THE PART PLAYED BY THE LUNGS IN THE OXIDATIVE PROCESSES OF THE BODY.

By C. LOVATT EVANS, D.Sc., and E. H. STARLING.

(*From the Institute of Physiology, University College.*)

In a series of four papers in the *Archives de Physiologie Normale et Pathologique*, Bohr and Henriques, in 1897, put forward evidence which they believed indicated that the seat of the oxidations was not confined to the tissues, but that a variable amount of the combustive processes were carried out in the lungs; according to them, the lungs receive from the tissues some metabolic products in an imperfectly oxidised condition, and the complete conversion of these bodies into the final end-products is only achieved in the lungs themselves, as these products are carried through them in the blood.

Bohr and Henriques based their view on the observation that the amount of carbon dioxide carried away from the lungs by the expired air was much greater than the amount of that gas which was carried to the lungs by the venous blood (2). Similar relations applied to the oxygen absorptions, the discrepancy amounting to from 0 to 66 % of the total amount. Of somewhat less importance, but yielding similar indications, were the facts that the respiratory quotients as determined in the air and blood simultaneously were different (4), and further that on occlusion of the aorta at the arch, so that the greater part of the body was served by the circulation of blood through small collaterals, the total respiratory exchange was not depressed so much as would be expected on the assumption that the oxidative changes were exclusively confined to the tissues (1). These results have been criticised by Zuntz and Hagemann (5) and by Loewy and Zuntz (6), who doubt whether the blood-samples collected really were representative ones. Some of the experiments of Bohr and Henriques have been repeated by Rulot and Cuvelier (7): quite recently Puetter (8) has attempted to prove from experiments on man that much of the oxidative processes may occur in the lungs: these

experiments have been criticised by Zuntz(9). These discussions turn chiefly on whether, in exercise, the heart is capable of supplying enough blood to allow of the transport to the tissues of an amount of oxygen equal to that actually absorbed from the lungs. The experiments of Bornstein(10) on man and of Knowlton and Starling(11) on animals indicate that the systolic output can be much increased with a rise of venous pressure, and Krogh and Lindhard(12), by the nitrous oxide modification of Bornstein's method, arrive at the same conclusion. Bohr(13) and Yandell Henderson and Barringer(14), are of the opinion that the output depends chiefly on the rate of the heart, and that the output per unit of time is not sufficiently increased during exercise to enable the tissues to obtain the required amount of oxygen.

Against the theory of Bohr and Henriques, little direct experimental criticism has been directed. It has indeed been said by Loewy (*Oppenheimer's Hdb. Biochem.* IV. (1st), p. 96) that such is at present not possible. In the first rank is the work of Morawitz(15) on the presence of reducing substances in the blood. He concludes that even in extreme asphyxia, such oxidations as occur are completed in the tissues themselves; he is unable to confirm the presence of substances which can be oxidised by contact with air, or by contact with living cells and air together.

In the experiments to be described here, we have studied the phenomena of oxidation by means of the heart-lung preparation made according to Starling's method(11), and also by the use of the isolated lung preparation. The methods employed in the determination of the gaseous exchange are similar to those used by Evans in a previous communication on the metabolism of the heart and lungs(17). In the course of the description of the experiments, we shall introduce some criticisms of the methods used by Bohr and Henriques.

THE METABOLISM OF THE LUNGS.

As pointed out by Barcroft(16), Bohr and Henriques did not make any allowance in their calculations for the metabolism of the lungs themselves, although, according to Bohr's views regarding the secretory nature of pulmonary activity, it might be considerable[1].

The experiments of Evans(17) indicate that the metabolism of the blood-perfused lung is not especially high, and that it amounts to about

[1] According to theoretical calculations by A. V. Hill (*Phys. Proc.* XXVII. 1913; this *Journal*, XLVI.) the amount need not be especially great.

1·0 c.c. of oxygen for the lung tissue corresponding to 1 grm. of heart[1]. As, however, we wished to take the normal metabolism of the lungs as our starting point, we have somewhat modified the perfusion apparatus used by Evans, and have thus been enabled to make longer series of determinations and to use a much smaller volume of blood, thus eliminating the chief source of error in the experiments. By this method we have also succeeded in diminishing the tendency to pulmonary œdema which so often occurred with the earlier form of the apparatus[2].

Method. The apparatus employed is illustrated in Fig. 1. *M* is a reservoir for the defibrinated and hirudinised blood: this is drawn out along the tube *N* and pumped into *B*, which is a bubble-trap, by means of the rubber syringe (a small antrum syringe of about 50 c.c. capacity). The syringe is rhythmically compressed by means of an eccentric cam treadle worked by a small motor. We shall refer to this syringe as the "artificial heart." The tube *H*, with the screw-clip *K*, serves as a bye-pass, by means of which the flow along *D* may be controlled. The side-tube *C* leads to a manometer by which the pressure may be determined. The cannula *E* is introduced into the pulmonary artery, and the temperature of the ingoing blood is indicated by the thermometer *T*; the temperature can be regulated by placing *M* in a water-bath at any required temperature. The large cannula *F* is tied firmly into the left auricle and thus the blood returns to the reservoir. We find that it is not necessary to exclude air from the blood in *M*, since the surface of the blood is practically stationary, and since, moreover, the tensions of the blood gases are not widely different from those in the air.

The pressure in the pulmonary artery as recorded by the manometer connected with the side-tube *C* was from 15 to 25 mm. in "systole" and was usually zero in diastole.

With this apparatus, we have found that the metabolism was of about the same order as was found in the previous work. The following experiments are typical (cf. Table I, p. 416).

The higher initial respiratory quotients are due to the fact that the blood is not in complete equilibrium with the air which is circulating in

[1] We find that it is of no value to weigh the lungs at the end of an experiment, since there is always more or less œdema after some hours. The weight of the heart is therefore recorded instead of that of the lungs: usually in dogs the lungs are about 80 to 95 % of the weight of the heart.

[2] The superiority of the perfusion apparatus employed here over the one used in the previous experiments is also seen from the fact that we have in no case encountered the annoying cessation of flow of blood which was so often met with in the use of the former apparatus.

