THE PHYSIOLOGICAL RESPONSE OF THE CIRCULATORY SYSTEM TO EXPERIMENTAL ALTERATIONS.

II. The Effect of Variations in Total Blood Volume.

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Plates 33 and 34.

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"The blood volume should be regarded, not as aliquot part of the body weight, but as a physiological variable which is adjusted to the work required of it and to the size of the 'bed' which it occupies." Thus wrote Barcroft (1) in his interpretation of the intimate relationship of the spleen to the vascular system.

In our studies of peripheral fistulæ (2) and of intracardiac fistulæ (3), a definite increase in blood volume was demonstrated. This increase paralleled a gradually enlarging vascular bed as manifested by a dilating but efficiently working heart and by a dilatation of those vessels through which the blood, shortcircuited by the fistula, flowed.

Additional experiments were undertaken to determine the interdependence of the size of the heart and the total circulating blood volume, and to test further the validity of the hypothesis that "the heart and blood vessels place themselves in harmony with an increased volume flow of blood through them, the former by dilatation and by hypertrophy, and the latter by dilatation."

Method.

The experiments consisted of massive blood letting in one animal, and the transfusion of the whole blood so obtained into another animal. The experiments were performed under ether anesthesia without preliminary medication. The femoral vessels in each groin were exposed, one artery was connected with a mercurial manometer and the other was cannulated for bleeding. The right femoral vein was connected with an infusion bottle from which was introduced

either citrated blood or normal salt solution. Roentgenograms of the heart were taken with the tube fixed 5 feet above the dog and the plate at a fixed distance beneath. This permits accurate comparisons between successive roentgenograms. The exposure was sufficient to cover a complete cardiac cycle, including both systole and diastole. The results are presented in the following protocols.

RESULTS.

Experiment 1. Weight of dog 15 kilos.[1]

	Pulse.	Systolic blood pressure.	Transverse diameter of heart.
			cm.
Normal	192	152	8.4
300 cc. blood removed from right femoral artery	218	68	7.9
300 cc. more blood removed	228	50	6.7

The dog was then allowed to recover until the blood pressure was restored to a systolic level of 100 mm. Hg.

	Pulse.	Systolic blood pressure.	Transverse diameter of heart.
			cm.
400 cc. more blood removed	180	44	6.7
750 cc. salt solution infused in vein	198	96	8.0
250 cc. more salt solution infused	192	130	—
200 cc. blood removed	234	80	7.0
200 cc. blood removed	210	54	6.8
1300 cc. salt solution infused	204	116	8.6

The entire experiment lasted 2½ hours. The animal was saved and showed no ill effects from the loss of 1400 cc. of blood, an adequate circulating blood volume being evidently maintained by accessions from the tissue and organ fluids. The normal blood volume for a 15 kilo dog is about 1500 cc. of blood.

Experiment 2. Weight of dog 13 kilos.

The whole blood obtained from the preceding experiment was introduced into the left femoral vein, and the following observations were made (Fig. 1).

[1] In this and the following experiments all operations were performed under ether anesthesia.

	Pulse.	Systolic blood pressure.	Transverse diameter of heart.
			cm.
Normal	192	176	7.3 (Fig. 1 a)
450 cc. blood introduced	228	212	7.6 (Fig. 1 b)
450 cc. additional blood introduced	216	218	8.0
500 cc. additional blood introduced	214	196	8.1
800 cc. blood removed	180	106	6.9
300 cc. additional blood removed	164	70	6.7
300 cc. additional blood removed	192	54	6.1 (Fig. 1 c)
700 cc. blood reinfused	180	164	7.8
700 cc. additional blood reinfused	160	164	8.1
1100 cc. salt solution introduced	162	160	8.2 (Fig. 1 d)

The entire experiment lasted 2 hours. Adding 1400 cc. of whole blood to the circulation increased the diameter of the heart from 7.3 cm. to 8.1 cm. Removing the same volume of blood almost immediately resulted in a reduction in heart size from 8.1 cm. to 6.1 cm., indicating that the circulatory system had very rapidly disposed of part of the circulating blood volume to accommodate the blood added from without.

In the following experiment the animal was bled for 800 cc. of blood which was reinfused into the same animal 20 minutes later.

Experiment 3 (Fig. 2).

