The Lewis A. Connor Memorial Lecture
The Physiology of the Cardiac Output

By W. F. Hamilton, Ph.D.

The primary function of the heart is to supply an adequate stream of oxygenated blood to the body. Transportation of other nutrients and wastes is an easy task compared to the transportation of oxygen. Thus, even in the resting state, one fourth of the blood’s oxygen is depleted as the blood passes through the body and goes back to the lungs; whereas it picks up only one eighth of its content of carbon dioxide on the same trip. The nutrients and wastes such as blood sugar and urea have an even smaller arteriovenous difference in proportion to blood content.

Thus it would seem that oxygen transport is the strategic function of the circulation and, from that assumption and from many other facts, it can be argued unequivocally that the handicaps resulting from the sudden insufficiency of the circulation in syncope and shock stem directly from failure of oxygen supply. More equivocally, but with some degree of probability, it can be argued that failure of adequate oxygen transport is an essential factor in activating the renal and hormonal mechanisms which cause the kidney to conserve water and salt, and which lead to the edema and plethora of congestive failure of the circulation.1

The circulation fails not necessarily because of a weak heart but also because even a normal heart cannot meet the oxygen demand as a result of some maladjustment other than that of the valves or the myocardium. In thyrotoxicosis the oxygen demand is increased; in certain pulmonary diseases and anemia the blood cannot take up its fair load of oxygen2; and in certain cases of beriberi there is a subtle physiologic interference with the utilization of oxygen. In all of these conditions there may be failure of oxygen supply and consequent congestive failure while the heart is laboring strongly and doing twice the normal pumping job. For this reason it might be well to think of the syndrome in general as congestive failure of the circulation rather than congestive heart failure.

The circulation rate, or cardiac output, thus does not have simple and uncomplicated relation to the development of heart disease symptoms. In order to unravel the complications of the regulation of the normal circulation and its disturbances in disease it is best to review the methods and their adequacy for measuring the output of the heart.

William Harvey3 based his argument that the blood did circulate upon the arrangement of the valves of the heart to permit only flow from veins to arteries. As a first instance of the quantitative method in physiology he suggested that the left ventricle contains two or three ounces of blood and, on contracting, ejects all or part of it into the arteries. He was not impelled by the necessities of his thesis to argue for a two to three ounce stroke volume because a single dram per beat would defeat the Galenic tradition and accumulate in the arteries to burst them.

Among the pioneers of the study of the circulation we should also pay our respects to Stephen Hales4 who made casts of the left ventricular cavity and, assuming that each stroke emptied it, calculated to four figures the cardiac output, the velocity of the blood flow in the aorta and in its branches by dividing the output by the aggregate cross area of the arterial tree at various levels. He located the peripheral resistance—to use modern jargon—in the minute vessels and worked out an explanation for dropsy that needs little extrapolation to seem very modern.

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These earliest workers based their estimates upon anatomic considerations. They could better be called speculations rather than measurements. The first lead to a quantitative measurement that could be applied to a normally functioning animal or man was a brief note by A. Fick who, in 1870, first called attention to the fact that we were to know the oxygen consumption and the arteriovenous oxygen difference as it obtained in the heart, the bloodflow could be readily calculated. History has played a sardonic trick on this estimable and learned gentleman by scattering the dust of obscurity over the monumental treatises to which he gave his life, and attaching his name, in the minds of nearly every medical student, to an evanescent idea that he barely took time to put on paper and to which he never returned.

The subject must have been introduced well ahead of its time because contributions to the field were few and far between for 50 years. The first was an exasperatingly brief note in the Comptes Rendus in 1886 indicating, but not describing adequately, measurements of the cardiac output of dogs. This was followed in 1898 by the classic and meticulous study of the cardiac output of horses by Zuntz and Hagemann. Taking advantage of the fact that the blood of this creature is slow to clot, a catheter was introduced via the jugular vein down to the vicinity of the right auricle. Mixed venous samples were taken during rest, digestion and exercise. The contributions of these workers were of such great merit that Yandell Henderson felt that we should refer to the method of Zuntz and Hagemann rather than the method of Fick.

