REVIEW ARTICLE

BLOOD AND BLOOD PRODUCTS

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The use of blood and blood derivatives in medicine and surgery has greatly increased in this century, though it was the investigations of workers in the 17th century which first suggested that transfusion, rather than blood-letting, might be of value in the therapy of some conditions. Blood transfusion as practised before 1900 was fraught with dangers, which were largely overcome when Landsteiner[1] demonstrated the existence of blood groups. The introduction of effective anticoagulants, and finally the drying and preserving of plasma and blood products, enabled blood and plasma to be stored. This saved the tedious procedure of calling up a donor for each separate transfusion, and direct transfusion from donor to recipient.

It is well known that human whole blood and plasma are most valuable in the treatment of shock, burns, and certain diseases where there is a depletion of one or more of the plasma components. Pooled and convalescent plasma and serum have also been used in the prophylaxis or modification of some infectious diseases.

Whole Blood and Concentrated Red Blood Cells

The collection and storage of whole blood for transfusion purposes was contemplated and practised in a small way during the First World War. Rous and Turner[2] investigated the preservation of living red blood cells *in vitro*. They found that these cells could be washed most satisfactorily using Locke's solution containing 1/4 to 1/8 per cent. of gelatin. The addition of the gelatin protected the cells from breakdown, even when shaken, though it was necessary to transfer the washed cells to a fluid containing no gelatin, if they were to be kept without hæmolysing. The best results were obtained by using mixtures of Locke's solution and isotonic solutions of sugars in water. In such solutions they found that the cells assumed a spherical shape. Using rabbits as experimental animals, these workers were able to show that transfusions of "kept cells" were useful in replacing lost blood, and that the animal was able eventually to dispose of them without harmful results[3].

This led Robertson[4], in 1918, to use stored blood in the treatment of wound shock on the battlefield, and he obtained excellent results, even with cells that had been kept for as long as 21 days. However, it was not until the Spanish Civil War, of 1937-9, that the use of stored blood was fully exploited, and at the advent of the Second World War an elaborate Blood Bank system was developed in this country, which is

still in operation to-day. It is controlled by the National Blood Transfusion Service, under the Ministry of Health, and consists of 2 London and 11 Regional Centres in England and Wales, with Centres in Scotland and Northern Ireland.

Donors are bled from the median cubital vein directly into sterile vessels containing a suitable anticoagulant solution. The standard anticoagulant now used consists of 100 ml. of 2 per cent. disodium citrate solution and 20 ml. of a 15 per cent. glucose solution. This is sterilised in the transfusion bottle, to which 420 ml. of blood are eventually added. This citrated blood is then stored at a temperature of + 3°C., and distributed to the hospitals, where it may be used for transfusion at any time up to 21 days after it was taken. The blood after storage for 21 days is considered unfit for transfusion. The fragility of the red cells increases, and they may hæmolyse.

Mainwaring, Aylward and Wilkinson[5] have also found that after withdrawal of blood from the body there is an increase of plasma potassium and plasma inorganic phosphate, and because of the possibility of these substances producing toxic reactions they recommend that the plasma be separated from the cells as soon as possible. It is now possible to preserve the plasma from stored blood by drying it from the frozen state.

Whole blood is most valuable in the treatment of shock caused by hæmorrhage, as in surgery, and it has also proved useful in cases of intestinal obstruction with circulatory failure of the shock type, and in acute generalised peritonitis.

Concentrated red blood cells have been used in the treatment of anæmia, and McQuaide and Mollison[6] report fewer reactions with these than with whole stored blood. The cells may be washed with saline, and preserved after so washing for about 48 hours.

Whole Dried Plasma

The plasma from time-expired human citrated blood is collected into 10 donor pools, constituted so that to each 9 bottles of Group A, 1 bottle of Group B, or AB is included to remove isoantibodies. It is then syphoned, in 400 ml. quantities, into transfusion bottles. These minute bottles are stored at + 2°C., and then frozen, by spinning them on a vertical axis at about 1,000 revs. at − 25°C., in the current of air from a fan. In this way a cone is forced down through the liquid, spreading the plasma evenly round the inside periphery of the bottle, where it is supercooled, and then rapidly freezes. It is dried from the frozen state, first by vacuum and finally over phosphorus pentoxide, and gives a satisfactory and rapidly soluble product[7]. Bacteriological tests for sterility are carried out at each step and all infected bottles discarded.

