A year after the acute episode the blood-pressure was still 130/85 mm. Hg and the blood urea measured 36 mg./100 ml. and the endogenous creatinine clearance 39 ml./minute. After 16 hours' fluid deprivation the urine osmolarity rose to 485 mOsm/kg. The pH of the urine fell to 4.92 after oral ammonium chloride 0.1 g./kg. body weight (Wrong and Davies, 1959). The urine contained about 1 g. of protein per 24 hours.

Hepatic and Renal Biopsy.—Hepatic biopsy 12 days after the onset of the illness was of normal liver tissue. Biopsy of the right kidney (Dr. G. M. Berlyne) was carried out on the 28th day of the illness (Special Plate, Fig. 1). More than half the renal tissue was necrotic, with involvement of both glomeruli and tubules, and there was much calcium deposition. The remaining tissue showed much fibrosis with slight polymorphonuclear-cell infiltration. The appearances were those of cortical necrosis.

Radiology.—A plain film of the abdomen 15 days after the onset of anuria showed that the right kidney was 11 cm. long; only the upper pole of the left kidney was visible. No calcification was present. A year later widespread calcification was seen throughout both kidneys (Special Plate, Fig. 2), and on the medial side of the lower pole of the left kidney the calcification was of the "tramline" pattern described by Lloyd-Thomas *et al.* (1962). The right kidney was 9.5 cm. long and the left kidney 13.5 cm. On intravenous pyelography (Special Plate, Fig. 3) the left kidney excreted the dye satisfactorily and the caliceal pattern was normal. Although there was some secretion of the dye on the right, details could not be defined. **Necropsy Report on Stillborn Infant (Dr. J. Cocker).**—There was macroscopic evidence of anoxia: the lungs were large and congested; subpericardial petechiae were present; a small subdural haemorrhage—probably of anoxic origin—was found; there was absence of meconium from the gut.

It was thought, on a weight/length ratio and also on ossification centres, that the maturity of the infant was 36–37 weeks and not 32 weeks as the maternal history indicated.

Discussion

Although this patient's initial symptom of pain in the back may have been due to retroplacental haemorrhage, the renal cortical necrosis can almost certainly be ascribed to the severe post-partum haemorrhage and prolonged

hypotension. The feature of the illness which remains unexplained is the jaundice; this had been noted clinically before blood transfusion, and subsequent tests did not show incompatibility of this blood. It is probable that the jaundice was hepatocellular in origin, due either to viral hepatitis or to toxæmia of pregnancy.

Two previous instances of recovery from renal cortical necrosis with development of diffuse calcification radiographically have been reported. In the case described by Gormsen *et al.* (1955) the serum urea nine months later was 59 mg./100 ml. and the endogenous creatinine clearance 29 ml./minute. There was a much more severe degree of renal impairment in the other case described (Derot *et al.*, 1960); the blood urea never fell below 200 mg./100 ml. and the patient died 16 months after the acute illness.

Summary

A woman who developed renal cortical necrosis following post-partum haemorrhage recovered after artificial haemodialysis on three occasions. A year later the blood urea was within normal limits. Radiographs of the kidneys showed the development of diffuse calcification.

We are grateful to Mr. T. B. Fitzgerald and Professor D. A. K. Black for permission to publish this report. We also wish to thank Dr. S. de C. Baker for the interpretation of the renal biopsy and the photographic department of Manchester Royal Infirmary for the illustrations.

