THE REGULATION OF THE ENERGY OUTPUT OF THE HEART.

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Part I. The influence of mechanical factors.

Experiments carried out in this Laboratory have shown that in an isolated heart, beating at a constant rhythm and well supplied with blood, the larger the diastolic volume of the heart (within physiological limits) the greater is the energy of its contraction. It is this property which accounts for the marvellous adaptability of the heart, completely separated from the central nervous system, to varying load, to which attention was first called by Cohnheim. So important is this property of the heart for the processes of adaptation and compensation in the healthy and diseased organ that it was called by one of us "the law of the heart"(1) and regarded as a special instance of the law connecting energy of the contractile process with the initial length of muscular fibre (Blix(2), A. V. Hill(3)). The law as stated above applies only so long as the physiological state of the cardiac muscle can be regarded as unimpaired. As the heart tires it has to dilate continuously in order to maintain its mechanical performance constant, so that the heart *in situ* becomes inefficient, *i.e.* unable to carry on the circulation at the previous output and arterial pressure, so soon as further dilatation is prevented by the heart, during diastole, coming up against the pericardium(4). In such a case freeing the heart from the pericardium will allow it to continue its function and to carry on the circulation as efficiently as before for a certain further period of time. It was shown by Lovatt Evans(5) and his fellow-workers that any increase in the work thrown upon the heart in the heart-lung preparation, whether by increasing the arterial resistance or by augmenting the inflow into the heart, caused a corresponding increase in the gaseous metabolism of the organ, whether measured by oxygen intake or by CO_2 output. It was therefore assumed that the increased energy of contraction incident on greater diastolic volume was attended by and due to increased chemical change. Thus

the amount of this latter should also be a function of the initial length of fibre, as has been shown to be the case for voluntary muscle, when the total chemical change is measured by the heat production (6). Direct proof of this relation was lacking. In Lovatt Evans's experiments no direct measurements were made of the pulmonary arterial pressure or of the coronary flow—both of them highly variable factors when the work of the heart is altered by changing the inflow or the arterial resistance—while alterations in the volume of the heart were inferred by the rough method of observing changes in the level of the blood in the venous reservoir of the heart-lung apparatus. It seemed to us that the gaseous metabolism of the heart was of sufficient importance to deserve reinvestigation by improved methods, profiting by the increased knowledge of the mechanical factors involved in the heart beat which have been brought out by subsequent investigation and measuring directly those quantities which had been simply inferred in Evans's experiments.

In this present investigation we have confined our attention to the oxygen consumption of the heart, since this serves as a sufficient measure of the total energy set free in the heart during its activity. It is a necessary condition of the continuance of the activity of the heart that the process of oxidative recovery during the diastolic period keep pace with the anaerobic breakdown which previously occurs during systole. The measurement of the oxygen consumption of the heart is thus equivalent to a measurement of the total heat production during the periods of contraction and recovery.

Cardiac muscle offers certain advantages over other forms of muscle for such a study. One is the ease of maintaining an adequate circulation through the muscle of a blood well oxygenated, in which the *p*H and the CO_2 content are maintained constant. In the heart-lung preparation the frequency of the beat, provided the *p*H of the blood is constant, depends only on the temperature of the pace-maker, so that by keeping the temperature of the entering blood constant, we can be assured of a regular rhythm throughout the whole of the experiment. It is easy, moreover, to maintain the work of the heart constant, or to alter it within very wide limits by changing the inflow or the arterial resistance. Finally, the heart may present great variations in diastolic volume and therefore in initial length of fibre within the physiological limits of its activity, accompanied by only minimal alterations in initial tension.

Previous work on the gaseous exchanges of the heart have not succeeded in establishing definite relationships between the mechanical

conditions under which the heart is placed and its oxygen consumption. The work of Evans and his collaborators has shown that as the work of the heart is increased its oxygen consumption rises. In different experiments, however, the relation between the work done and the oxygen consumption was extremely variable, and they failed to establish any definite relation between the volume of the heart and its oxygen consumption. Experiments such as those of Rohde(7), in which the mammalian heart is fed by saline solutions, are not adapted to solve the questions at issue, though this method may yield results when used with a cold-blooded heart. Observations on the oxygen consumption of the cold-blooded heart have been made by Weizsäcker(8) and by Lüscher(9), and we shall show later that the data obtained by Lüscher, when recalculated, tend to confirm the conclusions arrived at by us as the result of experiments on the dog's heart.

Methods. A new and simple method for the study of the oxygen consumption of the heart-lung has been devised. In principle it consists of a measurement of the decrease in the volume of air in a closed system circulating air to and from the lungs, removing the CO_2 continuously, while special precautions are taken to prevent variations in the volume of residual air in the lungs themselves after each deflation. The latter is achieved by the simple expedient of allowing the lungs to deflate themselves by their own elastic tension. Several other methods of achieving this end were tried, but none of them was found satisfactory, each introducing large errors. There are several possible errors in the method of allowing the lungs to deflate themselves. The first is that the elastic tension of the lung itself may change over a period of time. This has not been made the subject of a special study in this work because it has been possible to cancel out the possible effects of change in volume by repeating identical observations at various steps in almost all experiments; but if very long periods of observations on one preparation were to be conducted with the method here described it would become necessary to allow for the changes in the elastic tension of the lungs. Lung œdema would be a source of great error in our measurements if it were not so easy to detect the beginning of it upon our records. In Fig. 1 is shown a portion of a record of an experiment in which œdema of the lungs occurred. Just after the point *A* there can be seen a change in the slope of the oxygen consumption record, and from that point the slope becomes more precipitous. We have always found lung œdema to have a rapid onset like that illustrated. The detection of such a change is never in doubt, and when it occurs an experiment must be terminated immediately. The beating of the heart freed from the pericardium against the lungs tends to make the spirometer record uneven and difficult to measure, and in such cases we have found it necessary to fix the heart in a cardiometer in order to obtain consistent results. A further precaution we have found essential is to ensure against any portion of the lungs being collapsed at the time of beginning an experiment. It is perhaps needless to say that the lungs must not be handled, or even touched, during the course of a measurement. It is apparent that very many errors must be guarded against if this method is to be found sensitive and satisfactory, and it may be well to mention that we spent four months eliminating sources of error before any useful data were obtained.

