THE GASEOUS METABOLISM OF THE MAMMALIAN HEART. Part I. By JOSEPH BARCROFT and W. E. DIXON.

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THERE are, so far as we know, only two previous observations on the gaseous metabolism of the heart.

Yeo[1] observed that the frog's ventricle imbibed considerably more oxygen from a hæmoglobin solution enclosed in it, when beating than when still.

Fletcher[2] noted the carbonic acid output of the excised heart of the tortoise. He did not observe any appreciable decrease in the CO_2 when the vagus was stimulated; but his more recent researches suggest that muscular metabolism does not run the same course in excised organs exposed to air as in the well oxygenated tissues of the living body.

Method. Our method of obtaining a heart which beats efficiently for a considerable period of time was based on that of Heymans and Kochmann[3]. The heart of one animal was excised and connected with the circulation of a larger anæsthetised animal of the same species.

The following description of the technique employed is valid for cats as well as dogs. In most experiments dogs were the animals employed.

In some preliminary experiments we used dogs which had been pithed. These we found unsatisfactory on account of their low arterial pressure. The anæsthesia in all the cases described was established with chloroform and maintained with urethane (about 1 grm. per kilo). Cannulæ were placed in the trachea; in the left carotid artery, and jugular vein, for connexion to the artificially perfused heart; in the right femoral artery for recording blood-pressure; and in the left

[1] This *Journal*, VI. p. 93. 1885.

[2] Schäfer's *Text-Book*, I. p. 911.

[3] *Arch. Pharm. et de Thérap.* XIII. p. 379. 1904.

femoral artery and vein for obtaining samples of arterial blood, and for injections into the animal respectively.

The heart which we were about to investigate was then prepared. For this purpose a dog as small as possible was chosen, generally a puppy. It was killed instantaneously by pithing and a tube was placed at once in its trachea so that artificial respiration might be kept up and the circulation maintained for as long a time as possible. Cannulæ were next placed in the aorta and in the left pulmonary artery and all other vessels and connexions were ligatured. The heart was then removed and suspended by the aortic cannula apex downwards; the aorta and pulmonary artery of the excised heart were connected with the carotid artery and jugular vein of the large dog, the connecting tubes being filled with salt solution. On removing the bull-dogs from the vessels the circulation through the transfused heart began and the heart commenced to beat. For the purposes of analysis it was necessary to render the blood non-coagulable and the only satisfactory method which we have found for this was by injection of hirudin[1] (of Jacobi); peptone and the other methods which we have casually employed having proved unsuitable. It was found advisable to administer the hirudin by injection directly into a vein of the larger dog some minutes before the excised heart is put into the circulation.

In our later experiments we made an additional improvement. Not infrequently, when the blood reaches the perfused heart it sends the heart into fibrillary twitchings which involve a great expenditure of time and patience to remove and always leave the heart feeble and unsatisfactory. This may be, to some extent, prevented by administering a little hirudin to the smaller animal whilst its own circulation is yet intact.

A graphic record of the heart-beat was obtained by attaching the apex to a suitably weighted lever and recording directly on a smoked drum.

In the experiments in which the action of the vagus upon the heart was studied, the technique was altered and is described later.

For the experiments with dogs we used five cubic centimetres of blood for each analysis (except in Exp. 1), for those with cats one cubic centimetre. The blood was taken from a T-tube in connexion with the tube running from the pulmonary artery of the perfused heart to the jugular vein of the perfusing animal. A few drops were allowed to

[1] Manufactured by E. Sacchse & Co., Leipzig.

escape before this connexion with the graduated tube was made, in order to gain time for the rate of flow, which was momentarily upset by these manipulations, to readjust itself. It has been our practice to return blood lost from this or accidental causes into the femoral vein.

The rate of blood-flow through the coronary system was obtained by direct observation. A pipette consisting of a glass tube drawn off at the end was inserted into the rubber on the free end of the T-piece: it is important that the broad end of the pipette be inserted as the fine end causes a resistance to the flow of blood. The pipette was suitably graduated between two marks to 5 c.c. for dogs or 1 c.c. for cats. The person collecting the blood gave the signal when the meniscus passed each mark and an attendant with a stop-watch observed the time occupied. Having filled the pipette with blood, it was detached from the rubber and poured into the blood-gas bottle, the clamp being at the same time removed from the jugular vein so that the blood from the excised heart passed once more into the jugular vein of the intact animal.

When we studied the action of drugs these were injected into the rubber tube leading to the perfused heart. In this way a dose could be given which was large enough to affect the heart but not so large as to affect the general condition of the animal.

RESULTS.

Adrenalin. Our first concern was to produce the most obvious change in the activity of the heart in the easiest manner. For this purpose we used adrenalin. This experiment was performed on a dog and the blood was examined during four periods; in the first three of these no drug was given, whilst in the fourth the heart was under the influence of adrenalin. The following are the figures obtained.

As Exp. 1 is of a preliminary character it is advisable to add some brief comment on it. In the first place it should be noticed that the arterial samples at the four periods differ by very little, 22·0, 21·3, 21·5, 21·8 %. These differences are within the error of the Barcroft-Haldane[1] apparatus, and it may be taken that throughout this and all other experiments we have kept the oxygen in the blood at a constant figure. To ensure this factor being constant it has been our practice to keep up artificial respiration throughout the whole of the experiment.

[1] Barcroft and Haldane. This *Journal*, XXVIII. p. 232. 1902.

Considerable variations in the amount of oxygen present in the blood are not *a priori* likely to exist in these experiments to the same degree as when working with such organs as the kidney and pancreas, where large injections are made into the blood; or the salivary gland, where escape currents from the sympathetic to the vagus may influence the respiratory centre.

Exp. 1. Dog, 10·4 kilos. Puppy's heart, 16·7 grms.

