THE INFLUENCE OF VENOUS FILLING UPON THE RATE OF THE HEART. By F. A. BAINBRIDGE.

(*From the Physiological Laboratory, University of Durham, and the Institute of Physiology, University College, London.*)

It is well known that when plethora or hydræmic plethora is produced in the normal animal the venous inflow to the heart increases, the venous pressure rises and the output of the heart becomes larger. At the same time the heart beats more frequently and the increase in the rate of the pulse may be very considerable. Krogh(3) has pointed out that, when the venous inflow to the heart is so large that the right ventricle contains as much blood as it can hold before systole occurs (he terms this an adequate supply to the heart), the output of the heart per minute depends chiefly on its frequency. Patterson and Starling(6) have shown with the heart-lung preparation that, if the venous inflow is steadily increased, the output of the heart is correspondingly raised until the venous pressure reaches a level at which the heart is so dilated at the end of diastole that it is working at a mechanical disadvantage during systole; its output then begins to fall and unless the venous flow is diminished it may fail altogether. Further they find that when the heart is made to beat more frequently not only is its maximum output, that is its range of efficiency, increased, but also that if the inflow is kept constant the venous pressure falls. The observations of Evans and Matsuoka(1) also make it clear that, for a given venous inflow, the venous pressure is higher and the output of the heart is smaller when the pericardium is intact than when it is removed, so that removal of the pericardium increases the maximum output of the heart. Evans and Matsuoka's experiments have been confirmed and extended by Kuno, who finds that, if the venous inflow is increased, the venous pressure rises more rapidly and abruptly when the pericardium is intact than when it is opened. Kuno has also shown that, owing to the action of the pericardium in limiting the venous filling of the heart, a rise in the pulse rate is much more

effective in increasing the output of the heart when the pericardium is intact than when it is removed.

The quickening of the heart which occurs in plethora or hydræmic plethora must be of value not only in increasing its output when the venous filling of the heart is very rapid but also in lessening the risk of its becoming so engorged that it becomes mechanically inefficient. There does not appear, however, to be any definite evidence as to the means by which the acceleration of the heart is brought about, and the cause of the acceleration which accompanies increased venous filling of the heart forms the subject of the present enquiry.

Methods. All the experiments were made on dogs anæsthetised with a mixture of chloroform and ether after a preliminary dose of morphia. The pulse rate was recorded by means of a Hürthle manometer attached to one limb of a cannula inserted into the carotid artery; the other limb of the cannula was connected with a mercury manometer which recorded the blood pressure. In order to measure the venous pressure, an iliac vein was exposed without opening the peritoneal cavity, and a cannula was placed in the vein close to its opening into the inferior vena cava; the cannula was connected with a manometer containing hirudin dissolved in normal saline solution. A piston recorder was attached to the upper end of the manometer so that variations in venous pressure could be graphically recorded. The readings of the manometer were also observed directly. The zero of the venous pressure was obtained usually by opening the inferior vena cava close to the heart and occasionally by opening the right auricle. In either case, the venous pressure readings here recorded represent only approximately (probably within 1–2 cm.) the true venous pressure at the opening of the vena cava into the heart.

The fluids injected into the circulation were either normal saline solution or blood; the latter was either undiluted or diluted with one-third to an equal volume of saline solution. The fluid to be injected was placed in a reservoir which was immersed in water maintained at a suitable temperature and was connected with a cannula placed in a jugular vein. A thermometer inserted into the cannula recorded the temperature of the fluid as it entered the vein; the cannula was also provided with a side tube whereby, when the vein was clamped, fluid could be allowed to flow at will through the cannula from the reservoir.

In confirmation of Newell Martin(5), Knowlton and Starling(2) have pointed out that the temperature of the circulating blood greatly

influences the rate of the isolated heart; and in the present enquiry great care was taken to keep the temperature of the injected fluid at, or just below, the rectal temperature of the animal. Immediately before each injection the rectal temperature was observed, and the fluid in the reservoir and cannula was adjusted to the same temperature as the rectal temperature. The injection was then made and the thermometers in the reservoir and cannula were again read at the close of the injection; the reading of the cannula thermometer was sometimes the same as that of the rectal thermometer, but was more often about 0·5° C. lower than the rectal temperature owing to cooling of the fluid during its passage from the reservoir to the cannula.

The level of the fluid in the reservoir was usually 25–30 cm. above the point at which it entered the jugular vein. The rate at which the fluid was allowed to enter the vein was regulated by opening more or less widely a screw clip placed on the rubber tubing connecting the reservoir with the cannula. This method was adopted because otherwise the rate at which fluid entered the heart during a prolonged injection diminished owing to the rise of venous pressure. It had the further advantage that when the arterial pressure began to rise during an injection the rate of inflow could be slowed. Owing to its greater viscosity as compared with saline solution the injection of blood was made under a higher pressure than that used for saline solution.

In the experiments in which changes in the volume of the heart were studied, the ventricles were enclosed in a glass cardiometer of Henderson's type; this was attached to a large piston recorder.

In the figures given in this paper, the numbers on the pulse tracings represent the pulse rate per minute; the numbers on the venous pressure tracings indicate the pressure in millimetres of water, and the time marker records seconds.

Results.

