Methods of Raising a Low Arterial Pressure.

By W. M. Bayliss, F.R.S.

(Received August 29, 1916.)

(From the Physiological Laboratory, University College, London.)

CONTENTS.

In the course both of physiological experiments and of clinical practice a low arterial pressure may be due to two different causes, apart from failure of the heart.

After hæmorrhage, the blood pressure is low on account of deficiency of blood in circulation, so that the output of the heart is decreased and is insufficient to keep up a due supply in the arteries to take the place of that flowing through the capillaries. Now, while it is obvious that constriction of the arterioles would raise the pressure in such cases, by diminishing the rate of outflow through the capillaries, the result would be to decrease the supply of blood to all organs whose arterioles are affected, so that no real gain would be obtained. In such cases, what is needed is to increase the volume of blood, without constricting arterioles.

But the arterial pressure may be low, although the volume of the blood is normal. Supposing that the heart is beating efficiently, the low pressure is, in such cases, due to peripheral vaso-dilation. Such a condition is met with when the spinal cord is cut high up, as in the "spinal animal," and also in cases which are called "shock." Here, what is required is clearly to restore the normal tonic contraction of the arterioles. An increased volume of blood may be useless or even harmful, if the heart cannot correspondingly increase its output.

It is, nevertheless, the usual practice to treat both kinds of state by the intravenous injection of saline solutions, sometimes by transfusion of blood. But the unsatisfactory effect of saline injections suggested that a more efficient fluid might be found and the following investigation was undertaken with that object.

Loss of Blood.

I will consider first the restoration of arterial pressure after loss of blood.

Experiments were made to begin with in order to analyse the effects produced by injection of pure saline solutions.

A cat was anæsthetised by chloroform and ether and afterwards by urethane intravenously (1 grm. per kilogramme body weight), given slowly. Cannulæ were placed in the carotid artery for the registration of the arterial pressure, in the external jugular vein for the introduction of liquids from a burette, and in the femoral artery for the withdrawal of blood. The vagus nerves were cut in order to avoid cardiac and depressor reflexes. The blood pressure at the beginning of the experiment was 158 mm. of mercury. This was reduced to 46 mm. by the removal of 66 c.c. of blood. The same volume of Ringer's solution, warmed to 38° C., was then run into the vein. The blood pressure returned for a brief period to 128 mm.; that is, there was a restoration of three-quarters of the amount by which it had fallen. The size of the heart beats, which had been greatly reduced by the loss of blood, became as large as at first. But this partial recovery was only maintained for about five minutes and by the end of 24 minutes the pressure had fallen again to 80 mm., being only half of the original height.

In other experiments of the same kind, it was found that the fall of blood pressure resulting from hæmorrhage was restored by about two-thirds to three-quarters of the amount by which it had fallen. Of course, by the injection of amounts of saline solution greater than the volume of the blood removed, a temporary rise to the normal value may be obtained. But it is undesirable to augment the total volume of blood on account of the strain on the heart, and it is important to know why the restoration of the blood to its normal quantity, if done by saline injection, does not result in a return to the corresponding initial pressure.

Downs (12) found that, if the arterial pressure had fallen to three-eighths of the normal by hæmorrhage, injection of saline could only raise it to about two-thirds again. He gives detailed measurements of the relative effects obtained in various degrees of loss of blood.

As will be seen presently, there are two separate phenomena requiring explanation. Why is saline solution relatively ineffective in restoring pressure? And, secondly, why does the pressure actually produced fall again more or less rapidly to a value very little higher than that before the injection.

In regard to the former problem, we know that, the cardiac output being supposed constant, the height of the arterial pressure depends on the

resistance in the peripheral arterioles and that this resistance is entirely due to the internal friction or viscosity of the blood. The rate of flow is inversely proportional to the viscosity and directly proportional to the driving pressure, by Poiseuille's law. This law has been shown by Du Bois-Reymond, Brodie, and Müller (1) to apply to the circulation, contrary to the objections of Heubner and others. The output of the heart being constant, by hypothesis, the rate of flow through the blood-vessels must also be constant, and therefore if the viscosity of the blood decreases, the driving pressure must decrease also. Otherwise, the current through the capillaries would be larger than that supplied by the heart. In other words, the arterial pressure must fall. Although this fact seems obvious, I thought it of interest to test it in a model made of indiarubber tubing connected with a glass tube of 0·97 mm. bore and 27 cm. long. Through this a current of gum solutions of various concentrations and viscosities was driven by means of a small pump of constant delivery of 0·3 c.c. per stroke. The outflow from the capillary was found to be constant, although the driving pressures ranged from 178 mm. of mercury, when the viscosity was 3·7 times that of water, down to 45 mm. of mercury with water itself.

