cain and potassium chlorid are relatively inefficient. Alkalinization increases the efficiency from two to four times. The solutions of the anesthetic salts may therefore be mixed with an equal volume of 0.5 per cent. sodium bicarbonate, without loss of efficiency, and with a saving of one half of the anesthetic. The mixtures, however, do not keep well, and should be recently made.

The addition of epinephrin does not increase the efficiency, and is probably useless.

2. For infiltration and injection anesthesia, the relative efficiency is shown in Figure 1A. Cocain, novocain, tropacocain and alypin are about equally efficient. Beta-eucain and quinin-urea hydrochlorids are intermediate; apothecin and potassium sulphate (or chlorid) are relatively inefficient.

The efficiency is not increased by alkalinization. Epinephrin greatly prolongs the action, and should always be added (except to tropacocain).

The anesthetic action of potassium sulphate or chlorid is not great enough to be of real value.

A 1 per cent. (that is, isotonic solution) would be equivalent to about 0.125 per cent. of cocain or novocain. However, it may well be used in place of sodium chlorid for making anesthetic solutions, as suggested by Braun.

Several of the synthetic anesthetics can completely take the place of cocain. In view of this fact, it would be feasible to prohibit entirely the importation, manufacture, sale and use of the habit-forming cocain, except for scientific purposes.

FLUID SUBSTITUTES FOR TRANSFUSION AFTER HEMORRHAGE

FIRST COMMUNICATION *

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AND

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There exists at present a great and urgent need for an injection fluid that can be satisfactorily employed instead of blood for transfusion in cases of hemorrhage. It is common knowledge that casualty clearing stations, after a "push," are crowded with men who have lost too much blood to be operated on, who cannot be revived by means of salt solution and supportive measures, but who would undoubtedly respond to transfusion. For the latter neither time nor donors are available.

A number of fluid substitutes for transfusion have recently been suggested. Our work relates, first, to what may be expected of a substitute, and, second, to the relative merits of some of the substitutes proposed.

THE LIMITS OF SUBSTITUTION FOR HEMOGLOBIN

That severe acute hemorrhage, even to apparent exsanguination, does not entail permanent damage to the organism is shown by the rapid and complete recovery that usually follows transfusion. May one expect some such recovery when another fluid than blood is used? Or is this essentially dependent on the new supply of corpuscles and plasma?

The importance of the plasma has been investigated by Abel, Rowntree and Turner,¹ who demonstrated

that the healthy body will withstand and quickly repair great losses of the fluid. The ability to withstand similar losses of red cells only—or, more properly speaking, of functioning hemoglobin—has not been inquired into. This point was the first taken up in our work. Animals have been bled repeatedly, and the blood bulk at once restored by the injection of compatible plasma.

Rabbits were used because their rapid exsanguination and injection involves only minor operative procedures. All possible blood was taken by cardiac aspiration with strong suction, and then through an ear vein warmed plasma was run in containing the minimum of sodium citrate that would prevent clotting (about 0.5 per cent.). At the first bleeding, somewhat more than half of the total calculated blood bulk (5.5 per cent. in the rabbit²) was usually obtained in from one to three minutes. It was replaced with exactly the same amount of plasma. After a wait of a few minutes, to give time for part of the citrate to leave the circulation, a second bleeding and injection was carried out. Thus from three quarters to four fifths of the total hemoglobin was abruptly replaced.

The results were surprising. When the hemoglobin was reduced by not more than three fourths—as, for example, from 80 to 20 per cent.—and the rabbit replaced in its cage, no marked change was noted in its behavior. The respirations were for a few minutes somewhat quickened, and the ears for many hours were cold, with vessels contracted; yet the animal moved about normally, and immediately after the operation would eat when supplied with food. The blood gradually returned to normal in the course of the next few weeks, and the only inconvenience noted was that during the days of severest anemia, the least exertion would cause the animal to pant heavily.

