THE EFFECTS OF THE PATENT DUCTUS ARTERIOSUS ON THE CIRCULATION¹

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The operation for ligation of the patent ductus arteriosus, as described by Gross and Hubbard (1), presented an opportunity to study the circulatory dynamics of this congenital anomaly. A patent ductus arteriosus is a vascular communication between the aorta and the pulmonary artery. Because the blood pressure is normally higher in the aorta than in the pulmonary artery, and because the arterial blood of patients with patent ductus arteriosus has been found to be saturated with oxygen to a normal degree, it has been assumed that in uncomplicated cases the flow of blood through the ductus is in the main from aorta to pulmonary artery. The amount of blood passing through the ductus per unit of time was calculated by Plesch in 1909 (2); however, he used a method which in the light of present knowledge is not valid.

The purpose of this paper is to report the results of quantitative studies of the circulation in patients with patent ductus arteriosus. The problem is further elucidated by measurements in animals in which a situation similar to a patent ductus arteriosus has been brought about by operation.

In normal individuals and in those with certain types of cardiac abnormalities the output of the heart may be determined by the foreign gas method of Marshall and Grollman (3), provided that samples of the foreign gas from the lung-bag mixture are obtained *after* equilibrium has been reached and *before* recirculation to the lungs has occurred. This method is not applicable to patients with patent ductus arteriosus because, when such patency is present, a portion of the foreign gas absorbed by the blood during its passage through the capillaries of the lung is almost immediately returned to the lungs through the ab-

normal vessel, making it practically impossible to obtain samples before recirculation occurs. This criticism appears to apply to other indirect methods also, such as the ethyl-iodide method of Starr and Gamble (4) or the oxygen-carbon dioxide method of Burwell and Robinson (5). The possibility of obtaining blood from aorta and pulmonary artery at the time of operation leads to a consideration of the applicability of the so-called "direct" method, depending upon the principle of Fick (6). This principle may be stated as follows: Given the amount of oxygen per 100 cc. of blood entering a given vascular area, the amount of oxygen added to or subtracted from the blood during its passage in a unit of time, and the amount of oxygen per 100 cc. of blood leaving the area, the volume of blood flow through it during that time may be calculated. The calculation is made according to the formula

$$C = \frac{O}{A - V}$$
in which C is the volume of flow (cardiac output) per minute, O is the oxygen absorbed per minute, A is the arterial oxygen content, and V is the venous oxygen content.

In people with no abnormal connection between peripheral and pulmonary circuits the volume of blood passing through the lungs is (essentially) the volume of blood put out by the right ventricle, which is necessarily the same as the volume put out by the left ventricle. Neither of these statements, however, need be true in a patient with a patent ductus arteriosus. As we shall show, the flow through an uncomplicated patent ductus arteriosus is from aorta to pulmonary artery and, therefore, blood expelled from the left ventricle may pass via the ductus and the pulmonary blood vessels back to the left ventricle without having passed through the right. Clearly, under these circumstances the output per minute of the left ventricle may be greater than that of the right (Figures 1 and 2).

¹ Read in part at the thirty-second annual meeting of the American Society for Clinical Investigation, May 6, 1940, at Atlantic City.

FIG. 1. A DIAGRAM OF THE NORMAL CIRCULATION

FIG. 2. A DIAGRAM OF THE CIRCULATION WHEN THE DUCTUS ARTERIOSUS IS PATENT

When a patent ductus arteriosus permits the passage of blood from the aorta to pulmonary artery, the output of the *right* ventricle is made up of blood which comes to this ventricle *from the peripheral circulation*² and *from no other source*. The volume of the peripheral flow and the output of the right ventricle are identical. The volume of the peripheral blood flow can be calculated if the oxygen consumption per minute, the oxygen content of blood in the aorta, and the oxygen content of blood in the right ventricle (mixed venous blood) are known.

² The term "peripheral circulation" includes, of course, the flow through the coronary system.

The output of the left ventricle in patients with patent ductus arteriosus is made up of two components: the blood from the right ventricle and the blood entering the pulmonary artery by way of the ductus arteriosus. These confluent streams pass through the lungs and enter the left side of the heart. Since the blood entering the lung capillaries is thus only partly blood from the right ventricle, the oxygen content of the right ventricle blood cannot be used in calculating the pulmonary blood flow. This calculation requires knowledge of the oxygen content of blood taken from the pulmonary arterial system at a point where mixture of the two streams has occurred.

If there are at hand figures expressing the oxygen consumption per minute, the oxygen content of arterial blood, the oxygen content of mixed venous (right ventricle) blood, and *the oxygen content of the mixed arterial and venous blood in the pulmonary artery*, the output of each ventricle may be calculated according to the Fick formula. Obviously, the difference between the outputs of the two ventricles is the volume of the blood which passes through the ductus.

The operations by Gross (7) presented an opportunity to obtain directly from the pulmonary artery and other vessels the crucial samples of blood³ which permitted calculation of the outputs of the two ventricles. Similar studies have been made in dogs in which a connection between aorta and pulmonary artery has been established by operation. In subsequent portions of this paper the terms "pulmonary blood flow" and "peripheral blood flow" will be used. It should now be clear that these volumes are equivalent to the outputs of the left and right ventricles, respectively.

OBSERVATIONS ON THE FIRST PATIENT

The application of these principles to the study of the circulation in a patient may be exemplified by a brief presentation of the findings in the first case so studied.

Case 1 (F. S.) was a girl of six years. She appeared thin, fragile and underdeveloped for her age. The left chest was more prominent than the right and a widespread pulsation lifted the chest wall as far out as the nipple line. A precordial thrill, which was of maximum intensity in the second left interspace, could be felt throughout the cardiac cycle but was most evident in systole. In the pulmonary area, a continuous murmur was heard which had a systolic accentuation.

The diagnosis of patent ductus arteriosus was made and operation advised. (The criteria for diagnosis and for the selection of patients suitable for operative treatment have been defined by Hubbard, Emerson, and Green (10)). Operation in this patient was carried out in November 1938 under cyclopropane anesthesia. Expo-

³ In all determinations of oxygen content, the manometric apparatus of Van Slyke was used and duplicate determinations were made by the same observer. All samples of blood were taken under oil with potassium oxalate as an anticoagulant. It was not necessary to modify the method on account of the anesthesia when cyclopropane (8) was used; when ether was the anesthetic, appropriate changes in analytic methods, as described by Shaw and Downing (9) were applied.

sure of the heart and great vessels revealed the presence of a patent ductus 7 mm. in diameter and 7 to 8 mm. long. The heart was beating rapidly and vigorously. A thrill was felt over the ductus and pulmonary artery. Compression of the ductus between the fingers resulted in the abolition of the thrill and visible diminution in the amplitude of the cardiac excursions. Samples of blood were obtained from the femoral artery, the pulmonary artery when the ductus was open (opposite the entrance of the ductus), and the pulmonary artery within 15 seconds of temporary closure of the ductus.⁴ The ductus was then ligated. Some minutes later samples of blood were obtained from the femoral artery and from the pulmonary artery to determine what the situation was after the ductus had been ligated.

When these samples were analyzed it was found that the oxygen content of blood taken from the pulmonary artery (with the ductus open) approached that of femoral artery blood so closely that the question arose as to whether this sample actually represented the blood which was entering the lungs. It was considered that this pulmonary artery sample might have been taken from the stream of arterial blood entering by way of the ductus before it was thoroughly mixed with blood from the right ventricle. This possibility prompted the series of animal experiments herein described in which it was possible to make more complete observations than in patients.