REFERENCES

- Boucot, N. G., Guild, W. R., and Merrill, J. P. (1957). *New Engl. J. Med.*, **257**, 416.
 Crook, A. (1927). *Proc. roy. Soc. Med.*, **20**, 1249.
 Derot, M., Prunier, P., Roudier, R., and Prunier, M. (1960). *Bull. Soc. méd. Hôp. Paris*, **76**, 812.
 Gormsen, H., Iversen, P., and Raaschou, F. (1955). *Amer. J. Med.*, **19**, 209.
 Lauer, D. P., and Schreiner, G. E. (1958). *Ibid.*, **24**, 519.
 Lloyd-Thomas, H. G., Balme, R. H., and Key, J. J. (1962). *Brit. med. J.*, **1**, 909.
 Ober, W. E., Reid, D. E., Romney, S. L., and Merrill, J. P. (1956). *Amer. J. Med.*, **21**, 781.
 Wrong, O., and Davies, H. E. F. (1959). *Quart. J. Med.*, **28**, 259.

INFUSION OF NON-AUTOLOGOUS PLASMA

EFFECTS OF CHLORPHENIRAMINE, PREDNISOLONE, AND ADRENALINE

BY

J. L. HUTCHISON, M.D., F.R.C.P.(C.)

Research Associate

University Medical Clinic, Montreal General Hospital, Montreal, Canada

A. S. V. BURGEN,* M.D., M.R.C.P.

Deputy Director

Reactions to transfusion of whole blood have been a serious problem since this form of therapy was initiated. Improvements in erythrocyte typing and in cross-match technique have made reactions attributable to red-cell incompatibility a rarity. More recently it has been shown that antibodies to leucocytes and platelets may develop after transfusion or pregnancy, and may be associated with reactions in subsequent blood transfusions. Apparently unrelated to these reactions involving cell-type incompatibility are the allergic-type reactions following plasma transfusions in individuals who have not previously received a transfusion.

These were first demonstrated in dogs by Bliss, Johns, and Burgen (1959), who found that non-autologous plasma caused cutaneous and other reactions, as well as being an inferior expander of the circulation as compared with autologous plasma. Similar findings were described by

Remington and Baker (1959). Subsequently it was found that similar reactions occurred in man and could often be correlated with a deficient retention of the transfused plasma within the circulation (Hutchison, Freedman, Richards, and Burgen, 1960). Skin-sensitivity to non-autologous human plasma was also shown by intradermal testing (Freedman, Bliss, Hutchison, and Burgen, 1960).

It seems likely that plasma reactions of this type constitute a major group of the reactions to transfusion of whole blood which are seen. The present study was accordingly undertaken to see if the therapeutic agents previously used in dealing with transfusion reactions—namely, antihistamines, adrenal steroids, and adrenaline—were effective. We have examined the value of chlorpheniramine, prednisolone, and adrenaline given prior to transfusion of non-autologous plasma in reducing the incidence and severity of cutaneous and systemic reactions as well as increasing the blood-volume expansion.

*Now at the Department of Pharmacology, Cambridge.

Materials and Methods

Most of the subjects used in this study were healthy young volunteers; in a few of the earlier studies, young hospital patients free of diseases likely to influence the blood-volume dynamics or capillary permeability were used. None had previously received blood transfusions. In all, 73 studies were made. Five individuals served as controls, receiving only small amounts of saline or citrate and saline, 19 received non-autologous plasma, and 14 had autologous plasma. One-half of the autologous group were subsequently restudied as part of the non-autologous group. Thirty-one persons received non-autologous plasma together with chlorpheniramine (9 subjects), prednisolone (8 subjects), combined chlorpheniramine and prednisolone (6 subjects), and adrenaline (8 subjects). Four individuals received adrenaline but were not transfused with plasma.

Blood for the study was collected in silicone-treated bottles (Baxter) containing disodium citrate 2 g. in 30 ml. of water. Between 550 and 600 ml. was usually obtained and immediately centrifuged at 4° C. for 30 to 60 minutes at 1,700 r.p.m. The separated plasma was usually frozen and held at -23° C. until used, but in a few instances fresh plasma was used. Prior to freezing such plasma contained approximately 100 erythrocytes and 10 leucocytes per c.mm. Platelet concentrations were usually about 150,000/c.mm. In all but a few of the earliest non-autologous studies, single-donor transfusions were used. Each donor was bled twice to obtain the 500-600 ml. of plasma required. In all cases only ABO and Rh D compatible blood was used. Except in the earliest cases, a complete cross-match was carried out.