Period	Condition of heart	Nature of blood	Time taken for 1 c.c. to pass through coronary system	Oxygen in blood p.c.	Oxygen consumed per min. by the heart	Oxygen consumed per gr. per min.
I.	No drug, tonus	Venous	6 secs.	19·4	·26 c.c.	·016 c.c.
		Venous	6	18·8	·32	·019
		Arterial	—	22·0	—	—
II.	No drug	Venous	19	16·7	·15	·009
	Diminished tonus	Venous	18	15·2	·20	·012
		Arterial	—	21·3	—	—
III.	No drug	Venous	25	14·2	·17	·010
	Diminished tonus	Venous	22	15·4	·17	·010
		Arterial	—	21·5	—	—
IV.	Adrenalin	Venous	8	11·6	·76	·045
		Venous	15	8·0	·60	·036
		Arterial	—	21·8	—	—

There is one unsatisfactory feature about the figures of Period I, the blood-flow was a little fast, 1 c.c. going through the vessels in six seconds. The error in measuring this is relatively large and the difference between the oxygen in the arterial and venous bloods 22 % and 19·4 % respectively is small. The former difficulty we have obviated in dogs by using 5 c.c. of blood for each determination. In most of the subsequent experiments therefore it will be found that the difference between the oxygen in the arterial and venous bloods has been considerable.

But despite this source of error the oxygen consumption in the heart is fairly steady as shown by the two determinations in Period I. These determinations were made at four minute intervals. With regard to the effects of adrenalin it is immaterial as a first approximation whether the first or second determination in Period I be compared with the first or second determination of Period IV, although these latter two are not comparable with one another as is seen from the rate of blood-flow. The effect is decided in all cases; adrenalin greatly increases the oxygen consumption of the heart. It is clear also

that this increased metabolism is not in any way dependent upon changes in the rate of blood-flow.

At first we were disappointed at the disparity between the figures for the oxygen consumption in Periods I, II and III, especially so as the excursions of the recording lever were smallest in Period I; in neither period was any drug administered.

But when the portions of the tracing corresponding with these periods were placed side by side (Fig. 1) the interpretation became obvious. The fixed horizontal line appears at the top of the figure; the upstroke of the curve represents cardiac systole and the downstroke diastole. The small excursion in Period I is due not to deficient contraction but to diminished relaxation, in other words the diastolic tonus

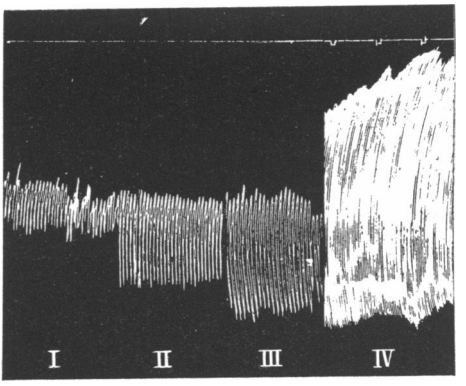

Fig. 1. Puppy's heart. Upstroke = systole. Between Periods III and IV an injection of adrenalin was made into the tube leading to the heart. Time = 12 seconds.

of the heart is considerably greater in Period I than in Periods III or IV; and it seemed obvious that this fact accounted for the greater oxygen consumption during Period I. We have verified this fact on several subsequent occasions and there is no doubt that increased cardiac tonus is a more potent factor in the consumption of oxygen than increased cardiac activity with good relaxation in diastole.

We did not obtain carbonic acid results of value in Exp. 1 as there proved to be too much CO_2 in the air of the operating room. In all subsequent experiments the gas analysis apparatus was kept in the adjacent room which was thoroughly ventilated. If the analysis is performed in fresh air the amount of extraneous carbonic acid in the blood-gas bottles is reduced to about ·012 c.c. and is constant throughout

the various determinations. With the precaution mentioned we have therefore neglected it in comparative results.

In Exp. 2 we confirmed the result of adrenalin injection and subsequently reduced the metabolism of the heart with pilocarpine. The following are the figures which were obtained.

Exp. 2. Anæsthetic and operation as in Exp. 1. Weight of dog, 13·8 kilos. Puppy's heart, 30 grms.

Period	Condition of heart	Nature of blood	Time taken for 5 c.c. to pass through coronary system	Oxygen in blood p.c.	CO_2 in blood p.c.	Oxygen consumed (*a*) per minute (*b*) per grm. per min.	CO_2 given out (*a*) per minute (*b*) per grm. per min.
I.	No drug	Venous	12 secs.	13·8	23·6	(*a*) **1·2** c.c.	**1·15** c.c.
		Arterial	—	18·6	19·0	(*b*) ·040	·038
II.	Adrenalin	Venous	11	10·7	23·6	(*a*) **2·15**	**1·26**
		Arterial	(see Period I)			(*b*) ·083	0·42
III.	Later stage of the same dose	Venous	18	9·6	27·8	(*a*) **1·50**	**1·46**
		Arterial	(see Period I)			(*b*) ·050	·048
IV.	Pilocarpine	Venous	65	12·9	21·1	(*a*) **·30**	**·10**
		Arterial	(see Period I)			(*b*) ·010	·003

Adrenalin induced an increase of metabolism in Exp. 2 which was very much less than in Exp. 1. In the latter the oxygen metabolism was increased about four-fold (cp. Periods III and IV), whilst in the former it was not doubled, being 1·2 c.c. per minute in Period I as compared with 2·15 in Period II whilst it fell off to 1·5 in Period III. The tracing, Fig. 2, at once shows that the increase in the activity of the heart produced by the adrenalin was very much less in Exp. 2 than in Exp. 1, and that this oxygen consumption is roughly the index of the change in functional activity.

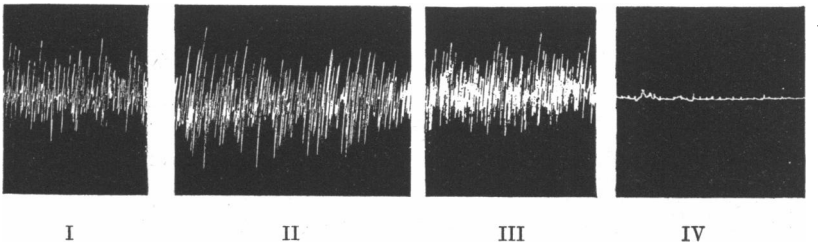

Fig. 2. Record of puppy's heart. Upstroke = systole. Period I represents normal. Periods II—III represent the condition after a small dose of adrenalin. Period IV shows inhibition produced by pilocarpine. Speed of drum is 1 mm. per second.

Pilocarpine and atropine. Period IV of Exp. 2 shows the effect of pilocarpine; the heart has been reduced almost to a standstill and the metabolism and blood-flow have been considerably reduced and represent a very low figure. The oxygen intake has come down to a quarter of its normal figure; the carbonic acid given out is even more decidedly decreased, whilst the blood-flow, which in Period I was 25 c.c. per minute, is now reduced to under 5 c.c. per minute.