OBSERVATIONS ON ANIMALS

What was sought in these dog experiments was to bring about a situation in which the circulation would resemble as closely as possible that of a patient with a ductus arteriosus. Accordingly, the following operation was carried out:

Under anesthesia with pentobarbital sodium or alpha chloralose, the chest was opened and the left lung partially collapsed. Respirations were maintained by posi-

⁴ This sample requires explanation. What was sought was a sample of blood having the oxygen content of the right ventricle blood ("mixed venous blood") when the ductus was open. This could have been obtained directly, if one had been willing to puncture the right ventricle. It is technically preferable to take this sample from the pulmonary artery. This can be done, provided the ductus is temporarily clamped to prevent the entrance of blood from the aorta. Since this manipulation and sampling were completed within 15 seconds (*i.e.*, probably before recirculation could take place), the sample drawn should represent the right ventricular blood during the time when the ductus was open.

FIG. 3. METHOD EMPLOYED FOR PRODUCING AN AORTA-PULMONARY ARTERY FISTULA IN DOGS

The left subclavian artery was freed from its bed along the dotted line and then divided high in the thorax. The proximal portion of this artery was then turned downward and anastomosed to the pulmonary artery. Lower sketch shows position of the operative incision.

LP—Left pulmonary artery. RP—Right pulmonary artery. PA—Pulmonary artery. SC—Left subclavian artery.

tive pressure. Samples of blood were drawn from the pulmonary artery and the aorta. The left subclavian artery was then divided about 3 cm. above its origin from the aorta and the proximal portion sutured into the pulmonary artery just above its bifurcation (Figure 3). In this way a communication was made between the aortic arch and the pulmonary artery. When this anastomosis was completed, the action of the heart became much more vigorous and a thrill could be felt over the pulmonary artery. Samples of blood were drawn from the heart and from various points in the great vessels. Oxygen consumption was determined at the end of the experiment by the Benedict-Roth apparatus, using a Blalock mask (11). In some experiments blood volume determinations were carried out by the method of Gibson and Evans (12).

In some cases the pressures in the aorta and pulmonary artery were directly measured by connecting manometers with the needles inserted into the vessels. It was found convenient to use a mercury manometer for the determination of aortic pressure and a water manometer for that in the pulmonary artery.

Table I summarizes the results obtained in the first dog. These observations show that, after the communication is established, the pulmonary

TABLE I

Observations on the circulation of Dog number 4-39 before and after the establishment of a communication between aorta and pulmonary artery, including studies of the mixture of the confluent streams

Dog number 4-39

Source of blood	Oxygen content	Arterio-venous oxygen difference	Blood flows	Oxygen capacity
	cc. per liter	cc. per liter	liters per minute	cc. per liter
JANUARY 7, 1939*				
CIRCULATION INTACT				
Aorta.....	186.2	49.2	2.05 (Pulmonary or peripheral blood flow)	241.1
Pulmonary artery.....	137.0			
AORTA-PULMONARY ARTERY COMMUNICATION ESTABLISHED				
1. Left ventricle.....	201.6	35.7	2.83 (Pulmonary blood flow)	240.5
2. Pulmonary artery near valves.....	150.2			
3. Pulmonary artery opposite communication.....	171.3			
4. Left pulmonary artery at root of lung.....	165.8	74.2	1.36 (Peripheral blood flow)	240.1
5. Right pulmonary artery at root of lung.....	165.9			
6. Right ventricle.....	127.4			
7. Pulmonary artery immediately after temporary occlusion of communication..	136.3	65.3	1.55 (Peripheral blood flow)	

* Basal oxygen consumption = 101 cc. per minute.

artery contains blood with a higher oxygen content than that of the blood in the right ventricle. This is evidence that blood from the aorta is entering the pulmonary artery through the artificial connection.

To determine the degree of mixture of the two streams of blood at various points, samples were taken from several parts of the pulmonary artery between the pulmonary valves and the lung roots. The oxygen content of a sample taken from the pulmonary artery near the pulmonary valves was 150.2 cc. per liter, while that of a sample taken immediately opposite the entrance of the stream from the transplanted subclavian artery was 171.3 cc. per liter. However, samples taken from the left and right branches of the pulmonary artery (several centimeters distal to the entrance of the fistula) gave values which were *essentially identical* (165.8 and 165.9 cc. per liter). These results are shown graphically in Figure 4. This agreement in oxygen content of blood going to both lungs would appear to indicate that at these points

FIG. 4. THE OXYGEN CONTENT OF BLOOD IN VARIOUS PARTS OF THE HEART AND GREAT VESSELS OF DOG NUMBER 4-39 AFTER THE ESTABLISHMENT OF A COMMUNICATION BETWEEN AORTA AND PULMONARY ARTERY (SEE TABLE III)

mixture had occurred. Since this was so, *samples which are to be used in the calculation of the pulmonary blood flow in patients with patent ductus arteriosus should be taken from the pulmonary artery at a point as far as possible distal to the entrance of the ductus.*

A theoretical source of error concerns the time of the cardiac cycle during which blood samples are taken. It is probable that the flow from aorta to pulmonary artery continues through both systole and diastole, perhaps with diminishing volume in diastole. The flow from right ventricle into the pulmonary artery is limited to systole. Therefore, we might expect to find a difference between samples obtained from the pulmonary artery in systole and in diastole. However, the usual sample requires over 10 seconds to draw, and represents sampling during 15 or more complete cardiac cycles. This suggested error is probably minimal.

The calculations in Table I concerning blood flow in the dog are illuminating. In the intact animal, the output of both the right and the left ventricle was 2.05 liters per minute. With the

shunt established, the output of the left ventricle increased to 2.83 liters per minute, while that of the right, representing the flow through the periphery, fell to 1.36 liters per minute. Thus the amount flowing through the shunt is calculated to be 1.47 liters per minute, or 52 per cent of the left ventricle's output.

The experiments in the dog also present an opportunity to test the validity of the method used in obtaining "mixed venous blood" in patients when the ductus is open (Cf. footnote 4). Sample 7 in Table I was obtained in accordance with this method (temporary occlusion of the artificial ductus); the oxygen content of this blood was within one volume per cent of the oxygen content of blood directly aspirated from the right ventricle. A similar agreement was observed in another dog. The figures for the oxygen content of "mixed venous blood" when the ductus is open are therefore only approximate; it will be realized that these values may be slightly higher but are never lower than the true oxygen content of "mixed venous blood."

A second set of observations made on this dog after a period of 3 months, with the communication open, showed a smaller but nevertheless definite difference between the left and right ventricular outputs. Again, blood samples taken from the left and right pulmonary arteries below the bifurcation showed that essentially complete mixing of the aortic and pulmonary artery blood had occurred at these points.

A similar operation in a second, third, and fourth dog produced circulatory changes which are outlined in Tables II, III, and IV.