Subjects for the studies lay down on a bed at rest for at least 20 minutes before the start of the experiments and remained recumbent for the duration of the experiment. Neither donors nor recipients were fasted. All sampling and infusions were carried out through a small-calibre polyethylene catheter placed in the antecubital vein. A slow drip of saline was used to maintain patency of this catheter. Between 50 and 80 ml. of saline was usually required for this purpose during the course of an experiment.

Immediately before the infusion of plasma, the plasma volume was determined, using radioactive iodinated serum albumin (R.I.S.A.) as previously described (Hutchison *et al.*, 1960). Haematocrits (Wintrobe) were done on three separate samples of the blood obtained for the plasma-volume determination. The plasma infusions were carried out over a 30-minute period using a constant-flow infusion pump. When the infusion was half completed 50 mg. of Evans blue dye (T 1824) or 200 mg. of sodium anoxynaphthionate ("coomassie blue") was given intravenously to make the recognition of urticarial lesions easier. One hour

after completion of the infusion the plasma-volume determination was repeated, using a second injection of R.I.S.A. and the haematocrit measured again in triplicate. In certain of the cases serial haematocrits were determined throughout the study. The results of the serial haematocrit changes have been reported (Hutchison *et al.*, 1960). Plasma-protein determinations were made, using a micro-Kjeldahl method (Hawk, Oser, and Summerson, 1947), on plasma samples obtained at the time of the two plasma-volume determinations and also on the donor plasma. In a few of the earliest cases the biuret method (Gornall, Bardawill, and David 1949) was used. The subjects were observed for cutaneous and systemic reactions both during and after the experiment. In the treatment group medication was given 10 minutes before the start of the plasma infusion and consisted of (a) chlorpheniramine maleate 10 mg. intravenously, (b) prednisolone sodium hemisuccinate 100 mg. intravenously, (c) chlorpheniramine 10 mg. and prednisolone 100 mg. intravenously, or (d) adrenaline 0.3 mg. subcutaneously.

Results

In order to permit comparison of plasma retention between subjects of different initial plasma volumes and receiving different volumes of plasma infusion, a plasma-volume index was used to make allowance for these factors. This was computed as follows:

$$\text{Plasma-volume index} = \frac{\text{Final volume} - \text{initial volume}}{\text{Volume infused} - \text{plasma withdrawn in sampling}} \times 100$$

An index of 100% indicates full expansion, an index of zero no expansion, and negative indices denote a net loss of plasma volume.

Haematocrit changes were evaluated as an alternative measure for assessing plasma retention. A haematocrit index was derived from the haematocrits, the pre-transfusion plasma volume, and volume of plasma infused, to permit comparison of results between different individuals (Hutchison *et al.*, 1960).

$$\text{Haematocrit index} = \frac{\text{Actual haematocrit change}}{\text{Predicted haematocrit change}} \times 100$$

An index of 100% indicates the predicted fall in the haematocrit, an index of zero no change; a negative index denotes a rise in the haematocrit. It has been assumed in these studies that the red-cell mass has not varied appreciably and that the venous haematocrit is not significantly different from the total body haematocrit index. We had in fact found previously (Hutchison *et al.*, 1960) that there was a good correlation between plasma-volume indices and the haematocrit indices.

