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THE XANTHINES (THEOBROMINE AND AMINOPHYLLINE) IN THE TREAT- MENT OF CARDIAC PAIN

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An endeavor was made in this study to secure evidence on the question of whether the xanthines relieve cardiac pain.

SELECTION OF PATIENTS

The subjects were 100 ambulant patients in attendance at the cardiac clinic, in whom the diagnosis of arteriosclerotic heart disease with cardiac pain was made, in accordance with the nomenclature and criteria adopted by the New York Heart Association.¹

They were selected from a total case load of approximately 700 patients, representing an average sample of the cardiac clinic population, comprising several racial groups, both native and foreign born. The study was conducted during a period of five years. The duration of the study in any given case varied from two to fifty months, the average being fifteen months.

Some of the characteristics of the whole group are listed in table 1.

None of these patients had signs of congestive heart failure. Only patients with pain on effort were studied, although it was realized that some cases of true cardiac pain were excluded by this restriction. However, this measure served further to insure against the inclusion of patients in whom the thoracic pain might be of non-cardiac origin.

The severity of the pain varied greatly, from mild substernal pressure or discomfort induced by moderate effort, only slightly interfering with the patient's ability to carry on (1+), to excruciating pain induced by the slightest effort, occurring also when the patient was at rest, so as to cause almost complete incapacity (3+).

Careful questioning of the patient at every visit to the clinic made it possible to exclude those cases in which there was reason to believe that cooperation in the uninterrupted use of whatever drug was issued and in the accurate reporting of any omissions was not sufficiently faithful for the purpose of this study.

If the xanthine should produce a moderate improvement in the efficiency of the coronary circulation, the

effect of this might conceivably escape detection in individuals engaged in very heavy work. From this point of view our subjects were particularly favorable for this study, since most of them, as shown in the table, were not engaged in any occupation.

GLYCERYL TRINITRATE TEST

Early in the course of the study it was believed desirable to restrict the selection of patients to those who could establish their qualifications for service in such a study as this by their ability to distinguish between the efficacy of glyceryl trinitrate taken under the tongue and a soluble placebo tablet taken in the same manner for relief during attacks of pain. The discovery of several patients who found the two equally effective among those who had suffered an attack of coronary thrombosis and were subject to thoracic pain on effort led us to abandon this restriction.

The results obtained in sixty patients in whom the glyceryl trinitrate test was made are of some interest. These patients received glyceryl trinitrate tablets, $\frac{1}{100}$ or $\frac{1}{150}$ grain (0.6 or 0.4 mg.), which they were directed to take under the tongue at the onset of an attack of pain. In many of these cases, periods of glyceryl trinitrate testing were alternated with periods in which a soluble placebo was dispensed. The duration of these periods was from one week to several weeks in each case. The results are presented in table 2. Of the sixty patients, forty-nine (82 per cent) reported relief by the use of glyceryl trinitrate during attacks. Of eighteen cases in which the soluble placebo was also used, fourteen (78 per cent) reported relief of symptoms. This is not a strictly valid comparison of the relative effectiveness of the placebo and glyceryl trinitrate because of the small number of cases in which the placebo was used. Nevertheless these results give some idea of how often a placebo taken under the tongue may be judged by the average clinic patient to afford relief during attacks of cardiac pain.

The qualification of the patient to testify regarding the efficacy of a vasodilator drug is, no doubt, best established in those cases in which the attack of pain is such as to enable the patient always to distinguish between the glyceryl trinitrate and the placebo. However, the fact that the patient believed that he obtained partial or even complete relief with the placebo during brief attacks of pain does not necessarily disqualify his testimony in a study of theobromine. A patient who is subject to brief attacks of cardiac pain on effort which necessitate immediate interruption of the physical activities and which, in turn, leads to rapid cessation of pain, may easily be in error in judgment regarding the efficiency of a drug used to terminate the attack. Such a patient, however, need not necessarily have difficulty in distinguishing a potent from an inert agent when the

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Faithful cooperation was rendered throughout the course of this study by Miss Kathleen Scott, (social worker, Hospital for Joint Diseases) and Miss Margaret Slevin, (social worker, Beth Israel Hospital).

1. Criteria for the Classification and Diagnosis of Heart Disease.

results compared are changes in the frequency of attacks and in the capacity for effort without distress. These individuals, therefore, are entirely suitable for the study of the effects of a drug like theobromine, which is presumed to act over a protracted period.

DRUGS AND OTHER TREATMENT

Most of these patients had been in attendance at the clinic for a long time when the study was started, and many of them were already subject to restrictions in

TABLE 1.—Classification of One Hundred Patients with Arteriosclerotic Heart Disease and Cardiac Pain

Average age	57.6 years
Age range	40-82 years
Number of males	85
Number of females	15
Number with hypertension (25 males, 9 females).....	34
Number with electrocardiographic changes indicating myocardial damage	51
Number with coronary thrombosis (30 males, 3 females)..	33
Classification of pain based on severity, duration and frequency of attacks, and degree of physical limitation:	
Slight (1+)	9
Moderate (2+)	45
Severe (3+)	46
Occupation:	
Number not working	75
Number working (15 women doing limited housework; 7 men engaged in light part-time work; 3 men engaged in light full-time work).....	25
Range of periods of study.....	2-50 mos.
Average period of study.....	15 mos.

diet and effort. No advice was given for modification of habits or activities during the course of this study.

