5. ———, *ibid.*, 1952, v27, 265.
6. Astrup, T., *Biochem. J.*, 1951, v50, 5.
7. Astrup, T., and Sterndorff, I., *Nature*, 1952, v170, 981.
8. Astrup, T., and Müllertz, S., *Arch. Biochem. Biophys.*, 1952, v40, 346.
9. Müllertz, S., *Acta Physiol. Scand.*, 1952, v26, 174.
10. Kocholaty, W., Ellis, W. W., and Jensen, G., *Blood*, 1952, v7, 882. Lewis, J. H., and Ferguson, J. H., *Am. J. Physiol.*, 1952, v170, 636. Jacobsson, K., *Acta Chem. Scand.*, 1953, v7, 430.
11. Ginsburg, I., de Vries, A., and Katchalski, E., *Science*, 1952, v116, 15.
12. de Vries, A., Feldman, J. D., Stein, O., Stein, Y., and Katchalski, E., PROC. SOC. EXP. BIOL. AND MED., 1953, v82, 237.

Received January 12, 1954. P.S.E.B.M., 1954, v85.

## Blocking Effect of Ethyl Chloride Spray on Cardiac Pain Induced by Ergonovine.* (20871)

SEYMOUR H. RINZLER, ISIDORE STEIN, HYMAN BAKST, JOSEPH WEINSTEIN, ROBERT GITTLER, AND JANET TRAVELL.

*From the Cardiovascular Research Unit, Beth Israel Hospital, the Veterans Administration, Regional Office, Brooklyn and the Department of Pharmacology, Cornell University Medical College, New York.*

Under suitable conditions ethyl chloride spray has proved effective in blocking the somatic component of cardiac pain when this occurs in acute myocardial infarction, angina pectoris and the shoulder-hand syndrome associated with coronary insufficiency(1-5). In initial trials by one of the authors (I.S.) ethyl chloride spray also relieved the angina induced by ergonovine in patients with effort angina and a normal electrocardiogram (Stein ergonovine test(6-8)). In such subjects with pre-existing coronary insufficiency, the intravenous injection of ergonovine induces electrocardiographic changes and/or pain which matches in character and location that induced by exertion; nitroglycerin promptly stops the pain and reverses the changes in the S-T segment and T-wave. The purpose of this investigation was to study more systematically the blocking effect of ethyl chloride spray in such patients with impaired coronary circulation and a positive Stein test.

*Materials and methods.* Thirty-six tests were done on 7 patients (44 to 70 years, 5 males and 2 females) who had a history of angina of effort and a normal resting 12-lead electrocardiogram. Three patients had moderate hypertension. One had a history of old myocardial infarction. None had congestive failure. At each test, the exact location of pain induced by walking was noted. A control blood pressure, pulse rate and resting electrocardiogram were taken. Leads I, II, III, aVr and $V_4$ were recorded on a direct-writing 2-channel Viso-cardiette. While Lead $V_4$ alone or Leads II and $V_4$ were being recorded, a colorless solution containing U.S.P. ergonovine maleate, 0.2 mg per ml of distilled water, was injected intravenously at the rate of 1 ml per minute. Injection was stopped when either pain or electrocardiographic changes appeared. Leads I, II, III, aVr and $V_4$ were repeated and blood pressure and pulse rate again determined about 1, 5 and 10 minutes after the end of the injection. When the test became positive, a sublingual dose of nitroglycerin (0.6 mg) was administered to terminate pain and/or electrocardiographic changes. This was usually given 6 to 8 minutes after the ergonovine, but occasionally only 2 minutes afterward if chest pain was intense. Electrocardiograms were taken until record became normal, usually 2 to 5 minutes after the nitroglycerin. At the first trial no more than 0.2 mg of ergonovine was injected. If 0.2 mg did not produce a positive effect, the

* This investigation was supported by the National Heart Institute of the National Institutes of Health, Public Health Service, the Josiah Macy, Jr. Foundation and the Loyal League Philanthropies.

