from cutting of the tissues by sutures in the first four or five days after operation.

DR. GEORGE A. HENDON, Louisville, Ky.: I set about trying to find a simple way to close incisional hernias and to eliminate mortality. I chose a method by which I could perform the operation without opening the peritoneal cavity unless there was a specific reason to do so. When this was done the opening was immediately closed. I proceeded on the basis, which is an essential and vital factor in all plastic surgery, of obtaining contact without tension. I also realize the importance of the principle in plastic surgery that, other things being equal, the chances of success are in proportion to the area of fresh surfaces that are brought into contact. Therefore, the problem is to increase the area of contact and reduce the degree of tension. For that purpose the superficial abdominal fascia around the hernia protrusion is exposed for at least an inch from the margin of the ring. A suture is started as far back as possible and is carried through the fascia to emerge about one-fourth inch from the margin of the ring. The needle is then made to jump over the hernia opening and is again started into the fascia about one-fourth inch from the margin of the ring and emerges from the fascia as far back as the exposure will allow. A mattress suture may be used if one wishes to do so. When the sutures thus introduced are tied, there is a shelf of tissue turned inside the abdomen which divides the tension and increases the area of surfaces in contact. Pressure on the shelf will push it against the inner surface of the abdomen and tend to strengthen the closure. One thus avoids the morbidity, shock and danger incident to the opening of the peritoneal cavity. There is no danger of including the intestine in the suture line, because it is pushed away when the peritoneal and transversalis fascia is turned in. I often use this method of closure in the primary operation.

MEDICINAL TREATMENT OF THE COMMON COLD

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MINNEAPOLIS

Although the public takes more medication for colds, both on prescription and without prescription, than for the treatment of any other illness, little of real significance has been written concerning the treatment of colds. The Thomsons,¹ in their exhaustive review of over 2,000 papers on the common cold, devote only about five out of 700 pages to the subject of general medicinal treatment and then conclude concerning the various drugs which they mention that "no doubt all of these are of some value. Nevertheless, they frequently fail to produce the desired effect so that one cannot be by any means certain of their efficiency." In view of such knowledge, it seems like distinct temerity to suggest that certain well known drugs are of definite value in the treatment of colds; but this is what it seems one must conclude, tentatively at least, from the results of a controlled study of the treatment of colds which has been in progress for approximately a year at the Students' Health Service of the University of Minnesota.

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From the Students' Health Service and the Department of Preventive Medicine and Public Health of the University of Minnesota.

1. Thomson, David, and Thomson, Robert: *The Common Cold*, *Annals of the Pickett-Thomson Research Laboratory*, London, Baillière, Tindall & Cox, and Baltimore, Williams and Wilkins Company 8, 1932.

The reason for inaugurating this study was the consistently good results I obtained in the treatment of my own colds with morphine.² A one-fourth grain (16 mg.) tablet by mouth at bedtime on two consecutive nights was the usual dosage taken, although on several occasions complete relief followed a single dose. It was in order to determine whether similar results would occur in other persons that the study was undertaken.

EXPERIMENTAL PROCEDURE

The agency through which this study is being conducted is the dispensary of the Health Service of the University of Minnesota, to which students come for medical advice and treatment. The following bulletin to the physicians of the Health Service Staff will explain the procedure followed in the study:

A STUDY OF THE TREATMENT OF COLDS

As explained at the staff meeting on Nov. 2, 1932, it is proposed to determine the therapeutic value or lack of value of a certain drug which gives some indication of being useful for the treatment of acute head colds.

The plan to be followed is this: select for this study students who have acute coryza, preferably of one or two days' duration. Tell these students about the study and explain that we will be glad to give them the medication which we are trying if they will report what effects, if any, they observe. Unless students are willing to report results, do not include them in this group.

The nose and throat of each student who is to receive this medication should be examined and notes made on the student's dispensary record as to symptoms, date of onset of cold, and objective findings. A prescription giving the student's name, address, and weight should then be written for "Cold Medication." The pharmacist will fill this prescription according to directions. With the medication the student will receive a card upon which to report results, but in addition to this report he should be requested to return to the Health Service in two or three days for another inspection of the nose and throat. At this time the examining physician's impression as to whether or not there has been improvement objectively should be recorded.

The instructions to the pharmacist were to fill these "cold prescriptions" alternately with cold medication A and cold medication B. Cold medication A consisted of morphine sulphate in the following dosage: weight less than 100 pounds, (45.5 Kg.) $\frac{1}{8}$ grain (8 mg.) at bedtime; weight 100 to 149 pounds (45.5 to 67.6 Kg.) $\frac{1}{8}$ grain (10 mg.) at bedtime; weight 150 pounds (68 Kg.) or more, $\frac{1}{4}$ grain (16 mg.) at bedtime. Cold medication B consisted of lactose tablets of the same size, shape and color as the morphine tablets. The directions issued with the lactose tablets were the same as with the morphine. Two tablets were given on each prescription with the following directions: "Take one tablet, and only one, with water before retiring. If symptoms of cold are present the following evening, take the second tablet. Do not give either of these to any one else." No instructions were given in regard to diet, rest, hot baths, gargles and the like. The box containing the tablets was enclosed in an envelop in which was printed the instructions given in figure 1.

DETERMINATION OF RESULTS

The card for reporting results which was filled out by the person who received the medication is shown in figure 2.

