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ISINGLASS AS A TRANSFUSION FLUID IN HÆMORRHAGE

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ON general physiological grounds whole blood is, of course, the ideal transfusion fluid, and plasma or serum has proved a very satisfactory substitute. These fluids, nevertheless, possess certain disadvantages from a practical point of view. Chief among these are incompatibility and storage difficulties of whole blood and the difficulty of having adequate supplies on hand of either blood, plasma or serum, to meet the requirements of a large number of casualties. When one considers that a severe case of hæmorrhage or of shock may require the transfusion of 2 litres of fluid and that each donor furnishes 400 c.c. of blood (or about 200 c.c. of serum) the need for a blood substitute becomes apparent. It has been amply proved that the prime requirement in hæmorrhage is to fill the vessels and so maintain the blood pressure. Compared with the reduction in the volume of the blood the loss of red cells is of very secondary importance as an immediate threat to life. Further, so far as we know at present, it is certain physical properties of the transfusion fluid rather than any biochemical characteristics it may possess which are essential for its success in the treatment of hæmorrhage or shock.

In order to restore and maintain the volume of circulating fluid a transfusion fluid must answer the following requirements. (*a*) The molecule of the dissolved substance must be of such a size that the fluid will not leave the vessels too freely. (*b*) The solution must exert an osmotic pressure and possess a viscosity approaching as closely as possible that of whole blood; these qualifications depend upon molecular size and shape. (*c*) It should be as nearly as possible isotonic with the contents of the erythrocytes. (d) It must, of course, be non-antigenic and innocuous in every respect. In addition, it should be readily available, preferably cheap, and capable of being quickly and easily prepared for intravenous administration. Provided it is suitable in the respects just listed there appears to be no valid objection to the use of some fluid other than blood or serum to fill the vessels after hæmorrhage.

A 7 per cent solution of ordinary gelatin in 0.9 per cent saline solution meets all but the last (*d*) of the foregoing specifications. Recalling the common sources of animal gelatin (bones, tendons, skins, etc.) it is no surprise that many instances should have been cited in the literature[1, 2, 3] in which it has been responsible for infection with the germs of tetanus. There is also a real fear of anthrax infection. It occurred to us that the danger of tetanus or anthrax infection could be avoided by the use of fish gelatin. Fish gelatin or isinglass is prepared from the sounds or swimming bladders of various species (sturgeon, hake, sea trout, etc.) and is used commercially in large quantities, chiefly by the brewing industry in the fining or clarifying process. The sounds as obtained from brewery supply houses appear as compressed thin translucent sheets or large shreds. They dissolve readily in warm water, but globules of an oily material collect on the surface of the solution and are mainly responsible for the latter's very disagreeable fishy smell. The crude commercial material is relatively cheap.

This material, even after removing the fatty impurities and freeing it from anything but a slightly fishy odour, was mildly toxic. When transfused into dogs after bleeding an initial

rise followed by a fall in blood pressure occurred. The method described below has proved successful in freeing the material from toxicity.

Two artificial solutions — saline and gum acacia—have been used in the past to restore the blood volume reduced as a result of hæmorrhage or shock. Saline, though effective in states of dehydration, is almost useless as a transfusion fluid when whole blood or plasma has been lost. Its failure is due to two causes. In the first place it is unable, except in excessive amounts, to raise the blood pressure to the pre-hæmorrhage level because its viscosity is no greater, practically, than that of water. Secondly, it diffuses freely from the vessels; any rise in pressure which does follow the transfusion of saline is therefore very evanescent. During the last war Bayliss[4] advocated gum acacia as a blood substitute. It was used as a 6 per cent solution in physiological saline. The osmotic pressure and viscosity of this solution are closely similar to those of blood and the fluid is retained in the circulation for a considerable time; it enjoyed a high degree of success in the treatment of shock and hæmorrhage. Keith,[5] who had a wide experience of its use in France, considered this fluid to be as valuable as whole blood itself in the treatment of these conditions. Nevertheless, gum acacia has come into disfavour within recent years, for it is believed to cause chronic liver damage. Yuile and Knutti,[6] for example, have reported enlargement of the livers of dogs to from 5 to 6 times the normal weight after weekly injections of a 6 per cent solution of gum acacia. The livers contained from 8 to 10 per cent of acacia. Further, the plasma proteins, especially fibrinogen, were profoundly depressed and remained below normal for several months after the acacia injections had been discontinued. Such effects are not surprising for, unlike gelatin (or rather the mother substance of gelatin, collagen) acacia is foreign to the animal body. It is a carbohydrate (pentosan) which apparently the body is unable to metabolize. The fate of isinglass after its introduction into the blood stream is now being investigated; it is probably broken down and used by the tissues.