These very striking results of pilocarpine have been confirmed by Exp. 3 in which the drug was given directly to a puppy's heart. It was administered in two doses, which were followed by two doses of atropine. The results of the experiment are as follows:

Exp. 3. Weight of dog, 12 kilos. Puppy's heart, 22 grms.

Period	Condition of heart	Nature of blood	Through coronary vessels, blood flow per min.	Oxygen in blood p.c.	CO_2 in blood p.c.	Oxygen consumed (*a*) per minute (*b*) per grm. per min.	CO_2 given out (*a*) per minute (*b*) per grm. per min.
I.	No drug	Venous	12·0 c.c.	11·4	34·2	(*a*) ·72 c.c.	·91 c.c.
						(*b*) ·033	·041
II.	Pilocarpine 1 c.c. ·5 %	Venous	11·5	14·7	33·6	(*a*) ·31	·80
						(*b*) ·014	·036
III.	Pilocarpine 1 c.c. 2 %	Venous	5·6	13·9	27·7	(*a*) ·20	·07
						(*b*) ·009	·003
IV.	Atropine 2 c.c. 2 %	Venous	6·6	12·4	28·2	(*a*) ·33	·12
						(*b*) ·015	·005
V.	Atropine 3 c.c. 2 % more	Venous	6·4	10·8	29·1	(*a*) ·42	·17
						(*b*) ·021	·008
Between I and II		Arterial	—	17·8 *	lost	—	—
After V		Arterial	—	17·0 *	26·4	—	—

* The mean of these readings 17·4 has been used as the basis of this calculation.

Fig. 3 shows the activity of the heart in the five periods of Exp. 3. The general correspondence between the oxygen metabolism and the change in activity is clear. There are one or two points which require notice. The atropinised heart appears to be beating at least as actively in Period V as was the normal heart in Period I; the rate remains almost exactly the same, the atropinised heart to the normal heart being as 28 to 29 beats. Nevertheless the oxygen metabolism though doubled by the administration of atropine is not restored to its original level. This effect is due, we believe, to loss of tonus due to the action of atropine on the cardiac muscle, but which we failed to record accurately.

The experiment shows another point for consideration, namely a tendency for the carbonic acid output to lag after the change in functional activity and oxygen intake. By comparing the last two columns of the preceding table it will be seen that the administration of pilocarpine which took place at 2.33 caused an instant drop in the oxygen intake but only a trivial drop in the carbonic acid given out. (The figures of Period I apply to 2.35.) At 2.40 (Period III) the heart had almost ceased to give out carbonic acid, and whilst atropine caused a sudden rise in the oxygen intake it produced only a gradual rise in the output of carbonic acid. This phenomenon if constant will be of importance in the interpretation of other blood-gas problems[1].

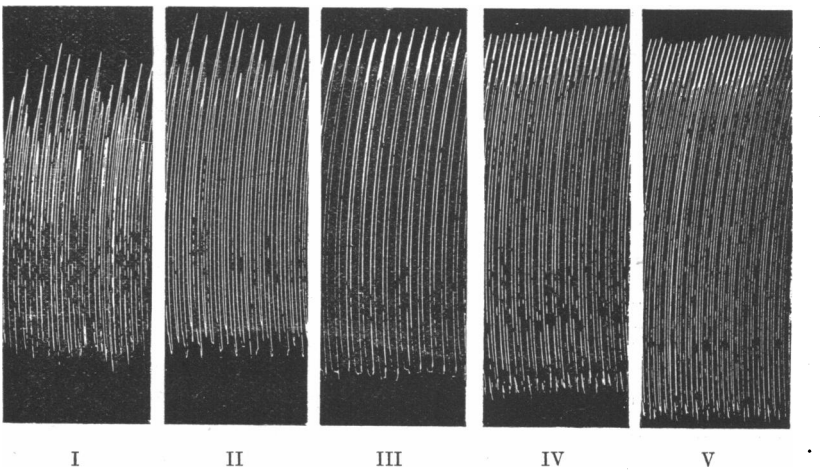

Fig. 3. Record of puppy's heart. Upstroke = systole. Period I is normal. Period II shows the effect after injecting 5 mgs. of pilocarpine and Period III after 20 mgs. Periods IV and V show the recovery of the heart after two successive doses of 0·4 mg. of atropine.

Tonus. Exp. 1 at once directed attention to the importance of tonus in the consideration of functional activity. Exp. 4 was undertaken to test how the metabolism of the heart was altered by drugs which are known to directly excite or depress cardiac muscle. For this purpose barium chloride and potassium chloride were selected respectively. Potassium chloride very greatly weakens the force of cardiac contraction and diminishes tonus, ultimately producing death in the most complete diastole. Barium chloride increases the force of the heart-beat, increases tonus, and in large doses causes death in systole.

[1] Barcroft and Brodie. This *Journal*, xxxi. p. 67. 1905.

Exp. 4. Weight of dog, 11·9 kilos. Weight of puppy's heart, 27 grms.

Period	Condition of heart	Blood flow per mm. through coronary vessels*	Nature of blood	Oxygen in blood p.c.	CO_2 in blood p.c.	Oxygen consumed (*a*) per minute (*b*) per grm. per min.	CO_2 given out (*a*) per minute (*b*) per grm. per min.
I.	No drug	14 c.c.	Venous	10·3	42·3	(*a*) ·8 c.c.	1·65 c.c.
						(*b*) ·030	·061
II.	KCl	12	Venous	10·4	40·2	(*a*) ·73	1·27
						(*b*) ·027	·048
III.	KCl	9	Venous	10·2	36·0	(*a*) ·55	·53
						(*b*) ·020	·020
IV.	KCl	11	Venous	13·2	36·2	(*a*) ·33	·67
						(*b*) ·012	·025
V.	$BaCl_2$	12	Venous	7·1	35·7	(*a*) 1·09	·66
						(*b*) ·040	·010
VI.	$BaCl_2$	9	Venous	7·4	34·4	(*a*) ·80	·38
						(*b*) ·030	·013
Between VI & V	—	—	Arterial	16·2	30·2	—	—

* Correct to the nearest cubic cm.

Two portions of the tracing are reproduced in Fig. 4.

The lower represents the transitional stage from Period I to Period II that is from a period in which the heart was beating somewhat feebly to one in which both the force of the beat and the tonus were very greatly reduced. This change was caused by potassium chloride.