2. Morphine was first used by the author to treat a cold merely as a substitute for powder of ipecac and opium (Dover's powder), but reference to prior use of this drug in colds is given by the Thomsons, who quote Watson as follows: "The treatment I find most useful is a single dose of morphine, gr. $\frac{1}{8}$, made up with a little capsicum and ol. menth. pep. (a small dose of nitroglycerin is also advantageous), in two hours 10 grains of aspirin and a hot bath. The following morning a purgative dose of magnesium sulphate is given to clear away the intestinal contents held back by the morphine."

When these report cards were returned they were checked for accuracy with the physician's notes on the dispensary record and classified as to type of cold and as to results of treatment. Classification as to type of cold was into one of the following groups: (1) acute coryza, i. e., colds of not more than four days' duration with serous discharge from the nose and with or without sore throat, headache, fever or other symptoms; (2) subacute or chronic head colds, i. e., colds with mucopurulent nasal discharge or with a serous discharge of more than four days' duration; (3) influenza,

COLD MEDICATION	
You will find enclosed some medication for the treatment of your cold. Our experience indicates that certain prescriptions which we are using are beneficial to most people but we want to check this carefully and request that you assist us in so doing by reporting results critically, favorable or unfavorable, on the card which will be sent to you in a few days thru the University mail.	
After filling in the card, return it to the Health Service thru the University mail.	
If you should fail to get relief by the time that you have taken all of this medicine please return to the Health Service for a different prescription. If relief is obtained with this medicine but symptoms recur, return for a refill of the same prescription.	

Fig. 1.—Instructions to patients.

i. e., acute infections of the upper respiratory tract characterized by headache, fever and general aching but without nasal discharge; (4) pharyngitis, i. e., a sore throat, with or without fever, headache, and the like but without nasal discharge; (5) other acute respiratory infections.

Any classification such as this based on symptoms is, of course, subject to inaccuracies, for an acute respiratory infection may be a pharyngitis today and a rhinitis, laryngitis, tracheitis or bronchitis tomorrow. Furthermore, coryza is a frequent complication of various respiratory infections such as influenza and pharyngitis. This tends to make the acute coryza group somewhat heterogeneous; but since, as the report will show, the inclusion of cases that were primarily influenza or pharyngitis tends to diminish rather than increase the proportion of good results, the classification will serve reasonably satisfactorily for these purposes.

Name.....
Date of beginning of cold.....
Symptoms before taking medicine:—watery discharge from nose:— (check) sore throat—thick yellow discharge from nose —headache—fever—general aching
Other.....
Date of first taking medicine:—.....
Condition next day (Note marked change)
.....
Was medicine taken on this day?.....
Condition on following day.....
Impressions as to effectiveness of treatment; i. e., did this cold run its usual course; if not, in what way was it different?

Fig. 2.—Card for reporting results of medication.

The cards reporting results were rated as indicating "definite improvement," "questionable improvement" or "no improvement." The ratings were made by me and independently by another physician without either of us knowing what medication had been given to the person making the report. Finally, the report from the pharmacist was obtained and the medication given to each patient was recorded.

These ratings, of course, represent merely the combined judgment of two physicians as to whether or not distinct improvement occurred immediately after treatment. No attempt was made to judge whether the

improvement, if any occurred, was the result of the medication, because the inclusion of a control group served to indicate how much improvement should be considered as due to spontaneous recovery. Some unselected examples of reports which were rated as showing "definite improvement," "questionable improvement" and "no improvement" are as follows:

DEFINITE IMPROVEMENT

1. First day, "very little change"; following day, "much better."
2. First day, "much improved"; following day, "all symptoms relieved."
3. First day, "improvement noticeable"; following day, "cold about gone."
4. First day, "better"; following day, "cold much relieved and almost gone."
5. "Complete cure," after first dose.

QUESTIONABLE IMPROVEMENT

1. First day, "cold was worse"; second day, "a little better." Comment: "The cold seem to disappear in a day or two less than usual."
2. First day, "no marked change"; second day, "slight improvement."
3. First day, "no marked change, headache gone"; second day, "a little better, voice clearer."
4. First day, "general aching eliminated perceptibly, other symptoms continued."

NO IMPROVEMENT

1. First day, "no improvement"; second day, "usual improvement."
2. First day, "no noticeable change, throat still sore"; second day, "about same as first day."
3. First day, "no improvement"; second day, "no change: cold ran usual course."
4. First day, "no better"; second day, "about the same."

As will be seen from these illustrations, there could be no question about the ratings that should be given to most reports. A few, however, are borderline and probably would be rated differently by different individuals. This might make some difference in absolute percentages of favorable and unfavorable results but, since the ratings were given without knowledge as to the medications received, it is probable that the differences between the results with the various medications would remain practically the same no matter by whom the ratings were given.

In figure 3 it will be seen that the proportion of reports rated as "questionable improvement" tends to increase as the proportion rated "definite improvement" decreases. This probably is due to the fact that some improvement usually occurs from day to day in the regular course of acute colds and, since many students had heard favorable reports of the treatment, there was a tendency for them to report the usual progress of the cold as "slight improvement." For this reason only reports rated as "definite improvement" are considered of much significance.

MEDICATIONS STUDIED

Although this study was instigated for the purpose of determining whether morphine is of value in the treatment of acute colds, the scope of the investigation was extended as soon as it became evident that this question could be answered in the affirmative. Codeine, papaverine, dilaudid (dihydromorphinone hydrochloride) and powdered opium were tried in the hope that they might prove more beneficial and less toxic than morphine.