Method of Preparation of Isinglass

A very simple method has been used in the preparation of the isinglass solutions for intravenous administration. Briefly it is as follows. The dried fish sounds are dissolved in about 5 times their weight of water, kept at about 60° C. The solution is then acidified with hydrochloric acid to approximately pH 4.0. Cellite (Johns Manville) is added to facilitate filtration, which is carried out with suction through linen. Occasionally it has been found necessary to refilter through a fluted filter paper to remove small amounts of particulate material. Sodium chloride is added to the clear solution which is then poured into cold ethyl alcohol. The precipitate is collected on a Buchner funnel, washed with 95 per cent alcohol, and finally dried *in vacuo* over calcium chloride. This dried material dissolves in warm water readily and completely. It has been used as a 7 per cent solution in isotonic saline. For every 7 g. 10 c.c. of a solution containing 2.5 per cent $NaHCO_3$ and 7.5 per cent NaCl has been used and the total volume made up to 100 c.c. with distilled water. In this way the solution is isotonic with respect to NaCl and has a pH of about 7.2.

In our experiments these solutions have been made up immediately before they were required. Solutions prepared as just described from different isinglass preparations have been tested by our colleague Dr. R. Hare and have been found to be sterile after boiling for five minutes. Further work is in progress to determine the efficacy of this simple sterilization procedure which might be employed in certain emergencies. It has been found by Mr. Knowles, of the Connaught Laboratories, that the above solutions may be filtered with tolerable speed through a sterilizing Seitz pad if the solution be kept warm.

Molecular Weight of Gelatin, Osmotic Pressure and Viscosity Determinations

The molecular weight of mammalian gelatin, as determined by different workers varies from 10,000 to 96,000.[7, 8, 9, 10, 11] This great variability in molecular weight of animal gelatins from different sources which, of course, will be reflected in their physical properties, has been an additional drawback to the use of this material as a transfusion fluid. Smith obtained a value of around 11 mm. Hg. for the osmotic pressure of a 0.5 solution of an ash-free sample of commercial gelatin. We have carried out osmotic pressure observations on a 7 per cent solution of isinglass prepared as described above. The osmometer used consisted of a small sausage-shaped cellophane bag fastened to the lower end of a long vertical glass tube (2 mm. bore). The solution was run into the bag until it rose in the tubing to a height somewhat below that expected to result from the fully developed osmotic pressure. The bag was then suspended in a 0.9 saline solution. The osmotic solution determined in this manner amounted to about 38 mm. Hg. This is, of course, considerably higher than that of blood plasma. The osmotic pressure of plasma separated by a semi-permeable membrane from a solution isotonic with its non-protein constituents is from 25 to

30 mm. Hg. The plasma owes its osmotic pressure mainly to serum albumin, to a less extent to the globulin fraction, and to a very minor degree to fibrinogen. We have not determined the osmotic pressure of serum (*i.e.*, plasma less fibrinogen) but this should be only slightly less than the value generally accepted for plasma. The relatively high osmotic pressure of a 7 per cent solution of isinglass is, however, we believe, an advantage rather than otherwise. One may reasonably assume that such a solution would act in a manner similar to that of concentrated plasma or serum, namely, to hasten the withdrawal of fluid from the extravascular spaces into the blood stream.