The mean plasma-volume index after infusion of non-autologous plasma was +33%, while the haematocrit index was +24%. Two of the cases had extremely large losses

TABLE 1.—Plasma-volume and Haematocrit Changes after Infusion. Index of Expansion (100% = predicted full expansion)

	No. of Cases	Index	+100% +149%	+50% +99%	0 +49%	-1% -50%	-51% -100%	-101% -350%	No Data	Mean Index
Non-autologous	19	{ P.V. Hct.	2 2	7 8	4 3	1 1	0 1	2 2	3 2	+33% +24%
Autologous	14	{ P.V. Hct.	3 6	10 6	1 1	0 0	0 0	0 0	— 1	+80% +85%
Non-autologous with chlorpheniramine	9	{ P.V. Hct.	2 1	3 5	4 3	0 0	0 0	0 0	— —	+63% +56%
Non-autologous with prednisolone	8	{ P.V. Hct.	0 0	3 5	3 3	2 0	0 0	0 0	— —	+37% +50%
Non-autologous with prednisolone and chlorpheniramine	6	{ P.V. Hct.	0 0	1 0	4 5	1 1	0 0	0 0	— —	+37% +17%
Non-autologous with adrenaline	8	{ P.V. Hct.	4 5	4 2	0 1	0 0	0 0	0 0	— —	+106% +109%

See text for details. * Number of subjects. P.V. = Plasma volume. Hct. = Haematocrit.

of plasma. In one the expansion was 1,500 ml. less than anticipated and in the other 989 ml. less. These two results weighted the mean rather heavily, but even if they are excluded the mean plasma-volume index was only +59% and the haematocrit index +61%. This contrasted with the autologous group, in which a mean plasma-volume index of +80% and haematocrit index of +85% were found. These results and those of the treatment groups are described in detail in Table I. Of the treatment groups, the most striking change was found with adrenaline, the plasma-volume index increasing to +106% and the haematocrit index to +109%. Chlorpheniramine by itself may have caused a marginal improvement, but no significant change was found in the other two treatment groups. The five individuals who served as controls and who received only saline or citrate and saline had increases in plasma volume ranging from 70 to 171 ml., with a mean gain of 116 ml.

The retention of the plasma protein infused was assessed by an index of protein retention computed in a manner analogous to the volume indices. The results obtained are shown in Table II, in which the changes in plasma-protein concentration are also given.

In the non-autologous group the mean index of protein retention was +53% (if the two cases showing massive protein losses are excluded the index rises to +82%). On the other hand, for autologous plasma it was +71%. It can be seen that little change of the index of protein retention accompanies the larger differences of volume retention between the autologous and non-autologous groups. This dissimilarity is reflected in the more marked rise of plasma-protein concentration in the non-autologous series, presumably a consequence of extravascular loss of transfused fluid without a corresponding loss of transfused protein. The only treatment apparently producing a change in the index of protein retention was adrenaline, which raised the index to 109%—that is, to well above the value found with autologous plasma.

Both cutaneous and systemic reactions were encountered during these studies. The cutaneous reactions took the form of a characteristic urticarial weal and flare. In some cases only one or two lesions were noted, while in others

extensive and confluent lesions covered a large portion of the body. These lesions generally appeared by the end of the infusion, or within 30 minutes thereafter. The most common systemic reaction was headache with chills and fever. However, in a number of instances nausea, weakness, faintness, nasal stuffiness, and fullness of the head were also encountered. In one individual severe joint pain occurred several hours after completion of the infusion. Another had urinary urgency and diarrhoea. For purposes of comparison cutaneous reactions were graded as + if only a few scattered lesions were present, or ++ if there was more generalized involvement. Systemic lesions were graded + if the reaction was restricted to headache, chills or fever. If other symptoms were present in addition the reaction was graded ++. These results are reported in Table III. Of the 19 subjects in the untreated non-autologous group, 12 had cutaneous reactions and six systemic reactions. None of those receiving autologous plasma had cutaneous or system reactions. No change in the frequency of reactions was seen with adrenaline or chlorpheniramine. In the prednisolone group cutaneous reactions were common but no systemic reactions were encountered. However, in one subject who had received both chlorpheniramine and prednisolone a severe systemic reaction occurred. It seems fortuitous, therefore, that no systemic reactions were encountered in the prednisolone group.

In general, a good correlation existed between the extent of the reactions and a poor expansion of plasma volume. This has been described previously (Hutchison *et al.*, 1960).