If 200–400 c.c. of saline solution are injected into the circulation during a period of 1½–4 minutes, the heart begins to quicken at a variable period after the beginning of the injection and its rate gradually increases until just after the injection is finished. It then continues to beat rapidly for a time, and may not slow down to its original rate for a considerable period. The arterial pressure may remain unaltered both during and after the injection, though it tends to rise unless the rate of injection is slow. If the arterial pressure is allowed to rise

considerably, and particularly if the initial pressure is high, quickening of the heart is less marked and may be quite trivial. Acceleration of the heart can also be brought about by the more rapid injection of smaller amounts of fluid, and it is possible to evoke definite quickening by injecting 40–50 c.c., provided the rate of injection is sufficiently rapid (Fig. 1). Every gradation exists between these two extremes in the volume of the injection, so that the cause of the acceleration must be the same whether it is produced by the rapid injection of a

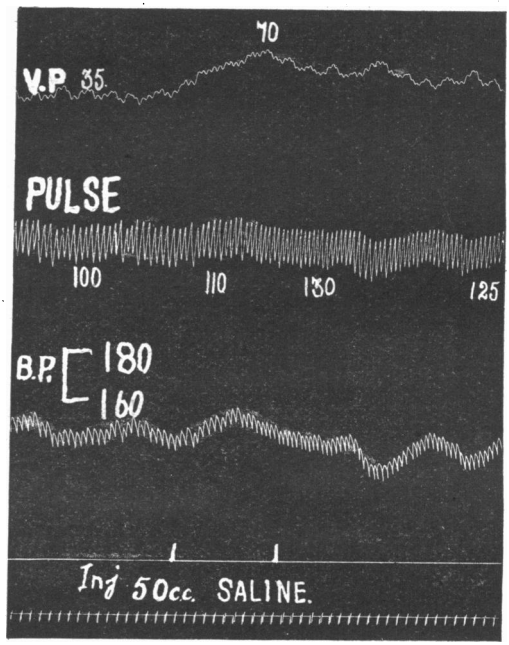

Fig. 1.

small amount of fluid or the slow injection of a large amount. When a small amount of fluid is injected, the acceleration of the heart may be quite as marked as that caused by a large injection; but the acceleration is less prolonged than when the injection is large, the heart usually returning to its original rate a few minutes after the close of the injection. Unless the injection of small amounts of saline solution is made too rapidly or under too high a pressure, the arterial pressure remains steady or rises very slightly; if the rate of injection is very rapid, the arterial pressure is apt to fall.

Acceleration of the heart also occurs when plethora is produced by the injection of blood either undiluted or diluted with a third to an equal quantity of saline solution. Probably owing to its greater viscosity, the injection of blood may cause a considerable rise of arterial pressure if a large amount is injected. It is possible, however, to inject 150–250 c.c. of blood with a comparatively small rise of pressure, provided the injection is made very slowly; in these circumstances the acceleration is well marked (Fig. 2).

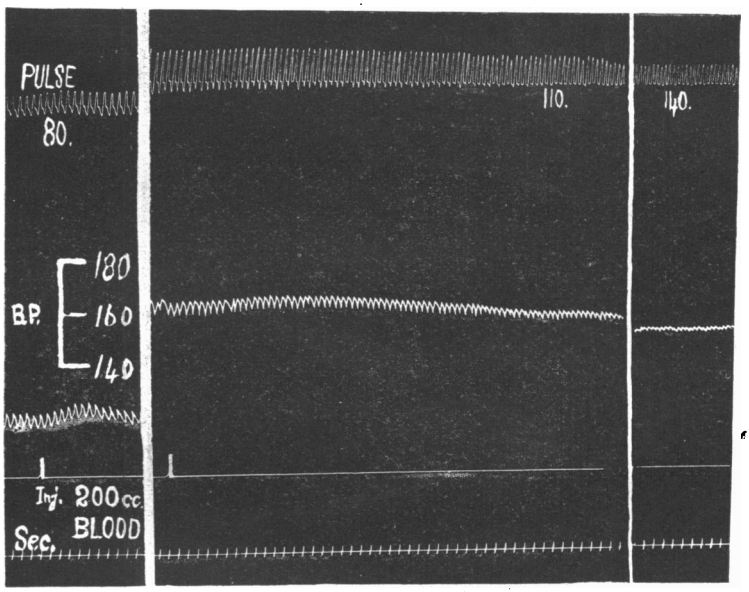

Fig. 2. Interval between first and second parts of tracing is 1′ 40″; interval between second and third parts of tracing is 15″.

Acceleration also occurs when small amounts of blood are *rapidly* injected (Fig. 3).

It is most important to avoid or at least to reduce to a minimum any alteration in arterial pressure, whether a small or large amount of fluid is injected, since changes in arterial pressure are in themselves sufficient (in accordance with Marey's law) to alter the rate of the heart. Every effort has therefore been made in these experiments to keep the arterial pressure constant during the injection of fluid.

In many experiments the respiratory movements were recorded in addition to the pulse rate and the arterial and venous pressures. As

a rule the injection of blood or saline solution had no appreciable influence upon the rate or depth of respiration (Fig. 3). The injection of large amounts of saline solution occasionally led to a slight increase in the depth and rate of breathing, but the changes were always too small to have any direct effect upon the rate of the pulse. Marked alterations in respiration were never observed.