This was the only study of the cardiac output in the intact animal by direct measurement which attempted to follow physiologic response to changed conditions from 1870, when Fick wrote his famed paragraph, until the 1920's when there was a revival of interest in the control of cardiac output. It was hoped that a key, such as blood pH, would be found to regulate the circulation just as it was thought to regulate the respiration. Search for such a key was naive because the cardiac output seems to be regulated as the summation of the demands for blood by the several organs of the body, each in control, so to speak, of its own blood supply. Much interesting work was done in this period by workers who followed changes in blood flow of animals resulting from drugs, arteriovenous fistulas, hemorrhage, trauma, and pneumonia, to instance a few of the numerous studies.

At the turn of the century no one had the temerity to puncture the human heart or to catheterize its cavities. Credit is due Loewi and von Schrotter for thinking of using the lungs as an aerotonometer to measure the gas tensions of the mixed venous blood and, hence, its gas content. Not only were these authors the first to use the lungs in this manner, but also they were the only ones to use the principle in a nearly impeccable manner. They blocked off a small part of one lung and allowed time for complete equilibrium of the air in that part with the returning venous blood. Others to follow attempted to arrive at equilibrium between the pulmonary air and the venous blood before recirculation and after blocking fresh air away from both lungs.

The results reported by these authors varied between 4 and 8 liters per minute, and it was not clear why they were so erratic. During the twenties and thirties of the present century the computation of the cardiac output from respiratory data became stylized about the procedure of Grollman who promulgated the doctrine that the human circulation time was 25 to 30 seconds (correct figure 10 to 18 seconds) and hence that a respiratory mixture could be left in the lungs for that length of time without exposure to recirculated blood. The figure for cardiac output, had by this method, was 2.2 liters per square meter per minute—about two-thirds the correct figure. It is perhaps fortunate that the procedure overwhelmingly in vogue pin-pointed a figure that was so dramatically in error. Had this not been the case the proponents of respiratory methods would not have given up so easily and the literature would have been stultified with controversy.

It is hardly necessary here, except for completeness' sake, to discuss the brilliant and dramatic story of cardiac catheterization. It
was introduced in 1929 by the intrepid Forssman who, using an ordinary varnish catheter, catheterized his own heart several times. The next year Klein drew mixed venous blood from such a catheter and calculated the cardiac output. Cardiac catheterization was applied during the next decade to the visualization of radiopaque substances injected into the cardiac cavities. Another significant advance was made in that a nonwettable plastic catheter was developed that minimized the danger of intravascular clotting. The time was ripe in 1941 for Courand and his co-workers to open up a new book: the study of the cardiac output in man, the unraveling of the pressure and flow relationships in the cardiac chambers and the great vessels of the pulmonary and systemic circulations. With the work of groups led by Stead, Bing, Dexter, McMichael and others, as well as with the continued work of the Bellevue group working with Courand, the pages of the new book have been filled with accounts of circulatory dynamics in normal man, in shock, in congenital heart disease, under the influence of drugs and in cardiac and pulmonary failure.

Attention has recently been called to a source of error which is inherent in the Fick procedure—and in all other “dilution” procedures—when the subject is not in an absolutely steady state. It is easily imaginable that cyclic changes in a heart with a congenital anomaly or sudden vasomotor changes would result in a change in the oxygen content of a venous sample so that the arteriovenous difference would change from 40 to 80 cc. per liter. The sample might be a mixture of the two bloods in equal proportion and would indicate an average arteriovenous difference of 60 cc. per liter. Assuming an oxygen consumption of 240 cc. per minute this average arteriovenous difference would correspond to a bloodflow of 4 liters per minute. This conclusion is based on the false implied assumption that the flows, when the arteriovenous difference was high and when it was low, can be taken as equal to each other and hence averaged together. As a matter of fact the flow during one period was at the rate of 6 liters per minute and, during the other period, at the rate of 3 liters per minute, and the volume average, as distinguished from the time average, is 4.5 liters per minute instead of 4.

This error in the Fick calculation tends to be minimized by two things. First, the time average tends to follow the direction of change in the volume average, clinging more closely than it should to the lower of the two figures. Second, any mixing of blood in the cardiac, venous, or arterial stream would tend to make the sample a true volume average. Thus, in calculating the pulmonary bloodflow in case of a shunt from left to right, cyclic changes in oxygen concentration of blood would be less in pulmonary artery samples if the shunt were in the ariule than if it were in the ventricle, and less in this case than if a patent ductus were involved.