Discussion

It was previously reported that there is a great difference in the response to non-autologous plasma transfusions as compared with autologous (Hutchison *et al.*, 1960); the present series extends and confirms this observation. When autologous plasma was infused no cutaneous or systemic reaction occurred, and the retention of the infused plasma was nearly complete. This was not the case with non-autologous infusions, in which reactions were common and sometimes severe and in which a smaller volume of the infused plasma was retained within the circulation.

TABLE II.—Plasma-protein Changes after Infusion

	No. of Cases	Index of Protein Retention (100% = Predicted Retention)								Change in Plasma-protein Concentration (g./100 ml.)				
		+100 +149	+50 +99	0 +49	-50 -100	-51 -100	-101 -200	No Data	Mean Index	+0.50 +0.99	0 +0.49	-0.01 -0.50	No Data	Mean Change
Non-autologous ..	19	3*	9	1	1	0	2	3	+53%	4*	11	2	2	+0.31
Autologous ..	14	2	7	4	0	0	0	1	+71%	1	7	5	1	+0.11
Non-autologous with chlorpheniramine ..	9	2	5	2	0	0	0	—	+71%	1	4	4	—	+0.14
Non-autologous with prednisolone ..	8	1	7	0	0	0	0	—	+85%	4	4	0	—	+0.53
Non-autologous with chlorpheniramine and prednisolone ..	6	0	6	0	0	0	0	—	+66%	4	2	0	—	+0.56
Non-autologous with adrenaline ..	8	5	3	0	0	0	0	—	+109%	1	6	1	0	+0.23

See text for details. * Number of subjects.

TABLE III.—Reactions

Degree of Reaction	Score	Non-autologous		Autologous		Non-autologous with Chlorpheniramine		Non-autologous with Prednisolone		Non-autologous with Chlorpheniramine and Prednisolone		Non-autologous with Adrenaline	
		Cut.	Syst.	Cut.	Syst.	Cut.	Syst.	Cut.	Syst.	Cut.	Syst.	Cut.	Syst.
++	2	6*	3	0	0	2	1	3	0	0	1	2	0
+	1	6	3	0	0	4	2	4	0	3	0	3	3
0	0	7	13	14	14	3	6	1	8	3	5	3	5
Mean score	—	0.95	0.47	0	0	0.94	0.49	1.25	0	0.50	0.33	0.88	0.38

* Number of subjects. See text for details. Figures in parentheses are number of cases.

The reason for the difference in response to autologous and non-autologous plasma has been discussed previously (Hutchison *et al.*, 1960). Isoagglutinins clearly cannot be responsible, since only typed plasma was given; nor are reactions to immune red-cell antibodies probable, as none were detected by cross-matching, neither had any of the recipients received previous transfusions. Furthermore, it is improbable that the reactions could be related to the infusion of red cells or lytic products, as the plasma was virtually free of red cells and no gross evidence of haemolysis was present. Likewise, although it is known that leucocytes may produce reactions in sensitized individuals (Brittingham and Chaplin, 1957; Payne and Rolfs, 1960), it is not known that they can produce reactions in non-sensitized individuals, and, in any case, so few leucocytes were present in the infused plasma that they could not possibly account for reactions of the magnitude found.

Platelet antibodies have been detected in a wide variety of diseases as well as in response to repeated transfusions and to some drugs (Harrington and Arimura, 1961). However, naturally occurring iso-antibodies appear to be very uncommon, and it is exceedingly unlikely that they could account for the reactions that were detected in over half of the subjects receiving non-autologous infusions. It must be admitted, however, that the considerable number of platelets in the infused plasma may leave a residual doubt about whether they can be entirely excluded from involvement in the reactions, but in similar experiments in the dog comparable reactions to non-autologous plasma transfusions have been found (Bliss *et al.*, 1959) even though the administered plasma had been Seitz-filtered to ensure that all cells had been removed. In this case we can exclude the participation of whole platelets in the reaction, although one cannot exclude the presence of soluble products of platelet breakdown. Before the use of disposable transfusion equipment, reactions to pyrogens from unclean equipment were often implicated. In the present study only disposable equipment was used, and, besides, such arguments cannot explain the distinction between autologous and non-autologous infusions.