When an animal in a state of plethora is bled slowly the rate of

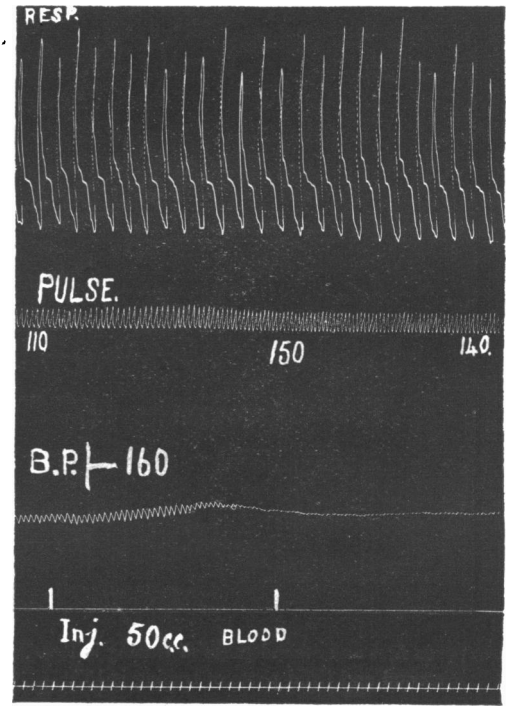

Fig. 3.

the heart decreases, and two or three minutes after the conclusion of the bleeding the pulse rate and blood pressure may be almost the same as they were before plethora was induced. By reinjecting the blood slightly diluted with saline solution plethora can once more be set up and can again be abolished by a second bleeding. This process can only be repeated once or twice in any one experiment, since the abdominal viscera gradually become œdematous and the circulatory conditions become abnormal. The following figures show the effects

of the production of plethora and of subsequent bleeding of the animal upon the arterial pressure and pulse rate:

TABLE I.

		Pulse rate per min.	Arterial pressure in mm. Hg.
(1)	Dog, normal	90	130
	Just after injection of 200 c.c. saline	130	138
	Shortly after being bled 100 c.c. ...	95	140
(2)	Dog, normal	120	88
	Just after injecting 300 c.c. saline	160	90
	Just after bleeding 150 c.c. ...	130	85
(3)	Dog normal	120	160
	Just after injecting 400 c.c. saline	150	168
	Just after bleeding 250 c.c. ...	130	154
(4)	Dog, cardiac accelerators divided	90	84
	Just after injecting 300 c.c. saline	120	108
	Later	130	96
	Bled 150 c.c.	110	90

The rapid injection of small amounts of fluid is more convenient for the study of the cause of the quickening of the heart, since it may be repeated a number of times without unduly increasing the volume of the circulating blood. One or two preliminary injections are sometimes necessary, however, to ascertain what rate of injection will quicken the heart without disturbing the blood pressure. The fall of arterial pressure which is sometimes noticed with a very rapid injection seems to be due to extreme dilatation of the heart and a diminished output. Even in these cases acceleration of the heart precedes the fall of pressure.

The quickening of the heart which normally accompanies hydræmic plethora no longer takes place when this is produced after division of the vagi and cardiac accelerator nerves and ligature of the suprarenal veins. Further, Knowlton and Starling(2) have shown that the rate of the mammalian heart, when isolated from the central nervous system, is not influenced either by variations in the rate of venous inflow, or by alterations in the endocardiac pressure. Hence the acceleration must be reflex in origin.

The efferent path.

There is no evidence that the suprarenal glands play any part in the quickening which occurs in hydræmic plethora. In the first place. after extirpation of these glands hydræmic plethora produces as marked acceleration of the heart as that observed in the intact animal, and secondly after division of the vagi and cardiac accelerator nerves, the

suprarenal glands being left intact, hydræmic plethora has no influence on the rate of the heart. This is shown in the following protocol:

Protocol 1. Dog ♀, weight 8 kilos. Cardiac accelerator nerves divided on both sides. Rectal temperature 35·5° C. Injected 300 normal saline solution into jugular vein. Pulse increased from 90–120 per minute. Blood pressure rose from 84 to 108 mm. Hg. Later the pulse rate fell to 90. After section of the vagi the pulse rate was 130. Later the pulse rate was 115.

150 c.c. of equal parts of blood and saline were injected. Pulse rate remained at 115.

The efferent path of the reflex must therefore be either the vagi or the cardiac accelerators, or both these nerves. There is no doubt that the acceleration is due largely to diminution or disappearance of vagus tone. This can be demonstrated by ligaturing the suprarenal veins, and dividing the accelerator nerves, so that the heart is connected with the central nervous system solely by the vagi. In these circumstances the production of hydræmic plethora, or of plethora, leads to a definite quickening of the heart (Fig. 4).

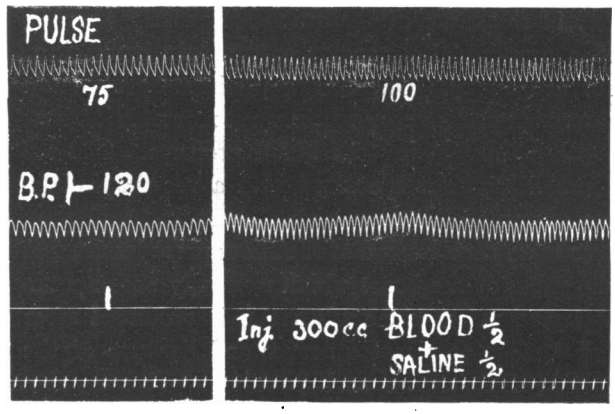

Fig. 4. Interval of three minutes between the two parts of the tracing.