The choice of a xanthine presented a problem. The results of animal experiments dealing with their effect on the coronary circulation are conflicting. Smith, Miller and Graber² found theophylline preparations more effective than other xanthines. In contrast, Gilbert and Fenn³ and Heathcote⁴ found theobromine preparations more effective than those of theophylline. There is also considerable divergence of opinion in the clinical literature on the relative merits of different members of the xanthine group. It has been stated⁵ that therapeutic effects may be produced by one member when another has failed. Each has its adherents (diuretin,⁶ theophylline,⁷ theobromine⁸). The one that appears to be most popular at the present time is theophylline with ethylenediamine, although some⁵ maintain that theobromine or its preparations are equally effective and sometimes more effective.

The drugs were dispensed in the clinic. In this study theobromine in the form of a 5 grain (0.3 Gm.) tablet was used in all the cases, and in twelve of them tests with aminophylline (theophylline with ethylenediamine), given in 1½ grain (0.1 Gm.) tablets, were also carried through. The total daily dose of theobromine varied from 15 to 60 grains (1 to 4 Gm.), given in single doses of from 5 to 15 grains (0.3 to 1 Gm.) at intervals of about six hours. The highest daily dosage of theobromine was from 15 to 25 grains (1 to 1.6 Gm.) in

26 per cent of the cases, 30 grains (2 Gm.) in 53 per cent, and between 40 and 60 grains (2.6 to 4 Gm.) in 21 per cent. The highest total doses of aminophylline were 9 and 12 grains (0.6 and 0.8 Gm.) daily in all cases except one, in which the highest dose was 6 grains (0.4 Gm.). These were given in single doses of 3 grains (0.2 Gm.) three or four times a day. These doses correspond to the high doses given by others and exceed the doses used in the majority of reports in the literature.

The xanthines were given in courses lasting from one to twenty-five weeks, the average lasting three and one-half weeks. Some patients received as many as seven courses; the average was two courses for each patient. Several courses of treatment with the xanthine and the placebo were carried through, especially in those cases in which obvious factors that might vitiate a valid comparison existed, such as a change of weather or of work. In all, 209 courses of treatment with the xanthines were given. Each course was alternated with a period in which the patient received various agents such as sodium salicylate, acetylsalicylic acid, calomel, quinidine, cascara, mixture of rhubarb and soda (N. F.), digitalis, phenobarbital or codeine. In each case a comparison was also made of the efficacy of the xanthines with that of lactose.

The physical characteristics of the oral placebo that we used as a routine, a tablet of lactose, were not identical with those of the xanthine. It was not considered necessary to have them identical for those patients who reported no improvement while taking a xanthine. However, it was essential to take the factors of size, shape and taste into account in the subsequent testing in cases in which improvement occurred during the use of the xanthine but which failed to continue when the medication was changed. The validity of the control was materially enhanced by the fact that the duration of the courses with the placebo and the xanthines was fairly long and that courses of each were

TABLE 2.—Efficacy of Glyceryl Trinitrate and Placebo in Providing Relief During Cardiac Pain

Number of Patients	Glyceryl Trinitrate	Placebo
34.....	+	0
2.....	+	—
8.....	—	0
9.....	+	+
4.....	+ or —	+ or —
2.....	—	—
1.....	—	+
Total.....	60	18

(+) Attacks always relieved; (—) not relieved; (0) not tested; (+ or —) sometimes relieved and sometimes not.

repeated frequently, at different seasons of the year, and under other conditions as nearly comparable as possible.

METHOD OF SECURING DATA

The method of securing data proved to be by far the most laborious aspect of the whole work. The validity of the results in this study depends chiefly on the nature of the questions that the patient was asked and the accuracy of the answers. No effort was spared in the endeavor to secure the patient's most accurate judgments, since these judgments regarding changes in the severity of a subjective symptom formed the factual data on which the analyses are based. It was fully realized that the study could be no better than this part of the work.

2. Smith, F. M.; Miller, G. H., and Graber, V. C.: The Effect of Caffeine Sodio-Benzozate, Theobromine Sodio-Salicylate, Theophylline and Euphylline on the Coronary Flow and Cardiac Action of the Rabbit, *J. Clin. Investigation* **2**: 157 (Dec.) 1925.
3. Gilbert, N. C., and Fenn, G. K.: The Effect of the Purine-Base Diuretics on the Coronary Flow, *Arch. Int. Med.* **44**: 118 (July) 1929.
4. Heathcote, R. St. A.: The Action of Caffeine, Theobromine and Theophylline on the Mammalian and Batrachian Heart, *J. Pharmacol. & Exper. Therap.* **16**: 327 (Dec.) 1920.
5. Gilbert, N. C., and Kerr, J. A.: Clinical Results in Treatment of Angina Pectoris with the Purine-Base Diuretics, *J. A. M. A.* **92**: 201 (Jan. 19) 1929.
6. Breuer, R.: Zur Therapie und Pathogenese der Stenokardie und verwandte Zustände, *München. med. Wehnschr.* **49**: 1604, 1902.
7. Smith, F. M.; Rathe, H. W., and Paul, W. D.: Theophylline in the Treatment of Disease of the Coronary Arteries, *Arch. Int. Med.* **56**: 1250 (Dec.) 1935.
8. Willius, F. A.: Newer Methods in the Treatment of Diseases of the Heart, *Collected Papers of the Mayo Clinic* **18**: 670, 1926.

