MECHANISM OF THE ARTERIAL HYPERTENSION INDUCED BY PAREDRINOL (α–N–DIMETHYL–p–HYDROXYPHENETHYLAMINE)

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In arterial hypertension the cardiac output, the metabolic rate, and the usual blood chemical constituents are essentially normal. Experimental hypertension in man, however, is usually attended by alterations in some of these measurements. Epinephrine produces hypertension in normal subjects, but at the same time it usually increases the heart rate and cardiac output. It elevates the basal metabolism, the blood flow in the muscles, the blood sugar and the blood lactic acid, and also causes great vasoconstriction in the skin vessels. This hypertension is therefore in no way comparable to that observed in disease. The study to be reported indicates that in normal subjects paredrinol sulphate[1] (α-N-dimethyl-p-hydroxyphenethylamine sulphate) produces a type of hypertension which has many features in common with clinical hypertension. For this reason the circulatory adjustments following the administration of this drug are of particular interest.

The pharmacology of paredrinol, a sympathomimetic drug closely allied in structure to ephedrine, has been studied extensively in animals. Rein (1, 2), in an investigation of the action of paredrinol on dogs anesthetized with morphine and pernocton, found that both the arterial pressure and the minute volume output of the heart were elevated. The drug acted first on the venous side of the circulation, and produced a greater venous return to the heart by increasing the venous tone and probably by emptying out the liver. This was followed in a few seconds by a slow increase in arterial tone and, shortly thereafter, by a powerful discharge of blood from the abdominal organs, particularly the spleen. Rein claimed that this intense discharge of blood from the abdominal venous reservoirs indicated that the main cause for the rise in arterial pressure was an increase in venous return to the heart, rather than an increase in peripheral resistance. He demonstrated that the blood flow in the extremities and in the abdominal viscera was never greatly decreased and at times was increased. Since the drug did not cause blanching when introduced into the human skin, he concluded that the capillaries were not constricted and that the arterial tone was increased in the larger vessels.

Heymans and Bayless (3), on the basis of experiments conducted on anesthetized dogs, concluded that the vascular effect of the drug was characterized by slight peripheral vasoconstriction and pronounced splanchnic vasoconstriction. When the physiological reflexes for the proprioceptive regulation of blood pressure were depressed by means of barbiturates, they were not restored by paredrinol, even though the blood pressure was raised. Lindner (4), working with isolated cats' hearts, demonstrated that paredrinol in concentrations of 1 to 1,000,000 increased the frequency and strength of the heart beat.

Numerous observations have been made on the effect of paredrinol in human subjects. The drug was found to be active by oral, rectal, subcutaneous, intramuscular, and intravenous routes (5, 6, 7). It caused a rise in blood pressure, a fall in heart rate, and palpitation (5, 7). There were no other symptoms unless the blood pressure rose excessively, in which event a sensation of severe pressure in the head and of precordial discomfort was experienced (5, 7, 8, 9). The venous pressure was increased by about 20 mm. of water (7), and one observer reported that the rise in venous pressure occurred after the rise in arterial pressure (9). The skin of the subjects showed no change in color (5). Nodal rhythm and ventricular extrasystoles occurred in certain instances (10). There was no change in the level of the

[1] The paredrinol sulphate used in this study was obtained through the courtesy of the Smith, Kline, and French Laboratories. This drug has been reported in the German literature under the trade names "veritol" and "H 75" (Knoll).

blood sugar (5). A transient rise in oxygen consumption has been reported (7) following the intravenous administration of paredrinol. It was suggested that this increase in oxygen consumption was the result of a heightened flow from the large veins and venous reservoirs, and that the mobilization of blood from venous reservoirs, which Rein had demonstrated in the dog, also occurred in man. The cardiac output was increased (11) when determined by the method of Broemser and Ranke, but in man this method was found to be unreliable in this laboratory. Several authors (8, 9, 11) believe that the rise in blood pressure was produced both by an increased venous return to the heart and by an increase in the peripheral resistance. The previous injection of atropine (12) prevented slowing of the heart and caused the blood pressure to rise to a higher level than that observed after the administration of paredrinol alone. Paredrinol is the N-methyl derivative of paredrine (β-4-hydroxyphenylisopropylamine). The effect of paredrine on the heart rate, blood pressure, and skin temperature has been reported by Abbott and Henry (13).