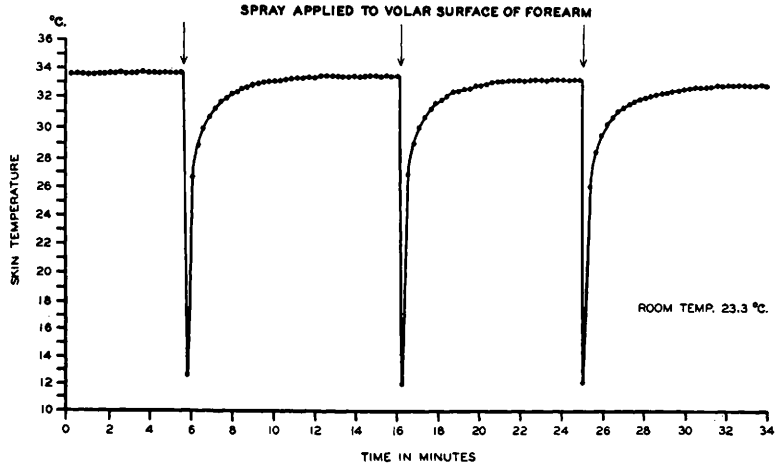


FIG. 1. Effect of 3 sweeps of ethyl chloride on temperature of skin surface as recorded by an iron-constantan thermocouple (Leeds and Northrup Speedomax).

patient was tested again with 0.4 mg one week later. No patient needed more than 0.4 mg. Thus, the threshold dose of ergonovine producing a positive test was determined for each patient. Criteria for positivity of the ergonovine test(6) are appearance of pain and/or S-T depression which amounts to at least 0.75 mm in limb leads and 1.5 mm in chest leads, or inversion of T-wave. Precautions in carrying out this test have been outlined(7). A control injection of physiologic saline was given each patient at some subsequent visit. Procedure was the same as for ergonovine and the same volume of solution used. In another series of tests on the 7 patients, 0.4 or 0.6 mg of nitroglycerin was given sublingually just before injection of ergonovine. In additional tests, ethyl chloride was sprayed over those areas of the chest, shoulders, arms or neck where pain had been produced by the ergonovine on an earlier occasion. The spray was applied in one series just *before* the dose of ergonovine was injected, and in another series when pain had appeared *following* ergonovine injection. Technic of applying ethyl chloride spray for relief of deep pain has been described (9,10). The jet stream is swept slowly over pain area in one direction; timing is such that one sweep lasts about 5 seconds with a 5 second break between sweeps. Since successive sweeps are applied to adjacent skin areas, any particular region is usually covered by the spray only once or perhaps twice. This manner of applying ethyl chloride spray may be visualized by inspection of the temperature curve from the skin surface during a single sweep (Fig. 1). The skin is not frosted. Perception of pinprick and light touch is retained in the sprayed area when tested immediately after completing such a single sweep.

*Results.* Results are shown in Table I. Pain and significant electrocardiographic changes were produced in all 7 patients by intravenous injection of ergonovine maleate. In Case 6, duplicate tests about 2 weeks apart yielded similar results (Table II). After intravenous injection of physiologic saline, no patient developed either pain or an abnormal electrocardiogram.

Nitroglycerin, 0.4 mg or 0.6 mg, given sublingually just before ergonovine, prevented pain in 5 and electrocardiographic changes in 6 of the 7 patients.

When the effective dose of ergonovine was administered and predicted pain appeared, ethyl chloride spray was applied to the pain areas. In 4 of 6 patients complete relief of pain occurred in from 30 to 60 seconds after start of spraying; 2 patients had partial relief (diminished intensity).

