

REVIEW ARTICLE

Production of human albumin solution: a continually developing colloid

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Albumin has a long history of clinical use in colloid replacement therapy dating back over 50 yr. It is currently used in greater volume than any other biopharmaceutical solution that is available, and worldwide manufacturing is of the order of 100s of tonnes annually. However, as with many therapies, the clinical use of albumin has often had its critics. Some of these⁶ have concluded that albumin therapy may carry an increased risk of death, relative to crystalloid solutions, in some critical care situations.

When assessing the place for albumin in critical care therapy, the nature of the product being infused should be considered. Less pure preparations, such as plasma protein fraction, have been replaced by purer preparations with lower associated adverse reactions. Many of the earlier studies of albumin use were conducted in the 1970s and 1980s. Since that time, human albumin solution has been refined by developments and improvements to manufacturing processes, so that modern albumin is far removed from the solutions infused in earlier decades.

Albumin solution for therapy should be as near as possible to the native protein found in the plasma, given the need for purification and viral assurance. This review outlines key changes in the production of albumin for clinical use, focusing in particular on the substantial improvements in purity and tolerability that have been achieved in the last 20 yr. It also provides an up-to-date profile of a continually improving product.

Properties and clinical use of albumin

Albumin is a highly water-soluble protein (molecular weight 66 000 Da) with considerable structural stability. It is an important component of plasma, making up 60% of the total protein. At normal physiological concentrations of plasma proteins, albumin contributes 80% of the colloidal

osmotic (oncotic) pressure of the plasma, and its function as a carrier for hormones, enzymes, fatty acids, metal ions and medicinal products is much reported.³²

Human albumin has been used as a therapeutic agent for over 50 yr. Its key indication is the restoration and maintenance of circulating blood volume in situations such as trauma, surgery and blood loss, burns management and plasma exchange.²⁶ The ideal product for this purpose would be monomeric albumin of very high purity, free from contamination with other plasma proteins, endotoxins, metal ions, albumin aggregates and prekallikrein activator (PKA), as such impurities appear to influence the tolerability of albumin infusion.¹¹

Experience with albumin products of the older generation suggests that high endotoxin concentrations may be implicated in febrile reactions, while high concentrations of PKA can cause hypotension.² Aluminium concentrations need to be kept very low to avoid accumulation in neonates and patients with impaired renal function.²³ Contamination with trace proteins may result in undesirable aggregation when albumin is being pasteurized.¹⁸ The goal for manufacturers in recent decades has therefore been to minimize or eliminate such impurities.

Virus safety

The safety record of albumin products with respect to virus transmission over the past 50 yr has been excellent. Pasteurization at 60°C for 10 h was introduced in the 1940s^{13 14} and has been shown to inactivate a range of lipid-enveloped and non-enveloped viruses,²⁷ including hepatitis A, B and C and HIV. The inclusion of stabilizers ensures that the albumin solution is not denatured on heating. Pasteurization in the final container after filling removes the potential for late contamination.