METHOD

This study of the action of paredrinol was carried out on subjects with normal cardiovascular systems. The arterial blood pressure was determined in the upper arm by the auscultatory method, using a mercury manometer. The heart rate was counted by arterial palpation. The blood flow in the hand, foot, forearm, and calf was measured by the plethysmographic methods previously described (14, 15, 16). When measurements were made on the forearm and calf, the circulation to the hand and foot distal to them was occluded by pressure cuffs below the plethysmographs (16, 17). The venous tone in the hand was measured by the method of Capps (18), and the venous pressure by the direct method of Moritz and Tabora (19). The cardiac output was measured by the acetylene method (20), and the basal metabolism by oxygen consumption. The histamine method was used for determining the circulation time (21). Skin temperatures were measured by a thermocouple. The paredrinol was injected intramuscularly after the subjects had rested quietly in the horizontal position for at least 30 minutes. The effects of the upright position on the circulation were determined by tilting the table on which the subjects rested to an angle of from 30 to 75 degrees above the horizontal.

RESULTS

Arterial pressure, venous pressure, and heart rate. In 10 normal subjects the intramuscular injection of 25 mgm. of paredrinol raised the arterial blood pressure from an average of 120 mm. Hg systolic and 76 mm. diastolic to 173 mm. systolic and 92 mm. diastolic (Figure 1). The height to which the arterial pressure rose varied greatly in different subjects. The minimum rise in arterial pressure was from 120 mm. systolic and 70 mm. diastolic to 148 mm. systolic and 72 mm. diastolic; the greatest was from 130 mm. systolic and 78 mm. diastolic to 200 mm. systolic and 104 mm. diastolic. There was also great variation in the results obtained in the same subject, the arterial pressure on one day rising from 114 mm. systolic and 80 mm. diastolic to 190 mm. systolic and 90 mm. diastolic, while a few days later the same amount of paredrinol caused a rise in pressure to only 148 mm. systolic and 72 mm. diastolic. The arterial blood pressure following intramuscular administration of 25 mgm. of paredrinol began to rise in from 3 to 9 minutes (average 5 minutes). The maximum height was reached in from 8 to 20 minutes (average 16 minutes). The blood pressure returned to the resting level in from 40 to 70 minutes (average 57 minutes). The heart rate in these 10 subjects dropped from an average of 72 to an average of 63 beats per minute. Three cases showed no significant change in heart rate. The maximal change was from 81 to 54 beats per minute.

In 3 normal subjects, from 35 to 40 mgm. of the drug were given intramuscularly; the arterial blood pressure rose from normal to 180, 186, and 214 mm. systolic, and to 80, 108, and 110 mm. diastolic, respectively. In 1 subject the arterial blood pressure was maintained above 190 mm. systolic and 110 mm. diastolic for 30 minutes by the repeated administration of smaller doses of paredrinol. In a second subject an arterial pressure of from 180 to 196 mm. systolic and 86 mm. diastolic was maintained for 30 minutes.

In 3 normal subjects the venous pressure was measured by the direct method and was found to increase by from 30 to 40 mm. of water above the resting level. The arterial and venous pressures began to rise at approximately the same time, but as neither determination was absolutely continuous it was not possible to say which was the first to increase. In one subject, who had received 3 mgm. of atropine subcutaneously before the intramuscular injection of 25 mgm. of paredrinol, the