It is not feasible to describe in detail the technic of the questioning; it varied from patient to patient. It should be stated, however, that the hurried interrogation of the average clinic routine history proved entirely inadequate for our purpose.

Some general principles that we endeavored to take into account may be mentioned:

The study was started during a period which the patient regarded as representing pain of average severity or the habitual status. The condition on the previous visit served usually as the point of reference in plotting the subsequent course. However, when the visits were more infrequent and the patients seemed uncertain of this point of reference, they were directed to relate the severity of the symptoms to their habitual status. Patients were also directed to consider in their judgment the frequency, the severity and the duration of the pain, and any change that they might have been able to detect in their ability to carry on their usual affairs without pain. The record of each visit included the patient's estimate of the entire period since the last visit and not merely one or two days during the period or the last day of the period.

It was found that, in the initial reply regarding changes in pain, patients often failed to take into account all the necessary factors on which the judgment was to be based, and, not infrequently, more thorough questioning resulted in their revision of their first appraisal. Therein was appreciated an important source of error of another kind; namely, the leading question. Various devices were employed to guard against directing the patient's judgment. Usually they were frankly informed that the examiner was uncertain as to whether the medicine would prove helpful or not, and the idea was conveyed to them that, in any case, subsequent planning for their treatment depended on the accuracy of their statements regarding their condition during the period that had elapsed. In a further attempt to eliminate the possibility of bias, the questioner usually refrained from informing himself as to the agent that had been issued until after the patient's appraisal of the period had been obtained.

The intensity of the pain was graded and charted. Three grades in each direction were considered: increase of pain, slight, moderate or marked; decrease of pain, slight, moderate or marked.

CAUSE AND EFFECT

The plan of the study included a consideration of the manner in which cause and effect were to be established.

Interesting data on this point are provided by the patients themselves. Their statements often represent not only matters of fact but their reflections on causes and effects. Patients were encouraged to disclose their own belief regarding the influence of the drug. Some expressed strong impressions that the agents exerted no beneficial effects, and the lack of disposition on the part of many patients to continue to keep their clinic appointments and to take the medicine regularly may usually be considered as an expression of opinion having a similar significance. Some expressed a definite conviction at times that it was the drug which was responsible for the relief. That that drug was often the lactose placebo, and that some patients insisted on its efficacy, protesting against any suggested change, justifies all the circumspection one can exercise in accepting a patient's judgments in a study of this sort. In some cases this type of questioning served to direct attention to extraneous factors which the patient clearly

perceived as a possible cause of the improvement, such, for example, as a change in the weather or in the amount of work.

The data obtained in this way proved to be entirely unreliable as a basis for establishing the efficacy of theobromine. Several possible causes for change in symptoms, some additive, some antagonistic, practically always coexisted. It seemed futile to attempt to unravel and evaluate the various factors, many of which are unknown, that might be responsible for the relief of pain.

The method we employed for determining cause and effect was more objective and relatively free of personal judgments. The procedure was based on this general formulation; namely, if the relief of pain during the

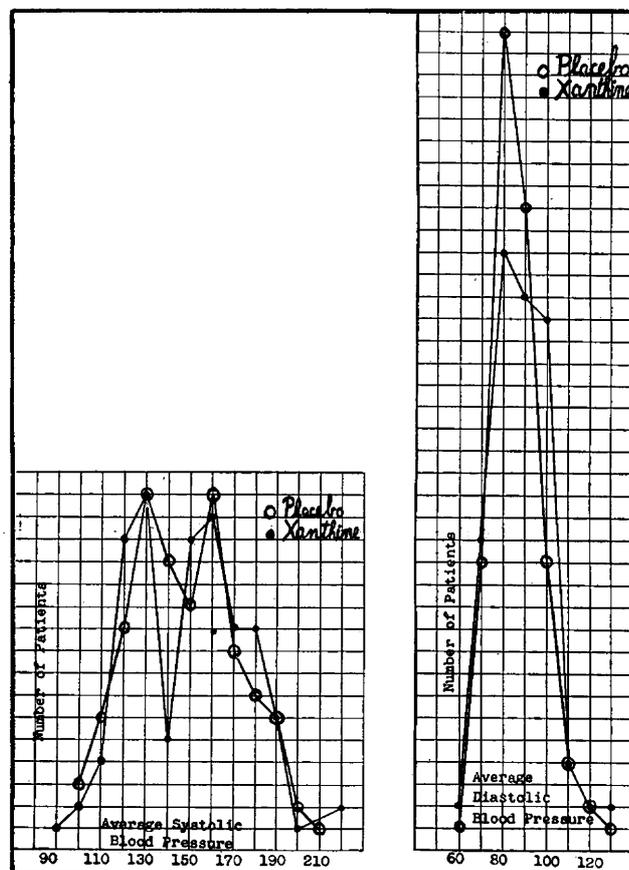


Chart 1.—Frequency distribution of average systolic and diastolic blood pressures in the 100 cases during the use of a placebo compared with that during treatment with a xanthine.

use of the xanthine is due to the specific action of the drug, the patient should be able to distinguish its effects, and to do so repeatedly, from the effects of a placebo given under similar conditions and in such form as to preclude its detection by the patient through any means other than the relief of pain.

