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EFFECT OF CHLORPROMAZINE ON ADRENALINE VASOCONSTRICTION IN MAN

BY

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Chlorpromazine is a synthetic alkyl amino derivative of phenothiazine, with a chemical structure very similar to that of promethazine. It has, however, less antihistaminic activity and is a more powerful central depressant. Antagonism to adrenaline has been described in animals (Courvoisier, Fournel, Ducrot, Kolsky, and Koetschet, 1953), and in man (Foster, O'Mullane, Gaskell, and Churchill-Davidson, 1954), but the nature of this action has not been fully elucidated.

The present study is a quantitative assessment of the antagonism between chlorpromazine and adrenaline in the blood vessels of the hands of healthy human subjects.

METHODS

Twenty-two tests were performed on nine male medical students and colleagues aged from 21 to 50 years. Each subject lay at rest on a comfortable couch in the laboratory for at least half an hour before the start of the test. The blood flow in both hands was measured regularly at half minute intervals by venous occlusion plethysmography under standard conditions: the laboratory temperature was maintained at 22–24° C., and the metal plethysmographs were filled with water (Barcroft and Edholm, 1943) kept at 32–34° C. (Duff, 1952). Blood flow was calculated and expressed as ml./100 ml. hand volume/min.

After anaesthetizing the overlying skin, a unilateral intra-arterial infusion of saline (0.9% w/v NaCl soln.) was given through a needle inserted into the brachial artery on one side just above its bifurcation at the elbow. Saline was delivered at the rate of 3 ml./min. by an electric infusion machine from one or other of two 50 ml. syringes, connected to the intra-arterial needle by a polythene tube and adaptor. Intravenous infusions were similarly given into a superficial vein of the opposite arm, using a second machine. Solutions of adrenaline (synthetic (−)-adrenaline tartrate, B.D.H.) and chlorpromazine ("Largactil," M. & B.) were prepared by serial dilution with saline. The potency of the adrenaline was maintained by adding 0.1 mg. ascorbic acid to each pint of saline used in the infusions (Gaddum, Peart, and Vogt, 1949).

The effect of chlorpromazine on the peripheral constriction caused by adrenaline was studied in two series of experiments. In the first of these the effect of *intra-arterial* chlorpromazine on the vasoconstriction produced by intra-arterial and by intravenous adrenaline was measured; this study also enabled the direct action of chlorpromazine alone on the calibre of the vessels to be assessed. In the second series of experiments, the effect of *intravenous* chlorpromazine on the constriction produced by intra-arterial adrenaline was studied.

Action of Intra-arterial Chlorpromazine on the Effects of Intra-arterial and Intravenous Adrenaline

The course of a typical experiment is illustrated in Fig. 1. After a control period of approximately 10 min. during which saline alone was given, three 4-min. infusions of adrenaline were alternated with control saline infusions for at least 4 min. Two infusions of adrenaline in a concentration of 0.5 μg./min. were given intra-arterially and one infusion of adrenaline (10 or 15 μg./min.) was given intravenously. Chlorpromazine was then infused into the artery in a total dose of 1.2 mg. at the rate of 200 μg./min. for 6 min. This amount was calculated to be the approximate fraction of a 50 mg. i.v. dose which would be expected to reach the brachial artery at the elbow (Barcroft and Swan, 1953). The intra-arterial and intravenous infusions of adrenaline were then repeated in the same concentration and order as before the chlorpromazine.

The blood flow in both hands normally fluctuates from moment to moment, as the result of systemic influences—especially variations in sympathetic activity—affecting both hands about equally (Cooper, Cross, Greenfield, Hamilton, and Scarborough, 1949; Duff, 1952). These phasic variations are not influenced by intra-arterial or intravenous infusions of saline alone, but allowance must be made for them before changes in hand blood flow can be attributed solely to the action of substances infused into the brachial artery. Thus, in the experiment depicted in Fig. 1, the mean flows, in the control period before the first intra-arterial infusion of adrenaline, averaged (*A*) 15.1 ml./100 ml. hand volume/min. in the test right hand and (*a*) 17.1 ml. in the control left hand. During the infusion of 0.5 μg./min.

