

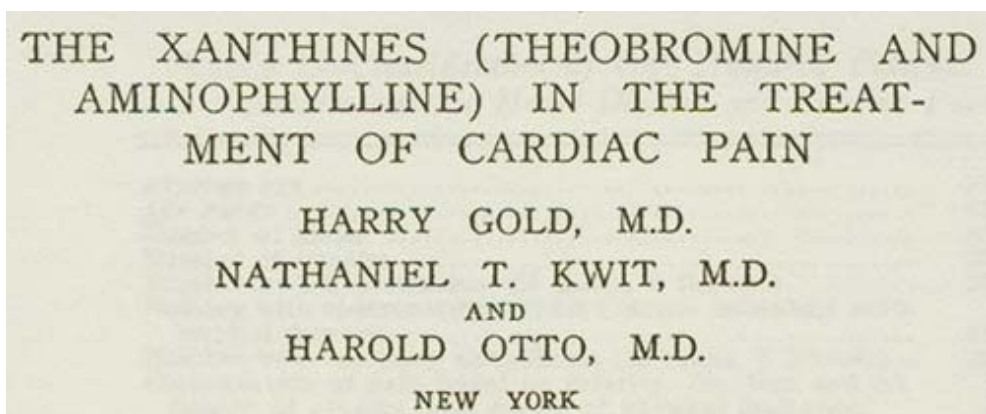
Records

Key Passage(s) Context

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[Gold H, Kwit NT, Otto H \(1937\)](#). The xanthines (theobromine and aminophyllin) in the treatment of cardiac pain. JAMA 108;2173-2179.

Key passages



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 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.

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.

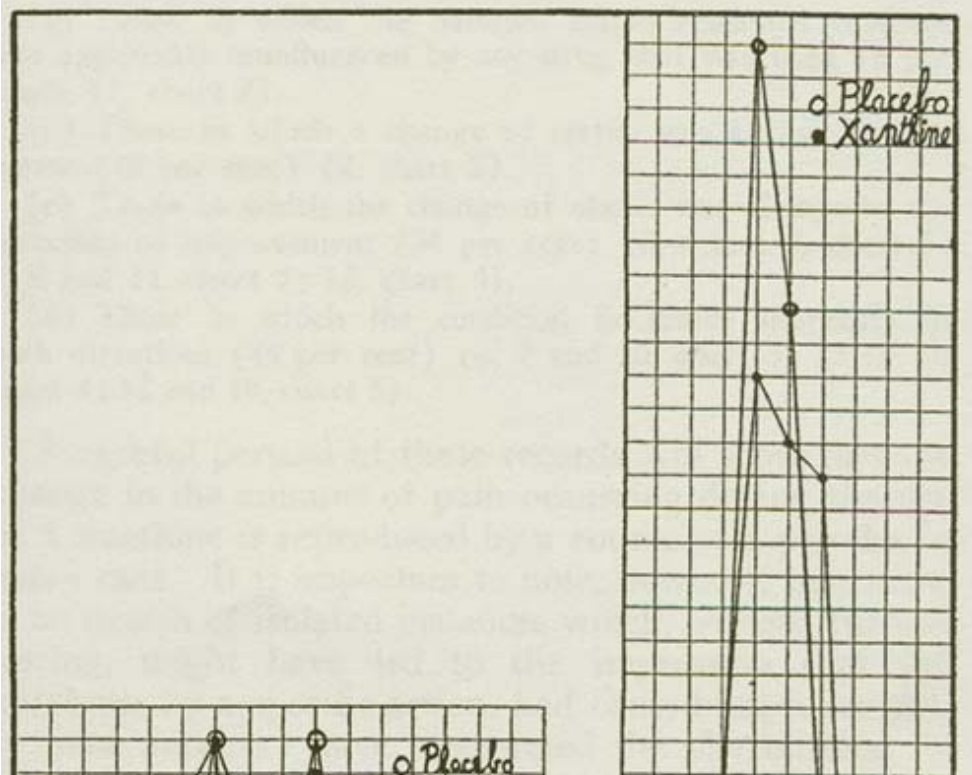
Interesting data on this point are provided by the patients themselves. Their statements often represent not only matters of fact but their reflections on causes and effects. Patients were encouraged to disclose their own belief regarding the influence of the drug. Some expressed strong impressions that the agents exerted

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



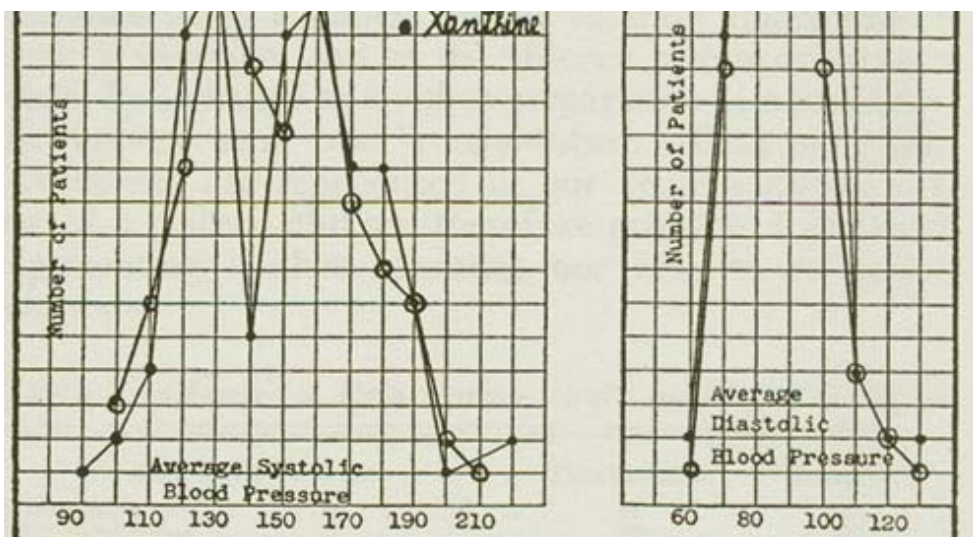


Chart 1.—Frequency distribution of average systolic and diastolic blood pressures in the 100 cases during the use of a placebo compared with that during treatment with a xanthine.

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.

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."