THE PHYSIOLOGICAL RESPONSE OF THE CIRCULATORY SYSTEM TO EXPERIMENTAL ALTERATIONS.

I. The Effect of Intracardiac Fistulæ.

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Plates 31 and 32.

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The cause of cardiac hypertrophy and dilatation continues to be a subject of opposing hypotheses and divergent opinions. Careful study of the heart and circulation in so called cardiovascular renal disease has failed to solve the puzzle of its many conflicting manifestations. Arteriosclerosis—increased peripheral resistance—cardiac hypertrophy is an alleged sequence of events, the many exceptions to which make an exact interrelationship difficult to determine. "Idiopathic hypertrophy of the heart" and "essential hypertension" represent additional familiar entities that remain unexplained.

In studies on arteriovenous fistulæ, both peripheral and intracardiac, evidence has been obtained indicating that an increased volume flow through the chambers of the heart is an effective stimulus to dilatation and hypertrophy, in spite of the decreased peripheral resistance incident to the fistula. Following the establishment of a large peripheral arteriovenous communication, as between the femoral or iliac vessels, the blood flow through the heart is practically doubled (1). Clinically and experimentally, dilatation and hypertrophy invariably follow such a fistula if it is sufficiently large (2) and of sufficiently long duration (3).

A long standing patent ductus arteriosus, unaccompanied by other complications, affects the heart in one of two ways, depending upon the direction of the blood flow through the abnormal communication (4). If the blood passes through the open ductus from pulmonary artery to aorta, a greater stream flows through the right

heart than through the left heart, and when the opening is sufficiently large, a dilatation and hypertrophy of the former are observed. On the other hand, if the blood deflected through the ductus flows from aorta to pulmonary artery, the greater stream passes through the left heart only, and the resulting dilatation and hypertrophy are limited to the left chambers.

Similar clinical observations have been made in the presence of other cardiac anomalies, as patent interventricular septum and patent foramen ovale, which frequently are associated also with pulmonary and aortic stenosis (5). The effect of these abnormalities is to direct the major stream of circulating blood through certain chambers and their corresponding vessels, the rest of the heart receiving a smaller volume of blood. Commensurate with this relatively increased blood flow, there occurs a dilatation and hypertrophy limited to these chambers, and a retarded development in that part of the heart receiving the lesser stream.

These clinical and experimental observations were sufficiently uniform and invariable to justify the presentation of the following hypothesis. 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.

Following an analysis of the circulatory effects produced by a congenitally patent septum, we undertook to establish such a lesion in the adult animal in order to observe the subsequent cardiac response, and to test the validity of the above hypothesis.

Method.

The experiments were performed under the strictest aseptic precautions. Some investigators in the physiology of the circulation have disregarded the obvious fact that "sacrifice" experiments cannot be accepted as telling the whole story in any study of physiological pathology, nor can the results of such experiments be applied to any pathological condition which requires the elapse of time for the development of the compensatory adaptation to its presence. This is particularly true in the complex and flexible circulatory system, which adapts itself in such an extraordinary manner to altered conditions within it. It is, therefore, only the survival experiment that can tell the true sequence of events, and such experiments require, in many instances, the technical equipment and operative skill of the trained surgeon.

The experimental methods used were those developed by Cutler and his co-

workers, Levine and Beck, in their studies on mitral stenosis and mitral insufficiency (6). The animals were anesthetized with ether by the intratracheal insufflation method with the Erlanger apparatus. The heart was exposed by an incision parallel to the left fifth rib, with or without resection of the rib. The pericardium was opened by a longitudinal incision parallel to the phrenic nerve. An apex stitch was applied for aid in manipulating the heart, and a knife valvulotome was introduced into the left ventricle through an avascular area at the apex. The interventricular septum was pierced preferably in its midportion, and an incision made toward the apex of the right ventricle in the longitudinal axis of the heart.

There were many technical difficulties. Several deaths occurred at the beginning, probably due to injury of the bundle of His. Some hearts were precipitated into "circus motion" with abrupt termination of contraction. One death was attributed to the complete division of an aortic leaflet, with the immediate development of aortic regurgitation in addition to the interventricular leak. Another death was due to mitral insufficiency following division of the chordæ tendineæ of the anterior mitral leaflet. Other deaths followed the establishment of septal defects that were excessively large.

RESULTS.

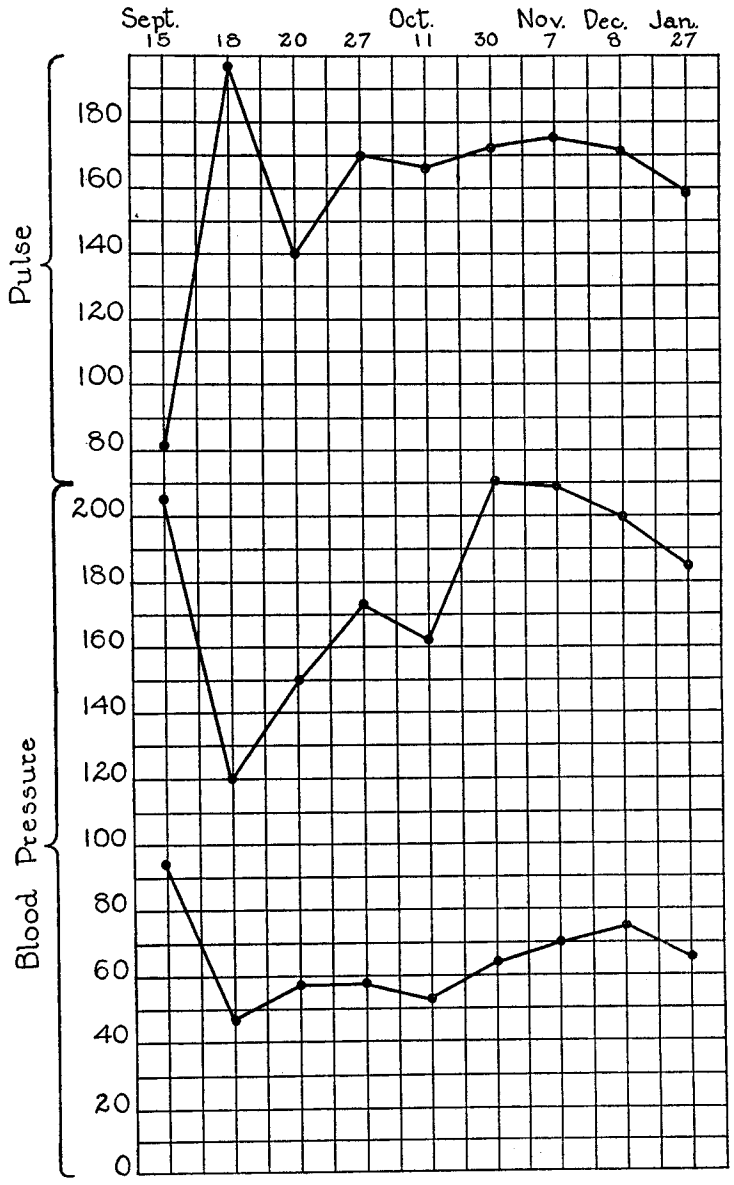
The following protocols present the important observations that were made.