One other special point of technique remains to be considered. The observations just presented on dogs showed that subclavian blood entering the pulmonary artery proximal to or at its bifurcation was evenly distributed between right and left pulmonary artery branches. Occasionally, the ductus arteriosus of humans enters the *left* pulmonary artery. The opening of the ductus into the left pulmonary artery is usually close to its origin from the main trunk. According to Gérard (13), it is almost always in close relation to the bifurcation, but in one of the patients studied (Case 4) the ductus (observed at autopsy) was found to enter the left branch of the pulmonary artery 15 mm. beyond the bifurcation. It is obvious that a duc-

tus in such a position might distribute different amounts or mixtures of blood to the two lungs, and hence be a source of error if a sample is taken from only one branch of the pulmonary ar-

TABLE II

Observations on the circulation of Dog number 17-39 after the establishment of a communication between aorta and pulmonary artery

Dog number 17-39

Source of blood	Oxygen content	Arterio-venous oxygen difference	Blood flows	Oxygen capacity
	cc. per liter	cc. per liter	liters per minute	cc. per liter
JANUARY 27, 1939*				
1. Left ventricle.....	168.4			179.5
2. Pulmonary artery opposite communication.....	132.0			
3. Left pulmonary artery at root of lung.....	127.2	41.2	6.19 (Pulmonary blood flow)	
4. Right ventricle.....	81.0	87.4	2.92 (Peripheral blood flow)	185.6
MARCH 1, 1939†				
1. Aorta.....	143.0			
2. Left pulmonary artery at bifurcation.....	107.6	35.4	5.73 (Pulmonary blood flow)	
3. Right ventricle.....	65.6	77.4	2.62 (Peripheral blood flow)	

* Basal oxygen consumption = 255 cc. per minute.

† Basal oxygen consumption = 203 cc. per minute.

TABLE III

Observations on the circulation of Dog number 55-39 before and after the establishment of a communication between aorta and pulmonary artery

Dog number 55-39

Source of blood	Oxygen content	Arterio-venous oxygen difference	Blood flows
	cc. per liter	cc. per liter	liters per minute
APRIL 12, 1939*			
CIRCULATION INTACT			
Aorta.....	166.1		
Right ventricle.....	122.7	43.4	4.02 (Pulmonary or peripheral blood flow)
AORTA-PULMONARY ARTERY COMMUNICATION ESTABLISHED			
1. Aorta.....	175.4		
2. Right pulmonary artery.....	132.9		
3. Left pulmonary artery.....	136.5	40.7	4.29 (Pulmonary blood flow)
4. Right ventricle.....	94.3	81.1	2.15 (Peripheral blood flow)

* Basal oxygen consumption = 174.5 cc. per minute.

TABLE IV

Observations on the circulation of Dog number 63-39 before and after the establishment of a communication between aorta and pulmonary artery

Dog number 63-39

Source of blood	Oxygen content	Arterio-venous oxygen difference	Blood flows	Oxygen capacity
	cc. per liter	cc. per liter	liters per minute	cc. per liter
JUNE 1, 1939*				
CIRCULATION INTACT				
Aorta.....	206.0			229.9
Right ventricle.....	152.1	53.9	2.31 (Pulmonary or peripheral blood flow)	
AORTA-PULMONARY ARTERY COMMUNICATION ESTABLISHED				
1. Aorta.....	229.4			252.3
2. Left pulmonary artery.....	206.6	22.8	5.47 (Pulmonary blood flow)	
3. Right ventricle.....	133.5	95.9	1.30 (Peripheral blood flow)	
JULY 26, 1939†				
1. Left ventricle.....	213.3			
2. Left pulmonary artery.....	187.4	25.9	5.23 (Pulmonary blood flow)	
3. Right ventricle.....	140.7	72.6	1.87 (Peripheral blood flow)	

* Basal oxygen consumption = 124.8 cc. per minute.

† Basal oxygen consumption = 135.5 cc. per minute.

tery. Accordingly, an attempt was made to reproduce such a situation in an animal.

The experiment was carried out in the same manner as the dog experiments already described, except that the anastomosis was made between the subclavian artery and the *left branch* of the pulmonary artery. The point of anastomosis was 15 mm. distal to the bifurcation of the pulmonary artery. After the establishment of the connection, samples of blood were obtained from the aorta, from the right ventricle, and from several points in the pulmonary artery and its main branches. The results are set forth in Table V.

This table shows that the oxygen content of blood in the main pulmonary artery is higher than that of blood in the right ventricle; the same is true of blood in the right branch. Therefore, some arterial blood which has entered the left pulmonary artery via the anastomosis is carried back into the main pulmonary artery and so gains access to the right lung. The difference in the oxygen content of blood in the two branches, however, makes it quite clear that more of the shunted

TABLE V

Observations on the circulation of Dog number 181-39 before and after the establishment of a communication between aorta and left branch of pulmonary artery

Dog number 181-39

Source of blood	Oxygen con- tent	Arterio- venous oxygen differ- ence	Blood flows	Oxygen cap- acity
	cc. per liter	cc. per liter	liters per minute	cc. per liter
NOVEMBER 21, 1939*				
CIRCULATION INTACT				
Aorta.....	172.7	81.4	1.60 (Pulmonary or peripheral blood flow)	202.2
Pulmonary artery.....	91.3			
AORTA-PULMONARY ARTERY COMMUNICATION ESTABLISHED				
1. Aorta.....	178.5	30.7	4.23 (?Pulmonary blood flow)	213.9
2. Main pulmonary artery...	147.8			
3. Left pulmonary artery....	156.9	21.6	6.02 (?Pulmonary blood flow)	
4. Right pulmonary artery..	148.6	29.9	4.35 (?Pulmonary blood flow)	
Right ventricle.....	104.9	73.6	1.77 (Peripheral blood flow)	

* Basal oxygen consumption = 129.5 cc. per minute.

blood is going to the left lung than to the right. If we could assume that equal volumes of oxygen are absorbed by the two lungs, the volume of blood flow through each lung could be calculated. In normal people, according to Björkman (14), about 53 per cent of the total oxygen is absorbed by the right lung and about 47 per cent by the left. But in patients or animals undergoing an operation of this type, the left lung is partly collapsed, and it is likely that less than its usual share of oxygen is being absorbed by it. Therefore, if the ductus enters the left branch of the pulmonary artery at a point much beyond the bifurcation, the calculations of pulmonary blood flow are not exact, although in the example cited in Table V the changes are still significant. One is not always certain, even after operative exposure, of the precise position of the opening of the ductus in relation to the bifurcation and it is possible, therefore, that in almost any given case it may open into the left branch. However, we have now made measurements in five patients and, while the ductus probably enters the pulmonary artery near the bifurcation in all of them, it is extremely improbable (13, 15) that it enters the left branch in more than the one that is known.

A few observations were made on the relative pressure in the aorta and the pulmonary artery of dogs before and after the establishment of the artificial communication. These are shown in Table VI. In two of the three animals the pressure in

TABLE VI

Pulmonary artery pressure before and after the establishment of a communication between aorta and pulmonary artery

Dog number	Time	Aortic pressure	Pulmonary artery pressure
		mm. of mercury	mm. of mercury
17-39	Before operation	116	16
	After operation		27
	5 weeks later		22
55-39	Before operation	124	16
	After operation	112	17
63-39	Before operation		16
	After operation		24
	8 weeks later	150	19

the pulmonary artery rose. In no case did it approach the pressures in the aorta, presumably because the resistance in the lung is relatively low, as pointed out by Levy and Blalock (16).