In detail, the respiration system employed is as follows: a single cylinder pump (Fig. 2, *B*) of variable stroke volume (Palmer's "ideal" respiration pump) was used, the

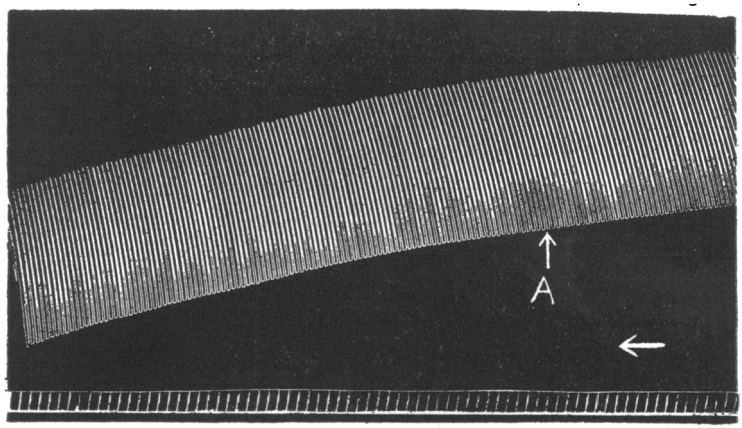

Fig. 1. Showing a portion of the spirometer record of an experiment in which œdema of the lungs occurred. The paper was moving from right to left, and the time signals mark each 10 secs. We always measure from the lowest points on the spirometer tracing, as they are much more regular than the highest points. Just after point *A* the slope loses its previous steady character and from that point on becomes steeper and steeper, corresponding with the development of the lung œdema.

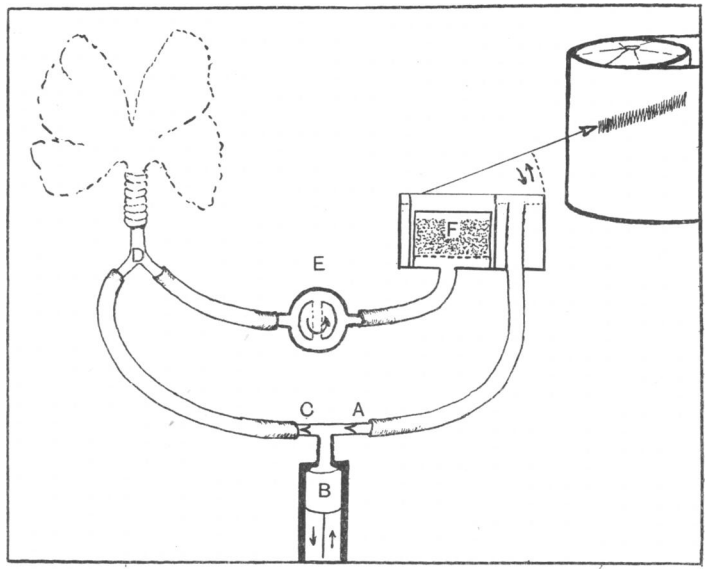

Fig. 2. Details of the respiration system employed, described in the text.

cylinder, piston and valves of which were very accurately ground to prevent any possibility of leakage at the pressures which come into play in filling the lungs. Air comes to the pump through the valve *A* from the spirometer *F* of 300 c.c. capacity, and is expelled through valvé *C* into the lungs, through the forked tracheal cannula *D*. While the pump is forcing air into the lungs the valve *E* is closed. As soon as the inflation is complete *E* is opened and the lungs deflate themselves. They force air into *F*, which is partially filled with soda lime, as in the Krogh apparatus, to absorb the CO_2 given up in the lungs. The spirometer float has a recording lever which writes on a moving paper, as also do a piston recorder connected with the cardiometer, and a manometer float. The system used is such that 1 mm. fall of the writing lever corresponds to a decrease of approximately 2·5 c.c. in the volume of the system. The change in volume during a single observation-period was never less than 50 c.c. Such a volume can be measured with an error of less than 5 p.c., since it involves making only two measurements, each accurate to $\frac{1}{2}$ mm. Repeated measurements always fell within that limit, and usually within $\frac{1}{4}$ mm. The latter gives a total error of $2\frac{1}{2}$ p.c. on a measurement of 50 c.c. A rather troublesome complication in measuring changes of volume resulted from the use of a lever writing on the arc of a rather small circle; at different positions of the lever a given fall corresponds to different volume changes, since it is the arc and not the perpendicular that is directly proportional to the volume. A correction must be made for the difference. The amount of the correction varies from 0 to 10 p.c. of the total value, the exact amount depending upon the angle the lever makes with the horizontal. The smaller the angle the less the correction.