	Pulse.	Systolic blood pressure.	Transverse diameter of heart.
			cm.
Normal	204	134	6.3 (Fig. 2 a)
800 cc. blood removed from left femoral artery.	174	28	4.9 (Fig. 2 b)
500 cc. blood reinfused 20 min. later	174	110	7.2 (Fig. 2 c)
300 cc. additional blood reinfused	144	132	7.2 (Fig. 2 d)
800 cc. blood removed	162	36	5.6
1200 cc. salt solution infused	156	90	7.7

Following the reinfusion of 800 cc. of blood into this animal it was noted that the swing of the lever recording the blood pressure had greatly decreased, suggesting a relatively greater increase in diastolic pressure than in systolic pressure with a diminution in pulse pressure. The exposed femoral arteries appeared to be dilated to twice their normal size and the roentgenograms gave evidence of a heart increased in diameter from 6.3 cm. to 7.2 cm. It is suggested that the diminished pulse pressure and the high diastolic pressure may be explained on the basis of an excessive filling of the entire vascular bed with blood.

In this instance, there occurred during bleeding a replacement of the blood volume by accessions from the tissues and probably also from such normal reservoirs of blood as the liver, spleen, and bone marrow By reinfusing the blood previously withdrawn there is a temporary increase in the blood mass contained in the vascular system as indicated by the dilatation of the heart and blood vessels.

It is also suggested that the diminished pulse pressure may be partly ascribed to the limiting action of the pericardium which prevents any great contractile excursion of a heart tensely dilated with blood.

Experiment 4. The whole blood obtained in Experiment 3 was infused into the femoral vein of a normal animal with the following results.

	Pulse.	Systolic blood pressure.	Transverse diameter of heart.
			cm.
Normal	156	96	7.8
500 cc. of whole blood infused	162	116	8.0
500 cc. more blood infused	162	124	8.6
1100 cc. salt solution infused	174	144	8.5
500 cc. blood removed	138	126	7.6
200 cc. additional blood removed	150	106	6.7

Immediately after completing the infusion of 1100 cc. of whole blood and 1100 cc. of salt solution, acute pulmonary edema developed, as shown by the loss of 200 to 300 cc. of frothy, bloody fluid from the mouth. The loss of this frothy fluid by mouth ceased immediately after the last bleeding.

DISCUSSION.

From the evidence obtained in these four experiments, the following conclusions are justified.

1. That the size of the heart conforms quite accurately to the volume of circulating blood.

2. That the addition of whole blood to the circulation of a normal dog increases the size of the heart, elevates the general blood pressure, and accelerates the pulse.

3. That massive blood letting reduces the size of the heart and lowers the general blood pressure to a degree commensurate with the volume of blood removed.

Interesting evidence was also obtained corroborating previous ob-

servations that the body has a rapidly adaptable mechanism for adjusting itself to an abrupt increase in blood volume. In Experiment 2, 1400 cc. of whole blood were added to the circulation with a rise in blood pressure and an increase in the size of the heart. Bleeding the animal almost immediately by an equal amount, 1400 cc., resulted in a marked reduction in the size of the heart and in blood pressure, indicating that the circulation had rapidly accommodated itself to the increased blood volume, not merely by a vasodilatation of the peripheral vessels (4), but by an actual egress of fluid from the circulatory system, presumably into the tissues or into the normal blood reservoirs, such as the spleen and the liver (5).

4. That the body has a remarkable blood volume reserve. In Experiment 1 the loss of 1400 cc. of blood had little effect upon the dog when the system was refilled with salt solution. In Experiment 3 the reinfusion of 800 cc. of whole blood, removed 20 minutes previously from the same dog, resulted in a marked dilatation of the entire vascular bed as indicated by an increase in the diameter of the heart from 6.3 cm. to 7.2 cm., and by a dilatation of the exposed vessels. As our other experiments have shown, a considerable volume of blood must be added to the circulation to produce such a dilatation. In Experiment 4 the addition of 500 cc. of blood increased the diameter of the heart only 2 mm., whereas 1000 cc. were required to increase the diameter 8 mm. The blood volume in Experiment 3 was increased temporarily following the reinfusion by an accession of blood and fluid from the tissues and from the normal blood reservoirs, accessions which were necessary during the bleeding to replace the blood withdrawn.

5. That massive plethora can produce an acute pulmonary edema with a transudation of blood through the pulmonary vessels (Experiment 4). This is probably the result of overdistention of the pulmonary vessels.