TABLE VII

Blood volumes in three dogs before and after establishment of a communication between aorta and pulmonary artery

Dog number	Time	Weight	Plasma volume	Red blood cell volume	Total blood volume	Hematocrit
		kgm.	cc.	cc.	cc.	per cent
17-39	Before operation	26.1	1280	1010	2290	44.0
	5 weeks after operation	24.7	1440	770	2210	34.8
	9 weeks later		1655	915	2570	35.6
55-39	Before operation	22.2	1225	795	2020	39.3
	4 weeks after operation*	19.7	1040	770	1810	42.4
63-39	Before operation	21.2	1078	897	1975	45.4
	8 weeks after operation	22.5	1890	1990	3880	51.4

* At this time the communication was found to be thrombosed.

Table VII summarizes studies of the blood volume in three dogs. In two dogs (number 17-39 and number 63-39) in which the evidence of the shunt persisted for 2 months or more, there was a significant increase in total blood volume, involving both plasma and cells. The dog (num-

ber 63-39) with the largest shunt (as shown by a pulmonary blood flow four times the peripheral flow) also exhibited the greatest increase in total blood volume—from 1975 cc. to 3880 cc. In one dog (number 55-39) in which the shunt closed spontaneously, this increase did not take place. In dog number 17-39 an increase in plasma volume took place in spite of an anemia due to infection, which apparently prevented an increase in cell volume.

CONCLUSIONS FROM FIVE DOG EXPERIMENTS

1. After the establishment of the aortic-pulmonary artery connection, the oxygen content of the blood in the pulmonary artery is always greater than that in the right ventricle. Therefore, the blood flow through the shunt is toward the pulmonary artery.

2. In two dogs, a comparison of the oxygen content of blood from the right and left branches of the pulmonary artery at the hili showed an approximate identity, indicating adequate mixture.

3. In each case, the shunt from the aorta to the pulmonary circulation was more than 50 per cent of the output of the left ventricle; the output of the left ventricle, therefore, was more than twice that of the right. In one animal (Table IV) the shunt was 75 per cent and the left ventricle was putting out four times the output of the right. The situation in this dog was essentially the same 8 weeks later.

4. In some animals, the left ventricular output was not greatly increased but the flow of blood to the periphery was diminished. In others the output of the left ventricle increased to such an extent that the volume expelled by the right was less severely reduced.

5. When the subclavian artery was anastomosed to the left branch rather than the main pulmonary artery, the arterial blood streams were not equally distributed to the right and left lungs. Under these circumstances, knowledge of the oxygen content in the left pulmonary artery did not allow the quantitative estimation of the pulmonary blood flow, although certain qualitative information was obtained.

6. In two of the three dogs in which the pulmonary blood pressure was measured before and after the subclavian artery was anastomosed with

the pulmonary artery, the pulmonary pressure rose.

7. In two animals with a large shunt a definite increase in total blood volume was observed.

OBSERVATIONS IN PATIENTS

In the patients to be considered now, each pulmonary artery sample was drawn from a point where, according to the animal experiments, mixture could be expected to have taken place; that is, from the left pulmonary artery as it entered the lung root. Under the conditions of this operation the right pulmonary artery is usually not accessible.

Observations were made on each of six patients subjected to ligation of a patent ductus arteriosus between November 1938 and December 1939. The data are presented in Tables VIII to XIX, inclusive, and consist of two parts: One part deals with the pulmonary and peripheral blood flow before and after ligation of the ductus and with the volume of the shunt. *The cardiac outputs were not basal. They were determined during anesthesia, and when the chest was open, and there is evidence (to be presented later) that they were much above the basal level. Therefore, these cardiac outputs cannot be compared with basal outputs in normal people or with other measurements of the circulation made in our patients under basal conditions.* The other part deals with other measurements before and after ligation, including height, weight, arterial blood pressure (basal and after exercise), venous pressure, circulation time, oxygen saturation of the arterial blood, plasma volume, red blood cell volume, vital capacity (basal and after exercise) and oxygen consumption. *Except where noted, these groups of data were obtained under standard basal conditions.* The exercise test varied somewhat with different individuals, but in general consisted of 1 to 2 minutes at 100 steps per minute over stairs. The venous pressure was measured by the direct method described by Lyons, Kennedy and Burwell (17); the circulation time was measured by sodium dehydrocholate; the blood volume by the method of Gibson and Evans (12).

PROTOCOLS

Case 1 (F. S.) has already been described. The results of the acceptable measurements of her circulation are summarized in Tables VIII and IX.

TABLE VIII

Observations on the blood flow in Case 1 before and after ligation of the ductus arteriosus

Case 1 (F. S.)

Source of blood	Oxygen content	Arterio-venous oxygen difference	Blood flows	Oxygen capacity
	cc. per liter	cc. per liter	liters per minute	cc. per liter
NOVEMBER 9, 1938*				
DUCTUS ARTERIOSUS PATENT				
Femoral artery.....	163.8			169.0
Pulmonary artery after temporary occlusion of ductus.....	135.2	28.6	4.9 (Peripheral blood flow)	
DUCTUS ARTERIOSUS LIGATED				
Femoral artery.....	166.8			168.8
Pulmonary artery.....	144.2	22.6	6.2 (Pulmonary or peripheral blood flow)	

* Basal oxygen consumption = 139 cc. per minute.

TABLE IX

Other observations in Case 1 before and after ligation of the ductus arteriosus

Case 1 (F. S.)

Observations	Pre-operative	Post-operative 4 months	Post-operative 14 months
Weight, <i>kgm.</i>	18.32	20.25	23.45
Height, <i>cm.</i>	117.0	117.0	126.1
Arterial blood pressure, basal			
Right arm, <i>mm. Hg.</i>	95/50	106/80	88/60
Left arm, <i>mm. Hg.</i>	98/40	100/70	92/70
Arterial blood pressure, after exercise (1½ minutes at 100 steps per minute over stairs), <i>mm. Hg.</i>	110/50*	118/60	
Venous pressure, <i>mm. H₂O</i>	130		
Vital capacity, <i>cc.</i>	1000	1100	1250
Oxygen consumption, <i>cc. per minute</i>	146	139	
	139		
	138		

* Sounds heard to zero.

Case 2 (M. F.), a girl of 17 years, was known to have had heart disease since early childhood. Because of dyspnea on exertion, palpitation, precordial distress and easy fatigue, her activities were seriously limited. On physical examination she appeared slender but reasonably well-developed. There were no remarkable abnormalities except for the heart. There was moderate cardiac enlargement, chiefly to the left. A vigorous systolic thrill could be felt in the pulmonary area. This thrill was accompanied by a loud continuous murmur which had a systolic accentuation. There was also a diastolic murmur at the apex which disappeared when the ductus was ligated.

On December 22, 1938, the ductus arteriosus measuring 9 mm. in diameter was ligated under cyclopropane anesthesia. Samples of blood were taken and analyzed for

oxygen content and capacity. The results of these and other measurements are collected in Tables X and XI. Six months after this ligation some degree of communication was reestablished, as judged by the reappearance of physical signs.

TABLE X

Observations on the blood flow in Case 2 before and after ligation of the ductus arteriosus

Case 2 (M. F.)