Protocol of Dog X 11.—Weight 14 kilos. On September 16, 1924, an opening[1] of considerable size was established between the ventricles, accompanied immediately by an intense systolic thrill palpated over the right ventricle. (In none of the intracardiac fistulæ was the thrill felt over the left ventricle. This is interpreted as indicating that the flow of blood occurred from the left to the right side of the heart.) 2 hours after the operation the pulse rate was 202. A marked systolic thrill was felt over the right side of the chest, accompanied by a loud systolic bruit.

The following day the dog lay quietly in his cage, obviously ill; respirations 96, pulse 186; no cyanosis. The postoperative behavior of the pulse and the blood pressure is recorded in the accompanying chart (Text-fig. 1).

December 8, the pulse rate was 176. On auscultation, it appeared to several observers that the pitch during inspiration was higher than during expiration, and that the rate was slightly retarded during inspiration. The explanation for this phenomenon is not apparent. It is probable that the increased filling of the heart from the venæ cavæ during the inspiratory phase, with its accompanying negative thoracic pressure, may diminish the amount of blood flowing

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



TEXT-FIG. 1. (Dog X 11.) Behavior of blood pressure and pulse following the establishment of a septum defect on September 16. Note fall in blood pressure and great acceleration in pulse rate persisting for several days with subsequent gradual recovery in blood pressure but permanent elevation in pulse rate.

through the defect and thus account for these changes in rate and pitch, an assumption dependent upon the observation that the bruit accompanying arteriovenous fistulæ is lower pitched in tone and the pulse rate more rapid when the flow through the fistula is large than when it is small. At no time were we able to recognize a second sound, either pulmonic or aortic, both being obscured by the systolic bruit.

On January 27 the animal was exercised. After a run of about 400 yards, it vomited and went into collapse. Immediately after the exercise the pulse was 220, and respirations 100.

Blood Volume Determinations.—The volume of the circulating blood was determined by the intravenous injection of brilliant vital red (7). Unfortunately, no dye was available for blood volume determinations before the operation for the establishment of the interventricular defect. The normal volume of a dog weighing 14 kilos, according to the dye method, is approximately 1400 cc., as the following figures indicate.

Weight of animal.	Blood volume.
kilos	*cc.*
11.1	1255
13.1	1357
13.6	1439
17.7	1867
20.0	2119
22.0	2166

On December 23, 1924, this dog had a blood volume of 2103 cc. A second determination made January 6 was 2096 cc. Compared with that of a normal dog of the same weight, the blood volume of this animal had increased 700 cc. Allowing 200 cc. as a margin of error which the method may entail, it is seen that the establishment of an interventricular communication must have been accompanied by a definite increase in the volume of the circulating blood.

Roentgenographic studies exhibited a gradual increase in the size of the heart (Fig. 1). Before operation the heart had a transverse diameter of 7.3 cm. October 14 this had increased to 8.3 cm., December 23 to 8.9 cm., and February 9 to 9.6 cm.

February 10 an attempt was made by operation to reverse the flow through the opening by applying an aluminum band to the pulmonary artery. When the heart was exposed at the operation it appeared enormous, the enlargement being due mostly to the increased size of both ventricles. However, it was manifest that the left auricle entered into this enlargement also—the ear was prominent and appeared at least four to five times the normal size. It covered the anterior aspect of the upper third of the left ventricle. In contrast to this was the very small right auricle, about one-half as large as the left auricle, whereas

normally it appears several times larger. The right auricle was almost completely obscured by the enlarged right ventricle and greatly dilated conus arteriosus. The attempt to reverse the flow through the septum defect was unsuccessful and the dog died while under the anesthetic.

At necropsy the heart was conspicuously large (Figs. 4 and 5). The ventricles were capacious, the walls were thicker than normal, particularly those of the right ventricle and the septum. The left auricle was large and prominent, as previously observed in the living state (Fig. 4). The opening between the two ventricles admitted a 30 mm. bougie. The aorta, where it left the heart, admitted a 24 mm. bougie, the pulmonary artery a 42 mm. bougie, indicating that these vessels had placed themselves in harmony with the volume flow of blood through them.