Although these are acute experiments, they manifest in many respects the same changes that characterize certain cardiovascular phenomena, as, for example, enlargement of the heart accompanied by hypertension. May not the phenomena observed in these experiments and in certain clinical entities have the same causative factor in common; *i.e.*, an increased total blood mass?

The Effect of Eliminating the Restrictive Action of the Pericardium.

In Experiments 3 and 4, it was noted that the acute dilatation of the entire vascular bed by plethora resulted in a diminished pulse pressure due, presumably, to a relatively greater increase in diastolic pressure than in systolic pressure. It was suggested that the dilated heart was limited in the excursion of its contraction by a restrictive action of the pericardium.

To determine what part the pericardium may play in limiting an acute dilatation of the heart and in restricting its contraction, the following experiments were undertaken.

Experiment 5 (Fig. 3).

700 cc. of whole blood were obtained from a normal animal. A second animal was anesthetized by intratracheal insufflation and the heart was exposed. The left femoral vessels were exposed and cannulated. The normal heart had a diameter of 7.2 cm. After the infusion of 1200 cc. of whole blood and salt solution, the diameter of the heart increased to 8.4 cm.

The pericardium was then opened by a longitudinal incision through which the heart bulged with almost explosive effort. It became markedly dilated and the left auricular ear became large and tense. Numerous dropped beats and extrasystoles marked the opening of the pericardium and the subsequent dilatation of the heart chambers. The excursion of the recording lever increased immediately from 7 mm. to 9 mm. and within 20 minutes to 15 mm. The heart was so large that an attempt to approximate the margins of the pericardium inclosed only one-half the heart. The roentgenogram showed a heart with a diameter of 9.1 cm. The dog was bled for 750 cc., and the diameter of the heart decreased to 6.4 cm. The pericardium was closed by interrupted silk sutures. The 750 cc. of blood were returned to the animal, resulting in an enlargement of the heart to 7.8 cm. (Fig. 3 a). At this point the amplitude of excursion of the recording lever had fallen from 7 mm. to 4 mm., accompanying the greatest filling of the vascular bed.

The pericardium was again opened, with the reappearance of numerous dropped beats and extrasystoles, and with an extraordinary dilatation of all the chambers of the heart. The transverse diameter of the heart increased to 8.7 cm. (Fig. 3 b).

The amplitude of the recording lever also increased immediately from 4 mm. to 7 mm.; within 3 minutes to 10 mm., and within 10 minutes to 12 mm., where it remained until the animal was killed.

Experiment 6.

The above experiment was repeated with the following observations. A heart

9.1 cm. in diameter was distended by the infusion of 800 cc. of whole blood to a transverse diameter of 9.6 cm., the pericardium being intact. Immediately after incising the pericardium the heart expanded to a width of 11.2 cm., with a tense dilatation of all its chambers.

CONCLUSIONS.

The pericardium presents a limiting or constricting action to acute dilatation of the heart. The diastolic pressure tends to approach the systolic pressure in a circulatory system distended with blood. The limiting action of the pericardium may be responsible for the small differences in the size of the heart noted by Meek and Eyster in their studies on the effect of plethora.

The views concerning the function of the pericardium are divergent. That it may restrict the heart in cases of acute dilatation is shown in the above experiments. If the tension upon the pericardium be exerted over a prolonged period of time, as occurs in cases of pericardial effusion, the pericardium readily enlarges. If, however, the intrapericardial pressure should at any time equal the pressure in the venæ cavæ, blood would no longer enter the heart and the condition would become fatal. In recovery experiments, pericardiectomy was followed by no demonstrable effect upon the general health of the dog, upon the response to exercise, or upon the size of the heart (6).

The Effect upon the Heart of a Redistribution of the Normal Blood Volume.

Previous experiments demonstrated remarkable changes in the size of the heart with variations in the total mass of the circulating blood. Equally significant effects upon the heart were produced by procedures which merely changed the *distribution* of the circulating blood without altering its volume. In general, the blood in the circulatory system is distributed between: (*a*) the heart and central vessels; and (*b*) the periphery, including the splanchnic area. Theoretically, an alteration in the peripheral system, either by a contraction or by a dilatation of its bed, should produce the reverse change in the heart. The following experiments were undertaken to test this point of view. Dilatation of the peripheral bed was effected by the inhalation of

amyl nitrite and by the injection of histamine. Contraction of the peripheral bed was accomplished by the injection of adrenalin or by an increase in intracranial pressure.