Since this source of error is involved in all dilution methods, it cannot be used to explain the fact that one dilution method gives an upward trend and another a downward trend. To evaluate this error in practical terms it is necessary to compare results with a volumetric method. This has been done and the two agree under the limited conditions tested.

Another and more serious source of error results from the storage in, or liberation of, gas from the body, including the lungs. A case of congenital heart disease with cyanotic episodes has been described in which lowering of the systemic resistance caused a cessation of lung blood flow and of oxygen uptake. The patient lived during this episode on her blood oxygen and by means of anaerobic metabolism. By the Fick calculation she would have no cardiac output and yet her heart was pumping strongly. As the organism goes into or comes out of an anoxic state the Fick calculation is dubiously related to the cardiac output.

The vagaries of cardiac output calculations from carbon dioxide production and venousarterial carbon dioxide difference are such that the measurement is commonly ignored. The unreliability of the Fick method when carbon dioxide is used may be related to the fact that small changes in ventilation strongly influence carbon dioxide storage by the body and a steady state is hard to reach.
In order to trace the growth of our subject in a logical fashion it is best to give an account of another method for measuring the cardiac output and cognate quantities. I refer to the injection method which, like the Fick method, is a dilution procedure. It was introduced into the literature by Stewart in 1897, and has been used by various authors since.

The substance by whose dilution the blood-flow is gaged is injected into the blood stream instead of being added to it or taken from it by physiologic process. An example will illustrate. Twelve milligrams of a substance such as a blood-volume dye, which remains in the vascular system, is injected into a vein. A series of samples is taken from an artery whose dye concentration—after the lapse of a few seconds—begins to increase, to reach a peak and then to descend exponentially until it rises again as a result of recirculation. From the nature of the exponential fall of concentration it is simple to plot the time concentration curve of dye on its first circulation. If the dye concentration curve persists over a period of 30 seconds and its average height is 4 mg. per liter, the 12 mg. injected has been diluted by 3 liters of blood in 30 seconds or by a cardiac output of 6 liters per minute (fig. 1).

This method has been checked against measured flow in models and against the Fick method both in dog and in man (fig. 2). Its errors in measuring the cardiac output are probably no greater than those of the Fick method and, in addition, the volume of blood in the heart, lungs, and great vessels (from the point of injection to the point of sampling) can be calculated from the dye concentration curve by multiplying the mean circulation time by the flow (fig. 1).

The accuracy of this volume calculation has also been checked by numerous experiments in models. There are large variations in the central volume which can be produced experimentally and are seen in disease. Our earlier idea was that the most distensible part of this vascular bed was that of the lungs. On this basis it was assumed that the huge increase in central volume seen in congestive failure, or after large doses of epinephrine in dogs, was the result of pulmonary congestion.

![Graph](http://circ.ahajournals.org/)

**Fig. 1.** Concentration curve resulting from the injection of dye into a vein at zero seconds. From this experiment the flow, the total circulation time, the mean circulation time, and the volume of blood in the heart, lungs, and great vessels can be measured.

![Graph](http://circ.ahajournals.org/)

**Fig. 2.** Plot of simultaneous measurement of the cardiac output in liters per minute by the direct Fick method and by the dye injection method.

Recent quantitative x-ray measurements have made it seem that enlargement of the heart by very large increases in residual blood will
account for all, or nearly all, of the changes in the central volume. Indeed, the heart of a dog who has received an overwhelming dose of epinephrine will contain 13 cc. per kilogram of body weight or 37 per cent of its lethal bleeding volume. The fact that increased pulmonary intravascular pressure does not necessarily result in increased pulmonary blood volume is borne out by measurements on man.44 An unfortunate misconception has gotten into the literature relative to the calculation of the mean circulation time. Ebert and his collaborators would have it that the planimetrically measured median circulation time can be used to calculate the capacity of the stream bed. This is true only if the dye concentration curve is symmetric. In a series of dye curves from dogs, use of the median circulation time to calculate central volume was in error by 50 per cent.* The mean circulation time, or the average time it takes all the dye to pass is computed as the center of gravity of the curve or:

\[ MCT = \frac{\sum CT}{\sum C} \]

Details of the calculation are shown in the paper referred to in reference 36.

