ABSTRACT OF
Contributions
TO THE
PHYSIOLOGY AND PATHOLOGY OF THE
MAMMALIAN HEART.¹

(From the Cambridge Pathological Laboratory.)

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IN studying the action of the mammalian heart we have sought to examine the organ under conditions, unexcised and intact, as nearly approaching the normal as are compatible with the employment of exact methods of research—in short, to make our observations approach in exactitude those which have been made upon the hearts of cold-blooded animals. And we have found two instruments of especial use—one, which we term the “cardiometer,” a form of cardiac plethysmograph or oncograph, which records the changes in volume of the whole heart; the other a myocardiograph, whereby we could record the contractions or expansions of any part or parts of the auricular or ventricular walls without interfering with the movements of the heart as a whole. In most cases we employed this instrument to obtain simultaneous records of the contraction of one auricle and one ventricle. These instruments are fully described in our complete paper which will shortly be published.

In order to interpret the results gained by any form of recording apparatus applied to the mammalian heart it is necessary to keep in mind continually certain elements of the mechanics of the subject, for neglect to do this has led to much confusion and erroneous statement. Thus the ventricles may be looked upon as roughly spherical, and it is most important to remember the relationship between the circumference and the cubic contents of a (elastic) sphere, according to variations in the diameter or circumference of that sphere. When such a sphere is enlarged a very slight diminution in its circumference is capable of throwing out a quantity of the contained fluid, whose expulsion in a sphere of smaller diameter would be associated with a very considerable diminution of circumference. For example, reduction by one inch in the circumference of a sphere of five inches in circumference is accompanied by a reduction of the contents equal in amount to that which accompanies the lessening by a quarter of an inch of the circumference of a sphere of ten inches in circumference, although in the one sphere the circumference is lowered one-fifth, in the other one-fortieth. It is important also to keep in mind that the strain on the walls of a hollow spherical shell increases uniformly with the circumference—in other words, that the resistance to contraction of the ventricular walls becomes greater as the circumference is increased. It is well also to note that a change of pressure in the aorta or pulmonary artery has the same effect on the resistance to contraction offered to the left or right ventricular walls as obtains in the case of a parallel-fibred voluntary muscle by increasing or lessening the weight against which it is made to contract by single induction shocks, causing maximal contractions. If the weight be increased, although the same amount of work be done, the extent of shortening in contraction is diminished, and *vice versa*. An analogous result takes place in the case of the ventricles. When from any cause the resistance to contraction is increased, or the force of contraction is reduced, their walls contract less completely, so that there is an increase in the amount of “residual blood” left in the cavities at the end of systole. The presence of such residual blood can be determined by the cardiometer, and,

indeed, by the naked eye, in a variety of conditions, among which, as we proceed to show, vagus excitation is to be included.

Studying the action of the vagus upon the heart, we find that excitation of this nerve slows and weakens or stops the auricular contractions, and this weakening or arrest is a potent factor in bringing about the increased systemic and pulmonary venous pressure and in modifying the action of the ventricles. Up to a certain point the ventricles tend to follow the “sinus” rhythm, and to this extent vagus slowing of the auricles induces ventricular slowing. But when the vagus excitation reaches a certain degree (varying in different animals), the ventricles begin to beat independently of the sinus and auricles; and this rhythm, which is at first slow and irregular, gradually becomes fairly rapid and almost completely regular. This rhythm, we show, must be looked upon as the same as that which, as Wooldridge and Tigerstedt observed, makes its appearance when the ventricles are severed from the auricles. We point out, however, that the independent ventricular rhythm of vagus action is characterised by the slowness with which it establishes itself. This characteristic is due to the lowering of the excitability of the ventricles produced by vagus action, and we adduce a considerable number of facts showing that the vagus *does* lower the excitability of the ventricles, and that, by means of muscarin and by discontinuous stimulation of the vagus, it is possible to isolate the influence of the vagus on the rhythm and force of the auricles from its influence upon the excitability of the ventricles. The power of the vagus to stop the ventricles temporarily can only be explained by this diminution of their excitability. We show that, with a certain degree of vagus excitation, irregularity of the ventricles necessarily results, in consequence of the sinus and the idio-ventricular rhythms interfering with one another; that this is the common cause of irregularity; and that irregularity may also be caused by the auricles not responding to all the impulses which reach them from the sinus.