It has been suggested that reactions might be due to the passive transfer of skin-sensitizing antibodies of the atopic type or to the transfer of allergens to which the recipient is sensitive. While this may be an occasional reason for reactions, it could not explain the high frequency of reactions encountered, many of them in individuals with no history of allergies. It seems more probable that there is a considerable degree of specificity among plasma, perhaps residing mainly in the gamma-globulin fraction. Recent work by Fudenberg and Kunkel (1961) has shown the presence of numerous gamma-globulin types which can react with the sera of other individuals. The number of types needed to explain the non-autologous reactions appears to be very high in view of the finding by Bliss, Stewart, and Fuller (1958) that reactions still occur even between highly inbred dogs of pure strain. The unusual nature of non-autologous reactions is evident in that they are immediate, and occur in a relatively high proportion of the population in good health and without previous sensitization.

Drug Treatment

The poor retention of infused plasma and the local and systemic reactions appear to be mediated, at least in part, by release of endogenous histamine. In the dog it has been shown that histamine is released in the skin when a triple response is induced by non-autologous plasma (Bliss and Walker, 1959) and also that a brisk secretion of gastric

acid occurs when non-autologous plasma is infused (Bliss *et al.*, 1959). The systemic symptoms encountered in man are characteristic of histamine-type reactions. This suggested that antihistamines might have some value in preventing reactions, although it is known that antihistamines are much less effective in countering the effects of endogenously released histamine than of injected histamine. Bliss *et al.* (1959) tested the effects of mepyramine in a dose of 5 mg./kg. in the dog and were able to prevent the occurrence of urticaria and to improve the plasma-volume expansion considerably, although this still did not reach the levels found with autologous plasma. This dose was the maximum tolerated, and produced somnolence and locomotor disturbance.

In the present study chlorpheniramine (10 mg. intravenously) was chosen because of its wide clinical usage and the general lack of side-effects at this dosage. It is possible that the plasma-volume expansion was slightly improved but not nearly to the extent found in dogs, and, further, no decrease in the incidence of reactions was found. It is possible that a larger dose might have been effective, but the incidence of side-effects makes this an impractical measure. It is also possible that other antihistamines in tolerated doses might have a more useful effect. Antihistamines have been used empirically for a number of years with the aim of preventing or cutting short blood-transfusion reactions (Seldon, 1956). The present results suggest that these drugs are not likely to be useful in reducing those reactions due to non-autologous factors whatever value they may have in the transfusion reactions of other origin.

Adrenal steroids of the cortisone group have been successful in the treatment of a wide range of allergic disorders although the mechanism of their action remains quite obscure. They have been reported by a number of authors to be useful in treating and preventing severe or recurrent transfusion reactions. Offenkrantz, Blaustein, and Babcock (1960) have found that intravenous prednisolone in the dose of 50–100 mg. given immediately before or during a transfusion was completely successful in preventing reactions. In the present study the same dose of prednisolone did not improve the plasma-volume expansion, nor did it in any way reduce the incidence or severity of skin reactions. Although no systemic reactions were encountered in the group treated with prednisolone alone, a particularly severe one occurred in a subject receiving both chlorpheniramine and prednisolone. The relatively small group studied with prednisolone makes it unwise to conclude that this drug necessarily has a significant effect in the incidence of systemic reactions. It must be emphasized again that the lack of effectiveness of prednisolone in countering the non-autologous reactions does not mean that this drug may not be valuable in dealing with other types of transfusion reactions.