Source of blood	Oxygen content	Arterio-venous oxygen difference	Blood flows	Oxygen capacity
	cc. per liter	cc. per liter	liters per minute	cc. per liter
DECEMBER 22, 1938*				
DUCTUS ARTERIOSUS PATENT				
Aorta†.....	176.9			195.8
Pulmonary artery at hilus of lung.....	169.3	7.6	25.0 (Pulmonary blood flow)	
Pulmonary artery after temporary occlusion of ductus.....	144.4	32.5	5.8 (Peripheral blood flow)	
Amount of shunt.....			19.2	
DUCTUS ARTERIOSUS LIGATED				
Aorta.....	176.9			195.8
Pulmonary artery.....	139.0	37.9	5.0 (Pulmonary or peripheral blood flow)	192.1

* Basal oxygen consumption = 190 cc. per minute.

† This sample obtained 16 minutes after the pulmonary sample; during this time there was no essential change in the general state of the patient.

TABLE XI

Other observations in Case 2 before and after ligation of the ductus arteriosus

Case 2 (M. F.)

Observations	Pre-operative	Post-operative 6 weeks	Post-operative 6 months
Weight, <i>kgm.</i>	42.83	42.64	46.40
Height, <i>cm.</i>	153.3	153.3	153.3
Arterial blood pressure, basal			
Right arm, <i>mm. Hg.</i>	122/54	104/70	114/64
Left arm, <i>mm. Hg.</i>	122/54	108/72	118/70
Arterial blood pressure, after exercise (1 minute at 100 steps per minute over stairs), <i>mm. Hg.</i>	154/40*	146/72	
Venous pressure, <i>mm. H₂O</i>	38	62	102
Circulation time, <i>seconds</i>	21.5-23.5	12.8	19.3
Arterial oxygen content, <i>cc. per liter</i>	169.3	185.3	
Arterial oxygen capacity, <i>cc. per liter</i>	178.0	195.5	
Arterial oxygen saturation, <i>per cent.</i>	95.1	94.8	
Total blood volume, <i>cc.</i>	3980	3280	3720
Plasma volume, <i>cc.</i>	2430	1980	2270
Red blood cell volume, <i>cc.</i>	1550	1300	1450
Hematocrit, <i>per cent.</i>	38.9	39.8	38.9
Vital capacity, <i>cc.</i>	2500	2200	1650
			2200†
Vital capacity after exercise, <i>cc.</i>	2200	2100	
Oxygen consumption, <i>cc. per minute</i>	192	185	190
	185	181	
	194	178	

* Sounds heard to zero.

† This determination of the vital capacity was made 12 months after operation.

TABLE XII

Observations on the blood flow in Case 3 before and after ligation of the ductus arteriosus

Case 3 (D. M.)

Source of blood	Oxygen content	Arterio-venous oxygen difference	Blood flows	Oxygen capacity
	cc. per liter	cc. per liter	liters per minute	cc. per liter
AUGUST 1, 1939*				
DUCTUS ARTERIOSUS PATENT				
1. Aorta.....	174.1	7.4	19.5 (Pulmonary blood flow)	186.9
2. Left pulmonary artery at hilus of lung.....	166.7			
DUCTUS ARTERIOSUS LIGATED				
3. Aorta.....	173.7	22.7	6.3 (Pulmonary or peripheral blood flow)	179.3
4. Pulmonary artery.....	151.0			

* Basal oxygen consumption = 144 cc. per minute.

TABLE XIII

Other observations in Case 3 before and after ligation of the ductus arteriosus

Case 3 (D. M.)

Observations	Preoperative	Post-operative 5 months
Weight, <i>kgm.</i>	25.88	30.00
Height, <i>cm.</i>	137.5	140.9
Arterial blood pressure, basal		
Right arm, <i>mm. Hg.</i>	70/40	90/66
Left arm, <i>mm. Hg.</i>	92/48	88/56
Arterial blood pressure, after exercise (1 minute at 100 steps per minute over stairs), <i>mm. Hg.</i>	108/40*	
Venous pressure, <i>mm. H₂O.</i>	unsatisfactory	
Circulation time, <i>seconds.</i>	17.6-19.8	
Total blood volume, <i>cc.</i>	2580	
Plasma volume, <i>cc.</i>	1655	
Red blood cell volume, <i>cc.</i>	925	
Hematocrit, <i>per cent.</i>	35.9	
Vital capacity, <i>cc.</i>	1600	1825
Vital capacity after exercise, <i>cc.</i>	1750	
Oxygen consumption, <i>cc. per minute.</i>	147	
	141	

* Sounds not heard to zero.

Case 3 (D. M.) was a delicate appearing, thin, undernourished girl of 11 years. She had led an unusually active life rather than one of limited activity. The heart was moderately enlarged to the left. A vigorous thrill of maximum intensity in diastole was felt in the second interspace. In this same area a loud, continuous murmur was heard. The physical examination was not otherwise remarkable.

On August 1, 1939, she was operated upon under cyclopropane anesthesia and the patent ductus arteriosus measuring 8 mm. in diameter was ligated. Unfortu-

nately, since a sample of mixed venous blood was not obtained, an estimation of the flow of blood through the periphery with the ductus open could not be made. The results of the studies are collected in Tables XII and XIII.

Case 4 (L. B.) was a girl of 15 years. For many years because of dyspnea she had been unable to run and play as strenuously as her friends. She was slender, small-boned, and short. Her fingers were long and hyper-extensible. The thorax was long, the respiratory excursions appeared limited and there was some precordial fullness. Vigorous pulsations could be seen in the suprasternal notch and in both supraclavicular spaces, especially on the right. The heart was moderately enlarged to the left and its action unusually forceful. In the second left interspace a thrill was felt, most marked in systole, but at times palpable throughout the cardiac cycle. There was a systolic murmur at the apex and a loud continuous murmur in the second left interspace. The peripheral arteries showed a collapsing type of pulsation and in the femoral region there was a loud pistol shot sound.

On October 22, 1939, she was operated upon under ether anesthesia and a large patent ductus measuring 8 mm. in diameter was ligated. The results of the studies of this patient are summarized in Tables XIV and XV. This patient died 9 days after operation and at post-mortem examination was found to have an extensive mediastinitis, pericarditis and left empyema. There had been erosion of the ligatures through the ductus and extensive hemorrhage into the pleural cavity. Staphylo-

TABLE XIV

Observations on the blood flow in Case 4 before and after ligation of the ductus arteriosus

Case 4 (L. B.)

Source of blood	Oxy- gen con- tent	Arterio- venous oxygen differ- ence	Blood flows
	cc. per liter	cc. per liter	liters per minute
OCTOBER 22, 1939*			
DUCTUS ARTERIOSUS PATENT			
1. Aorta.....	173.7	17.7	10.3 (Pulmonary blood flow)
2. Left pulmonary artery.....	156.0		
3. Pulmonary artery after temporary occlusion of ductus.....	120.5	53.2	3.4 (Peripheral blood flow)
Amount of shunt.....			6.9
DUCTUS ARTERIOSUS LIGATED			
4. Aorta.....	157.3	45.7	4.0 (Pulmonary or peripheral blood flow)
5. Pulmonary artery.....	111.6		

* Oxygen consumption = 183 cc. per minute.

TABLE XV

Other observations in Case 4 before ligation of the ductus arteriosus

(This patient died 9 days after the operation.)

Case 4 (L. B.)