In consequence of this slowing of the rhythm and lessened excitability of the ventricular walls, the ventricles become distended in diastole, this distension being also aided by the fact that the increased venous pressure must lead to a greater amount of blood being poured into the cavities between the beats. And this dilatation of the ventricles is not simply diastolic, but is also systolic—the ventricular cavities are relatively distended at the completion of systole. It must not, however, be thought that this increase in the residual blood indicates a lessened force of contraction of the ventricular muscle due to the action of the vagus. Of such weakening of the ventricular muscle we find no proof. A consideration of the principles enunciated at the beginning shows that residual blood is not a necessary indication of lessened force of contraction, and that, if the ventricles be dilated, a comparatively slight extent of contraction leads to the expulsion of a comparatively large quantity of blood. And, as a matter of fact, we find that, while through the slowing of rhythm which accompanies vagus excitation, the output of the heart—that is to say, the amount of blood expelled in a given time—undergoes considerable diminution, the “contraction volume” or amount of blood thrown out at each individual beat is not lessened, but, on the contrary, greatly increased. The diminution of arterial pressure does not suffice to explain this increase. We therefore conclude that, as stated above, the vagus does not lessen the force of contraction of the ventricles.

Studying the effect of direct excitation of the nervi augmentores (accelerantes) upon the heart, we show that the acceleration of the rhythm may be extremely slight if the heart be beating fast, and that the acceleration and augmentation of force of the heart bear no constant proportion to one another. The augmentor nerves increase the diastolic expansion of the auricles and also increase their systolic contraction; but these two effects do not go hand in hand. Excitation of the augmentors increases the output of the heart, owing to the increased force and frequency of the auricular contractions, the result of this being that the pressures in the systemic and pulmonary arteries rise, while the systemic and pulmonary venous pressures fall. If there be but little quickening, the contraction volume of the ventricles is increased. The augmentors, on direct stimulation, cause a slight increase in the diastolic expansion of the ventricles, which is passive

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in nature and due to the increased force of the auricular contraction. The force of the ventricular contractions is increased; they contract more completely, diminishing the amount of residual blood, in spite of the fact that the arterial pressure is usually somewhat raised. Reflex excitation of the vagus produces results which are the same as those of direct excitation of the nerve, and the curves are more typical and satisfactory than those obtained on direct excitation. Excitation of a mixed nerve like the sciatic usually produces effects on the heart similar in kind to those due to direct excitation of the augmentors, but the phenomena are complicated by the greater rise of the pressure in the systemic arteries. Sometimes the increase in force of the ventricle more than counterbalances this increased resistance to contraction, and the amount of residual blood in the left ventricle is reduced; in other cases the increase in force of the ventricular contractions is not sufficient to counterbalance the increased resistance, and the residual blood in the left ventricle is increased.

We show that excitation of the central end of a mixed nerve like the sciatic or splanchnic usually affects both the augmentor and vagus centres in the medulla, and that, in nearly all cases, the augmentor centre is the more strongly excited of the two, so that augmentor effects show themselves during the excitation, but are succeeded by vagus action on ceasing to excite the nerve. In many cases augmentor effects alone show themselves. When excited reflexly the augmentor centre ceases to act earlier than the vagus; the opposite, therefore, to what takes place with direct excitation. In rare cases the excitation of the vagus centre may be stronger than that of the augmentor from the first. Although, in the absence of any augmentor action, the vagus does not reduce the force of the ventricular systole, it does unmistakably have the power of inhibiting the strengthening influence which the augmentors exert upon the ventricular contractions. As to the part played by the vagus in the economy, we show that vagus excitation relieves the heart of work, and therefore of waste, to as great an extent as is compatible with a continuation of the circulation, and conclude that the vagus acts as a protective nerve to the heart, reducing the work thrown upon that organ when from fatigue or other cause such relief is required by it. The presence of fibres in the sciatic and other mixed nerves which cause reflex excitation of the vagus would seem to indicate that this nerve may be used by other parts of the body to diminish the output of the heart and lower the blood-pressure, thereby reducing the activity of the circulation as a whole. The influence of the blood-pressure in the systemic arteries on the degree of vagus activity and the readiness with which the vagus centre is called into play by raising the intracranial pressure indicate that the vagus mechanism is specially employed in lowering the circulation so as to limit cerebral congestion. The vagus acts chiefly in the interests of the heart and central nervous system. The power of the vagus over the heart is limited, and the idio-ventricular mechanism which comes into play when the vagus action exceeds a certain limit must be looked upon as the means by which arrest of the circulation and death is prevented, whenever from any cause the nerve exerts a maximum influence. The power of the vagus to lower the excitability of the ventricles makes their temporary arrest possible; but this reduction of the excitability of the ventricles cannot be kept up, no matter how strong the stimuli applied to the nerve, for a period long enough to endanger the economy.