The rapid injection of fluid also gives rise to a temporary acceleration of the heart (Fig. 5). This effect is illustrated in the following protocol:

Protocol 2. Dog, weight 10 kilos. Suprarenal veins ligatured; cardiac accelerator nerves cut on both sides; vagi intact.

(*a*) Rectal temperature 36·5° C. Injection of 300 c.c. equal parts of blood and saline solution; period of injection 3′ 28″. The pulse rate rose from 75 to 100 per minute; the arterial pressure was 105 mm. Hg before the injection and remained unchanged. The dog was then bled and the pulse rate gradually fell to 70.

(*b*) Rectal temperature 36° C. Injected 100 c.c. equal parts of blood and saline solution; injection period 16″. The pulse rate rose from 70 to 90.

The arterial pressure was 116 mm. Hg before and after the injection.

The acceleration produced by plethora or hydræmic plethora after division of the accelerator nerves is distinctly less persistent than in the normal animal; this fact suggests that the quickening in the normal animal is due not only to loss of vagus tone but also to some increase in accelerator tone. It is not easy, however, to obtain convincing evidence on this point. When the vagus endings are paralysed by atropin considerable accelerator tone is often present, and the rate of the heart may be 170 or even more; in these circumstances neither the production of hydræmic plethora, nor the rapid injection of small amounts of fluid has much effect upon the rate of the heart although the venous pressure rises. In some experiments the rate of the heart after the injection of atropin has been comparatively slow (130–140)

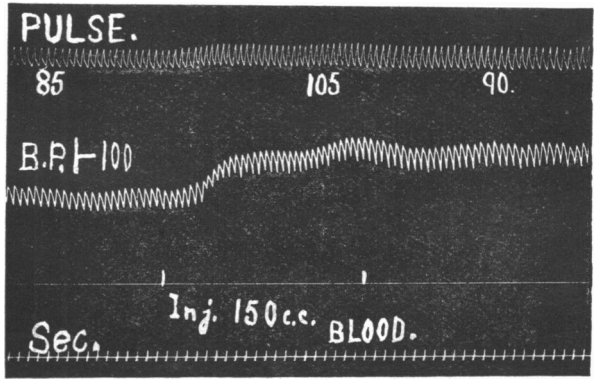

Fig. 5.

and the injection of large amounts of blood or saline solution has evoked a moderate increase in rate (Fig. 6). Such a result is shown in the following protocol:

Protocol 3. Dog; weight 11 kilos. Vagi and cardiac accelerator nerves intact. Initial pulse rate 90; after the injection of atropin 140. 300 c.c. saline solution injected during 2′ 50″. Pulse rate rose from 140 to 170. Blood pressure rose from 95 to 100, and later to 140. The dog was then bled 150 c.c.; the pulse rate fell to 150.

The results of other similar experiments are given in the following table, which shows the effect of plethora upon the pulse rate after the injection of atropin; at the end of each experiment the vagi were divided and their peripheral ends were stimulated in order to make certain that the vagus endings were paralysed. The cardiac accelerator nerves were intact.

TABLE II.

		Pulse rate	Arterial pressure	Venous pressure
Exp. 1. Injection of 300 c.c. equal parts of blood and saline solution	Before	110	110	—
	After	180	140	—
Exp. 2. Injection of 400 c.c. equal parts of blood and saline solution	Before	165	130	70
	After	190	154	170

Although the quickening is rarely very marked it seems to be a genuine effect, more especially as it is sometimes possible subsequently to diminish the accelerator tone by bleeding the animal. It is necessary, however, to inject large amounts of fluid and there is usually a rise of blood pressure amounting to 30–40 mm. Hg; the respiration is

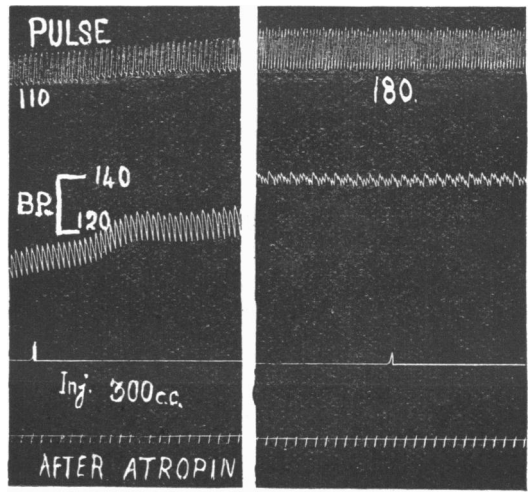

Fig. 6. Interval between two parts of tracing = 2′ 10″.

unaffected. It is probable, therefore, that plethora produces not only diminution or loss of vagus tone but also, under favourable conditions, some increase of accelerator tone, since the acceleration is not caused by increased activity of the suprarenal glands. If this is the case, the increase in the pulse rate brought about by increased venous filling of the heart falls into line with that occurring during muscular exercise or caused by the stimulation of many sensory nerves, and furnishes another instance of reciprocal action between the vagus and accelerator centres. Nevertheless the dominant factor is the loss of vagus tone.