TABLE I. *Lung metabolism in dog.*

Exp. 1. Weight of heart—51 grams. Pressure in manometer—4 (diastole) to 24 (systole) mm. Rate of artificial heart—46 per min. Temp. 36° C. Blood circulated for 1 hour before commencing the determinations.

Period (hours)	Rate of perfusion per min. (c.c.)	Per hour			Per gram heart per hour	
		O_2	CO_2	R.Q.	O_2	CO_2
1	250	49·7	46·5	·93	·98	·91
1	242	45·5	39·0	·86	·89	·77
1	231	48·1	39·0	·81	·94	·77
½	230	45·3	37·0	·82	·89	·73
Exp. 2.	Heart 111·5 grams.					
½	163	95·0	84·0	·88	·86	·75
½	150	90·0	70·0	·78	·81	·63
Exp. 3.	Heart 76 grams.					
½	106	63·4	51·0	·8	·83	·67
Exp. 4.	Heart 41·5 grams.	"Artificial heart" 103 per min.				
½	250	56·6	70·0	1·24	1·4	1·68
½	250	56·0	57·0	1·0	1·3	1·40
½	250	52·0	50·0	·96	1·2	1·20
½	250	56·0	50·0	·89	1·3	1·20
Exp. 5.	Heart 76 grams.					
½	176	73·0	69·0	·90	·96	·91
Exp. 6.	Heart 51·5 grams.					
½	220	46·0	44·0	·96	·89	·85
½	220	46·2	38·2	·83	·89	·74
Exp. 7.	Heart 65 grams.	"Artificial heart" 130 per min.				
½	300	61·8	55·0	·89	·95	·85
½	300	64·0	53·0	·83	·97	·82
½	300	61·4	—	—	·95	—
				Mean of all exps.	1·00	0·94

Mean R. Q. = 0·94.

and out of the lungs. This is indicated by the fact that the oxygen maintains a fairly steady value throughout the whole period, and it is for this reason that we attach more weight to the determination of the oxygen than to that of the carbon dioxide. The washing out of carbon dioxide is seen very clearly in cases where freshly defibrinated blood is added to the blood in the circuit of the apparatus, as in the following experiment: the determinations of the amounts of carbon dioxide in the blood show clearly that we are dealing with such an effect, and not to processes of scission of unstable organic compounds with the production of carbon dioxide, as was thought to be the case by Bohr and Henriques.

Exp. 8. Dog 4·62 kg. Heart 30·2 grams.

Time	Temp.	c.c. CO_2 per hour	% CO_2 in blood	
12.17 to 12.47	35·0	35·6	16·2	
12.53 to 1.23	34·5	90·0	25·6	100 c.c. fresh blood
1.35 to 2.05	34·0	34·0	—	added at 1 p.m.
2.08 to 2.38	35·0	40·8	15·0	

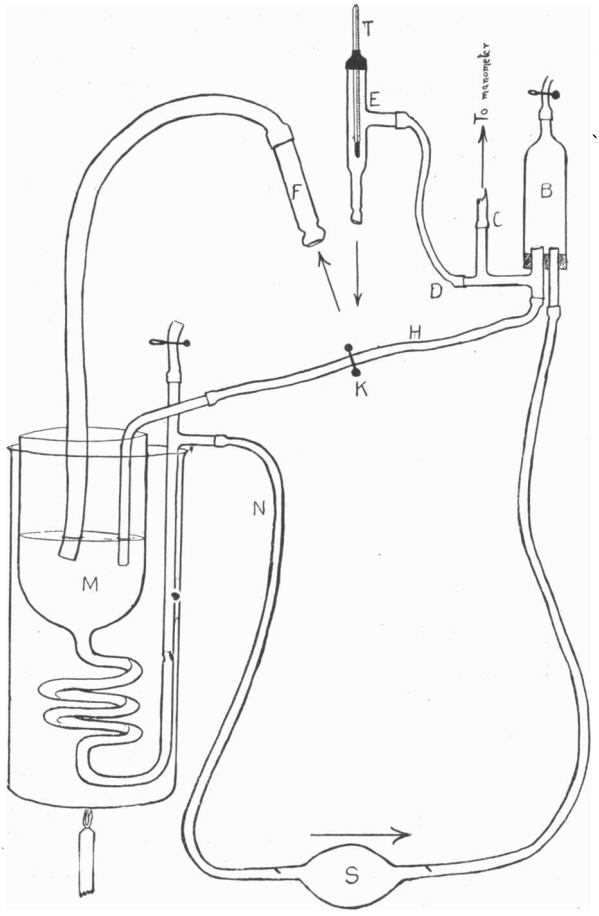

Fig. 1.

Usually we have kept up the artificial respiration for about half an hour before commencing the determinations; this was in order to remove most of the CO_2 from the blood. In some cases, this was not done; the results of such an experiment are given here, since they illustrate the same fact as experiment 8.

Exp. 9. Cat 2·55 kg. Heart 13·0 grams[1].

Time	Temp.	c.c. CO_2 per hour	% CO_2 in blood
2.39 to 3.09	35·3	65·4	12·1
3.13 to 3.28	34·5	44·8	—
3.30 to 3.45	34·0	16·4	—
3.47 to 4.02	34·2	17·6	—
4.04 to 4.19	34·3	16·8	8·7

Consideration of these results indicates, therefore, that there was no appreciable error introduced into the experiments of Bohr and Henriques by their having neglected the metabolism of the lungs.

The distribution of the blood in the coronary vessels.

There can be little doubt that the "factor of irrigation" which Bohr and Henriques used in calculating the flow of blood through the heart in their experiments was much too low; by the use of their factor the calculated flow was about 10 to 12 % of the amount passing along the aorta, and was deduced from the weight of the heart, which, however, is not given in their protocols. They allowed from 8 to 19 % of the weight of the heart as the volume of blood passing along the coronary arteries per minute. From recent experiments by Markwalder and Starling, we have learned that the amount is considerably more than this, and some of the experiments to be described here will serve to illustrate this point.