We do not know the size or shape of the molecule of our isinglass preparation. Unless it is of such a size and shape as to be retained within the capillary membrane *in vitro* determinations of osmotic pressure can be taken only as an approximate gauge of its effective osmotic pressure within the vascular system.

The *viscosity* of blood is a factor of the first importance in maintaining the arterial blood pressure. The chief constituents responsible for blood's viscosity are the cells and the plasma proteins, the latter contributing to only a minor degree. We have found that whole blood (both human and canine) has a viscosity over three and a half times that of serum or plasma. A number of determinations have been carried out upon the blood, plasma and serum of dogs, upon human whole blood and serum, and upon a 7 per cent solution of isinglass. The viscosity of the last is some three times that of water, about double that of human serum or plasma, though only a little better than half of that of human whole blood. From the point of view of viscosity an isinglass solution is therefore superior to plasma or serum as a transfusion fluid but much inferior, of course, to whole blood. A 7 per cent solution of our preparation of isinglass does not gel at room temperature.

METHODS AND RESULTS

Dogs were used in all our transfusion experiments. The animals were anæsthetized with nembutal and ether in the earlier acute experiments, and with ether alone in the survival experiments and controls. They were bled from the femoral artery of one side specially exposed for the purpose, or, as in the later experiments, from the same cannula in the femoral from which the blood pressure was recorded. When

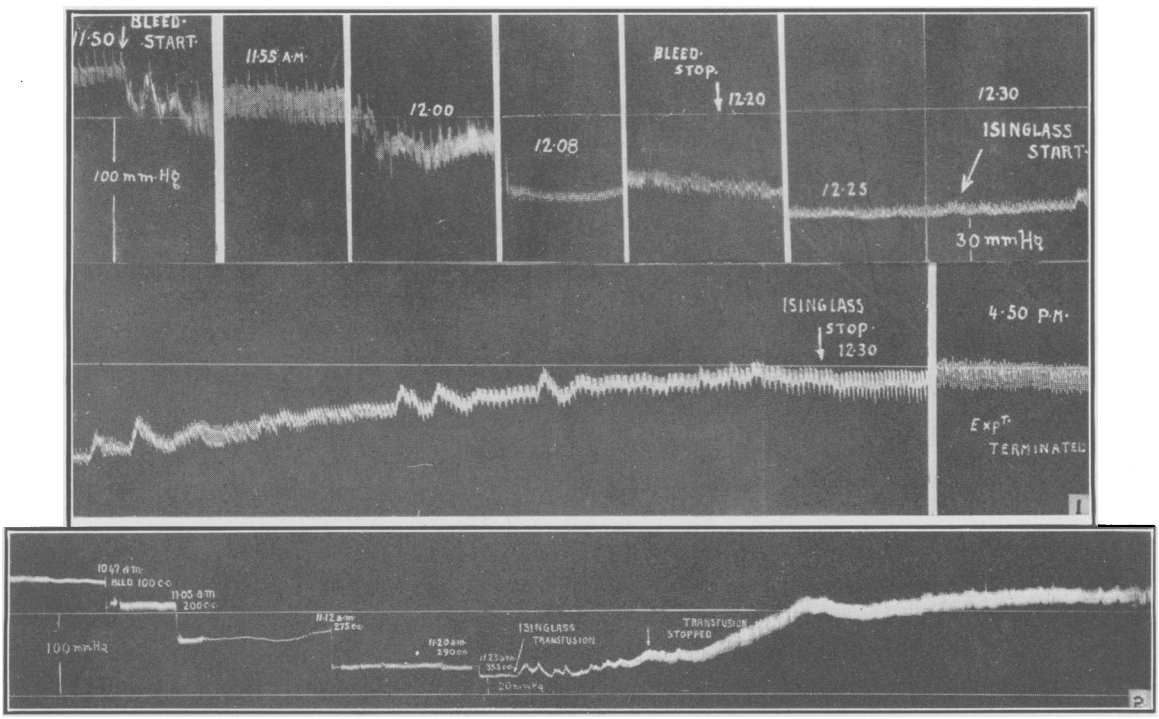

Fig. 1.—Showing the fall in blood pressure due to hæmorrhage, and its restoration and maintenance for several hours by the transfusion of a 7 per cent solution of isinglass. The sharp peaks in the tracings are caused by the too rapid injection of the solution. **Fig. 2.**—Showing the effect of the transfusion of a solution of isinglass on the blood pressure of a dog which had been bled to the extent of 47 per cent of its blood volume within 30 minutes. This animal recovered completely.