The combination of codeine and papaverine was introduced with the thought that the codeine and the papaverine might be effective in different individuals. Dilaudid and papaverine were combined on the suggestion of Dr. Raymond Bieter, associate professor of

TABLE 1.—Medications Studied and Dosages Used for Persons Weighing 150 Pounds

Medication	Dosage	Directions
Morphine sulphate.....	$\frac{1}{4}$ grain tablets	1 at bedtime
Lactose.....	Small tablets	1 at bedtime
Codeine sulphate.....	1 grain tablets	1 at bedtime
Papaverine hydrochloride...	$\frac{1}{2}$ grain capsules	1 in a.m.; 1 in p.m.; 3 at bedtime
Codeine-papaverine (1).....	$\frac{1}{4}$ grain codeine with $\frac{1}{4}$ grain papaverine	1 in a.m.; 1 in p.m.; 3 at bedtime
Codeine-papaverine (2).....	$\frac{1}{4}$ grain codeine with $\frac{1}{2}$ grain papaverine	1 in a.m.; 1 in p.m.; 2 at bedtime
Dilaudid (1).....	$\frac{1}{48}$ grain capsules	1 in a.m.; 1 in p.m.; 4 at bedtime
Dilaudid (2).....	$\frac{1}{18}$ grain capsules	1 in a.m.; 1 in p.m.; 3 at bedtime
Dilaudid (3).....	$\frac{1}{75}$ grain capsules	1 in a.m.; 1 in p.m.; 3 at bedtime
Dilaudid (4).....	$\frac{1}{100}$ grain capsules	1 in a.m.; 1 in p.m.; 4 at bedtime
Dilaudid-papaverine (1).....	$\frac{1}{75}$ grain dilaudid with $\frac{1}{4}$ grain papaverine	1 in a.m.; 1 in p.m.; 3 at bedtime
Dilaudid-papaverine (2).....	$\frac{1}{75}$ grain dilaudid with $\frac{1}{2}$ grain papaverine	1 in a.m.; 1 in p.m.; 2 at bedtime
Acetylsalicylic acid-acetphenetidin-caffeine	$3\frac{1}{2}$ grains acetylsalicylic acid, $2\frac{1}{2}$ grains acetphenetidin, $\frac{1}{2}$ grain caffeine	1 in a.m.; 1 in p.m.; 3 at bedtime
Powder of ipecac and opium (1)	$2\frac{1}{2}$ grain capsules	1 in a.m.; 1 in p.m.; 3 at bedtime
Powder of ipecac and opium (2)	5 grain capsules	1 after lunch; 3 at bedtime
Opium powder.....	$\frac{1}{2}$ grain capsules	1 after lunch; 3 at bedtime
Sodium bicarbonate.....	10 grain capsules	3 after each meal; 4 at bedtime
Acetylsalicylic acid.....	5 grain capsules	1 every 2 hours first day and three times a day thereafter
Morphine-papaverine.....	$\frac{1}{16}$ grain morphine with $\frac{1}{2}$ grain papaverine	1 in a.m.; 1 in p.m.; 2 at bedtime

pharmacology, that papaverine might reduce the toxicity of the dilaudid. Later, papaverine was used in combination with morphine for the same reason.

Several other drugs extensively used in the treatment of colds, viz., powder of ipecac and opium, acetylsalicylic acid, sodium bicarbonate, and acetylsali-

TABLE 2.—Reports Not Returned and Reports Discarded

	Number Not Reporting	Percentages Not Reporting (of Totals Who Received Medication)	Number Discarded	Percentages Discarded
Morphine.....	27	8.1	26	9.1
Lactose.....	28	12.3	17	9.5
Dilaudid.....	2	1.9	8	7.8
Codeine.....	13	9.2	9	7.3
Powder of ipecac and opium.....	1	1.2	5	6.2
Acetylsalicylic acid-acetphenetidin-caffeine.....	2	2.7	4	5.8
Opium powder.....	0	0.0	2	4.9
Dilaudid-papaverine.....	1	1.0	4	4.2
Codeine-papaverine.....	9	2.9	8	2.8
Sodium bicarbonate.....	2	3.5	1	1.7
Acetylsalicylic acid.....	6	10.0	1	1.7
Papaverine.....	5	7.1	1	1.5
Morphine-papaverine.....	0	0.0	0	0.0
	96	5.9	86	5.8

cyclic acid-acetphenetidin and caffeine were added to the list of medications studied in order that their effectiveness might be evaluated in relation both to the control tablet and to the other drugs used. A complete list of the drugs studied and the dosages used for persons of average size is given in table 1.

Perhaps I should add that before any new drug combination was prescribed for students it was taken, in

larger dosage than was eventually used, by me and frequently also by other members of the health service staff.

REPORTS NOT RETURNED OR NOT RATED

Students who failed to report results within a week were sent follow-up notices with urgent requests for a report. As shown in table 2, a small percentage of students failed to respond even to these notices. Most

Constipation and diarrhea, the frequency of which is indicated by the following percentages, were not considered as significant toxic symptoms: constipation was reported after morphine by 2.6 per cent of the subjects, after codeine by 1.7 per cent, after opium powder by 4.6 per cent, after sodium bicarbonate by 4.2 per cent, after acetylsalicylic acid by 3.3 per cent, after dilaudid-papaverine by 2.1 per cent, after codeine-papaverine by 2.4 per cent, and after lactose by 1.2 per cent. Diarrhea was reported after morphine by 1.1 per cent, after opium powder by 2.3 per cent, after dilaudid-papaverine by 1 per cent, and after codeine by 1.7 per cent.

The frequency with which toxic effects were reported after the various drugs is shown in table 3. In considering this, allowance must be made for the fact that some of these symptoms, such as those reported after lactose, were caused by the infection and not by the medications that had been taken.

