BLOOD TRANSFUSION.*

BY

E. F. SKINNER, M.A., M.B., F.R.C.P.,
ASSISTANT PHYSICIAN, SHEFFIELD ROYAL HOSPITAL.

THE most obvious indication for blood transfusion is previous loss of blood, and the present revival of the operation is due largely to the brilliant results following this procedure in battle casualties. The shock condition produced by severe haemorrhage is due to two factors: (1) Loss of oxygen carriers, and (2) loss of blood volume; but whereas the latter can be quickly made good by the tissues pouring out fluid, except in those cases where the tissues themselves are drained of their fluids to such an extent that there is none left to replace blood loss, the former is only made good very slowly, and whilst by the injection of suitable solutions into the circulation the deficiency in blood volume can be replaced, the only means of replacing oxygen-carrying capacity is by means of blood transfusion.

Haemorrhages, whether sudden and severe, as in injuries and obstetric cases, or long-continued slight bleedings, equally benefit by transfusion, whilst the clinical anaemias, whether primary or secondary, are improved, and though in the case of the primary anaemias no permanent cure may yet be recorded, almost every observer has been struck with the occurrence of dramatic recoveries. But besides these conditions there are many others where blood transfusion may be of great value—for instance, in seriously ill persons before an obligatory operation the administration of 200 or 300 c.cm. of blood might entirely alter any possible end-result of surgical interference¹; the terrible mortality of influenza and pneumonia² occurring in epidemic form might be lessened, and a number of successful cases have been recently reported from France. In the blood diseases—haemophilia, purpura haemorrhagica, and the like—there is again an obvious indication for blood transfusion, and Graham,³ in a paper read before the Edinburgh Medico-Chirurgical Society, reported a series of 75 blood transfusions, amongst which were a number of instances of these conditions. Blair Bell⁴ advocates its use in eclampsia, whilst Ramsay⁵ refers to its gratifying employment in cases of acute nephritis. The employment of transfusion in septicaemic cases is advocated by some authors but deprecated by others, and Lewisholm⁶ utters a warning against its routine use in septicaemia, but reports good results in staphylococcal osteomyelitis.

When such a varied list of diseased conditions is studied it is clear that the action of the blood is not the same in each case: that whereas in haemorrhage and anaemia probably the increased oxygen capacity of the circulating fluid is responsible for the benefit, this cannot apply to osteomyelitis, and in this type of case the possibility of "complement" or "antibody" transference must not be lost sight of.

The catastrophes that from time to time were observed to follow the intravenous administration of blood remained unexplained until it was discovered by Landsteiner⁷ that when the blood serum of one individual was brought into contact with blood corpuscles from another individual there sometimes occurred a clumping of the corpuscles, with the formation of little conglomerate masses quite easily visible to the naked eye, and at once it was realized that in this phenomenon lay the explanation of these catastrophes—in other words, that there is an incompatibility of bloods of certain individuals, and that two such incompatibles cannot act as "donor" and "recipient" respectively in a transfusion operation, whence it follows that before each such operation the compatibility of the two bloods must be determined.

Compatibility of Blood.

In 1901 Landsteiner examined a large number of blood serums from the point of view of their property of agglutinating red blood cells, and as a result of his observations he stated that human beings could be divided into three classes according to the agglutinin content of their blood; these classes he called A, B, and C, in which the serum of Class A agglutinated the corpuscles of Class B, the serum of Class B agglutinated the corpuscles of Class A, whilst the serum of Class C agglutinated the corpuscles of both A and B classes (Fig. 1).

Moss⁸ in 1910 repeated this work, but found that three groups were insufficient to cover all cases of agglutination, that if in a large number of different bloods the serum of each was mixed with the corpuscles of every other there were

		CORPUSCLES		
		A.	B.	C.
SERUM	A.		+	
	B.	+		
	C.	+	+	

FIG. 1.—Landsteiner's original 3 group classification.

		CORPUSCLES			
		1.	2.	3.	4.
SERUM	1.				
	2.	+		+	
	3.	+	+		
	4.	+	+	+	

FIG. 2.—Moss's 4-group classification.

certain exceptions to Landsteiner's grouping, and he found that a four-class grouping was necessary to cover all cases, which groups he called I, II, III, and IV—a classification which is still adhered to for convenience and which is shown in Fig. 2.