When we first started to study the coronary circulation in the heart-lung preparation, which we did by means of the cannula used by Morawitz and Zahn(18) for introduction into the coronary sinus, it soon became evident to us that this cannula did not drain off all the blood of the coronary circulation; in other words, the veins which do not open into the coronary sinus carry a good deal of blood into the right auricle. These veins are the posterior cardiac vein, the veins of Thebesius, and some small veins which open into the walls of the auricle, but which are not easily visible to the naked eye. It was therefore necessary to obtain some idea of the contribution of these veins to the total coronary flow, before we could draw any conclusions from experiments with the coronary cannula. The following method was employed for this purpose.

A heart-lung preparation was made from a dog of about 12 kg. in the usual manner: this preparation we may call the feeder (Fig. 2, *F*). Another smaller dog was now taken, and anæsthetised, and the chest

[1] In the cat the lungs are usually not less than 150 % of the weight of the heart. The values of CO_2 per gram of lung per hour are therefore similar to those in the dog.

opened: a cannula (*A*) was tied tightly in the aorta, directed towards the heart, as in the well-known perfusion method of Heymanns and Kochmann(19). This cannula was then connected with a side-tube from the arterial tube of the feeder, so that blood from the feeder could be passed at normal arterial pressure through the coronary arteries of the second or subject heart (*S*). After passing through the coronary vessels this blood flows from the right ventricle, so that if we ligature

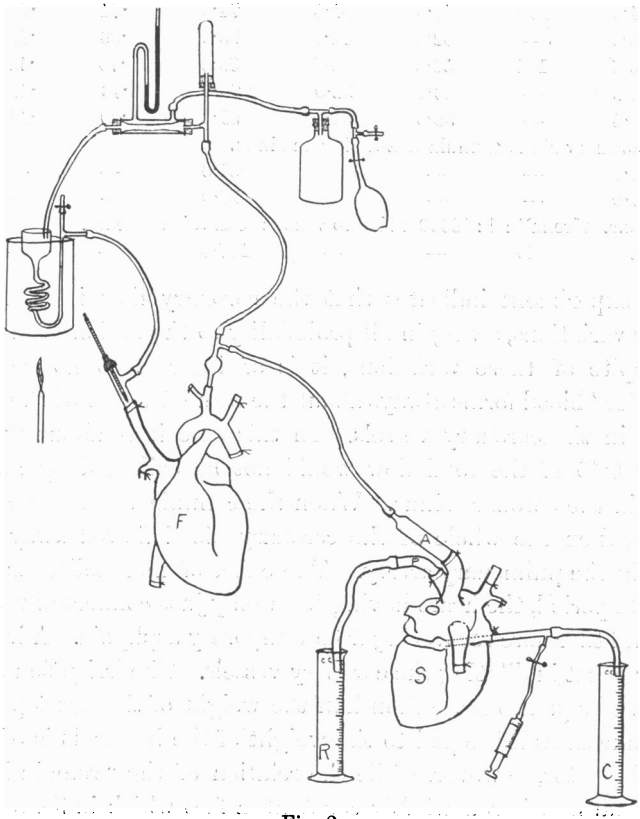

Fig. 2.

all the other vessels on the right side of the subject heart, and introduce a cannula (*P*) into the pulmonary artery, the coronary blood will emerge from this cannula and can be measured. The cannula was then introduced into the coronary sinus in the usual way, and the coronary flow observed; the blood which now issues from the pulmonary artery represents that which has passed by means of veins which do not open into the coronary sinus: this has been called the "remainder."

The details of some experiments are given below:

EXP. 10. Weight of subject heart 139 grams. Arterial pressure of feeder 75 mm.

Time	Temp. of blood	Rate of beat of subject heart	Flow c.c. per min. Coronary sinus (S)	Remainder from pulm. art. (R)	Total $[R+S]$	R/S	$R/R+S$	Irrigation coefficient %
1.5	31·5	—	66·5	73·0	139·5	1·1	·53	100
1.9	31·5	—	Venous pressure raised in feed heart to increase output.					
1.12	32·0	120	51·0	49·5	100·5	·96	·49	72
1.20	34·0	105	42·5	31·5	74·0	·74	·42	53
1.22	33·5	—	52·5	41·0	93·5	·80	·44	67
1.25	35·5	114	56·5	42·5	99·0	·75	·43	72
1.30	36·2	—	43·5	32·0	75·5	·73	·42	55
1.33	36·4	—	38·5	31·0	69·5	·80	·45	50
1.38	Coronary sinus cannula removed from sinus.							
1.39	36·7	—	—	—	61·0	—	—	44
1.40	37·0	—	—	—	77·0	—	—	56
1.45	1 c.c. adrenalin 1 : 10000 added to venous reservoir of feeder.							
1.46	36·3	245	—	—	117·0	—	—	84

This experiment indicates that the coronary flow is liable to considerable variations, owing in all probability to the action of metabolites. But in spite of these variations, it is of interest to notice that the "remainder" blood forms always about the same fraction of the total flow of blood in the coronary vessels. In this case it is about 0·45, *i.e.* as much as 0·45 of the total flow would not be collected by means of a cannula in the coronary sinus. When the cannula was taken away from the sinus, then the whole of the coronary blood flowed away from the cannula in the pulmonary artery. The effect of metabolites is well seen in the first period, the heart having been only just connected up with the feeder, and therefore recovering from temporary asphyxia. Adrenalin has the same effect in dilating the coronary vessels. The irrigation coefficient is seen to be equal to more than half the weight of the heart per minute, and in some cases it is equal to the weight of the heart; it is of necessity a variable factor, however, while the relation of the "remainder" blood to the total flow is remarkably constant, a fact which indicates that the "remainder" blood cannot be regarded as due to a leak away of blood around an imperfectly fitting coronary cannula.

The next experiment was made in the same manner.