The right ventricular wall was definitely hypertrophied. It measured 6 mm. at its narrowest portion, and the right ventricular cavity measured 23 mm. in diameter. In a normal animal of the same weight and size, the right ventricular wall measured 4 mm. at its narrowest portion, and the cavity was only 8 mm. in diameter. The heart weighed 162 gm., whereas the heart of the normal animal weighed 118 gm. The lungs showed discolored areas of congestion. They were firmer than normal, and the trachea and bronchi contained white frothy fluid which was not blood-tinged. Microscopic sections of the lung revealed a marked and intense edema and congestion, with some fibrin deposits in the alveoli suggesting a long standing edema. There was only a moderate congestion of the liver and kidneys, without edema. The heart muscle showed large nuclei with square ends, corroborative microscopic evidence of a cardiac hypertrophy (8).

Protocol of Dog X 7.—Weight 18 kilos. On September 14, 1924, a septum defect was made in the usual manner. The heart rate was increased from 156 to 198, but the thrill and bruit immediately following the operation were only of moderate intensity. The pulse rate on the following day was 105, the thrill had disappeared, and only a slight systolic bruit was present. It was inferred from these observations that only a minor leak had been established. Accordingly, on September 29, on which date even the systolic bruit was no longer audible, the dog was reoperated upon and a second interventricular opening was made. The heart rate before operation was 100; after operation 210. A well marked thrill and bruit were present after the operation. The next morning the animal was found dead. At necropsy, 10 cc. of bloody fluid were found in each pleural cavity. The lungs everywhere were dark red in color. The bronchi contained considerable frothy fluid. The heart was dilated, and both ventricles were capacious. The opening between the ventricles admitted a 34 mm. bougie. The weight of the heart was 135 gm. Microscopic sections of the lung showed intense pulmonary edema and congestion. The liver and spleen showed only slight congestion.

Protocol of Dog X 10.—Weight 10.4 kilos. The usual technique for the establishment of an interventricular leak was employed. The pulse rate increased immediately from 120 to 220. The animal died during the night, within 12

hours after the operation. Thin bloody fluid had escaped from the nose. The lungs were markedly congested, with the consistency of liver. The interventricular opening admitted a 30 mm. bougie. Weight of heart 71 gm. Microscopic sections of the lungs showed very marked edema and congestion, whereas the edema and congestion of the liver and spleen were insignificant.

Protocol of Dog X 23.—Weight 12.2 kilos. On December 16, 1924, an opening between the ventricles was established, with an increase in pulse from 153 to 180, and the appearance of a faint thrill and an intense bruit. Following operation, the animal was very ill. 8 days later there was considerable purulent discharge from the nose and eyes, indicative of a severe attack of distemper. Death occurred on January 3. At necropsy, a little free purulent fluid was present in each pleural cavity. There were multiple circumscribed areas of discoloration and consolidation in both lungs about 1 cm. in diameter. The heart was not enlarged. On opening the heart the left ventricular cavity was normal. The opening between the ventricles, the entire right ventricular cavity, and the pulmonary artery were filled with a friable, yellowish vegetative mass, which was adherent to the sides of the ventricular opening, to the wall of the right ventricle, and to the pulmonary valves. Microscopically, this mass was made up of necrotic material, infiltrated with polymorphonuclear white cells and round cells. Sections stained for bacteria were negative. The presence of a purulent nasal discharge, due to distemper, with the subsequent development of endocarditis, is an interesting experimental duplication of the frequent clinical observation that death in many cases of congenital cardiac anomalies is due to a superimposed endocarditis. The lungs showed multiple areas of embolic consolidation. The absence of cardiac dilatation in the presence of a septum defect 26 mm. in diameter is dependent upon the obstruction to blood flow through the defect due to the vegetative mass filling the opening, the right ventricle, and the pulmonary artery.

Protocol of Dog X 25.—Weight 11.2 kilos. Preoperative pulse 76. On December 15, an interventricular defect was established, with an immediate increase in pulse from 136 to 156, and the appearance of a thrill over the right ventricle. The right and left ventricles appeared definitely larger at the end of the operation as compared with their appearance at the beginning. On January 8 a bruit and thrill of only moderate intensity were recorded. The pulse rate was 148.

Roentgenographic studies showed a moderate increase in the transverse diameter of the heart from 7.1 to 8.2 cm. On February 9 the animal was found dead following a fight with another dog. The heart was larger than normal (Figs. 4 and 5). The right ventricle was dilated, as was also the left auricle, which was abnormally large. The left ventricle was capacious. The opening between the ventricles was lined by glistening endothelium, and admitted a 26 mm. bougie. The aorta admitted a 34 mm. bougie, and the pulmonary artery a 40 mm. bougie. The heart weighed 152 gm. Microscopically, the lungs showed marked edema, with some congestion. The liver was not congested. This

animal survived the establishment of the defect only 7 weeks. The extent of the circulatory changes wrought by a defect depend not only upon its size, but also upon its duration.

Protocol of Dog X 26.—Weight 14.1 kilos. An opening was made between the ventricles, with the development of the usual thrill and bruit, and with an acceleration in pulse rate. The animal was found dead 18 hours later. Blood-tinged froth had escaped from both nostrils. There was no free fluid in the pleural cavity. The lungs were dark red throughout, and firm. The bronchi were filled with pink froth. The interventricular opening admitted a 32 mm. bougie. The heart weighed 122 gm. Microscopic sections revealed an intense edema and congestion of the lungs, and only moderate congestion of the liver and spleen.

Protocol of Dog X 27.—Weight 13.4 kilos. On January 8 an interventricular defect was established, with an immediate acceleration of pulse from 150 to 180, and the development of a thrill and bruit over the right ventricle. On January 9 the animal had a cough, but seemed in fair condition. The pulse rate was 180. It died 40 hours after operation. At necropsy a bloody mucous discharge from the mouth was noted. 3 ounces of blood-tinged fluid were present in each thoracic cavity. The left lung was firm and dark in color, with no air-containing areas. The right lung showed normal areas alternating with firm congested areas. The liver and spleen showed areas of congestion and increased consistency, alternating with normal areas. The right heart was dilated. The opening between the ventricles admitted a 32 mm. bougie. The heart weighed 119 gm.