Moss assumed the possession by the blood corpuscles of his groups of three different agglutinogens, each reacting with a specific agglutinin in the serum of another group, but this explanation is now simplified by an adaptation of Landsteiner's original conception worked out by von Dungern and Hirschfeld.⁹

This view is now known as Landsteiner's law of iso-agglutinins, and it sets forth that there are present in human blood two agglutinable substances, A and B, which react with specific agglutinins *a* and *b*, and that if any one blood contains an agglutinable substance it will contain the agglutinin which reacts with the alternative agglutinable substance; thus a blood which contains A agglutinable substance will contain the *b* agglutinin and vice versa. By the variation of these factors in the blood the four classes are determined and the supposed arrangement may be shown diagrammatically as in Fig. 3.

Group II.	Group III.	Group IV.	Group I.

FIG. 3.—Landsteiner's law of iso-agglutinins (after Hirschfeld).

In the figure the English and American numerical groups are indicated and it will be seen that Group II possesses the agglutinable substance A and agglutinin *b*, Group III the agglutinable substance B and agglutinin *a*, whilst Group IV has both agglutinins but no agglutinable substance, and Group I has both agglutinable substances A and B but neither agglutinin. Therefore Landsteiner's law may be shortly stated thus: "In any blood there are always present agglutinins against the agglutinable substance absent from the same blood."

It is stated that shortly after birth¹⁰ the blood takes up the characters of one of the four groups, and these apparently persist throughout life unchanged. In a personal investigation of this point I have found that at the moment of birth the child's blood may possess an agglutinable substance quite different from that of the mother's blood. Out of 17 such cases investigated this year, in 11 cases the blood of the child contained the same agglutinogens as the blood of the mother, whilst in 6 cases they were different.

Technique of Agglutination Tests.

The compatibility of any two bloods is shown by the non-appearance of agglutination when the serum of each is mixed with the corpuscles of the other, and by referring again to Moss's table (Fig. 2) it will be seen that by means of the serums of Groups II and III all samples of blood can be grouped according to their agglutinating properties; thus if a sample of blood is mixed with a little serum from a Group II blood and also with serum from a Group III blood, and agglutination occurs in both mixtures, the drop of blood comes from a Group I individual; if, on the other hand, no agglutination occurs in either mixture, then the blood being tested belongs to Group IV; if agglutination occurs with serum II the blood belongs to Group III, and if agglutination takes place in the serum III the blood under investigation is a Group II. With samples of serum from known Groups II and III it is possible to test out quickly any blood, and before a transfusion operation this must always be done. It is found that it is sufficient for practical purposes that the corpuscles of the blood from the donor should not be agglutinated by

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the recipient's serum, for though theoretically the donor's serum may agglutinate the recipient's corpuscles this serum is so largely diluted that this does not prove any great danger and need not be considered.

Since the corpuscles of Group IV are agglutinated by no serum of any other group, the members of this group are spoken of as "universal donors," and generally such a Group IV blood is chosen for transfusion purposes if possible.

The testing out of the compatibility or otherwise of bloods is extremely simple, and can be done at the bedside. There are many ways of carrying out the test, but the simplest, and at the same time most reliable, is as follows:

Into a small test tube such as is used for the Wassermann reaction is placed a small quantity of N/10 sodium citrate in normal saline, and four or five large drops of blood, obtained by pricking the finger, are mixed with this citrate solution, giving an emulsion of r.d. blood corpuscles. On to one end of a microscope slide is placed a drop of serum from a Group II blood, and on to the other end of the slide a drop of Group III serum, to each of which is then added a little of the corpuscle emulsion, each mixture being stirred with a smooth glass rod and the slide gently rocked to and fro. If agglutination occurs, it is quickly and unmistakably visible to the naked eye, and appears as a fine deposit resembling brick-dust, the particles of which often gradually get larger and larger as more and more corpuscles are agglutinated, until in some cases there appear a few deep crimson dots floating in clear serum.

Before any blood is used for transfusion it is essential to exclude the possibility of conveying any blood-borne disease, so that a Wassermann reaction should be carried out to exclude syphilis, and a careful history of all previous illnesses obtained; donors should be healthy adult males between the ages of 30 and 40 if possible, and during the next decade the possibility of conveying blood parasites should be kept in mind, in view of the large number of adult men who have been abroad during the war and contracted various tropical diseases—for example, malaria, filariasis, etc. Syphilis is said to have been conveyed by blood transfusion.¹⁰ The previous occurrence in an individual of such conditions as acute rheumatism, trench fever, pneumonia, cerebro-spinal fever, typhoid, etc., should prevent such individual acting as a blood donor from the point of view of danger to the recipient, whilst albuminuria, even though transient, any cardiac debility, or marked obesity in a prospective donor should negative his employment on account of danger to himself.