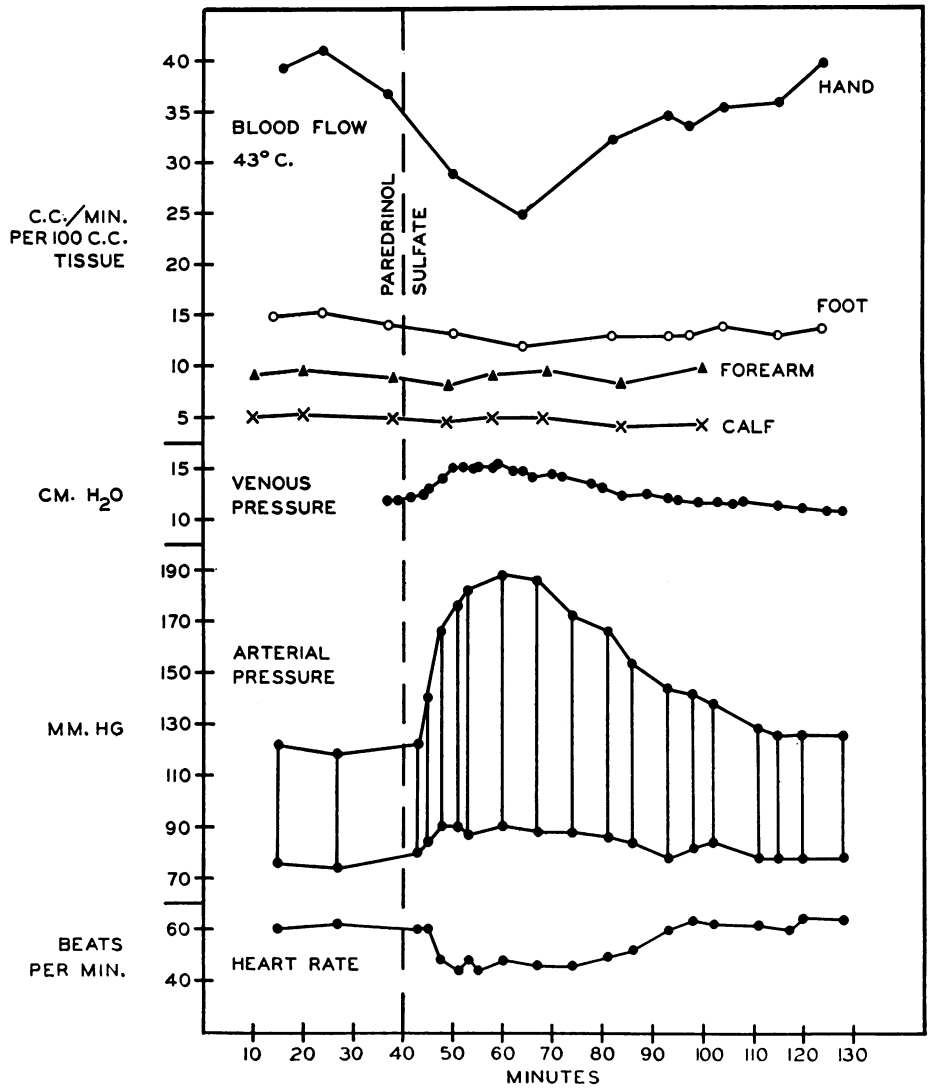

FIG. 1. EFFECT ON HEART RATE, ARTERIAL PRESSURE, AND VENOUS PRESSURE IN A NORMAL SUBJECT OF THE INTRAMUSCULAR INJECTION OF 35 MGM. OF PAREDRINOL. EFFECT ON THE BLOOD FLOW IN HAND, FOOT, FOREARM, AND CALF IN THE SAME SUBJECT OF 25 MGM. OF THE SAME DRUG.

spinal fluid pressure rose from 170 mm. to 230 mm. of water.

Symptoms and signs. Palpitation, which was experienced by all the subjects, was usually the only symptom noted. The drug caused no pain at the site of injection. There was no evidence of excitement, cerebral stimulation, or tremor. The color of the hands and face did not change. The force of the apex impulse was greatly increased. The arterial pulsations in the neck were quite marked. Pistol shots were occasionally heard in the femoral vessels. No disturbances in cardiac rhythm were observed. Three of the subjects complained of occipital headaches at pressures of 180, 214, and 220 mm. systolic, and at 100, 110, and 150 mm. diastolic. One subject complained of mild precordial discomfort.

Electrocardiograms and phonocardiograms. In 4 normal subjects the electrocardiographic tracings showed no change except in the T-waves (Figure 2). The T-waves were usually increased by from 1 to 2 mm. in height in Leads 1, 2, and