RESULTS

Blood Pressure.—Records of the blood pressure were taken with the mercury manometer at almost every visit throughout the study. Very marked variations, as high as 70 mm. systolic and 30 mm. diastolic, were found in some individuals at different times. The highest and lowest systolic pressures for any individual in a given period were averaged similarly for the diastolic pressures. The averages for the systolic and diastolic pressures in the placebo and xanthine periods are com-

pared in a frequency distribution curve (chart 1). This discloses no significant effect of the xanthine on the blood pressure.

Electrocardiograms were not taken systematically as part of this study. There were several electrocardiograms for each patient, but in only nine cases was a tracing taken during the use of the xanthine. In these, the form of the deflections, their voltage and the time intervals are indistinguishable from those in the patients' control tracing.

Toxic Effects.—Fourteen patients at some time during the study complained of one or more of the following symptoms: dizziness, light-headedness, headache, weakness, nausea, vomiting (in one case) and heart-burn. It is not possible to be certain in how many of these cases the symptoms were due to the xanthine. In five cases the symptoms disappeared even though the theobromine was continued in the same or in higher daily doses (from 30 to 60 grains). In three the symp-

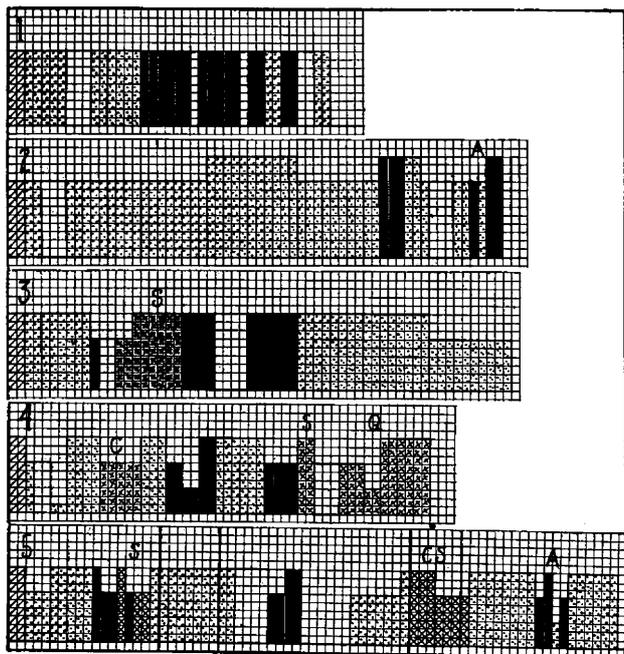


Chart 2.—Course in cases 1 to 5. The first column of each chart is made to represent the habitual status of the patient. It is arbitrary, nine squares high, and a column of the same height may refer to pain of different severity in different patients. The periods between individual clinic visits are marked off by the dark lines, or by white lines between black columns. An increase in pain is indicated by an upward direction of the column and a decrease in pain is indicated by a downward direction (change of column by three squares); marked (change of column by six squares); moderate (change of column by eight squares). The solid black columns always indicate a xanthine; it is theobromine, except when labeled *A* (aminophylline). The dotted columns always indicate a placebo. The cross-hatched columns always indicate active agents and are labeled as follows: *S* (sodium salicylate), *C* (calomel), *Q* (quinidine sulfate), *CS* (cascara sagrada), *Co* (codeine sulfate), *B* (barbital), *P* (phenobarbital), *R* (mixture of rhubarb and soda [N. F.]), *D* (digitalis). Blank columns indicate periods without medicine.

toms disappeared when the doses were reduced from 40 to 20 grains daily. One patient complained of nausea while taking a daily dose of 9 grains of aminophylline.

Effect on Pain.—The effect on cardiac pain of the first course of treatment with the xanthine was compared with that of the first course of a placebo, and the results are given in table 3. As may be seen, most of the patients reported no change, a small number reported that the pain was worse and about one fourth of the patients in each group reported improvement. Of those who reported improvement, eight belonged to both groups.

The full significance of these observations is not appreciated until one examines the complete record of the various cases. It is not feasible to present a detailed account of all the cases, but several typical cases that have been selected and are shown in charts 2 to 5 will suffice to demonstrate the results, as well as the manner in which the study was pursued to determine whether a patient can identify a xanthine by its influence on cardiac pain from among other agents either inert or known to be of little or no value in this condition.

The records of the hundred cases studied in this way fall into four types:

(a) Those in which the habitual status remained constant and apparently uninfluenced by any drug that was used (8 per cent) (1, chart 2).

(b) Those in which a change of status was always for the worse (12 per cent) (2, chart 2).

(c) Those in which the change of status was always in the direction of improvement (34 per cent) (3, 4 and 5, chart 2; 8, 9 and 11, chart 3; 12, chart 4).

(d) Those in which the condition fluctuated markedly in both directions (45 per cent) (6, 7 and 10, chart 3; 13 to 17, chart 4; 18 and 19, chart 5).

A careful perusal of these records will show that the change in the amount of pain occurring during the use of a xanthine is reproduced by a course of a placebo in every case. It is important to note, however, that there is no dearth of isolated instances which, without further testing, might have led to the impression that the xanthine, by a specific action, had caused improvement.