Observations	Preoperative
Weight, <i>kgm.</i>	32.28
Height, <i>cm.</i>	147.1
Arterial blood pressure, basal	
Right arm, <i>mm. Hg.</i>	120/48
Left arm, <i>mm. Hg.</i>	132/30
Arterial blood pressure, after exercise (1½ minutes at 50 steps per minute over stairs), <i>mm. Hg.</i>	170/20*
Venous pressure, <i>mm. H₂O.</i>	38
Circulation time, <i>seconds.</i>	19
Arterial oxygen content, <i>cc. per liter.</i>	172.4
Arterial oxygen capacity, <i>cc. per liter.</i>	182.9
Arterial oxygen saturation, <i>per cent.</i>	94.2
Total blood volume, <i>cc.</i>	2870
Plasma volume, <i>cc.</i>	1650
Red blood cell volume, <i>cc.</i>	1220
Hematocrit, <i>per cent.</i>	42.7
Vital capacity, <i>cc.</i>	1300
Vital capacity after exercise, <i>cc.</i>	1300
Oxygen consumption, <i>cc. per minute.</i>	164
	170

* Sounds heard to zero.

coccus aureus was cultured from the blood before and after death.

Case 5 (D. S.) was a small but normally developed girl of 6 years. There were no symptoms of cardiac disability. Her physical examination was not remarkable except for the usual continuous murmur and thrill in the second left interspace and a soft systolic murmur at the apex.

On December 18, 1939, she was operated upon under cyclopropane. A patent ductus arteriosus 7 mm. in diameter was ligated. The results of the studies of this patient are presented in Tables XVI and XVII.

Case 6 (M. S.) was a young woman of 26 years of somewhat limited mental capacity. She had always had dyspnea and easy fatigue on exertion and was unable to lie flat without respiratory discomfort. She appeared ruddy and healthy. Both little fingers were deformed; the right showed contracture and the left lacked a terminal phalanx. The heart was enlarged to the left. There was an apical systolic murmur and a continuous murmur in the second left interspace which was accompanied by a thrill. The pulmonary second sound was accentuated. In the supine position, the facies became suffused but no remarkable distention of the jugular veins occurred.

She was operated upon on December 22, 1939, under ether anesthesia. The ductus measuring 8 mm. in diameter was ligated. The results of studies of this patient are set forth in Tables XVIII and XIX.

DISCUSSION OF OBSERVATIONS ON PATIENTS

In these six patients the diagnosis of patency of the ductus arteriosus was confirmed at the operation. In each the patent ductus arteriosus was the only demonstrable anomaly. It is to be emphasized that this is a group of patients selected for operation on the basis of impressive signs or symptoms. Therefore, these ducti (which measured from 7 to 9 mm. in diameter) were presumably larger than many that are recognized.

The discussion of the observations on these six patients will, for convenience, be taken up in two

TABLE XVI

Observations on the blood flow in Case 5 before and after ligation of the ductus arteriosus

Case 5 (D. S.)

Source of blood	Oxygen content	Arterio-venous oxygen difference	Blood flows	Oxygen capacity
	<i>cc. per liter</i>	<i>cc. per liter</i>	<i>liters per minute</i>	<i>cc. per liter</i>

DECEMBER 18, 1939*
DUCTUS ARTERIOSUS PATENT

1. Aorta.....	157.9			171.6
2. Left pulmonary artery at hilus of lung.....	145.6	12.3	8.7 (Pulmonary blood flow)	
3. Pulmonary artery after temporary occlusion of ductus..	135.6	22.3	4.8 (Peripheral blood flow)	
Amount of shunt.....			3.9	

DUCTUS ARTERIOSUS LIGATED

4. Aorta.....	159.8			170.9
5. Pulmonary artery.....	127.6	32.2	3.3 (Pulmonary or peripheral blood flow)	

* Basal oxygen consumption = 107 cc. per minute.

TABLE XVII

Other observations in Case 5 before ligation of the ductus arteriosus

(Postoperative observations were not possible.)

Case 5 (D. S.)

Observations	Preoperative
Weight, <i>kgm.</i>	15.55
Height, <i>cm.</i>	101.5
Arterial blood pressure, basal	
Right arm, <i>mm. Hg.</i>	98/40
Left arm, <i>mm. Hg.</i>	114/58
Oxygen consumption, <i>cc. per minute.</i>	107

TABLE XVIII

Observations on the blood flow in Case 6 before and after ligation of the ductus arteriosus

Case 6 (M. S.)

Source of blood	Oxygen content	Arterio-venous oxygen difference	Blood flows	Oxygen capacity
	cc. per liter	cc. per liter	liters per minute	cc. per liter
DECEMBER 22, 1939*				
DUCTUS ARTERIOSUS PATENT				
1. Aorta.....	174.8	10.8	14.1 (Pulmonary blood flow)	177.0
2. Left pulmonary artery.....	164.0			
3. Pulmonary artery after temporary occlusion of ductus.....	149.3	25.5	6.0 (Peripheral blood flow)	
Amount of shunt.....			8.1	
DUCTUS ARTERIOSUS LIGATED				
4. Aorta.....	173.7	24.3	6.3 (Pulmonary or peripheral blood flow)	
5. Pulmonary artery.....	149.4			

* Oxygen consumption = 153 cc. per minute.

TABLE XIX

Other observations in Case 6 before and after ligation of the ductus arteriosus

Case 6 (M. S.)

Observations	Preoperative	Post-operative 1 month
Weight, <i>kgm.</i>	52.20	54.45
Height, <i>cm.</i>	154.6	
Arterial blood pressure, basal		
Right arm, <i>mm. Hg.</i>	128/66	115/80
Left arm, <i>mm. Hg.</i>	118/62	
Arterial blood pressure, after exercise.....	unsatisfactory	
Venous pressure, <i>mm. H₂O</i>	101	82
Circulation time, <i>seconds</i>	13.8-15.0	11.6
Arterial oxygen content, <i>cc. per liter</i>	161.4	
Arterial oxygen capacity, <i>cc. per liter</i>	171.2	
Arterial oxygen saturation, <i>per cent</i>	94.2	
Total blood volume, <i>cc.</i>	4130	3720
Plasma volume, <i>cc.</i>	2520	2260
Red blood cell volume, <i>cc.</i>	1610	1460
Hematocrit, <i>per cent</i>	38.9	39.0
Vital capacity, <i>cc.</i>	2700	2300

parts: The first part (A) deals with the direction and volume of the flow through the ductus and with the output of the two ventricles. The second part (B) deals with a variety of other measurements made before and after ligation of the ductus.

A. Observations concerning blood flow

The patients were not in a basal state when the observations on pulmonary and peripheral blood

flow were made. They were anesthetized, the chest was opened, and the respiration carried on under positive pressure. It is known that the output of the heart may be altered by various anesthetic agents. Regarding ether, Blalock (18) has studied the problem in dogs by one method and Snyder (19) in humans by another. It appears that at moderate levels of surgical anesthesia, there is an increase in the cardiac output while, at deeper levels an actual decrease may occur. Robbins and Baxter (20) have demonstrated that when cyclopropane is used, the cardiac output is increased as much as 45 to 50 per cent under conditions of surgical anesthesia. These increases are presumably related to dilatation of the peripheral vascular bed and are not due to a large increase in the oxygen consumption. In two cases in which the oxygen consumption during ether anesthesia was determined at the time of operation, it was not significantly different from that observed under standard conditions. When cyclopropane was used, a determination of the oxygen consumption under anesthesia was not made. However, it was shown by Robbins and Baxter (20) that, in dogs, the amount of oxygen used under basal conditions and under cyclopropane anesthesia does not differ by a significant amount.