The influence of asphyxia on the coronary flow is especially interesting and agrees well with the results of Markwalder and Starling. In spite of the very great increase in the flow of blood in the coronary vessels, the value $R/R+S$ remains constant, showing very conclusively that we are dealing with a true accessory circulation and not with

Exp. 11. Subject heart 48 grams. Blood-pressure of feeder 80 mm. Hg.

Time	Temp.	Pulse	*S*	*R*	*S*+*R*	*R*/*S*	*R*/*R*+*S*	Irrigation coefficient
2.55	34·0	—	21·4	11·9	33·3	·56	·36	69
2.58	34·8	—	20·7	11·9	32·6	·57	·37	68
3.04	36·0	—	23·5	11·9	35·4	·51	·34	73
3.06	36·4	133	21·3	—	—	—	—	—
3.10	1 c.c. adrenalin 1 : 10000 added to blood of feeder.							
3.12	36·4	213	34·5	21·6	56·1	·62	·38	117
3.14	—	196	45·5	23·2	68·7	·51	·34	140
3.17	36·0	187	36·6	23·3	59·9	·64	·39	123
3.18	Artificial respiration of feeder stopped to induce asphyxia.							
3.20	35·5	162	34·5	21·5	56·0	·62	·38	117
3.22	36·0	150	37·0	24·3	61·3	·66	·40	127
3.24	36·0	154	43·7	28·3	72·0	·65	·39	150
3.27	36·0	158	89·5	60·0	149·5	·67	·40	302
3.28	35·7	150	111·0	66·5	177·5	·60	·37	370
3.29	Feeder beginning to fail.							

a side leak in the coronary cannula, in which case the amount would remain constant, so that the ratio would be disturbed. Here again the "remainder" blood contributes about 0·4 of the total coronary flow.

The high value of the irrigation coefficient is remarkable, especially in asphyxia: since Bohr and Henriques certainly were dealing with a condition in which there was more or less asphyxia, it is evident that their coefficients were much too low: even under conditions where the heart is supplied with very well arterialised blood, the coefficient is quite high. The next experiment gives similar results, but the flow is smaller owing to the fact that the pressure of the "feeder" is less than in the previous cases.

Exp. 12. Weight of subject heart 49 grams. Pressure on arterial side of feeder 65 mm. Hg.

Time	Temp.	Pulse	*S*	*R*	*S*+*R*	*R*/*S*	*R*/*R*+*S*	Irrigation coefficient
12.03	37·0	109	22·6	10·1	32·7	·45	·31	50
12.06	37·5	115	23·6	9·7	33·3	·41	·29	51
12.16	1 c.c. adrenalin in 1 : 10000 added to blood in reservoir.							
12.18	37·0	187	35·7	23·8	59·5	·67	·40	92
12.20	37·0	200	45·8	29·3	75·1	·64	·39	116

In another case the total coronary flow was determined by merely connecting the two hearts up in the usual manner, but without introducing the coronary sinus cannula.

Exp. 13. Total coronary flow. Dog heart weight 53 grams.

Time	Temp.	Total flow c.c. p. min.
11.55	33·0	81·0
12.00	33·0	77·0
12.14	37·0	34·0
12.16	37·0	32·0
12.20	37·5	30·5

We may assume, therefore, that the "remainder" blood forms about 0·4 of the total coronary flow, and that in all probability the coefficient of irrigation is somewhere of the order of 50%; we would not lay too much stress on the latter figure, but would merely indicate that it is of this order and subject to considerable variations according to the amount of venosity of the blood with which it is supplied, and to a considerable extent according also to the temperature of the blood. There can be no doubt, however, that the results can be considered to represent a closer approach to normal values than those determined, for example, by Bohr and Henriques(20), in which the hearts only beat for a few minutes (from one to four).

The hearts in the present case beat well for a number of hours, as was the case also in the similar preparations used by Barcroft and Dixon(21).

The respiratory exchanges of the heart.

If we determine the gaseous exchanges of the heart-lung preparation by the air circulation as used by Evans (*loc. cit.*), fairly constant values are obtained when we calculate the gaseous exchange per gram of heart per hour. If now, the tissue of the heart is the seat of the oxidations we should obtain the same values by means of an analysis of the arterial and coronary blood, by Barcroft's method, as was done by Barcroft and Dixon(21). This we have attempted to do. Since the metabolism of the lungs is so constant for a given weight of heart, the external exchanges in the expired air can readily be corrected for the lung metabolism. As regards the blood-gas analyses, two methods have been used. We can perfuse the heart by Heymans and Kochmann's method, and measure and analyse the coronary blood, in exactly the same way as was done by Barcroft and Dixon: or, we can draw off the coronary blood by means of the Morawitz cannula, and analyse it. In the latter case, we must allow for the "remainder" blood from the data already deduced, in order to ascertain the amount of the coronary flow. It might be objected that in doing this, we make the unwarranted assumption that the "remainder" blood has the same composition as the coronary sinus blood, but the results of differential blood-gas analyses by Barcroft's method indicate that there is not any very great difference. A compensatory advantage is that by this method the heart is filled and contracting under normal arterial pressure, whereas in the blood-perfused heart the ventricles are empty.

In the two tables given below, the results of such experiments are given: the first table gives the "*external respiration*" of the hearts, *i.e.* the coefficients in c.c. of oxygen per gram of heart per hour, after due correction for the lung metabolism. In the second table we have the results of direct determinations by blood-gas analyses, these are called the "*internal respiration*" coefficients.

In the case where these have been determined by the analysis of blood drawn from the coronary sinus by means of the Morawitz cannula, the metabolism as deduced from the rate and composition of the sinus blood has been multiplied by the factor 1·67 in order to allow for the blood not included in the flow from the sinus, as mentioned in the last section (the factor is obtained from the ratio 0·6 : 1 : 1 : 1·67).

The results obtained by this method are if anything lower than those found by the perfusion method in which the whole coronary blood was collected and analysed, which indicate that the factor of 1·67 is by no means too high.