A very different condition was seen after four fifths or slightly more of the hemoglobin had been removed. On its release from the operating board, the animal lay panting, with the accessory muscles of respiration actively employed, and made at first no attempt to rise. Soon, however, the respirations became less frequent, though still rapid, and when touched the animal would get on its feet. At first, following the outside stimulus, it sat like a normal rabbit with head up, ears back, and legs drawn well together; but soon the head nodded, the ears drooped, the legs sprawled out irregularly, and if undisturbed the animal sat somnolent for a long time. When touched it would straighten up and assume an alert posture, only in the course of a few minutes to relax again. These animals died in from three to six hours.

We have spoken of proportional amounts of hemoglobin rather than of absolute quantities, because of indications that, within limits, it is the proportional loss that most affects the results. A rabbit with an initial hemoglobin of 80 per cent., Sahli, will withstand a reduction to 20 per cent., whereas this is fatal to an animal having 100 per cent. to begin with. The symptoms described can scarcely be due to the citrate in the plasma, since this was varied freely in cases yielding similar results, and because, furthermore, the same effects were obtained when a noncitrate fluid, namely, horse serum, was used instead of plasma. The lowest absolute hemoglobin percentage to which we have reduced an animal without death was from 17 to 18 per cent., Sahli. Horse serum was the fluid

* From the Laboratories of the Rockefeller Institute for Medical Research.

1. Abel, J. J.; Rowntree, L. G., and Turner, B. B.: *Jour. Pharmacol. and Exper. Therap.*, 1914, 5, 625.

2. Boycott, A. E., and Douglas, C. G.: *Jour. Path. and Bacteriol.*, 1909, 13, 256.

used to replace the blood withdrawn. In this instance, the hemoglobin value did not rise during several days.

The ability of rabbits in which anemia is gradually produced, as well as that of patients with chronic anemia, to survive with only 20 per cent. of hemoglobin or less is usually ascribed to gradual bodily adjustments. But the present experiments show that in reality the body can tolerate an abrupt change to a very low figure.

Such great losses of hemoglobin as were accomplished in our rabbits are never brought about by hemorrhage. As is well known, a loss of slightly more than half the total blood bulk is usually fatal to man. This fact is true also of rabbits. The loss of hemoglobin is never so great as that of blood bulk, for the reason that as hemorrhage proceeds the blood is diluted with fluid previously extravascular. The dilution occurs so rapidly that the last blood to flow from a cut carotid is appreciably thinner than the first. Thus a relative retention of hemoglobin is brought about. This point is well indicated in the recent work of Depage and Govaerts.³ They studied the hematologic indications for transfusion on wounded soldiers, and state that when wounds do not involve the abdomen, and the red cells fall below 4,500,000 per cubic millimeter in the first three hours, or 4,000,000 in eight hours, or 3,500,000 in the first twelve hours, the patient will probably die unless transfusion is performed. In such instances, the full loss of hemoglobin is doubtless not indicated by the counts, since there is an attendant loss in blood bulk. Yet, even allowing for this, the total reduction in hemoglobin is not sufficient to account for the impending death. The amount of the pigment retained in the body under the circumstances of the most severe acute hemorrhage is always far above that which, as the present experiments have shown, will support life. The objection may be made that under the circumstances of clinical hemorrhage, no such immediate replacement of blood bulk occurs as in our bled and infused rabbits, and that the losses of hemoglobin may not be so well supported by animals rendered acutely anemic for some hours. But, as has already been pointed out, the results of transfusion in exsanguinated individuals show clearly that ordinary hemorrhage does not of itself produce lasting injury.

The view, therefore, seems justified that, however desirable it may be, it is not essential to supply blood corpuscles in ordinary cases of *acute* hemorrhage. Even in the worst example, the body retains at least twice the minimum functioning hemoglobin which, if other factors are favorable, will support life.