Microscopic sections of the lung showed marked edema and engorgement of the blood vessels, with congestion. The liver and spleen showed congestion.

Protocol of Dog X 42.—Weight 14 kilos. Preoperative studies showed a pulse of 98, a blood pressure of 220/90. On March 4 an interventricular defect was established, with an immediate increase in pulse rate from 164 to 202. On the following day the blood pressure was 105/45, pulse 188. 2 days later the blood pressure had recovered to 130/70, pulse 168. A thrill and murmur were present over the right chest. Within 4 days the pulse rate dropped to 148, and by March 17 it had dropped to 92. On April 1 a blood pressure of 170/70, and a pulse of 90 were recorded. Upon this date the thrill and bruit had become very faint. These observations, together with the rapid recovery in blood pressure and pulse, indicated that only a small leak was present. On April 21 the bruit had become almost inaudible, and the thrill had entirely disappeared. On February 26, before operation, the blood volume was calculated as 1430 cc. On April 24, 7 weeks later, when practically all clinical evidences of a septal leak had disappeared, it was 1200 cc. On April 27 the animal was found dead, having been killed in fighting.

Both by roentgenographic and by direct examination, the heart had increased little in size. The right ventricle, however, appeared slightly larger than normal. The heart was opened and only a small scar indicated the location of the septum defect. It was covered by endothelium, but a 10 mm. bougie could be passed

after breaking through this delicate endothelial obstruction. The aorta admitted a 32 mm. bougie, the pulmonary artery a 36 mm. bougie.

Protocol of Dog X 2.—Weight 18.4 kilos. A large ventricular defect was established on September 8, 1924, accompanied by the immediate development of a marked thrill, an intense bruit, a lowered blood pressure, and a rapid pulse.

	Blood pressure.		Pulse.
	Systolic.	Diastolic.	
Sept. 8, 1924 (before operation)	180	90	72
Sept. 9, 1924	130	44	162
Sept. 11, 1924	166	56	162
Oct. 3, 1924	170	60	144

During the subsequent months, up to the time of the animal's death, the blood pressure readings remained at a systolic level of 160 to 180, and a diastolic level of 65 to 76. The pulse, however, remained abnormally rapid for several months only. On January 3 the rate was 148. There then occurred a gradual return to a normal rate of 80 to 110, as compared to a previous rate of 140 to 160. Repeated roentgenograms following the operation showed a gradual increase in the width of the heart shadow (Fig. 2). The transverse diameter of the heart before operation was 7.3 cm. September 29 this had increased to 8.3 cm.; October 30 to 8.7 cm.; November 29 to 9 cm.; January 8 to 9.4 cm.; April 1 to 10 cm. The activity of the heart was plainly visible over the chest wall, and the systolic thrill and bruit were always intense. As in X 11, this bruit was higher pitched during inspiration than during expiration, and the rate was slightly but definitely retarded during inspiration.

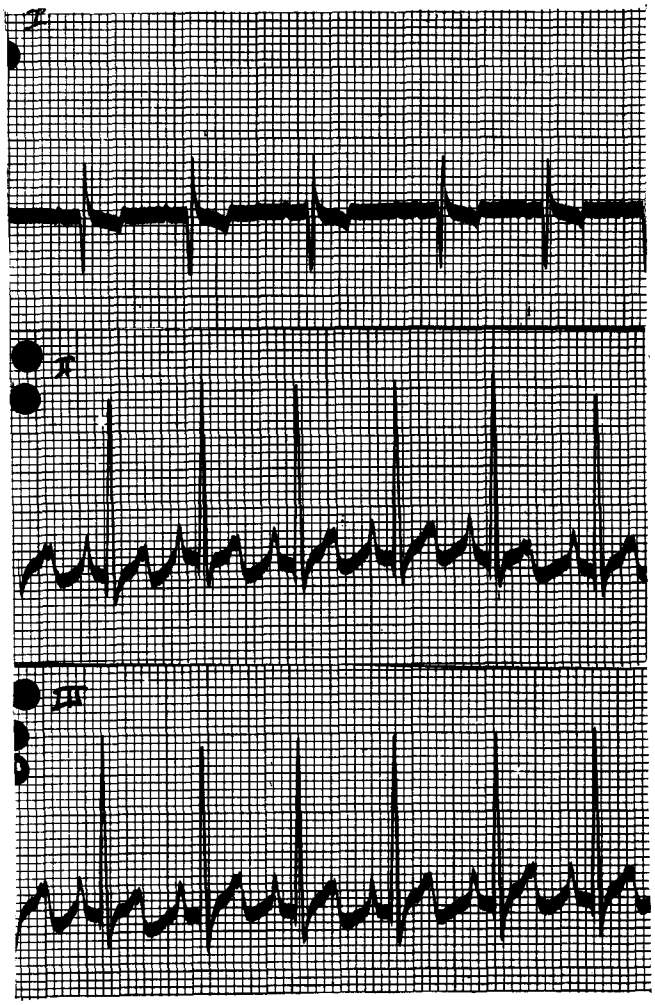
The blood volume determinations were as follows:

	cc.
Dec. 23, 1924	1635
Mar. 3, 1925	2075
Apr. 14, 1925	2100
May 8, 1925	2460

The increasing size of the heart was paralleled by a steadily increasing total blood mass. On April 27 an electrocardiogram revealed a relative right ventricular preponderance (Text-fig. 2).