the blood pressure had fallen to a dangerously low level the isinglass solution was transfused not too rapidly (over a period of from 15 to 20 minutes) into a femoral vein through a cannula connected by tubing with a pressure bottle. In a few experiments the fluid was injected by means of a syringe into a superficial leg vein. The quantity of fluid transfused was equal in most instances to only from 50 to 70 per cent of the quantity of blood which had been lost.

In most of the experiments hæmatocrit determinations were made, samples of blood being taken before hæmorrhage and again a few minutes after the injection of the solution. A comparison of the cell volume of these two samples afforded a certain check on the proportion of the blood volume which according to calculation had been lost. The hæmatocrit readings could, however, only tell us the minimum proportion of blood which had been withdrawn. It is obvious that only if the blood volume had been restored exactly to the pre-hæmorrhage level, either by the transfusion fluid or by fluid passing into the vessels from the tissues, could a precise estimation of the blood loss be obtained from the hæmatocrit determinations. Since the quantity of isinglass transfused was considerably less in most instances than the quantity of the blood which had been lost, and the quantity of tissue fluid which entered the vessels to dilute the blood during the bleeding period was found in control experiments to be insufficient to make up the difference, we can be sure that the hæmatocrit readings indicate the least quantity of blood which had been removed. The enrichment of the blood in red cells by contraction of the spleen would also tend in the same direction and give a lower rather than a higher estimate of the quantity of blood lost.

Acute experiments.—In the earlier experiments the blood pressure after it had been raised by the isinglass solution was recorded for several hours. It was remarkable how readily the pressure was elevated and how well it was maintained (see Fig. 1). The animals in these earlier experiments did not survive indefinitely. They died either on the table some hours later or within 24 hours in their cages. A number of causes probably contributed to the failure of the animals in these earlier experiments to recover completely. In the first place the first samples of fish gelatin which we prepared undoubtedly possessed toxic properties, to a moderate degree at least. Further, the anæsthetic (nembutal) was unsuitable. This drug, according to Moon,[12] and to Robinson and Parsons[13] is capable itself of inducing a shock-like state. These experiments, which are summarized in Table I, were nevertheless profitable in demonstrating that isinglass is capable of restoring and maintaining the blood pressure for several hours after it has been reduced by hæmorrhage to a very low level.

TABLE I.

ACUTE EXPERIMENTS SHOWING EFFECT OF A SOLUTION OF RATHER CRUDE ISINGLASS IN RESTORING THE BLOOD PRESSURE AFTER HÆMORRHAGE—ANÆSTHESIA; NEMBUTAL AND ETHER

Dog	Date	Body weight kg.	Calculated blood volume c.c.	Quantity of blood lost c.c.	Percentage blood volume	Duration of bleeding minutes	Mean blood pressure mm. Hg.		After transfusion mm. Hg.	Maintenance of blood pressure (to end of experiment)	Remarks
							Before bleeding	End of bleeding			
1	8/1/41	15.00	1,200	545	45.4	5	125	24	90	9½ hours	Killed.
2	9/1/41	23.1	1,848	1,125	60.0	..	160	40	140	2½ "	Killed.
3	15/1/41	16.5	1,320	750	56.8	..	128	22	90	3 "	Death on table due to accidental slipping of ligature from femoral artery.
4	4/2/41	18.0	1,440	720	50.0	..	140	50	135	3½ "	Died during night.
5	7/2/41	18.0	....	....	....	..	140	32	140	3 "	Died during night.
6	10/2/41	15.5	1,240	340	27.4	..	130	50	133	2 "	Died on table after sudden sharp fall in blood pressure.
7	19/2/41	19.0	720	260	36.1	..	130	30	105	4 "	Died during night.