THE LIMITS OF SUBSTITUTION FOR PLASMA

To determine the limits of possible substitution for plasma is difficult for the reason that the body possesses immediate fluid reserves as well as the ability to manufacture fresh plasma in a few hours. This, of course, is not the case with hemoglobin. Only after the depletion of the fluid reserves does an injected liquid play an essential part in an animal's recovery. And even then the results must be discounted because of the organism's activity in furnishing for itself a new plasma. The limits of substitution are directly dependent on the time taken for the plasma's removal and that allowed for recovery.⁴ When both are gen-

erous, the possibilities as regards plasma withdrawal and substitution are practically unlimited. Unfortunately, in cases of hemorrhage the depletion is extremely rapid and involves both cells and plasma. New fluid is required, not merely to replace the plasma, but also to make up the total blood bulk.

BLOOD BULK AND BLOOD SUBSTITUTES

Hemorrhage depletes, not merely the blood, but the fluid reserves as well—a fact long recognized by physiologists. The results may be clearly seen in rabbits bled at intervals of fifteen minutes. The effect on a good sized animal of a first bleeding of 20 c.c. is to lower the blood pressure only temporarily. A second similar bleeding causes a greater fall and a somewhat slower recovery, but soon the normal is reached again. A third bleeding of only 10 c.c. may now bring about a great drop in pressure, from which there is practically no return. In such an instance, not only have all physical means of adjustment, such as vasoconstriction, been pressed into play, but the fluid reserves have been so exhausted that nothing is forthcoming to replace the blood bulk. Under such conditions, the effects of a substitute for the blood can be directly observed.

Unfortunately, the fluid reserves and other compensatory mechanism differ so much in animals of the same size that often one cannot tell how far recovery is dependent on the character of an injected fluid and how far on the organism's natural resiliency. For this reason, as well as to save time, we have employed the rapid exsanguination by suction already referred to. Half or more of the total blood—and blood not diluted as when it flows from a vessel—is rapidly removed and replaced through an ear vein with the fluid under test. Aspiration from the femoral artery has proved safer than that from the heart, and quite as rapid. A large blunt needle is thrust far up the vessel, and then suction applied. The blood pressure is recorded from the carotid artery with mercury manometer and kymograph.

The ability of plasma to replace whole blood was first studied. When more than half of the total calculated blood volume had been taken, and the carotid pressure had fallen to a physiologic zero (from 10 to 20 mm. of mercury), it was instantly and permanently restored to the normal by the injection of an equivalent quantity of plasma. This was the case, too, when horse serum was used. A saline solution, on the other hand (Ringer's fluid), brought about only a slight, transient recovery of the pressure. Sometimes, nevertheless, the animal survived for the half hour or more necessary for the successful utilization of its own fluid resources.

The reasons for the failure of saline solution, as thus indicated, have been variously given, but the most important, undoubtedly, is that it leaves the vessels for the tissues and the urine almost as soon as it is injected. The same is true to a less extent of many fluids better than salt solution, but not so good as plasma. After the injection of such a fluid, the blood pressure may be immediately restored to normal; but it does not remain there. Almost at once the pressure begins to fall as the fluid leaves the vessels, and only after a greater or less period, as the organism itself furnishes a blood substitute, does the fall cease and the pressure rise gradually to normal. If the fluid is a fairly good substitute for blood, the depth of the curve expressing the pressure changes is not great

3. Depage and Govaerts: *Presse méd.*, 1917, 25, 602.

4. Hurwitz, S. H.: *Intravenous Injections of Colloidal Solutions of Acacia in Hemorrhage*, *THE JOURNAL A. M. A.*, March 3, 1917, p. 699. Abel, Rowntree and Turner (Footnote 1).

(from 15 to 20 mm. of mercury), and return to the normal pressure is complete within one-half hour.

THE RELATIVE MERITS OF BLOOD SUBSTITUTES

Gelatin-containing fluids have often been used as blood substitutes. Hogan⁵ advises 2.5 per cent. gelatin and Bayliss,⁶ 6 per cent. We have tested several fluids made with gelatins which answered to Hogan's requirements for purity and ability to "gel." They were made up carefully according to his formula, and rabbits were used as in his experiments. But though these solutions undoubtedly restored blood pressure better than did salt solution, their effect was soon lost, the pressure falling off in the course of fifteen or twenty minutes nearly to the level to which the bleeding had originally reduced it. In these results there is no necessary contradiction to Hogan's findings. He took the rate of secretion of urine as the index of the ability of his solution to stay in the vessels, and found that it was not increased. But, as Bogert, Underhill and Mendel⁷ have shown, loss of fluid into the tissues is often far more important for blood volume than that through the kidneys.