Now, the viscosity of blood is considerably higher than that of water or of a dilute saline solution. In the cats used in my experiments it was usually about three times that of water, but in one case it was only 2·2 times, and in another it was as high as four times. The viscosity of Ringer's solution, on the other hand, is practically the same as that of water. It follows that, if part of the blood is replaced by such a saline solution, the resulting viscosity is correspondingly reduced, and, other things equal, the arterial pressure must decrease. Thus, in one experiment, the viscosity was reduced to 1·6 times that of water by replacing half of the blood by Ringer's solution. In another case it was reduced from 2·2 times to 1·8 times by the replacement of 47 per cent. of the calculated blood volume by the saline solution.

The viscosities were determined at 38° in an apparatus similar to that described by Scarpa (2), in which a known volume is driven first upwards through a capillary tube by pressure and then allowed to run back downwards. The mean of several pairs of readings was taken. The advantage of this method is that no correction need be made for specific gravity or surface tension, since these factors correct themselves by acting in opposite directions in upward and downward movement.

The blood volume was taken to be 48 c.c. per kilogramme of body weight.

In one experiment several samples of blood of 45 c.c. each were removed and replaced by saline in series, so that the viscosity decreased each time. The height of the arterial pressure, compared with the viscosity in each stage, was as follows:—

Table I.

Blood pressure.	Viscosity relative to water.	Relative blood pressure.	Relative viscosity.
136	3·0	100	100
128	2·65	94	89
104	2·3	77	77
82	2·0	60	66

It is evident that the diminution of viscosity is a sufficient explanation of the inefficiency of saline solutions, so far as the immediate effect is concerned. If, therefore, the viscosity of Ringer's solution could be raised by the addition of some innocuous substance, a much better result would be obtained. There are several substances which might be used for this purpose.

Soluble starch has the disadvantage of not having sufficient viscosity, except in concentrated solutions. It does not give very homogeneous solutions, and alters by keeping, even in the cold. The solution becomes acid, as shown by Wolff and Fernbach (3), by separation of phosphoric acid, so that neutralisation is necessary each time that it is used. It has, further, the objection of a very small osmotic pressure. The importance of this fact will be seen presently.

Amylopectin, prepared by precipitation of ordinary starch with acetone, in the manner of Wolff and Fernbach, has a high viscosity, but an insignificant osmotic pressure.

Agar requires too high a temperature to melt the jelly, and is practically devoid of osmotic pressure.

Gum acacia in 7-per-cent. solution has a viscosity about equal to that of blood. The commercial samples consist partly of the calcium salt. I find that the one used in my experiments had a calcium content equal to 2·23 per cent. of calcium chloride. A 7-per-cent. solution would therefore contain 0·16 per cent. This is too high for a normal physiological solution. It is advisable to precipitate by the addition of the necessary amount of phosphoric acid; 7 grm. of the gum referred to require 9·38 c.c. of decimolar phosphoric acid. On making just alkaline to neutral red with sodium hydroxide, the calcium phosphate is precipitated and falls on standing. The solution consists now of the sodium salt of the gum acid, saturated with calcium phosphate. A saturated solution of calcium phosphate was found by Ringer to contain the optimal concentration of calcium. The sodium salt has the further advantage of a slightly higher viscosity than the calcium salt. To complete the solution, the correct amount of potassium

chloride is finally added. For clinical use, sterilisation by heat does not perceptibly diminish the viscosity. The mucilage of the British Pharmacopœia, when diluted by adding 400 c.c. of water to 100 c.c., makes a 7-per-cent. solution.

Finally, *gelatin* is very convenient in many ways, as solutions are quickly made. If the maximum viscosity is required, a temperature above 40° C. should not be employed in making the solution. If heated to 100°, as Moore and Roaf (4) showed, the osmotic pressure rises. The decrease of viscosity on heating is a disadvantage for clinical use, since sterilisation is indispensable, owing to the usual presence of micro-organisms, especially those of tetanus.