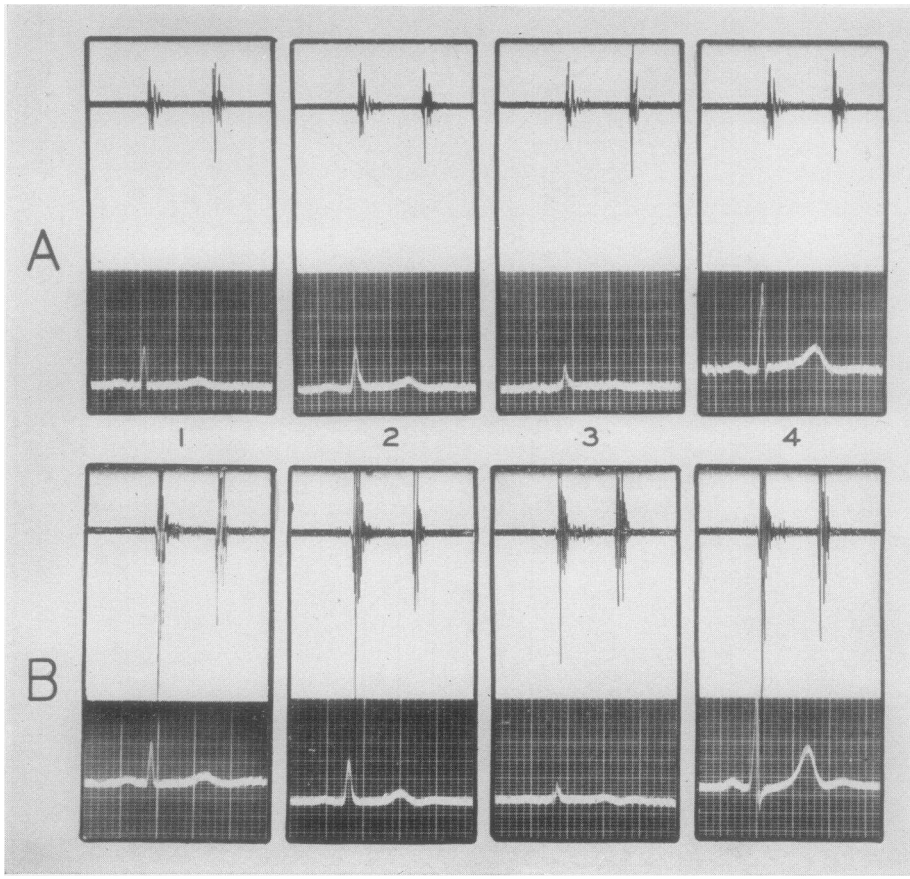

FIG. 2A. SIMULTANEOUS ELECTROCARDIOGRAM AND PHONOCARDIOGRAM OF A NORMAL RESTING SUBJECT.

FIG. 2B. SIMULTANEOUS ELECTROCARDIOGRAM AND PHONOCARDIOGRAM OF THE SAME SUBJECT AFTER THE INTRAMUSCULAR INJECTION OF 25 MGM. OF PAREDRINOL.

3, although this change was not uniform and at times occurred in only one or two of these leads. In Lead 4 the T-waves were consistently higher, the average increase being 5 mm. In 3 cases with inverted T-waves in certain leads, the T-waves never became any deeper, usually they became less inverted and at times they became upright. Phonocardiograms (Figure 2) illustrated the great increase in the intensity of the heart sounds.

Blood flow, vasomotor reactions, and venous tone. In 5 subjects the blood flow in the hand at 43° C. showed a definite, though not marked, fall after the intramuscular administration of 25 mgm. of paredrinol; the flow dropped from an average of 34 cc. to an average of 27 cc. per minute per 100 cc. of tissue. In 2 subjects the hand flow at 37° C. also showed a moderate decrease. No significant change in the blood flow in the foot was demonstrable when measured at 43° C. (4 subjects), at 37° C. (2 subjects) and at 32° C. (1 subject). In 3 subjects the blood flow in the forearm and calf at 43° C. showed no change. The spontaneous fluctuations in vasomotor tone became much less marked in the hand after administration of paredrinol, while in the foot there was only a slight decrease in vasomotor activity. Typical vasoconstriction (22), however, was obtained in both organs with such stimuli as a deep inspiration or pinching the skin. The venous tone was definitely increased in the 4 subjects tested. Two of these were normal subjects while the other 2 had had preganglionic sympathectomies. The increase in venous tone was of about the same magnitude as that observed following the administration of epinephrine. When paredrinol was pricked into the skin or injected

TABLE I

Effect of paredrinol on the cardiac output (acetylene method)

Subject and age	Date	Blood pressure	Pulse rate	Oxygen consumption	Basal metabolic rate	Arteriovenous oxygen difference	Cardiac output			
years	*1939*	*mm. Hg*	*per minute*	*cc. per minute*	*per cent*	*cc. per liter*	*liters per minute*	*cc. per beat*	*liters per 100 cc. of oxygen consumed*	*liters per square meter of surface area*
A. Y. 26	February 3	120/86	62	219	−17.5	58.1 56.0	3.84	62.0	1.75	1.98
	February 3	200/116	50	243	− 7.2	60.8 63.7	3.91	78.2	1.61	2.02
	February 3	194/116	54			59.0 58.4	4.14	76.6	1.70	2.13
E. A. S. 30	February 27	112/78	60	218	−24.0	82.9 85.6	2.59	43.2	1.19	1.24
	March 8	182/86	52	253	−10.0	83.0 88.4	2.95	56.7	1.17	1.41

intracutaneously in concentrations of 1 to 40, a wheal surrounded by a flare was produced, which was usually attended by itching.

Cardiac output, circulation time, and basal metabolism. The cardiac output was determined in 2 subjects with the blood pressure elevated to 200 mm. and 194 mm. systolic, and 116 mm. and 86 mm. diastolic, respectively (Table 1). In neither subject was there a rise in minute output of the heart, though as the stroke volume increased the heart rate decreased. The basal metabolic rate was measured 7 times in 3 subjects, with an average increase of 7 per cent above the basal level. The histamine circulation time was measured 3 times in 2 subjects at the height of the blood pressure response and in neither subject did it differ from the values obtained at normal blood pressure levels.