The upper portion of the tracing corresponds to the condition between Periods V and VI. In Period V the heart was beating very forcibly as a result of administration of barium chloride, whilst a second dose, given at the moment representing the beginning of the tracing, very soon sent the heart into a condition of almost complete tonus. It was in this condition that the blood of Period VI was taken for analysis. The figures tabulated above show how considerable is this continued effect of potassium chloride in reducing the oxygen consumed in the heart. This drug does not however cut out the carbonic acid production to a comparable figure, and in this respect it bears comparison with chloroform; and these two drugs will be further considered when we contrast their effect with that of pure cardiac inhibition. This experiment confirms the conclusion arrived at in Exp. 1, namely that the degree of tonus, as well as the aptitude of contraction, influences the gaseous exchange of the heart.

Isotonic and isometric contraction. The same facts are shown in another way in Exp. 5. The tracing shown in Fig. 5 was obtained from a heart in which the aortic semilunar valves were incompetent. The cavities on the left side of the heart were distended with blood and the volume of the organ was much enlarged. The heart was endeavouring to contract but the resistance to the outflow of blood (*i.e.* the pressure

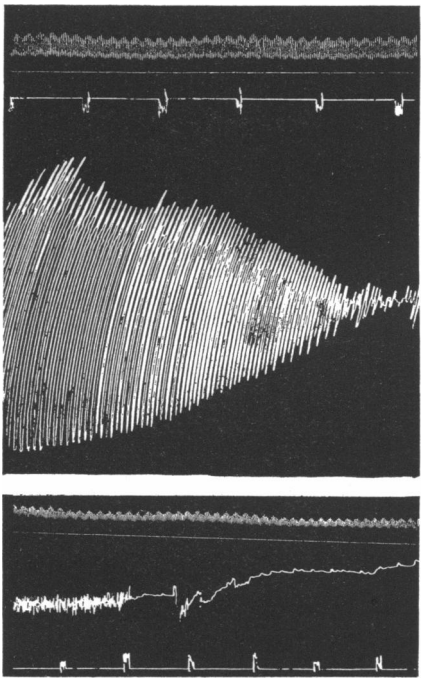

Fig. 4. Record of puppy's heart, and blood-pressure of mother taken with Hürthle's manometer. Lower tracing shows the effect of KCl (1 c.c. of 1 % solution) on the feeble and irregularly beating heart. It causes complete standstill in diastole. Sufficient KCl was not administered to effect the blood-pressure of the "mother."

The upper tracing shows the effect of the second of two injections of $BaCl_2$ ($\frac{1}{2}$ c.c. of a 1 % solution) given to the same heart. This drug causes systolic standstill from which the heart does not recover. Time = 12 seconds.

in aorta) being greater than the force of contraction, it was performing a series of approximately isometric movements. At the point where the tracing changes its character the resistance to the outflow was abolished by introducing a tube through the wall of the left auricle into the left ventricle so that now the heart could drive its blood up this tube at each contraction. In the first period the condition of the heart has

some resemblance to an enlarged heart with incompetent semilunar valves, such as occurs in mitral regurgitation: this is characterised by the rapid pulse and the failure to produce effective contractions. In the isotonic period the rhythm had returned to its normal rate and the contractions were well marked. The oxygen consumption in the first period was ·174 c.c. per minute, in the second ·169. Another point of interest arises in that the slightly greater oxygen consumption was associated with a reduced blood-flow. In the isometric period the blood passing through the coronary system was 1·9 c.c. per minute, in the isotonic it was 2·6.

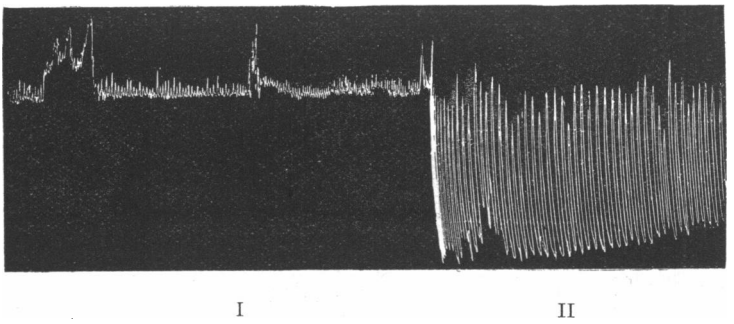

Fig. 5. Record of puppy's heart. Period I shows the condition during the incompetence of the aortic semi-lunar valves (*i.e.* the isometric condition). Period II shows the recovery after a tube had been introduced into the left ventricle (*i.e.* the isotonic condition).

Exp. 5. Weight of puppy's heart, 27 grms.

Period	Condition of heart	Nature of blood	Rate of flow through coronary vessels	Oxygen in blood p.c.	CO_2 in blood p.c.	Oxygen consumed (*a*) per minute (*b*) per grm. per min.	CO_2 given out (*a*) per minute (*b*) per grm. per min.
I.	Isometric	Venous	2·2 c.c.	7·5	34·0	(*a*) **·174** c.c.	**·22** c.c.
						(*b*) ·0064	·0081
II.	Isometric	Venous	2·61	9·2	37·3	(*a*) **·169**	**·35**
						(*b*) ·0062	·013
Between II & III		Arterial	—	15·7	23·8	—	—

Chloroform. In Exp. 6 there were two periods. During the first of these the heart was beating normally; at the point indicated by the arrow ·12 c.c. of chloroform-water was injected. The heart responded almost at once by contracting less forcibly, and when the maximum effect was established the sample of blood was taken for analysis; the period when this was done is indicated by the white horizontal line. Below the

heart tracing is a record of the arterial pressure of the feeder; it will be seen that by injecting the chloroform directly into the vessel leading to the perfused heart a striking effect was produced upon the heart without any immediate effect upon the general arterial pressure of the dog. Chloroform reduces the metabolism of the heart very considerably, the oxygen metabolism being reduced to a much lower figure than the CO_2 metabolism.