The animal was killed on May 8. The necropsy revealed a greatly enlarged heart which weighed 224 gm. (Figs. 4 and 5). The heart of a normal large framed Airdale weighing 18 kilos appeared to be half the size of this heart, and weighed 162 gm. The left auricular ear was distended with blood and unusually prominent. The two ventricular cavities were capacious and dilated (Fig. 5). The pulmonary artery admitted a 40 mm. bougie, the aorta a 34 mm. bougie. The interventricular opening admitted a 28 mm. bougie, being slightly smaller

than the opening in X 11. The liver was enormous, firm, blue-black in appearance, and weighed 840 gm. The spleen was somewhat firm, not conspicuously congested, and weighed 48 gm. The liver of a normal dog of approximately the



TEXT-FIG. 2. Right ventricular preponderance observed in X 2, 8 months after establishment of septum defect.

same size weighed 390 gm., the spleen 36 gm. The lungs were firmer and darker in color than normal. Microscopic sections revealed an intense edema and congestion of the lungs, the alveoli and bronchi being filled with fluid. There

was also a marked congestion of the liver, spleen, and kidneys. The heart also exhibited microscopic evidences of hypertrophy, as indicated by the large nuclei with square ends. This evidence was more pronounced in the right ventricle than in the left ventricle.

Protocol of Dog X 34.—Weight 17.3 kilos. The preoperative blood pressure reading was 170/65, pulse 120. On January 31 an interventricular defect was established. 5 days later the blood pressure was 115/55, with a pulse of 176. March 3 slight recovery had occurred, the blood pressure being 150/70, the pulse 146, and on May 8 the blood pressure was 180/75, pulse 126, indicating a comparatively early return to normal readings. Roentgenographic studies revealed a well marked increase in the transverse diameter of the heart from 7.3 cm. on January 30, to 9.2 cm. on May 8 (Fig. 3).

The following blood volume studies were made.

	cc.
Jan. 28, 1925	1770
Mar. 3, 1925	1820
Apr. 14, 1925	1880
May 8, 1925	2140

An electrocardiogram on April 27 revealed a moderate relative right ventricular preponderance, which was not so striking as in X 2.

That the septum defect in this dog was smaller than in either X 2 or X 11 was evidenced by the rapid recovery of blood pressure, the early return of the accelerated pulse to a normal rate, the moderate enlargement of the heart, the lessened intensity of the thrill and bruit, and the moderate increase in blood volume.

The animal was killed on May 8. The heart was somewhat larger than normal (Figs. 4 and 5). It weighed 183 gm., whereas the heart of a normal similarly built animal weighed 162 gm. The ventricular cavities were moderately dilated; the pulmonary artery admitted a 38 mm. bougie, and the aorta a 34 mm. bougie. The left auricular ear was prominent. There were two small septum defects, one admitted a 16 mm. bougie, and the other a 10 mm. bougie. It is apparent that the combined cross-section size of these two openings was considerably smaller than the defect in either X 2 or X 11. The clinical manifestations in the latter two animals were much more pronounced than in X 34, and the effects upon the circulatory system observed at necropsy were less conspicuous in the presence of the smaller defect.

DISCUSSION.

From the foregoing protocols, it is apparent that the establishment of a defect in the interventricular septum resulted in certain invariable effects upon the circulatory system and particularly upon the heart, these effects depending entirely upon the size of the defect, and upon its duration. A defect larger than 30 mm. in circumference

in a heart 120 to 140 gm. in weight (X 7, X 10, X 26, X 27) was invariably fatal within 12 to 36 hours. The fatal issue was attended by the development of marked pulmonary edema and congestion. This congestion had the appearance of so called passive congestion, but it is evident that in these instances it followed not a *passive* but an *active* state of the circulation. The liver and spleen were frequently free of any congestion or edema.

The thrill and bruit which followed the establishment of the defect were directly proportional to the size of the defect, and, therefore, to the volume flow of blood through it. In the exposed heart they were limited to the right ventricle, and in the surviving animal they were most pronounced over the right side of the chest. They were limited to systole and completely obscured both the aortic and pulmonic second sounds.

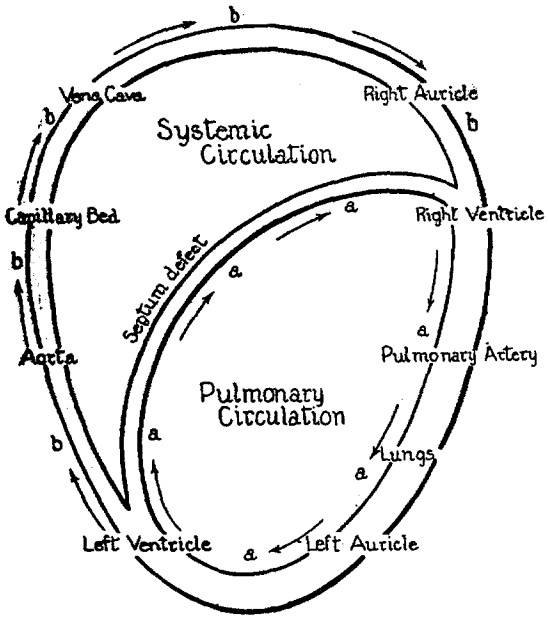
In the presence of the larger defects there was a slowly progressive dilatation of the heart, limited to the chambers and vessels through which the shortcircuited blood passed; namely, the left ventricle, right ventricle, the pulmonary artery, and the left auricle. The enlargement of the heart was demonstrable by roentgenograms and at necropsy. The right auricle and the aorta were unaltered or smaller than usual, conforming in size to the relatively decreased volume flow of blood through them. This was demonstrated most clearly in X 11.

There was a definite hypertrophy of the heart shown by an increase in the weight of the heart, and by an obvious thickening of the right ventricular wall (X 2, X 11, X 25, X 34). This hypertrophy is interpreted as being the physiological response to the increased effort necessary to propel forward an increased volume of blood. It cannot, in these instances, be due to an increase in peripheral resistance since this remains unaltered in relation to the right ventricle, and definitely decreased in relation to the left ventricle. Nor can it be due to pericardial adhesions, since numerous observations upon other experimental animals indicate that the adhesions, which invariably form following the opening and resuturing of the pericardium, have no effect upon the size of the heart.