Survival experiments.—Our later experiments were directed toward the survival of the animals after a proportion of the blood volume which would almost certainly have caused death in an untreated animal was withdrawn and partially replaced by a 7 per cent isinglass solution. The isinglass used in these experiments was quite

free from toxicity. The animals were anæsthetized with ether alone. The quantity of blood withdrawn varied in different experiments from 35 to 63 per cent of the calculated blood volume. The bleeding was done rapidly, over a period of from 15 to 36 minutes, and in one instance in 3 minutes. As a basis for our calculations the blood volume was taken as 8 per cent of the body weight. Dogs vary considerably in respect to the proportion of their blood volume which must be lost to cause death, and we have found in a number of control experiments, presently to be described, that the blood-pressure level is a much more reliable criterion of an animal's chances of survival. The results of these survival experiments are given in Table II. A typical blood pressure tracing is shown in Fig. 2.

None of the animals was given any special after-care. They were returned to their cages at the end of the experiment, and beyond being provided with a bowl of milk they received no further attention. As a rule they were able to walk about as soon as they had recovered from the anæsthetic, and appeared remarkably little affected by the considerable loss of blood which they had sustained.

It must be emphasized that the transfusion fluid should not be given at too rapid a rate. If this precaution be not taken the sharp rise in blood-pressure which follows almost immediately upon the injection of the first few cubic centimetres is succeeded by an equally sharp fall. The pressure may drop below the critical level and continue to decline until the death of the animal. In all probability this untoward result is due to cardiac failure from acute distension of the right ventricle. Possibly anoxia of the cardiac muscle, due to the filling of the coronary system with blood highly diluted with the isinglass solution, is a contributory factor.

CONTROLS

A number of control experiments were done to determine the proportion of the blood volume which must be lost to cause death within a short time if the animal is not transfused (Table III).

TABLE II.

SURVIVAL EXPERIMENTS IN WHICH BLEEDING WAS FOLLOWED BY THE TRANSFUSION OF 7 PER CENT SOLUTION OF ISINGLASS

Dog	Date	Body weight kg.	Calculated blood volume c.c.	Quantity of blood lost c.c.	Percentage blood volume	Duration of bleeding (min.)	Gelatin transfused. c.c.	Mean blood pressure mm. Hg.			Hæmatocrit cell volume percentage			Subsequent history
								Before bleeding	End of bleeding	After transfusion	Before bleeding	End of bleeding	After transfusion	
8	10/2/41	9.1	728	365	50	3	350	90	40 after injecting adrenaline	86	43	..	19—23 after 19 hrs.	Lived for 21 hrs.
9	24/2/41	10.0	800	280	35	15	160	114	28	..	44	..	..	Complete recovery
10	25/2/41	8.6	688	382	56	36	200	100	33	76	44	..	..	Complete recovery
11	26/2/41	7.9	632	293	46	35	230	96	32	70	46	..	..	Complete recovery
12	27/2/41	9.6	768	415	54	30	230	99	22	78	50	..	..	Complete recovery
13	3/3/41	17.5	1,400	625	45	30	305	128	28	80	..	..	..	Complete recovery
14	4/3/41	9.7	776	415	54	32	160	..	20	..	52	..	..	Lived for 3½ hrs.
15	5/3/41	16.0	1,280	580	45	35	307	170	20	120	56	..	30	Lived for 7 hrs.
16	10/3/41	13.7	1,096	610	56	30	500	130	24	100	47	42	25	Complete recovery
17	18/3/41	9.5	760	355	47	32	330	142	20	134	48	41	23	Complete recovery
18	18/3/41	10.5	840	485	58	17	350	76	19	80	50	..	22	Complete recovery
19	19/3/41	10.4	832	480	57	20	450	90	14	88	50	..	23	Complete recovery
20	24/3/41	13.2	1,056	660	63	29	400	106	18	84	54	48	23	Lived for 10 hrs.
21	27/3/41	14.0	1,120	620	55	17	500	92	14	84	52	..	27	Complete recovery
22	28/3/41	19.2	1,536	770	50	15	475	118	18	114	47	..	29	Complete recovery

