It has been pointed out that in army practice the precise diagnosis of peptic ulcer by clinical means alone is difficult. Radiological evidence supporting the diagnosis of ulcer is essential. For this reason the only acceptable radiological evidence of ulcer is the demonstration of an ulcer crater.

The treatment of ulcer was along the usual lines. A small controlled group of cases—on aluminium hydroxide—did not do as well as those on routine treatment. The rigid control of smoking on the gastric ward was felt to be of definite value.

It would appear evident from this series that all cases of active duodenal ulcer should be invalided from the services in England. The majority of the cases in this series were so dealt with. Of 40 cases treated to healing, and returned to duty in England, 24 have returned to hospital within three months of their discharge. It is obvious that these men are ineffective, and cannot carry on satisfactorily in the Service in England. It is by no means certain that they will be effective in the Service at home.

The large group of functional dyspeptics presents an interesting problem. Two-thirds of all the cases studied fell into this group. It is of interest that a very marked increase in their numbers occurred during the winter months (Chart 1). This was in contrast to the cases of peptic ulcer which showed little seasonal variation. Few of the functional dyspeptics appear to have developed organic disease. The majority are still on duty with their units. It would seem that unless these complaints render the soldier continuously ineffective he should be kept on duty.

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A COMPARISON OF ISINGLASS AND GELATIN AS BLOOD SUBSTITUTES

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RECENTLY it was reported (Taylor and Waters[1]) that a solution of isinglass prepared from the swimming bladders of fish possessed a number of the essential properties of a blood substitute. Further it was shown that this solution when injected into dogs which had just undergone a severe hæmorrhage promptly restored the blood pressure of these animals and enabled them to make an uneventful recovery from the otherwise fatal loss of blood. The isinglass, however, was mildly antigenic. This was demonstrated by injecting a second dose of the isinglass about 10 days after the dogs had been bled and treated with relatively large amounts of the isinglass. With a number of animals a moderate fall in blood pressure occurred, indicating a mild degree of sensitization.

Since then I have been able to show that heating the original acid solution of the dried swimming bladder to 90° C. for a few minutes considerably reduces the already low antigenicity of the isinglass. Two dogs were bled in the manner already described and were then given a transfusion of the original isinglass, prepared by extraction of the swimming bladder at 60° C. When these dogs were reinjected ten days later with 50 c.c. of a 7 per cent solution of isinglass prepared by extraction of the swimming bladder at 90° C. for 5 minutes, no decrease in blood pressure occurred, but when 10 minutes later an equal quantity of the original material prepared by extraction at 60° C. was injected there was a prompt fall in blood pressure of about 20 mm. Hg. Dogs which received a large initial injection of the heated preparation failed to give any response when subsequently injected with 50 to 100 c.c. of the same material, except in one experiment when there was a decrease of 35 mm. Hg. with a return to normal within 6 minutes. Probably the antigenicity could be completely removed by continuing the heat treatment at 90° C. for a few minutes longer.

Objection to isinglass as a blood substitute on the grounds that it is antigenic does not therefore apply. Because of the anticipated ease of preparation of isinglass from the swimming bladders of fish, it was originally hoped to obtain a uniform product of sufficiently high mole-

cular size to warrant its use as a blood substitute. The experiments reported below do not support these earlier hopes.

Attention has therefore been paid to the possibility of using a high grade animal gelatin for such purposes. Eastman's purified gelatin, made from green stock calf skin, was selected and some of the results of experiments with this material are shown below and are to be compared with those obtained with isinglass.

In order that a substance shall function as a blood substitute in the maintenance of blood pressure it must remain within the blood vessels until such time as it takes for the return of sufficient normal protein to maintain the necessary level of blood pressure. Therefore one good criterion of an efficient blood substitute is the length of time it remains in the circulation of the injected animal. Making use of the fact that isinglass or gelatin is not precipitated by trichloracetic acid, but is precipitated together with the plasma proteins by tungstic acid, I have been able to distinguish between the normal plasma proteins of a sample of blood and any isinglass or gelatin it may contain. In this way it has been possible to follow the rate of disappearance of the isinglass and of gelatin from the blood of an injected animal. At the same time one can follow the rate at which the plasma proteins return to their original concentration, and this general method of procedure may lend itself to studies in plasma regeneration.

METHODS AND RESULTS

Method of estimating gelatin in plasma: 0.05 c.c. of oxalated plasma was pipetted into a pyrex test tube. The plasma was washed down the side of the tube with 1 c.c. of distilled water, then treated with either 1 c.c. of 10 per cent trichloracetic acid solution or with tungstic acid solution prepared by adding 0.25 c.c. 10 per cent sodium tungstate and 0.25 c.c. 2/3 N.H_2SO_4. The trichloracetic acid precipitate consisted of plasma proteins, while the tungstic acid precipitate contained those proteins as well as the isinglass or gelatin present in the plasma. The precipitated solutions were allowed to stand in the refrigerator for two hours, oftentimes longer. They were then centrifuged and the supernatant fluid decanted. The trichloracetic precipitates were washed with 0.5 c.c. 5 per cent trichloracetic acid solution and again centrifuged and the supernatant fluid well drained from the precipitate. It is not worth while to attempt to wash the tungstic acid precipitates, for the amount of nitrogenous substances in the solution adhering to them is negligible. The precipitates are then digested in the same pyrex tubes in the usual way with 1 c.c. concentrated sulphuric acid in the presence of a little copper salt, and the amount of ammonia produced finally estimated by distillation in the micro Kjeldahl apparatus. All estimations were carried out in duplicate. The results checked well when the method was tested with mixtures of plasma and gelatin solutions.