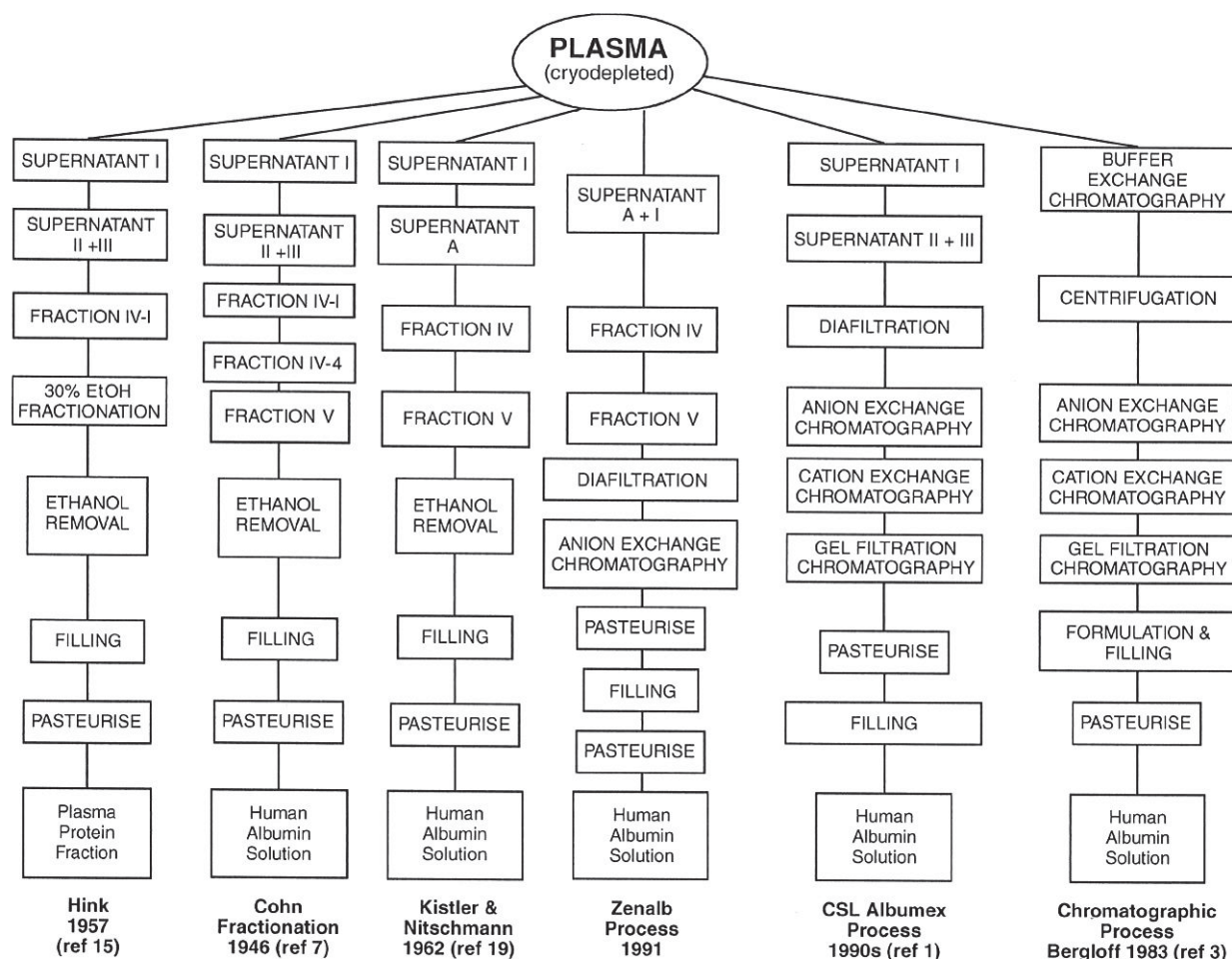


Fig 1 Schematic flow diagram comparing traditional methods for the preparation of plasma protein fraction and human albumin solution^{1 7 15 19} with modern processes which incorporate chromatography (Zenalb® BPL and Albumex CSL) and those which are wholly chromatographic (Bergloff). Details of the processes are given in the references cited beneath each process.

Methods of preparation

Albumin is now predominantly derived from human plasma, although both time-expired blood and, in some countries, placental material have been used as sources in the past. The rise in the use of packed red cells rather than whole blood transfusions means that the amount of albumin derived from time-expired blood has declined markedly, while the use of placental material was abandoned because of difficulties in ensuring donor traceability, particularly in terms of viral status.

Albumin products fall into two categories. The plasma protein fraction (PPF)¹⁵ is broadly similar to human albumin solution (HAS) and is derived (Fig. 1) by a higher-yielding process but has a lower minimum albumin purity (>85% for PPF *vs* ≥95% for HAS). Its main disadvantage is the presence of hypotensive contaminants, particularly PKA.^{20 30} Consequently, and with greater supplies of plasma becoming available, PPF has fallen in popularity and is no longer listed in the British

Pharmacopoeia. Some PPF products are still available outside the UK.

The traditional method for the purification of albumin for therapeutic use has been cold ethanol fractionation, as described by Cohn and colleagues in 1946⁷ and its later variants. Since then, some pharmaceutical providers have chosen to supplement this process with additional purification steps¹ while others have moved towards an alternative, predominantly chromatographic separation method.⁴⁰ A schematic representation of the different processes is shown in Fig. 1.