Electrocardiographic studies on X 2 and X 34 revealed a relative

preponderance of the right ventricle, more pronounced in X 2, which possessed the larger defect.

In the presence of the large defects (X 2, X 11), a considerable increase in total blood volume was demonstrated. Dog X 34, with a moderate defect, showed only a moderate increase in blood volume. In Dog X 42, with a small defect which healed completely, no increase in blood volume was exhibited.



TEXT-FIG. 3. Scheme of circulation in presence of septum defect established experimentally in an adult animal.

The sequence of events subsequent to the establishment of a septum defect is interpreted as follows:

The presence of this direct communication between the arterial and venous systems provides two routes for the circulating blood (Text-fig. 3): (*a*) left ventricle, septum defect, right ventricle, lungs, left auricle; (*b*) left ventricle, aorta, capillary bed, right heart, lungs, left auricle. The difference in peripheral resistance between the pulmonic and systemic capillary beds, and the preponderance of the

left ventricle over the right, result in a division of the blood stream in the left ventricle, a part of the circulating blood being diverted through the defect during systole, the quantity depending upon the size of the opening. Commensurate with the volume of blood abstracted from the systemic circulation there occurs a marked fall in general blood pressure. If the amount of blood deflected is too large (Dogs X 7, X 10, X 26, X 27), the animal succumbs either from an excessive pulmonary congestion and edema, or from a lowered general blood pressure, or from a combination of both factors. If the animal survives the immediate effects of the defect, a gradual recovery in blood pressure is observed until the systolic pressure has again reached a normal level.

The factors to which may be attributed the reestablishment and maintenance of a blood pressure compatible with life are several. The pulse rate is immediately accelerated. That this great increase in pulse rate may gradually subside over a period of months was illustrated in our experimentally produced peripheral fistulæ, and also in the intracardiac fistulæ. In X 11, with a large defect, the pulse never returned to normal during the 6 months of observation. In X 2, with a slightly smaller defect, the pulse returned to normal after 5 months. In X 34, with a still smaller defect, the pulse returned to normal within 2 months, and in X 42, with a defect which closed spontaneously, the pulse returned to a normal rate within a month. This gradual return to a normal pulse rate is explained as follows:

The increased cardiac output necessary to compensate for the shortcircuited flow through the fistula is at first achieved by a more rapid rate of contraction of the heart. With the increased filling of the heart, provided by the diversion of the circulating blood into Circuit A, the heart is enabled to increase its output by this increased frequency of heart beat. This is the first, and the immediate compensatory adjustment for the abnormal leak. If the septum defect is large the volume of blood deflected into the shorter circuit is considerable. Whence its source? Immediately following the establishment of the fistula, it is obtained at the expense of the volume of blood flowing through the rest of the body; *i.e.*, through Circuit B. If the volume deflected is excessive the animal obviously cannot

survive, and a number of our experiments terminated fatally within 12 to 36 hours. The animals that survived were ill for a number of days, with a very low general blood pressure and a rapid pulse. A gradual recovery followed, due, according to our observations, to a second compensatory adjustment in the form of a gradual increase in total blood mass. The normal volume flow through Circuit B, temporarily decreased by diversion of a considerable part of the circulating blood into Circuit A, is slowly reestablished by increasing the total volume of blood. As this increase in blood volume approaches the point of full compensation for the shortcircuited flow, the pulse again returns to a normal rate.[2] The increased cardiac output necessary to maintain a normal general blood pressure is now attained by a slower rate of contraction, since the left ventricle, already dilated by a greatly increased filling, has developed a systolic discharge entirely sufficient to provide both for the septal leak and for the systemic circulation. Under these circumstances, complete equilibrium has been reestablished between Circuits A and B. The rapidity with which this equilibrium is reestablished depends primarily upon the size of the defect. The resistance offered to the flow of blood through the shorter circuit is the sum of that presented by the pulmonary bed and that provided by the septum defect itself. When any further increase in the volume flow through the shorter circuit is prevented by the limited size of the defect, resistance in the two

[2] The question of venous pressure in peripheral arteriovenous fistulæ is probably also dependent for a satisfactory explanation upon the basis of a *gradual adjustment*, much in the same way that the accelerated pulse rate returns to normal when complete equilibrium has been reestablished in the circulation. Immediately after the establishment of a peripheral fistula there is an increase in venous pressure proximal to the fistula, as numerous experiments have shown. As the vessels proximal to the fistula, including both the feeding artery and the *receiving vein*, undergo gradual dilatation to accommodate the increased flow through them, the increased quantity of blood delivered to the heart is maintained by an increase in the cross-section of the column of blood entering it. As a result, the increased venous pressure subsides without, however, any decrease in venous filling. Clinically, the cases of arteriovenous fistulæ in which the circulation has reached an equilibrium may show a normal *venous pressure*, as Lewis and Drury (9) contend, although actual *venous filling* per unit of time may be greatly augmented by an increase in the size of the column of blood entering the heart.

circuits is equalized. There will then be no further increase in the volume flow of blood through Circuit A, no further dilatation of that part of the circulatory system through which the deflected flow passes, and no further increase in total blood volume. It may then be said that complete compensation for the leak has occurred. In Dog X 11, in which a large defect was established, and in which the pulse never returned to a normal rate, it is assumed that complete compensation had not been attained when the animal was killed. The slightest effort in this animal produced complete collapse. It is likely that overdilatation of the heart through the mechanism of an increasing blood flow through Circuit A, and of an increasing total blood volume, might eventually have resulted in cardiac decompensation in this dog. May not decompensation be an inevitable development whenever dilatation outstrips hypertrophy?