Experiment 7. The effect of amyl nitrite, adrenalin, and histamine upon the size of the heart (Fig. 4).

	Pulse.	Blood pressure.	Transverse diameter of heart.
			cm.
Normal	198	120	7.1 (Fig. 4 a)
Amyl nitrite (three ampules inhaled)	204	56	6.5 (Fig. 4 b)
Partial recovery from amyl nitrite	204	96	6.8
Complete recovery	192	120	7.0
15 minims adrenalin (1:1000) intravenously.			
25 sec. later	210	190	7.3
90 " "	180	176	7.0
130 " "	204	74	6.4
Recovery.			
20 min. later	180	116	6.2
12 mg. histamine intravenously	144	44	6.2
90 sec. later	150	50	5.9
10 minims adrenalin intravenously	140	108	6.7

Experiment 8. The effect of amyl nitrite and adrenalin upon the size of the heart.

	Pulse.	Blood pressure.	Transverse diameter of heart.
			cm.
Normal	145	120	8.0
Amyl nitrite by inhalation	205	96	7.7
Recovery	175	140	7.7
Amyl nitrite	225	120	7.2
Recovery	195	136	7.2
Adrenalin, 15 minims intravenously	150	280	8.2
3 min. later	180	96	7.3
Recovery	190	110	7.3

Experiment 9. The effect of histamine and adrenalin upon the size of the heart (Fig. 5).

	Pulse.	Blood pressure.	Transverse diameter of heart.
			cm.
Normal	156	110	6.5 (Fig. 5 a)
10 minims histamine intravenously.			
50 sec. later	168	46	6.0
150 " "	156	44	5.6 (Fig. 5 b)
30 min. "	150	100	6.1 (Fig. 5 c)
7 minims adrenalin intravenously.			
50 sec. later	198	178	7.1 (Fig. 5 d)
180 " "	192	100	6.2
40 min. "	174	110	6.3

Experiment 10. The effect of adrenalin upon the size of the heart.

	Pulse.	Blood pressure.	Transverse diameter of heart.
			cm.
Normal	186	122	6.3
10 minims adrenalin.			
60 sec. later	180	196	7.0
20 min. "	192	104	6.4

It is interesting to note a confirmation in these studies of an observation made by Gordon and Wells that after the first effect of the injection of adrenalin has subsided, there is a temporary fall in blood pressure below the level preceding the injection of adrenalin. Accompanying this fall there is a definite demonstrable reduction in heart size as our records show.

As the blood pressure again recovers, there is a recovery also in the size of the heart. The fall in pressure is explained on the basis of a dilatation of the peripheral bed following the very temporary constriction by adrenalin, evidence which contraindicates the use of adrenalin as a means of combating shock.

Experiment 11. The effect upon the heart of increased intracranial tension produced acutely by the injection of normal salt solution into the extradural spaces of the skull (Fig. 6).

	Pulse.	Blood pressure.	Transverse diameter of heart.
			cm.
Normal	168	112	6.6 (Fig. 6 a)
Moderate increase in intracranial pressure	156	120	7.3 (Fig. 6 b)
Great increase in intracranial pressure	120	156	7.7 (Fig. 6 c)

Experiment 12.

	Pulse.	Blood pressure.	Transverse diameter of heart.
			cm.
Normal	180	136	7.5
Increased intracranial pressure	120	180	7.8
Release of pressure	156	150	7.4
Increased pressure	132	212	7.8
Increased pressure to point of circulatory failure. Readings 20 sec. before failure	198	210	8.0

DEDUCTIONS.

Certain deductions are admissible from an analysis of the preceding experiments.

1. Alterations in the peripheral circulatory bed, either by the inhalation of amyl nitrite, or by the intravenous injection of histamine, result in a marked reduction in the size of the heart, due, it is suggested, to a decrease in the volume of blood contained in the central circulatory bed incident to a dilatation of the peripheral bed. Gordon and Wells (7) have observed similar variations in heart size in the rabbit and suggested that they were intimately related to blood pressure and made no reference to changes in blood volume distribution. The variations in heart size could not be attributed merely to the altered rate of cardiac contraction (8) since there was no invariable interrelationship established.