Dog — *General remarks*

8. This animal had been sensitized 2 weeks before to horse serum and had been given a second injection of serum just before being bled. Mild anaphylactic shock developed. After bleeding an injection of adrenaline and artificial respiration required to revive; was then transfused.
9. Hæmatocrit 28 per cent cell volume 3/3/41; 32 per cent 5/3/41.
11. 160 c.c. gelatin given immediately after bleeding; 70 c.c. 4 hours later.
12. This animal had been sensitized 2 weeks previously with horse serum and had been given a second injection. Mild anaphylactic shock. Bled after blood pressure had nearly regained pre-shock level. 150 c.c. isinglass solution given immediately; 80 c.c. 3½ hours later. In excellent condition.
13. Hæmatocrit 29 per cent 11/3/41; 41 per cent 25/3/41.
14. Insufficient quantity of transfusion fluid given.
15. Seemed to recover fully. Walking around half hour after removal from table.

As already mentioned, the animals varied widely in this respect. The rate of bleeding is a very important factor and in order to weight the scales in favour of the animals not treated with isinglass the period of bleeding in most of the control experiments was made considerably longer (35 to 60 minutes). We have been unable to predict even approximately what proportion of the calculated blood volume it is necessary to withdraw to cause death. In one animal it was necessary to cause the loss of 59 per cent of its blood volume to cause death, whereas in one other a 29 per cent loss was fatal. As already mentioned, it is much easier to predict the extent of the blood pressure fall which will prove fatal. A pressure around 30 mm. Hg. is critical. No untreated animal has survived for more than a short period after its blood pressure immediately after hæmorrhage had fallen below 34 mm. Hg.

TABLE III.

CONTROL EXPERIMENTS

Dog	Date	Body weight kg.	Calculated blood volume c.c.	Quantity of blood lost c.c.	Percentage blood volume	Duration of bleeding (min.)	Mean blood pressure mm. Hg.		Hæmatocrit		Time of death from end of bleeding period
							Before bleeding	End of bleeding	Before bleeding	End of bleeding	
23	6/3/41	22.25	1,760	510	29	25	180	24	..	..	6 minutes.
24	10/3/41	22.50	1,800	800	44	35	150	22	..	..	20 minutes.
25	12/3/41	10.20	816	440	54	42	140	30	66	53	13 minutes.
26	13/3/41	14.25	1,140	625	55	55	140	24	60	48	15 minutes.
27	14/3/41	8.25	660	370	57	60	130	23	38	33	90 minutes.
28	17/3/41	11.70	936	430	46	33	130	46	59	47	17½ hours.
29	17/3/41	9.7	776	330	43	18	82	28	51	..	Less than 1 min.
30	18/3/41	9.2	736	310	43	38	160	34	53	46	Complete recovery
31	20/3/41	17.0	1,360	520	38	32	132	32	47	42	5 minutes.
32	20/3/41	16.2	1,296	727	56	60	120	42	52	44	Complete recovery
33	21/3/41	11.2	896	455	51	43	144	34	62	50	Complete recovery
34	21/3/41	14.7	1,176	695	59	35	130	40	48	53	12 minutes.
35	28/3/41	15.5	1,240	650	52	30	175	41	..	..	30 minutes.

