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The effect of ethyl alcohol and chlorpromazine on the response of the hand blood vessels to cold

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Summary

1. The response of hand blood flow to a measured cold stimulus was determined using venous occlusion plethysmography in normal subjects, before and after orally administered alcohol, and in patients on chlorpromazine therapy.

2. The average resting hand blood flow of the patients taking chlorpromazine, as well as the constriction of these blood vessels to cold, was the same as in the normal subjects.

3. Oral alcohol caused a rise in resting hand blood flow in the normal subjects and also modified the response of the hand blood vessels to cooling.

4. A patient with a completely denervated hand was also studied. Oral alcohol did not increase the blood flow through the part, but it modified the hand vascular response to cold.

5. These results suggest a diminished reactivity of the hand blood vessels to cold in the presence of alcohol.

Introduction

Certain drugs, including alcohol (von Euler, 1961) and chlorpromazine (Lewis, 1964), reduce the ability of man and warm-blooded animals to maintain body temperature in the cold. The effect of these drugs on the thermoregulatory heat balance is not clear. Fewings, Hanna, Walsh & Whelan (1966) have shown that alcohol, given by mouth, causes peripheral vasodilatation and attributed this phenomenon to an inhibition of sympathetic vasomotor tone due to an action of alcohol on either the vasomotor centres or sympathetic ganglia. Chlorpromazine has also been shown to cause peripheral vasodilatation (Kollias & Bullard, 1964), but the mechanism of this dilatation has not been fully elucidated.

In the present study, a graded cold stimulus has been applied to one hand of normal subjects before and after drinking alcohol and to patients taking large doses of chlorpromazine.

The average blood flow of the patients taking chlorpromazine, as well as the constriction of the blood vessels of the hand to cold, was the same as in the normal subjects. Oral alcohol caused a rise in resting hand blood flow and the response to cooling was modified.

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Methods

The subjects for these studies were eight normal volunteers, six patients on chlorpromazine therapy, and one patient who had a chronic traumatic loss of motor, sensory and sympathetic nerves to the right hand.

The experiments were carried out at laboratory temperatures ranging from 29° to 32·5° C, the subjects lying recumbent on a couch for at least 30 min before observations were made, during which time the recording apparatus was applied. In all cases, a minimum of 2 h had elapsed since the last meal or cigarette.

Hand blood flow was measured simultaneously on both sides by venous occlusion plethysmography, using water-filled plethysmographs initially maintained at a temperature of 32°–33° C (Greenfield, 1954), three or four records of flow being obtained each minute. After recordings had been made at this temperature, the water in the plethysmograph on the right hand was rapidly aspirated and replaced with colder water at a preselected temperature. This procedure took approximately 1 min. Six minutes later the cold water was aspirated and replaced with water to return the temperature of the plethysmograph to 32° C. The water temperature in contact with the hand was recorded just before aspiration. Three cooling periods of different intensities were administered to each subject in a randomized pattern. In two of the subjects, cooling was repeated on a second day to check the reproducibility of the flow changes and the responses were found to agree within $\pm 4\%$.

The effects on hand blood flow produced by the cold were determined from the averaged flow values during the 2 min before the stimulus was applied and the fifth and sixth minutes of contact of the hand with the cool water. The absolute and percentage falls in flow on both the treated and untreated sides were calculated, as well as the percentage fall of the cooled right hand corrected by subtraction of changes in the left hand, to account for the systemic effects produced by the cold and also spontaneous fluctuations (Duff, 1952). The changes in flow were then plotted against the final water temperature producing the fall. The times taken for the blood flow to recover to resting levels on both the treated and untreated sides were also determined. These results were plotted in a similar fashion.