In the presence of a peripheral or intracardiac fistula, the conditions in the heart conform exactly to the requirements which, according to Fick, are considered essential for the development of cardiac hypertrophy. Fick "holds that muscles elicit more or less work according to the degree to which they are stretched. He believes that hypertrophy can occur only if the stimulus to contraction, or the contraction itself, results in a stretching greater than normal" (10). The deflection of a considerable volume of blood into the shorter circuit provides for an increased filling of this part of the circulatory bed including the left auricle, the left and right ventricles. During each cardiac cycle, therefore, there occurs a greater stretching of the muscle fibers in these chambers than under normal conditions, and hypertrophy is an inevitable sequence to the large fistula, both theoretically and experimentally. It is apparent, however, from our experimental observations that hypertrophy of the heart is responsible only in small part for the cardiac enlargement that occurs. It is mainly a dilatation.

The mechanism that determines the various manifestations that follow in the wake of a fistula, whether peripheral or intracardiac, is the same in all cases, and is dependent upon an increased flow of blood through the shorter circuit. Our experiments indicate that the extent of these manifestations and the subsequent pathological changes depend upon the size of the fistula and upon its duration.

Additional evidence is presented by these experiments to substantiate the hypothesis that the heart and blood vessels place themselves in harmony with the volume flow of blood through them, the former by dilatation and by hypertrophy, and the latter by dilatation.

SUMMARY.

An abnormal communication, experimentally produced between the right and left ventricles, causes a deflection of part of the blood stream into the shorter pulmonary circuit. Proceeding *pari passu* with the increase in volume flow of blood through this shorter circuit, there occurs a gradual enlargement of the heart limited to that part of the circulatory system through which the deflected blood passes; namely, the left ventricle, the right ventricle, the pulmonary artery, and the left auricle. There is also a demonstrable hypertrophy of the right and left ventricles, which presumably is the result of the increased effort necessary to propel forward an increased volume flow of blood, since it cannot be attributed to an increased peripheral resistance.

Immediately after the production of the defect, the right auricle and aorta become smaller than usual, conforming in size to the decreased volume flow of blood through them. As full compensation for the deflected flow occurs by an increase in total blood volume, they return to their normal size. If full compensation has not occurred they remain smaller than normal (Dog X 11).

The changes incident to the establishment of an opening in the septum are entirely dependent upon the size of the defect, and hence, upon the extent of the volume of blood deflected into the shorter circuit. Commensurate with the volume of blood deflected, there is a fall in general blood pressure. If the animal survives the immediate fall in blood pressure, certain compensatory adjustments occur which reestablish a more normal blood pressure: (*a*) an immediate increase in pulse rate; (*b*) a gradual increase in total blood mass. The increase in blood volume is directly commensurate with the size of the defect. The pulse returns to a normal rate when complete compensation through an increase in blood volume has been attained.

It is suggested that the enlargement of the heart seen clinically in

so called "idiopathic hypertrophy," "essential hypertension," and also in certain cases of cardiorenal disease, may be due to an increase in total blood mass following some interference with the mechanism for its control. The seat of this impairment in blood volume control may be: (*a*) in a chemical alteration in the blood; (*b*) in a diseased function of the kidneys which may be responsible for a decreased elimination, or for a change in the chemical composition of the blood; or (*c*) in an abnormal stimulation of the organs producing the cellular elements of the blood.

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EXPLANATION OF PLATES.

PLATE 31.

FIG. 1. Increase in size of heart following establishment of septum defect on September 16: (a) September 15, 1924; (b) February 9, 1925.

FIG. 2. Great enlargement of heart in X 2 as revealed by roentgenogram. Defect established on September 8, 1924: (a) August 27, 1924; (b) March 9, 1925.

FIG. 3. Roentgenographic evidence of enlarged heart in X 34, following establishment of septum defect of 3 months duration: (a) January 30, 1925; (b) May 8, 1925.

PLATE 32.

FIG. 4. Hearts removed at necropsy illustrating marked enlargement in X 11 and X 2 with large septum defects, and less though definite enlargement in X 25 and X 34 with smaller defects of shorter duration. Note increase in size of ear of left auricle.

FIG. 5. The cardiac enlargement is due mainly to dilatation, and only partly to hypertrophy. Note thickness of right ventricular wall in X 11.

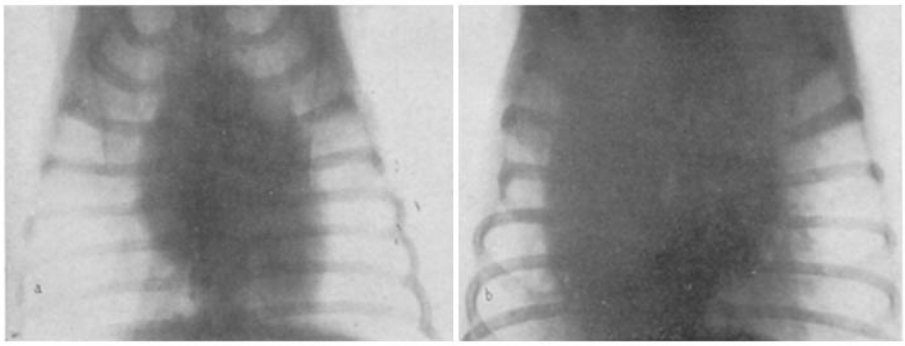

FIG. 1.