The reason that a greater blood loss is required to depress the blood pressure below the critical level when the bleeding is slow than when it is rapid is indicated by the hæmatocrit findings. With the slower hæmorrhage, time is allowed for a partial restoration of the blood volume by fluid entering the vessels from the extravascular spaces. The later bleedings of a long bleeding period withdraw diluted blood and in consequence a smaller proportion of red cells. It is interesting to examine the blood pressure record from the point where the critical level is reached to the death of the animal. The tracing remains flat for several minutes but then commences to decline rather rapidly, which suggests that the heart or some vital nervous structure, *e.g.*, the vasomotor centre, has as a result probably of powerful vasoconstriction, been deprived of an adequate blood supply and thereby suffered irreparable damage. It may be recalled that a large proportion of the blood volume normally is contained in the heart and larger vessels—about 75 per cent according to the experiments of Mann.[14] It is therefore evident that in order to maintain a pressure even of 30 mm. Hg. a large proportion of the reduced blood volume must still be held in the heart and larger vessels, for the capacity of this part of the vascular tree cannot undergo any great reduction. This means that the minute vessels upon which the blood supply of the tissues depends must be very powerfully constricted. Therefore, if the hæmorrhage amounts to 50 per cent or so of the blood volume vital tissues may be almost completely deprived of oxygen. With a blood pressure of around 25 mm. Hg. in the femoral artery that in the capillaries must be near the vanishing point and certainly far below the osmotic pressure of the plasma; it follows, therefore, that the passage of fluid from the blood to the tissues is in abeyance.

ATTEMPTS TO SENSITIZE ANIMALS TO ISINGLASS

There is general agreement that gelatin is non-antigenic. However, we have considered it worth while to carry out some experiments to be sure that our preparations of isinglass are non-antigenic. It is possible that while gelatin injected in the usual form is free from antigenicity, the use of a gelatin precipitate obtained by means of alum might make possible the successful sensitization of guinea pigs (Caul-

feild *et al.*[15]). We have used this more rigid test of antigenicity. A 10 per cent solution of isinglass was partially precipitated with iron alum and injected subcutaneously into guinea pigs, using either 5 or 2 c.c. The "shock" dose of isinglass was injected either intravenously or intracardially 5½ weeks later. In some preliminary experiments on 12 guinea pigs no evidence of sensitization by this procedure has been observed. Also dogs which had been bled and the blood volume restored with relatively large injections of isinglass have later been anæsthetized with ether and reinjected with an isinglass solution. Of the animals thus treated two showed mild but typical anaphylactic reactions. These animals were tested 12 days after the first injection of isinglass. Those tested after a longer interval (3 to 4 weeks) have shown no evidence of sensitization. It appears therefore that our isinglass preparations, at present, are capable of conferring upon dogs injected with relatively massive doses a mild degree of sensitization which is detectable so far within the first two weeks only of the first injection. This sensitization is to be attributed probably to fish protein contaminating our isinglass preparations, rather than to the isinglass itself. The very mild procedures adopted in the preparation of the isinglass from the dried fish sounds were calculated to preserve the molecular complexity of the isinglass. It is probable that more vigorous treatment is necessary to rid the product of all contaminating protein. Methods are now being tried whereby both objects will as far as possible be achieved—the isolation of an isinglass which has suffered little molecular degradation and which is freed of all contaminating fish protein.

DISCUSSION

A comparison of the data in Tables II and III will show that though the rate of bleeding in the transfused animals was on the whole considerably more rapid than in the controls, the former survived after the loss of a somewhat greater proportion of their calculated blood volume. The greatest blood loss that an animal was able to overcome unaided was 56 per cent of its calculated blood volume; the smallest hæmorrhage which proved fatal in this group was 29 per cent of the blood volume. Three other control animals succumbed to a loss amounting to less than 45 per cent of their total blood and only one survived after a loss of over 55 per cent. In this experiment (dog no. 32) the bleeding period was much longer (60 minutes) than in any of the survival experiments. It will also be observed that the blood pressure (42 mm. Hg.) of this animal was not depressed to the critical level. In the series of transfused animals, on the other hand, none succumbed after a blood loss amounting to less than 45 per cent of the blood volume, and four survived after a loss of over 55 per cent. Of these, two recovered completely after a loss of 58 and 57 per cent, respectively. Even those animals of the transfused group which succumbed made an excellent immediate recovery and did not die until several hours later. One of the four fatalities (dog no. 14) in this group undoubtedly received an insufficient volume of the transfusion fluid and the others could probably have been saved by careful nursing. In the control series, on the contrary, death occurred in most instances within a few minutes after the termination of the bleeding.