Adrenaline and related drugs represent a third group that have found use in the treatment of allergic phenomena, particularly asthma, urticaria, and angio-oedema. In the present study a rather modest dose (0.3 mg. subcutaneously) was used to obviate significant symptoms due to adrenaline itself. This dose did not modify the incidence of cutaneous or systemic reactions but it did produce a remarkable improvement in the degree of plasma-volume expansion, which in fact even exceeded that found with autologous plasma. The possibility existed that the improvement in expansion was due to an increase in plasma volume produced by adrenaline which had no direct relation with the infusion of plasma. Ebert and Stead (1941) and Kaltreider, Meneely, and Allen (1942) found that after

subcutaneous injection of adrenaline in man the plasma volume fell and the haematocrit increased. We have studied the effect of adrenaline without subsequent plasma infusion in four individuals. There was a mean increase of +60 ml. in plasma volume and a fall of 1.02% in the haematocrit index. This increase in plasma volume is too small to account for the marked improvement in the response to autologous plasma transfusions. It is more likely that the changes of the small blood-vessels produced by adrenaline modify the handling of added plasma after transfusion. Recent work by Folkow, Johansson, and Mellander (1961) has shown that the often puzzling effect of adrenaline on the peripheral circulation can be explained on the basis of a differential effect on resistance and capacitance vessels.

Among the non-autologous transfusion results a proportion of subjects seem to retain the infused plasma as well as autologous plasma and in addition showed neither cutaneous nor systemic reactions; at the other extreme were individuals who suffered severe cutaneous and systemic reactions and profound losses of fluid from the circulation. It might be thought that the first group represents individuals either lacking the ability to respond to non-autologous plasma or that the non-autologous plasma in these cases did not contain the reaction-provoking factor. However, it has been shown by skin-testing that 80% of individuals will respond to plasma taken from a random donor (Freedman *et al.*, 1960). In dogs, Bliss *et al.* (1958) did not find a single case in which an animal failed to respond to the local injection of non-autologous plasma into the skin. These considerations make it more likely that the difference between the subjects reacting adversely to transfusions of non-autologous plasma and those not reacting is not an absolute one, but may depend more on the concentration of non-autologous factor in the donor plasma and in individual variations in sensitivity of the recipients.

These conclusions are important because in the present series a rather large volume of plasma has been administered rapidly; it is probable that a number of the subjects reacting to non-autologous plasma might have been free of reactions if a smaller volume had been infused or the infusion had extended over a longer period of time. Such large transfusions of plasma are not commonly given so rapidly except in haemorrhage or in the treatment of shock. Elias, Gurd, Hampson, and Burgen (1963) have shown that in hypovolaemic dogs the non-autologous reaction is suppressed. It seems likely, therefore, that in normal transfusion practice the incidence of non-autologous reactions is lower, because when the blood volume is normal the volume of plasma transfused is small and is usually administered slowly, whereas large and rapid transfusions are usually restricted to patients with oligæmia, in which some protective mechanism reduces the incidence of reactions. These considerations account for the lower incidence of allergic reactions reported by various investigators (Offenkrantz *et al.*, 1960), although we suspect that closer observation might uncover many reactions that would previously have been missed. One of the advantages of studying normal individuals is that reactions are readily detected and are not confused with or attributed to coexistent disease processes.

Summary

Normal human volunteers have received infusions of plasma from single donors. A high incidence of cutaneous and systemic reactions was seen when the plasma was derived from another individual, while no reactions were

found on retransfusion of an individual's own plasma. The plasma-volume expansion, as measured by labelled albumin and by haematocrit changes, was much below that expected when non-autologous plasma was used, but near to the predicted value with autologous plasma.

Within the conditions of this experimental study chlorpheniramine 10 mg. intravenously, prednisolone 100 mg. intravenously, or the two together fail to lower the incidence of reactions. Also, no significant improvement in plasma expansion was noted. Subcutaneous adrenaline in a dose of 0.3 mg. did not produce a clinically significant diminution of reactions, although a marked improvement in plasma retention was noted.