The Table below gives numerical data of the properties of various solutions, so far as they concern us here.

Table II.

	Viscosity ($H_2O=1$).	Viscosity in dynes $\times 10^3$ ($H_2O=6{\cdot}6$).	Osmotic pressure against water.	Osmotic pressure against Ringer solution.
			mm. Hg.	mm. Hg.
Blood of cat	3·0	19·8	—	—
Ox serum	1·5	9·9	116	36–40
Soluble starch (Kahlbaum) 4 per cent.	1·7	11·2	—	14–16
Soluble starch (Kahlbaum) 4 per cent., after cold storage	2·26	16	—	—
Wheat starch, 2 per cent.	2·65	17·5	—	—
Amylopectin, 1·72 per cent.	4·8	32	—	—
Gum acacia, 7 per cent., Ca salt	3·1	20·5	—	—
Gum acacia, 7 per cent., Na salt	3·4	22·5	218	39
Gelatin, 6 per cent.	4	26·4	95	38·5
Gelatin, 6 per cent., after heating to 100°	3	19·8	—	63

Although some of these figures are to be found in the literature, I thought it better to determine them all with the solutions actually used in my experiments, and under similar conditions at 38°. Many of the data are new. Others differ somewhat from previous determinations, as would be expected from the variability of colloidal substances.

In experimental test, it was found that injection of Ringer's solution containing one or more of these substances in sufficient quantity to raise the viscosity to that of blood, even when injected only in amount equal to that of the blood lost, brought back the arterial pressure to its original height,

and sometimes temporarily above this height. The explanation of this latter fact will be seen immediately. Thus:—

A cat with a blood pressure of 110 mm. of mercury had about half of the calculated amount of its blood removed. The pressure fell to 40 mm. It was brought back at once by the injection of an equal volume of Ringer's solution containing gum in sufficient quantity to raise its viscosity to 3·1 times that of water. In the course of two or three minutes the pressure rose further to 145 mm. Although it soon commenced to fall slowly, it was still at its initial value of 110 mm. at the end of 43 minutes. It had only fallen to 102 mm. in an hour and to 98 mm. in 75 minutes. Similar results were obtained with gelatin.

We see that by raising the viscosity of the injected fluid to that of blood by the addition of gum or gelatin, the blood lost can be replaced by an equal volume of the solution, with a return to its original height. Further, that this height is maintained for an hour or so, and even then has only fallen to an unimportant degree.

Pure Ringer's solution, as shown above, is very inefficient in maintaining the blood pressure even at that height to which it at first raises it. Why do gelatin and gum behave differently in this respect? It is clear that viscosity alone is not a sufficient explanation. The fact that gelatin solutions caused a more permanent rise of blood pressure than pure saline was noted by J. Hogan and Martin H. Fischer (9), and Bogert, Underhill, and Mendel (17) found that saline solutions containing 2 per cent. of gelatin did not leave the blood-vessels as rapidly as pure saline.

A partial explanation of these facts is given by Knowlton's experiments on the secretion of urine (5). Starling (6) had shown that if the osmotic pressure of the blood colloids, to which the membrane of the glomerulus is impermeable, be reduced by dilution of the blood, diuresis results. This is the case when a pure saline solution is injected. But Knowlton showed that by the addition of a colloid which has an osmotic pressure, such as gelatin, the effect of the dilution is greatly decreased. Further, if a colloid which has no perceptible osmotic pressure, such as the soluble starch used by him, be added, instead of gelatin, the diuresis is as great as with saline. This is confirmed by the following experiment:—

A cat with a blood pressure of 180 mm. of mercury had one-third of its blood removed. An equal volume of 5-per-cent. soluble starch in Ringer's solution was injected when the blood pressure was 70 mm. It was brought back, temporarily, to 160 mm., the viscosity of the solution being only 2·2 times that of water. The blood pressure then began to fall, becoming 130 mm. in 18 minutes, and 62 mm. in 40 minutes. At the end of the

experiment, 50 c.c. of urine were found in the bladder, while 30 c.c. had been passed in the course of the experiment.