Atropine. Three subjects were given from 3 to 4 mgm. of atropine subcutaneously (Figure 3). The heart rate increased from an average of 71 to an average of 117 beats per minute. After the rate had become constant 2 of the subjects were given 25 mgm., and the third 35 mgm., of paredrinol intramuscularly. The heart rate increased to an average of 135 beats per minute and the blood pressure reached an average height of 205 mm. systolic and 130 mm. diastolic. In these subjects the blood flow in the hand and foot at 43° C. and in the foot at 40° C. showed no significant change.

Posture. In normal subjects the high arterial blood pressure produced by paredrinol showed little change when the subject was tilted from the horizontal position to an angle of from 50 to 75 degrees above the horizontal. The oral administration of 3 grains of sodium nitrite had no effect on the development of the paredrinol hypertension in the horizontal position, but the arterial blood pressure fell rapidly to either normal or subnormal levels when the subjects were tilted to the upright position (Figure 4).

Arteriosclerotic gangrene and preganglionic sympathectomy. In 2 subjects with early arteriosclerotic gangrene of the lower extremities and without hypertension, the systolic blood pressures were maintained at levels of 186 and 200 mm., respectively, for at least 1 hour; no change in skin temperature was observed. In 2 subjects with preganglionic sympathectomies the decrease in hand flow produced by paredrinol was greater than that in the normal subjects.

Comparison of the effect of paredrinol and paredrine (β-4 hydroxyphenylisopropylamine) on the cardiovascular system. Three of the above subjects were given 20 mgm. of paredrine hydrobromide intramuscularly. Their arterial blood pressures rose to an average of 176 mm. systolic and 91 mm. diastolic; the heart rate slowed from an average of 66 to an average of 49 beats per minute. The subjects experienced no pain at the site of injection, but they were soon aware of