Cold ethanol fractionation

Albumin has some unique properties that allow relatively simple and effective purification by precipitation methods. It has the highest solubility and the lowest isoelectric point (the pH at which it bears no net charge) of the major plasma proteins. Adjustments to pH, temperature, ionic strength,

Table 1 Comparison of changes in some of the pharmacopoeial requirements for human albumin over the period 1988–1999. Information derived from the relevant year's pharmacopoeia. IEP = immunoelectrophoresis

Criterion	BP 1988 Plasma protein fraction	BP 1988 Human albumin solution	BP 1993 Human albumin solution	BP 1999 Human albumin solution	EP 1997 Human albumin solution
Source material	Plasma/serum	Plasma/serum/placenta	No change	Plasma	No change
Albumin purity	≥85%	≥95%	No change	No change	No change
Albumin concentration	4–5%	15–25%	No change	No change	No change
Stabilizer	Octanoate	Octanoate	No change	3.5–5%	No change
Sterility	Octanoate	Octanoate	Octanoate	Octanoate and/or <i>N</i> -acetyl tryptophan	Octanoate and/or <i>N</i> -acetyl tryptophan
Antimicrobial agent	Passes test	No change	No change	No change	No change
Pasteurization	None	No change	No change	No change	No change
Sterility check 30–32°C	10 h at 60°C	10 h 60 ± 0.5°C	No change	No change	≥10 h at 60 ± 0.5°C
Sterility check 20–25°C	Incubate ≥14 days	No change	No change	No change	No change
Appearance	Incubate ≥4 weeks	No change	No change	No change	No change
	Clear pale yellow liquid	Almost colourless or amber	No change	Almost colourless, yellow or green	No change
Human identity (using specific antisera)	Precipitation/IEP. Electrophoretic profile distinct from HAS	Precipitation/IEP. Electrophoretic profile distinct from PPF	Precipitation/IEP. Electrophoretic profile distinct from PPF	Precipitation/IEP	Precipitation/IEP
pH	6.7–7.3	No change	No change	No change	No change
Alkaline phosphatase activity (u g ⁻¹)	≤0.1	No change	No change	Not required	No change
Haem content:	≤0.15	No change	No change	No change	No change
absorbance at 403 nm, 1% solution					
Prekallikrein activator	Not defined	No change	No change	≤35 iu ml ⁻¹	No change
Aggregates	Unretained peak ≤10% of total nitrogen content run on dextran gel	Unretained peak ≤5% of total nitrogen content run on dextran gel	No change	Aggregate peak area/2 ≤5% (HPLC)	No change
Potassium (μmol g ⁻¹)	≤50	No change	No change	No change	No change
Sodium (mmol litre ⁻¹)	≤160	No change	No change	No change	No change
Abnormal toxicity	Pass	No change	No change	Not required	No change
Storage in dark	5 years 2–8°C, 3 years ≤25°C	No change	No change	No timescales given	No change
Aluminium (μmol litre ⁻¹)	Not defined	No change	No change	No change	No change
Indication of suitability for dialysis and in premature infants	Not stated	Not stated	≤200 if for use in premature infants or for dialysis Stated on label	No change	No change
Origin of albumin	Not stated	Stated on label	No change	No change	Not stated
Pyrogenicity	Test in rabbits; dose 3 ml kg ⁻¹ body weight	Test in rabbits; dose 3 ml kg ⁻¹ body weight	Test in rabbits; dose 3 ml kg ⁻¹ body weight	Test in rabbits; dose 10 ml kg ⁻¹ (5% product), 3 ml kg ⁻¹ (20% product)	No change