TABLE II. *External respiration of dog's heart.*

Weight of heart, grams	Temp.	No. of periods	c.c. of O_2 per grm. heart per hour	Weight of heart, grams	Temp.	No. of periods	c.c. of O_2 per grm. heart per hour
41·0	36·0	3	1·90	56·0	36·0	4	2·55
47·5	36·0	5	2·15	41·0	36·0	3	2·05
76·0	36·0	3	1·10	58·5	36·0	5	2·93
52·6	36·0	5	4·17	89·5	36·0	2	2·40
64·5	36·0	4	2·88	52·0	36·0	4	4·30
37·5	36·0	4	4·30	57·0	36·0	2	3·03
57·5	36·0	1	3·50	41·0	36·0	2	3·15
39·5	36·0	1	4·00	57·0	36·0	2	2·90
33·0	36·0	2	3·55	55·0	36·0	3	2·20
50·5	36·0	3	2·60				
		Mean =	3·015			Mean =	2·85

Maximum = 4·30. Minimum = 1·10.

We may therefore take as the coefficient of external respiration of the dog's heart about 2·9 c.c. of oxygen. The values in the above table vary considerably according to the temperature and to the amount of work which the hearts are performing. There is also perhaps some relation between the weight of the heart and the activity of the gaseous interchange. The minimum figure is 1·1 and the maximum is 4·30.

TABLE III. *Internal respiration of dog's heart.*

Weight of heart	Temp.	Coronary flow, c.c. per min.	Diff. in O_2 per c.c. of blood	c.c. O_2 per grm. heart per hour	
67	35·2	25·4	·061	2·31	Cannula in coronary sinus.
67	35·0	24·2	·061	2·31	
126	35·0	40·5	·097	3·12	
126	35·0	62·5	·057	2·85	Cannula in coronary sinus.
126	35·0	57·5	·057	2·62	
126	35·5	83·0	·133	8·80	After adrenalin.
41	36·1	14·5	·082	2·91	Cannula in coronary sinus.
41	37·1	20·0	·029	1·44	
97	36·3	33·6	·060	2·07	
97	35·0	120·0	·014	1·74	Cannula in coronary sinus.
108	39·0	19·6	·134	2·43	Cannula in coronary sinus.
108	36·0	35·8	·065	2·17	
108	35·9	96·0	·035	3·12	
139	35·5	56·5	·085	2·08	Total coronary blood collected by the perfusion method. (Heart empty.)
49	37·0	33·3	·076	3·10	Total coronary blood collected by the perfusion method. (Heart empty.)
49	37·0	75·1	·077	7·00	After adrenalin.

These results are of the same order as those obtained in the more extended observations on the external respiration of the heart. The mean value, exclusive of the periods in which adrenalin was given, is 2·43, which is sufficiently near to the value obtained in the last series of experiments, when we consider that the total coronary flow is in these experiments only approximately known. Had the lungs participated in the combustion processes, we should have expected a larger margin.

In order, however, to exclude the variations involved by these experiments in which different hearts are employed, we have attempted to determine in the same heart at as nearly as possible the same time, the oxygen usages by both methods. In carrying out these experiments, the heart-lung preparation was connected up with the respiration apparatus in the usual way, and the cannula introduced into the coronary sinus; the tube leading from this cannula was connected to the side-tube leading from the venous reservoir to the right auricle, so that the coronary sinus blood was led back into the right side of the heart, but so that samples of it could be taken at intervals for analysis (Fig. 3). The results of the two series were then compared. The

metabolism as determined from the sinus blood was multiplied by 1·67 as before, while the allowance for the metabolism of the lungs was made, in the case of the external metabolism, in the usual way. In the following table the values are expressed as before, as the volume of oxygen in cubic centimetres per gram of heart per hour. These figures are given in the last two columns.

TABLE IV. *Simultaneous determinations of "internal" and "external" respiration of heart of dog.*

EXP. 14. Heart 97 grams. Blood analyses by the differential method.

Temp.	Coronary flow, c.c. per min.	Diff. in O_2 per c.c. of blood	O_2 by coronary sinus per hour	O_2 by heart and lungs per hour	c.c. of O_2 per gram of heart per hour corrected: By blood (internal)	By air (external)	
36·3	33·6	·060	200	210	2·07	1·16	
35·0	120·0	·014	169	278	1·74	1·76	
EXP. 15. Heart 95 grams.							
36·0	15·5	·110	103	231	1·80	1·42	
36·0	26·7	·062	99	128	1·04	1·35	
EXP. 16. Heart 80 grams.							
36·0	19·0	·076	87	170	1·81	1·13	
36·0	27·3	·039	64	170	1·34	1·13	
EXP. 17. Heart 41 grams.							
36·1	14·5	·082	71·5	168	2·91	3·10	
37·1	20·0	·029	35·0	179	1·44	3·30	
35·7	38·2	·083	190	413	7·8	9·10	After adrenalin.
36·0	39·0	·065	153	417	6·3	9·2	

The agreement between these figures by the two methods simultaneously is sufficiently near to indicate that there is no considerable combustion of partly oxidised products in the lungs: thus the values 1·74 and 1·76, 2·91 and 3·10 are practically identical; in some cases it is true that the external respiration is in excess of the internal, but the reverse is also true in other cases. In all probability, this discrepancy is to be explained by the fact that we only collect a sample of the coronary blood and measure its rate once or twice in each period, assuming that the flow and composition remain constant during that period; a glance at the figures will show that this cannot be the case. In other cases, too, the differential analyses of the two samples of blood indicated but small differences between the arterial and venous blood: in these cases the flow was large, and therefore an error in the blood-gas determinations would be much multiplied[1].

[1] The blood-gas analyses were performed in duplicate.

Determination of the gaseous metabolism of the heart by a differential method.