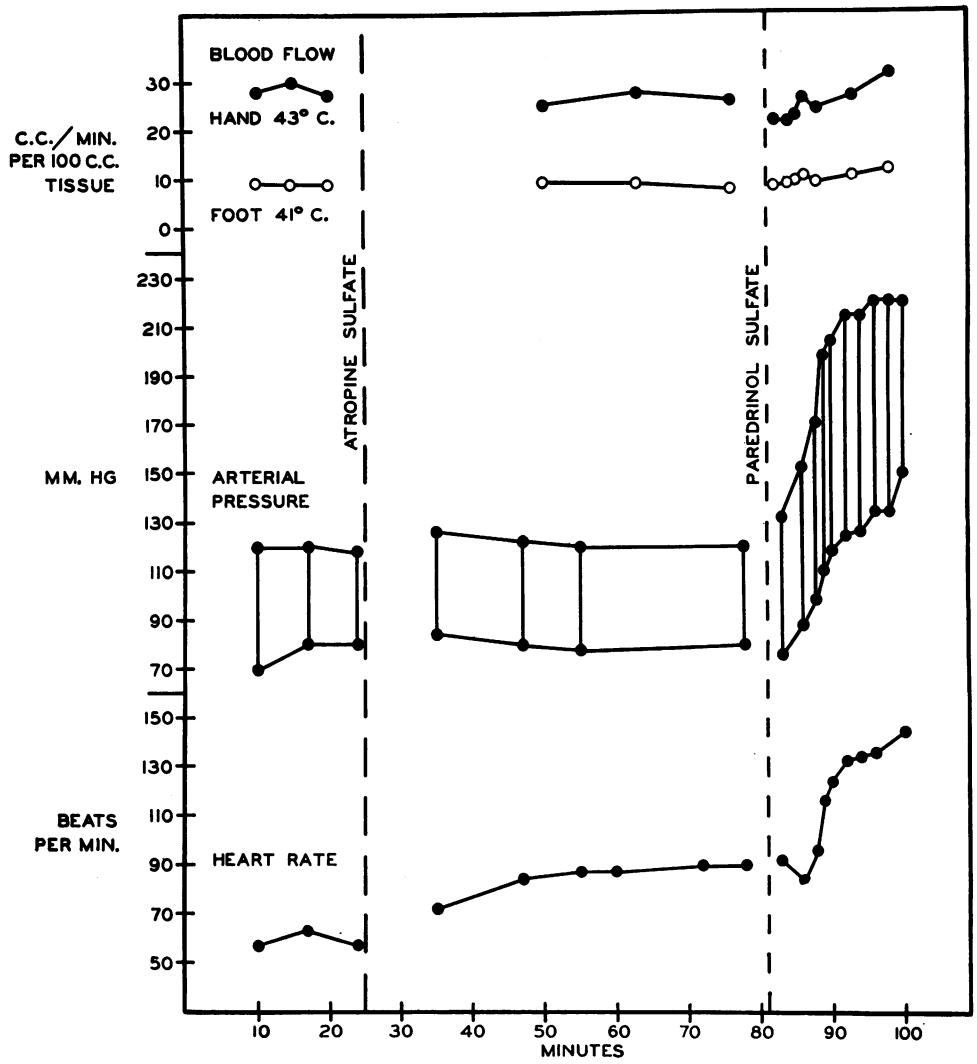

FIG. 3. THE EFFECT OF INTRAMUSCULAR INJECTION OF 25 MGM. OF PAREDRINOL IN A NORMAL SUBJECT WHO HAD PREVIOUSLY RECEIVED 4 MGM. OF ATROPINE SUBCUTANEOUSLY

palpitation. No change in color of their skin was observed. The effect produced on the blood pressure and heart rate of these 3 subjects by the administration of 20 mgm. of paredrine was similar in nature and intensity to that produced by 25 mgm. of paredrinol.

DISCUSSION

Paredrinol in normal subjects produces a type of hypertension in which the only outstanding abnormalities regularly observed are the forceful apex beat, loud heart sounds, and the high arterial pressure itself. The heart rate is usually, but not always, slower than in normal subjects at rest. Palpitation is the only symptom experienced by most of the subjects. Other changes in the circulation are detectable only if the resting values for the individual subjects are known. While the blood flow and vasomotor reactions in the hand are decreased after administration of the drug, they are still within the normal range. Likewise, while the elevation of the venous pressure is definite and easily demonstrated by frequent determinations, the rise is not enough to produce an abnormal venous pressure unless the resting venous pressure is close to the upper limits of normal. Occipital headache, resembling that described in clinical hypertension, occurs when the blood pres-

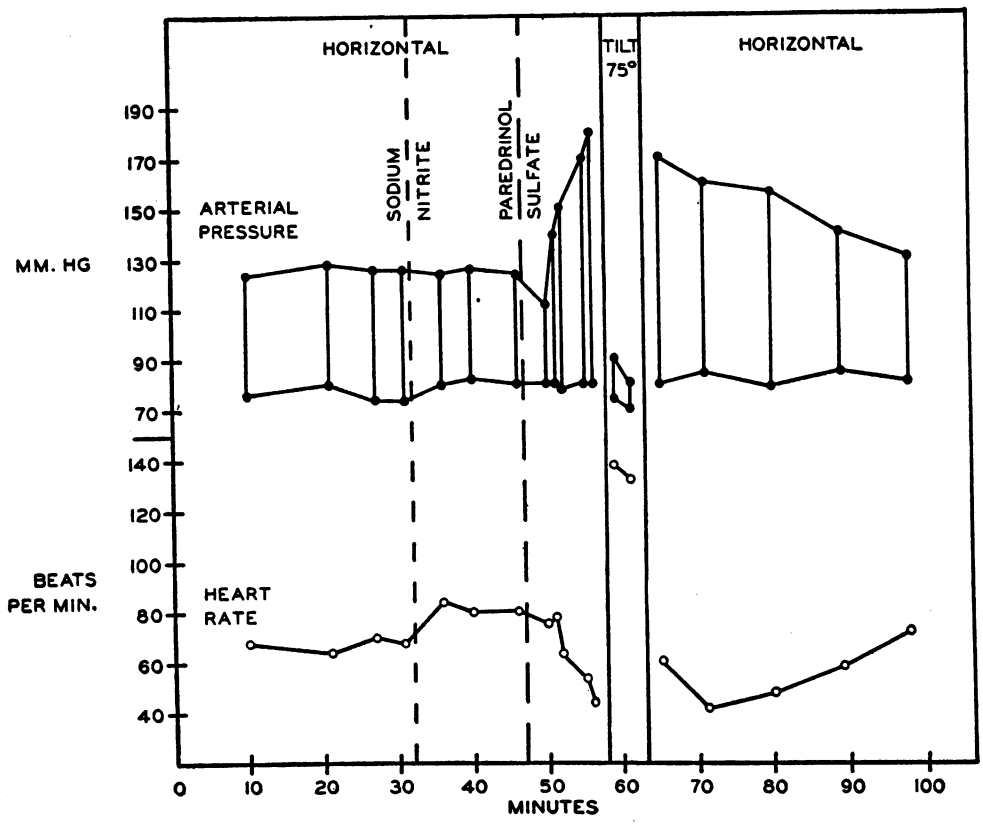

FIG. 4. THE EFFECT ON A NORMAL SUBJECT WITH PAREDRINOL HYPERTENSION OF THE ORAL ADMINISTRATION OF 3 GRAINS OF SODIUM NITRITE FOLLOWED BY TILTING TO THE UPRIGHT POSITION.