The determination of the rate of disappearance of injected isinglass or of gelatin was carried out in dogs treated in the following manner. A fasted dog was anæsthetized with ether and one of its femoral arteries cannulated. This cannula was used, not only for the recording of blood pressure but also for bleeding the animal. The dog was bled fairly rapidly, usually 100 c.c. of blood being removed during each 5 minutes of the time of bleeding. In this way approximately half the blood volume would be removed and the blood pressure would be reduced to a dangerously low level. One dog behaved exceptionally. It weighed 12.8 kilos and when bled of 550 c.c. over a period of 33 minutes showed no decrease in its blood pressure; for a short time there was even a slight increase. Within 3 or 4 minutes of the end of bleeding the animals were given a transfusion of a 7 per cent solution of isinglass or of gelatin in isotonic saline equal in volume to the blood withdrawn. The blood pressure was promptly restored to a more or less normal value. The incision in the groin was sutured and the anæsthetic discontinued. Blood samples were then taken at various times to ascertain, by the above described procedure, the amount of foreign protein remaining in the circulation. The first sample after the transfusion was not taken until 15 to 30 minutes later in order to be sure that uniform mixing of blood and transfusion fluid had taken place.

Some representative results, showing the rate of disappearance of isinglass and of gelatin are given in Tables I and II. It will be seen that the isinglass disappears very quickly. The gelatin leaves the blood stream much more slowly; appreciable amounts remain 24 hours after the transfusion.

From one dog anæsthetized with ibatal and weighing 10 kilos, 360 c.c. of blood were removed in 15 minutes. Four minutes later a transfusion of an equal volume of 7 per cent isinglass was begun. The blood pressure was 134 mm. Hg. before bleeding, 158 mm. Hg. a few minutes after isinglass, 116 mm. Hg., the minimum value recorded, 2 hours after and 120 mm. Hg. 4½ hours after transfusion. Plasma protein nitrogen was 8.4 mg./c.c. before bleeding, 4.1 mg./c.c. with isinglass, 2.7 mg./c.c. 22 minutes after the end of transfusion and 6.0 and 0.7 mg./c.c. for plasma protein and isinglass respectively 4½ hours after transfusion. Immediately after this later sample 48 c.c. of urine were removed by catheter. When left in the refrigerator the urine formed a fairly firm gel. It contained no albumin but gave a tungstic acid precipitate which indicated isinglass to be present in a concentration of 11.5 per cent. Evidently there is a rapid excretion of isinglass by the kidney.

Rabbits, as well as dogs, have been injected intravenously with solutions of isinglass and gelatin. In none of these experiments has there been evidence of acute toxicity of either kind of solution, except that most of the animals, dogs and rabbits, receiving the isinglass solution developed febrile reactions which sometimes lasted for a few hours. This was rarely the case when gelatin solution was used. It should be pointed out, however, that the isinglass preparations were deliberately made in the simplest possible manner and no effort has been made to develop a more homogeneous product until it could be shown to be worth while for the purpose in mind, namely for transfusions. One dog, weighing 10.5 kilos, was injected with 1,200 c.c. of a 7 per cent solution of isinglass over a period of 19 days. This animal was sacrificed the day after the last injection. The liver showed mild fatty infiltration. No other abnormalities were detected.

TABLE I.

RATE OF DISAPPEARANCE FROM THE BLOOD OF ISINGLASS TRANSFUSED INTO DOGS AFTER HÆMORRHAGE

	Blood samples		*Proteins of plasma*		
No.	*Time after isinglass injected*	*Cell volume percentage*	*Plasma protein nitrogen mg./c.c.*	*Isinglass nitrogen mg./c.c.*	*Further details*
Dog S. 1.	Before bleeding	50	9.0	0	Dog S. Weight 7.5 k. Calc. blood volume (8 per cent) 600 c.c. Blood removed 285 c.c. in 15 minutes. Volume of 7 per cent isinglass used 290 c.c. Dog made good recovery.
2.	37 minutes....	31	4.3	3.0	
3.	6 hours.....	35	6.5	<0.3	
4.	9½ hours.....	..	7.0	Nil	
Dog G. 1.	Before bleeding	38	9.0	0	Dog G. Weight 10.5 k. Calc. blood volume (8 per cent) 840 c.c. Blood removed 465 c.c. in 20 minutes. Volume of 7 per cent isinglass used 400 c.c. Dog made good recovery.
2.	16 minutes....	20	4.5	2.7	
3.	4 hours.....	25	6.8	0.4	
4.	18 hours.....	21	7.3	Nil	

TABLE II.