Some authors⁵ have interpreted the phenomenon as tolerance when a patient ceased to show improvement from a xanthine, and as the absence of cross-tolerance when, by a change to another preparation of a xanthine, the improvement was reestablished. Both of these phenomena are reproduced in our records during the use of a placebo and are therefore probably fortuitous, representing neither tolerance nor absence of cross-tolerance.

TABLE 3.—Changes in Pain During First Course of Treatment

	Number of Patients	Theobromine	Placebo
Pain unchanged.....	63	69	
Pain diminished.....	22	25	
Pain increased.....	15	6	
Duration of course.....		1.6 weeks (1-4 weeks)	2.6 weeks (1-8 weeks)

There was one patient (19) who gave strong indication that he was capable, by the relief of pain, of differentiating the xanthine in a variety of forms (tablets and solutions of various colors and tastes) from among a number of other agents. This experiment yielded results that were almost conclusive, but the patient also appeared able to distinguish clearly the taste of the theobromine from that of other agents, even when masked. Before the experiment was carried through to exclude that factor the patient died, and with that there vanished the possibility of conclusive proof in what might have been our only positive case.

COMMENT

Askanazy⁹ appears to have been the first to direct attention to the use of the xanthines in angina pectoris. In the period of about forty years that has elapsed, their use for this purpose has gained momentum and at the present time it is probable that few sufferers with

9. Askanazy, S.: Klinisches über Diuretin, Deutsches Arch. f. Klin. Med. 56: 209, 1895.

cardiac pain escape a course of treatment with a xanthine at one time or another.

Numerous reports have been published on the use of these agents for the relief of cardiac pain.¹⁰ These reports do not all show the same degree of optimism. Breuer⁶ declared the introduction of theobromine for the treatment of cardiac asthma and angina pectoris "to be the most praiseworthy therapeutic achievement

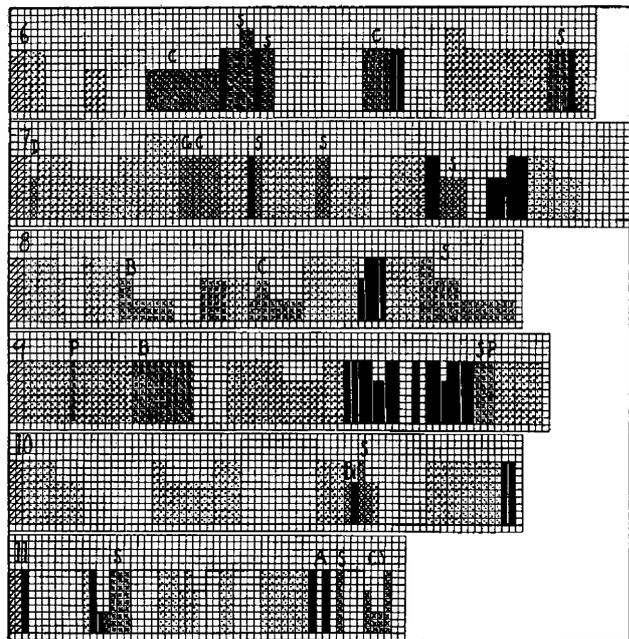


Chart 3.—Course in cases 6 to 11.

of the last decade." Gilbert and Kerr⁵ concurred in this statement "with equal emphasis." They reported relief in 83 per cent of a group of eighty-six patients with angina pectoris. On the other hand, Dock¹⁰ observed that "in most cases of angina pectoris no relief was given, but in an important minority relief was immediate and complete." The experience of different observers regarding the time it takes to secure the full therapeutic effects also shows wide divergence. For example, Dock¹⁰ stated that, if decided benefit is not noted within three or four days, further administration is useless. On the other hand, Smith, Rathe and Paul⁷ observed that, in order to insure the maximum benefit from the drug, its administration should be continued for a long time, and Musser¹⁰ found that pain is relieved and the pressure is distinctly lowered "after theophylline-ethylenediamine has been taken for weeks or months."

With one exception,¹¹ the clinical reports have two characteristics in common: first, they all advocate the use of the xanthines and report beneficial results in numbers up to about 80 per cent of the cases in different series; second, they are reports of clinical experience rather than of controlled investigations and represent observations made under conditions that fail to meet essential standards of scientific evidence.

10. Dock, William: The Use of Theobromine for Pain of Arteriosclerotic Origin, *California & West. Med.* **25**: 636 (Nov.) 1926. Musser, J. H.: Theophylline-Ethylenediamine in Heart Disease Associated with Pain, *J. A. M. A.* **91**: 1242 (Oct. 27) 1928. Guggenheimer, H.: Zur Herzbehandlung bei Erkrankungen der Koronargefäße, *Deutsche med. Wchnschr.* **49**: 1007 (Aug. 3) 1923; Ueber die Wirkungsweise des Euphyllins bei kardiovaskulärem Cheyne-Stokes und Asthma cardiale, *Ztschr. f. Kreislaufforsch.* **25**: 98 (Feb. 1) 1933. Gilbert and Kerr.⁵ Breuer.⁶ Smith, Rathe and Paul.⁷ Willis.⁸ Askanazy.⁹

11. Evans, William and Hoyle, Clifford: The Comparative Value of Drugs Used in the Continuous Treatment of Angina Pectoris, *Quart. J. Med.* **26**: 311 (July) 1933.