The function of the augmentor in the economy is to increase the work and tissue waste of the heart as part of the mechanism by which the nervous system governs the circulation, and the augmentor mechanism sacrifices the heart in order to increase the output of the organ and enable the ventricles to pump out their contents against a heightened arterial pressure. Such excessive action of the heart is limited by the vagus, which, as we have seen, readily steps in so soon as the call for an increased supply of blood has ceased. It may do so earlier, presumably because the increased blood-pressure or the fatigue of the heart calls for vagus intervention.

Considering the mode of interaction of the vagi and augmentores, we point out that when the vagi are paralysed by section or atropine, the augmentores have no control over the cardiac rhythm, and that therefore they can only act by inhibiting the influence of the vagi on the rhythmic centre of the heart. When neither nerve is acting on the

auricles they contract with a certain force, which is increased by the augmentores and diminished or inhibited by the vagi. The force of the ventricular contractions is increased by augmentor action; this increase can be inhibited by vagus excitation, which latter has otherwise no power to reduce the strength of ventricular contractions. The force of the heart's contractions is influenced by other factors than the vagi, augmentores, and other nerves. The pressure of the blood in the coronary arteries is one of the most important of these factors. If this be lowered, the contractions of both auricles and of ventricles diminish in strength, while a rise of pressure in the systemic arteries causes an increase in the force of the heart's contractions, so that the force of the heart's contractions is to a certain extent regulated automatically by changes in the blood-pressure in the aorta, which is one of the variable quantities affecting the work of the left ventricle. Change in the volume of blood in the body affects greatly the contraction volume and output of the heart. Injections into the veins of a volume of defibrinated blood equal to one-tenth of the total blood in the body may double the output. It is important to note here that there is no increase in the strength of the ventricular contractions; increase in the work, therefore, of the ventricles due to increase in the output has no tendency to automatically increase the force of the ventricular contractions, as is the case with rise of pressure in the systemic arteries. We refer to the bearing of this in cases of plethora. Increase of the watery constituents of the blood increases the contraction volume and output to the same extent (though only temporarily) as does transfusion of blood, but acts more unfavourably on the heart, seeing that the work done by the ventricles is increased, while the nutritive value of the blood supplied to the coronaries is diminished. The increased output of the heart both in plethora and in hydræmia is due to rise of pressure in the systemic veins, increasing the volume of blood which enters the right ventricle during diastole. We refer to the bearing of these facts upon the treatment of chlorosis and heart disease.