The heart-lung preparation was made in the usual way (Knowlton and Starling(10)), except that it was converted into a closed system to prevent loss of gases from the blood. This was done by using a collapsible rubber sleeve, immersed in a warm water bath, as the venous reservoir. (A similar system has been employed by Daly(11) for another purpose.) A further change in the ordinary technique of the heart-lung preparation was the insertion of a Stolnikow stromuhr in the pulmonary artery. In order to avoid clotting in the stromuhr this was done after the heart-lung circuit had been established. The Stolnikow stromuhr has been described, in the form used, by Anrep(12). In order to measure the volume of the heart a Henderson cardiometer has been employed, fitted with a special rubber sleeve of very thin material, which lay snugly against the heart and made an absolutely air-tight seal around the ventricles without compressing the atrioventricular ring. The volume change was recorded with Palmer's large glass piston recorder. We have measured only the volume of the ventricles, since the atria make up less than 10 p.c. of the weight of the heart, and it seemed reasonable to simplify the problem by neglecting the influence of changes in that small fraction of the total metabolism of the heart upon the final values. Ultimately it may become necessary to reckon with it, but with the present methods, involving a possible error of 5 p.c. in metabolism values, the error involved may probably be neglected.

We have of necessity included in our measurements of oxygen consumption of the heart the oxygen used by the lungs themselves. If the metabolism of the lungs does not alter under the experimental conditions we have used, as the work of Evans and Starling(13) indicates, we are justified in assuming it a constant in a given experiment. The metabolism of the lungs, therefore, appears as a constant value added to the real oxygen consumption of the heart. It will in no way interfere with the validity of interpretations or calculations we have made.

In our experiments on the effect of mechanical factors on the energy output we maintained the heart rate constant by keeping the temperature of the heart constant. Previous work has shown that the hydrogen ion concentration in the blood, its CO_2 content, and its lactic acid content do not change appreciably during the course of an experiment, after

the first quarter hour. This preliminary period we have never employed for oxygen measurements.

The pulmonary arterial pressure was measured by a saline manometer, connected with a branch from the cannula in the pulmonary artery. The aortic pressure was measured by a mercury manometer. In both cases the mean pressure was taken as the basis of the calculations of the work done by the heart.

Results. The general plan of all our experiments was to determine whether any relation could be established between the consumption of oxygen by the heart and the mechanical conditions of its beat. The resistance to the contraction is determined by the pressures in the pulmonary artery and aorta, so that alterations in these pressures would cause corresponding alterations in the maximum pressures attained in the ventricles during the process of contraction. The work of the heart depends on the output and on the arterial resistance and can be altered therefore by varying either of these two factors. The diastolic volume of the heart will be increased by any increase in either or both of the factors, arterial resistance and venous inflow. The results of our experiments are presented in graphic form, each figure given being a sample of several experiments which yielded corresponding results.

We may deal first with the influence of changes in arterial resistance. In a heart in good condition alterations in the arterial resistance cause

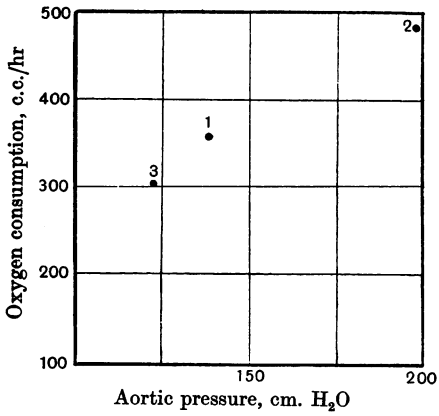

Fig. 3 *a*

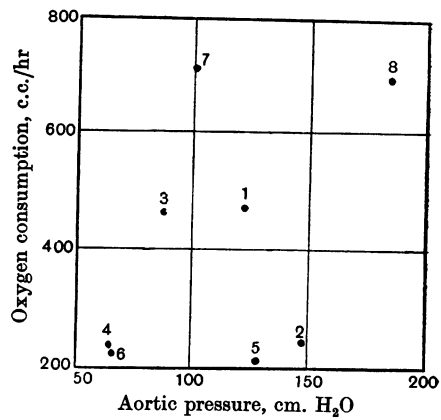

Fig. 3 *b*

Fig. 3. Fig. 3 *a* shows data on the oxygen consumption of a heart whose total output was kept constant at 375 c.c. per min., while the aortic pressure was changed. The points are numbered in their time sequence. The oxygen consumption is observed to increase or decrease with the corresponding changes in aortic pressure.

Fig. 3 *b* shows data from another heart whose output was changed as well as the aortic pressure. In this experiment there is no proportionality whatsoever visible between aortic pressure and oxygen consumption.

corresponding alterations in the oxygen consumption of the heart. The results of one such experiment are shown in Fig. 3 *a*, in which changes in the arterial pressure are plotted against changes in the total oxygen consumption of the heart lung preparation. The figures over the dots representing the oxygen consumption indicate the order in which the observations were made. It will be seen that the increase in oxygen consumption is, within the limits of the observations, directly proportional to the increment in aortic pressure. Since the isometric part of the intracardiac pressure curve is determined by the arterial resistance it might be thought that here we had a direct relation between the pressure attained in the isometric portion of the curve and the oxygen consumption. Reference to Figs. 3 *b* and 4 shows, however, that the aortic pressure by itself is not the determining factor. In the experiments, the results of which are given in Fig. 3 *b*, the venous inflow, instead of being maintained constant as in Fig. 3 *a*, was altered, and now it will be seen that there is no relation at all between the aortic pressure and the oxygen consumption. With increasing inflow there is a corresponding increase in the pulmonary arterial pressure but the relationship between oxygen consumption and arterial resistance is not altered if with varying inflow, as in Fig. 4, we plot the oxygen consumption against the *sum* of the pressures in the pulmonary artery and aorta respectively.