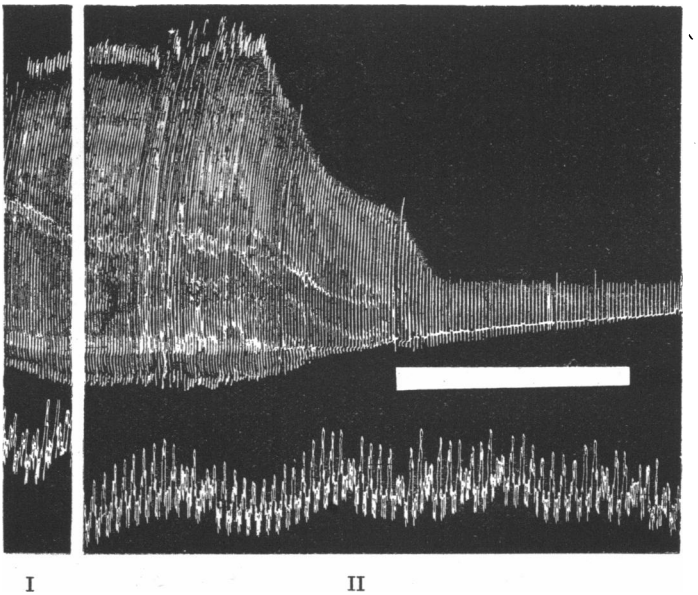

Fig. 6. Upper tracing represents record of puppy's heart. Lower tracing = blood-pressure of the perfusing animal. Period I = normal. Period II shows the effect of injecting 20 minims of $CHCl_3$ water. The signal mark represents the time during which the sample of blood was taken.

The data associated with this tracing are tabulated below:

Exp. 6.

Period	Condition of heart	Nature of blood	Rate of flow through coronary vessels	Oxygen in blood p.c.	CO_2 in blood p.c.	Oxygen consumed per minute	CO_2 given out per minute
I.	No drug	Venous	30·0 c.c.	5·2	71·8	**3·0** c.c.	**3·8** c.c.
II.	Chloroform 20 minims of chloroform water	Venous	9·1	11·6	63·0	**·37**	**1·9**
		Arterial	—	15·6	42·2	—	—

Chloroform, like potassium, exerts its toxic action on the ordinary musculature of the heart and the results obtained with drugs of this class show a close resemblance to one another.

Vagus. The most interesting method of reducing the contractions of the heart is by stimulation of the vagus nerve. In these experiments it proved to be much the most difficult. So far we have succeeded in obtaining a good effect only in cats.

It was necessary to keep up the circulation and the artificial respiration in the small animal to a much later period in experiments on the vagus than in others. It was not possible to use puppies, as the air passages became blocked and the heart stopped from lack of oxygen. When the circulation was satisfactory the chest was opened, the azygos vein and superior vena cava were ligatured and the lung on the right side tied off about $\frac{1}{4}$ inch from the root. Ligatures were then placed round the inferior vena cava, the two branches of the pulmonary artery, the aorta, and the various lobes of the left lung. Some care is needed in placing the ligatures round the aorta as some of the fibres of the vagus may be included in the ligature. During this period the neck of the animal was kept warm by means of hot sponges. The pericardium was not incised until ligatures were placed round the aorta and pulmonary arteries and then a transverse incision was made about $\frac{1}{2}$ inch long.

Up to this stage the circulation remained intact and the heart was beating well; at this point the arterial respiration was stopped; the left lung, inferior vena cava, and one branch of the left pulmonary artery were ligatured and cannulæ were inserted into the aorta and the other branch of the left pulmonary artery. No ligature was placed round the main root of the pulmonary artery. If the circulation from the feeder was now commenced the vagus was usually found to be quite active. But in spite of these precautions the irritability soon ceased and excitation of the nerve rarely produced an effect half an hour after the commencement of the perfusion, so that the experiment should be performed as rapidly as possible.

Another point of importance was the type of cannula for the pulmonary artery. This cannula was very likely to get blocked by a portion of the vessel wall acting as a valve. To avoid this we used, successfully, a glass cannula or rather catheter containing a large number of openings all round it, which was passed into the right ventricle.

In these experiments (Figs. 7 and 8) a different system of recording

the heart-beat was employed. A receiving tambour was prepared with a suitably bent pin rigidly connected to its centre, and this was brought into proximity with the centre of the left ventricle. In this way movements of the ventricle were communicated through the pin to the tambour and were in turn communicated to a second or recording tambour; so that when the heart contracted, the receiving tambour was driven inward and the recording tambour connected to it was driven outward, causing the lever to rise. In these tracings therefore the upstroke is the systole and the downstroke is the diastole.

During the inhibition in Exp. 7, the rate of the heart is diminished by about a half; and the force of the beat, represented in the figure by the height of the contractions, is considerably reduced.

Exp. 8 is not reproduced; the effect of the vagus on the heart was as marked as in Exp. 7; there was no after effect. We considered Exp. 8 especially satisfactory so far as the manipulations were concerned as it ran a particularly even course throughout. The following are the results of these experiments.

Exp. 7. Cat, 4 kilos. Small cat, 2·1 kilos. Heart, 15 grms.

Period	Condition of heart	Nature of blood	Rate of flow through coronary vessels per min.	Oxygen in blood p.c.	CO_2 in blood p.c.	Oxygen consumed (*a*) per minute (*b*) per grm. per min.	CO_2 given out (*a*) per minute (*b*) per grm. per min.
I.	Normal	Venous	6·7 c.c.	10·5	54·9	(*a*) ·21 c.c.	·58 c.c.
						(*b*) ·014	·38
II.	Vagus	Venous	4·6	10·9	47·6	(*a*) ·13	·07
						(*b*) ·009	·005
III.	After vagus	Venous	6·0	8·0	49·8	(*a*) ·34	·22
						(*b*) ·022	·015
After III.	—	Arterial	—	13·7	46·2	—	—

Exp. 8. Cat, 3 kilos. Kitten's heart, 4·1 grms.

I.	Normal	Venous	2·14	10·6	39·4	(*a*) ·092	·12
						(*b*) ·022	·03
II.	Vagus	Venous	1·04	9·7	39·2	(*a*) ·054	·056
						(*b*) ·013	·014
After II.	—	Arterial	—	14·9	33·8	—	—

In each of the above experiments there is an obvious reduction in the gaseous exchange of the heart, and therefore direct expression of a chemical basis for inhibition. In each case vagus stimulation cuts the oxygen consumption down to six-tenths of its previous value, whilst the CO_2 output is even more considerably reduced.