The afferent path.

In attempting to ascertain the seat and nature of the stimulus which gives rise to quickening of the heart, when the venous inflow is increased, it is necessary to consider first whether it can be accounted for by any of the recognized causes of acceleration. In the first place, the production of plethora or hydræmic plethora is not accompanied by any constant or definite alteration of respiration. The respiratory movements are either unaffected or are increased to a trivial extent, insufficient to produce any direct effect upon the rate of the pulse. Hence the quickening of the heart cannot be attributed to any influence of the respiratory centre by irradiation to the cardio-inhibitory centre. Secondly the circulation through the brain must be practically unaltered since the arterial pressure often remains unchanged and rarely rises more than a few millimetres. Nor is there any reason to suppose that the composition of the injected fluid is responsible for the increase in the pulse rate; this takes place whether the injected fluid be saline solution or blood from another dog or the animal's own blood. Thirdly plethora is not accompanied by visible muscular movements. It is probable, therefore, that the acceleration of the heart does not depend either on stimuli arising in the brain itself or upon changes in the composition of the circulating blood, but that it is brought about by impulses set up peripherally in the circulatory system.

The effects produced by plethora or hydræmic plethora upon the circulation include not only an increase in the pulse rate, but also a rise of venous pressure and dilatation of the heart; their occurrence has been confirmed in the present enquiry and the following example may be given:

Protocol 4. Dog; 5 kilos. Cardiac nerves intact. Rectal temp. 33·5° C.

		Pulse rate	Venous pressure	Arterial pressure
Inj. 200 c.c. saline solution in 104″ Temp. 33·0° C.	Just before injection	120	8	146
	Just after injection	160	112	150
	3½ mins after injection	140	45	130

Similar changes accompany the *rapid* injection of small amounts of blood or saline solution. Although the rapid injection of 50 c.c. of fluid into a large dog, the volume of whose blood may be 500 c.c., does not notably increase the volume of the blood, it causes both a rise of venous pressure and quickening and dilatation of the heart. The venous pressure rises rapidly during the injection, begins to fall as soon as the injection is ended and gradually returns to its original level

(Fig. 1). On the contrary, the *slow* injection of a small amount of fluid does not raise the venous pressure and does not evoke any acceleration of the rate of the heart. This is seen in the two following protocols:

Protocol 5. Dog ♀; weight 5·5 kilos. Cardiac nerves and suprarenal glands intact. Rectal temp. 38·25° C.

		Pulse rate per min.	Venous pressure in mm. saline	Arterial pressure in mm. Hg.
(1) Injection of 50 c.c. saline in 2′ 20″	Before	105	35	148
	After	105	35	152
(2) Injection of 50 c.c. saline in 0′ 11″	Before	100	35	146
	After	130	70	150

The zero of the venous pressure was observed after opening the vena cava near the heart.

Protocol 6. Dog; 6 kilos. Cardiac nerves and suprarenal glands intact. The zero of the venous pressure was observed after opening the vena cava near the heart. Rectal temp. 38·5° C.

		Pulse rate per min.	Venous pressure	Arterial pressure
(1) Injection of 50 c.c. saline in 104″	Before	80	40	86
	After	80	45	86
(2) Injection of 100 c.c. saline in 20″	Before	80	70	80
	After	100	160	84

The close association between a rise of venous pressure and quickening of the heart is also seen when the period at which they occur in the course of an injection is observed. In one experiment, 100 c.c. saline solution were injected during 20 seconds; during the injection, the arterial pressure rose from 82 to 86 mm. Hg. The heart began to quicken 10 seconds after the beginning of the injection; at this moment, the venous pressure had risen approximately 45 mm. The venous pressure and the rate of the heart continued to increase until the injection was finished. In a second experiment, 200 c.c. saline solution were injected during a period of 112 seconds; during the injection the arterial pressure rose from 130 to 138 mm. Hg. The heart began to quicken 65 seconds after the injection began; at this time the venous pressure had risen 35 mm. The heart continued to quicken and the venous pressure rose until the end of the injection. Other experiments yielded similar results.

It seems clear that the quickening of the heart, when the venous inflow is increased, does not depend upon the amount of fluid injected, that is to say, upon the increased volume of the blood, since a small injection may cause acceleration of the heart whereas a larger one may fail to do so. There is, however, a constant relation between a

definite rise of venous pressure and quickening of the rate of the heart; as a rule the quickening begins when the rise of venous pressure is from 30–60 mm. of water. The actual rise of venous pressure at the onset of acceleration of the heart varies considerably in different animals, but the stability of the vagus centre is doubtless influenced both by the initial dose of morphia and by the general condition of the animal.

After the completion of an injection, whether this be large or small, the venous pressure gradually falls and the rate of the heart diminishes. When a small amount of fluid is injected, the venous pressure often sinks to its original level and the pulse returns to its original rate within five minutes after the end of the injection. The relation between the fall of venous pressure and the diminution of pulse rate is illustrated in the following experiment:

Protocol 7. Dog; 6·5 kilos. Cardiac nerves intact. Rectal temp. 38·25° C.