If the central blood volume or some definite part of it were simultaneously and homogeneously mixed with the injected substance, one could calculate the magnitude of this volume from the slope of the downstroke or washout of the dye concentration curve.44 We have never felt that the initial assumption was satisfied in the animal and have shown that in ordinary conditions of flow in models the volume which determines the slope is rather remotely related to the total volume.36 We therefore have little faith in the calculation of physiologic volumes from the washout slopes of dye concentration curves.

This is even more to be emphasized by the fact that pulmonary flow is in all probability entirely different from flow through a chamber.

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* Dow, P. Personal communication.
where dye and blood are completely or even incompletely mixed. In the perfused lungs there is a long wait after injection for the dye to appear; in the mixing chamber it appears instantly. Moreover tubular flow does not give a simple exponential washout type of curve and the curve from lung perfusion experiments resembles that from tubular flow rather than that from chamber washout (unpublished work). The exponential washout curve obtains, however, when heart and lungs are perfused in series.

The laborious measurement of dye concentration in many samples has contributed a technical hazard that has served to make the method relatively unpopular. There are in process of development several procedures for measuring the concentration curve of dye in the arterial stream by means of a photoelectric cell and a recording galvanometer. The blood is put in front of the photoelectric cell either in a heated ear pinna or in a translucent tube connected to the artery by a puncture needle. The dye concentration read from a curve made in this manner is hard to quantitate, but the method promises to be a very useful one. A similar labor saving approach is to attach a radioactive atom to an injectable substance which remains intravascular.

Besides the dilution methods for measuring the circulation rate we have methods in which the aortic stream may be metered volumetrically by the cardiometer, or electromagnetically. To use these methods it has been necessary to open the thorax and to make the measurements of an abnormal circulation. Nevertheless, a great many important advances have been made by these methods.

The methods considered so far are best called primary methods in that, if reasonable assumptions are granted, they are direct measures of the cardiac output. Contrasted to these are methods which are best referred to as empiric methods, methods which achieve their validity from constants derived by comparison with a primary method. Among these are ballistocardiography, x-ray kymography, electrokymography, and the calculation of the cardiac output from the pulse pressure curve. Time will permit the discussion only of the last of these methods.

Evaluation of the stroke volume from the pressure pulse was first suggested by Erlanger and Hooker. Quantitative adjustments were made against the ethyl iodide method in a few subjects by Bazett and his co-workers and against the nitrous oxide method by Liljestrand and Zander. A few years ago careful measurements were made of the vol-
to avoid the complications of a pulse wave velocity correction, such as used by Bazett and by Broemser and others, and simply relate pulse pressure to stroke volume. This was done for a series of patients from the direct Fick measurements made in Courmand’s laboratory and a smaller series from the Georgia laboratory (fig. 5). By a strange coincidence it was found that the best fit was given when 1 cc. of stroke index was made equivalent to 1 mm. Hg of pulse pressure. Thus if the arterial pressure is 120/80 the average stroke index would be predicted to be 40 cc. These values hold only at ordinary pressure levels. The prediction of the stroke volume is of about the same order of accuracy as that made by the ballistocardiograph. It could no doubt be made more accurate if, at the beginning of an experimental procedure, an actual output measurement (for example, dye curve) were made to “calibrate” the distensibility of the subject’s arteries. After such a calibration the stroke volume could be followed from beat to beat during an experimental procedure.

Since dogs die young and their arteries rarely show the effects of aging and disease, a potent cause for the random variation in the relation between stroke volume and pulse pressure is not seen in these creatures. Careful measurement has shown that all aortas of dead dogs are very much alike as to their size in relation to the size of the body and as to their distensibility.

This fact justified the attempt to measure in detail the amount of blood required to expand the arterial tree as the pulse wave passes out over the arteries (fig. 6). It is necessary because the contour of the pulse wave differs very greatly in various experimental conditions. In some cases the pressure at the moment of aortic valve closure is very high and the aortic arch greatly expanded. In other cases the pressure in the arch has gone back to the diastolic level when the valves close; and the pulse volume is stored in the aorta and its branches farther down.

These considerations caused us to measure the distensibility of the four main subdivisions of the arterial tree (arch, head, viscera, legs) and find what part of the pulse wave has arrived at each of the subdivisions at the time the aortic valve has closed. This gives us the effective pulse pressure in each part of the arterial tree. Knowing the distensibility of these parts and the effective pressure change brought about by the pulse wave, the total uptake of the aorta and its branches (corrected for body size) could be summed.