Other experiments were made with the insertion of a cannula in the bladder, and records made by means of an electrical drop recorder. It was found that while saline solutions produced diuresis, this was not the case with gelatin. For example, only 14 c.c. were excreted in 68 minutes, against 2·5 c.c. in six minutes (=14 c.c. in 34 minutes) before the bleeding.

The loss of the injected fluid by renal excretion does not, however, explain the phenomenon of the fall of blood pressure. It was sometimes found in my experiments that very little urine was produced after the saline injection. This was probably due to the kidney having suffered from want of oxygen during the period of low blood pressure following the removal of blood. In fact, it was noticed in one case that a slow renal secretion subsequent to a saline injection was considerably increased by a more vigorous artificial respiration, although there had been no signs of asphyxial stimulation of the nerve centres. It is well known that the kidney is sensitive to deficient supply of oxygen. But what concerns us for the present purpose is the fact that, although there may be no increased loss of fluid by renal excretion, yet the arterial pressure falls rapidly after saline injections.

The additional factor is, no doubt, passage of fluid into the tissues. Bogert, Underhill and Mendel (17) have shown that saline solutions pass into the tissues rapidly and that the kidney is not necessary for the removal of excess of fluid from the circulation after intravenous injections into the normal animal. Moreover, the production of œdema by perfusion with Ringer's solution is familiar to all who have made such experiments. The liver, in particular, swells to a great extent when saline solutions are injected. This is obvious to the eye, and in some plethysmographic experiments on a lobe of the liver which I made some years ago, I noticed a very considerable increase in volume under such circumstances. In the experiments to be referred to below, in which a limb was perfused with Ringer's solution containing 7 per cent. of gum acacia, the absence of œdema was noticeable. We have also seen above that the blood pressure remains high for a long time after the injection of gum or gelatin, but falls after starch solutions. In what way, then, do gum and gelatin differ from starch? Clearly in the possession of osmotic pressure. Starling (7) has emphasized the importance of the osmotic pressures of the protein content of blood and tissue fluids in the passage of water from one to the other. The protein content of the blood plasma is higher than that of the tissue lymph, so that there is a continual attraction of water from the tissues to the blood. This is, however, normally balanced by filtration in the other direction, which occurs where the pressure in the

blood-vessels exceeds the difference between the osmotic pressure of their contents and that of the tissue fluids. If, on the other hand, the blood is diluted, so that the osmotic pressure of its colloids is lowered, an internal pressure of the same height as before will cause greater filtration, and, at the same time, the difference between the osmotic pressure of the blood and that of the tissue fluid being less, there is a decreased osmotic attraction of water by the blood from the tissues. The two causes combine to produce œdema. The colloid added to increase the viscosity of an intravenous injection must therefore possess an osmotic pressure equal to that of the colloids of the blood. Table II, above, includes some determinations of the osmotic pressures of certain solutions of interest in the question. These were all made under the same conditions with Moore and Roaf's osmometer, arranged for changing the outer fluid as required, practically as described by me in a previous paper (8). It will be noticed that the value found for serum against Ringer's solution is the same as that found by Starling, but that against distilled water the reading is considerably higher. The water and the saline solution used were made just faintly alkaline to neutral red in order to approximate to the reaction of the blood, and also to avoid the loss of cations from the colloidal salt which occurs when the outer solution becomes acid from any cause, such as absorption of carbon dioxide from the air (see my paper [10, p. 251]). The fact that the osmotic pressure of gelatin is lowered by salts was noticed by Moore and Roaf, and interpreted as due to the aggregation of the colloid. I accepted this explanation at first, but subsequently found that a sufficient explanation is to be found in the unequal distribution of the salts between the two sides of the membrane, when the colloid is itself a salt of a colloidal acid with a diffusible cation. The explanation is discussed in my 'General Physiology' (pp. 120, 160, 161). Owing to the small molecular weight of the salts in Ringer's solution, a very small difference of concentration in favour of the outer fluid suffices to produce a considerable fall in the apparent osmotic pressure of the colloid. In the case of the sodium salt of gum, for example, there is a difference of 180 mm. of mercury between the osmotic pressures against Ringer's solution and against water. Supposing the sodium chloride in the former case were 90 per cent. dissociated, a difference in concentration between the inner and outer liquids of 0·034 per cent. in sodium chloride, or 3·8 per cent. of the total concentration, would account for the difference in osmotic pressure. Thus, the osmotic pressure of the contents of the osmometer is the sum of those of the colloid and the salts; the osmotic pressure of the outer fluid is that of a solution of the salts of a slightly higher concentration; the pressure shown by the manometer is the difference between the two. It is interesting

to note that the difference referred to is greater in the case of gum than in the case of serum proteins or in that of gelatin. I take it that this is due to the acid of the gum being a stronger one than those of the proteins, so that its salts are more dissociated electrolytically. The difference in the case of congo-red is still greater.