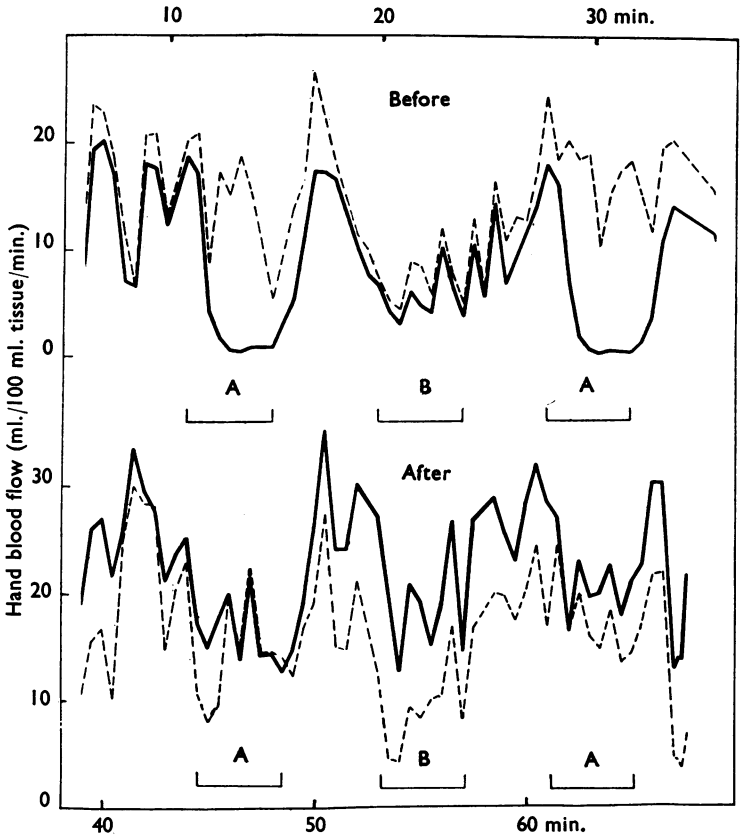

FIG. 1.—Response of hand blood flow in one subject (O. R., ♂) to adrenaline, intra-arterially (A, 0·5 μg./min. for 4 min.) and intravenously (B, 10 μg./min.) before (upper records) and after (lower records) chlorpromazine (1·2 mg. in 6 min., starting at 37 min. on the record) infused into right brachial artery. Solid lines, right hand; broken lines left hand.

adrenaline, the corresponding values were (*B*) 1.3 ml. and (*b*) 12.6 ml. for the right and left hands respectively.

Since, normally, *A*/*a* approximately equals *B*/*b*, an estimate of *B* is given by the expression *Ab*/*a*, assuming adrenaline to have had no effect on the blood flow in the test hand. This estimate is denoted by the symbol $E \simeq Ab/a$ and averaged 11.1 ml. in this instance. The measured value for *B*, however, was 1.3 ml. The difference between these two values—that is, between the estimated or expected value *E*, derived from *Ab*/*a*, and the measured value *B*—represents the net effect of adrenaline on the flow in the test right hand. Thus, $B-E=1.3-11.1=-9.8$, and indicates a net reduction in flow of nearly 10 ml. during the infusion of adrenaline. When this is expressed as a percentage, $[B-E/E]\%$, the infusion of 0.5 μg./min. adrenaline can be said to have caused a decrease in mean flow of $\frac{9.8\times100}{11.1}$ or 88% of the expected value. Similarly, with the second intra-arterial infusion of adrenaline (Fig. 1), the mean decrease in flow was 84% of the expected value. This method of analysis (Duff, 1952) was applied to the results of *all* intra-arterial infusions.