In view of these facts it is clear that no hypothesis to account for inhibition can hold good which regards it as a phase of increased anabolism. Its only certain chemical expression is decreased katabolism. But beyond this statement we can discuss probabilities. It has been suggested that the carbonic acid which is produced normally by muscular contraction is a post-functional product, and that oxidation is not a manifestation of the chemical action which liberates the energy of the contraction but a subsequent scavenging of the waste products of activity. In other words contraction is independent of oxidation but oxygen is necessary to destroy waste products. If this view be held in its most extreme form it would follow that gaseous exchange would give no clue to the extent of the anabolic processes, and the data before us would be no evidence as to whether anabolism was increased or diminished. Increased oxidation would however be evidence of increased katabolism as the increase of the scavenging process would

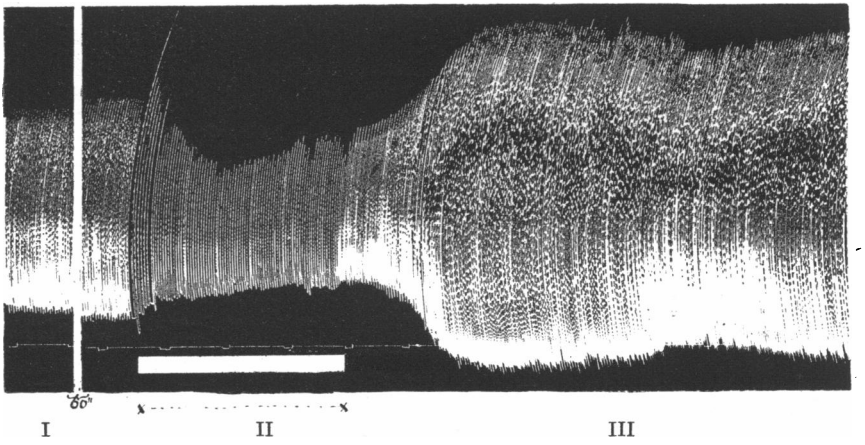

Fig. 7. Record of the movements of the heart of a small cat perfused from the circulation of a large cat. Upstroke = systole. Period I = normal. In period II the signal mark represents the time of vagus stimulation (coil at 10 cms.). The third period corresponds to the after effect and in this period the third sample of blood was taken.

indicate an augmented output of waste products. The theory is built for the most part upon the experiments of Hill and of Fletcher; the former has not, so far as we know, published the data which he obtained, and the latter has never expressed any public adherence to the interpretation which others have put upon his experiments. Fletcher[1] has

[1] Fletcher. This *Journal*, xxviii. p. 474, 1902, and xxx. p. 414. 1904.

made it abundantly clear that in excised muscle the products of fatigue —of which lactic acid was supposed to be important and which Hopkins and Fletcher have recently shown is important—are abolished by oxygen, a result which is quite in harmony with experiments along similar lines performed in Richet's[1] laboratory. But it has not been demonstrated that the carbon in the fatigue products of anærobic contraction is equal in quantity to that in the CO_2 of normal contraction. Indeed the recent work of Fletcher and Hopkins[2] lends itself to a very different hypothesis from the extreme view stated above.

It is more usually held that oxidation is directly responsible for the energy of contraction by the combustion of some body of very high potential energy which breaks up, giving carbonic acid as one product. If this be the case then it does not matter to our argument whether the oxygen is supplied directly and a certain store of oxygenated material formed, or whether the oxygen is held by carrier till required, for in both cases the oxygen is closely bound up with the anabolic process. On any such view the figures we are considering would suggest decrease of both anabolism and katabolism.

In the foregoing remarks we have postulated only ærobic conditions since these are the only ones with which we have yet experimented. In both Exps. 7 and 8 there was ample oxygen in the venous blood, and it may therefore be claimed that the needs of the tissue for oxygen were always abundantly satisfied. Yet it is significant that in one of these experiments and in both of the experiments in which pilocarpine (presumably a vagus stimulant) was used, the carbonic acid output is reduced to a much greater extent than the oxygen intake.

	Pilocarpine		Vagus	
	Exp. 2	Exp. 3	Exp. 7	Exp. 8
Oxygen taken in	·30	·21	·13	·024
Carbonic acid given out	·10	·09	·07	·056

Comparison of vagus and pilocarpine with potassium chloride and chloroform.

We think it is important to compare the exchange during vagus inhibition, both when caused by stimulation of the nerve or by drugs, with that obtained by treating the heart with potassium salts and with chloroform.

[1] Richet's *Dictionnaire de Physiologie*, VI. p. 129.

[2] See this number of the *Journ. of Physiol.*

	KCl small dose	KCl large dose	Chloroform
Oxygen taken in	·55	·33	·37
Carbonic acid given out	·53	·67	1·9

In the two last of these cases the oxygen taken in is reduced to a much smaller figure than the carbonic acid given out.

The metabolism of the heart may conveniently be divided into two portions: (1) that connected with the beat, (2) that which is akin to the metabolism of resting muscle. Now the beat of the heart is much reduced or even abolished by a large dose of KCl or of chloroform and correspondingly with this there should be a great reduction of oxygen intake and carbonic acid output; but the carbonic acid output is not reduced so much as the oxygen intake. This may be the result of the direct effect of chloroform on the residual metabolism of the heart. In harmony with this is the fact that chloroform increases the carbonic acid output of the resting gastrocnemius (Fletcher). In other words both chloroform and potassium chloride in toxic doses produce not only depression of the cardiac muscle as shown by the falling off of the beat but also dissolution, that is a breakdown of tissue into relatively simple bodies of which carbonic acid is the only one with which we are concerned here. The effect is very similar to the changes which immediately follow death of the organ. This effect is in contrast to nervous inhibition whether produced by stimulation of the vagus nerves or by the administration of pilocarpine; in these the physiological inhibition is associated with an output of carbonic acid that is smaller than the amount of oxygen absorbed. This affords another proof that the action of such drugs as pilocarpine and potassium on the heart is entirely different, and to our mind tells strongly against the recent hypothesis of Howell[1] that vagus inhibition is due to the action of potassium salts.

Rate at which the equilibrium of carbonic acid is reached.

The figures under consideration are worth recording for yet another reason. In some experiments by one of us[2] in collaboration with Dr T. G. Brodie it was found that there was often an excessive output of carbonic acid at the beginning of the experiments. One suggestion made to account for this fact was that during manipulation the blood-flow had been slowed, and that carbonic acid was only slowly washed away and accumulated in the kidney. In other words that there was a

[1] Howell. *Amer. Journ. Physiol.* xv. p. 281. 1905–6.