When a patient declares that pain has diminished during the use of the xanthine the cause might be the specific action of the drug, but it might also be any one of a number of other factors, such as:

1. Spontaneous variations in the course of the pain.
2. Change in the weather.
3. Change of occupation or amount of work.
4. Change of diet.
5. Change in eating habits with increase in the amount of rest before and after meals.
6. Condition of the bowels.
7. Emotional stress.
8. Change in domestic affairs.
9. Confidence aroused in the treatment.
10. Encouragement afforded by any new procedure.
11. A change of the medical adviser.

Authors have clearly appreciated the numerous sources of error, but they have failed to take many of them sufficiently into account or have minimized their importance in the final evaluation. An interesting example of this is the important study by Gilbert and Kerr.⁵ In their report they referred to angina pectoris as "a symptom complex so readily influenced by nervous factors, and in which there are so many unknown variables," and in regard to treatment they stated: "Reassurance alone is a therapeutic aid of no mean value. Some patients tend to improve from a decrease in emotional strain and from other factors unknown." The regimen in their cases consisted in observation in

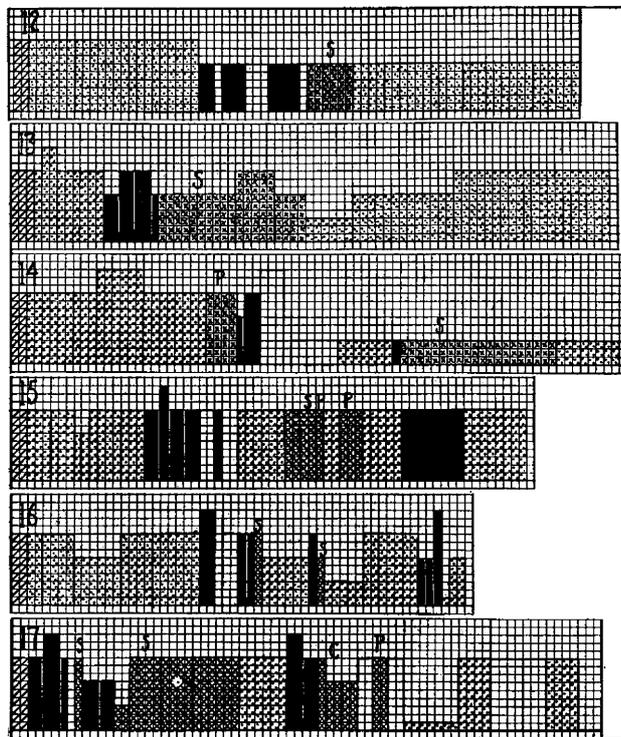


Chart 4.—Course in cases 12 to 17.

the hospital for a few days and the following routine after discharge: regulation of the bowels with liquid petrolatum or three or four glasses of warm water on rising, rest one-half hour before meals and one-half to one hour after meals, withdrawal of "foods which in their experience caused gas," and a dose of a xanthine four times daily. Here, therefore, are five measures, each in itself competent to exert a beneficent influence on cardiac pain, and when in a high proportion of the

eighty-six cases relief was obtained the result was ascribed to the xanthines, without proof that a placebo given under similar conditions would not have accomplished as much.

A word about the experimental basis for the use of the xanthines in the treatment of cardiac pain: Perhaps it is unnecessary to state that the strength of the proof supplied by animal experiments cannot materially enhance the validity of inadequate clinical observations. Clinical reports on the xanthines in cardiac pain lean very heavily on the results of the studies with the isolated heart and in anesthetized animals. These show fairly consistently that the xanthines dilate coronary arteries,¹² and the belief prevails that the soundness of their clinical use is secured in these pharmacologic studies. The indications for the use of the xanthines are, in fact, derived from a combination of current theory as to the mechanism of cardiac pain and the means by which it may be relieved, and dubious inferences from the results of animal experiments; for not one of them is free of objections as a basis for the assumption that the xanthines produce an increase in the capillary or collateral flow through the heart.¹³ The bias created by the undue emphasis placed on the clinical significance of the experimental results is undoubt-

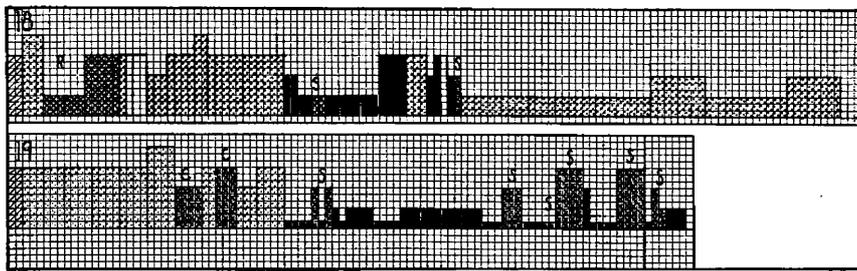


Chart 5.—Course in cases 18 and 19.

edly responsible, at least in part, for the fact that the question whether the xanthines actually relieve cardiac pain in patients with coronary disease has received so little satisfactory independent examination.

Mention has been made of one study in the literature in which exception is taken to the general belief regarding the efficacy of the xanthines in angina pectoris. This is the paper by Evans and Hoyle,¹¹ which appeared while our study was in progress. In that investigation ninety patients were treated with a variety of agents, including xanthines, and their efficacy compared with a placebo. The influence on the pain was determined not only by an estimate of the patient regarding his status but by a written record kept by the patient of the frequency of attacks. As the result of this work they stated that they were unable to convince themselves that the xanthines (as well as the other drugs which they tested) are worthy even of trial in the routine treatment of cardiac pain.