The arterial uptake is only a part, but a significant part, of the stroke volume (stroke index). In addition, there is the blood which drains out through the arterioles during systole. Arteriolar outflow follows quite closely the law of Poiseuille, that is, it is the product of pressure and time if the arterioles remain the same. Since the uptake is known and must drain out the arterioles during diastole, it is possible to calculate the arteriolar drainage in cubic centimeters per millisecond per millimeter of mercury from the diastolic part of the curve and apply it to the systolic part of the curve. This systolic drainage plus the uptake is the stroke volume (stroke index).

This formidable calculation has been stylized by means of tables and graphs so that it may be accomplished in 15 minutes or so. When dogs are under the influence of drugs, hemorrhage, neurogenic or renal hypertension, or
traumatic shock, the pulse pressure method gives results which compare closely with those of the Fick procedure or the dye injection method (fig. 7). This has been confirmed by the Baylor group (fig. 8). It was checked against the rotameter in dogs by Longino and Gregg and found to give rather close agreement when the rotameter was placed in the pulmonary artery (fig. 9).

When, however, the rotameter is placed in the right auricle and vena cava the pulse contour calculations become too large. The arterial uptake under this and other severe conditions is much less than it is normally with the same pulse pressure. The aorta has suddenly become less distensible, has gone into rigor. Unfortunately no change in pulse wave velocity indicates the change in aortic rigidity.

It has been rather a disappointment to find that the pulse contour method will not calculate the cardiac output under all conditions, even though it will under most conditions. Every bafflement is a stimulus to further work and, I hope, greater insight will result. Why is it that the arteries lose their distensibility, go into rigor? Is it a reversible phenomenon? What is its fundamental cause? Why is the change always a decrease, never an increase, in distensibility? I hope that these questions will be answered before long.

After having spent so much time evaluating the methods of measuring the cardiac output we are justified in raising questions relative to

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**Fig. 6.** Diagram of two pulse curves and of the distensibility of four divisions of the arterial tree. The vertical lines referred to the ordinate scale indicate the pulse pressure in millimeters of mercury distending the different parts of the arterial tree at the time of aortic valve closure. These pulse pressures are laid off on the proper distensibility curve and the uptake of the parts summated to make the total uptake as read on the lower scale in cubic centimeters per square meter body surface. The upper pulse wave, with its greater pulse wave velocity, distends all four arterial divisions. The lower pulse curve, with its shorter duration and slower pulse wave transmission, distends only two parts when the valve closes. For calculation of stroke index from uptake see text.

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our insight into fundamental mechanisms by means of which the cardiac output is regulated. That there is such regulation, that it is adaptive and serves the ends of the organism is beyond dispute. The cardiac output can change from a resting figure of 6 liters per minute to a value of 15 in mild exercise, and probably much more with heavy exercise. The increase is brought about by an increase in stroke volume as well as by an increase in rate. The increase in stroke volume is minor, as was long held by Y. Henderson. Under conditions of circulatory handicap, such as hemorrhage, the cardiac output may be reduced to half the resting figure or even less. Thus the circulation rate may be varied sixfold or more but regulation is such that the driving force, that is, the mean blood pressure, varies comparatively little (10 to 50 per cent).

The fact that there is a relatively constant blood pressure in the face of large changes in flow implies a regulation of the cardiac output to match the peripheral resistance or vice versa. It can be shown, I think, that the circulation rate is governed primarily by the peripheral resistance and that the output of the heart is secondarily regulated so as to maintain a relatively constant arterial pressure.

The peripheral demand for blood expresses two needs: the need for oxygen by active tissues and the need to dissipate heat. Both of these demands are satisfied by local dilation, under local or specific control. When muscles, glands or viscera become active their arterioles dilate and their blood supply increases. This is mainly in response to local chemical influences and is dependent, to little or no degree, upon reflex adjustment of vascular tone. When we become overheated, hypothalamic reflexes are activated which cause cutaneous dilation and heat is dissipated. Both of these vasodilator mechanisms are prepotent, that is will hold
vessels open in spite of vasoconstrictor outflow from the medulla.