With intravenous infusions, any drug effect involves both hands. Hence the change in flow in either hand, expressed as a percentage of the previous level of flow in that hand, provides an estimate of the peripheral constrictor or dilator effects of drugs given intravenously.

Thus, in the experiment depicted in Fig. 1, the effect of the first intravenous infusion of adrenaline (10 μg./min.) on the flow in the right test hand, as given by the expression $[B-A/A]\% = [5.5-12.7/12.7]\%$. Similarly, the effect of this infusion on the flow in the left hand is obtained from $[b-a/a]\% = [6.2-15.9/15.9]\%$. The mean percentage reduction in flow with this intravenous infusion of adrenaline was therefore 57% in the right hand and 61% in the left hand.

Action of Intravenous Chlorpromazine on the Effects of Intra-arterial Adrenaline

In these experiments, an infusion of adrenaline (0.5 μg./min. for 4 min.) was given before and after an intravenous infusion of chlorpromazine (50 mg. in 10 min.).

In view of the possible dangers attending systemic administration of both substances together, subjects receiving intravenous chlorpromazine were not given intravenous adrenaline.

RESULTS

Action of Intra-arterial Chlorpromazine on the Effects of Intra-arterial Adrenaline

The results of thirteen intra-arterial infusions of adrenaline (0.5 μg./min.) before and after the infusion of 1.2 mg. chlorpromazine into the brachial artery are summarized in Table I. In each test, *A* and *a* are the *mean* values of six flows recorded simultaneously in test and control hands respectively *before* the infusion of adrenaline: *B* and *b* are the *mean* values of six flows similarly recorded in these hands *during* the adrenaline infusion.

Before chlorpromazine, intra-arterial adrenaline caused a decrease in flow in the test hands which averaged 75% (Table I, col. *B*–*E*/*E*). After 1.2 mg. chlorpromazine had been infused into the brachial artery, the level of flow in the test hand increased;

TABLE I

RESPONSE TO INTRA-ARTERIAL ADRENALINE (0·5 μG./MIN. FOR 4 MIN.) BEFORE AND AFTER INFUSING CHLORPROMAZINE (1·2 MG. IN 6 MIN.) INTO THE BRACHIAL ARTERY

A, *a* = means of 6 measurements of hand blood flow during 3 min. before adrenaline in test and control hands, respectively; *B*, *b* = corresponding means during first 3 min. of adrenaline period; *E* = *Ab*/*a*. Mean blood flows in cols. *A*, *B*, *a*, *b*, in ml./100 ml. tissue/min.

Expt. No.	Before Chlorpromazine					After Chlorpromazine				
	Test Hand		Control Hand			Test Hand		Control Hand		
	A	*B*	*a*	*b*	$\frac{B-E}{E}$	*A*	*B*	*a*	*b*	$\frac{B-E}{E}$
1	10·9	4·9	5·9	5·1	−48	18·0	9·7	10·2	6·5	−16
2	9·2	1·4	3·9	4·9	−88	19·5	16·4	12·7	16·4	−35
3	15·1	1·3	17·1	12·6	−88	20·1	16·3	14·5	16·8	−30
4	12·9	2·2	16·1	16·9	−84	24·1	19·9	20·5	16·5	−02
5	7·3	2·0	5·9	6·9	−76	20·9	14·7	8·7	8·5	−28
6	8·9	2·2	9·8	9·5	−74	17·6	10·2	9·6	9·1	−39
7	16·4	2·7	12·7	13·9	−85	26·9	20·9	16·6	14·1	−08
8	8·9	2·2	9·8	9·5	−74	14·8	7·7	7·5	7·4	−47
9	17·2	3·9	16·7	11·7	−68	29·0	19·1	25·0	21·9	−25
10	3·4	0·9	3·5	3·1	−70	9·8	5·3	2·3	2·0	−38
11	22·7	1·2	17·8	12·9	−93	38·9	15·4	17·9	16·4	−57
12	3·4	0·9	3·5	3·1	−70	10·7	7·3	1·9	1·4	−08
13	12·1	3·3	8·7	6·1	−61	13·0	13·7	9·3	12·8	−23
Mean	11·4		10·1		−75	20·3		12·1		−27