Our study, carried out under substantially similarly controlled conditions, has yielded similar results, and our conclusion is in accord with theirs; namely, that the xanthines exert no specific action that is useful in the routine treatment of cardiac pain.

12. Fowler, W. M.; Hurevitz, H. M., and Smith, F. M.: Effect of Theophylline Ethylenediamine on Experimentally Induced Cardiac Infarction in the Dog. *Arch. Int. Med.* 56: 1242 (Dec.) 1935.

13. Wiggers, C. J., and Greene, H. D.: The Ineffectiveness of Drugs upon Collateral Flow After Experimental Coronary Occlusion in Dogs. *Am. Heart J.* 11: 527 (May) 1936. Gold, Harry; Travell, J., and Modell, W.: The Effect of Theophylline with Ethylenediamine on the Course of Myocardial Infarction in Experimental Coronary Occlusion, to be published.

SUMMARY

1. The effect of theobromine and aminophylline on cardiac pain was studied in a group of 100 ambulant patients with angina pectoris.

2. These patients were selected on the basis of proof of organic heart disease, cardiac pain on effort, little or no physical work, and faithful cooperation.

3. An attempt to include only patients who could distinguish relief afforded by glyceryl trinitrate from relief by a soluble placebo tablet taken in the same way during an attack of pain was abandoned, because a fairly large number of patients with cardiac pain were found who could not distinguish between the two. This is due to the transient character of effort pain in a large proportion of the patients.

4. The effect studied was the influence on the severity and frequency of attacks and on the capacity for effort without pain, not relief during attacks of pain.

5. The data consisted of the patients' judgments regarding changes in pain. These data were secured in a manner relatively free of bias by the use of the "blind test."

6. In all, 209 courses of treatment with the xanthines were given, each course being alternated with a course in which a placebo (or some other agent) was used.

7. The doses of the xanthines were from 15 to 60 grains daily of theobromine, and from 9 to 12 grains daily of aminophylline.

8. Changes in the amount of pain were charted. Cause and effect were established by a method relatively free of personal judgments; namely, by comparing sections of the chart representing periods in which a placebo of lactose (or some other agent) was taken with those in which a xanthine was administered.

9. The xanthines were without appreciable influence on the blood pressure.

10. Every type of change in pain observed during the use of a xanthine was reproduced in the same individual by a period in which a placebo was used.

11. The results show, therefore, that patients with cardiac pain are unable to distinguish the effects of a placebo from those of a xanthine when measures are taken to preclude the identification of the agent by any means other than the relief of pain. It is concluded that the xanthines exert no specific action which is useful in the routine treatment of cardiac pain.

REPORT OF CASES

CASE 1 (F. W., a woman, aged 58).—The diagnosis was arteriosclerosis, hypertension, enlarged heart, coronary thrombosis, regular sinus rhythm, bundle branch block. The habitual status was pain 3+. The duration of study was thirty-seven weeks. The daily dosage of theobromine in order of visits was 15 grains the first week and 30 grains thereafter.

CASE 2 (L. F., a man, aged 41).—The diagnosis was arteriosclerosis, hypertension, enlarged heart, coronary thrombosis, regular sinus rhythm. The habitual status was pain 2+. The duration of study was sixty weeks. The daily dosage of theobromine in order of visits was 30 grains and 15 grains. The daily dosage of aminophylline in order of visits was 12 grains and 9 grains.

CASE 3 (M. A., a man, aged 62).—The diagnosis was arteriosclerosis, coronary sclerosis, sclerosis of the aorta, regular sinus rhythm. The habitual status was pain 2+. The duration of study was fifty-nine weeks. The daily dosage of theobromine in order of visits was 30, 30 and 15 grains.

CASE 4 (J. G., a man, aged 51).—The diagnosis was arteriosclerosis, enlarged heart, coronary thrombosis, regular sinus rhythm. The habitual status was pain 1+. The duration of study was forty-nine weeks. The daily dosage of theobromine in order of visits was 20 grains for the first two and 30 grains thereafter.

CASE 5 (M. S., a man, aged 68).—The diagnosis was arteriosclerosis, hypertension, enlarged heart, coronary thrombosis, regular sinus rhythm. The habitual status was pain 3+. The duration of study was seventy-one weeks. The daily dosage of theobromine in order of visits was 20 grains for the first two and 30 grains thereafter. The daily dosage of aminophylline in order of visits was 12, 12 and 6 grains.

CASE 6 (M. C., a man, aged 61).—The diagnosis was arteriosclerosis, enlarged heart, coronary sclerosis, regular sinus rhythm, bundle branch block. The habitual status was pain 3+. The duration of study was eighty-three weeks. The daily dosage of theobromine in order of visits was 20 grains for the first week and 30 grains thereafter.

CASE 7 (A. B., a man, aged 60).—The diagnosis was arteriosclerosis, enlarged heart, coronary sclerosis, regular sinus rhythm. The habitual status was pain 2+. The duration of study was eighty-eight weeks. The daily dosage of theobromine in order of visits was 20, 20, 30 and 30 grains.

CASE 8 (S. K., a man, aged 70).—The diagnosis was arteriosclerosis, enlarged heart, coronary thrombosis, regular sinus rhythm. The habitual status was pain 3+. The duration of study was seventy-two weeks. The daily dosage of theobromine in order of visits was 30, 30 and 45 grains.