The effect of these local dilations, mediated by mechanisms which have no relation to the control of the heart beat, is to lower the peripheral resistance and, hence, the arterial pressure, and to set in action reflexes originating in the aortic arch and carotid sinus which accelerate the heart and restore the arterial pressure, but with an increased output. Peripheral constrictor mechanisms such as cold, abatement of activity, and vasoconstrictor drugs bring about the opposite re-

Fig. 10. Schema to illustrate the theory that the primary control of the output of the cardiac pump rests in the variable resistance controlled at the level of the peripheral organs and that cardiac regulation is secondary to pressure changes in the arterial reservoir.

response by the peripheral resistance and, hence, secondarily by the heart. The pressure rises but is reflexly restored toward normal by cardiac slowing and a reduced cardiac output. It must be recognized that these relationships are often hidden by other things going on at the same time. Thus in exercise the peripheral resistance is half that in rest; in a study of the effects of exercise the arterial pressure increased 50 per cent, and the cardiac output more than doubled while the oxygen consumption increased about sixfold. The fact that the heart rate doubled cannot be due to a lowered peripheral resistance because the arterial pressure has just increased. Nervous and hormonal stimulation of the heart, arising directly from the excitement of the effort, seem to have played a prepotent role over the reflex slowing which usually accompanies a rise in pressure.

Moreover, the nervous tensions of anxiety and other emotional states alter the peripheral resistance, and this alteration, acting through the secretion of epinephrine and the direct action of the sympathetic system, is different in different species. Thus, in man, anxiety and emotional disturbances dilate blood vessels in the muscles and reduce the peripheral resistance as does the injection of epinephrine. On the other hand it is difficult to demonstrate a primary reduction of resistance upon the injection of epinephrine into dogs.

In addition to this psychogenic anticipatory pressor pattern there is another response which, acting at the same time, tends further to complicate the simple relation between increase or decrease in peripheral demand and increase or decrease in cardiac pumping. This is the pattern of arterial pressure regulation through changes in the peripheral resistance as well as through changes in cardiac pumping. Thus the arterial stretch receptors are connected reflexly to produce vasoconstriction when the arterial pressure is low and to produce vasodilation when the arterial pressure is high. If there should be a local demand for blood (oxygen) at the same time that general blood pressure regulation demands vasoconstriction, there is a contest for prepotence between the two tendencies. This contest is decided beforehand by the vasculature of the brain and heart. These blood vessels cannot constrict so as to deprive the vital organs of a steady oxygen supply as can the blood vessels of the leg and to a lesser extent those of the viscera. Even in the vascular beds that are best able to constrict we can well think of a constant conflict between the effect of anoxic chemical changes producing vasodilation (provided the arterial pressure is high enough to prevent the elastic closure of minute blood vessels) and the tendency for constriction under central blood pressure regulation.

The conflict between the effects of local
demand and of general regulation can be illustrated by the following. When one lies recumbent, gravity returns blood to the heart more easily, filling it better, and mechanically increasing its pumping action. At once the heart is reflexly slowed and vasoconstrictor tone is lessened because more impulses are being generated by the arterial stretch receptors in response to a small and aborted rise in arterial pressure. This pattern of response results in a lowered peripheral resistance and an increased cardiac output in spite of the fact that the metabolic demand for blood is lessened.

Conversely the results of trauma or hemorrhage handicap the venous return and lessen the pumping action of the heart. In response to lowered arterial pressure the heart accelerates and the arterioles constrict. This happens in spite of the fact that a very low venous oxygen tension indicates that the tissues are greatly in need of oxygen. This response may not be in the best interests of survival, as witnessed by the fact that when the vasoconstrictor response is aborted by Dibenamine the animal endures the hypotension of shock better than without the drug.77, 78

Not only do adjuvant mechanisms complicate responses but the responses themselves are of extraordinary accuracy and delicacy. On injecting a small dose of epinephrine, or other constrictor drug, the heart often appears to slow before there is any visible rise in pressure. In interpreting this it has been suggested that the reflex slowing is teleologic and anticipatory. To quote a statement which has become "classic" in our discussions around the laboratory, "The decreased cardiac output... is attributed to reflex adjustments initiated by the threatened (sic.) increase in blood pressure which would result from constriction of cutaneous vessels."79 In contrast to this we may assume that the reflex slowing has a very delicate threshold and that the response is due to a rise in pressure that escapes notice—is in reality the same stimulus that seems logically to produce the slowing, a few seconds later, when the pressure rise is appreciable.