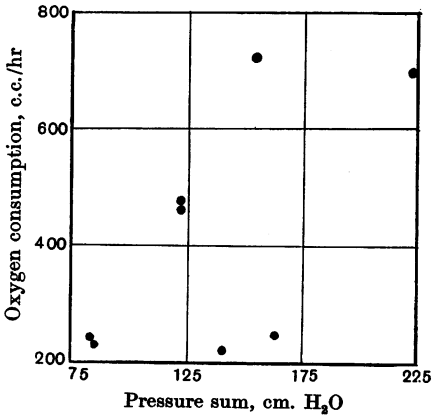

Fig. 4. Data of an experiment typical of many others, showing that the pressure sum, *i.e.* the numerical sum of the pulmonary arterial and the aortic pressures, does not govern the oxygen consumption of the heart.

In the experiment given in Fig. 3 *a*, since the inflow into the heart was maintained constant, alterations in the resistance were equivalent

to alterations in the total work of the heart, and if we multiply resistance by output so as to obtain the work of the heart and plot this figure against the oxygen consumption, as has been done in Fig. 5 *a*, we find a definite relation between oxygen consumption and the work. We may see from this and other experiments that as the total work of the heart increases there is a corresponding increase in oxygen consumption. The oxygen usage seems to increase more slowly as the work rises to a maximum, so that it would seem that the efficiency of the heart under these

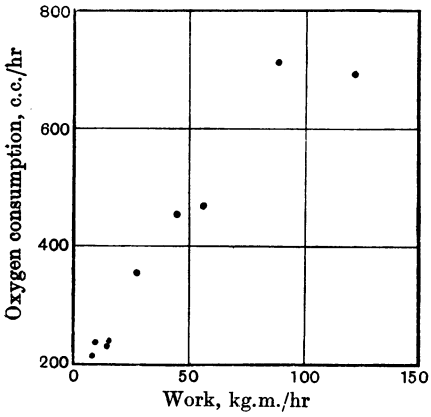

Fig. 5 *a*

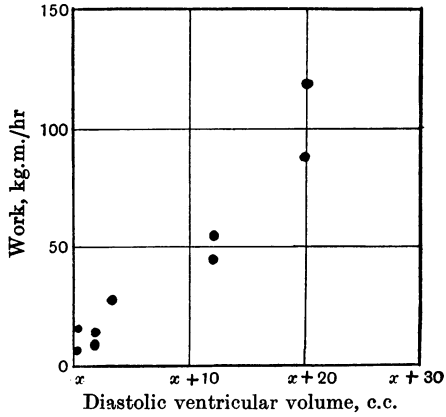

Fig. 5

Fig. 5. Figs. 5 *a* and 5 *b* present data from an experiment in which the work of the heart was varied by numerous changes in output and pressure. The outputs ranged from 200–1200 c.c. per min., and the pressures from 80–120 mm. Hg.

Fig. 5 *a* shows the work done plotted against the oxygen consumed. In calculating the work of the heart the velocity factor was neglected. The direct correspondence between the two is very definite in this experiment.

Fig. 5 *b* shows data from the same experiment, showing work plotted against the diastolic volume of the ventricles. The volumes are expressed as x + known values. The x represents the lowest value of the volume during the experiment, which is impossible to measure when a cardiometer is used to record heart volume. The cardiometer enables one to measure only an increase over this minimum value. The figure shows a direct correspondence between work done and ventricular volume.

conditions is higher at heavy than at light loads. A similar conclusion was arrived at by Evans. In the experiment given in Fig. 5 *a* the volume of the heart was recorded throughout the experiment, and in Fig. 5 *b* the alterations in diastolic ventricular volume are plotted against the work done by the heart in kilogram metres per hour. It will be seen that there was a steady rise in the diastolic volume as the work thrown upon the heart increased, whether this increased work was due to altera-

tions in the arterial resistance or in the cardiac output. (The absolute ventricular volume was not measured. The volume x indicates the smallest diastolic volume obtained throughout the experiment, and the increments of this volume are plotted along the abscissa against the total external work of the ventricles as obtained by multiplying the total output into the mean pulmonary and arterial pressures respectively.) In Fig. 6 the

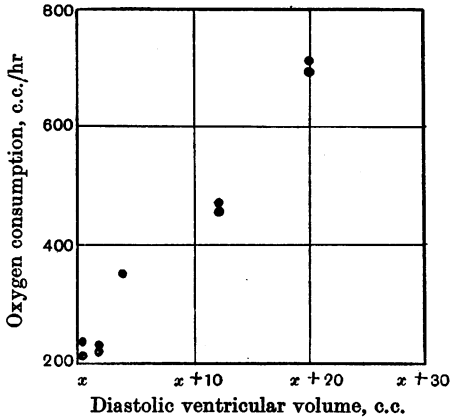

Fig. 6. Shows the oxygen consumption of a heart plotted against its diastolic ventricular volume. This figure is plotted from data from the same experiment from which Figs. 5 *a* and 5 *b* are taken. In the ventricular volumes x = the lowest volume obtained during the experiment. Many variations of pressure and output were employed. The changes in oxygen consumption are seen to vary directly with the changes in diastolic volume at all stages of the experiment.

oxygen consumption of the heart from which Figs. 5 *a* and 5 *b* were taken, is plotted against the diastolic ventricular volume; a direct proportionality is to be observed between the oxygen consumption and the increments in diastolic volume. These experiments thus lead us to the conclusion that the adaptation of the heart to increased load, whether due to raised arterial resistance or increased output, is effected by dilatation of the heart, this dilatation with the resultant increased diastolic length of fibre being responsible for an increase in the total energy set free at each contraction of the heart muscle.