RESULTS IN ACUTE CORYZA

As previously stated, our so-called acute coryza group includes all persons who reported symptoms of a "watery discharge from the nose" and whose symptoms had not been present more than four days before treatment. Certainly most of the persons in this group had primary acute coryza, but in some cases the coryza was secondary to pharyngitis or influenza (grip). The results obtained with the different medications in this group of cases are shown in figure 3.

The percentages of individuals who reported definite improvement or complete cure of their colds within from twenty-four to forty-eight hours after taking morphine, dilaudid, codeine-papaverine, dilaudid-papaverine and morphine-papaverine are essentially the same, the differences in percentages of good results

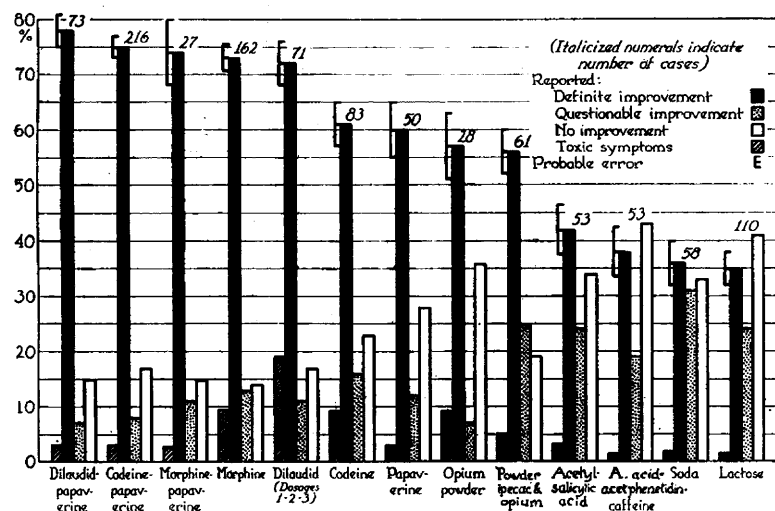


Fig. 3.—Various drugs in the treatment of acute coryza.

of the failures, however, occurred early in the study or during examination or vacation periods.

Of the reports received, eighty-six were discarded without ratings because of one of the following shortcomings: The medication had not been taken in accordance with directions; the medication was discontinued because of toxicity; the statements on the report card were too ambiguous for classification or the infection was in the lower rather than in the upper respiratory tract. Table 2 shows the numbers and percentages of reports discarded.

The relatively large proportion of reports discarded from persons who had received the morphine and lactose tablets is due to the fact that at the beginning of the experiment only one dose of the drug was given with instructions to return the following day to report results and to receive a second dose. However, because of the considerable proportion of patients who failed to return for the second dose, this plan was soon replaced in favor of the one that has been described. It will be noted also that the proportion of unsatisfactory reports is higher for the drugs which proved to be most toxic.

Although it would have been highly desirable to have all reports returned and rated, it is unlikely, in view of the distribution of the missing and discarded reports, that the results would have been much different had this been possible.

TOXIC EFFECTS OF THE DRUGS USED

A record was kept of all students who reported symptoms which they considered toxic effects of the drugs they had taken. The most common of these symptoms were nausea, vomiting, dizziness, "dopey feeling" and faintness or actual fainting. Fainting was reported to have occurred most frequently on rising in the morning after having taken the medicine the night before.

TABLE 3.—Toxic Symptoms Reported

	Percentage Reporting*						
	Total Reports Received	Vom- iting	Nausea With- out Vom- iting	Faint- ness or Faint- ing	Severe Head- ache	"Dopey or Feel- ing"	Percentage of Total Report- ing Sym- toms†
Dilaudid, dosages 1, 2, 3.	99	4.0	0.1	0.0	1.0	5.1	19.2
Morphine.....	279	2.6	3.7	1.4	0.4	1.1	9.4
Codeine.....	118	0.0	2.5	1.7	2.5	1.7	9.3
Opium powder.....	43	2.3	2.3	2.3	0.0	2.3	9.3
Powder of ipecac and opium.....	78	2.5	1.3	0.0	1.3	0.0	5.1
Acetylsalicylic acid.....	60	0.0	0.0	0.0	0.0	3.3	3.3
Papaverine.....	65	0.0	1.5	0.0	1.5	0.0	3.1
Dilaudid-papaverine.....	97	0.0	1.0	0.0	0.0	2.1	3.1
Codeine-papaverine.....	288	0.0	0.7	0.3	0.7	1.4	3.1
Morphine-papaverine.....	35	0.0	0.0	0.0	0.0	2.9	2.9
Sodium bicarbonate.....	58	0.0	1.9	0.0	0.0	0.0	1.9
Lactose.....	178	0.6	0.0	0.0	0.6	0.6	1.7
Acetylsalicylic acid-acet-phenetidin-caffeine.....	68	0.0	1.5	0.0	0.0	0.0	1.5

* Only the one symptom which seemed most outstanding in each case was tabulated.

† In making up these totals, constipation and diarrhea were not considered as toxic symptoms.

being without significance.^{2a} Codeine papaverine, dilaudid-papaverine and apparently morphine-papaverine, however, are preferable to morphine or dilaudid alone, because of their being distinctly less toxic (table 3).

2a. Some of the improvement after each of the medications is of course spontaneous and not the result of the treatment.