Larger concentrations of gelatin up to 6 per cent. act proportionately better than Hogan's solution. In some instances, 4 per cent. gelatin restores blood pressure permanently, but in others it does not. Six per cent. gelatin, in our experience, is always effective.

It has been interesting to determine the effects of hypertonic glucose and dextrin solutions, since these have been advised to draw fluid into the circulation. Under most circumstances, a pump for continuous injection, such as that employed by Erlanger and Woodyatt,⁸ will not be available, so we have contented ourselves with immediate large injections. Eight per cent. dextrin (Merck) in salt solution, and 5.4 per cent. glucose in Ringer's solution—a fluid with twice the tonicity of blood—have been found to exert only a slight transient effect to raise the blood pressure in the bled rabbits.

Bayliss, who originally advised either 6 per cent. gelatin or 7 per cent. gum acacia as blood substitutes, has recently advocated the latter,⁹ and for good reasons. It can be sterilized by boiling, whereas the autoclaving of gelatin is necessary in order to kill tetanus spores. It is more uniform in constitution than commercial gelatin, and, being protein free, it does not induce anaphylaxis or the severe reactions that often follow the latter. We can confirm Bayliss' statement that 7 per cent. gum acacia will permanently restore blood pressure to normal.

At the British front, where acacia solutions are now used, there has been an avoidance of the higher percentages in favor of a 2 per cent. fluid, and the results, while encouraging, have not been convincing. The reason for this is well seen in our experiments. A 2 per cent. acacia solution, like Hogan's fluid, at first raises the pressure to normal, but it drops off within a few minutes to the danger point. Four per cent. is more satisfactory, as the secondary drop in pressure, being slow, is better compensated. But neither the 4 per cent. nor the 5 per cent. solution recommended by Hurwitz⁴ is effective in all cases. Six or 7 per cent.

is required if one is to bring back the normal pressure in an organism depleted of its fluid reserves.

Mention has already been made of horse serum. The indications are that it would be an effective blood substitute, except for the risk of inducing sensitization or causing anaphylactic shock. In nonsensitive animals (rabbits, dogs), it acts as well as the plasma of the same species. But large quantities of it bring about serum sickness. A rabbit that had three quarters of its blood replaced by horse serum died on the sixth day, and showed extensive liver necroses. In a sensitive man, as we have had opportunity to observe, the injection of 2 c.c. induced a fall of twenty points in the systolic pressure, which was repaired only after several hours. In a nonsensitive man, the effect of the injection of 90 c.c. was to raise the pressure slightly for a few minutes. Horse serum injections, under the conditions of the battlefield, might well save many lives, but they would probably cause death in some cases.

BLOOD SUBSTITUTES AND THE INDIVIDUAL CASE

The needs for a blood substitute may in individual cases be widely different. When the hemorrhage has been rapid and has been completely checked, almost any harmless isotonic solution will tide the patient over. It matters little that the fluid will soon leave the vessels, for the patient's own fluid reserves are almost intact, as is his ability to manufacture a plasma rapidly. At the other extreme are those instances in which the blood has been draining steadily away and there remains in the body no source of an immediate restoration of fluid. Here half-measures cannot suffice. A fluid must be furnished which will take the place, over many hours, of the lost blood bulk. Except for the blood or plasma of other human beings, fluids containing from 6 to 7 per cent. of gum acacia are the best at present available for the purpose. Their use when death threatens and transfusion cannot be performed is worth the taking of risks. Intermediate cases can undoubtedly be much helped by a 2 or 3 per cent. acacia solution or perhaps by Hogan's solution. In view of our ignorance of the after-effects of these foreign substances, it is certainly advisable not to inject more than the needs of the case may demand.