This principle of accurate physiologic adjustment is illustrated in the control of blood-flow through the Goldblatt kidney. The clamp, when it is first applied to the renal artery, must in the nature of things reduce the bloodflow to the kidney. Soon, by hormonal mechanisms, the blood pressure rises and, when a steady state is reached, the renal bloodflow is back within normal limits. Is it not reasonable to believe that physiologic compensations are accurate and delicate enough to bring the renal bloodflow back to a figure that, to our crude measures, seems normal? What other compensatory function would the hypertension have?

Thus we might assume as a working hypothesis, that whatever variable is held most constant is the key to natural physiologic regulation. The wisdom of the body is such that by the time a steady state is reached, under new demands, the important variable, the one with survival value, is regulated within physiologic limits. Thus in looking at the regulation of respiration we would hunt, not for something that is abnormal when the respiration is increased or decreased, but rather for something which has been returned to normal by the changed respiration. The answer on this hypothesis of accurate regulation would be the hydrogen ion concentration of the blood for respiration, kidney blood flow for renal hypertension, and arterial pressure for the regulation of the circulation.

In discussing the control of cardiac output, the classic experiments of Starling and his collaborators must be taken prominently into account.80, 81 Starling's experiments were made on the heart-lung preparation, a preparation in which the heart could respond only by means
of its intrinsic myocardial mechanism. His evidence showed conclusively that when the heart is deprived of the natural reflex mechanisms, when its rate is held constant and hormonal stimuli are not acting, an increase in the aortic pressure or in the venous return brings about an increase in diastolic cardiac size. He showed moreover that within physiologic limits, this increase in diastolic size was self limiting because it also brought about an increase in the effectiveness of cardiac pumping and an increase in oxygen consumption by the heart.

These same physiologic reflexes which control the rate of the heart also control its strength of beat. Sympathetic stimuli which accelerate the heart augment its strength of beat and make it empty more completely and become smaller. Under sympathetic stimulation, then, the heart is smaller, not only because it is faster, but also because it is stronger.

An opposite effect results from parasympathetic stimulation. Vagus beats in man, if not in the dog, are weaker than normal beats and the heart under parasympathetic influence is larger, not only because it is slower and fills more, but also because it is weaker and empties

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**Fig. 12.** Left: The relation of cardiac blood volume to filling time. The various symbols indicate experimental procedures such as buffer nerve section, epinephrine infusion, vagus stimulation, and others. These procedures do not indicate significantly different trends or slopes.

Right: Relation of net heart size to venous pressure. The group indicated by the lower arrow are slowly beating hearts which become large with low venous pressure; those indicated by the upper arrow are rapidly beating hearts that remain small in spite of high venous pressures.

It is not the purpose of the following paragraphs to cast doubt upon the fundamental truth of the insight into cardiodynamics which is embodied in "Starling's Law of the Heart," but rather to inquire into the manner in which the reflex adjustments available to the intact animal enable him to safeguard his heart from stresses which illustrate Starling's law.

In making adjustments to changes in flow and in aortic pressure the most obvious physiologic change is in heart rate. It has been known for more than a century. It is in response to pressure changes in the aorta and carotid sinus, and brings about changes in heart size that are of theoretic importance in relation to the diastolic size of the heart and Starling's law. In exploring in the normal animal such aspects of cardiac action as stroke volume, cardiac work, systolic and diastolic pressure, and heart rate, it was found that only heart rate clearly and uniquely correlated with diastolic size as computed from x-ray silhouettes. When the heart accelerates—pumps more blood—it becomes smaller and when it slows it fills more and becomes larger. Changes in rate then work against any application of the Starling law in the intact animal.
less. Changes due to sympathetic and parasympathetic stimulation thus guard the heart against the stresses implied in the application of Starling's law.

Caution must be urged against gaging diastolic heart size from the venous pressure. In the first place there are two venous pressures, right and left, and if we are to measure heart size at all we must measure that of the two hearts together. In the second place when the heart rate is rapid the venous pressure may rise to great heights and the heart still remain small.\textsuperscript{81} It seems that the process of myocardial relaxation prevents cardiac filling unless there is plenty of diastolic time for the relaxation to take place. Thus large, slow hearts are seen with low venous pressure, and rapid, small hearts are seen with high venous pressure (fig. 12).