adrenaline then caused a reduction in flow averaging only 27%. This change in mean percentage reduction with adrenaline, from 75% before to 27% after chlorpromazine, is considerable (Table I). The effect of adrenaline on the hand blood flow, before and after chlorpromazine, in each of the thirteen tests, is shown diagrammatically in Fig. 2.

The *net* change in flow during the infusion of adrenaline can be calculated from Table I, using the formula *B*–*E*. The mean change in flow with intra-arterial adrenaline was 7.9 ml. before and 5.7 ml. after chlorpromazine: the difference between these means is not significant (S.E. = 1.33, $t = 1.7$). Adrenaline therefore caused much the same *net* reduction in flow before and after the drug infusion.

The blood flow in the hand which had been infused with chlorpromazine always increased (Table I, col. *A*). The increase started before the end of the drug infusion, and the raised level of flow was still present at the end of the experiment. The amount of vasodilatation varied in different subjects; the average increase in flow in the hand which had received chlorpromazine was from a mean of 11.4 ml. to a mean of 20.3 ml. After accounting for any bilateral changes in flow, this represents a mean rise in flow of 49% due to chlorpromazine alone.

The flow in the opposite (non-infused) hand rose in ten experiments and fell in three during the infusion of chlorpromazine (Table I, col. *a*): the mean change in flow, however, was only 3.1 ml. It may therefore be assumed that the amount of chlorpromazine reaching the general circulation was not sufficient to influence the flow appreciably in the non-infused hand.

The mean changes in flow in both hands during these infusions are shown in Fig. 3.

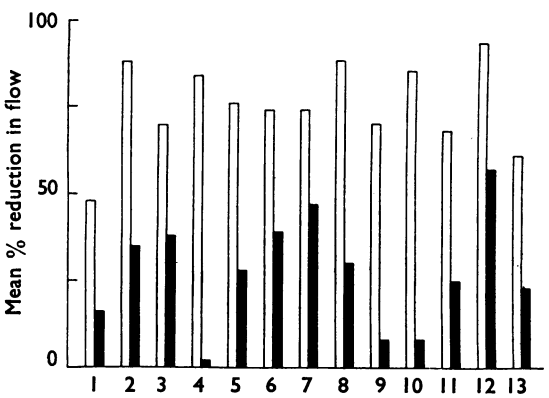

FIG. 2.—Blood-flow responses, in 13 different hands, to intra-arterial adrenaline (0·5 μg./min. for 4 min.) before (open rectangles) and after (solid rectangles) intra-arterial chlorpromazine (1·2 mg. in 6 min.).

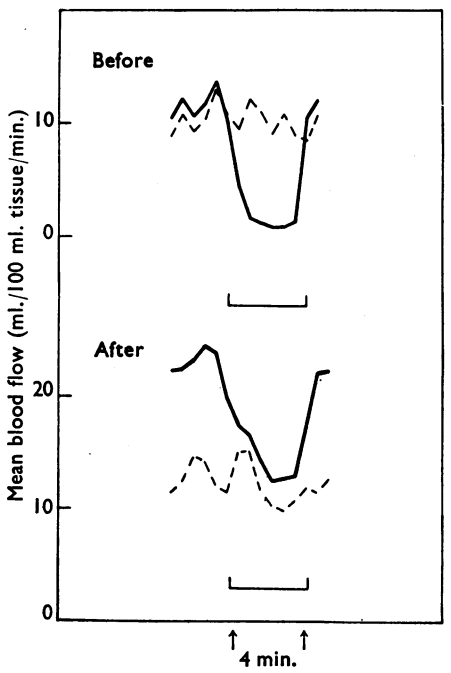

FIG. 3.—Mean blood flow in test hands (solid lines) and control hands (broken lines) during infusions of intra-arterial adrenaline (0·5 μg./min. for 4 min.) before (upper records) and after (lower records) intra-arterial chlorpromazine (1·2 mg. in 6 min.).