Thus plasma, which otherwise would have had to be discarded as unfit for use, may now be preserved in a dried state and reconstituted with pyrogen-free distilled water as it is required. In this way plasma can be stored for periods up to 5 years, and hence is always available in an emergency, or when there is delay or difficulty in obtaining fresh

blood. The dried plasma may be transfused to a patient of any blood group. This is of great importance when the time lost in the sampling and typing of a patient's blood may result in a deterioration of his condition, and even when a transfusion of whole blood is indicated the interim use of reconstituted plasma is often beneficial in tiding the patient over this period of delay. Human serum also may be preserved by freeze drying.

Liquid Plasma and Serum

The preservation of liquid plasma and serum has presented many difficulties, largely due to the fact that these liquids are normally rather opaque and tend to form a sediment on standing, particularly when shaken, thus making it impossible to distinguish between sterile and non-sterile material. Aseptic conditions are always adhered to during the collection and preparation of plasma and serum for transfusion purposes, but it is essential to be able to detect any infection that may inadvertently occur.

At first it was thought that Seitz filtration would remove any bacteria, and by clarifying the liquids enable them to be stored satisfactorily. It was found that plasma and serum contain unstable lipoid substances and in the case of plasma the difficulties of preparation are further enhanced by the fact that filtration, due to the activation of prothrombin by the magnesium of the asbestos of the filter pad and the subsequent conversion of the fibrinogen to fibrin, caused clots and shreds to appear in the filtered plasma. Bushby and Whitby[8] suggested a method of overcoming this post-filtration clotting by alkalinisation of the plasma prior to filtration, and then readjusting the *p*H with carbon dioxide. This was not entirely satisfactory, and it seemed that the complete removal of fibrinogen was the only answer to the problem.

Several workers have suggested methods for accomplishing this. Clegg and Dible[9] prepared a transfusion material by recalcifying citrated plasma. The fibrin clot was broken up by shaking with glass beads, and the serum was then sterilised by passing it through a Seitz filter. They found that this material gave no skin reaction when injected intradermally, and provided a satisfactory transfusion fluid.

Reid and Bick[10] recommend the production of serum by recalcification of centrifuged plasma, as they were able to demonstrate the presence of muscle-stimulating and vasoconstrictor substances in serum formed by the clotting of whole blood. They thought that the transfusion reactions occasionally seen after transfusion of serum were due to these. Toxic symptoms following the transfusion of serum have also been reported by some other workers, but the evidence is by no means clear.

Maizels[11] has described a procedure for removing the fibrinogen from plasma by adsorption on kaolin. The process involves five steps, the kaolin is autoclaved in bottles, plasma is added, shaken and the kaolin allowed to settle. The plasma is then removed, passed through a paper pulp filter, and finally sterilized by passage through an antibacterial filter pad. This material gave excellent clinical results, and Maizels claims

that its use was so particularly free from reactions that it has been suggested that kaolin may also remove pyrogens or other toxic substances sometimes present in plasma.

It was found that after a single absorption this fluid was still not stable in the liquid state, and the technique was found most useful for plasma drying, although Maizels reported that a second and third treatment with kaolin produces a more stable material.

The use of alcohol and ether at low temperatures has proved the most satisfactory means of obtaining a stable liquid for transfusion. This was first suggested by Hardy and Gardiner[12] who added serum or plasma to a large volume of alcohol or acetone at $-8°C.$, and then washed the precipitate with ether. Bick[13] describes a modification of the method, and precipitates serum proteins with a mixture of alcohol and ether at $-12°$ to $-14°C.$ McFarlane[14] has claimed that the unstable lipoids are removed from serum by freezing it with ether below $-25°C.$ Electrophoresis of serum treated 3 times in this manner showed that the concentration of beta globulin had been reduced, and when the process was applied to plasma, the fibrinogen had been completely removed. The resultant fluid was crystal clear, and had good keeping qualities.