We have also attempted to obtain some light on the question of pulmonary oxidations by means of what may be called the differential method, or the method of the sum and difference. If we arrange a heart-lung preparation connected with the respiration apparatus in the usual way, we can insert a cannula into the coronary sinus (Fig. 3),

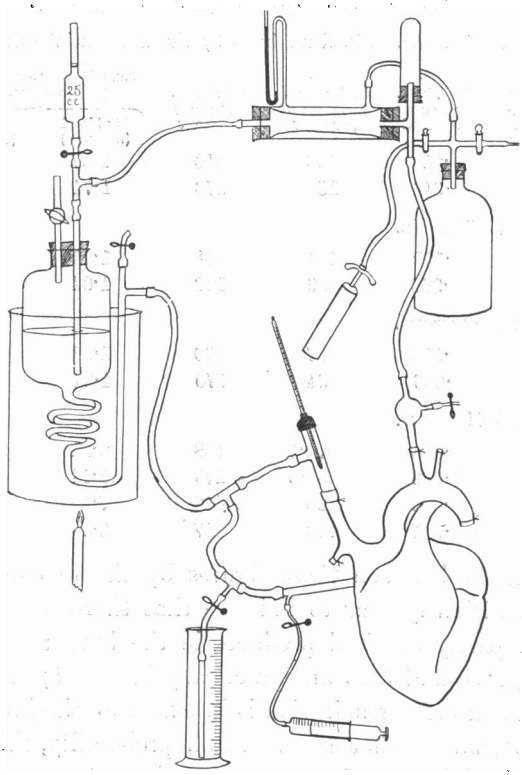

Fig. 3.

and allow the coronary sinus blood to escape during a period. The difference between the oxygen absorption during this period, as compared with that during a normal period, should give us the metabolism of the heart, after due allowance for the "remainder" blood which has been entering the right auricle during the whole time. At the end of the period during which the coronary blood has been flowing away, the tube from the coronary cannula is attached once more to the

inlet from the venous reservoir, so that the sinus blood once more enters the right auricle: with these arrangements another "normal" period is now taken for comparison with the first.

During the next period, we add the coronary blood which was drawn off after having made an analysis of it by Barcroft's method. We now have the normal metabolism of the heart and lungs plus the added coronary blood. If now, this blood contains "reducing substances" which are capable of being oxidised in the lungs, the oxygen absorption due to the addition of this blood should be greater than that calculated from the volume and composition of the added coronary blood.

In other words, if (a) represent the metabolism of the lungs, (b) that of that part of the heart drained by the coronary sinus, and (c) that of the "remainder" of the heart, then in a normal period we have $(a+b+c)$; in the period in which the sinus blood is flowing away $(a+c)$; and in the period in which the coronary blood is added to the circulation $(a+2b+c)$, assuming that the periods are all of equal length. (When this was not the case, the results have been reduced accordingly in order to give comparable figures.) In calculating the oxygen absorption by the "remainder" blood, the coronary sinus flow is multiplied by the factor $\cdot 4/\cdot 6 = \cdot 66$ (roughly) in order to obtain the flow by veins other than those opening into the coronary sinus. From these results we can compare the values of (b) as found by the direct method (analysis of blood and measurement of flow) and the indirect method, *i.e.* by the difference between the normal period and the $(a+c)$ period $(a+b+c)-(a+c)=b$, and also from the difference between the $(a+2b+c)$ and the normal period, or $b=(a+2b+c)-(a+b+c)$.

For the sake of brevity, we shall refer to the period in which the whole heart-lung metabolism is taken from the air-circuit as the "normal period," to that in which the coronary blood is flowing away as the $(a+c)$ period, and to that in which the coronary blood is added during an otherwise normal period, as the $(a+2b+c)$ period.

These results indicate on the whole that the oxygen absorption which takes place in the lungs is not greater than that calculated from the oxygen deficiencies of the coronary blood. In one or two cases the lung absorptions are greater, but in several cases the blood figures are the greater. In four cases the agreement is fairly good.

The results therefore cannot be said to afford evidence that the lungs have participated in the oxidative processes to any appreciable extent. The discrepancies which have been observed may be accounted for by the complicated nature of the experiments, and especially by the

TABLE V. *Metabolism of the heart by the sum and difference method.*

Type of period	Duration of period	Coronary sinus flow, c.c. per min. (observed)	"Remainder" flow, c.c. per min. (calc.)	Total coronary flow	Diff. between art. and venous blood	Per hour: O_2 used, calc. from blood	Per hour: O_2 abs. from lungs (observed)	Per hour: O_2 by breath, calc. from abs. from lungs	Remarks
Exp. 18. Heart 57 grams. Arterial pressure = 90 mm. Hg.									
Normal	20·0	—	—	—	—	—	229	172	
$(a+c)$	10·0	18·2	12·1	30·3	·078	**143**	124	**152**	(152 = 124 − 57 + b)*.
Normal	10·5	—	—	—	—	—	242	185	
$(a+2b+c)$	10·5	—	—	—	—	**143**	329	**145**	[(329 − 242) × 1·67] = 145.
—	—	—	—	—	—	—	—	129	(329 − 57 − 143).
Normal	20·0	—	—	—	—	—	234	177	
$(a+c)$	10·0	33·0	21·8	54·8	·019	**64**	147	**90**	
$(a+2b+c)$	11·0	—	—	—	—	**64**	313	**97**	(313 − 254) × 1·67.
Normal	20·0	—	—	—	—	—	254	197	
Exp. 19. Heart 97 grams. Temp. 36·0. Arterial pressure 80 mm. Hg.									
Normal	20·0	33·6	22·2	55·8	·060	**200**	210	**113**	
$(a+c)$	7·0	35·6	23·5	59·1	·060	**213**	188	**128**	(188 − 97 + b)*.
Exp. 20. Heart 95 grams. Arterial pressure 80 mm.									
Normal	10·0	15·5	10·2	25·7	·110	**172**	231	**136**	
$(a+c)$	10·0	17·5	11·5	29·0	·090	**159**	147	**141***	
Normal	10·0	—	—	—	—	—	179	84	
$(a+2b+c)$	10·0	26·7	17·6	44·3	·062	**165**	307	**214**	
Normal	10·0	—	—	—	—	—	175	80	
Exp. 21. Heart 80 grams. Arterial pressure 55 mm.									
Normal	20·0	—	—	—	—	—	213	133	
Normal	20·0	—	—	—	—	—	182	102	
$(a+c)$	10·0	19·0	12·6	31·6	·076	**145**	117	**124***	
Normal	10·0	—	—	—	—	—	166	86	
$(a+2b+c)$	10·0	—	—	—	—	**145**	222	**94**	
$(a+c)$	10·0	27·3	18·1	45·4	·039	**107**	102	**86**	
Normal	10·0	—	—	—	—	—	170	90	
$(a+2b+c)$	10·0	—	—	—	—	**107**	204	**57**	

* The second are the best, because whole blood taken.

fact that some of the periods were so short that the errors are multiplied up considerably in calculating the oxygen consumption per hour.