The effect of alcohol on the hand vascular response to cold was studied in five of the eight normal subjects and in the patient with the denervated hand. The alcohol was administered in the form of 100 ml brandy (diluted with ginger ale) and was consumed over a period of 1–5 min. The responses of the blood vessels of the right hand to the cold stimulus were then determined in an identical fashion to the control run. At the conclusion of the experiment, which was approximately 1·5 to 2 h after the alcohol had been ingested, samples of venous blood were withdrawn and their alcohol content determined by the method of Williams, Linn & Zak (1958). Fewings *et al.* (1966) have shown that the blood alcohol is still maintained at a maximum level at this time. In one subject, the alcohol study was repeated on a second day and the results found to be reproducible.

The patients on chlorpromazine were selected from the population of a mental hospital. The selection was directed to obtain: (*a*) patients able to understand the nature and purpose of the study and to co-operate in the use of the plethysmograph; (*b*) patients who were on high doses of chlorpromazine but, as far as possible, not on any other medication which had vasoactive properties; (*c*) patients who had been on chlorpromazine therapy for a period of at least 10 days.

Table 1 summarizes the drug therapy of the six patients. Four of these were on chlorpromazine alone, and they had been on this regime of treatment for a considerable period of time (usually months or years). One patient was receiving 100 mg of phenytoin sodium three times a day, and another 10 mg of trifluoperazine and 50 mg of orphenadrine hydrochloride three times a day in addition to chlorpromazine. Their patterns of vascular response to the cold were identical to that of the other four subjects.

Results

The average resting hand blood flow of the eight normal subjects was (9·8 ml/100 ml)/min (S.E.M. ± 1·09).

The effect of cooling one hand of the members of this group was to cause vasoconstriction in both that hand and also of the opposite uncooled hand. Figure 1

TABLE 1. *Drug therapy of patients participating in the study on vascular response to cold*

Initials	Age (years)	Drug and dosage
O.E.V.W.	65	Chlorpromazine 25 mg t.d.s.
M.E.D.W.	36	Chlorpromazine 200 mg q.i.d.
A.H.E.S.	41	Chlorpromazine 200 mg q.i.d. Phenytoin Sod. 100 mg t.d.s.
L.S.	56	Chlorpromazine 100 mg t.d.s. Trifluoperazine 10 mg t.d.s. Orphenadrine HCl 50 mg t.d.s.
A.B.	20	Chlorpromazine 200 mg q.i.d.
T.P.	58	Chlorpromazine 200 mg q.i.d.

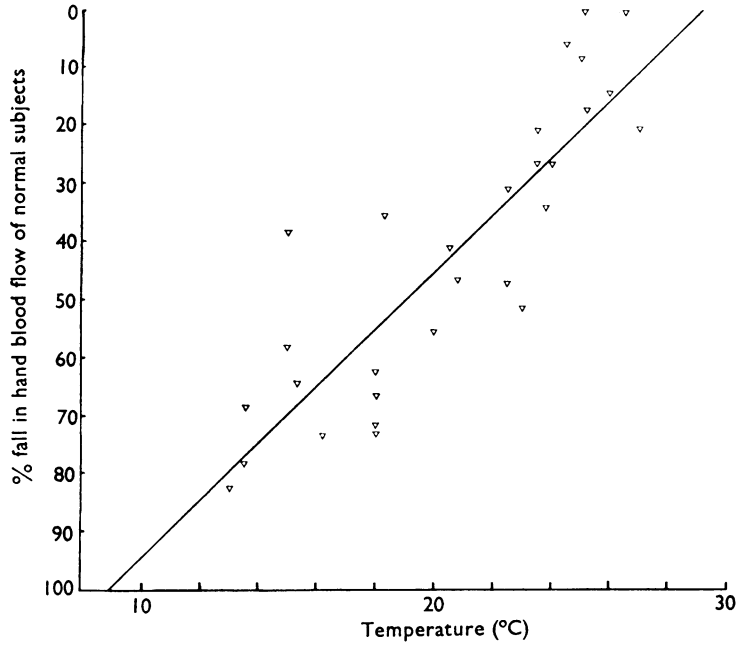

FIG. 1. Corrected percentage falls in hand blood flow of eight normal subjects in response to cooling, plotted against the final temperature of the water in the plethysmograph producing the fall. The calculated regression line for the points is shown.