Further attempts to devise blood substitutes may be expected in the next few months. The fact may, therefore, be pointed out that it is not vital to success, as Bayliss has assumed, that a fluid substitute have the viscosity of whole blood; for plasma, which has only about half this viscosity, substitutes perfectly. Indeed, the advisability of raising the blood pressure after hemorrhage beyond a certain point by making an injected fluid difficult to push through the vessels may well be questioned. In order that a diminished number of red cells may carry on the body's normal work, it would seem that a brisker circulation is requisite.

Our experiments have brought out no indication of a special stimulating influence on blood pressure of either plasma or serum. That these fluids possess special characters which render them preferable to any possible substitute is obvious. But the important point is that their use is not essential.

SUMMARY

The animal organism will withstand an abrupt reduction in hemoglobin to almost, if not quite, the low percentage that is tolerated in chronic anemia. Roughly speaking, three quarters of the total hemo-

5. Hogan, J. J.: The Intravenous Use of Colloidal (Gelatin) Solutions in Shock, *THE JOURNAL A. M. A.*, Feb. 17, 1915, p. 721.

6. Bayliss, W. M.: *Proc. Roy. Soc.*, B, **89**, 380.

7. Bogert, L. J.; Underhill, F. P., and Mendel, L. B.: *Am. Jour. Physiol.*, 1916, **41**, 219.

8. Erlanger, Joseph, and Woodyatt, R. T.: Intravenous Glucose Injections in Shock, *THE JOURNAL A. M. A.*, Oct. 27, 1917, p. 1410.

9. Bayliss, W. H.: *Arch. méd. belge*, 1917, **70**, 793.

globin may be safely removed, provided the blood bulk is maintained. If four fifths is suddenly withdrawn, the animal becomes apathetic, shows symptoms of air hunger, and dies in a few hours. The amount of hemoglobin which remains after fatal acute hemorrhages is far above the minimum requirement of the body. As Abel and his co-workers have shown, great losses of plasma are soon repaired by the organism, if only the blood bulk is maintained. Taken together, these facts show that however desirable transfusion may be (especially to furnish the elements needed in clotting, to lessen acidosis, to improve oxygenation, etc.), it is not essential to recovery from even the severest acute hemorrhage, if only the blood bulk can be restored in other ways.

Of the several fluid substitutes for transfusion which have recently been suggested, all are preferable to salt solution. Bayliss' 7 per cent. gum acacia solution is up to the present the best, and its use should save life in many instances. In less urgent cases, from 2 to 3 per cent. acacia solution, or Hogan's 2.5 per cent. gelatin solution, are to be preferred to salt solution. But these fluids leave the circulation relatively soon, and when the organism has been drained of its fluid resources their injection restores the blood pressure to the normal level for only a few minutes. Permanent betterment cannot be expected in cases of severe hemorrhage with solutions containing less than from 5 to 7 per cent. gum acacia.

It is not essential that a blood substitute should possess the viscosity of whole blood.

FATAL RESULT FOLLOWING INJECTION TREATMENT OF HEMORRHOIDS

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The grave complications frequently arising from seemingly simple methods employed in the treatment of dispensary patients leads to the presentation of one such treatment and its undesirable result.

The rectal mucosa cannot be effectively freed from pathogenic organisms, which may be carried deeper by a hypodermic needle. The liquid injected reduces tissue resistance, and furnishes a good medium for the growth of organisms. If an anesthetic agent is injected, pain and the defensive reflexes it arouses are abolished. Hence, the mechanical spread of the infection is unretarded. The patient's walking, jolting in cars and sitting in chairs all aid in spreading the infection. Dispensary patients, therefore, are subjected to a double risk.

REPORT OF CASE

History.—For ten years, a chauffeur, aged 38, had had external and internal hemorrhoids, which had bled six years. He was constipated. January 31, in a dispensary, three large internal hemorrhoids were injected with quinin and urea hydrochlorid. They later sloughed off. That night, he had a severe headache; the next, a severe chill. These symptoms recurred to the end. Pain in the right hypochondrium commenced the fourth day.