The anesthetic agents used in the dog experiments, according to the available information (21), do not increase the cardiac output and may decrease it. This difference is to be kept in mind when comparing the observations in dogs with those in patients.

The analyses of blood from the aorta and the pulmonary artery in these patients offer the first direct demonstration of the direction of the flow of blood through the patent ductus, a point hitherto the subject of many assumptions. In these patients the blood in the pulmonary artery contains more oxygen than the blood in the right ventricle; therefore, arterial blood must enter the pulmonary artery by way of the ductus. Moreover, the oxygen saturation of femoral artery blood (shown in Tables X, XIV and XVIII to be from 94.2 to 95.1 per cent) indicates that there is no significant flow of venous blood in the reverse direction. This, of course, explains the absence of cyanosis

in patients whose only lesion is a patent ductus arteriosus.⁵

Are there any circumstances under which the flow will be from pulmonary artery to aorta? The obvious answer is that such flow will occur when the pressure in the pulmonary artery exceeds that in the aorta. The resistance necessary for the development of such an elevated pulmonary pressure will usually be back pressure from a failing left ventricle, or may occasionally be some form of pulmonary vascular disease. Obviously, this resistance must be *distal* to the origin of the ductus if it is to cause a flow of mixed venous blood through it.⁶

TABLE XX

The blood flows of six patients before and after the ligation of the patent ductus arteriosus

(The blank spaces indicate that certain samples of blood either were not obtained or were technically not acceptable.)

Patient number	Blood flow before ligation		Volume of shunt	Percentage of left ventricular output shunted through ductus	Peripheral and pulmonary blood flow after ligation
	Peripheral	Pulmonary			
	<i>liters per minute</i>	<i>liters per minute</i>	<i>liters per minute</i>		<i>liters per minute</i>
1	4.9				6.2
2	5.9	25.4	19.5	77	5.1
3		19.1			6.2
4	3.4				4.0
5	4.8	8.7	3.9	45	3.3
6	6.0	14.1	8.1	57	6.3

The volume of the flow is quite as interesting as the direction and much more unexpected. Table XX summarizes the essential measure-

⁵ A contrary view has been expressed by Koza and Mělka (22) who found an arterial saturation of 84 per cent in one patient who was said to exhibit the classical signs of patent ductus arteriosus.

⁶ Holman (23) has assumed that the propulsive force exerted by a hypertrophied right ventricle can produce a blood pressure in the pulmonary artery greater than the pressure produced in the aorta by a less well-developed left ventricle. The experiments of Levy and Blalock (16), and those reported in the early part of this paper, show that even when a powerful left ventricle is pumping large volumes of blood into the pulmonary artery, the pressure in the pulmonary artery does not rise to anything like that in the aorta. The obvious explanation is that the resistance in the lung is much less than in the periphery.

ments.⁷ In the patients studied, from 4 to 19 liters of blood per minute are found to be flowing

⁷ Certain possibilities of error exist which may affect the results in any given case. Ideally, blood samples to be used in the calculation of cardiac output should be drawn simultaneously. Under the conditions of operation this is not practicable, but with one exception (Table X) the samples in each patient were obtained within a few minutes of one another. The errors attributable to inadequate mixing of the two currents of blood in the pulmonary artery are presumably met by taking this sample from near the pulmonary hilus where our observations on animals indicate that mixture has occurred.

In the observations on humans, "mixed venous blood," when the ductus was open, was obtained by a method already described.⁴ This method, while not absolute, has been shown in the dog experiments to offer an acceptable approximation.

There is also the occasional occurrence of a ductus which enters the left branch of the pulmonary artery, a point already considered in the observations on animals. These various sources of error have been recognized and attempts have been made to eliminate them. It is believed that the general order of figures is essentially correct. This conclusion is borne out by the similarity in the measurements in humans and dogs and by the impressive diminution in the cardiac excursion with occlusion of the ductus, as shown both by direct observation at the operating table and by comparison of x-ray kymograms made before and after operation.

In Case 2 the pulmonary flow of 25.4 liters per minute approaches the volume considered by Bainbridge (24) to represent the upper limit of cardiac capacity. It should be noted that this volume was observed during operation and that this patient exhibited the most severe symptoms—the largest heart, the greatest amplitude of cardiac excursion and the largest ductus.

Another point already obvious to those who have worked with cardiac output is that the smaller the arteriovenous difference the greater the effect of analytical errors. Thus, if the oxygen consumption is 200 cc. per minute, and the arteriovenous oxygen difference is 50 cc. per liter, the cardiac output will be 4 liters per minute. If the arteriovenous difference changes from 50 cc. to 52 cc., the calculated cardiac output will become 3.8 liters, an inconsiderable change. However, if the oxygen consumption is 200 cc. and the arteriovenous difference is 10 cc. per liter, the calculated output will be 20 liters per minute. At this level if the arteriovenous difference changes from 10 to 12, i.e. by 2 cc. per liter, the calculated output will become 16.6 liters, a major change. Thus, when large outputs are calculated, such as those which are reported in Case 2, they are bound to have a greater error than when the arteriovenous difference is larger. This criticism does not affect the general significance of our results, but does mean that figures at this level of output are less precise than those obtained at lower levels.

from the high pressure area in the aorta to the relatively low pressure area in the pulmonary artery. These volumes constitute 45 to 75 per cent of all the blood entering the aorta from the left ventricle. This arterial blood flows through the ductus to the pulmonary artery and via the lungs back to the left ventricle without having passed through the peripheral circulation and through the right ventricle.

The cardiac output is increased by the circumstances under which the observations were made. This is shown by the fact that the cardiac output, after ligation of the ductus (Table XX), was above the basal level in every patient. In several patients it was as much as 100 per cent above the calculated basal values. The figures for the output were obtained by the reliable direct Fick method immediately after ligation without the complications of mixing and timing which exist when the ductus is open. These are the figures which are to be compared with the figures for pulmonary and peripheral blood flow when the ductus is open.

The total flow through the lungs in these patients was from 10 to 25 liters per minute. This flow represents the output of the right ventricle plus that part of the output of the left which is shunted through the ductus. Since the lungs, and consequently the left ventricle, have these two sources of blood, and the right ventricle only one (*i.e.*, the periphery), there is a difference in the output of the two ventricles. These inequalities in their output must affect the work performed by the two ventricles. In the patients studied, the left ventricle was putting out at the time of the observations from two to four times the volume expelled by the right.

The work of the right ventricle is probably not greatly changed, since it is certainly not pumping more than the usual amount of blood and may often be pumping less. The pulmonary pressure against which this blood is pumped may be elevated to some degree in the presence of a patent ductus, but probably when the lungs are normal this increase is not great.

These speculations are in accord with the observation that right ventricular preponderance is seldom found after the age of infancy when a patent ductus arteriosus is the only congenital cardiac abnormality.