Technique of Transfusion.

When a suitable blood donor has been obtained the actual operation of transfusion presents little difficulty, at any rate if the "citrate method" is employed, and as this method has the outstanding merit of being a "one-man" procedure, whereas the other methods, whether Kimpton's paraffin tube or any of the syringe methods, require skilled surgical team work, it will be the only one described here.

The apparatus required is a large wide-necked bottle capable of holding 700 to 800 c.cm. graduated in 50 c.cm., and provided with a rubber cork with three holes through which pass three glass tubes, the middle one of which is ground and tapered to fit the stem of a small separator funnel. To one of the side glass tubes, A, a length

FIG. 4.

of rubber tubing of about 18 inches is attached carrying at its other end a needle with a fairly wide bore (from 1 to 1.5 mm.), whilst to the other side tube, B, is attached a double action bulb giving either a negative or positive pressure. On the centre tube, C, fits the special funnel, which has a capacity of 30 c.cm., and marked on the glass at the half-way or 15 c.cm. level, and provided with a stopcock, E. The apparatus is shown in sketch form in Fig. 4.

After sterilizing the whole apparatus blood is obtained from the donor in the following way. A solution of sodium citrate (3.5 per cent.) is poured into the bottle and allowed to run out through the

needle by simply inverting the bottle, the other tubes being meanwhile stopped by means of short pieces of rubber tube clipped by "bulldog" artery forceps, and after the tube A has been thoroughly flushed the bottle is turned over again, leaving 15 c.cm. of citrate solution in the bottom. The funnel is next placed in the centre glass tube and filled with citrate solution up to the 30 c.cm. mark, the stopcock E being shut and the suction bulb attached to the other glass tube B, the tube A being clipped. The bottle is exhausted to a mild degree and the whole apparatus is ready for use.

The donor, lying down on a bed or table, has the arm cleansed and swabbed with iodine or picric acid, and after the antecubital veins have been rendered prominent by means of a tourniquet, or arm band, the needle is pushed directly into the vein, preferably in a distal direction, though this point is not of much importance, and the tube clip removed. Blood immediately flows into the bottle, and as soon as the 100 c.cm. mark has been reached the tap on the citrate funnel is turned and a further 15 c.cm. allowed to run in, the funnel being again filled up to the 50 c.cm. mark, and as each 50 c.cm. of blood runs into the bottle 15 c.cm. of citrate is allowed to pass in from the funnel. This is better than putting a large bulk of citrate into the bottle first, as one may not always obtain the total quantity of blood counted on. When the blood has been collected and thoroughly mixed with the citrate (the bottle should be kept constantly agitated whilst the collection is proceeding, being also warmed by standing in water at 100° F.), the funnel is detached and a small length of rubber tubing, suitably clipped, is substituted. The suction bulb is replaced by a similar piece of tubing and clip, and a somewhat finer needle is substituted for the collecting needle.

The recipient is similarly prepared as to the arm, and generally it is unnecessary to dissect out a vein, though at times in very collapsed patients this has to be done, so that it is always advisable to have at hand a little local anaesthetic, hypodermic syringe, scalpel, forceps, ligatures, etc. The bottle of blood is inverted and a little of the contents allowed to run out of the needle, which is then clipped off, whilst the clip on the middle tube is released to allow air to pass up into the bottle. The needle is then pushed into the recipient's vein, in the proximal direction, and the citrated blood allowed to run in slowly. Gravity is, as a rule, quite sufficient for the purpose, but occasionally a little positive pressure must be exerted, in which case the pressure bulb is attached to the centre tube, and if positive pressure is being used it is as well to have the cork fastened down, as otherwise it will be forced out. In Fig. 5 the bottle is shown in position for the gravitational giving of citrated blood.*

The actual amount of blood to be transfused at any one time will depend upon a variety of circumstances, and at present this aspect must be left to the discretion of the operator, as no unanimity has been reached, nor does the amount of citrate solution, within reason, seem to matter practically. This, however, is a point on which further light might be thrown with advantage, as I have seen one case in which unexpected symptoms developed during a transfusion within a few seconds of the blood beginning to flow, symptoms which were repeated four times as, for various reasons, four successive veins were punctured; and it was not until the following day that it was discovered that, owing to a clerical error, the citrate solution was being used in a strength of 30 per cent. instead of just over 3 per cent. The strength of the citrate solution when mixed with the blood in the way described above gives a resulting mixture of about 1 per cent. sodium citrate, and the time taken to infuse 500 c.cm., which may be looked upon as an average amount of citrated blood, should be from fifteen to twenty minutes, a slow transfusion being less liable to produce reactions and symptoms than a rapid one.