shows the percentage fall in blood flow of the cooled hand in the eight normal subjects, corrected for concomitant changes in the control hand, with the calculated regression line for the plotted values. The latter has the equation:

$$\% \text{ fall in hand blood flow} = 143{\cdot}8 - 4{\cdot}95 \times (\text{final plethysmograph temperature } °C)$$

$$r = 0{\cdot}865 \quad P < 0{\cdot}001$$

Figure 2 shows the corrected percentage falls in flow of the cooled hand in the six patients who had been treated with chlorpromazine. The regression line for the responses is shown as well as the regression line of the normal subjects. Neither the slopes nor the intercepts of these lines are significantly different from each other (Table 2). The average initial blood flow of this group was (8·5 ml/100 ml)/min (S.E.M. $\pm$1·11) which is not significantly different from the normal group. Neither the percentage falls (uncorrected) nor the absolute fall ((ml/100 ml)/min) of either the cooled or the uncooled hand was different from normal. The time for return of the blood flow to resting levels of both the cooled and the control hand after the cooling was stopped was the same as the normal subjects.

Percentage fall in flow has been used to make it possible to compare changes in flow in subjects with differing initial blood flows (Cooper, Fewings, Hodge & Whelan, 1963). In our study, the five normal subjects who ingested alcohol had an average initial blood flow of (8·55 ml/100 ml)/min (S.E.M. $\pm$1·09) before taking the spirit and (13·34 ml/100 ml)/min (S.E.M. $\pm$0·71) afterwards. There is a significant difference in these values (t=3·306, P<0·01), and the higher flows in the latter may be attributed to the vasodilator effect of alcohol produced by its inhibiting

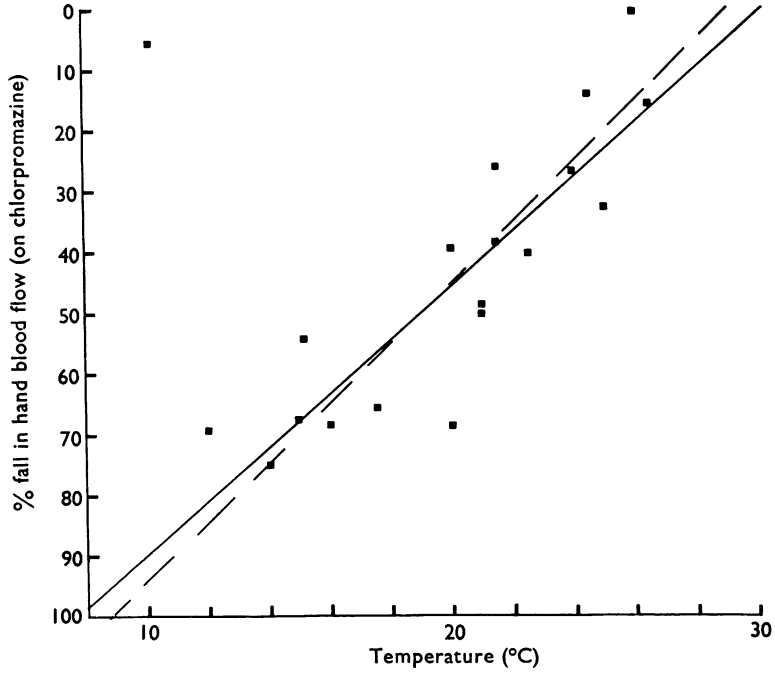

FIG. 2. Corrected % fall in hand blood flow of the patients on chlorpromazine therapy, plotted against the final water temperature producing the fall in flow. The solid line is the regression line for the patients and the broken line that for the normal subjects.