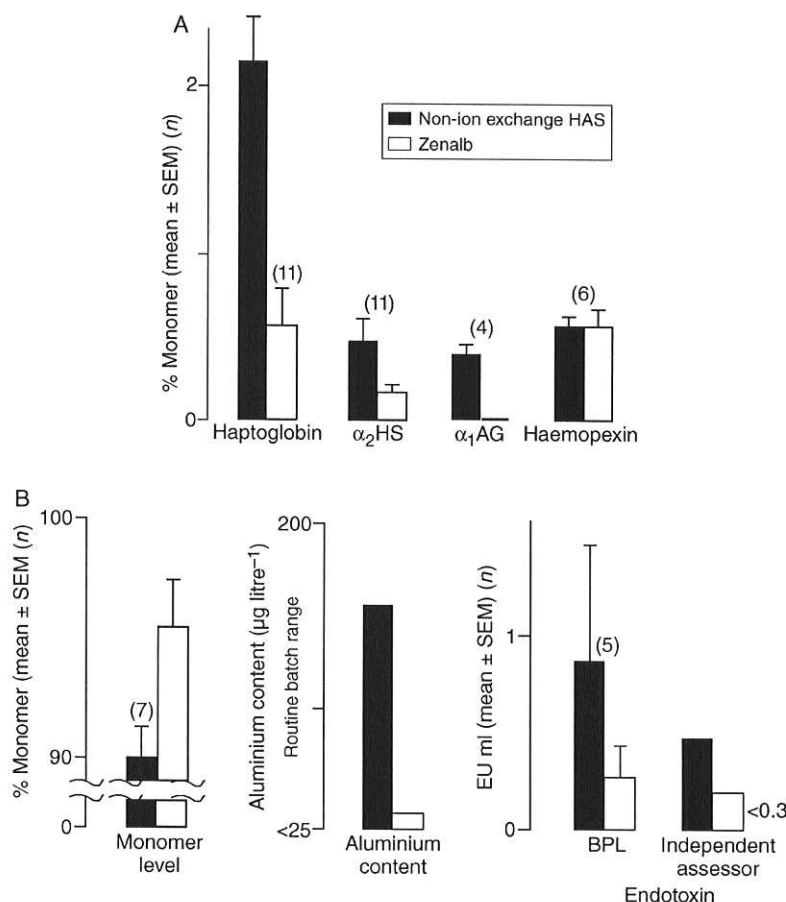


Fig 2 (A) Comparisons of previous BPL human albumin solution and the Zenalb® product. Concentrations of four common plasma protein impurities measured by radial immunodiffusion for the laboratory-scale process. α_2 -HS = α_2 -HS glycoprotein; α_1 -AG = α_1 -acid glycoprotein. (B) Some properties of albumin produced at production/pilot batches for previous BPL human albumin solution and Zenalb®. Monomer content was measured by FPLC (Pharmacia) size exclusion chromatography, aluminium content by atomic absorption spectrometry and endotoxin concentrations by the *Limulus* amoebocyte lysate assay.

ethanol concentration and protein concentration therefore allow the separation of albumin from the other plasma proteins. Seventeen disulphide bonds along the single polypeptide chain confer considerable structural stability, so that under conditions in which other valuable plasma proteins would be totally denatured, albumin is recovered relatively undamaged.

There are two cold ethanol fractionation processes in common use; these are compared in detail elsewhere.²⁸ Many American suppliers have retained the original Cohn process.⁷ The Kistler and Nitschmann process, which uses fewer protein precipitation steps and hence less ethanol, is more cost-effective,¹⁹ and has been favoured by some European fractionators (Fig. 1). The valuable coagulation factors are removed as cryoprecipitate on initial thawing of the plasma before cold ethanol fractionation. With either method, an initial low ethanol precipitation stage removes the fibrinogen from the source plasma. Subsequently, by raising the ethanol concentration to 25% at pH 6.9 for the Cohn method or 19% at pH 5.85 for the Kistler and

Nitschmann method, the immunoglobulins are precipitated while the albumin remains in solution. Albumin is then isolated from the majority of the other plasma contaminants (mainly α and β globulins), which are precipitated by the further addition of ethanol to a final ethanol concentration of 40%. This is carried out in two stages in the Cohn process but as a single step in the Kistler and Nitschmann method. In a final step, the albumin is itself precipitated near its isoelectric point. The precipitate paste (fraction V) can be held frozen before further processing.