Reactions.

Certain reactions, however, do occur, and even in carefully tested bloods, where the agglutinin contents seem quite compatible, there is a slight risk which has been stated to be as high as 1 per cent.—a risk at present unexplained. If a reaction occurs it generally manifests itself during the actual operation, the recipient complaining of pain in the chest and difficulty of breathing, which may be accompanied by nausea or vomiting and sometimes the appearance of an urticarial rash and even loss of consciousness, but generally only the first stage of this reaction is seen and if the transfusion is stopped for a few moments and then allowed to proceed more slowly no more trouble is encountered.

Quite frequently, some thirty or forty minutes after the operation there is a "late" reaction, ushered in by a shiver or rigor, which may be slight or severe, accompanied by a mild pyrexia up to 100° F., lasting perhaps for twelve hours, and

* Messrs. Allen and Hanbury have made a very convenient outfit for me on these lines.

FIG. 5.

symptoms are more likely to occur if the operation is hurried; the more quietly everything is done and the fewer the number of persons present the better will it be tolerated; at present the method is looked upon as somewhat of a therapeutic curiosity and tends to attract too much attention.

Results.

It is as yet difficult to estimate the value of blood transfusion apart from its use in haemorrhagic shock, where its value is incontrovertible, since it is only too frequently resorted to as a last desperate hope. If it is to be of real assistance it must be used much more frequently and early, for its final value will not depend on the cases of gastric ulcer snatched from death, nor the occasional miraculous recovery of the pernicious anaemia patient, but rather on a sound understanding of its rationale and method of action, and such can only be discovered by frequent observations in large numbers of varying conditions. In those conditions where unknown metabolic processes are at work—for example, haemophilia, purpura haemorrhagica, haemorrhagic necrosis, etc.—much might be learned both of the value of blood transfusion, and even of the underlying factors of these pathological conditions, by carefully carried out observations; and, again, its rôle in such chronic infections as tuberculosis might be found to be not entirely useless.

REFERENCES.

- ¹ Williamson: BRITISH MEDICAL JOURNAL, 1920, i, 603. ² *Presse Médicale*, April, 1919. ³ Graham: BRITISH MEDICAL JOURNAL, 1920, ii, 820. ⁴ *Ibid.*, 1920, i, 625. ⁵ *Ibid.*, 1920, i, 766. ⁶ Lewisohn: *Amer. Journ. Obstet.*, 1918. ⁷ Landsteiner: *Wien. klin. Woch.*, 1901, No. 14. ⁸ Moss: *Johns Hopkins Hospital Bulletin*, 1910. ⁹ Von Dungen and Hirschfeld: *Zent. f. Immunitätsforschung*, 1911, 526. ¹⁰ Rendle Short: *Medical Annual*, 1919, 15.

THE COMPOSITION OF THE GASES IN ARTIFICIAL PNEUMOTHORAX.

BY

LEONARD HILL, M.B., F.R.S.,

AND

J. ARGYLL CAMPBELL, M.D., D.Sc. EDIN.

(From the National Institute for Medical Research, Hampstead.)

ON several occasions during the past year we have had the opportunity to obtain samples of gas from the thoracic cavity in patients with artificial pneumothorax. As our interest was thereby stimulated we carried out several experiments in which we produced artificial pneumothorax in animals—cats, rabbits, and a goat. We studied the composition of the air in the thoracic cavity, using Haldane's apparatus for the analysis of oxygen and carbonic acid. Our observations, although fairly numerous, form but a small contribution to the total, since the previous researches on this subject are extensive. We have made a study of the previous literature and consider that a critical review will be useful, seeing that the conclusions reached by different observers were so varied. As we are at present carrying out a research on the changes in composition of air injected into other body cavities and tissue spaces, and obtaining thereby rather striking results, we feel we are perhaps fortunately placed for a review of the afore-mentioned subject, and attempt herein to bring the different results, previously obtained, into line.

A very early research was that of Davy,¹ who in 1823 studied the gases in a case of pneumothorax. He obtained some of the gas from the thoracic cavity after the death of the patient. It was found that air had passed freely from the lung into the pleural cavity through a valvular ulcerated opening in the upper part of the superior lobe; the valvular opening prevented the air escaping again. Davy found 8 per cent. of carbon dioxide and 92 per cent. of nitrogen in the gas. He carried out numerous experiments on animals, injecting various gases and mixtures of gases—air and carbon dioxide, hydrogen and carbon dioxide, hydrogen and nitrous oxide gas. In the light of modern research, the older observers appear to have been much handicapped as regards the accuracy of their results owing to crude analytical methods. It seems hardly fair, then, to criticize their pioneer work.