Codeine-Papaverine.³—One hundred and sixty-one of the 216 individuals, 75 per cent, who took the codeine-papaverine combination for acute coryza, reported definite improvement or complete cure in from twenty-four to forty-eight hours. This is 14 per cent more than reported similar results from codeine alone, and 19 per cent more than from papaverine alone. With such differences, the odds are 45 to 1 that the codeine-papaverine combination is more beneficial than codeine alone, and 79 to 1 that the same combination is more beneficial than papaverine alone.⁴ Codeine and papaverine were tried together in several proportions and dosages, the chief of which are shown in table 1 as dosages 1 and 2. The difference in the percentages of good results with these two dosages, however, 74 and 76 per cent, respectively, is not sufficiently great to be of significance. Hence the smaller dosage, $\frac{1}{4}$ grain of codeine with $\frac{1}{4}$ grain of papaverine, is now in use. The specific directions given with this codeine-papaverine combination to persons of various weights are as follows:

75 to 99 pounds: 1 after breakfast; 2 at bedtime.

100 to 129 pounds: 1 after breakfast; 3 at bedtime.

130 to 169 pounds: 1 after breakfast; 1 after lunch; 3 at bedtime.

170 pounds and over: 1 after each meal and, depending on weight, 3 or 4 at bedtime.

The change most frequently observed by persons who reported improvement was a prompt decrease or a complete disappearance of the nasal discharge and congestion. In many cases relief of the coryza was permanent following the first dose of the medicine, and even when there was a recurrence of congestion or discharge between doses the relief that followed the medication lasted for several hours. Furthermore, although the excessive secretion was controlled, the unpleasant dryness that usually occurs when atropine is taken for this purpose was not experienced. The pharyngitis, laryngitis and tracheitis that occur with certain colds were not materially affected by the medication. The relief of the coryza, however, very definitely reduced the discomfort and incapacity and in most cases seemed practically to eliminate the protracted period of mucopurulent discharge. This was particularly noticeable when the medication was taken at the very beginning of symptoms.

Unpleasant symptoms, such as nausea, dizziness, headache and fainting, were infrequent following the codeine-papaverine combination (table 3).

When one is prescribing derivatives of opium, a question as to the danger of habituation naturally arises. Concerning addiction to papaverine, New and Non-official Remedies⁵ says that "its toxicity is low, and neither tolerance nor habituation has been reported." Addiction to codeine may occur, but it is so rare that Wolff⁶ states that "codeine is not practically dangerous from the point of view of habituation and, like papav-

erine, does not come under the German opium law." Furthermore, the use of these drugs for the treatment of colds is occasional and for only short periods of time. Hence it would seem that one need have no concern in regard to habituation when using this drug combination for the treatment of acute colds.

Dilaudid-Papaverine.—The results obtained with dilaudid-papaverine were practically identical with those reported for codeine-papaverine, the differences that appear in figure 1 being too small to be of significance. In at least two cases, however, dilaudid-papaverine gave prompt and permanent relief after the codeine-papaverine combination had produced only temporary improvement. Whether or not one of these combinations will tend to be effective in any considerable number of cases when the other is ineffective is being investigated. The proportion of patients who reported "definite improvement" after the dosages of dilaudid-papaverine (shown in table 1) were 77 and 80 per cent, respectively, a difference not sufficiently great to be significant. The specific directions given to the several weight groups for the use of the dilaudid-papaverine combination are the same as for the use of the codeine-papaverine combination.

The proportion of patients who reported toxic results after dilaudid-papaverine was approximately the same as after codeine-papaverine. The total incidence of toxic symptoms after dilaudid-papaverine, however, was only about one sixth as great as after dilaudid alone. These results, as well as those with the codeine-papaverine and morphine-papaverine combinations, strongly suggest that papaverine may be effective in reducing the toxicity of morphine, codeine and dilaudid. The danger of habituation from the dilaudid-papaverine combination in the dosage used is certainly negligible if not absolutely nil.

Morphine-Papaverine.—The number of cases treated with this combination is too small to justify generalizations, but since the results with it are no better than with codeine-papaverine or dilaudid-papaverine, there does not seem to be any reason for continuing its use. The toxic effects from the morphine-papaverine combination appear to be distinctly less than those from morphine alone.

Morphine.—This drug, with which our study was started, is apparently of definite value in the treatment of acute coryza. However, the larger proportion of toxic results after it and the hesitancy of physicians to prescribe morphine because of the danger of addiction make it less desirable for extensive use than the several combinations already discussed.

Dilaudid (dihydromorphinone hydrochloride).—Beneficial results with dilaudid alone, in the larger dosages used, were approximately as frequent as with the other effective drugs or drug combinations, the proportions of "definite improvement" reported after dosages 1, 2, 3 and 4 (table 1) being 76, 69, 65 and 47 per cent, respectively. However, the large proportion of unpleasant effects after dilaudid (table 3) caused its discontinuance in favor of the less toxic combination of dilaudid with papaverine.

Concerning the dangers of habituation to dilaudid, Wolff⁶ says that "it has been shown both experimentally and clinically that it leads more slowly to habituation and addiction than morphine and its devotees are therefore more easily cured."

3. A patent application has been filed to enable the University of Minnesota to control the preparation and sale of the new drug combinations indicated by this study to be of value in the treatment of the common cold. Specifically these combinations are codeine with papaverine, dilaudid with papaverine, and morphine with papaverine. It is not intended, however, that this patent shall interfere with the use of these drugs in the compounding of prescriptions written by physicians for their patients.

4. Pearl, Raymond: Medical Biometry and Statistics, Philadelphia, W. B. Saunders Company, 1933.

5. New and Nonofficial Remedies, Chicago, American Medical Association, 1933, p. 307.

6. Wolff, Paul: Drug Addiction: A World-Wide Problem, J. A. M. A. 98: 2175 (June) 1932.

Codeine.—Codeine is evidently of definite though less value than morphine in the treatment of acute coryza. Toxic effects after codeine were just as frequent as after morphine.