We may therefore summarise by saying that at present whole blood, washed concentrated red cells, liquid filtered plasma and reconstituted dried plasma are available for transfusion in this country. Whole blood is used for surgical shock and the replacement of blood lost. Concentrated red cells are used in the treatment of anæmia, and plasma and reconstituted plasma in emergency treatment, when the delay in finding a suitable blood group might be dangerous. Plasma is most valuable in the treatment of burns[15] where there is a fluid loss into the tissues and a rapid and extensive loss of protein accompanied by hæmoconcentration. Transfusion with plasma will reduce this hæmoconcentration and restore the circulating blood volume.

The Fractionation of Plasma

In the treatment of some conditions it will be realised that all the constituents of plasma are not equally effective, and indeed whole plasma may be less effective and less economical than the use of the separated components. Among the constituents of plasma that have thus far been concentrated are the antibodies against infectious diseases, two of the components of complement, the anti-A and anti-B isohæmagglutinins and Rh antibodes, hypertensinogen, thyrotropin, fibrinogen and thrombin, and the various groups of electrophoretically defined globulins and albumins.

It is most important that any process of plasma fractionation shall not irreversibly alter the plasma components, as such proteins would be foreign to the human body, and their introduction into the circulation may result in the production of undesirable reactions. The methods of separation that have been developed depend upon differences in the physicochemical properties of the plasma proteins. It is possible to isolate

proteins by electrophoresis, but only on a small scale, so this method finds most useful application in the control and improvement of the bulk fractionation methods. The solubility of proteins in aqueous solution is determined by such variables as *p*H, salt concentration, temperature, total protein concentration, and in some procedures, solvent concentration.

Earlier methods of protein precipitation depended on varying the salt concentration—the so-called "salting-out" procedures. However, the necessity of afterwards removing the precipitating salt by dialysis makes it difficult to maintain sterility and, as interactions betwen proteins and salts appear to be more specific at low salt concentrations, the effects tend to be masked at the high concentrations needed for salting out. Both these disadvantages are overcome by using a solvent to precipitate the protein. A solvent like alcohol or ether can be added under sterile conditions and is, indeed, often bacteriostatic in itself. Its volatility ensures its complete removal during the freeze-drying of the final product, and the process can be carried out at low electrolytic concentrations where effects are more specific. Solvent precipitations must be performed at low temperatures, between 0° and −10°C., to prevent denaturation and subsequent loss of biological activity of the protein. Methyl alcohol, ethyl alcohol, acetone, dioxane and ether have all been used in the fractionation of proteins from aqueous solution, but of these ethyl alcohol and ether are now in most common use.

Electrophoretic studies show that normal human plasma is composed of albumin 55 per cent., alpha globulin 14 per cent., beta globulin 13·5 per cent., gamma globulin 11 per cent. and fibrinogen 6·5 per cent. In the production of protein fractions for clinical use, biological activity is more important than physico-chemical purity, though the fractions prepared do correspond fairly closely with the electrophoretic components.

The Fractionation of Plasma by Ethyl Alcohol

The development of the ethyl alcohol method of plasma fractionation by Cohn[16] and his co-workers in Harvard originated from the war-time need for a process for the production of concentrated human albumin for transfusion. By varying *p*H, ionic strength, and alcohol concentration Cohn prepared 5 main fractions from normal pooled human plasma

TABLE I

Fraction	*p*H.	Ethyl alcohol per cent.	Temp. °C.	Ionic Concentration
I	7·4	8	−3	0·14
II & III	6·8	25	−5	0·09
IV	5·8	40	−5	0·09
V	4·8	40	−5	0·11

(Table I). These fractions, when examined electrophoretically, showed the following compositions, in g. of protein/litre of plasma (Table II).

TABLE II

Fraction	Plasma	I	II & III	IV	V	VI
Albumin	33·2	0·2	0·7	1·0	29·0	0·3
α Globulin ...	8·4	0·2	1·8	5·4	0·6	0·3
β Globulin ...	7·8	0·8	6·2	3·1	—	
γ Globulin ...	6·6	0·5	6·0	0·2	—	
Fibrinogen ...	4·3	2·6	1·6	—	—	

Preparation of Plasma Products by the Ether Fractionation Process

In this country plasma fractionation is now carried out using ether as a precipitating agent. McFarlane[14] in 1942 found that the extraction of plasma and serum with ether at low temperatures produced a stable transfusion fluid, and electrophoresis of the plasma treated in this way showed that beta globulin had been reduced and fibrinogen removed. This led Kekwick, Mackay and Record[17] to investigate the possibility of using ether to prepare biologically active fibrinogen and thrombin for clinical use. The process has now been developed to give gamma globulin also[18].