Ethyl chloride spray, when applied to appropriate skin areas just *before* ergonovine, prevented pain in 4 of 7 patients, delayed the onset of pain in 3 patients, but did not prevent the electrocardiographic changes in any (Table I). An illustrative test with prior

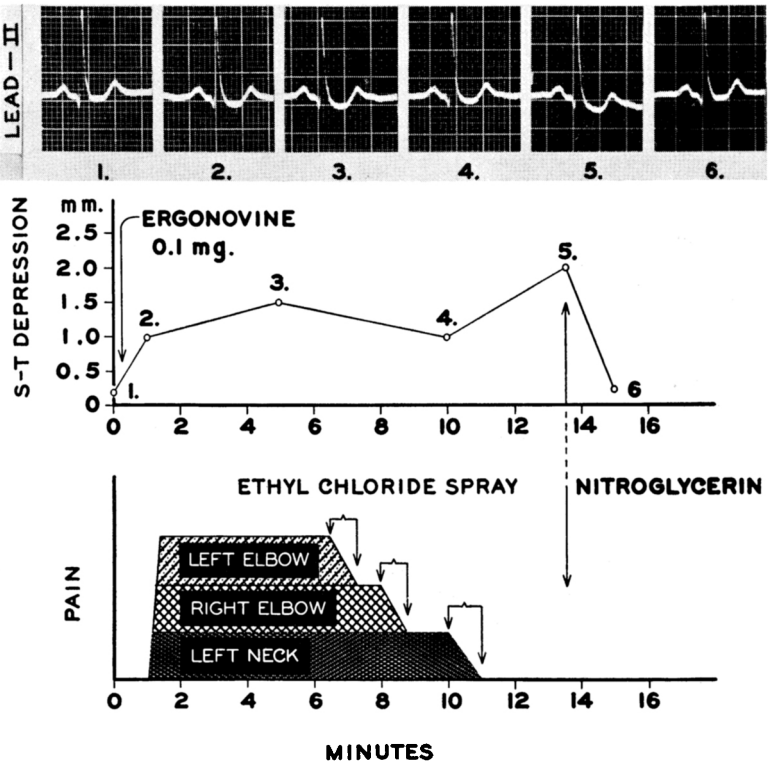


FIG. 2. Effect of ethyl chloride spray on ergonovine angina in B.G., a 49-year-old male. Note that as spray was applied to each painful area in turn, it stopped pain in that region within a minute. S-T segment remained depressed by 1 to 2 mm until nitroglycerin was administered 13½ min. after ergonovine injection. (In Fig. 2 and 3, time on the abscissa starts at *end* of ergonovine injection which occupies about 1 min.; control electrocardiogram was taken shortly before *start* of injection.)

application of ethyl chloride spray is shown in Fig. 3. In another patient, duplicate tests with prior spray showed essentially the same delay in onset of pain as compared with two control tests (Table II).

*Discussion.* The title of this paper implies that pain induced by ergonovine represents cardiac pain. This conclusion is based

TABLE I. Effect of Ethyl Chloride Spray on Pain and Electrocardiographic Changes Induced by Ergonovine in 7 Patients with Effort Angina and a Normal Resting Electrocardiogram.

| | Ergonovine | | Saline | | Nitroglycerin-ergonovine | | Spray-ergonovine | | Ergonovine-spray | |
|---|---|---|---|---|---|---|---|---|---|---|
| Ergonovine dose, mg | Pain | ECG changes | Pain | ECG changes | Pain | ECG changes | Pain | ECG changes | Pain relief | Persistent ECG changes |
| .1 | Yes | Yes | None | None | Yes | Yes | None | Yes | P* | Yes |
| .2 | " | " | " | " | " | None | " | " | C | " |
| .4 | " | " | " | " | None | " | " | " | C | " |
| .2 | " | " | " | " | " | " | " | " | | |
| .2 | " | " | " | " | " | " | Yes | " | C | " |
| .1 | " | " | " | " | " | " | " | " | C | " |
| .1 | " | " | | | | | " | " | | |
| .2 | " | " | " | " | " | " | " | " | P | " |

* P = partial; C = complete.