The question is, then, Are we to take as the required colloidal osmotic pressure of our ideal injection fluid, that against water or against Ringer's solution? If the wall of the blood-vessels consists of a membrane permeable to crystalloids, impermeable or nearly so to colloids, it will behave as the parchment paper membrane of our osmometer, and we must take the osmotic pressures as measured against Ringer's solution as those which come into play. We require a solution of a colloid which gives under these conditions an osmotic pressure of about 40 mm. of mercury. This, as Table II shows, is given by a 7-per-cent. solution of gum or a 6-per-cent. solution of gelatin. As it happens, the viscosity of such solutions is only very little higher than that of blood. If stronger solutions are used, water is attracted from the tissues and the blood is diluted. This was actually found to be the case when 8-per-cent. gelatin was injected. The viscosity of a sample of blood taken immediately after the injection was 4·2 times that of water; after an hour the viscosity had decreased to 3·4 times that of water.

As already pointed out, with equal cardiac output, the rate of blood flow through the organs remains the same, although the arterial pressure may be higher, if this rise of arterial pressure is due to increased peripheral resistance from rise of viscosity. It might be thought that increased viscosity is not desirable, since the work of the heart is increased thereby. In practice, however, the output of the heart falls with a low blood pressure, partly owing to insufficient inflow from the veins, partly owing to the heart muscle suffering from deficient supply of oxygen.

It is desirable, therefore, to increase both the viscosity and the colloidal osmotic pressure of solutions used for intravenous injection after loss of blood. This can be done effectively by the addition of 6 per cent. gelatin or 7 per cent. gum acacia to Ringer's solution.

Loss of Vascular Tone.

We pass on to those cases where the arterial pressure is low on account of vascular dilatation, without diminution of the volume of blood in circulation. This condition was obtained in my experiments either by dividing the spinal cord at the foramen magnum, or by decapitation in Sherrington's manner. It was found that, although solutions containing gum or gelatin

were more effective than pure Ringer's solution, the rise in arterial pressure did not remain at any considerably raised level for more than 5 mins. or so. It appears from Boycott's experiments (11) that increase in the total volume of blood, at least in rabbits, is apt to lead to heart failure, presumably from over-distension. The cat's heart does not so readily suffer in this way, and it is to be expected that a rise in venous pressure would be found to occur if the falling blood pressure were due to this cause. I have made several observations by connecting a cannula in the vena cava end of the renal vein with a small indiarubber recording tambour filled with half-saturated sodium sulphate solution. The results obtained were rather contrary to my expectation, in that signs of heart failure were not obvious. For example, in a small cat, the arterial pressure after section of the cord was 40 mm. of mercury, and the venous pressure 47 to 50 mm. of sodium sulphate solution of a density of 1·047. The injection of 50 c.c. of Ringer's solution containing 6 per cent. of gum and 3 per cent. of soluble starch raised the arterial pressure to 110 mm. of mercury, but it fell again in 18 mins. to 80 mm. The immediate effect of the injection was to raise the venous pressure to 100 mm. of Na_2SO_4. But, as the arterial pressure fell, the venous pressure also fell along with it, and when the former was 80 mm. of mercury the latter had returned to its original value. Moreover, the heart beats were no smaller than the initial ones, and even greater than those before the injection of the gum. In experiments in which a membrane manometer was used to record the arterial pressure, it was clear that the fall of blood pressure was not accompanied by any decrease in the vigour of the cardiac contractions. On two occasions on which œdema of the lungs came on in the course of the experiment, a rise in venous pressure up to 160 mm. or more of sodium sulphate solution occurred, as would be expected. In the spinal cat, the rise of arterial pressure produced by injection of gum solutions appears to last for a shorter time than when the cord is merely cut. But here again, although the pressure may have fallen to its original value, the heart beats were larger. There was no considerable rise of venous pressure, but by repetition of injections a permanent rise in it could be produced, and sooner or later heart failure came on. The general impression one obtains from these experiments is that the failure of gum injections to maintain for any considerable length of time the temporary rise of blood pressure is not to be accounted for by heart failure resulting from over-distension of the vascular system.