Our study of the volume and the oxygen consumption of the heart under these varying conditions thus tends to confirm conclusions already arrived at by Anrep as a result of experiments on the cold-blooded as well as on the mammalian heart, namely, that the diastolic volume of the heart depends, not on arterial resistance or on venous inflow alone, but in every case on the product of these two factors, namely, the external work done by the heart at each contraction.

These results, however, apply only to a certain proportion of our experiments. In others, such as that of which the results are given in Figs. 7 *a* and 7 *b*, the relation between the oxygen consumption and

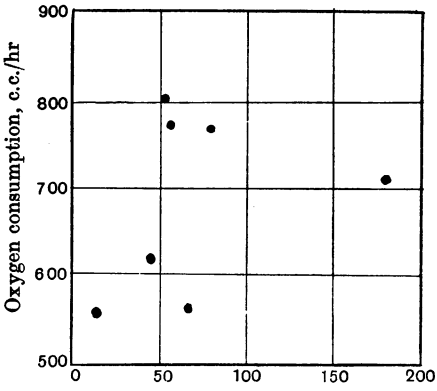

Fig. 7 *a*

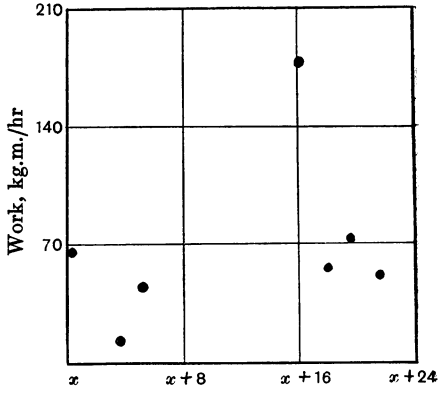

Fig. 7 *b*

Fig. 7. Fig. 7 *a* shows data from an experiment in which the pressure and output of the heart were varied widely, the pressure from 80–160 mm. Hg, and the output from 200–1000 c.c. per min. In this heart, which was not in good functional condition (*i.e.* it did not recover to the same volume when it was given the same load after a period of high work), there is nothing more than a random relationship between work done and oxygen consumed.

Fig. 7 *b* shows the relation between the diastolic ventricular volume and the work done. The random relationship is to be contrasted with the proportionality in Fig. 5 *b*.

work done by the heart or between the work of the heart and the diastolic volume, seems to be entirely random. In order to obtain the results given in Figs. 3–6 it is essential that the heart be in good condition and remain in good condition over the period of the observations. The test for "good condition" is that the diastolic volume of the heart remain at a steady level so long as the mechanical conditions of inflow and arterial resistance are unaltered, and that, after changes in volume have been brought about by increase in either of these two factors, the diastolic volume return to its previous level on restoring the previous mechanical conditions. In no case does the heart in a heart-lung preparation remain throughout the experiment in this good physiological state, though in many cases during the first one to one and a half hours it deviates but little from this ideal condition. Generally, however, from the very beginning of the experiment the heart, under even a moderate load, shows a steady slow dilatation although the load is maintained constant,

and the rate at which this dilatation occurs is much increased by further increase in the strain to which the heart is subjected. These are the conditions under which the random relationships between work, oxygen consumption and diastolic volume, such as those shown in Figs. 7 *a* and 7 *b*, are obtained. One relationship, however, remains unaltered during this process of deterioration of the physiological condition of the heart muscle, namely, the relation between diastolic volume and oxygen consumption. In the experiment of which the results are given in Fig. 8 the work done by the heart was maintained constant for a period of four hours. During this time the heart dilated continuously, the dilatation affecting both diastolic and systolic volumes so that the output at each beat and the total work remained constant. The oxygen consumption also increased steadily, so that, when the oxygen consumption is plotted against the diastolic ventricular volume, we find an approximately

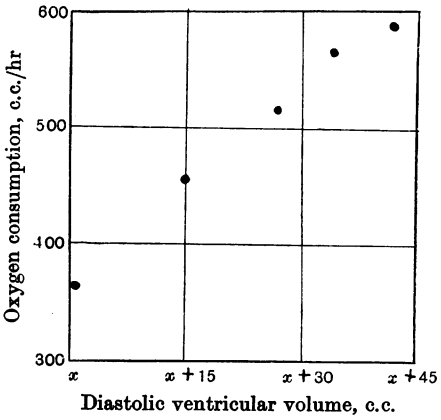

Fig. 8

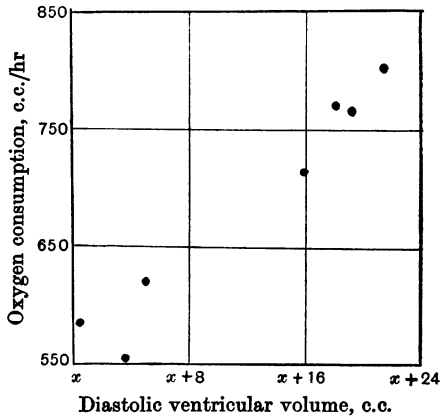

Fig. 9

Fig. 8. In the experiment here shown the arterial pressure was held constant at 100 mm. Hg and the output at 450 c.c. per min., over a period of 4 hours. The figure shows that there was an increase in oxygen consumption concomitant with and proportional to the degree of dilatation of the heart during the experimental period.

