of prophylaxis should not be practised universally so that it will eventually supersede the less satisfactory method of horse-serum administration.

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The Royal Society of Health held a sessional meeting in London last November at which a number of papers were read on the subject of "The Design of Health Buildings." In an introductory paper Dr. CHRISTIE W. GORDON stated that the National Health Service is founded upon the family and its doctor, and suggested that in the future development of hospital services out-patient departments should be considered as an extension of the facilities available to the general practitioner in his surgery. The in-patient departments of the hospital might be organized into an admission unit and special departments, supported by neighbourhood homes and a country annexe. The neighbourhood homes would receive patients from the special departments of the hospital as soon as they could be moved, and there they would be cared for by their general practitioner. A trained nurse would be in charge of the homes, which would so far as possible be maintained by the patients themselves, members of their family, and voluntary workers.

CARDIOVASCULAR ACTIONS OF CHLORPROMAZINE

WITH PARTICULAR REFERENCE TO PERIPHERAL VASCULAR DISEASE

BY

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Since its introduction by Laborit and Huguenard (1951) chlorpromazine has been found to have a variety of interesting actions. It is a powerful anti-emetic and produces hypothermia. It has been used in the treatment of various psychiatric conditions and as an adjuvant in general anaesthesia to combat the shock syndrome.

Despite much experimentation with laboratory animals certain of its pharmacological effects in man have not yet been fully elucidated. It has been shown to cause profound circulatory changes in the hands, forearms, and calves of healthy subjects (Foster *et al.*, 1954) as a result of both central and peripheral actions. The present paper concerns the effects of intravenous chlorpromazine on the general circulation and on the blood vessels of hands, feet, and forearms of both healthy subjects and patients with peripheral vascular disease.

Methods

Throughout each experiment the subject reclined comfortably on a couch in a laboratory in which the ambient temperature was kept between 22° and 24° C.

FIG. 1.—Effect of intravenous infusion of 25 mg. of chlorpromazine on blood flow in the left hand and right foot of a healthy man.

Repeated measurements of blood flow in one or more extremity (hand, forearm, foot) were obtained by intermittent venous occlusion plethysmography, using metal plethysmographs filled with water maintained at $34 \pm 1^\circ \text{C}$. (Duff and Swan, 1951; Duff, 1952). The skin temperature of other extremities was recorded by thermocouples, and at intervals the oral temperature was taken. The arterial blood pressure in one arm was determined regularly by sphygmomanometry, and the heart rate and rhythm were recorded by electrocardiography.

After making control observations for half to one hour an infusion of a specific amount of chlorpromazine ("largactil"), based on the subject's weight, was given intravenously. Measurements of blood flow, blood pressure, temperature, etc., were then repeated regularly for one and a half to four hours. The blood flow was calculated and expressed as the volume flowing in millilitres per minute per 100 ml. of tissue (hand, forearm, or foot) volume (ml./100 ml./min.).

Results

1. *Effect of Chlorpromazine on Cutaneous Blood Vessels (Hands and Feet) of Healthy Subjects.*—Healthy volunteers and patients with no evidence of circulatory impairment in tested extremities were studied. In all a marked increase in blood flow occurred soon after the start of the chlorpromazine infusions (Fig. 1). The amount of vasodilatation varied greatly irrespective of the dose of the drug (Table I), but the average change was from 5.4 to 21.5 ml./100 ml./min.—an increase of almost 300%.

2. *Effect on Diseased Vessels.*—This group comprised 10 limbs with gross evidence of inadequate circulation, such as ischaemic ulceration, coldness and discoloration of the skin, and intermittent claudication. All but two were men between 25 and 52 years of age, diagnosed severally as suffering from arteriosclerosis, Buerger's disease, and

advanced Raynaud's disease. In most chlorpromazine caused little (Fig. 2) or no (Fig. 3) increase in cutaneous blood flow (Table II, A). In some, as in Fig. 3, the infusion was followed by an actual reduction of blood flow in the limbs studied. In one subject with right femoral artery thrombosis but otherwise comparatively healthy vessels chlorpromazine caused vasodilatation in both feet, though of less degree in the right (Fig. 4).

3. *Effect on Muscle Vessels (Forearm).*—Observations were obtained from three patients whose vascular disorder appeared to be confined to the skin (Raynaud's disease) or else mainly affected the lower limbs (arteriosclerosis and Buerger's disease). It could therefore be inferred that in these patients the vessels of the forearms were affected comparatively slightly. In all three a definite increase in blood flow occurred within half an hour of starting chlorpromazine infusions, as in Fig. 2. The average change was from 1.9 to 3.3 ml., an increase of almost 100%. A fourth patient with advanced Buerger's disease had a reduction of forearm blood flow (Table II, B) presumably because blood was diverted into more relaxed vessels in regions (other than the limbs) less affected by the disease.