sure is excessively elevated. The blood flow in the foot, forearm, and calf shows no change, and the minute cardiac output remains unaltered. The decrease in heart rate is not the primary cause for the unchanged cardiac output and peripheral blood flow, for if the cardiac slowing accompanying paredrinol administration is prevented by atropine the blood flow to the hand and foot does not become greater than the normal resting flow. Following the administration of paredrinol the circulation time is unchanged. The basal metabolic rate is not affected significantly. Thus if a subject is seen shortly after the administration of the drug he presents a condition closely resembling clinical hypertension, for typically in this condition, except for the arterial blood pressure, all measurements of the various aspects of the circulation and of the other body functions are normal.

Hypertension induced by paredrinol can be explained by two possible mechanisms, either singly or combined: (*1*) Primary constriction of certain portions of the minute vessels which regulate peripheral resistance (arterioles, capillaries, or venules); (*2*) primary venoconstriction and emptying of the vascular reservoirs, causing an increased venous return to the heart and a redistribution of the blood in the arterial and venous portions of the circulation. The observations recorded indicate that increased peripheral resistance does occur for, in spite of the greatly increased arterial pressure head, blood flow through the tissues and cardiac output remain essentially normal. It does not necessarily follow, however, that the primary action of the drug is to cause such an increase in the peripheral resistance by a direct vasoconstrictor effect, for the constriction demonstrated may be a secondary response to an earlier, primary change in the venous system. Evidence against the direct vasoconstrictor action of paredrinol is the observation that, when the drug is injected or pricked into normal skin in concentrations as high as 1 to 40, a wheal surrounded by a

flare results. The cutaneous wheal with the sensation of itching is not unlike that observed after the injection of histamine. This is in sharp contrast to the white spot formed by the intracutaneous injection of epinephrine. Too much emphasis, however, cannot be placed on the failure of paredrinol to produce visible vasoconstriction after intracutaneous injection, for the drug may act on the larger arterioles rather than on the capillaries or venules.

There is considerable evidence that the main action of paredrinol is on the venous reservoirs. Hypertension may therefore result from an increase in the arterial circulating blood volume because of a change in the distribution between the arterial and venous parts of the vascular bed. Rein believes that his experiments on dogs have demonstrated this to be the main factor in the production of the hypertension. In man, the venous pressure rises by from 30 to 40 mm. of water while the arterial pressure is increasing. The venous tone in the extremities, as demonstrated by plethysmographic measurements, is also increased. The important effect of the quantity of circulating blood on this type of hypertension is clearly shown in postural experiments after the oral administration of 3 grains of sodium nitrite. In subjects whose venous systems respond to sodium nitrite with a decrease in venous tone, the drug has no measurable effect on the paredrinol hypertension while the body is in the horizontal position; when the upright position is assumed, however, the blood pressure falls from hypertensive levels either to normal or greatly subnormal levels. When the horizontal position is resumed, the blood pressure immediately returns to the hypertensive level which existed before tilting. The venous pooling induced by the combination of sodium nitrite and the upright position so reduces the circulating blood volume that the arterial blood pressure falls sharply. Thus, in these experiments with sodium nitrite, specific antagonistic changes are induced; hence the paredrinol hypertension is abolished. This is also of great practical importance because it offers a method of controlling the hypertension induced by paredrinol if the blood pressure rises to alarming heights or if a headache develops. The blood pressure is instantly lowered by amyl nitrite in the horizontal position and the headache quickly disappears. The effect, however, lasts for only a minute. By tilting the subject upright the effect is greatly prolonged and a normal pressure can be maintained without difficulty.

On *theoretical* grounds one can account for the development of the hypertension induced by paredrinol by assuming a decrease in volume of the venous reservoirs and veins. This produces an increased venous return to the heart. As far as is known, the blood flow in the tissues is regulated chiefly by the requirements for metabolism and for heat conservation and dissipation. If the blood flow through the tissues is increased momentarily beyond these requirements by a rise in cardiac output resulting from the increased venous return, the vessels may well contract sufficiently to restore the blood flow to the normal level. Under such circumstances an initial increase in cardiac output will produce hypertension. The rise in blood pressure will tend to increase the work of the heart and reduce the cardiac output. When equilibrium is reached the increased arterial blood pressure will have reduced the cardiac output to normal and the tissue blood flow will also be at the normal level. As yet, sufficient evidence has not accumulated to determine whether the hypertension caused by paredrinol is produced (*1*) by the direct action of the drug on the small vessels controlling the peripheral resistance; or (*2*) by the direct action of the drug on the veins and venous reservoirs, causing primarily an increased venous return to the heart and a secondary increase in peripheral resistance. Neither of these mechanisms is necessarily antagonistic and both may play a part in the production of the hypertension.