TABLE II

RESPONSE TO INTRAVENOUS ADRENALINE (10 TO 15 μG./MIN.) BEFORE AND AFTER INFUSING CHLORPROMAZINE (1·2 MG. IN 6 MIN.) INTO THE BRACHIAL ARTERY

A, B, a, b, as in Table I. Blood flows in ml./100 ml. tissue/min.

Expt. No.	Before Chlorpromazine						After Chlorpromazine					
	Test Hand		Control Hand				Test Hand		Control Hand			
	A	*B*	*a*	*b*	$\frac{B-A}{A}$%	$\frac{b-a}{a}$%	*A*	*B*	*a*	*b*	$\frac{B-A}{A}$%	$\frac{b-a}{a}$%
1	10·3	4·9	6·6	2·5	−52	−65	20·1	10·2	9·4	3·1	−49	−67
2	12·7	5·5	15·9	6·2	−57	−61	27·5	16 9	18·3	7·8	−39	−57
3	15·0	6·2	10·2	4·4	−59	−57	35·9	19 8	16·3	5·9	−45	−65
4	4·9	1·9	4·8	2·5	−61	−46	21·3	7·7	8·7	3·4	−64	−61
5	16·7	4·6	10·6	3·9	−72	−63	30 2	13 9	20·3	6·9	−54	−66
6	3·1	1·5	2·6	1·3	−52	−50	14·1	7·8	2·5	1·1	−45	−56
Mean					−59	−57					−49	−62

Action of Intra-arterial Chlorpromazine on the Effects of Intravenous Adrenaline

Adrenaline was given intravenously to six subjects before and after an intra-arterial infusion of 1.2 mg. chlorpromazine. The characteristic effects of systemic adrenaline, such as tachycardia and pallor, occurred in all subjects, three of whom received 10 μg./min. and three 15 μg./min. The blood flow in the hands (Fig. 1 and Table II, cols. *B–A/A* and *b–a/a*) decreased on average by 59% on one, and by 57% on the other, side.

When intravenous adrenaline was given after infusing chlorpromazine into the brachial artery, the reduction in flow averaged 49% in the test hand (Table II, col. *B–A/A*). The difference between the reduction of 59% before and 49% after chlorpromazine, though small, is significant (S.E.=3.0, t=2.8). By contrast, the opposite hand, which had not received chlorpromazine, responded to the second intravenous infusion of adrenaline with a reduction in flow of 62% (Table II, col. *b–a/a*). This value is not significantly different from the previous mean of 57% (S.E.=2.8, t=1.5).

The effect of intravenous adrenaline was therefore slightly but significantly reduced in the hand that had been infused with 1.2 mg. chlorpromazine.

Action of Intravenous Chlorpromazine on the Effects of Intra-arterial Adrenaline

The effect of intravenous chlorpromazine on the response to intra-arterial adrenaline was tested in three subjects (Table III). In the control period before chlorpromazine, the reduction in flow (Table III, col. *B–E/E*) with intra-arterial adrenaline averaged 75% in the test hand. The mean percentage reduction was only 22% after intravenous chlorpromazine, when the level of flow had increased by at least 300%.

The *net* reduction in flow with adrenaline, *B–E*, was not, however, affected by chlorpromazine; the mean value was 4.5 ml. both before and after the chlorpromazine infusion.