Many important researches have been published in modern times. In 1914 Webb, Gilbert, James, and Havens² made extensive series of observations, mainly with the object of determining from a clinical point of view the best gas to inject to produce artificial pneumothorax, and concluded that, as Haldane had predicted, little, if any, clinical advantage was

gained by the employment of nitrogen rather than atmospheric air for the production of artificial pneumothorax. Although they did not pay any great attention to or discuss fully the reasons for the changes in the composition of the injected gases, they gave very complete details of the analyses after the injection of oxygen, nitrogen, and air. Their figures for carbon dioxide in the imprisoned gas after many hours varied between 2.64 and 13.59 per cent., and the figures for oxygen varied between 0.41 and 8.66 per cent., except when pure oxygen was the gas injected into the thorax, the figures for oxygen percentage after forty-eight hours being then as high as 24.04 per cent. The remaining percentage, and therefore much the highest percentage, was made up by nitrogen. To quote these authors:

"The oxygen cases are especially noteworthy from the discovery of the large addition of nitrogen which must have diffused into the pleural space. Since blood contains only a small percentage of nitrogen (about 2.4 per cent.), diffusion must take place between alveolar air and pleural space to establish equilibrium. It would, therefore, seem certain that, whatever gas is used for the production of pneumothorax, it does not long remain pure; for Nature rapidly changes it until an analysis yields the equivalent of alveolar air. At our elevation (6,000 feet) alveolar air averages carbon dioxide 6 per cent., oxygen 14 per cent., and nitrogen 80 per cent.

"In general the longer the time between injections the higher the percentage of carbon dioxide and the lower the percentage of oxygen, the former tending to reach 10 per cent., and the latter 1 per cent. to zero."

The second paragraph just quoted contradicts the first paragraph as far as the oxygen is concerned. The first paragraph says the oxygen should be the same as in the alveolar air—that is, 14 per cent.—whereas the second paragraph states that the oxygen tends to reach from 1 per cent. to zero. It is quite obvious that their explanations are not sufficient to cover the variations given in their tables. They carried out an experiment under strictly physiological conditions with two monkeys. The right lungs of two monkeys of equal size and weight were collapsed under ether, one with 125 c.cm. of air and the other with the same amount of nitrogen. Forty-eight hours after positive pressure had been induced in this way the amount of gas still present in the monkey injected with air was 83 c.cm., and on analysis it gave carbon dioxide 8.06, oxygen 4.24, and nitrogen 87.70; whereas the amount of gas still present in the monkey injected with nitrogen was 92 c.cm., and on analysis it gave carbon dioxide 8.52, oxygen 5.61, and nitrogen 85.87. The figures show slight variation, but no conclusion may be drawn from them unless it was known that the lung in each monkey was collapsed to the same extent, or in other words that the circulation was similarly altered in both. These observers appear to have left the gases in the blood out of consideration, but, as has already been stated, the composition of the gases was not their main theme.

The blood gases have been very fully considered by Rist and Strohl³ in their conclusions. They made a very careful physical study of the volume changes of the gases and of the changes in absolute quantities of the gases in the thoracic cavity following the injection of air, nitrogen, oxygen, and carbon dioxide. They represented these changes by means of graphs showing the variations in quantities and also in partial pressure at definite intervals after the injection of each gas. They concluded that several days after the operation for artificial pneumothorax—not complicated by purulent exudate—analysis of the gases contained in the pleural cavity proves that the composition of the gases is the same in all cases. The phenomena which occur after the injection of gas into the pleural cavity, according to these observers, are explained completely by the exchange of gases which takes place in the living body, and which consist of a diffusion through the pleural membrane with rapidity proportional to the coefficient for each gas, and depending on the partial pressure of each gas on each side of the membrane. Equilibrium, they state, is established between the gases of the pleural cavity and the venous blood, and they hold that their graphs show why different results have been obtained at different phases before the establishment of this equilibrium. It is well known that carbon dioxide diffuses twenty-five times more rapidly through tissues than does oxygen, and obviously allowance must be made for this and similar physical laws. Rist and Strohl found that after the injection of nitrogen and oxygen the total quantity of gas was increased for a short period, probably owing to the rapid diffusion of carbon dioxide out of the blood; thus is the phenomenon of over-compression explained. Some of our own experiments illustrate very clearly how rapidly the percentage of carbon dioxide rises in