TABLE II. Duplicate Ergonovine Tests with and without Ethyl Chloride Spray (Patient 6).

| Test No. | Date | Time to pain after ergonovine, min. | S-T depression (Lead II), max change, mm |
|---|---|---|---|
| | | Ergonovine alone | |
| 1 | 6/ 1/53 | 2 | 3. |
| 3 | 6/13 | 1 | 2. |
| | | Ergonovine preceded by ethyl chloride spray | |
| 2 | 6/ 6 | 6 | 2. |
| 4 | 6/22 | 4 | 3. |

on a number of observations: The angina of ergonovine has a marked resemblance clinically to angina of effort in character, intensity and location of pain and also in such concomitants as sweating, pallor and extrasystoles or coupling. Similar electrocardiographic changes attend both effort and drug induced attacks. Nitroglycerin, which is known to dilate the coronary arteries, promptly stops pain and reverses the electrocardiographic changes after both exercise and ergonovine; it may also prevent these acute effects of ergonovine. It is reasonable to infer that angina of ergonovine depends on a coronary vasoconstrictor mechanism, especially since ergonovine fails to cause a significant rise in blood pressure or acceleration of heart rate as an accompaniment of pain.

That ethyl chloride spray blocks pain induced by ergonovine is in line with numerous observations concerning relief of pathologic cardiac pain by procedures altering the flow of nerve impulses from the somatic reference zone(1-4,11-13). So far as we know, however, the only other studies which show that standardized visceral pain may be *prevented* by treatment of somatic reference zone are those of Theobald(13) and Lindgren(12).

In our study, dissociation of cardiac pain and electrocardiographic changes characteristic of coronary artery disease is clearly shown in the combined effects of ergonovine and ethyl chloride spray. Russek *et al.*(14) also note such a dissociation at times in their standard exercise test. Another example of the divergence of pain and electrocardiographic changes is the clinically silent, acute myocardial infarct.

What is the mechanism by which ethyl chloride spray relieves cardiac pain when applied to the somatic reference zone? Promptness of relief afforded by the spray after ergonovine and after acute myocardial infarction(3) suggests interruption of a reversible neurogenic process responsible for maintaining the pain cycle independent of initiating cause. It seems likely that the mechanism is mainly that of counterirritation. Thus, the initial cold shock sets up an intense barrage of afferent impulses, followed by post-stimulatory depression and alteration of the central excitatory state. This is in line with Gammon and Starr's(15) finding that if counterirritant drugs and physical agents such as cold are to relieve pain effectively, the degree of initial stimulation must be of high intensity and close to that which produces pain. The intermittent application of cold (ice) was the most effective of the agents tested. Another factor in the relief of pain by ethyl chloride spray may be a brief hypesthesia due to cold, momentarily reducing the stream of afferent cutaneous impulses, in phase with subnormal (post-stimulatory) state of conduction in the central nervous system. It is further postulated that such a brief interruption of the neurophysiologic process responsible for pain can lead to permanent relief.

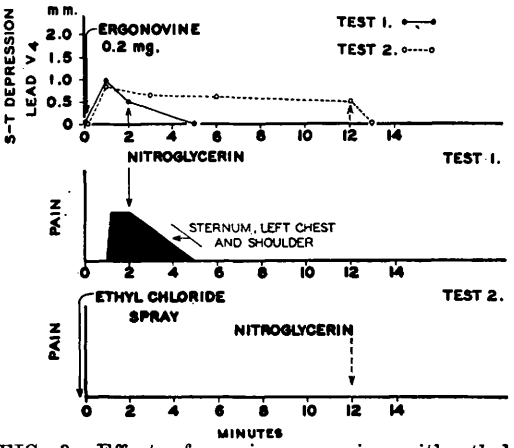


FIG. 3. Effect of previous spraying with ethyl chloride (Test 2) on pain and electrocardiographic changes induced by ergonovine (Test 1) in A.F., a 61-year-old female. Note: (1) S-T depression was similar in both tests; (2) after spraying sternum, left chest and shoulder, pain did not appear, and (3) electrocardiographic changes persisted in absence of pain for 12 min. (until nitroglycerin).