Papaverine.—Papaverine, which seems to be practically nontoxic, gives approximately the same proportion of good results as codeine (57 per cent of fifty-two cases and 61 per cent of eighty-three cases, respectively).

Powder of Ipecac and Opium.—This powder, consisting of 10 per cent powdered opium and 10 per cent powdered ipecac, seems to have been first proposed for the treatment of colds by Dover,⁷ an English physician, in the seventeenth century. For many years it was extensively used, but pharmacists state that recently it has been almost completely replaced by the more actively promoted antipyretics, alkalis and the like. However, Cecil,⁸ in his book on colds, recommends powder of ipecac and opium as the medication of choice in the general treatment of colds.

The dosage in which powder of ipecac and opium was first used in this study was that ordinarily prescribed by physicians (dosage 1, table 1). Later the dosage was increased (dosage 2, table 1), so that the amount of available morphine which it contained was approximately the same as the amount of morphine that was being prescribed when morphine was given alone. With the larger dosage, however, there was no significant improvement in results, "definite improvement" being reported after dosages 1 and 2 by 54 and 58 per cent of cases, respectively.

The results (figure 3) with this time-honored remedy indicate that it has real merit. However, since powdered opium alone gives as good results as the powder of ipecac and opium, it would seem that its value lies in the ability of the opium to relieve the nasal congestion and secretion and not, as commonly supposed, in the stimulation of secretions and sweating produced by the combination of the opium and ipecac.

A few individuals reported nausea and vomiting following the powder of ipecac and opium, but the percentage of these was small.

Opium Powder.—Powdered opium was tried in order to compare the results with it to those obtained with morphine and with powder of ipecac and opium. The dosage of opium used was such that it contained approximately the same amount of available morphine as that administered when morphine was used alone. This also was the same amount of opium as was contained in the larger dosage of powder of ipecac and opium.

The percentage of persons reporting "definite improvement" with the powdered opium was less than with morphine, but the same as with powder of ipecac and opium (fig. 3). Why opium should be less beneficial than morphine or morphine-papaverine or codeine-papaverine is not clear, although it is possible that smaller proportions of these alkaloids are absorbed when opium is used than when the alkaloids are taken separately.

The proportion of toxic symptoms from the opium was the same as from morphine or codeine but greater than from the codeine-papaverine combination. The possibilities of addiction to opium are too well understood to need comment, but certainly there is no danger

of developing habituation when the drug is used as it was in this study.

Lactose.—It seemed essential at the beginning of this study to have reports from a series of patients who thought they were taking some presumably effective medication but who in reality received no medication whatever. For this purpose tablets and capsules of lactose were employed. The proportion of good results (35 per cent) reported after lactose is indicative of the spontaneous improvement in acute colds for which any medication that happens to be taken is given credit. It is because this percentage is so large that it is possible to convince the public that practically any preparation is of value for the prevention or treatment of colds. In fact, some of the comments that were made on the report cards by persons who had received only lactose tablets would serve admirably as testimonials concerning the value of these tablets for the treatment of colds.

It would have been desirable, of course, to continue this control group throughout the year, but after reports

UNIVERSITY OF MINNESOTA—STUDENTS' HEALTH SERVICE	
Name.....	
Will you be good enough to answer a few more questions in order to help us to determine the value of the medication which you received for a cold on.....? These questions are:	
1. How many days or half days were you absent from classes or work because of this cold?	
(a) before treatment.....days.	(b) after treatment.....days.
2. Did you "stay in" any other time over a week-end or holiday because of this cold?	
(a) before treatment.....days.	(b) after treatment.....days.
3. What was the approximate total duration of this cold?.....days.	
4. Did you observe any unpleasant effects which seemed to be due to the medication, such as diarrhea, constipation, etc? If so, what?	
After filling in the answers to the above questions, please drop this card in the University mail.	
If you received treatments for colds, other than the one noted above, additional cards will be sent you.	
H. S. DIEHL, M.D., Director	

Fig. 4.—Follow-up report on results of treatment.

from a hundred patients had been received we did not feel justified in continuing it further.

Acetylsalicylic Acid-Acetphenetidin-Caffeine.—The proportion of persons (37 per cent) who reported beneficial results from this drug combination is not significantly greater than that reporting benefit from the sugar capsule. A few stated that headache was relieved but that other symptoms continued unchanged. The majority, however, seemed to get no benefit whatever.

Acetylsalicylic Acid.—Because acetylsalicylic acid is so widely used in the treatment of colds, it was tried alone. The proportion of good results (42 per cent), however, was not significantly greater than that with the sugar capsule.

Sodium Bicarbonate.—During the past few years the so-called alkalization treatment of colds, by means of sodium bicarbonate, other mild alkalis or citrus fruits, has been much advocated. Some of this has been based on medical writings,⁹ but most of it on the promotion of medicinal preparations or citrus fruits by advertisers.

In our study, sodium bicarbonate in dosages of 130 grains (8.5 Gm.) a day for the adult of average size was used (table 1). This amount was believed suffi-

7. Stedman, T. L.: Medical Dictionary, New York, William Wood & Co., 1928.

8. Cecil, R. L.: Colds: Cause, Treatment and Prevention, New York, D. Appleton & Co., 1927.

9. Cheney, V. S.: The Common Cold: Etiology, Prevention and Treatment, Am. J. Pub. Health 18:15-20 (Jan.) 1928.

cient to produce at least as much "alkalization" as is usually obtained with this treatment. The results, as shown in figure 3, are approximately the same as those reported after acetylsalicylic acid, the acetylsalicylic acid-acetphenetidin-caffeine combination, and lactose. In other words, this study gives no evidence that alkalinization is of value in the treatment of the common cold.