		Pulse rate	Venous pressure	Arterial pressure
Injection of 100 c.c. saline solution in 20″. Temp. 38° C.	Just before injection	80	70	80
	At end of ,,	100	160	86
	½′ after injection	100	130	90
	2½′ ,, ,,	100	95	96
	5½′ ,, ,,	90	80	92
	7′ ,, ,,	80	70	84

After the injection of large amounts of fluid, the venous pressure falls rapidly at first and then more slowly, and may not decline to its original level for 15–20 minutes after the injection; the acceleration of the heart produced by the injection also passes off gradually as the venous pressure approaches or reaches its initial level.

The fall of venous pressure can be rapidly induced by bleeding the animal to a moderate degree, and in these circumstances the pulse rate and venous pressure diminish simultaneously, as is seen in Figs. 7 and 8. Fig. 7 shows the effect upon the pulse rate and venous pressure of injecting

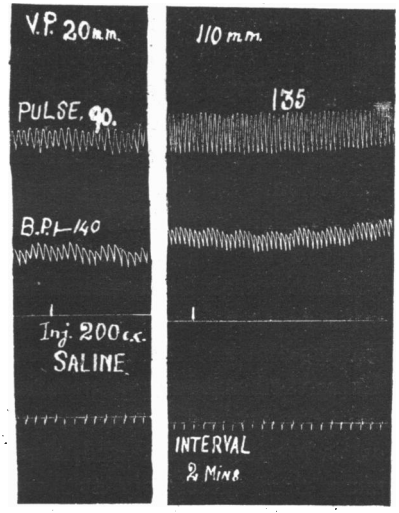

Fig. 7.

200 c.c. saline solution. Two minutes after the end of the injection, the venous pressure had fallen to 50 mm. of water and the pulse rate was 130; this is shown in the first part of Fig. 8. The animal was then bled to the extent of 50 c.c., and the second part of Fig. 8 shows the pulse rate and venous pressure two minutes after the bleeding.

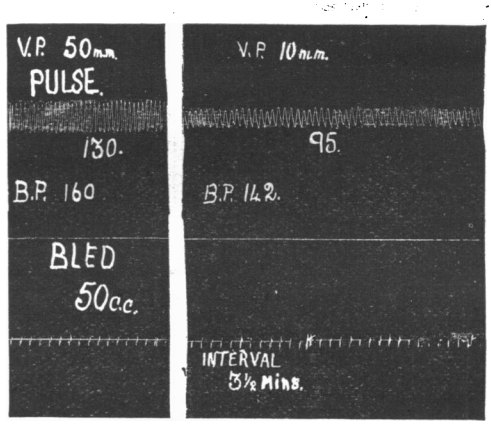

Fig. 8.

The rate at which the venous pressure and pulse rate fall after an injection depends not only upon the volume of fluid injected, but also upon the initial volume of the blood. If the animal has already received one or two injections, even a small injection of fluid may cause a comparatively prolonged rise of venous pressure, whereas if the blood volume has been lessened by hæmorrhage, the rise of venous pressure produced by a large injection of fluid rapidly passes off after the injection.

It is evident from the foregoing experiments first that the acceleration of the rate of the heart produced by increasing the venous inflow is constantly associated with a rise of venous pressure, and secondly that the acceleration begins when the rise of venous pressure reaches a definite point and that it passes off again as the venous pressure falls.

Using the heart-lung preparation, Patterson and Starling(6) have shown that, when the arterial resistance is constant and the venous inflow is gradually increased, a point is reached at which the venous pressure rises sufficiently to become an effective factor in actively distending the ventricles during diastole and that it ultimately produces dilatation of the heart. Provided the arterial pressure remains

constant and the heart is not fatigued, dilatation of the heart, therefore, is simply an expression of, and is secondary to, increased venous and diastolic pressure. It seemed desirable, however, to make some observations as to the effect of the rapid injection of small or moderate amounts of blood or saline solution upon the volume of the heart in the normal animal. When the chest is opened and the heart placed in a cardiometer, its rate is often so rapid that it is not easy to obtain further quickening by the injection of small or moderate amounts of fluid into the circulation. Acceleration took place, however, in some

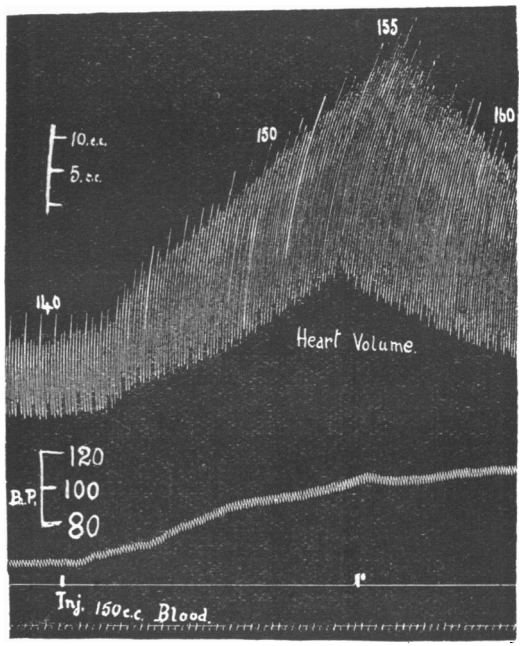

Fig. 9.

experiments, and its occurrence was accompanied by definite and considerable dilatation of the heart (Fig. 9); conversely, an injection which was too slow to dilate the heart did not give rise to quickening. Although cardiometer experiments are unsatisfactory for investigating acceleration of the heart during increased venous filling, they show that the rise of venous pressure which accompanies quickening of the heart, when the venous inflow is increased in the normal animal, is almost certainly sufficient to raise the diastolic pressure and to cause some dilatation of the heart.