The subjects were given 50 mg. chlorpromazine intravenously over 10 min. and rapidly became apathetic and drowsy. A rise in flow in both hands was apparent within 2 min. of the start of the infusion: the highest level of flow was recorded after about 6 min., when only half the total dose had been given. The rise varied between 300 and 400% in each hand (Table III, cols. *A* and *a*) and persisted until the end of the experiment.

TABLE III

RESPONSE TO INTRA-ARTERIAL ADRENALINE (0·5 μG./MIN. FOR 4 MIN.) BEFORE AND AFTER INFUSING CHLORPROMAZINE (50 MG. IN 10 MIN.) INTRAVENOUSLY

Col. headings as in Table I. Blood flows in ml./100 ml. tissue/min.

Expt. No.	Before Chlorpromazine					After Chlorpromazine				
	Test Hand		Control Hand			Test Hand		Control Hand		
	A	*B*	*a*	*b*	$\frac{B-E}{E}$%	*A*	*B*	*a*	*b*	$\frac{B-E}{E}$%
1	4·1	1·3	4·0	3·5	−64	19·9	14·8	22·0	19·3	−15
2	5·4	1·2	3·4	2·9	−74	27·8	20·6	27·6	25·1	−19
3	7·9	1·3	5·7	6·5	−86	21·7	15·4	20·9	20·7	−28
Mean					75					22

Discussion

Peripheral vasodilatation after chlorpromazine has been clearly demonstrated. Intra-arterial infusions of 1.2 mg. produced a mean rise in flow in the infused hand of 49%. This is the increase attributable to the drug alone, for the analysis (Methods and Table I) has taken account of any bilateral changes in flow. A similar increase in hand blood flow was found by Foster *et al.* (1954): intra-arterial infusions of 0.06 to 0.8 mg. chlorpromazine caused an average increase in flow in the infused hand of 50%. There is therefore good evidence that the drug has a direct action on the peripheral vessels.

When chloromazine was infused intravenously, in a dose (50 mg.) calculated to give approximately the same local concentration in the hand as in the intra-arterial experiments, the increase in flow was much greater, and averaged three or four hundred per cent in either hand. Intravenous chlorpromazine, therefore, produced a rise in hand blood flow almost eight times that found after comparable doses given intra-arterially. A similar disparity between the degree of vasodilatation after comparable intravenous and intra-arterial infusions was noted by Foster *et al.* (1954). Duff, McIntyre, and Butler (1956) found vasodilatation of a similar order. Peripheral vasodilatation after intravenous chlorpromazine would therefore appear to result from both local and systemic actions. Laborit and Huguenard (1951) suggested that many of the cardiovascular effects of chlorpromazine could be explained by a central inhibition of autonomic activity. Holtzbauer and Vogt (1954) have shown, however, that one form at least of central sympathetic activity is not inhibited by chlorpromazine—the stimulant action of morphine on hypothalamic sympathetic centres in cats. In the small group of subjects given intravenous chlorpromazine in this investigation, it was noted that the stimulant effect of a distended bladder caused subjective effects and a temporary decrease in hand blood flow. Moreover, all three subjects, though drowsy and disinclined to move, were able to stand and compensate for any postural hypotension within half to three-quarters of an hour of the end of the infusion. Chlorpromazine does not, therefore, cause complete inhibition of central vasomotor activity. Peripheral vasodilatation after intravenous chlorpromazine may result in part from other actions of the drug and may possibly involve changes in metabolism. Whatever the mechanism, the striking changes in peripheral flow should not be ignored when chlorpromazine is given in clinical practice.