TABLE 4.—Duration of and Time Lost on Account of Acute Colds

Medication	Num-ber of Cases	Average Time Lost After Treatment, Days		Percentages Who Lost No Time		Average Duration of Symptoms, Days	
		From School or Other Work	Usual Activities, Total	From School or Other Work	Usual Activities, Total	Before Treatment	After Treatment
Codeine-papaverine...	129	0.2	0.5	87.1	78.0	2.8	4.3
Dilaudid-papaverine...	42	0.3	0.5	85.3	80.5	2.6	2.8
Papaverine.....	29	0.3	0.4	79.3	62.1	2.8	6.2
Acetylsalicylic acid...	20	0.3*	0.6*	83.3*	66.7*	2.6*	5.8*
Morphine.....	85	0.3	0.7	80.0	64.2	2.4	4.0
Codeine.....	62	0.4	0.7	72.7	59.3	2.7	5.4
Powder of Ipecac and opium.....	42	0.4	0.8	79.5	67.4	2.9	8.4
Morphine-papaverine...	11	0.5*	0.6*	63.7*	63.7*	2.3*	4.3*
Sodium bicarbonate...	27	0.5	0.9	72.0	68.0	2.9	5.3
Opium powder.....	16	0.5*	0.9*	50.0*	33.3*	2.7*	4.1*
Lactose.....	61	0.6	1.2	72.6	62.9	2.6	6.7
Acetylsalicylic acid-acetphenetidin-caffeine.....	36	0.6	1.5	73.0	51.4	2.8	4.6
Dilaudid (dosages 1, 2 and 3).....	42	0.8	1.1	64.3	47.2	2.9	4.4

* Based on less than twenty-five cases; hence, unreliable.

VARIATION IN RESULTS THROUGHOUT THE YEAR

Since no single medication was used continuously, it is impossible to speak with certainty of variation in results throughout the year. However, the results suggest that colds tend to become more severe as the winter progresses. This may be due to an increase in the virulence of the infections or, what is more likely, to a decrease in resistance of the victims.

TABLE 5.—Results in Subacute and Chronic Colds

Medication	Total Cases	Percentages Reporting*		
		Definite Improvement	Questionable Improvement	No Improvement
Codeine-papaverine.....	47	36	21	39
Dilaudid-papaverine.....	13	31	31	46
Morphine-papaverine.....	8	25	13	62
Morphine.....	50	48	24	28
Dilaudid.....	15	47	26	27
Codeine.....	21	43	33	24
Papaverine.....	13	38	31	31
Opium powder.....	10	50	10	40
Powder of Ipecac and opium	8	38	12	50
Sodium bicarbonate.....	8	63	12	25
Acetylsalicylic acid-acetphenetidin-caffeine.....	10	30	30	40
Acetylsalicylic acid.....	11	55	27	18
Lactose.....	48	35	31	34

* Most of the percentages in this table are subject to considerable variability because of the small number of cases on which they are based.

A marked decrease in the proportion of reports of "definite improvement" in May with all medications was coincident with, if not actually due to, the prevalence among the student body of a severe infection of the upper respiratory tract characterized primarily by an acute pharyngitis. Many of these patients developed coryza and so were classified in the acute coryza group.

In December there was an epidemic of mild influenza, or grip, among the students. Some of these patients

developed coryza and so were given the "cold medications" in use at that time. One of these was the control tablet, and since most of these infections were very mild and of short duration, the proportion of persons reporting definite improvement following the lactose tended to increase during this period.

INFLUENCE OF TREATMENT ON TIME LOST AND ON TOTAL DURATION OF ACUTE COLDS

After this experiment had been in progress about a month, it was decided to check the results by comparing the amount of time lost and the total duration of colds following the various medications. Information relative to this was obtained from a card (fig. 4) which was sent to university students three weeks after treatment.

As may be seen by comparing totals in figure 3 and table 4, these reports of time lost were not received from nearly all the persons treated. For this there are several obvious reasons: viz., the loss of interest on the part of students because of the long interval of time between treatment and the request for this report; the occurrence of vacation periods at the time this report was due; a lack of follow up if the first card was not returned, and the sending of these cards only to certain students in order that all reports would be from individuals under similar regulations in regard to absence from class.

TABLE 6.—Results in Influenza

Medication (4)	Total Cases	Percentage Reporting		
		Definite Improvement	Questionable Improvement	No Improvement
Acetphenetidin.....	33	48	30	22
Morphine-acetphenetidin....	37	42	29	29

The considerable proportion of these reports which are lacking introduces such a large element of possible error that the validity of results indicated by the tabulation is questionable. On the other hand, there is no reason to think that the comparative results with the different medications are not of some significance.

In table 4 are presented the average amounts of time lost from usual activities by patients who received the various medications, the proportion of each group who lost no time, and the average duration of symptoms before and after treatment. From this tabulation it appears that the loss of time by persons who received the medications indicated by figure 3 to be most beneficial and least toxic is significantly less than by those who received the least effective group of drugs.¹⁰ For example, the average amount of time lost from school or work by students who took codeine-papaverine (0.23 day) or dilaudid-papaverine (0.25 day), was approximately half as great as the amount of time lost by those who took sodium bicarbonate, lactose or the acetylsalicylic acid-acetphenetidin-caffeine combination, 0.52, 0.61 and 0.65 day, respectively. The total amount of time after treatment lost from all usual activities is in approximately the same ratio, viz., one-half day after codeine-papaverine or dilaudid-papaverine as compared to from one to one and a half days after sodium bicarbonate, lactose and the acetylsalicylic acid-acetphenetidin-caffeine combination.