FIG. 2.—Little or no increase in foot blood flow of patient with intermittent claudication following intravenous chlorpromazine; slight vasodilatation of the forearm.

FIG. 3.—In this patient with advanced Buerger's disease 10 mg. of chlorpromazine was followed by a slight reduction of the circulation in the feet and forearm.

TABLE I.—Effect of Intravenous Chlorpromazine on Blood Flow Through Healthy Skin Vessels

Subject	Limb	Total Drug mg.	Dose: mg. stone (6.35 kg.) Body Weight	Mean Blood Flow (ml./100 ml./min.)		
				Control	Hours After Drug	
					0-½	½-1
P.B.	Left hand	25	2	7.7	40.0	16.0
A.B.	"	8	1	5.9	11.2	
J.M.	Left foot	45	4	1.9	21.0	9.0
P.B.	Right foot	25	2	3.0	12.7	8.4
A.H.	"	11	1	12.6	23.5	14.6
L.M.	Left foot	16	1	2.8	19.0	12.1
A.B.	Right foot	8	1	4.1	23.1	
Averages				5.4	21.5	12.0

TABLE II.—Effect of Intravenous Chlorpromazine on Blood Flow Through Diseased Skin Vessels of Feet, and Skeletal Muscles of Forearms

Subject	Condition	Total Drug Dose mg.	Dose: mg. stone (6.35 kg.) Body Weight	Mean Blood Flow (ml./100 ml./min.)		
				Control	Hours After Drug	
					0-½	½-1
A. Feet						
G.R.	Buerger's dis.	10	1	7.3	6.6	6.4
J.J.	Arterio-sclerosis	13	1	4.0	4.2	6.5
E.H.	Buerger's dis.	10	1	8.5	7.0	6.7
E.H.	"	10	1	10.1	7.5	8.0
D.D.	Raynaud's dis.	9	1	3.7	2.3	
L.M.	Femoral thrombosis	16	1	3.7	10.4	
Averages				6.2	6.3	7.0
B. Forearms						
G.R.	Buerger's dis.	10	1	1.8	3.2	2.0
J.J.	Arterio-sclerosis	13	1	1.7	2.9	2.7
B.D.	Raynaud's dis.	9	1	2.4	3.8	
E.H.	Buerger's dis.	10	1	6.5	3.3	3.2

FIG. 4.—Chlorpromazine caused vasodilatation in both feet, though less marked on the side of the femoral artery thrombosis.

4. *Effect of Chlorpromazine on Heart and Blood Pressure.* Immediately following chlorpromazine infusions moderate fluctuations in heart rate occurred (Table III, A); thereafter the rate tended to be slightly above the control levels. No change in electrocardiographic pattern was observed with the doses used. Some fall in blood pressure occurred, especially in those receiving larger doses; but even with the largest dose (45 mg.) the fall in pressure was not excessive (Table III, B). The blood pressure remained slightly below normal for an hour or more after the infusions.

5. *Effect on Body Temperature.*—Shortly after infusing chlorpromazine the oral temperature began to fall, and during the next hour or two reached a level some 0.5 to 1.5° F. (0.3–0.9° C.) below the control temperature (Table III, C). In several subjects the temperature of the skin of the hands and feet was measured by thermocouples. After the infusions the temperature of these extremities rose more or less in parallel with the recorded increase in volumetric blood flow.

TABLE III.—*Effect of Intravenous Chlorpromazine on Heart Rate, Arterial Blood Pressure, and Oral Temperature*