[2] Barcroft and Brodie. This *Journal*, xxxii. p. 26. 1902.

very long lag between the carbonic acid production and its appearance in the blood. The results which we have tabulated with potassium chloride and chloroform might be explained in this way were it not for the pilocarpine and vagus results. In Exp. 7 for instance time was all important and the utmost expedition was used (the clock marked every 12 seconds); it will be clear from this tracing that the carbonic acid put into the blood was cut down very rapidly and that the lag between carbonic acid production and expulsion was relatively short.

Rate of flow through the coronary vessels.

The blood-flow through the coronary vessels is obviously influenced by several factors. An increase in the rate of heart-beat, or an increase in the blood-pressure at the mouths of the coronary arteries will of itself tend to influence the blood-flow. It will also be influenced by the power of the beat, an increase of tone of the heart causing a decrease of flow (other things being equal). Thus in Fig. 8 it will be noticed that a rise of the arterial pressure of the perfusing animal is accompanied by increased tone of the perfused heart and a simultaneous decrease of blood-flow.

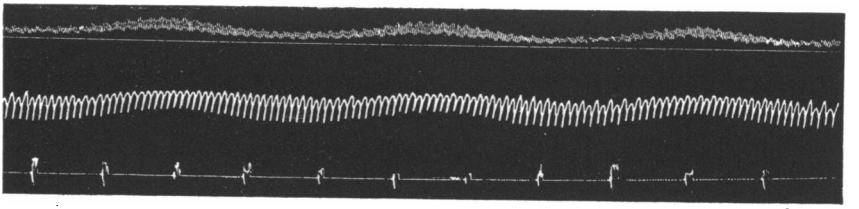

Fig. 8. The upper tracing represents the arterial pressure of the dog (Hürthle's manometer). Lower tracing shows the movements of the perfused heart. Upstroke = systole. The alterations of tone in the heart are synchronous with the Traube-Hering curves caused by injection of the $BaCl_2$. Time = 12 seconds.

The factors named above do not however explain the alterations in blood-flow which are recorded. We follow Schäfer in his observation that there is no evidence of vaso-motor nerves to the coronary system; it therefore becomes necessary to consider those cases of alteration in the rate of flow for which we find no reason on the ground of general blood-pressure or of the direct effect of the cardiac rhythm.

Arterial Pressure. The arterial pressure has been maintained so nearly constant in those experiments in which it was registered that we have no reason to suppose that any sudden change in the recorded rate

of flow was due to change of arterial pressure. It is possible that over the whole time which was occupied by an experiment changes in general arterial pressure may have been a factor for consideration. In considering the rates of blood-flow between two consecutive periods of an experiment we may eliminate the question of general arterial pressure and look to the heart itself for the cause of regulation of the blood-flow.

Alterations in the rhythm. The important changes in blood-flow which are unexplained by the alterations in the heart's rhythm are as follows.

1. As between Periods I and II of Exp. 1 there is nothing in the rate of the rhythm which would cause a decrease in the rate of blood-flow from 10 c.c. per minute to 3·3, *i.e.* a 66 % decrease. The relation of the tonus would tend to quicken the flow.

2. As between Periods II and III of Exp. 1 the same observation is true in a minor degree.

3. As between Periods I and II of Exp. 3 there was a considerable change in the rate of the beat. The pulse was 35 % faster in the first period than in the second, yet the rate of blood-flow was only about 4 % faster in the first.

4. As between Periods II and III of Exp. 3 there was the same change in the pulse, which in III was 35 % slower than in II. In this case the blood-flow was reduced by 40·6 %.

5. As between Periods III and IV of Exp. 4 there was no increase in activity of the heart, which was almost entirely quiescent, yet there was an increase of 22 % in the blood-flow.

6. As between Periods IV and V in Exp. 4 there was an enormous change in the activity produced by the injection of barium chloride and an increase of only 9 % in the blood-flow.

7. In Exp. 7 we may compare Periods I and III although they are not consecutive, for we have ascertained that the blood-pressure was constant and the periods were only separated by about two minutes. In Period I the blood-flow was 12 % more rapid than in the third period, though the heart was beating much more actively in the third period than in the first.

Out of 21 possible comparisons given in this paper, 7 are not explained on the grounds which we have considered. It remains therefore to seek some other factor which can exert an influence upon the calibre of the arterioles.

Gaskell[1] and others have suggested that the products of the

[1] This *Journal*, I. pp. 108 and 262. 1878–9.

metabolism of an organ exercise such a function. In such organs as the hearts which we have perfused the CO_2 output will be a measure of the general production of metabolites and it is, itself, probably an important dilator agent. We have therefore plotted out the relation between the CO_2 production and the rate of flow through the coronary vessels.

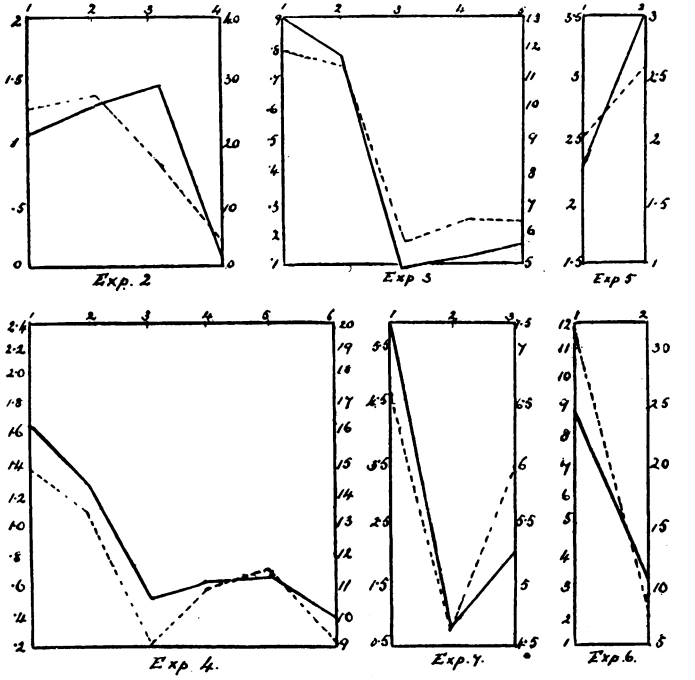

Fig. 9 shows the rate of flow through the coronary vessels (dotted line); and the output of carbonic acid (continuous line). The figures along the ordinates are in each case c.c. per minute, those on the left-hand side of each curve refer to the continuous line, those on the right-hand side to the dotted line. The periods are arranged along the abscissa.

The CO_2 output and the flow of blood follow one another with great regularity.