The marked increase in the output of the left ventricle implies an increase in work unless there is a corresponding diminution in the mean aortic blood pressure. This mean pressure is somewhat lowered in these patients but not sufficiently to prevent a considerable increase in the work of the ventricle. This work may be further increased by still another factor; that is, the velocity imparted to the blood. This factor becomes increasingly important when dealing with such a large volume per minute as is put out by the left ventricle in these patients. Since these data are not at hand, it is not possible to make precise calculations of the work of the left ventricle. However, it is probably justifiable to conclude that the work of the left ventricle is considerably increased. This suggestion is borne out by the observation that, when heart failure occurs in these patients, it is usually predominantly left-sided failure, and by the fact that the x-ray film commonly shows a dilatation or hypertrophy of the left ventricle. Indeed, it is surprising that preponderance of the left ventricle is not more common in the electrocardiographic tracing than the observations of Schnitker (25) and ourselves have shown it to be. It appears that in these patients the response of the left ventricle to the demand for increased work is like the response in patients with arteriovenous fistula; that is, it is mainly a reversible dilatation and only ultimately does hypertrophy occur.

The observations on blood flow throw light on the problem of the adjustment of the circulation to the abnormal situation created by the patency of the ductus arteriosus. Theoretically, the diversion of a considerable volume of blood per minute from the aorta to the pulmonary artery may result in: (1) a diminution in the blood supply to the periphery, (2) an increase in the output of the left ventricle, or (3) a combination of the two.

Actually, in every patient and in every dog in which studies of the blood flow were made there was an increase in the output of the left ventricle. This increase, even in the presence of a large leak, was in some patients sufficient to maintain the peripheral flow at or near its normal level. In other patients, however, this compensation was not complete. The evidence for this is that the

peripheral flow increased in two patients when the ductus was ligated.

Examples of both types of adjustment are shown by the measurements of the blood flow in dog number 63-39 (Table IV). After the establishment of the artificial communication, the output of the left ventricle rose and the flow to the periphery fell. After 7 weeks during which there

tors, including the size of the ductus. In the patients reported, the ductus was 7 mm. or more in diameter and the changes in the circulation were severe. When the ductus is smaller, the changes are probably less severe and the required adjustments less extensive. Other factors as yet unknown may also affect the adjustment of the circulation to this lesion.

FIG. 5. ARTERIAL BLOOD PRESSURES IN CASE 2 UNDER VARYING CIRCUMSTANCES BEFORE AND AFTER LIGATION OF THE DUCTUS ARTERIOSUS

was an increase in the total blood volume, the output of the left ventricle was still 5.2 liters and the flow to the periphery had risen from 1.3 to 1.9; that is, it approached the control value of 2.3.

Thus, the patient with a large patent ductus arteriosus must either suffer a decrease in the blood supplied to the organs by the peripheral circulation or there must be extra work on the part of the left ventricle. This increase in work must limit the cardiac reserve and in the long run may be a factor in the onset of failure of the left ventricle.

The degree and kind of compensatory adjustment may be presumed to vary with many fac-

B. Other observations

Arterial blood pressure. Studies of the blood pressure in these six patients (some of whom have been reported by Gross and Hubbard (1) and by Gross (26)) show a low diastolic level and a wide pulse pressure (determined according to the standard procedure defined by the American Heart Association) as constant findings. This is in accordance with the observations of Bohn (27). The level of the diastolic pressure is comparable to that seen in patients in whom there is a leakage of blood from the arterial system by way of an arteriovenous fistula. In our six patients the initial low diastolic level was found to be still lower

after mild exercise. The exercise consisted of walking over steps at a rate of about 100 steps a minute for 1 minute, a degree of exertion which in normal people produces no change or even a slight rise in the diastolic pressure. Not only was there a fall in the diastolic pressure but also the arterial sounds were often heard to zero. Ligation of the ductus was followed by immediate and striking rise in the diastolic blood pressure. The changes are illustrated in Figure 5.

Venous blood pressure. This measurement by the direct method was made before and after operation in a few patients. No constant changes were observed and all the readings were within limits accepted as normal.

Circulation time. Before operation the circulation time was from 14 to 23.5 seconds. That is somewhat longer than the expected time in children. In the two cases in whom satisfactory measurements were made after operation it was shorter than before operation. In Case 2, in whom there was a partial recurrence of the leak, the circulation time was 21 to 23 seconds before operation, 13 seconds 6 weeks after operation, and 19 seconds 5 months later when recurrence had taken place. Since pulmonary congestion (increase in the amount of blood in the lungs) is of constant occurrence in these patients, it is probable that these suggestive changes in circulation time are to be explained on this basis.

Total blood volume. This measurement was made with the generous collaboration of Dr. Gibson. Satisfactory observations before and after ligation were obtained in two patients and in both of them the hematocrit reading remained essentially constant. In Case 2, the total blood volume was 3980 cc. before ligation, 3280 cc. 6 weeks after operation and 3720 cc. 6 months after operation when some recurrence of the leak had taken place. In Case 6 the total blood volume was 4130 cc. during the control period and 3720 cc. 1 month after ligation of the ductus. These observations are in accord with the rise in the total blood volume which was observed in dogs after establishment of an aortic-pulmonary artery fistula. The two patients in whom these changes in total blood volume were observed had symptoms which limited their activity and were considered to be in mild congestive heart failure.

Vital capacity. There were no constant changes

in this measurement, in spite of an impressive diminution in the x-ray signs of pulmonary congestion following ligation of the ductus. The absence of significant change may be related to the fact that many of the patients were children and all of them had some difficulty in vigorous chest movement for a considerable period after operation.

Nutrition and growth. The relation of the ligation of the ductus to the state of nutrition and to rate of growth has been discussed by Gross (26). For the sake of completeness the height and weight figures are included in our tables. These figures indicate that ligation of the ductus may be followed by accelerated growth and improved nutrition. These gains suggest that abolition of the shunt has permitted a larger amount of blood to be distributed to the periphery. Such enhanced peripheral flow was actually demonstrated in two patients.

In general, the circulatory measurements that have been made in patients emphasize the extent of circulatory changes and the severity of the burden imposed on the heart when the ductus is large. They support the viewpoint that ligation of the ductus may be indicated for the purpose of relieving the heart of an eventually disabling burden and they explain quite clearly the benefit which follows operation in patients with disability from diminished reserve or congestion.

SUMMARY

Studies of the circulation made on six patients before and after surgical closure of an uncomplicated patent ductus arteriosus show that:

1. When the ductus arteriosus is open the blood flow is from the aorta to the pulmonary artery.
2. There is no flow of blood from pulmonary artery to aorta. Therefore, these patients do not have arterial unsaturation and are not cyanotic.
3. The volume of blood flowing from aorta to pulmonary artery varied from 4 to 19 liters per minute, which is 45 to 75 per cent of all the blood pumped into the aorta by the left ventricle. These flows occurred in patients with large ducti and under temporary conditions which are known to elevate the output of the heart.
4. The left ventricle expelled from two to four times the volume of blood expelled by the right ventricle in a given period of time.

5. Adjustment of the circulation to the patent ductus may be made by an increase in the output of the left ventricle. If this is not sufficient to compensate completely for the leak through the ductus, there may be, in addition, a diminution in the blood flow to the periphery.

Comparable studies in dogs with an artificial aorta-pulmonary artery fistula showed similar circulatory adjustments.

Knowledge of the circulatory changes which occur with patency of the ductus permits a better understanding of the signs and symptoms associated with this condition. Furthermore, these studies of the circulation supply direct evidence of the beneficial effects of operative closure of the ductus in improving the peripheral circulation in some of the patients and in reducing the work of the heart in all of them.

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