TABLE 2. *Regression of % fall in hand blood flow against temperature (°C)*

Treatment	Number of observations	Intercept (*A*)	Standard deviation (*A*)	Statistical significance	Slope (*B*)	Standard deviation (*B*)	Statistical significance	Regression
Chlor. subjects	18	135·7956	12·5217	—	−4·5309	0·6071	—	−0·8814
Normal controls	29	143·8262	11·5574	—	−4·9541	0·5509	—	−0·8658
Pooled regression	47	140·8555	8·4372	—	−4·7988	0·4048	—	−0·8703
Alcohol subjects	17	100·4755	16·5779	<0·001	−3·8753	0·8459	—	−0·7637
Alcohol controls	17	148·3637	12·4077		−5·0699	0·5985	—	−0·9095
Pooled regression	34	116·7690	14·1179	—	−4·1017	0·6998	—	−0·7195

vasomotor tone on the hand blood vessels (Fewings *et al.*, 1966). As would be expected, the hand flow of the patient whose right upper limb was totally denervated did not increase in response to orally administered alcohol.

Figure 3 shows the corrected percentage fall in blood flow of the cooled hand in the five subjects who each consumed 100 ml of brandy. The regression line for the results is also shown. The dotted line represents the regression line for the corrected percentage falls in hand blood flow in the same subjects before their drinking alcohol. Although there is no significant difference between the slopes of the regression lines, the intercepts of these are significantly different (Table 2) ($P<0{\cdot}001$), and this indicates that the percentage fall in hand blood flow, in response to the application of a cold stimulus after alcohol, is less at all temperatures. (Table 3 shows the blood alcohol contents in the five subjects.)

TABLE 3. *Blood alcohol level of the five control subjects and the patient with the denervated hand, each of whom consumed* 100 *ml of brandy*

	Subject	Sex	Blood alcohol level (%)
1	G.C.	M	0·07
2	J.C.	F	0·12
3	J.W.	M	0·09
4	J.D.	M	0·07
5	L.K.	F	0·15
	Patient		
1	P.B.	M	0·06

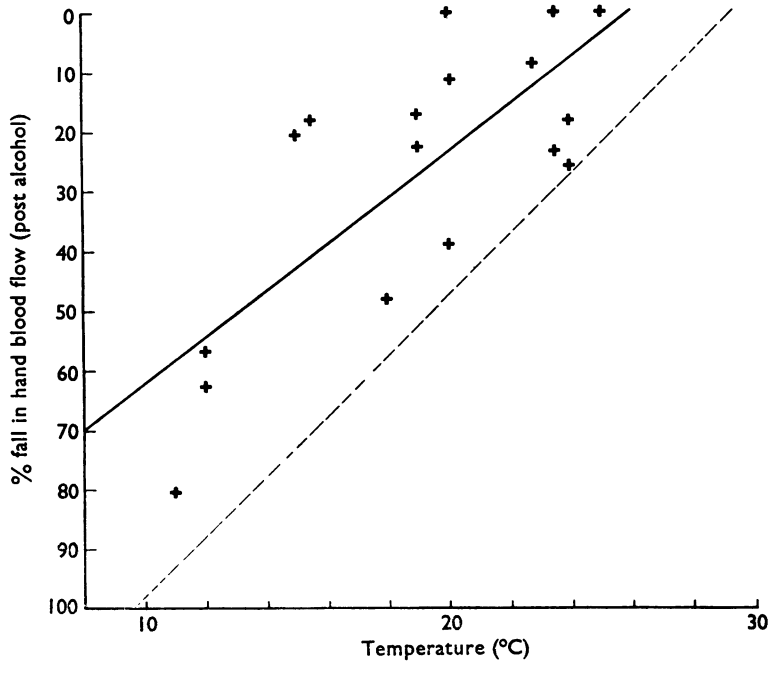

FIG. 3. Corrected percentage falls in hand blood flow of the five subjects who each consumed 100 ml of brandy, plotted against the final water temperature producing the fall, with the calculated regression line. The broken line is that calculated for the results from the same subjects before alcohol was consumed.

Figure 4 shows the uncorrected percentage falls in blood flow of the cooled hand. There is some overlap between the responses of the vessels before and after alcohol. However, the distribution suggests that the percentage falls in hand flow in the subjects were less after the alcohol.