CASE 9 (A. K., a man, aged 53).—The diagnosis was arteriosclerosis, enlarged heart, coronary thrombosis, regular sinus rhythm. The habitual status was pain 3+. The duration of study was seventy-six weeks. The daily dosage of theobromine in order of visits was 20 grains for the first five and 40, 40, 60, 60 and 15 grains thereafter.

CASE 10 (A. N., a man, aged 62).—The diagnosis was arteriosclerosis, enlarged heart, coronary thrombosis, sclerosis of the aorta, regular sinus rhythm. The habitual status was pain 3+. The duration of study was seventy-two weeks. The daily dosage of theobromine in order of visits was 20 grains. The daily dosage of aminophylline in order of visits was 12 and 9 grains.

CASE 11 (F. B., a man, aged 65).—The diagnosis was arteriosclerosis, hypertension, coronary sclerosis, aortic sclerosis, regular sinus rhythm. The habitual status was pain 3+. The duration of study was fifty-four weeks. The daily dosage of theobromine in order of visits was 30, 30 and 30 grains. The daily dosage of aminophylline in order of visits was 12 and 9 grains.

CASE 12 (G. S., a woman, aged 56).—The diagnosis was arteriosclerosis, hypertension, enlarged heart, sclerosis of the aorta, regular sinus rhythm. The habitual status was pain 1+. The duration of study was seventy-one weeks. The daily dosage of theobromine in order of visits was 15, 20 and 20 grains.

CASE 13 (H. R., a man, aged 55).—The diagnosis was arteriosclerosis, hypertension, enlarged heart, coronary thrombosis, sclerosis of the aorta, regular sinus rhythm. The habitual status was pain 2+. The duration of study was seventy-four weeks. The daily dosage of theobromine in order of visits was 20, 30, 30 and 40 grains.

CASE 14 (J. C., a man, aged 40).—The diagnosis was arteriosclerosis, enlarged heart, coronary thrombosis, regular sinus rhythm with premature contractions. The habitual status was pain 2+. The duration of study was seventy-six weeks. The daily dosage of theobromine in order of visits was 30, 30 and 30 grains.

CASE 15 (S. O., a man, aged 55).—The diagnosis was arteriosclerosis, enlarged heart, coronary thrombosis, regular sinus rhythm. The habitual status was pain 3+. The duration of study was sixty-four weeks. The daily dosage of theobromine in order of visits was 15, 30, 30, 20, 40 and 20 grains.

CASE 16 (L. L., a man, aged 44).—The diagnosis was arteriosclerosis, enlarged heart, coronary sclerosis, sclerosis of the aorta, regular sinus rhythm. The habitual status was pain 3+. The duration of study was fifty-six weeks. The daily dosage

of theobromine in order of visits was 20, 15, 30 and 20 grains. The daily dosage of aminophylline in order of visits was 12, 12 and 12 grains.

CASE 17 (S. N., a man, aged 53).—The diagnosis was arteriosclerosis (diabetes) enlarged heart, coronary thrombosis, aortic sclerosis, regular sinus rhythm. The habitual status was pain 3+. The duration of study was seventy weeks. The daily dosage of theobromine in order of visits was 20, 40, 40, 30, 40, 30 and 15 grains.

CASE 18 (M. G., a man, aged 56).—The diagnosis was arteriosclerosis, enlarged heart, coronary thrombosis, regular sinus rhythm. The habitual status was pain 3+. The duration of study was 120 weeks. The doses of theobromine in order of visits were 20, 40, 20, 30, 15, 15, 15, 30, 30 and 40 grains.

CASE 19 (C. E., a man, aged 68).—The diagnosis was arteriosclerosis, enlarged heart, coronary sclerosis, regular sinus rhythm with ventricular premature contractions. The habitual status was pain 3+. The duration of study was ninety-seven weeks. The doses of theobromine in order of visits were 30 grains for the first four visits; 25, 15, 30, 15 and 30 grains; the following twelve visits, 15 grains.

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TECHNICAL FACTORS AFFECTING THE TUBERCULIN TEST

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It has been known for some time that tuberculin is extremely heat resistant and that it adheres to glass and other materials after they have been washed and sterilized. Attention has been called to this fact by such workers as Zieler,¹ Smith,² Parish and O'Brien³ and Schick,⁴ and similar facts have been demonstrated for other allergens by Rackemann and Simon.⁵ Krause,⁶ in recalling experiments performed some years ago, has recently called attention to the precautions necessary to secure trustworthy results in immunologic experiments with extracts of tubercle bacilli. We have ourselves repeatedly secured positive reactions in tuberculin-hypersensitive persons when only physiologic solution of sodium chloride (0.85 per cent) was used in syringes previously employed for tuberculin, although these syringes had been washed and boiled and autoclaved. However, it has become increasingly evident to our two groups that insufficient attention is paid to this factor, and we have therefore decided to present jointly further data bearing on this subject.

The danger from such contamination may be illustrated by the following incident: A young physician whose Schick test had been negative several months previously stated that he was now Schick positive. On questioning it was discovered that the Schick test had been made with a syringe previously employed for

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2. Smith, C. H.: Tuberculin Skin Reactions, *Tr. Am. Pediat. Soc.* **38**: 81, 1926.

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