Fig. 9. Showing the direct proportionality between increments in diastolic ventricular volume and in oxygen consumption in the same experiment from which Figs. 7 *a* and 7 *b* are taken. The correspondence between heart volume and energy liberated, even when the work done bears no constant relation to either, is very striking.

linear relation between the oxygen consumption and the increment in diastolic volume. And the same relation is found when the work of the heart is varied in the course of the experiment. In Fig. 9 the diastolic volume in the experiment of which the results are given in Figs. 7 *a* and

7 *b*, is plotted against the oxygen consumption, and here we find that the random relationship has disappeared and that increase in oxygen consumption goes *pari passu* with increase in diastolic ventricular volume. And in all our experiments similar relations are to be observed (Fig. 10).

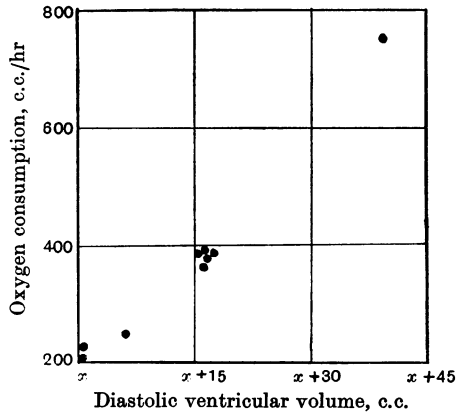

Fig. 10. Showing data from another experiment similar to that in Fig. 9. Wide variations of arterial pressure and cardiac output were used. The direct proportion between the changes in diastolic volume and those in oxygen consumption is again to be noted.

Provided that the other conditions of the heart muscle, *e.g.* temperature, composition and *p*H of circulating blood be maintained constant, the oxygen consumption by the heart increases and diminishes with the diastolic volume of the heart. Throughout a long experiment it is possible to keep the diastolic volume constant by gradually reducing the load, and it seems immaterial for the purpose whether this reduction be effected by diminishing the inflow or by diminishing the arterial resistance, provided the arterial resistance is sufficient to maintain an adequate flow of blood through the coronary arteries. Under these conditions it is found that the oxygen consumption of the heart remains at a constant level.

Thus, among the mechanical factors of the heart beat which we have studied, the diastolic volume, *i.e.* the initial length of the cardiac muscular fibres, seems to be the determining factor for the oxygen consumption of the heart, *i.e.* for the total energy set free at each contraction. It is interesting that a similar conclusion may be deduced from the experiments of Lüscher on the frog's heart, the only ones recorded in the literature in which an accurate measurement of ventricular volume has been made simultaneously with a measurement of oxygen consumption. Lüscher believed on *a priori* grounds that the

oxygen consumption of the heart should be directly proportional to the pressure and the ventricular volume. He therefore sought to find if the ratio $\frac{O_2 \text{ used}}{\text{pressure} \times \text{volume}}$ were a constant. He found as much as 30 p.c. variation in the value of the ratio and considered this a fair agreement in spite of the fact that he was able to reproduce quantitative results with an accuracy of 10 p.c.

Apparently it did not occur to him to test the relationship between simply the ventricular volume and the oxygen consumed. For if one takes his published data (Exps. 1, 2 and 3 in Table VII, p. 120) and determines the value of the ratio $\frac{O_2 \text{ used}}{\text{ventricular volume}}$ one finds it to be constant to within 10 p.c. for a given heart. These values are shown in Table I.

TABLE I.

Table showing the constancy of the ratio $\frac{O_2 \text{ used}}{\text{ventricular volume}}$ in Lüscher's experiments on the frog's heart, and comparing it with the ratio $\frac{O_2 \text{ used}}{\text{pressure} \times \text{volume}}$, which he considered a satisfactory constant. Each experiment was upon a separate heart, and he gives only two determinations on each heart. The second ratio is seen to be nearly constant for each heart.

Exp. no.	$\frac{O_2 \text{ used}}{\text{pressure} \times \text{volume}}$	$\frac{O_2 \text{ used}}{\text{volume}}$
1	7·4	5·9
	9·8	5·4
2	7·5	7·3
	10·0	7·1
3	8·8	7·3
	10·7	7·0

The facts here presented enable us to give greater precision to the general relationships formulated as the law of the heart, namely, that within physiological limits the larger the volume of the heart the greater are the energy of its contraction and the amount of chemical change at each contraction. We can now state that under all conditions of load, output and fatigue the total energy liberated at each beat is determined by the diastolic volume of the heart and therefore by the muscle-fibre length at the beginning of contraction. This inter-relation between physical dimensions and the amount of chemical change taking place is the explanation of the adaptability of the isolated heart with respect to its load. Under physiological conditions, *i.e.* so long as the functional capacity of the heart muscle remains unchanged, the mechanical energy of the heart's contraction, as measured by the work it can do, will increase or diminish with the total chemical energy liberated. Thus under

these conditions we may say that the work done by the isolated heart at each beat is determined by its diastolic volume. As the heart tires or as its physiological capacity diminishes in the course of a long experiment, especially when it is given a heavy load, the heart has to dilate more and more in order to carry out the work. This dilatation, as we have seen, is associated with an ever-increasing oxygen consumption, so that the relation of the mechanical work done by the heart in its contraction to the total energy liberated becomes continually smaller. Fatigue of the heart muscle or diminished physiological capacity is therefore determined, not by a diminution in the total energy liberated, but by a diminution in the mechanical efficiency of the muscle regarded as a machine, *i.e.* in the proportion borne by the mechanical work to the total energy liberated.