Fresh citrated plasma is clarified by passing it through a paper pulp filter and then, at the normal *p*H and ionic strength of plasma, 11 vols. per cent. of ether are added slowly, with stirring, at a temperature of 0° to −0·5°C. The resulting precipitate, which consists largely of fibrinogen, is allowed to settle overnight at 0°C. It is centrifuged and may be dissolved in citrate saline for conversion to fibrin foam, or washed with ether citrate saline, dissolved, and freeze-dried as fibrinogen.

To prepare fibrin foam, the crude fibrinogen solution is whipped to a froth by a spinning metal disc, thrombin is injected, and the material is poured into metal trays, where it is allowed to set, and then dried from the frozen state. It is finally baked and dispensed in pieces of convenient size.

Prothrombin is separated from the supernatant liquid after the fibrinogen precipitation by adjusting the *p*H to 5·35 at 0°C. The resulting precipitate is washed twice with distilled water, dissolved in citrate saline, and converted to thrombin at *p*H 7·0 by the addition of thromboplastin and Ca ions. After filtration the thrombin solution is freeze-dried in quantities to give 50, 250, and 500 units per ampoule. The supernatant liquid from the prothrombin separation is now diluted with 3 volumes of

sterile distilled water, and the beta and gamma globulins precipitated at an ether concentration of 18·5 vols. per cent., *p*H 5·75 and temperature – 3°C. The mixed precipitate is suspended in distilled water, and dissolved in buffer, and the beta globulins separated at *p*H 5·0, ionic strength 0·01, and an ether concentration of 9 vols. per cent., at 0°C. The gamma globulins which remain in solution are then precipitated by bringing the ether concentration up to 18 vols. per cent. at *p*H 6·70, and temperature – 3·5°C. This precipitate is dissolved and dried from the frozen state in quantities to give about 250 mg. per ampoule. In the freeze-drying of small volumes of protein solutions the ampoules are loaded directly into the drying chamber, and frozen by centrifugal vacuum spin freezing[7] so that the freezing and drying processes are combined in the one operation.

Clinical Uses of Plasma Products

Fibrinogen.—The fibrinogen-containing fraction of plasma is largely used, in conjunction with thrombin, for the promotion of fibrin clots in certain surgical procedures. The great advantage of human fibrin is that it may be introduced into the body and left *in situ* without fear of its behaving as an antigen and producing undesirable reactions. In America it is also used for the preparation of fibrin clots, fibrin films and fibrinogen plastics. These are made in a great variety of shapes, sizes and mechanical properties, and treated in such a way as to modify their susceptibility to attack by proteolytic enzymes, as well as their rate of absorption in living tissues. Morrison and Singer[19] find that untreated fibrin films persist in tissue for a period up to 5 days, but fully treated films have been known to last for more than 80 days. With films of extended persistence time, an encapsulation occurs between 10 and 30 days after implantation. Bailey and Ingraham[20] have tested fibrin films for their suitability in the repair of dural defects and the prevention of meningocerebral adhesions, and they claim that they seem superior to metal foil, preserved dura, fascialata, rubber, gutta-percha or amniotic membrane. In the formation of plastics[21] the fibrinogen is not clotted with thrombin, or even separated from the accompanying globulins, but Cohn's entire Fraction I is subjected to an irreversible moulding treatment. Fibrinogen and thrombin have also been used for the surface treatment of burns[22,23] for nerve suturing, skin grafting, and in coagulum pyelolithotomy. In the latter case, the fibrinogen solution is injected into the renal pelvis, and converted to fibrin by the subsequent injection of thrombin. The calculi are enmeshed and removed with the coagulum. Dees[24] has reported that this fibrinogen coagulum has several advantages in the operative removal of renal calculi, as it ensures the removal of all free stones, it avoids fragmentation of the stones during removal, trauma to the kidney is reduced to a minimum and complete surgical mobilisation of the kidney may be unnecessary.