Some experiments were made to discover whether an increase of the viscosity of the blood, without increasing its volume, would be more effective. This was done by removing a portion of the blood, defibrinating, centrifuging,

and suspending the deposit of corpuscles in a sufficient volume of 7-per-cent. gum solution to make up the volume removed. Since, as Table II shows, the viscosity of the blood is mainly due to the corpuscles, such a solution as that mentioned would have a considerably greater viscosity than that of the blood, because that of the gum solution alone is equal to that of blood. It is somewhat surprising, however, that these solutions of high viscosity have no better effect than those whose viscosity is no higher than that of blood. It is possible that the heart may be overloaded, although the venous pressure did not rise higher than 36 mm. of sodium sulphate solution. Even after 50 c.c. more gum solution and 25 c.c. of saline, the venous pressure was only 60 to 70 mm. of sodium sulphate solution, although in asphyxia it rose to 100 mm. We may call to mind the experiments of Evans and Ogawa (13), in which it was found that the output of the heart-lung preparation was decreased by increase in viscosity of the blood above the normal value. These observers hold that the effect is mainly due to increased resistance to inflow through the tubes supplying the heart. The practical point is that no advantage is to be gained by increasing the viscosity of the blood above its normal value.

This statement applies also where the blood pressure was low on account of hæmorrhage. If the viscosity of the fluid run in to replace the loss was increased by the addition of corpuscles from centrifuged blood, the rise of pressure was no greater than if the solution had only the normal viscosity of blood. It is probable that the accommodation mechanism to be referred to below comes into play under such circumstances.

My experiments fail to supply an answer to the question why the effect of intravenous injections, even of gum solutions, is so much less lasting when the low pressure is due to vaso-dilatation than it is when due to loss of blood.

Since the fall of pressure in the former case is due to arterial dilatation, it is natural to test whether the administration of a substance which causes vaso-constriction, such as adrenaline, is what is needed. But the effect of adrenaline is very transitory, so that it would be necessary to give it continuously or in repeated doses. Barium chloride is advocated by Langley (14), and has a more prolonged action. I am able to confirm its value. In doses of 2 mgrm. per kilogramme of body weight in the cat, it does not affect vaso-motor reflexes, and produces a large and prolonged increase in arterial pressure. It may, with advantage, be combined with a moderate amount of gum solution, and given in 1 mgrm. doses, as the following experiment shows:—

Cat of 1·25 kgrm. weight. Cord cut at foramen magnum and vagi cut.

Arterial pressure 41 mm. of mercury. Heart beats very small. Three cubic centimetres of 0·04-per-cent. barium chloride given intravenously (=1 mgrm. per kilogramme). Pressure raised to 63 mm. Twenty cubic centimetres of gum solution were then given. The pressure was raised to 96 mm. It remained high for 7 or 8 minutes, but slowly fell, until in 27 minutes it was 54 mm. A further dose of barium chloride did not raise the pressure much. The vaso-constrictor mechanism was found finally to respond to asphyxial stimulation.

It appears that in physiological experiments the injection of barium chloride combined with gum solution will be found useful. Whether it would be admissible for clinical use, I am unable to state.

Accommodation of the Vascular System.

Some incidental observations made in the course of the preceding research are of interest.

It has long been known that after hæmorrhage there is a gradual rise of blood pressure, and also that an artificially produced rise of pressure causes a reflex vaso-dilatation. The latter is generally regarded as due to stimulation of receptor endings of the depressor nerves. Heidenhain appears to have thought that the vasomotor centres are directly sensitive to rise and fall of arterial pressure. But very little direct evidence has been obtained towards solution of the problem. Johansson and Tigerstedt (15) state that loss of blood results in vaso-constriction, but I have been unable to find the experimental evidence in their paper.