The slow heart rate frequently encountered after the administration of paredrinol is caused by stimulation of the carotid sinus and aortic nerves. After atropine the fall in cardiac rate no longer occurs. If the subject is completely atropinized and the pulse allowed to become constant, paredrinol causes a further distinct rise in pulse rate. When the vagus is active, however, it masks the direct stimulating effect of paredrinol on the heart rate. After the administration of atropine, paredrinol causes a greater and more prolonged rise in arterial blood pressure, particularly in the diastolic level. This great rise in diastolic pressure (up to 150 mm. Hg) is

caused by the marked increase in heart rate. Diastole becomes very short and consequently there is not sufficient time for the pressure to fall to the usual diastolic level before the next systole occurs. If the blood flow were appreciably increased, the diastolic pressure would not rise so steeply. Blood flow determinations on the hand and foot indicate that the peripheral resistance merely increases as the pressure rises and that the blood flow is not increased.

In view of the conclusion drawn by Rein from animal experiments that paredrinol increases the blood pressure chiefly by acting in the veins and venous reservoirs, it was hoped that by increasing the pressure head the blood flow could be increased in the extremities in cases of arteriosclerotic gangrene without hypertension. The experiments with atropine and paredrinol had previously demonstrated that the blood flow could not be increased through the normal hand and foot by raising the blood pressure to great heights. In the presence of incipient gangrene, however, it was possible that enough dilating substances would be present locally to maintain vasodilatation and permit an increase in flow. Skin temperature studies on 2 such cases revealed no change after the administration of paredrinol. Similar results have been reported in cases of Buerger's disease in which hypertension was induced by paredrine (13). The possibility still remained that the increased peripheral resistance resulted from central stimulation of the vasoconstrictor nerves. That this was not the case was demonstrated by finding that the blood flow was slowed to an even greater degree in the sympathectomized than in the normal hand.

SUMMARY AND CONCLUSIONS

1. Paredrinol (α-N-dimethyl-p-hydroxyphenethylamine) produces in normal subjects a type of acute arterial hypertension that closely resembles that observed in disease. The tendency to a slower heart rate, the vigorous apex impulse, the loud heart sounds, and the hypertension itself are the only outstanding abnormalities produced by the administration of the drug.

2. This hypertension differs greatly from that produced by epinephrine.

3. The arterial blood pressure response in different subjects, and in the same subject on different days, varies greatly. The average duration of the hypertension after the intramuscular injection of 25 mgm. of paredrinol is 1 hour.

4. The blood flow in the dilated hand is moderately decreased. The spontaneous fluctuations in vasomotor tone in the hand and foot are decreased. The venous tone in the hand is increased. The venous pressure is increased by from 30 to 40 mm. of water. The T-waves in the electrocardiogram become higher. These changes are usually not great enough to be detectable unless the resting values for the particular subject are known.

5. There is no significant change in blood flow in the foot, forearm, and calf. The cardiac output, circulation time, and basal metabolism are not significantly altered.

6. The decrease in heart rate results from an increase in vagal tone brought about by stimulation of the carotid sinus and aortic nerves, since if the vagal effect is removed by atropine, paredrinol causes an increase rather than a decrease in heart rate. When atropine is given before the injection of paredrinol the arterial pressure, particularly the diastolic, rises to higher levels than after paredrinol alone.

7. The combination of nitrite and tilting to the upright position pools sufficient blood to reduce the paredrinol hypertension to normal. Thus, if the arterial blood pressure rises to alarming heights, or if headache develops, the hypertension can be rapidly and permanently reduced.

8. The peripheral blood flow in subjects with arteriosclerosis and in subjects who have had a preganglionic sympathectomy is not increased by raising the arterial pressure head with paredrinol.

9. The hypertension produced by paredrinol may result from either or both of the following mechanisms: (*1*) A primary increase in peripheral resistance from a direct vasoconstrictor effect on the minute vessels (arterioles, capillaries, venules); (*2*) a primary increase in venous tone and an emptying of the splanchnic reservoirs, causing increased venous return to the heart and a secondary increase in peripheral resistance.

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