The use of fibrinogen and thrombin in skin grafting dispenses with the need for pressure dressings, and it has been found that the grafts vascularise with great rapidity, and the tendency to bronze pigmentation seems to be reduced. Cronkite, Lozner and Deaver[25] report several cases of skin grafting in which fibrinogen and thrombin were used,

and they emphasise that its great advantage is the time saved, due to quick control of hæmorrhage, fewer sutures and simplified dressings. Michael and Abbott[26] recommend the use of fibrinogen in reconstructive surgery, especially neurosurgery and tendon repair work, and Hawn, Bering, Bailey and Armstrong[22] have reported its use in the surface treatment of burns. Prepared fibrin film may be applied to the burnt area by means of freshly formed fibrin, and Macfarlane[23] found this gave satisfactory results.

It has been found that the fibrinogen fraction also contains enough of the antihæmophilic factor of normal plasma to make it most useful in preventing or arresting bleeding in hæmophiliacs, particularly when it is necessary to subject them to surgical treatment.

The existence of a substance in normal plasma which was effective in accelerating the coagulation of hæmophilic blood was noticed in 1937 by Patek and Taylor[27], and since then considerable work has been done in this field. Lewis and co-workers[28] carried out an *in vitro* and *in vivo* comparison of normal and hæmophilic blood plasma, and their derived plasma protein fractions, and they found the antihæmophilic factor was present in Cohn's Fractions I, II, III and IV—I of normal plasma. However, it is Fraction I, or the fibrinogen fraction of the ether process which is generally used in the clinical treatment of hæmophilia. Minot *et al.*[29] have tested the antihæmophilic activity of Cohn's Fraction I *in vivo*, and they report that the injection into a patient of an active globulin fraction had no influence on the effectiveness of subsequent injections of the material, though Laurence and Craddock[30] report the case of two hæmophiliacs who became refractory to further transfusion or injection of Fraction I.

Van Creveld and Mastenbroek[31] studied the effect on hæmophiliacs of a plasma fraction containing fibrinogen 82 per cent., albumin 2·3 per cent., gamma globulin 4·27 per cent., and 11·2 per cent. of " ill defined " globulins migrating in the alpha and beta region, and they found that a 2 per cent. solution of this protein mixture had a marked coagulation promoting effect *in vitro* and *in vivo*. Other clinical tests have shown that 10 ml. of a 2 per cent. solution of the fibrinogen fraction reduces the clotting time of a hæmophiliac's blood to within the normal range for about 48 hours. The material is equally effective when injected intravenously or intramuscularly.

Thrombin

Although thrombin solutions are usually used in conjunction with fibrinogen or fibrin foam, this protein has also been found valuable as a local hæmostatic agent in various surgical procedures. Tidrick, Seyers and Warren[32] used it in the control of bleeding from bone, the gall bladder and appendical bed, and following pyloro-plasty, mastectomy and biopsies. Experience using thrombin with and without soluble cellulose for local hæmostasis have been reported by Cronkite, Deaver and Lozner[33].

Fibrin Foam

Fibrin foam is a valuable hæmostatic agent in neurosurgical procedures, and as with the other fibrin products already mentioned, its great advantage is that it can be left *in situ* without exciting injurious tissue reaction. In this respect, it is superior to muscle. It is often used in conjunction with thrombin solution, in which it is soaked before being applied to the bleeding surface. The first record of the use of fibrin for hæmostasis was by Grey[34] who tried tampons made of animal and human fibrin, and later Harvey[35] used fibrin paper and films in surgery.

Bailey and Ingraham[36] report clinical and pathological studies on the use of fibrin foam as a hæmostatic in neurosurgery. They find it of great assistance in controlling continual oozing and even more vigorous bleeding from large venous channels, such as the dural sinuses and cerebral veins, but it is seldom effective in the arresting of bleeding from large arteries. It has proved of value in general surgery, and some workers have reported success in controlling hæmorrhage from the cut surface of liver and kidney and in prostatectomies Its usefulness has also been demonstrated in certain dental operations, particularly in hæmophiliacs.

Gamma Globulin

It has been shown that the antibodies of human plasma are largely concentrated in the gamma globulin, and so this fraction has found wide use in the prophylaxis and treatment of various diseases. Of these the most important is measles in children and many clinical tests have been carried out to ascertain the effectiveness of gamma globulin in the prevention and attenuation of this disease.