If a definite rise of venous and diastolic pressure is not merely associated with the quickening of the heart produced by increased venous inflow, but is the actual cause of the acceleration, the afferent impulses thus set up in the heart must travel up the vagi, since acceleration occurs when the heart is connected with the central nervous system solely by the vagi. Owing to the fact that the vagi are the chief efferent path of the reflex, it is almost impossible to obtain direct evidence that they also constitute the afferent path for the impulses which give rise to reflex quickening of the heart in hydræmic plethora. But some light

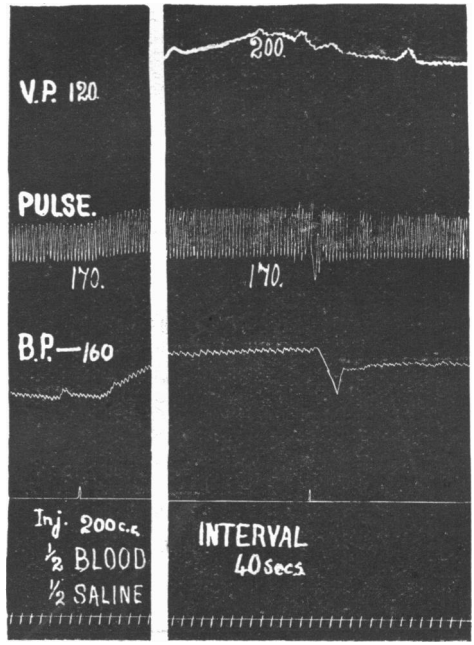

Fig. 10. Interval between two parts of tracing is 40″.

is thrown on this point by the difference in the effect of hydræmic plethora upon the rate of the heart on the one hand after the administration of atropin, and on the other hand after division of the vagi, the cardiac accelerator nerves being in each case intact. After the injection of a small dose of atropin, hydræmic plethora produces some acceleration of the heart unless its initial rate is very rapid, whereas after division of the vagi, hydræmic plethora has no effect upon the rate of the heart (Fig. 10). It is often necessary to employ artificial respiration after

division of the vagi, but the same result is obtained when the breathing is natural. That the rate of the heart was by no means maximal after section of the vagi was shown by the fact that considerable further acceleration could be produced by the injection of adrenalin. Further the amount of fluid injected was sufficient to cause a rise of 60–80 mm. in the venous pressure, both after the injection of atropin and after section of the vagi.

The essential difference between these two groups of experiments is that, while in both groups the influence of the vagus centre upon the heart is abolished, section of the vagi also eliminates afferent impulses from the heart, whereas atropin excludes, so far as is known, only the efferent vagus fibres. Evidence based on the dissociation of efferent and afferent fibres by means of a drug such as atropin is not entirely satisfactory, but, so far as they go, these experiments point to the conclusion that the afferent impulses which give rise to reflex acceleration of the heart when the venous inflow is increased probably arise in the heart and travel up the vagus.

The effect of plethora or hydræmic plethora upon the rate of the heart after section of the vagi is shown in the following protocol and table:

Protocol 8. Dog; weight 5·5 kilos. Vagi and cardiac accelerator nerves intact. Rectal temp. 38° C. Pulse rate 100; venous pressure 35 mm.

(*a*) 50 c.c. of saline solution were rapidly injected; at the end of the injection, the pulse rate was 130, and the venous pressure 70 mm.

(*b*) The vagi were divided and the pulse rate rose to 190 at first and gradually fell to 170; respiration was natural. The injection of 175 c.c. of saline solution at 38° C. yielded the following result:

	Just before the injection	Just after the injection
Pulse rate	170	170
Venous pressure ...	35	65
Arterial pressure ...	72	178

(*c*) On section of the cardiac accelerators, the pulse rate fell to 145–150.

(*d*) The maximal rate of the heart, determined by the injection of adrenalin, was 220–230.

TABLE III. In all these experiments, the cardiac accelerators were intact.

		Pulse rate per min.	Arterial pressure	Venous pressure in mm. saline
(1) (*a*) *Normal*				
Injection of 50 c.c. equal parts of blood and saline	Before	115	130	—
	After	150	150	—
(*b*) *After section of vagi*				
Injection of 50 c.c. equal parts of blood and saline	Before	150	200	—
	After	150	200	—
Maximum rate of the heart was 210.				

		Pulse rate per min.	Arterial pressure	Venous pressure in mm. saline
(2) (*a*) *Normal*				
Injection of 200 c.c. saline solution	Before	90	130	25
	After	130	138	115
(*b*) *After section of vagi*				
Injection of 200 c.c. blood and saline solution	Before	170	142	135
	After	170	160	215
Maximum rate of the heart, 190.				
(3) (*a*) *Normal*				
Injection of 300 c.c. saline solution	Before	120	90	—
	After	160	85	—
(*b*) *After section of vagi*				
Injection of 250 c.c. blood	Before	140	160	—
	After	140	180	—
Maximum rate of the heart, 190.				