On a previous occasion one of us has defined tone of the heart as "synonymous with physiological condition or fitness of the muscle fibre" and its measure as "the energy set free per unit length of muscle fibre at each contraction of the heart."(1) This statement is only correct if we insert the word "mechanical" before "energy set free." Probably a more correct definition of tone would be the mechanical efficiency of the muscle fibre, *i.e.* the relation of the mechanical energy to the total energy liberated: the latter, as we have seen, does not change with fatigue but only that portion of it, which can be utilised for the performance of work.

The conclusions we have formulated only hold good so long as the chemical and temperature conditions of the heart muscle are maintained constant. We have no evidence as yet as to the action of alterations in the *p*H of the circulating blood, which are known to cause changes in the diastolic volume and the rhythm of the heart, but we have definite evidence that adrenaline increases the energy output of the heart at a given fibre length. This it does proportionately at all fibre lengths, so that the relation of energy liberated to initial length of fibre still persists, the only change being that the oxygen consumption at any initial fibre length is increased as compared to the heart without adrenaline.

Till now we have given no experimental evidence that the systolic volume of the heart is not a factor in determining energy liberation. One can, by suitable manipulations of inflow and arterial pressure, alter the diastolic volume, holding the systolic constant. When one does so, the oxygen consumption is not constant, but varies in proportion to the diastolic volume. On the other hand, one can keep the diastolic volume

constant and change the systolic, when one finds that the oxygen consumption does not change but remains steady with the diastolic volume. Data on this point are presented in Table II.

TABLE II.

Table showing measurements of the oxygen consumption of the heart and of the volume of its ventricles in systole and in diastole. By suitable manipulation of venous inflow and arterial pressure the diastolic volume was changed without altering the systolic volume, and *vice versa*. It is seen that the oxygen consumption does not vary with systolic volume, but follows the diastolic volume of the ventricles.

Experiment	Oxygen consumption c.c./hr.	Systolic ventricular volume c.c.	Diastolic ventricular volume c.c.	Cardiac output c.c. per beat	Aortic pressure cm. H_2O	Pulmonary arterial pressure cm. H_2O
19. iii. 1926	240	$x+5$	$x+7{\cdot}6$	1·3	150	14
	462	$x+5$	$x+14$	4·5	88	35
	238	$x+5$	$x+7{\cdot}8$	1·4	65	16
22. iii. 1926	772	$x+10$	$x+15{\cdot}4$	2·7	216	23
	768	$x+4{\cdot}4$	$x+16{\cdot}0$	5·8	108	27

PART II. THE INFLUENCE OF THE HEART RATE.

In a study of the influence of the heart rate upon the energy cost of cardiac activity two important questions present themselves. First, is the energy output per beat, at a given diastolic fibre length, constant at all heart rates? And second, does the mechanical efficiency of the heart vary with the heart rate?

No satisfactory answer to either of these questions has been arrived at by previous work. Evans(14) experimented with changes in heart rate produced by altering the temperature of the heart, and found the oxygen consumption per beat increased at higher temperatures, at which the heart rate is increased. It is impossible to interpret that result, however, because the heart dilates at higher temperatures and hence one should expect a greater oxygen consumption on the basis of the data presented in Part I. Moreover, the effect of temperature upon the speed of the chemical processes in muscle contraction is not sufficiently well understood to permit one to compare beats at two temperatures under the assumption that they should be alike except for the rate. In fact, the work of Hartree and Hill(15) upon heat production in striated muscle makes such a comparison appear to be invalid. Evans recognized the complexity of the problem and did not attempt to draw a general inference regarding the relation between rate and the energy output per beat from his findings.

We have tried to solve the problem of the relation between heart rate and oxygen consumption per beat by changing the heart rate at a constant temperature, and by taking into account diastolic volume of the ventricles.

Methods. We have experimented with a number of methods of altering the heart rate. We have attempted to "drive" the heart by faradic stimulation of the sino-auricular node at a rate faster than the normal rhythm. That method was found unsatisfactory, for most hearts are unwilling to "follow" at a pace appreciably higher than their own. One frequently obtains partial contractions at each stimulus, when by comparing the blood-pressure with the myographic record of auricular contraction one finds that only half or a third of the beats are effective in expelling any blood from the ventricles. There is not actually a heart block since inspection of the ventricles shows that they are contracting at each stimulus, but only partially. It is highly improbable that such weak contractions would have the same energy output as a normal one, and consequently we have been forced to adopt other methods. Pilocarpine was tried, and although it reduces the heart rate satisfactorily, it has a stimulating action upon the bronchioles, contracting them and hindering deflation of the lungs, thus making metabolism study by the method we employed impossible. The method of altering heart rate which we have found satisfactory is that of vagal slowing. It has not been possible in the heart-lung preparation to stimulate the vagus nerves electrically for any length of time after the preparation is made. Consequently we kept the brain of the animal alive by perfusing it by means of a second heart-lung preparation. As Anrep and Starling(16) and Anrep and Segall(17) have shown, it is possible to slow a heart by increasing the blood-pressure in the brain. By means of the separate heart-lung we were able to vary that pressure, and consequently the heart rate, at will. There is no connection between the circulations in the brain and the heart-lung of the same animal, consequently the oxygen consumption of the brain was not included in that of the heart-lung. The heart rate was recorded by myographic registration of the auricular contraction upon a rapidly moving drum. In determining the rate every beat in a period was counted. The oxygen consumption of the heart-lung preparation was measured as described in Part I. The heart-lung preparation was made in the same manner as before, except that the Stolnikow stromuhr was placed in the aortic circuit instead of in the pulmonary artery. In that way we were unable to measure the coronary blood flow. That inability appeared to be of small consequence for this study. So far as the first question we have tried to settle is concerned, the cardiac output is of no consequence; for the second question the possible coronary flow changes are of some importance, for Anrep and Segall, in work as yet unpublished, have shown that the coronaries are constricted under vagus stimulation and hence the coronary flow is decreased. That effect is not large as compared with the total volume of blood our hearts put out, which was over 700 c.c. per minute, exclusive of the coronary flow. We kept the arterial pressure constant and hence the most important regulator of coronary flow was held steady. The possible effects of the changes in coronary flow will be discussed under the results.