2. Contraction of the peripheral vascular bed, either by the intravenous injection of adrenalin, or by an acute increase in the intracranial pressure, results in a demonstrable increase in the size of the heart, due, it is suggested, to an increase in the volume of blood contained in the central circulatory bed. Again, variations in the rate of

cardiac contraction alone cannot be considered responsible for these variations in heart size.

3. The size of the heart is commensurate with the volume flow of blood through it, whether the latter is altered by massive blood letting, by massive transfusions, or by a redistribution of the normal blood volume.

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EXPLANATION OF PLATES.

PLATE 33.

FIG. 1 (see Experiment 2). Changes in size of heart accompanying alterations in blood volume.

FIG. 2 (see Experiment 3). Changes in size of heart following the removal of 800 cc. of blood and its reinfusion 20 minutes later.

FIG. 3 (see Experiment 5). Limiting action of pericardium in acute plethora shown by marked increase in size of heart following incision of the pericardium. (a) Size of heart, pericardium intact, after injection of 750 cc. of whole blood. (b) Size of heart after incising pericardium.

PLATE 34.

FIG. 4. (see Experiment 7). Reduction in size of heart following inhalation of amyl nitrite.

FIG. 5 (see Experiment 9). Changes in size of heart accompanying redistribution of blood volume. (a) Normal. (b) Reduction following injection of histamine. (c) Recovery. (d) Enlargement following injection of adrenalin.

FIG. 6 (see Experiment 11). Marked enlargement of heart accompanying increased intracranial pressure which constricts the peripheral and splanchnic vascular beds, thereby increasing the volume of blood contained in the heart and large central vessels.

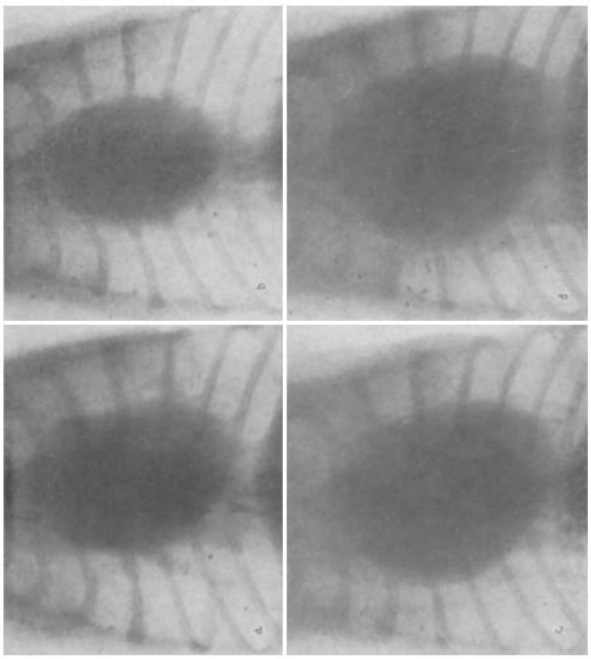

FIG. 2.

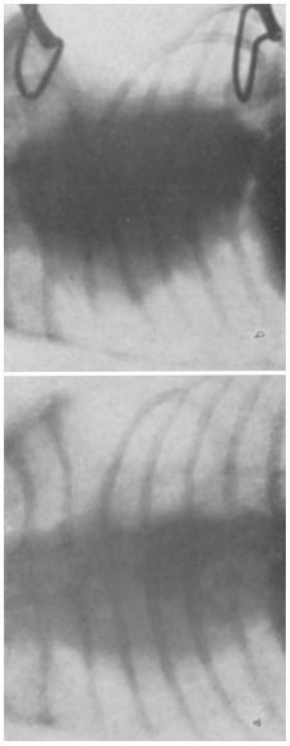

FIG. 3.