The sixth day, February, 5, while having a chill, he was admitted to the hospital, obviously acutely ill. His condition was septic. There were no signs of jaundice. Over the right lung, patches of harsh breathing, modified voice, and râles were heard. Examination of the heart was negative. Tenderness was elicited over the lower half of the abdomen

and over the right hypochondrium. Neither the liver nor the spleen was palpable. Rectal examination revealed several external hemorrhoids and a few ulcerated, tender, sloughing, internal hemorrhoids. The blood count revealed: white blood cells, 12,400; polymorphonuclear neutrophils, 93 per cent.; lymphocytes, 4 per cent.; transitionals, 3 per cent. Blood pressure ranged between 72 and 118 systolic.

The seventh day, February 6, the liver and spleen were palpable, and the tenderness was greatly increased. The eighth day, a light jaundice appeared. It increased rapidly. The patient's condition appeared more septic. Liver dulness reached the fourth space anteriorly, the sixth in the mid-axilla, and the scapular angle posteriorly. A needle inserted into the right eleventh space posteriorly found no pus. Two blood cultures were taken, the first February 6, directly into plain broth and agar plates, and the second, February 9, into sterile water, the sediment being centrifuged and planted in glucose broth. Both cultures remained sterile. The patient died the twelfth day, February 11.

Necropsy.—The diagnosis at necropsy was: ulcers of the rectum, following necrosis of internal hemorrhoids; phlebitis of the prostatic and possibly of the hemorrhoidal veins; thrombosis of the same veins; multiple abscess of the liver; septic infarct of the lungs, chronic pulmonary tuberculosis, which, however, was obsolete; parenchymatous degeneration of the heart, liver, kidneys, etc., and infection by *Bacillus aerogenes-capsulatus*.

Following is a summary of the detailed report:

The skin and conjunctivae were icteric. The heart was normal except for the fact that the myocardium was pale, grayish pink, opaque, soft and friable. There were no focal lesions. The chambers contained fluid blood intermingled with gas bubbles. Frothy blood escaped from the large thoracic vessels. The lungs were congested. There was a large septic infarct located in the left upper lobe anteriorly. Several small hemorrhagic foci with necrotic centers were found in the right lower lobe. The spleen was enlarged, weighing 11½ ounces, and though it showed a normal consistency, the capsule was doubled in thickness. The cut section was dark, brownish red, and the trabeculae and malpighian bodies were indistinct. The kidneys, weighing, respectively, 6 and 6½ ounces, were pale, grayish pink. After being stripped of the capsule, they were smooth, and revealed a normal consistency, a thickened cortex, and indistinct markings. The periprostatic plexus veins appeared dilated, and a creamy pus escaped when they were cut across. The rectal mucosa showed three sloughing ulcers each about 1 cm. in diameter. The hemorrhoidal veins were small and apparently clear. The pelvic and abdominal veins showed no thrombophlebitis, but they contained fluid, frothy blood. The liver was enlarged, weighing 6 pounds and 7 ounces. It was soft and friable, and was brownish red. Scattered throughout the organ were irregular, large, greenish-yellow, necrotic, fairly circumscribed foci, with softened centers. The nodules were as large as walnuts, and on pressure yielded a purulent discharge. Those just beneath the capsule did not project above the surface of the liver. The normal liver markings were gone. Frothy blood was found in the large veins of the liver. The gastro-intestinal tract was negative, and the stools were gray.

An emulsion of pus from one of the liver abscesses was injected into a rabbit, which later died. A beginning abscess in its liver yielded encapsulated bacilli with the characteristics of *B. aerogenes-capsulatus*. A blood culture from the rabbit's heart gave a pure culture of the same organism.

8 West Sixteenth Street.

Wounds in the Trenches.—In modern trench warfare, about 75 per cent. of the wounds are produced by shell-fire and 20 per cent. by rifle and machine-gun fire, this proportion, of course, varying with the nature of the action. In 100 wounded there will be: 10 to 20 head wounds, 5 to 10 chest wounds, 6 abdominal wounds, 60 wounds of extremities.—Lieut.-Col. T. H. Goodwin, R. A. M. C.