RATE OF DISAPPEARANCE FROM THE BLOOD OF GELATIN TRANSFUSED INTO DOGS AFTER HÆMORRHAGE

	Blood samples		*Proteins of plasma*		
No.	*Time after gelatin injected*	*Cell volume percentage*	*Plasma protein mg./c.c.*	*Gelatin nitrogen mg./c.c.*	*Further details*
Dog P. 1.	Before bleeding	49	8.9	0	Dog P. Weight 9.2 k. Calc. blood volume 736 c.c. Blood removed 445 c.c. in 14 minutes. Volume of 7 per cent gelatin used 440 c.c. Blood cell volume 20 days later = 36 per cent. Dog made good recovery.
2.	15 minutes....	19	3.0	4.1	
3.	6 hours.....	18	3.7	3.2	
4.	19 hours.....	19	4.8	2.4	
5.	3 days.....	20	6.6	1.2	
Dog B. 1.	Before bleeding	50	8.9	0	Dog B. Weight 6.6 k. Calc. blood volume 528 c.c. Blood removed 260 c.c. in 13 minutes. Volume of 7 per cent gelatin used 260 c.c. Dog made good recovery.
2.	32 minutes....	24	4.1	4.1	
3.	4½ hours.....	..	4.2	3.1	
4.	18 hours.....	23	5.4	2.5	
5.	2 days.....	..	6.6	1.5	
6.	3 days.....	22	7.4	0.8	

Mention has already been made of the very mild antigenic nature of the isinglass preparations. So far no instance of sensitization to the gelatin has been encountered.

Even after massive injections of either isinglass or gelatin have been made into dogs after severe hæmorrhage, there was no significant change in the clotting time of the blood compared to the rate prior to the bleeding. There is, however, a much increased sedimentation rate.

Experimental work is now in progress to determine if repeated injections of gelatin solutions over a period of weeks result in any harmful effects, especially to the liver and kidneys.

In all these experiments the gelatin solutions have been freshly prepared and kept at 100° C. for 10 minutes before being used. Solutions prepared in this way from three different lots of this brand of gelatin were found to be sterile by my colleague, Dr. R. Hare. Sterilization of a 7 per cent solution by Seitz filtration is not feasible, due evidently to the high viscosity of the solution. Mr. Knowles, of the Connaught Laboratories, tried Seitz filtrations at various temperatures up to 80° C. It is feasible to sterilize a 3½ per cent solution of gelatin by Seitz filtration. It may be pointed out that such a 3½ per cent solution of gelatin is still slightly more viscous than a 7 per cent solution of isinglass.

A 7 per cent solution of gelatin is, of course, quite fluid at 37° C. but when allowed to cool to room temperature its viscosity increases and gradually it forms a firm gel. Blood plasma containing gelatin quickly sets to a gel in the refrigerator and a simple test might well be developed on this basis to determine the presence of significant amounts of gelatin in the blood of a transfused individual. As pointed out earlier, a 7 per cent solution of isinglass remains fluid at room temperature. The lesser tendency to gel, the lower viscosity of the solutions and their more rapid elimination from the blood vessels of an injected animal in comparison with solutions of calf skin gelatin suggest that the isinglass has an average molecular weight appreciably below the average for the gelatin. It is possible that isinglass prepared from the swimming bladder of other species of fish may yield a product of higher molecular size than that used in these experiments.

CONCLUSION

It might be asserted that all that is necessary with a transfusion of a blood substitute is to supply an innocuous foreign substance to restore and maintain the blood pressure for just such a time as it takes for the adequate development of the body's own compensating mechanisms. In the experiments of Taylor and Waters it now appears that these compensating mechanisms come into play very quickly and the injection of an isinglass solution was quite sufficient to tide the bled animal over the relatively short danger period. But it may well be questioned whether such experimental conditions are sufficiently drastic to serve as a guide in the search for a blood substitute which one hopes to advocate for clinical trial in cases of hæmorrhage and of wound shock. It would seem that the use of solutions of a suitable animal gelatin rather than of isinglass offers greater assurance of effective maintenance of blood pressure because of the much longer time it remains in the blood stream of the transfused animal. It is suggested that solutions of calf skin gelatin may, in an emergency, prove useful as a blood substitute. Further experimental work is in progress to determine if calf skin gelatin is as innocuous as experiments to date suggest it to be.

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THE FACTORY WORKER IS IN THE FRONT LINE.—The worker who shirks today or obstructs is a Fifth Columnist; the worker who strikes is the same as the deserter from the front line. The worker who gives all that he has, and more, is the true Canadian patriot. —Beverley Baxter.

The cure of Scrophula by the Royal Touch is the most singular piece of quackery in the history of superstition. Lord Bacon says that imagination is next akin to miracle-working faith. There was seemingly some of both, and a little money to boot, to keep this remedy in fashion; and as each patient touched a bit of gold, we may suppose in this, as in other complaints, that some were cured of the king's evil who never had any other *evil* than that of poverty, which brought more patients and more fame to these royal practitioners than they deserved.—William Wadd.