In strictly physiological conditions, and in spite of the beautiful mechanism by which the force of the ventricular contraction is regulated, the heart, like the voluntary muscles of the body, is liable to fatigue when the work thrown upon it greatly exceeds that required to maintain the circulation under ordinary circumstances. We take as example the increased work thrown upon the organ during active muscular exertion, and show that exertion and endurance of fatigue are limited mainly by the limited power of the heart to continue supplying the increased amount of blood which is required by the acting voluntary muscles. We show that those luxuries which are forbidden or limited in "training," and which are known to hinder prolonged exertion, such as water, alcohol, tobacco, caffeine, all directly weaken the force of the heart's contractions, and, in the case of water, place the organ under a disadvantage; also that fatigue of the heart leads to dilatation of the organ. On comparing the power of fatigued ventricles to carry on increased work, as compared with well-nourished, unfatigued ventricles, it is found that not only is the strengthening effect of the augmentor nerves upon the individual contractions less in the former case, but also that the fatigued, and therefore dilated, heart is *per se* unfavourably placed for meeting increase in the work thrown upon it. An explanation is given of the reason why in heart disease failure takes place during exertion. The part played by the vagus in protecting the diseased heart from harmful overwork is referred to, and it is shown that irregularity of the heart in disease may be explained by the mode in which this nerve, when acting powerfully, releases the ventricles from the control of the rhythmic centre in the sinus. The chief forms of rhythmic and arrhythmic irregularity are considered, and it is shown that these correspond with the forms of irregularity which can be produced by vagus action. The irregular heart expends more energy, and its tissues therefore are more wasted, for a given amount of work than the heart which is beating regularly. The effect upon the heart of imperfect aeration of the blood is, first of all, to produce powerful vagus action from the medullary centre; this is usually, though not always, accompanied in curarised animals by diminution of the output of the heart. But reasons are given for assuming that the output would be increased in uncurarised animals, owing to the high venous pressure which results from

struggling. Besides the vagus action, it can be shown that asphyxia causes progressive weakening both of the auricles and of the ventricles, and attention is drawn to the fact that the considerable rise of pressure in the systemic arteries in asphyxia is accompanied by vagus effects upon the heart, and not by augmentor action, as is the case, so far as we know, in all other instances in which the vaso-constrictor centre is excited in the normal individual. It is noted that the change in the heart and circulation which takes place during asphyxia points to the conclusion that, when the total amount of oxygen in the blood is lowered, it is for the benefit of the economy that those organs, such as the central nervous system, whose continuous blood-supply is a vital necessity, should be richly furnished with blood by constriction of the vessels of the spleen, kidney, and digestive system, whose blood-supply can be cut off temporarily without danger to life, and also that the heart should carry on the circulation in a manner involving as little as possible waste of its own substance. This, as we have seen, it is the function of the vagus nerve to bring about.

Lecture

ON

TISSUE- OR CELL-FIBRINOGEN IN ITS RELATION TO THE PATHOLOGY OF BLOOD.

Delivered at the Theatre of the Laboratories of the Conjoint Colleges of Surgeons and Physicians, on Feb. 4th, 1892.

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THE first step in the direction of the acquirement of a control over the processes of coagulation in the living body was made by Wooldridge when he succeeded in demonstrating that intra-vascular coagulation could be obtained by the injection of solutions of tissue-fibrinogen. I do not think that I am over-estimating the importance of this discovery; for when it had been confessed by Schmidt's own pupils¹ that the injection of practically unlimited quantities of fibrin ferment into the vessels made the blood more liquid instead of producing coagulation in it, it became evident that there was no possibility of influencing the coagulability of the blood by following the lines of the fibrin-ferment theory. Now Wooldridge's work was a departure on new lines, and he succeeded in the most brilliant manner in demonstrating that it was possible by working upon these new lines to obtain a practical control over the phenomena of coagulation in the living body. It is to the facts that Wooldridge discovered, and to such others as I have been able to add to them or to bring into relation with them, that I would wish to direct your attention this afternoon. And to begin with, I would like to say that in ascribing the credit of the method of producing intra-vascular coagulation to Wooldridge I believe that I am only giving him what is strictly his due; for, although Groth,² one of Schmidt's pupils, had described the occurrence of intra-vascular coagulation in connexion with the injection of leucocytes in 1884—i.e., before the date of Wooldridge's publication—he had elicited the phenomena in a much less distinct manner, and he had not determined to what constituent of the leucocyte the intra-vascular coagulations were due. Instead of this he ascribed these coagulations to a production of fibrin ferment in the blood—that is to say, Groth ascribed his coagulation to a cause which we know to be quite ineffective. I think we need not therefore consider a question of priority here; but, on the other hand, we shall do well to keep in view the fact that Groth was successful in obtaining intra-vascular coagulations by the injection of the expressed juice of lymph-glands, and we have to note also that Groth regarded his experiments as conclusive as to the partici-

pation of leucocytes in the processes of coagulation. Groth's work thus opens up a number of important issues, which we shall have to consider in connexion with the production of intra-vascular coagulation by tissue-fibrinogen.