It has been mentioned that we have found in dogs a rather wide variation in the magnitude of the blood loss which is fatal. Other observers have remarked upon this fact. On this account the foregoing figures alone would not, perhaps, permit one to conclude positively as to the efficacy of isinglass as a substitute for lost blood. The blood pressure records provide a surer indication of its value. No animal of the control series whose blood pressure had fallen below 34 mm. Hg. survived, whereas several of those which had been transfused with isinglass solution and recovered, recorded a blood pressure of less than 24 mm. Hg. at the end of the period of bleeding and in five animals the pressure had fallen below 20 mm. Hg. In none of the fatalities of this series was the blood pressure before transfusion higher than 20 mm. Hg.

Dog No. 8 deserves special mention. This animal suffered mild anaphylactic shock after the injection of horse serum to which it had been sensitized some two weeks previously. When the shock had passed off, as indicated by the return of the blood pressure to near the pre-shock level, it was bled to 50 per cent of its blood volume. The blood pressure fell again, reaching a very low level, and breathing ceased. The animal was revived by artificial respiration and the injection of adrenaline, and was then immediately transfused with 350 c.c. of isinglass solution. It recovered and regained its strength

to a surprising degree. It survived for 21 hours. Had this animal not been transfused it is extremely unlikely that it would have even survived the anæsthetic.

In nearly all the experiments tabulated in Table II the isinglass solution was given in a single injection, but certain of our observations suggest that it would be of even greater benefit, and that some of those animals which died would have survived, had the total amount been given in two or three instalments at intervals of four or five hours. All that one need aim at in the transfusion operation is to tide the subject over the critical period and until his own restorative mechanisms have become effective. It is quite conceivable that if means exist for metabolizing isinglass, and if these means are competent to cause the disappearance of large quantities from the circulation, then smaller transfusions at intervals should extend the beneficial effect of the transfusion over a longer period.

SUMMARY

1. The properties of a 7 per cent solution of fish gelatin or isinglass in 0.9 per cent saline are described. This solution has been found to fulfil the rather rigid specifications of a transfusion fluid which have been listed in this paper.

2. As prepared from the sounds of fish by the method described, isinglass is soluble in water or saline, is without toxicity, and can be readily sterilized by raising its temperature to 100° C. for 5 minutes. It forms a perfectly clear pale yellow solution.

3. Experiments are reported in which a 7 per cent solution of isinglass in saline is capable of restoring the blood pressure after it had been lowered by hæmorrhage and of saving the lives of animals which, had no treatment been instituted, undoubtedly would have died. These animals made a complete and uneventful recovery.

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RÉSUMÉ

Dans l'hémorrhagie ou le shock l'essentiel est de redonner à la masse sanguine un volume suffisant. Pour atteindre ce but le liquide transfusé doit être une substance dissoute dont les molécules se maintiendront à l'intérieur des vaisseaux et dont la tension osmotique et la viscosité se rapprochent de celles du sang; ce liquide doit être isotonique avec le contenu des globules rouges; il ne doit pas être antigénique; il doit être inoffensif. La solution de gélatine doit être rejetée parce qu'elle peut véhiculer le tétanos ou le charbon. La gélatine de poisson ne fait pas courir ces risques. On la prépare avec les ouies et les vésicules natatoires de diverses espèces dont l'esturgeon et la truite de mer. Elle peut être stérilisée par l'ébullition pendant 5 minutes. Le sérum physiologique est trop vite absorbé pour rendre de véritables services. La solution de gomme acacia provoque des dégât hépatiques. La solution de gélatine de poisson à 7 pour cent dans du sérum physiologique salé à 0.9 pour cent a une tension osmotique un peu supérieure à celle du plasma sanguin; on ne connaît pas les dimensions et la forme de sa molécule; sa viscosité est supérieure à celle du plasma mais inférieure à celle du sang total. L'expérience chez le chien démontre que la transfusion de gélatine de poisson relève la tension artérielle abaissée par l'hémorrhagie et évite l'issue fatale certaine qu'eut entrainée l'abstention thérapeutique. La guérison des chiens ainsi traités s'est effectuée dans les délais normaux. JEAN SAUCIER