THE OXYGENATION OF VENOUS BLOOD IN THE LUNGS.

There remains now to be considered what we consider to be the crucial experiment, since it is more free from objections than any yet described here. It will be seen from the figures given in Table I that the metabolism of a particular isolated lung-preparation is remarkably constant from hour to hour. This being the case, one can add to such a preparation some venous or asphyxial blood of known composition and observe how much more oxygen is absorbed in the succeeding period. If there are in the blood substances which can be oxidised only by the lungs, then the oxygen absorptions by the lungs will be considerably greater than those which would be calculated from the oxygen percentages and oxygen capacities of the added asphyxial blood.

These experiments were performed in the following way. An isolated lung-preparation was set up, connected with the respiration apparatus, and the metabolism during one or two periods observed. A large dog was then anæsthetised and artificial respiration performed for some half-hour after having opened the thorax and divided the vagi. The animal was then asphyxiated until the right ventricle became very distended, and until there were signs of commencing heart failure ("heart-block"); there were usually strong spasms during the asphyxiation. When it was judged that the asphyxia had been carried as far as could safely be done without complete cessation of the circulation, blood was drawn from the right ventricle by means of a trochar, and was run into a few cubic centimetres of hirudin solution in a measuring cylinder. Usually 200 to 250 c.c. of the asphyxial blood was collected in this manner. A portion of about 100 c.c. was immediately added to the blood in the lung-preparation apparatus, samples having been taken previously for analysis. This blood is referred to as "blood A." The specimen of blood A was generally added to the circulation within two or three minutes of being drawn, and the oxygen absorption of the lung observed during a period of usually half an hour's duration. This time was quite long enough to allow the circulating blood to attain equilibrium with the alveolar air in the lungs, in fact the blood usually regained its arterial colour within ten minutes.

Meanwhile the second sample of asphyxial blood was well shaken up with air, or in some cases with oxygen, until it was saturated. This is

called "blood B." After taking a "normal" period for the lung once more, and ensuring that the first sample of asphyxial blood had been oxygenated in the lungs, about 100 to 150 c.c. of blood was withdrawn from the circulation, in order to keep the volume of circulating blood within reasonable limits, and the sample of blood B, previously warmed, was now added, and a further period of observation made.

Bohr was of the opinion that the action of the lungs was a specific one, *i.e.* that the lungs were able to effect oxidation of substances which could not be oxidised by simple exposure to air or oxygen, and this hypothesis can be tested by the addition of blood B, assuming that the results of the addition of blood A were in agreement with the view of Bohr and Henriques.

The results of the experiments are given below in tabular form.

TABLE VI.

	Blood A		Blood B	
No. of exp.	Oxygen required to saturate blood	Oxygen absorbed in lungs	Oxygen required by blood	Oxygen absorbed in lungs
22	16·5 c.c.	15·8 c.c.	0·0 c.c.	0·5 c.c.
23	19·0	21·0	0·0	—
24	18·5	? 26·3 (or 16·3)	0·0	1·3
25	11·7	9·5	—	—
26	21·1	19·4 (20·1)	0·0	0·0 (−3·9 c.c.)

The details of the experiments are given below.

Exp. 22. Lung-preparation (wt. of heart 41·5 grams. Perfusion rate 250 c.c. per minute. Rate of artificial heart 103 per minute. Temp. 36° throughout. Half-hour periods with the respiration apparatus.

1st period. O_2 absorbed 28·3 c.c.
2nd period. O_2 absorbed 28·0 c.c. } Mean 28·2 c.c.

93 c.c. of blood A were now added.

3rd period. O_2 absorbed 44 c.c. Increase 44·0 − 28·2 = 15·8 c.c.

The blood added contained no oxygen; its oxygen capacity was 17·8 %. Therefore 93 c.c. of it were capable of absorbing 16·5 c.c.

4th period. O_2 absorbed 26·0 c.c.

After removing about 100 c.c. of blood from circulation, 87 c.c. of blood B were now added.

5th period. O_2 absorbed 26·5 c.c.

6th period. O_2 absorbed 28·0 c.c. (normal period).

Increase in O_2 absorption on adding blood A	15·8 c.c.
Oxygen capacity of the blood added ...	16·5 ,,
Increase in absorption on adding blood B ...	0·5 ,,
Oxygen capable of absorption by blood ...	0·0 ,,

EXP. 23. Wt. of heart 26·5 grams. Perfusion 203 c.c. per minute. Artificial heart 102 per minute. Temp. 36°. Half-hour periods.

1st period. O_2 absorbed 31·5 c.c.
2nd period. O_2 absorbed 52·5 c.c. 90 c.c. of blood A had been added.
Increase in O_2 absorbed = 21·0 c.c.

The blood added contained 0·73 % of O_2
0·84 ,, ,, } Mean 0·8 %.

Oxygen capacity of blood added 21·9 %.
Therefore 90 c.c. would absorb 19 c.c. of O_2.
Observed absorption of O_2 = 21·0 c.c.

EXP. 24. Heart 51 grams. Rate of artificial heart 130 per minute. Rate of perfusion 220 c.c. per minute. Half-hour periods.

1st period. O_2 absorbed 23·4 c.c.
2nd period. O_2 absorbed 23·0 ,, } Mean 23·2.
3rd period. O_2 absorbed 49·5 c.c. 110 c.c. of blood A added.
% O_2 in blood = 1·97; O_2 capacity = 18·8 %. Therefore 110 c.c. can absorb 18·5 c.c.
Actual absorption 49·5 − 23·2 = 26·3 c.c.[1]
4th period. O_2 absorbed 23·1 c.c.
5th period. O_2 absorbed 24·4 c.c. 95 c.c. of blood B had been added.