First, with regard to the relation of white corpuscles to coagulation, we are met by the fact that Wooldridge not only did not consider that Groth's experiments proved the existence of any such relation, but he went further than this, and expressed it as his opinion that the leucocytes of the blood had not been shown to stand in any relation whatever to coagulation. Wooldridge based this view, for the one part, on certain defects in conclusiveness in the evidence which had been adduced by Schmidt and his pupils to implicate the leucocytes in the processes of coagulation. Schmidt had, for instance, described the superior coagulability of the so-called granular layer which is seen above the corpuscular layer in horse blood which has been kept from coagulation by cooling; and Schmidt had asserted the granules of that layer to be with certainty derivatives of disintegration of white blood-corpuscles, and upon this assumption he had concluded that the superior coagulability of the granular layer was evidence of the participation of the leucocytes in coagulation. Wooldridge, however, pointed out that there was a flaw in this evidence, inasmuch as Schmidt had not excluded the possibility of these granules being derivatives of the plasma—i.e., the possibility of their being simply a precipitate produced in the plasma by cooling. In this connexion Wooldridge showed that peptone plasma gives such a precipitate on cooling, and I may say that I have observed that a similar precipitate can invariably be produced by the action of cold upon decalcified plasma. It follows, I think, that the argument from the superior coagulability of the granular layer must be finally abandoned. Again, with respect to the experiments of Groth and afterwards of Krüger,³ in which an increased coagulability was observed after leucocyte injections, Wooldridge drew attention to the fact that the experiments were conducted with insufficiently isolated leucocytes, and pointed out that a fallacy was, in his opinion, introduced into them by the fact that the lymph plasma which was injected along with the lymph cells contained a coagulative substance—namely, tissue fibrinogen. Further, Wooldridge repeated the experiments of Groth and Krüger with washed leucocytes, and found that he obtained a diminution instead of an increase of coagulability in the blood. These appear at first sight to be very grave, if not fatal, objections to Schmidt's view of the important rôle of the white corpuscles in coagulation; still I hope to be able to show that it is possible to settle satisfactorily with them.

First, with regard to the defective isolation of the cells which was insisted upon by Wooldridge, it must be conceded that Groth's leucocytes were not at all isolated. They were simply injected along with the inter-cellular fluid of the lymph gland. With regard, further, to Krüger's attempt at isolation by means of filtering off the lymph plasma, Wooldridge is probably also correct in stating that this method is entirely ineffective, inasmuch as any attempt to filter off leucocytes from a solution of tissue fibrinogen would be rendered futile by the fact that a considerable amount of tissue fibrinogen would invariably be retained on the filter. It is evident, therefore, that we have to concede to Wooldridge that neither Groth's nor Krüger's experiments were performed with isolated leucocytes.

When we come to the second heading of the objection, which is based upon the fact that the lymph plasma contains tissue fibrinogen, and would thus introduce a fallacy if not effectually separated from the leucocytes before injection, we must, however, pause for consideration. It is not at all necessary to meet this objection by asserting that there is no tissue fibrinogen in the lymph plasma. Wooldridge was a very careful observer, and we may well accept the fact upon his statement; but we may, on the other hand, with advantage inquire how the tissue fibrinogen got into the lymph plasma; and when this question is once formulated, it is easy to see that the answer must be that the tissue-fibrinogen is almost certainly derived from the disintegration of leucocytes, inasmuch as Wooldridge himself has shown that the lymph cells contain this substance. We thus see that if the coagulative substance of the lymph plasma was derived from the leucocytes, the contamination of the leucocytes with this plasma

¹ Jabowicki, Birk, Köhler: Disserts., Dorpat, 1875, 1877, 1880. Edelberg's contradictory results (Archiv f. Exp. Path., 1880) may be neglected. They were obtained with extraordinarily impure fibrin-ferment solutions.

² Dissert., Dorpat, 1884.

³ Zeitschrift f. Biolog., 24, p. 189.