Subject	Total Drug Dose mg.	Dose mg./stone (6.35 kg.) Body Weight	Control	Hours After Drug		
				0-½	½-1	1-2
A. Heart Rate (per Minute)						
J.M.	45	4	83	68	100	108
P.B.	25	2	86	100	80	
A.H.	11	1	96	90		80
G.R.	10	1	71	90	70	
J.J.	13	1	65	86	60	
L.M.	16	1	64	72		
E.H.	10	1	91	128	116	
Averages		..	79	91	85	
B. Arterial Blood Pressure (mm. Hg)						
J.M.	45	4	130/70	100/70	98/65	98/65
P.B.	25	2	114/70	100/70	105/70	112/75
A.H.	11	1	120/70	120/80		120/75
G.R.	10	1	112/75	105/75	110/80	
J.J.	13	1	140/88	110/75	100/70	
L.M.	16	1	120/80	120/75		
E.H.	10	1	140/85	100/70		
Averages		..	125/77	108/73	103/71	
C. Oral Temperature						
P.B.	25	2	98.3° F. (36.85° C.)	97.1° F. (36.15° C.)	96.5° F. (35.85° C.)	
A.H.	11	1	98.7° F. (37.05° C.)		97.5° F. (36.35° C.)	
G.R.	10	1	98.0° F. (36.7° C.)	97.3° F. (36.25° C.)	97.1° F. (36.15° C.)	
J.J.	13	1	97.5° F. (36.35° C.)	97.2° F. (36.2° C.)	97.0° F. (36.1° C.)	
E.H.	10	1	98.5° F. (36.95° C.)	97.6° F. (36.4° C.)	97.3° F. (36.25° C.)	
B.D.	9	1	100.0° F. (37.8° C.)	98.6° F. (37° C.)		
Averages		..	98.5° F. (36.95° C.)	97.7° F. (36.45° C.)	97.2° F. (36.2° C.)	97.0° F. (36.1° C.)

Discussion

It has been shown that intravenous chlorpromazine increases the calibre of healthy blood vessels in the skin of the hand and foot and the muscles of the forearm. This confirms the conclusion of Foster *et al.* (1954) that the drug causes vasodilatation in normal hands and forearms. In the present series the healthy subjects had considerable increases in the blood flow to the extremities, three to four times the control level. The resultant warmth of the hyperaemic skin has been noted by Dobkin *et al.* (1954).

The relatively small change in heart rate and blood pressure suggests that the total cardiac output was but little affected. It must therefore be inferred that the increased circulation in the limbs reduced the blood available for other tissues, such as the abdominal viscera, in which vessels must have constricted, actively or passively.

The experiments were performed under conditions which prevented much loss of heat from the body surface, the exposed parts of which were covered by blankets. The fall in mouth temperature cannot, therefore, be attributed to the peripheral vasodilatation. It may be a direct result of the reduced visceral circulation or a more specific action on the temperature-controlling centres in the brain.

In patients with peripheral vascular disease the effects of chlorpromazine on heart rate, blood pressure, and oral temperature were similar to those of healthy subjects. In patients with moderately extensive involvement of the vasculature some increase in peripheral blood flow occurred, especially in less-affected regions. But the drug failed to improve the circulation in more severe cases of arteriosclerosis and Buerger's disease. Indeed, by lowering blood pressure and directing blood into less rigid vessels the circulation to the extremities was sometimes reduced. However, when the lesion was confined to the main artery and did not involve the peripheral vascular bed, chlorpromazine increased the circulation by opening up collateral vessels.

These findings may have practical implications. Chlorpromazine has been shown capable of dilating blood vessels in the muscles and skin of some patients with gross vascular disease of the extremities, increasing the circulation through vessels retaining some flexibility. The drug has an advantage over several other agents used for peripheral vascular disease in that it causes little increase in cardiac output but achieves its effect by preferentially dilating the limb vessels at the expense of other regions. This property would especially recommend the trial of chlorpromazine in vasospastic states. However, in view of the risk of toxic effects such as jaundice following prolonged administration, the drug had best be confined at present to more acute conditions such as arterial thrombosis or embolism. Finally, chlorpromazine might appropriately be used to determine what circulatory benefit might be expected from surgical sympathectomy.

Summary

Peripheral and central circulatory effects of intravenous chlorpromazine have been studied in healthy subjects and in patients with various vascular disorders of the extremities.

Increases in the volume of blood flowing through the skin (hands and feet) of healthy limbs were measured by venous occlusion plethysmography.

In patients with extensive disease of peripheral vessels little or no increase in cutaneous blood flow was demonstrated by the plethysmographs, but in some the circulation through a comparatively unaffected region (forearm) was augmented.

The heart rate, after some fluctuation, tended to remain slightly increased; a slight fall in systemic blood pressure occurred consistently.

The oral temperature regularly fell a little; by contrast the vasodilatation of the extremities was attended by increased warmth of the hands and feet and raised digital temperatures.

Certain pharmacological and clinical implications of these findings are discussed.

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A campaign to improve the rate of immunization against diphtheria was begun at the end of last month by the London County Council. It is estimated that of the children under 5 years of age in London little over half have been immunized, and it is this, which has prompted the L.C.C. to give public notice of the continued importance attached to diphtheria immunization. The medical officer of health of London has recently pointed out that in a county as large as London, with great numbers of migrants passing through each year, the possibility of imported infection is always present. The fall in the incidence of diphtheria has certainly been dramatic—in London there were only 12 cases with 2 deaths last year—but it would be dangerous for the parents of young children to think they were safe from infection.