Results. When the diastolic heart volume is held constant by adjusting the output, and the heart rate altered by central vagus stimulation of the innervated heart-lung, the total oxygen consumption per unit time is slightly less than at the higher heart rate. The relevant data from the experiments performed are given in Table III.

TABLE III.

Table showing the oxygen consumption of the heart per beat at low and high heart rates, at a constant diastolic volume. The low rates were produced by central vagus stimulation of an innervated heart-lung. The oxygen consumption per beat is higher at low heart rates than at high.

Experiment	O_2 consumed per hour c.c.	Heart rate beats per minute	O_2 consumed per beat per minute per hour c.c.
28. v. 1926	320	107	3·00
	335	125	2·63
	280	92	3·00
3. vi. 1926	333	103	3·23
	356	128	2·78

The concordance of the data in these experiments in which we have eliminated any source of confusion from heart volume changes makes it very probable that in reality a heart puts out less energy per contraction at the same initial fibre length when contracting frequently than when contracting less frequently.

In support of this belief we may say that experiments upon changes in rate by temperature, by driving, and by pilocarpine, all yield the same result. We have not placed complete reliance upon any of these other methods, for reasons outlined above, but when one obviates the difficulties in each, as we have been able to do somewhat satisfactorily, the end result always shows the same fact, namely, that the oxygen consumed per beat is higher, the slower the heart rate. We feel that the vagal stimulation experiments are the only entirely satisfactory ones, and we are, consequently, merely mentioning the other results as confirmatory evidence.

With regard to the efficiency of doing work at various heart rates we have found, as Table IV shows, that the heart uses somewhat less oxygen to do a given amount of work when the rate is slow than when it is rapid.

TABLE IV.

Table showing the influence of rate upon the efficiency of the heart under a constant load. The heart volume increased as the heart rate decreased in consequence of the fact that the heart had more work to do per beat. In each experiment the load put upon the heart was the same at high and low rates. The aortic pressure was 120 mm. Hg, and the aortic output about 700 c.c. per min. in each case.

Experiment	O_2 consumed c.c./hr.	Heart rate beats/min.	Diastolic ventricular volume c.c.	Remarks
28. v. 1926	325	151	x	
	275	92	$x+9$	Vagal stimulation
	490	168	$x+3$	
	320	107	$x+9·5$	Vagal stimulation
3. vi. 1926	414	128	x	
	333	103	$x+15$	Vagal stimulation

It was mentioned before that our failure to measure the coronary blood flow in these experiments makes them slightly imperfect, for there is the possibility of a 5 p.c. decrease in work done during the vagal excitation. Thus the decrease in oxygen consumed per unit of time under vagal inhibition may not represent quite so large an increase in absolute efficiency of the heart. Even allowing for a 5 p.c. change in the total work, which is ample to cover the possibilities, the hearts would still have been considerably more efficient at the low rates than at the high. Thus it appears that slowing the heart is a means of making it more efficient in carrying the small loads that it has to do when the body is at rest, normally. This is true in spite of the fact that each beat is more expensive at a given fibre length at slow rates than at more rapid ones. It implies that the saving effected by making each contraction do more work, and hence be more efficient mechanically, is more than enough to counterbalance the other effect.

Conclusions (Part I).

1. Under all the conditions we have studied, the oxygen consumption of the isolated heart, maintained under constant chemical and temperature conditions, is determined by its diastolic volume, and therefore by the initial length of its muscular fibres. This rule applies whatever the physiological condition of the heart. During the whole of an experiment the oxygen consumption at a given diastolic volume is always the same, whatever the work that the heart is performing at this volume.

2. In a heart functioning well, as at the beginning of an experiment, every increase or decrease in work done by the heart, is accompanied by a proportional increase or decrease in diastolic volume. The diastolic volume is constant for any given amount of work, whatever be the inflow and the arterial resistance. This is in confirmation of Anrep's findings.

3. It follows from (1) and (2) that any increase in the work demanded of the heart is met by a corresponding increase in the oxygen consumption of this organ, consequent on the increased initial length of its muscle fibres.

4. This interrelation between physical dimensions and the amount of chemical change taking place is the explanation of the adaptability of the isolated heart with respect to its load. But as the heart tires, and its functional capacity decreases, its mechanical efficiency is diminished: *i.e.* although the total energy (as measured by oxygen consumption) liberated at any given initial length of fibre remains unchanged, the fraction of this energy which can be utilised for the per-

formance of work progressively diminishes. To do the same amount of work the heart has therefore to dilate continuously, and the work is maintained constant at an ever-increasing cost in total energy.

5. The oxygen consumption of the heart has no relation to the systolic volume.

6. There is evidence that adrenaline increases the oxygen consumption at a given fibre length, without however altering the general correspondence between changes in diastolic volume and in oxygen consumption.

Conclusions (Part II).

1. At the same diastolic length of fibre, a heart uses more oxygen per beat when contracting at a low rate than at a high.

2. Slowing the heart enables it to do a given amount of work per unit time more economically.

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