Figure 5 shows the actual fall in hand blood flow ((ml/100 ml)/min) on the cooled side during the fifth and sixth minutes of cooling, plotted against the temperature

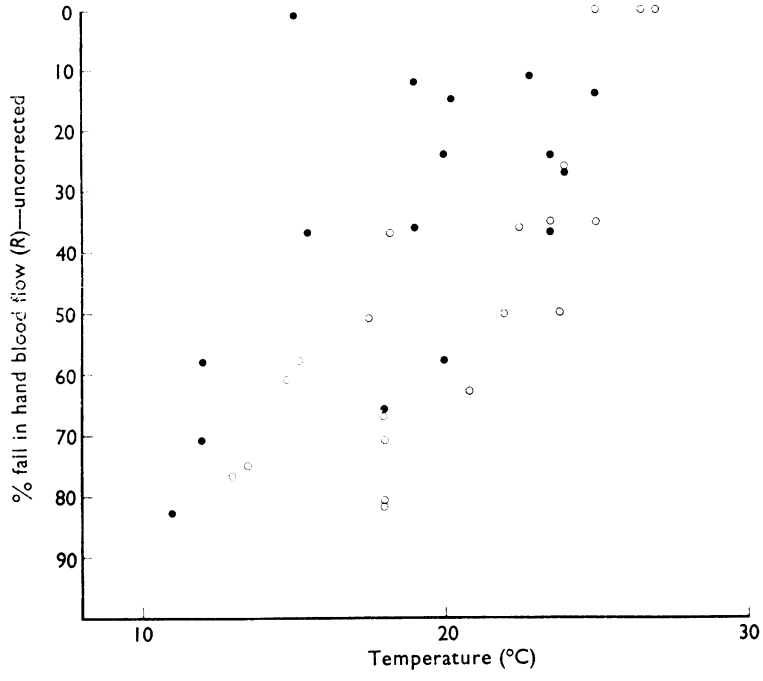

FIG. 4. Percentage falls in hand blood flow, uncorrected, plotted against the final water temperature producing the fall, before (○) and after (●) ingesting alcohol.

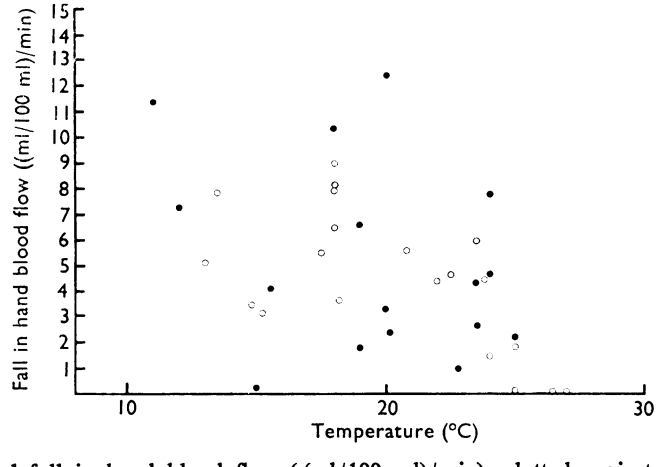

FIG. 5. Actual fall in hand blood flow ((ml/100 ml)/min), plotted against the final water temperature, before (○) and after (●) alcohol.

of water in the plethysmograph. The changes in flow appear to overlap and, in the light of the earlier findings, indicate that, though the percentage fall in hand flow is less in the alcohol treated group, the actual fall in (ml/100 ml)/min is the same. This may be explained in terms of the higher initial flow in the alcohol treated subjects where an equivalent fall in flow to that in the control experiment results in a smaller percentage change. There was no difference in the times taken for the flow of the cooled hand to recover after exposure to the cold before and after alcohol. There was also no difference in the percentage falls in hand flow or the time for the flow to recover on the control side in either study.