Summing up the foregoing evidence, it seems clear that the acceleration of the heart which takes place, when the venous inflow is increased by the injection of blood or saline solution into the normal animal, is not due either to alterations in respiration or arterial pressure or to changes in the composition of the blood, but that it is invariably associated with a definite rise of venous pressure. The quickening of the heart begins when the venous pressure has risen sufficiently to dilate the heart and to raise the diastolic pressure, and as the venous pressure falls the rate of the heart again diminishes; after exclusion of the afferent fibres of the vagi by division of these nerves a rise of venous pressure is no longer accompanied by acceleration of the heart. Further, the acceleration of the heart is not directly dependent upon the increased volume of the circulating blood since it may be produced by either a small or a large injection; and the injection of fluid seems to be effective in quickening the rate of the heart only in so far as it raises the venous pressure.

It may be concluded, therefore, that the reflex acceleration of the heart, which is brought about by increasing the venous inflow, is caused by a rise of venous pressure sufficient to raise the diastolic pressure and to dilate the heart. Moreover, since the injection of fluid into the circulation is merely a convenient means of raising the venous pressure, it is probable that an adequate rise of venous pressure, under whatever conditions it may occur, leads to acceleration of the heart, provided the cardiac nerves are intact and the arterial pressure is not raised.

The question as to whether the effective stimulus to the heart is the rise of venous (and diastolic) pressure or whether it is the increased tension in the muscle fibres of the dilated heart cannot be answered with

certainty. But the available evidence points to the rise of venous pressure as the essential cause of the acceleration of the heart. When the pericardium is closed, an increase in the venous inflow produces a considerable rise of venous pressure and a moderate dilatation of the heart, whereas when the pericardium is opened an increased venous inflow leads to a small rise of venous pressure and to great dilatation of the heart. It has been found in the present enquiry that the injection of both small and large amounts of fluid causes acceleration of the heart much more readily and certainly in the normal animal than after removal of the pericardium; the acceleration appears, therefore, to be correlated with increased venous pressure rather than with the dilatation of the heart evoked by the rise of venous pressure.

If these conclusions are correct, the heart is provided with a reflex mechanism whereby, when the venous filling is increased, the circulation can be maintained by the more rapid transference of blood from the venous to the arterial system and the risk of excessive dilatation and of failure of the heart is lessened. This mechanism must play a part in the quickening of the heart during muscular exercise, which is accompanied by increased venous inflow to the heart and by a rise of venous pressure. Again, Patterson and Starling(6) have shown that greater diastolic distension of the heart is needed to produce a given output when the heart is fatigued than when it is fresh; this distension can only be caused by a rise of venous pressure. Since the rise of venous pressure will lead to acceleration of the heart, if the cardiac nerves are intact, it follows that a fatigued heart must inevitably be a rapid heart.

Marey has shown that the pulse rate tends to vary inversely with the arterial pressure; consequently the pulse rate must be influenced in opposite directions by a rise of arterial and venous pressure respectively. The relationship between arterial pressure and pulse rate, however, has many limitations, and the extent to which it holds good in the normal animal is by no means clear. The relation between a rise of venous pressure and the pulse rate is not only more constant in its incidence, but appears to be more important for the continued well being of the heart and the maintenance of the circulation.

Conclusions.

(1) Increased venous filling of the heart, whether produced by the rapid injection of small amounts, or the slow injection of large amounts, of blood or saline solution, leads to a rise of venous pressure and to acceleration and dilatation of the heart; the arterial pressure rises slightly or remains steady.

(2) The quickening of the rate of the heart is reflex in origin since it no longer occurs after division of the vagi and cardiac accelerator nerves and ligature of the suprarenal veins.

(3) The acceleration of the heart is due chiefly to diminution of vagus tone and partly to increased accelerator tone; there is no evidence that the activity of the suprarenal glands is increased.

(4) The acceleration is not necessarily or usually accompanied by changes in arterial pressure or in the respiratory movements, nor does it depend upon the character or amount of the injected fluid except in so far as this raises the venous pressure.

(5) The acceleration is constantly associated with a definite rise of venous pressure, and begins when the rise of pressure is sufficient to raise the diastolic pressure and to dilate the heart; after section of the vagi, the cardiac accelerator nerves being intact, a rise of venous pressure is no longer accompanied by quickening of the heart.

(6) The reflex acceleration of the rate of the heart which takes place when the venous inflow is increased in the normal animal is caused by impulses arising within the heart, and the effective stimulus is an adequate rise of venous pressure.

The expenses of this research were partly defrayed by a grant from the Government Grant Committee of the Royal Society.

References.

(1) Evans and Matsuoka. This Journal, xlix. p. 378. 1915.
(2) Knowlton and Starling. Ibid. xliv. p. 206. 1912.
(3) Krogh. Skand. Archiv. Physiol. xxvii. p. 126. 1912.
(4) Kuno. This Journal, l. p. 1. 1915.
(5) Newell Martin. Phil. Trans. Roy. Soc. clxxiv. p. 663. 1883.
(6) Patterson and Starling. This Journal, xlviii. p. 357. 1914.