Clearly the only way in which direct evidence can be obtained is by observations on the state of the arterioles in an organ whose circulation is independent of that of the animal to which it belongs, while it is still in nervous connection therewith. Experiments of this kind have been made by Pilcher and Sollmann (16) on artificially perfused spleens. They found that hæmorrhage caused vaso-constriction, transfusion of blood caused vaso-dilatation.

The question seemed of sufficient importance to warrant further experiments, and on another organ. I chose the hind leg of the cat. The whole of the tissues, excluding the femoral artery and vein and the nerves, were tied off by a series of strong ligatures. As perfusion fluid, 7-per-cent. gum in Ringer's solution was used. This was aërated by blowing air through it and was driven through the limb under constant pressure by means of a small pump. A side outlet on the delivery side served to keep the pressure constant and was adjusted by means of a screw pinchcock. The pressure was also controlled by a manometer attached to the cannula in the femoral artery.

The rate of blood flow through the limb was recorded by an electrical drop recorder.

It has been already mentioned that, after blood has been removed, the arterial pressure rises again fairly rapidly to a certain degree, independently of the injection of any fluid. This rise appears to be too rapid to be accounted for, at all events in its initial stage, by absorption of fluid from the tissues. Indeed, I was unable to obtain evidence of dilution of the blood within 3 mins., although the arterial pressure had risen from 38 mm. of mercury to 66 mm. When the circulation through the perfused limb was observed during this period, there was seen to be a progressive slowing of the rate of flow, this slowing was replaced by an increased rate when injections of gum solutions were made into the jugular vein of the animal itself. The results of Pilcher and Sollmann were thus confirmed. It was noticed also, as would be expected, that the first stage of asphyxia was accompanied by a slowing of the circulation through the limb. The constriction passed off in the later stages, as the nerve centres become paralysed.

We see now why it was found in some cases that injection of gum solution, of equal volume and viscosity to that of the blood removed, caused a temporary rise of arterial pressure above that existing before the loss of blood. The injection was made into a system in which the arterioles were to some extent constricted by impulses from nerve centres.

The cause of the peripheral vaso-dilatation produced by rise of arterial pressure seems clear. The depressor nerves were intact, and a sufficient explanation is afforded by stimulation of their receptor endings in the aorta or heart. The peripheral vaso-constriction produced by fall of pressure is not quite so simply explained. Pilcher and Sollmann are inclined to attribute it to anæmia of the vaso-constrictor centre. The result of this is presumably a greater or less accumulation of carbon dioxide, not sufficiently rapidly removed by the blood current, and it has been shown that carbon dioxide excites nerve centres. I do not altogether understand whether these authors regard this as the cause. They state that they have excluded asphyxial effects by the insufflation of oxygen. But it does not follow that more oxygen is actually supplied to the nerve centres, since the blood may have been practically saturated already, and the rate of blood flow is not necessarily increased. There may, therefore, have been a slight rise in the carbon dioxide content of the centres, even when oxygen is insufflated into the lungs. The comparatively slow rate of onset of the vaso-constriction in my experiments is in favour of this explanation. A brief stimulation of the vagus nerve, so that the heart was stopped, did not result in any detectable change in the rate of flow through the limb.

Summary.

When the arterial pressure is low from loss of blood, it cannot be brought back, except to a certain degree, by the injection of saline solution in volume equal to that of the blood lost. But if the viscosity of such solutions is raised to that of the blood, a return to normal height is possible.

The effect of saline injections is also much less lasting than that of solutions containing gum or gelatin. The difference in this case is due to the osmotic pressure of the colloids, by which loss of water by the kidneys and to the tissues is prevented. Solutions containing gum do not produce œdema in artificial perfusion of organs.

When the fall of blood pressure is due to peripheral vaso-dilatation, gum or gelatin solutions, although more effective than pure saline, produce a much less permanent rise than in cases of loss of blood. No signs of heart failure could be detected and the cause of the fall of the raised pressure to its original height is still obscure. The combination of a small dose of barium chloride, as recommended by Langley, with a moderate amount of gum solution was found to be the most satisfactory method in such cases and no diminution of vaso-motor excitability resulted.

The view that fall of arterial pressure produces peripheral vaso-constriction by means of nervous channels and that rise of arterial pressure produces vaso-dilatation was confirmed by artificial perfusion of a limb.

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