In America, using Cohn's Fraction II, Stokes, Maris and Gellis[37] found that in a controlled group of cases with exposure within the family, gamma globulin from normal pooled adult plasma gave a rate of 71 per cent. protection, 27 per cent. modification and only 2 per cent. failure among 62 inoculated children, whereas of 46 uninoculated controls only 7 per cent. failed to contract measles. Of the remainder, 4 per cent. had the disease in a mild form, and 89 per cent. developed measles of average severity. Ordman, Jennings and Janeway[38] also carried out clinical tests, which further proved the value of this plasma fraction in the treatment of measles.

In this country, tests were performed to compare the effect of human serum gamma globulin, prepared in America by Cohn's process, with that of convalescent measles serum[39]. The gamma globulin was found to be about twice as potent as the convalescent serum. Apart from this increased potency, gamma globulin has a great advantage over serum in that there is always a risk of the latter transmitting homologous serum jaundice, whereas there has been no recorded instance of this disease following many thousands of injections of immune globulin. Using the ether fractionation process, gamma globulin is now produced in Great Britain, and clinical tests are proving most satisfactory. Several workers have investigated the effect of the gamma globulin-containing fraction on

other diseases. It has been claimed to be useful in the prophylaxis of infective hepatitis,[40] and Adams and Smith[41] have reported some success against upper respiratory infections.

A small number of patients suffering from mumps were treated with gamma globulin by Candel[42], and this appeared to reduce the incidence of orchitis as compared with untreated controls. This has been further borne out by Gellis, McGuiness and Peters[43] who administered gamma globulin, prepared from mumps convalescent serum, on the first day of the disease. Stokes[44], while emphasising the need for early diagnostic criteria of infection also found evidence that gamma globulin gave favourable results in several other diseases in man.

Albumin

During the war, it was the need for concentrated human albumin for clinical use that led to the development of Cohn's[16] method of plasma fractionation in America, and he was able to produce a precipitate that was shown to be 98 to 100 per cent. albumin by electrophoretic analysis. This material was used by the armed forces for the treatment of shock, œdema and hypoproteinæmia.

Albumin has been shown to have at least two known functions: it maintains the colloidal osmotic pressure of the blood, and plays a role in the nutrition of the tissues. Although it comprises only about 60 per cent. of the plasma proteins, it is responsible for nearly 80 per cent. of the colloidal osmotic pressure of plasma and blood, and so is the constituent of plasma that is most effective in the maintenance of blood volume. Scatchard, Batcheldar and Brown[45] have shown that each g. of albumin holds about 18 ml. of fluid in the blood stream, and therefore has an effect equivalent to about 20 ml. of citrated pooled plasma. In this respect it has proved most valuable in the treatment of shock, as it increases the blood volume without causing a fall in plasma concentration, as is the case when saline is used. However, it is recommended by Cournand *et al.*[46] that, because of the persistence of acute anæmia in many cases after albumin therapy, whole blood should be given subsequently when available.

Janeway *et al.*[47] have studied the use of albumin in the treatment of hypoproteinæmia. They find that albumin is usually the deficient plasma protein in hypoproteinæmia, and so favour its use, rather than whole plasma, in the therapy of this condition.

Salt-poor albumin has also been found to be of value in the treatment of nephrosis [48], and cirrhosis of the liver[49].

The Isohæmagglutinins

The A and B isohæmagglutinins which appear to be associated with beta globulin have been purified and concentrated from pools of plasma of suitable blood groups. High titre sera are required for accurate blood group testing, and methods of concentration make available the agglutinins from plasma whose titre is initially too low. Enders[50] reports that Cohn's Fractions II and III have isohæmagglutinin activity.

Plasma Substitutes

The difficulties associated with the collection and storage of plasma, and its dangers as a transmitter of disease, have led to a search for a material of non-human origin, which could be used as a plasma substitute. The main function of such a substitute would be to restore the circulating blood volume till the patient could replace the plasma protein lost, though it could never be more than a second best when blood rather than plasma had been lost.

The ideal blood substitute should possess certain properties. It must exert the same colloid osmotic pressure as whole blood, be readily sterilisable, non-toxic, and non-antigenic, and absolutely stable as a liquid at normal temperatures. Also it should show no deterioration on shaking, and thus be readily transportable. Probably most important of all, it should be only slowly destroyed in the body, and its elimination must be rapid and complete.