Because the flow after alcohol was increased in the normal subjects, a further study was performed in which three of the subjects were indirectly heated to produce resting blood flows comparable with that produced by the alcohol. One hand of these subjects was then cooled in the same fashion as previously. In each subject, the fall in blood flow in response to cooling was greater before alcohol than after it. Figure 6 is a representative result in one normal subject (J.A.D.) and in the patient (P.B.) with the denervated hand.

Discussion

Chlorpromazine has multiple pharmacological actions. It is widely used as a psychotropic agent, and some of the effects are said to be mediated through a depressant action on the ascending pathways of the reticular formation, the thalamus, the hypothalamus, and those parts of the brain which control autonomic activity (Lewis, 1964). In addition, it blocks α-adrenoceptors of peripheral blood vessels. The hypothermic action of chlorpromazine has been attributed, at least in part, to peripheral vasodilatation (Decourt, Brunaud & Brunaud, 1953 ; Kollias & Bullard, 1964), but it is not clear whether this effect is on the central nervous system or on the peripheral blood vessels themselves.

In the present study, which was conducted in a warm room, the hand blood flow of patients taking large doses of chlorpromazine was not different from the normals. The response to graded cooling, as measured by percentage fall in flow, whether corrected for changes in the control hand or not, fell within the comparable normal

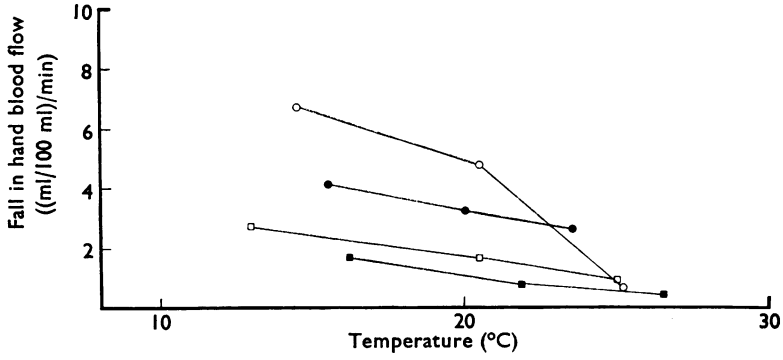

FIG. 6. Actual fall in hand blood flow ((ml/100 ml)/min) of a normal subject before (○) and after (●) alcohol and a patient with a denervated hand before (□) and after (■) alcohol, in response to the cold stimulus. The normal subject had been indirectly heated to produce a resting hand blood flow comparable with the level after alcohol.

range, as did the absolute falls in flow. The time taken for the flow to recover in both the cooled and uncooled hands was also normal. These results demonstrate that the hand blood vessels of the patients on chlorpromazine therapy are capable of responding to cold in a normal fashion. The similarity of the reflex changes in the uncooled hand in both patients and normal subjects does not lend support to the suggestion that the drug modifies peripheral thermoregulatory reflexes.

Alcohol infused directly into a blood vessel causes vasoconstriction (Hales, 1733 ; Fewings *et al.*, 1966), but the systemic effect of the drug is to cause widespread vasodilatation in the skin. This vasodilatation, mediated by an effect of the alcohol on the central nervous system (Fewings *et al.*, 1966), would enhance heat loss in the cold.

In this study, alcohol significantly increased hand blood flow in the normal subjects but not in the patient with the denervated hand. In every subject (both normal and denervated), the % constriction in response to cooling was less after alcohol than before. Table 2 shows the statistical analysis of the results. The slope of the regression line after alcohol was not significantly different from that of the control period, although the intercept of the line on the X (temperature) axis was significantly shifted to the left. These results would indicate a diminished reactivity of the vessels to the cold in the presence of alcohol. The similarity of the responses of the patient with the denervated hand and of the normal subjects supports the concept that the effect of the alcohol was, at least in part, directly on the vessels themselves.

It has been shown that even small doses of alcohol contribute to a fall in body temperature in the cold (Haight & Keatinge, 1970). In the light of the results here reported, a direct inhibitory effect of alcohol on the response of the peripheral vessels to cold should be considered in addition to its known neurological and metabolic actions.

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