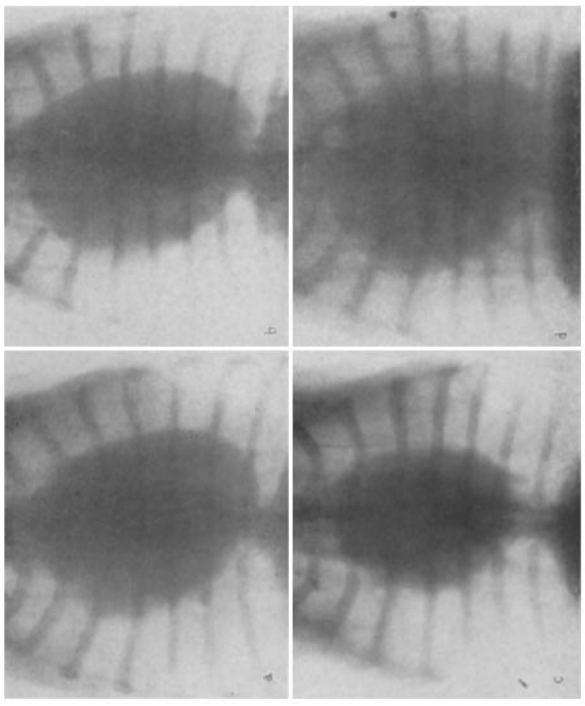

FIG. 1.

(Beck and Holman: Physiological response of circulatory system. II.)

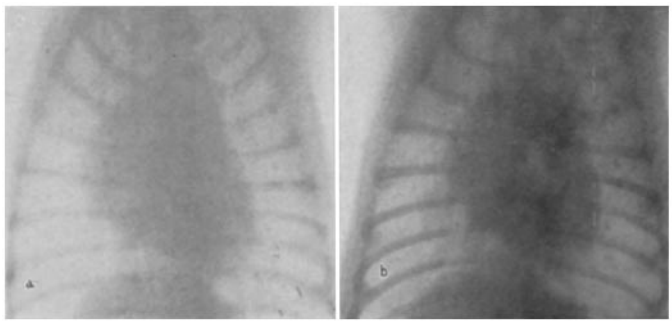

FIG. 4.

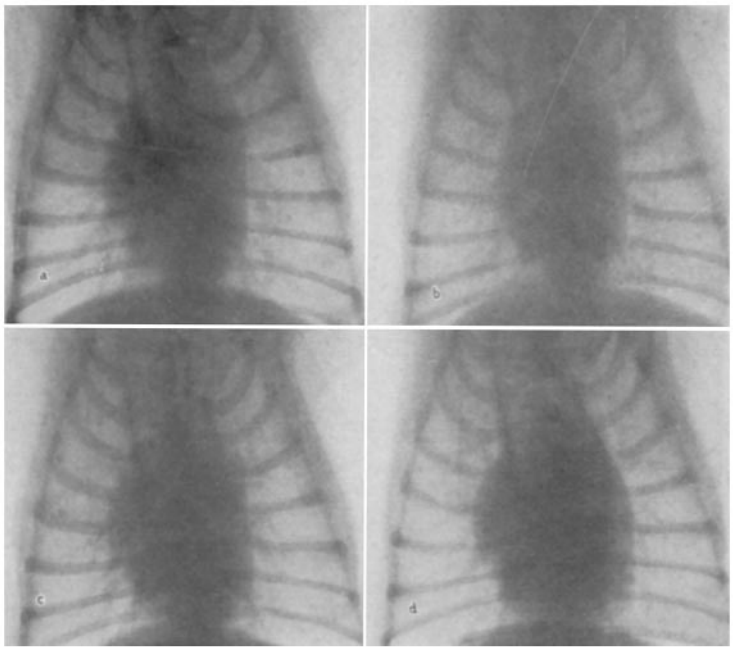

FIG. 5.

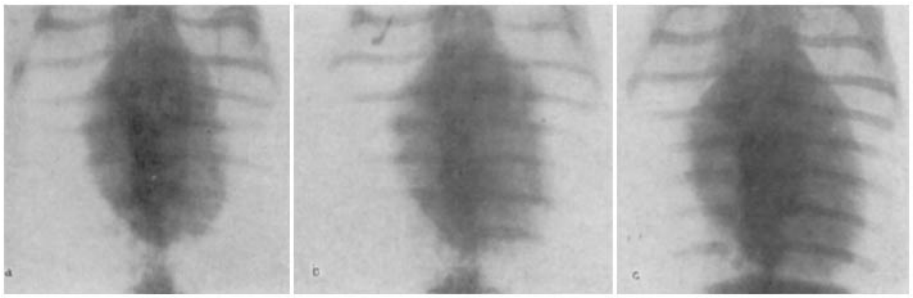

FIG. 6.