As a result of experience during the 1914-18 war, Bayliss[51] in 1919, tried the colloids soluble starch, dextrin and gelatin as blood substitutes, but these proved unsatisfactory. However, he found that a 6 per cent. solution of gum arabic in 0·9 per cent. sodium chloride had most of the desired properties, and this was introduced for general use. Various workers have since criticised the use of gum arabic on the grounds that it is stored in various organs, particularly the liver, and that it interferes with liver function. Similar storage phenomena have also been attributed to some other possible colloids for infusion, such as pectin, polyvinyl alcohol and methylcellulose.

During the 1939-45 war, the Germans introduced Periston[52], a synthetic colloid, polyvinyl pyrolidene, and they claimed this was well tolerated by the body, its action lasted for 2 days, and it was eventually excreted in 3 to 4 weeks. However, Bull and his colleagues doubt that molecules of the vinyl polymers which are large enough to be retained by the glomeruli can be metabolised by the body, and they suggest that some form of storage must take place here too.

Recently, in Sweden, " Dextran Ph " has been introduced and widely used as a plasma substitute[53]. This is a 6 per cent. solution of the polydispersoid glucose polymer dextran, in which most of the molecules have been hydrolytically given a molecular weight conforming to that of albumin. This material has certain theoretical advantages over the other non-protein colloids, because being free from acidic radicals it is not likely to form storage complexes, and it can be hydrolysed into glucose by acids and certain living organisms, suggesting that the living body may also be able to metabolize it slowly. Some tests have been carried out in this country both with the Swedish Dextran, and with material produced experimentally in Britain, and a comprehensive report has been published[54].

It is claimed that dextran is well retained in the circulation, and can maintain the osmotic pressure till its place is taken by plasma proteins. However, it is desirable to prepare dextran with a defined range of molecular size, because if the molecular weight is insufficiently reduced during

acid hydrolysis, renal damage may result. On the other hand, its value as a substitute for plasma depends on the proportion of molecules of a size which will not pass the glomerular filter.

The fate of dextran in the body is still in doubt, though serological methods can detect it in the lymph glands and spleen when it is no longer apparent in the plasma. Further investigations on this most important aspect must be done before dextran can be unreservedly recommended for widespread use, though work up to date has shown that in all other respects it appears to be a most useful plasma substitute. It has also been claimed that gelatin, when produced under rigidly controlled conditions, may be useful as a substitute for plasma.

SUMMARY

The Blood Transfusion Service, organised as an emergency measure by the Medical Research Council in 1939, has now become an integral part of the National Health Service in England. Blood Transfusion Laboratories, under the Regional Hospital Boards, have been established in London and in the Provinces to collect blood, to carry out research and to provide specialised services in connection with blood transfusion.

A central Blood Group Reference Laboratory prepares and distributes grouping serum, and Units of the Medical Research Council have been set up to study problems associated with blood groups and blood transfusion. A combined Medical Research Council and Lister Institute Unit has been responsible for carrying out the research on plasma fractionation and for the routine preparation of plasma fractions and drying of plasma.

In the field of plasma fractionation the American workers have made many important advances in the theoretical and practical field, and their procedures have been developed commercially. In this country the emphasis has been laid on the production of those fractions most needed by clinicians, and because of the difficulty of getting equipment the scale of operations has been much smaller. The scheme is sponsored, and the expenses of the routine production are paid by the Ministry of Health, through the Medical Research Council. The collection of the necessary blood is arranged and carried out by the National Blood Transfusion Service. As the blood is a gift, the plasma fractionation products are not sold in this country, and in order to make sure that they are not wasted they are issued to clinicians through the Ministry of Health and may only be obtained by application to the Ministry. At present the use of fibrinogen is restricted to skin and nerve grafting, and the treatment of hæmophilia. Fibrin foam is used for brain and lung surgery in conjunction with thrombin, and gamma globulin has been successfully used in measles prophylaxis, in controlling the spread of the disease in hospitals, and other closed communities. At the same time, at the Lister Institute, research work to improve the different procedures goes on all the time, side by side with investigations into more fundamental problems.

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