We have no instance in which there is an increased blood-flow with a diminished CO_2 output, and one case in which there is a definitely increased CO_2 output with a diminished blood-flow (Exp. 2, Period III).

We find in the production of katabolites a factor which will explain the alterations of blood-flow that cannot be explained on other grounds, and we have not discovered any evidence which prevents us from

believing that they are among the influences which exert a controlling action upon the calibre of the vessels.

In our experiments CO_2 may be only an index of other metabolic products, such as lactic acid and purine bodies, which have a similar action. Severini has found however that CO_2 causes dilation of the blood vessels in the frog and although this was not confirmed by Roy (see also Tarchanoff, *Pflüger's Arch.*, IX. p. 413), it has been confirmed by us; Brodie and Locke, Sherrington and Miss Sowton, inform us that they have found similar effects in the coronary vessels.

Energy of the heart's contraction. If we assume that the energy of the heart-beat is derived from the oxidation of a carbohydrate constituent by the oxygen taken, the data obtained in the foregoing experiments as to the intake of oxygen afford a means of estimating the amount of energy set free by the heart. The data are collected in the following table.

Exp.:—	1	2	3	4	7	8
Normal oxygen intake per grm. per min.	0·017	0·040	0·033	0·030	0·014	0·022
Maximum do. ...	0·045	0·083	—	0·040	0·022	—
Minimum do. ...	0·010	0·010	0·009	0·012	0·009	0·013

1 c.c. of O_2 oxidises ·0013 grms. of sugar. The heat equivalent of a gram of sugar is approximately 4000 small calories. The mechanical equivalent of 1 calorie is 42,550 centimetre-gram units of work. In a dog of 12 kilos the weight of the heart is about 120 grms. Thus the energy set free per minute of the heart of a dog of 12 kilos would be $\cdot0013 \times 4000 \times 42550 \times 120$ multiplied by ·017 if estimated by the lowest normal intake of oxygen (Exp. 1), and multiplied by ·04 if estimated by the highest normal intake (Exp. 4). That is, the energy varies from about 445,000 to 1,048,000 cm.-grm. units. The average for four experiments is about 786,000 cm.-grm. units. Since the heart was not working against any considerable pressure the numbers are probably somewhat low.

The experiments of Stolnikoff[1], Tigerstedt[2] Zuntz[3], and Stewart[4] gave the quantity of blood passing through the heart per second as about ·0018 of the body-weight. Allowing the efficiency of the heart to be 30% and calculating the work of the heart by the following

[1] *Arch. f. Physiol.* p. 81. Leipzig, 1886.
[2] *Skandinav. Arch.* III. p. 145. 1892–3.
[3] Quoted in Schäfer's *Text-Book*, II. p. 48.
[4] This *Journal*, XXII. p. 159. 1897.

formula, $W = QH + \frac{PQV^2}{29}$, the energy set free per minute by the heart of a dog weighing 12 kilos is about 700,000 cm.-grm. units.

Our estimations then agree fairly closely with those arrived at by the observers mentioned, but they are distinctly lower than the earlier results of Volkmann.

In the cat the energy set free per gram per minute appears to be somewhat less than in the dog.

Comparison of the heart with other organs. The minimum values of oxygen intake are remarkably close to one another, and may be represented as ·01 per gram per minute. The heart, of course, in no case has entirely lost its rhythm, but still it may be compared with some other organs during rest. The following are the approximate amounts of oxygen taken in by the resting tissues of which we have data: pancreas = ·03—·05 c.c. per gram per minute, the submaxillary gland ·03 c.c. and the kidney ·03 c.c. The tissue of the heart, therefore, apart from its beat, has not more than one-third of the metabolic value of these organs.

The maximum values given above may be compared in the same way with the values of active organs; those of the highest for the dog's heart was 0·083 c.c. per gram per minute, under the influence of adrenalin, whilst two others from the dog were 0·045 c.c. and 0·40 c.c. The corresponding approximations for the active kidney are ·07 c.c., submaxillary gland ·09 c.c., and pancreas ·1 c.c. Here again the heart appears to undergo smaller metabolic changes than the glands, for although the figure ·083 c.c. for the heart is very close to those for the glands, it is much lower than the highest recorded figure for any one of the three glands above mentioned. The figures for the submaxillary and the pancreas are approximate only inasmuch as the actual glands were not weighed in each case, the average weight of glands in dogs of the size used being taken as the basis for calculation.

The experiments of Richet and others have shown the average oxygen consumption of the dog to be ·017 c.c. per gram per minute and of the cat ·010 c.c.[1]

[1] See Schäfer's *Text-Book of Physiology*, I. p. 707.

Conclusions.

1. By means of perfusion from a living hirudinised animal we have maintained a circulation of undiluted blood through the coronary system of an excised heart. This circulation has been efficient enough to keep the heart in good condition for several hours.

2. This procedure has enabled us to make determinations of the gaseous exchange of the heart muscle and of the rate of the flow through the coronary vessels under varying conditions.

3. There is a general relation between the oxygen taken up by the heart and its activity, a relation which has already been indicated by Yeo. The carbonic acid output also varies with the activity of the heart, but lags somewhat behind it. Hence the changes in carbonic acid output lag behind the changes in oxygen intake.

4. In estimating the activity of the heart account must be taken of tonus, as well as of the rate and amplitude of the contractions. Increase of tonus, such as can be obtained by administering barium salts augments the gaseous exchange; and decrease of tonus, obtained by potassium chloride or chloroform, diminishes it. Instances of augmented rhythm are afforded by adrenalin, atropine after pilocarpine, and the after effect of vagus stimulation; instances of diminished rhythm by pilocarpine and vagus stimulation.

5. There is a close relationship between the carbonic acid output and the rate of flow through the coronary vessels; we have given reasons to show that the liberation of metabolic products from the heart, of which carbonic acid is the chief, controls the vaso-motor changes in the coronary arterioles.

6. Our results yield a figure for the energy transformed in the heart, which is in entire agreement with the calculations of Zuntz, Tigerstedt, Stewart, and Stolnikoff, for the work done by that organ but which is not in agreement with those of Volkmann and Vierordt.

7. The heart is of lower metabolic value, weight for weight, than the kidney, the pancreas, or the submaxillary gland.

We desire to tender our thanks to the British Association for a grant which has defrayed much of the expense of the above research, and to the Government Grant Committee of the Royal Society which has accorded us a sum of money for the special object of obtaining hirudin.