Antagonism between chlorpromazine and adrenaline was first demonstrated by Courvoisier *et al.* (1953): the drug was found to abolish, and even reverse, the pressor action of adrenaline, and to afford some protection against its toxic effects. Hence chlorpromazine was described as a specific adrenaline antagonist, therein resembling dibenamine (Huidobro, 1954). Reduction of peripheral adrenaline vasoconstriction has been demonstrated in man (Foster *et al.*, 1954), but evidence of reversal was not conclusive (Foster *et al.*, 1954). The present investigation showed that the mean reduction in flow with intra-arterial adrenaline (Table I) was 75% before and 27% after intra-arterial chlorpromazine: chlorpromazine reduced the effect of adrenaline by about one half. These figures, however, represent responses to adrenaline expressed as a percentage of the control level of flow, after accounting for bilateral changes (see Methods). After chlorpromazine this control level was considerably greater. Calculation of the net alteration in mean flow (*B–E*), which simply measures the volumetric *reduction* in flow, showed no significant difference in the *net* effect of adrenaline after chlorpromazine. Thus adrenaline still caused much the same total reduction in flow, in the hand into which chlorpromazine had been infused; but since the initial level of flow was higher as the result of chlorpromazine the proportionate reduction was correspondingly less. The difficulty of deciding which is the more accurate measure of drug activity —the absolute or the relative change in response—arises in any biological assay. Since there was no change in the net response to adrenaline it might be

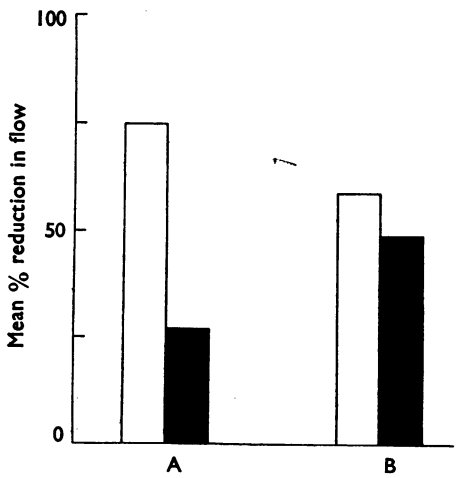

FIG. 4.—Mean response in all tests to adrenaline, intra-arterially (A, 0·5 μg./min. for 4 min.), and intravenously (B, 10 μg./min. for 4 min.), before (open rectangles) and after (solid rectangles) chlorpromazine intra-arterially (1·2 mg. in 6 min.).

argued that there is no antagonism, at least peripherally, between adrenaline and chlorpromazine in man. It may also be contended that much of the antagonism demonstrated in animals is attributable to peripheral vasodilatation, and not to a specific adrenaline antagonism. The increase in peripheral blood flow may therefore be an important factor in the protection afforded by chlorpromazine against adrenaline shock in animals.

It was interesting that chlorpromazine was much more effective against intra-arterial than against intravenous adrenaline (Tables I and III, Fig. 4). Reactivity to adrenaline may have been increased after a single intravenous dose (Cannon and Rosenblueth, 1949). The *net* change in flow was indeed greater by about 50% in both hands after the second intravenous infusion of adrenaline, but the *percentage* reduction in the hand which had *not* received chlorpromazine was not significantly increased. These results emphasize the complex nature of drug antagonism.

Summary

1. The effects of intra-arterial and of intravenous infusions of chlorpromazine on the blood vessels of the hands of healthy men have been assessed by venous occlusion plethysmography.

2. The volume of blood flowing through the hand increased by an average of about 50% after intra-arterial (1.2 mg.) and by about 400% after intravenous (50 mg.) chlorpromazine.

3. The percentage reduction in flow with intra-arterial (0.5 μg./min.) adrenaline averaged 75% before and 27% after the infusion of 1.2 mg. chlorpromazine into the brachial artery; but the *net* reduction in flow with intra-arterial adrenaline was not significantly different after chlorpromazine.

4. The average percentage reduction in flow in the hand with intravenous adrenaline was slightly but significantly decreased by the infusion of 1.2 mg. chlorpromazine into the brachial artery.

5. No reversal of peripheral adrenaline vasoconstriction was found even after intravenous chlorpromazine.

6. The results are discussed in relation to the problem of antagonism between adrenaline and chlorpromazine.

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