The myocardium is a contractile engine whose elastic properties enable it to do work against pressure. The amount of work which it does and, more importantly, the amount of blood which it ejects is dependent upon the pressure against which it works. Thus if the aorta is pressed shut the stroke volume and often the work per beat diminish with the next beat and before any reflex adjustments can have taken place. Similarly there is an immediate increase in stroke volume and often in work per beat when the occlusion is released.\textsuperscript{84} The same immediate mechanical control of the stroke volume obtains when an arteriovenous fistula or surgical arteriovenous shunt is occluded or opened,\textsuperscript{84, 85, 86} or when a massive vascular area is shut off until, through the process of reactive hyperemia, there is local vasodilation.\textsuperscript{86} Release of such occlusion results in an immediate increase in stroke volume even though cardiodynamics are not much changed by the occlusion itself.

The fact that the stroke volume will change twofold or more under these conditions necessitates the belief that there is a residual volume of blood in the heart ready for instant mobilization, and further reserve waiting in the venous reservoir. As the aortic pressure is lessened, the residual blood is evacuated, the heart becomes smaller, the stroke volume larger and the work increased. These changes all occur in reverse when the aortic pressure rises. These mechanisms, even though they are intrinsically myocardial in nature, also militate against a clear application of the Starling law.

It seems from the considerations above that the reflex influences to which the normal heart in the intact animal is subject cause the heart to accelerate and hence to decrease in diastolic size when there is a peripheral demand for an increased bloodflow, and to increase in size when the peripheral demand is lessened. Thus

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig13}
\caption{Circulatory changes resulting from occlusion and release of the aorta.\textsuperscript{4}}
\end{figure}

the normal heart is protected against, and does not react to, the stresses imposed upon it in Starling's experiments.\textsuperscript{50, 81}

What then is the role of Starling's law? We can say, as some have, that it operates when, consequent upon respiratory fluctuations in venous return and resulting fluctuations in filling pressure, there are parallel fluctuations in stroke volume.\textsuperscript{87} While this is technically an example of Starling's law the situation does not fulfill the implications of his
thesis. To my mind Starling's thesis is that the increased force of contraction and metabolism consequent upon myocardial stretching can enable the heart to overcome a real stress.

It was well known in Starling's time that sympathetic influences, hormonal and reflex, increase the heart beat and that parasympathetic influences decrease it. By means of his heart-lung preparation he ruled out these influences and held everything constant except increased diastolic size and its cardiodynamic consequences. When heart size, and heart size alone, was varied the conclusion was inescapable that the strength of the contraction varied accordingly. It increased as heart size increased up to a certain limit and then fell off.

In cases of heart disease the reflex reserves have been exhausted. The sympathetic influences which tend to keep the heart small have worked at their maximum but have not sufficed. The heart has fallen back upon the Starling mechanism and, by increased diastolic size, has compensated the weakness, or has been overloaded and given out.

The evolution of the intricate adjustments outlined in so cursory a fashion is very puzzling. It seems best to regard them as having been developed as responses to a stress or emergency that can be answered by muscular effort. Thus the need for conservation of water that leads to the oliguria of exercise leads also, in the continued and desperate effort to maintain life under the handicap of heart disease, to the inundation of the tissues in cardiac dropsy. Similarly the hyperpnea of exercise leads to the dyspnea of heart disease, and the excitation of the sympathetic system in exercise is linked with generalized vasoconstriction of traumatic shock.

These responses have evolved as useful stratagems in their original setting as emergency mechanisms, but they have no survival value as compensation for chronic degenerative conditions. This results from the fact that nature is indifferent to the survival value of things that develop after reproductive life is over. Neither an adaptation nor a handicap is relevant to the process of evolution if it develops late in life. For this reason vicious cycles are often the aftermath of degenerative disease. Thus it is customary for the physician to allay the dyspnea of heart disease with a sedative, though its analog, the hyperpnea of exercise, is regarded as a useful response. The dyspnea of heart disease is a vicious cycle, and the welfare of the patient demands that it be aborted. Similarly we abort the oliguria of heart disease with diuretics but not the oliguria of exercise. The former is a vicious cycle, a response that has not been culled from the stream of inheritance by the rigorous process of evolution.

It may well be that, as medicine turns more and more toward geriatrics, vicious cycles resulting from late degenerative disease will confront the physician more often. It will be truly a test of the intelligence of the physician and his fundamental background for him to tell the vicious cycle from the useful response, for him to learn to interfere with the one and help the other.

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