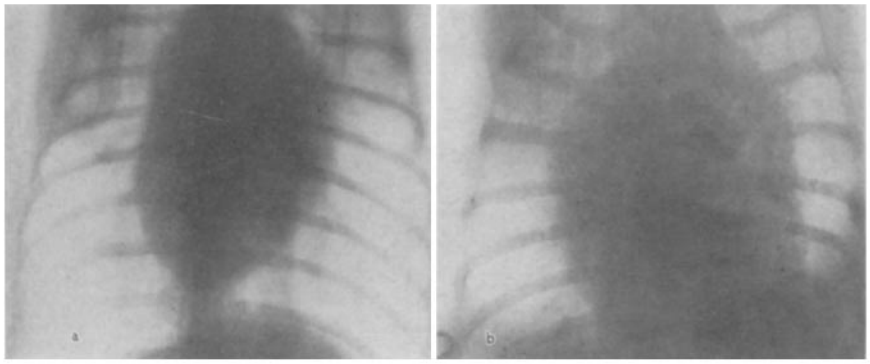

FIG. 2.

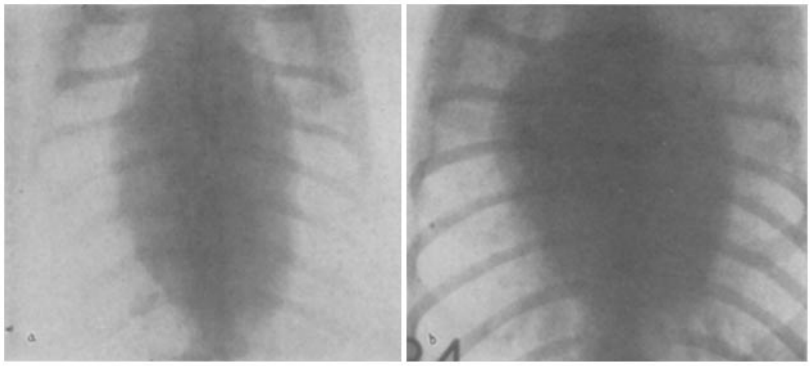

FIG. 3.

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

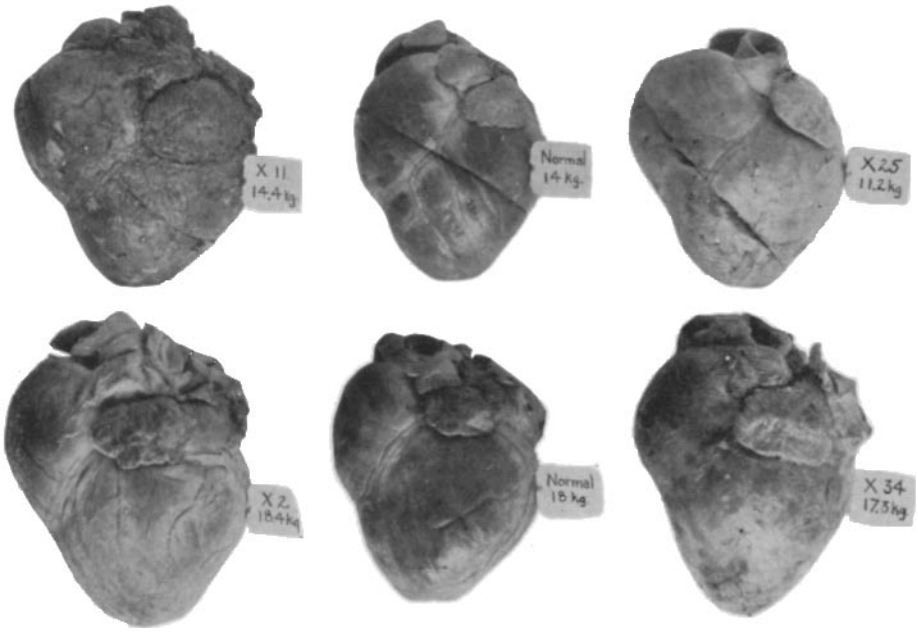

FIG. 4.

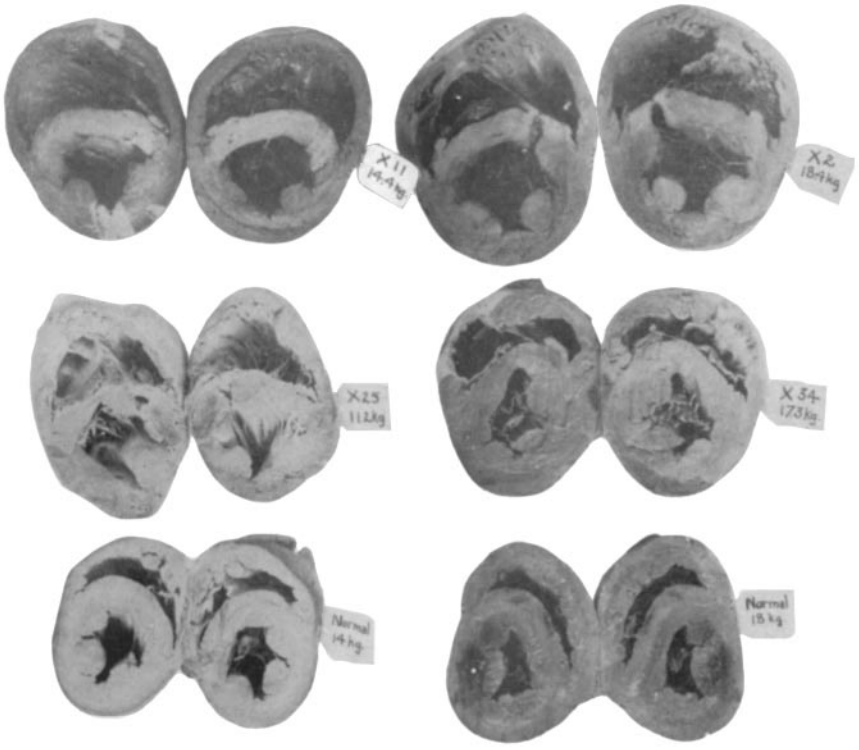

FIG. 5.

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