10. The only exception to this is acetylsalicylic acid, the loss of time after which is only about half as great as after lactose or the acetylsalicylic acid-acetphenetidin-caffeine combination, which, according to other reports, are of as much value as acetylsalicylic acid. Hence this difference is doubtless without significance and due to the small number of cases.

The figures in regard to the total duration of the colds are of less significance because it is difficult to determine the exact date of termination of a cold. In general, however, these average durations tend to show differences between the medications similar to those suggested by the amounts of time lost.

RESULTS IN SUBACUTE OR CHRONIC COLDS

The group of subacute or chronic colds consists for the most part of individuals with colds of more than four days' duration at the time of treatment, although cases of shorter duration were included if a "thick yellow nasal discharge" was reported. The results of treatment in these subacute or chronic colds (table 5) give no indication that any of the medications used are beneficial. The actual percentages rated "improvement" show considerable variability, but in view of the small numbers of cases on which these are based the differences are without significance.

RESULTS IN INFLUENZA

The effect of morphine in mild influenza without coryza was tested both in ambulatory and in bed patients. The ambulatory patients alternately received acetphenetidin and acetphenetidin plus morphine in the dosages shown in table 1. All the bed patients received the acetylsalicylic acid-acetphenetidin-caffeine combination, but in addition every second patient was also given morphine in the dosage previously indicated.

As to the proportion of influenza patients in whom coryza developed and who consequently were included in our acute coryza group, we have no information, but Doull and Bahlke¹¹ report that in an influenza epidemic among the resident nurses of Johns Hopkins Hospital, in the winter of 1928-1929, 51 per cent of the patients exhibited coryza as a "first day" symptom. In connection with the study here reported, several members of the health service staff who had influenza with symptoms of coryza and who took morphine reported relief from the symptoms of coryza but no other effect on the course of the infection.

The summary of the reports from the ambulatory patients appears in table 6. Results in the hospitalized patients were estimated by comparing the average number of days that the two groups were confined to bed. These were 2.6 days for twenty-four patients who had received the usual treatment and 2.4 days for sixteen patients who in addition had received the morphine. None of these results suggest any value for morphine in the treatment of influenza without coryza.

RESULTS IN PHARYNGITIS

The cases of pharyngitis are too few to justify conclusions, but the results do not suggest any value for the codeine-papaverine combination in this condition.

COMMENT

It seems quite definite from the results of this study that opium and the major alkaloids derived from it are of distinct value in the treatment of acute coryza. The chief result observed is a marked decrease or complete disappearance of the nasal congestion and discharge. This effect occurs promptly and is usually prolonged or permanent. Rest or sweating is not a factor, although it is reasonable to suppose that secondary infections are less likely to develop if general hygienic measures are followed.

The failure to get good results with any of the medications in cases of influenza and pharyngitis suggests that the variability in results throughout the year may be due, in part at least, to differences in the types of infections causing the coryza. The absence of good results in subacute and chronic colds seems to indicate that beneficial results can be expected only before secondary infections have set in.

SUMMARY OF RESULTS

1. This study shows the relative values of various drugs and drug combinations in the treatment of 1,039 cases of acute coryza, 262 cases of subacute or chronic colds, 114 cases of influenza and 53 cases of acute pharyngitis.

2. Of the drugs studied, only opium and certain alkaloids derived from it seem to be of value in the treatment of acute coryza.

3. Combinations of papaverine with codeine, papaverine with dilaudid, and papaverine with morphine were followed by "definite improvement" in from 74 to 78 per cent of the cases, and in the dosages used these combinations seem to be practically nontoxic.¹²

4. For general use a combination of codeine and papaverine seems most desirable because of the high per centage of good results obtained with it, its low toxicity, and the absence of danger, or at least of "practical danger," of habituation to it.

5. Morphine and dilaudid (dihydromorphinone hydrochloride) alone were followed by "definite improvement" in nearly as large a proportion of cases (73 and 72 per cent, respectively) but each was distinctly more toxic alone than when combined with papaverine.

6. Codeine, papaverine, powdered opium, and powder of ipecac and opium were followed by "definite improvement" in from 56 to 61 per cent of cases. The toxicity of these drugs is in the following order: codeine, powdered opium, powder of ipecac and opium and papaverine, with codeine practically as toxic as morphine.

7. Powder of ipecac and opium, although of value in the treatment of acute colds, is no more beneficial than the same amount of powdered opium without the ipecac.

8. Sodium bicarbonate, acetylsalicylic acid and a combination of acetylsalicylic acid-acetphenetidin-caffeine give little if any better results in the treatment of acute coryza than the lactose tablet used as a control, each being followed by "definite improvement" in from 35 to 42 per cent of cases.

9. A computation, based on incomplete reports of time lost from their usual activities by patients who received the various medications suggests that it may be possible with the codeine-papaverine or dilaudid-papaverine combinations to reduce very materially the amount of time lost as a result of acute colds.

10. None of the medications studied seem to be of benefit in subacute or chronic colds.

11. Morphine was tried in influenza but was of no value.

12. The number of cases of pharyngitis treated were too few to justify conclusions, but none of the drugs seemed of value.

Students' Hospital and Dispensary.

11. Doull, J. A., and Bahlke, Anna M.: Epidemic Influenza: A Comparison of Clinical Observation in a Major and Minor Epidemic, *Am. J. Hyg.* 17: 562 (May) 1933.

12. Further experience, since the preparation of this paper, with the dilaudid-papaverine combination shows it to be more toxic and of no greater benefit than the codeine papaverine combination.