EXP. 25. Heart 52 grams. Artificial heart 150 per minute. Perfusion rate 174 c.c. per minute. Temp. 36°. Half-hour periods.

1st period. O_2 absorbed 26·5 c.c.
2nd period. O_2 absorbed 24·5 c.c. Mean 25·5 c.c.
100 c.c. of blood A now added. O_2 in blood = 1·3 %.
Oxygen capacity of blood 13·0 %. (The volume of the hirudin solution was rather greater than usual in this case.) Therefore 100 c.c. of the blood can absorb 11·7 c.c. of O_2.
3rd period. O_2 absorbed 35·0 c.c.
Hence increase in O_2 absorbed 9·5 c.c.

EXP. 26. Heart 65 grams. Artificial heart 130 per minute. Perfusion rate 300 c.c. per minute.

1st period. O_2 absorbed 30·9 c.c.
2nd period. O_2 absorbed 32·0 c.c. Mean 31·4 c.c.
125 c.c. of blood A now added.
O_2 capacity 18·35 %.
O_2 per cent. 1·42 %.
Hence 125 c.c. can absorb 21·1 c.c. O_2.
3rd period. O_2 absorbed 50·8 c.c. Increase 19·4 c.c.
4th period. O_2 absorbed 30·7 c.c. (50·8 − 30·7 = 20·1 c.c.)
110 c.c. of blood B now added.
5th period. O_2 absorbed 26·8 c.c. (This small amount was owing to the fact that the temperature was accidentally lowered to 33—34° C.)

[1] This may perhaps be an error of reading. If it were 39·5 the difference would be 16·3 c.c.

In all these cases, with the possible exception of Exp. 24, the differences between the oxygen actually absorbed from the lungs, and the amount which was calculated on the assumption that the blood became saturated with oxygen in the lungs, are in all cases within the limits of experimental error. The case of Exp. 24 is an isolated one, and some doubt is felt as to the accuracy of the reading during the period following the addition of blood A. This doubt is strengthened by the fact that the amount of carbon dioxide which was evolved during the period (47·0 c.c.) was more in accordance with an O_2 absorption of 39·5 c.c., since in all the other experiments the CO_2 evolved in similar periods was invariably much higher than the oxygen absorbed. Thus for the oxygen absorptions of 44·0, 52·5, 35·0, and 50·8 c.c. there were respectively 61·0, 66·0, 57·0, and 67·5 c.c. of CO_2 evolved. If, therefore, we are to assume that the reading in Exp. 24 was correct, then we have the anomaly that in this case there is more oxygen absorbed than is required to oxygenate the blood completely, and yet at the same time there is less CO_2 produced than is the case in those experiments where no pulmonary oxidations were indicated. But even if we accept the reading of 49·5 c.c. as being correct and as indicating the occurrence of oxidative processes in the lung, the non-specific nature of the effect of the lung is seen in the fact that in the period where blood B was added, there was no increased absorption, except such as lay within the limits of experimental error.

We are therefore bound to conclude, with Morawitz (15), that in asphyxia there are not formed any substances which are capable of being oxidised in the lungs; these experiments go further than those of Morawitz, in that we have actually tested the supposed specific nature of the behaviour of the lung tissue, whereas Morawitz merely investigated the view held by Loewy (22) at that time, namely that there were substances which could be oxidised by any living tissues provided that the requisite oxygen tensions prevailed in order to render the change possible. Our experiments not only support the work of Morawitz, but they show that we cannot even ascribe to the tissue of the lungs any such specific activity in this respect as was attributed to it by Bohr.

Summary and conclusions.

1. The metabolism of the blood-perfused lung has been investigated by means of an improvement of the apparatus already described. It is found to be remarkably constant at constant temperature. Owing to the

fact that the lungs so readily become œdematous, the values cannot be given directly per gram of lung, but by weighing the heart an approximate idea can be obtained. These values relative to the heart are 1·00 c.c. of oxygen and 0·94 c.c. of CO_2 per gram of heart per hour, as the mean of seven experiments.

2. The distribution of the blood in the coronary vessels has been investigated. The coefficients of irrigation are much higher than those on which Bohr and Henriques worked, and in all probability may be taken fairly correctly as about 60 % of the weight of the heart per minute.

But the flow in the experiments of Bohr and Henriques was in all probability an ever increasing one, owing to the powerful dilating effect of metabolites on the coronary vessels.

3. By means of a simple modification of the perfusion method of Heymanns and Kochmann, the distribution of the coronary blood between the coronary sinus and the veins opening directly into the right auricle has been investigated. These experiments indicated that, if we call the flow in the whole coronary system unity, then the flow in the coronary sinus is 0·6 and that in the remaining vessels 0·4. If the rate of the coronary flow is altered in any way this ratio of distribution still holds.

It is therefore possible, by means of the coronary sinus cannula employed by Morawitz and Zahn, to obtain an idea of the whole coronary flow at any time.

4. The oxygen metabolism of the blood-perfused heart as estimated by the oxygen absorption from the lung in the isolated heart-lung-preparation, after due correction for the metabolism of the lungs, agrees sufficiently well with the metabolism as found by analysis of the arterial and coronary blood to indicate that the lungs do not participate in the oxidative processes.

5. The same result is obtained in the "differential" experiments in which the coronary blood is run away from the heart-lung-preparation while a respiration experiment is being carried on, and after being measured and analysed, again added to the circulation.

6. When asphyxial blood is added to the blood in the isolated lung-preparation, there is no evidence that any oxidative process occurred in it other than the absorption of the amount of oxygen required to (almost) fully saturate it.

7. The results of these experiments therefore all point in the same direction, namely, that not only in the normal tissues supplied with

the normal amount of oxygen, but even in conditions of extreme oxygen lack, such oxidations as are carried out are completed in the tissues.

The lungs do not exercise any general or specific activity in completing oxidations partially carried through in the other tissues.

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