Whether the drugs tested are of clinically significant value in the prophylaxis and treatment of reactions due to routine whole-blood transfusions cannot be settled on the basis of these studies because such transfusions may produce reactions due to minor undetected erythrocyte incompatibilities, leucocyte and platelet antibodies. Leucocyte and platelet antibodies are particularly important in the oft-transfused individual. However, if one accepts the premise that an unknown plasma factor is responsible for a considerable proportion of clinical transfusion reactions, the present study would make it appear unlikely that chlorpheniramine, prednisolone, or adrenaline in the dose commonly used will greatly alleviate reactions to whole blood.

This project has been supported by grants from the Defence Research Board of Canada and the Schering Corporation, Montreal. Mr. Robert May has given invaluable technical assistance. Chlorpheniramine ("chlor-tripolon") and prednisolone ("metacortelone") were kindly provided by Dr. W. K. MacDonald, of the Schering Corporation, Montreal; and sodium anoxynaphthionate ("coomassie blue") by Dr. Leighton Smith, of Ayerst, McKenna and Harrison Limited, Montreal.

REFERENCES

- Bliss, J. Q., Johns, D. G., and Burgen, A. S. V. (1959). *Circulat. Res.*, **7**, 79.
 ———, Stewart, P. B., and Fuller, J. L. (1958). *Brit. J. exp. Path.*, **39**, 30.
 ———, and Walker, J. D. (1959). *Canad. J. Biochem.*, **37**, 371.
 Brittingham, T. E., and Chaplin, H., jun. (1957). *J. Amer. med. Ass.*, **165**, 819.
 Ebert, R. V., and Stead, E. A., jun. (1941). *Amer. J. med. Sci.*, **201**, 655.
 Elias, G. L., Gurd, F. N., Hampson, L. G., and Burgen, A. S. V. (1963). *Circulat. Res.* In press.
 Folkow, B., Johansson, B., and Mellander, S. (1961). *Acta physiol. scand.*, **53**, 99.
 Freedman, S. O., Bliss, J. Q., Hutchison, J. L., and Burgen, A. S. V. (1960). *J. Allergy*, **31**, 134.
 Fudenberg, H. H., and Kunkel, H. G. (1961). *J. exp. Med.*, **114**, 257.
 Gornall, A. G., Bardawill, C. J., and David, M. M. (1949). *J. biol. Chem.*, **177**, 751.
 Harrington, W. J., and Arimura, G. (1961). *Blood Platelets*, p. 659. Little, Brown, Boston.
 Hawk, P. B., Oser, B. L., and Summerson, W. H. (1947). *Practical Physiological Chemistry*, 12th ed., p. 814. Blakiston, Toronto.
 Hutchison, J. L., Freedman, S. O., Richards, B. A., and Burgen, A. S. V. (1960). *J. Lab. clin. Med.*, **56**, 734.
 Kaltreider, N. L., Meneely, G. R., and Allen, J. R. (1942). *J. clin. Invest.*, **21**, 339.
 Offenkrantz, F. M., Blaustein, A., and Babcock, G., jun. (1960). *Anesth. Analg. Curr. Res.*, **39**, 390.
 Payne, R., and Rolfs, M. R. (1960). *Amer. J. Med.*, **29**, 449.
 Remington, J. W., and Baker, C. H. (1959). *Amer. J. Physiol.*, **197**, 193.
 Seldon, T. H. (1956). *Med. Clin. N. Amer.*, **40**, 1217.

A new British Standard for surgical dressing scissors has recently been prepared by the British Standards Institution at the request of the Ministry of Health. Scissors complying with this new specification will be marked with the name or trademark of the manufacturer or supplier and with the number B.S. 3646. Copies of B.S. 3646 may be obtained from the B.S.I. Sales Branch, 2 Park Street, London W.1 (price 5s. each; postage extra to non-subscribers).