The effect of ethyl chloride spray probably can not be ascribed to reflex circulatory changes in the myofascial structures of the reference zone since in other experiments(16) we found that the spray relieves deep pain due to ischemic muscle work while the circulation to the region remains occluded. Gammon and Starr(15) observed that subcutaneous pain also was relieved by intermittent cold during occlusion of the circulation.

*Summary.* Thirty-six tests were carried out on 7 patients with effort angina but a normal resting electrocardiogram, in whom intravenous injection or ergonovine (0.1 to 0.4 mg) induced angina and electrocardiographic changes. Nitroglycerin, 0.4 or 0.6 mg given sublingually just before ergonovine, prevented pain and electrocardiographic changes in most patients. When angina had been induced by ergonovine and ethyl chloride spray was applied to pain areas of chest, shoulders, arms or neck (reference zone of cardiac pain in each patient), pain was uniformly relieved. Relief of ergonovine angina by ethyl chloride spray required less time than by nitroglycerin. When ethyl chloride spray was applied to pain areas just *before* ergonovine was injected, pain failed to occur in the majority, and the onset of pain was delayed in the remaining patients. In combination with ethyl chloride spray, ergonovine caused depression of the S-T segment even in the absence of pain. These results afford additional evidence of the previously reported effectiveness of ethyl chloride spray for relief of the somatic component of cardiac pain.

The authors are indebted to Mrs. Mary P. Clapp and Miss Amelia Curcio for technical assistance.

1. Travell, J., and Rinzler, S. H., PROC. SOC. EXP. BIOL. AND MED., 1946, v63, 480.

2. Rinzler, S. H., and Travell, J., *Am. Heart J.*, 1948, v35, 248.

3. Travell, J., *Circulation,* 1951, v3, 120.

4. Rinzler, S. H., *Cardiac Pain,* Charles C. Thomas, Springfield, Ill., 1951, pp 23-25; 76-87.

5. Travell, J., *Connective Tissues,* Transactions of the Second Conference, Josiah Macy, Jr. Foundation, New York, 1952, pp 86-125.

6. Stein, I., *Am. Heart J.*, 1949, v37, 36.

7. Stein, I., and Weinstein, J., *J. Lab. Clin. Med.*, 1950, v36, 66.

8. ———, *New York State J. Med.*, 1953, v53, 1454.

9. Travell, J., *Arch. Phys. Med.*, 1952, v33, 291.

10. ———, *New York State J. Med.*, 1952, v52, 1550.

11. Weiss, S., and Davis, D., *Am. J. Med. Sci.*, 1928, v176, 517.

12. Lindgren, I., *Cardiologia,* 1946, v11, 207.

13. Theobald, G. W., *Lancet,* 1949, v2, 41.

14. Russek, H. I., Urbach, K. F., Doerner, A. A., and Zohman, B. L., *J.A.M.A.*, 1953, v153, 207.

15. Gammon, G. D., and Starr, I., *J. Clin. Invest.*, 1941, v20, 13.

16. Travell, J., and Rinzler, S. H., *Fed. Proc.*, 1949, v8, 339.

Received November 24, 1953. P.S.E.B.M., 1954, v85.

## Presence of Antidiuretic Material in Blood of Hypophysectomized Rats. (20872)

CHARLES W. LLOYD, ERICH LOEWY, SOPHIE PIEROG, KAROL BRADWICK, AND ROBERT SOSTHEIM.

*From the Department of Obstetrics (Division of Endocrinology), State University of New York Medical Center, Syracuse, N. Y.*

It has generally been accepted that removal of the posterior pituitary results in disappearance of antidiuretic hormone. Several investigators, using different assay technics (1-3), have reported the absence of antidiuretic material from the blood of hypophysectomized rats.

In the course of studies of turn-over of water and metabolism of posterior pituitary hormone of hypophysectomized rats which were a month or more postoperative, it was observed that an appreciable number of the animals had antidiuretic material in their blood. This was not found in the blood of