Chromatographic purification

An alternative to cold ethanol fractionation is the chromatographic purification of plasma to produce albumin. This method was first described in the early 1980s.^{3 8 40} After clarification, the plasma is buffer-exchanged by either column gel filtration or diafiltration to allow subsequent ion exchange chromatography. There follows one or more

Table 2 Summary of spontaneous adverse reaction reports for human albumin solution (HAS) received by the BPL Medical Department (1993–1997). *Serious adverse reactions include fatal or life-threatening reactions, or cause persistent or significant disability/incapacity, or result in or prolong hospitalization, or lead to congenital anomalies or birth defects. **One infusion estimated as 500 ml of 4.5% HAS or 100 ml of 20% HAS

Severity of adverse reactions	Body system	Human albumin solution 4.5%		Human albumin solution 20%	
		No. of symptoms	No. of patients	No. of symptoms	No. of patients
Non-serious*	Cardiac	9	8	0	0
	Dermatological	2	2	1	1
	Gastrointestinal	2	2	0	0
	General	23	11	1	1
	Musculoskeletal	1	1	0	0
	Neurological	4	3	0	0
	Respiratory	3	3	0	0
	Vascular	8	8	0	0
	Subtotal	52	17	2	1
Serious*	Cardiac	0	0	4	2
	Dermatological	1	1	0	0
	Gastrointestinal	3	2	0	0
	General	10	4	1	1
	Neurological	2	1	1	1
	Respiratory	0	0	7	4
	Vascular	2	2	2	1
	Subtotal	18	5	15	4
	Grand total	70	22	17	5
Total volume of albumin issued (litres)		602 000		133 000	
Approximate number of infusions**		1 204 000		1 330 000	
Total number of reported adverse reactions		70		17	
Incidence of adverse reactions per infusion		1:17 200		1:78 200	

column chromatographic purification steps, then further gel filtration chromatography or buffer exchange.

The appeal of chromatographic processing of plasma over cold ethanol fractionation in principle is its ease of automation, the relatively inexpensive plant required, and the ease of sanitizing and maintaining a Good Manufacturing Practice environment. The process is potentially less damaging to the protein than ethanol precipitation, and the concentration of aggregation resulting from processing is minimized. The yield of albumin is also generally higher by chromatographic methods (80–85% yield at >98% purity) than by cold ethanol precipitation (typically 60–70% yield and a 95% pure product).

Despite these potential advantages, chromatographic albumin purification has not been widely adopted until relatively recently because of the limited availability of the very large chromatographic equipment required to meet demand for the product.

Other methods

A combined method, whereby chromatographic purification steps supplement the cold ethanol fractionation process, has been adopted by a number of manufacturers. Single or multiple column steps can improve product purity by allowing convenient buffer exchange and depleting trace protein contaminants. Several other strategies for the purification of albumin have been evaluated over the past

50 yr but none has been adopted on a large scale. These are discussed more fully elsewhere.²⁸

Pharmacopoeial standards for albumin products

Human albumin is produced at two concentrations. The 4–5% albumin solution is an isotonic solution particularly suitable for fluid replacement in hypovolaemia. The 20–25% albumin is a hypotonic but hyperoncotic solution for the treatment of fluid loss where electrolyte or fluid load is contraindicated. The highly concentrated protein solution provides colloidal pressure while minimizing the additional salts and fluid volume that are infused. These low-salt, high-concentration albumin products are also used to treat patients with poor renal function, to avoid electrolyte disturbances, and in the treatment of neonates. Electrolyte balance can be maintained more accurately by tailoring the use of appropriate crystalloids with the 20% albumin solution.

An examination of the changes to the pharmacopoeial requirements for albumin products over the past decade provides an interesting insight into alterations in processing methodologies and the resulting product improvements. Thus, a review of the requirements of the British Pharmacopoeia (BP) dated 1988, 1993 and 1999 and the European Pharmacopoeia (EP) 1997 (Table 1) shows the move away from allowing placental sources, and the introduction of maximal permitted concentrations for PKA

and aluminium. Improvements in analytical technology are reflected in the use of HPLC (high-performance liquid chromatography) rather than soft gel chromatography for the measurement of aggregates. Screening of plasma pools for hepatitis C was introduced once the causative agent had been identified. Finally, the defined appearance of albumin solutions has been broadened to permit green coloration, as anion exchange-purified albumin generally has a green colour²⁵ resulting from the conversion of bound bilirubin to biliverdin by oxidation during the pasteurization step.

Developments in albumin fractionation

Any review of developments in albumin processing is hampered by the paucity of information; the detailed methods concern confidential industrial processes. For this reason, we will use the development of the albumin purification process at Bio Products Laboratory (BPL; a UK fractionator, which is part of the National Blood Service in England) to illustrate the general changes that have occurred in the industry over the past 20 yr. The albumin produced by BPL has long been of the standard required by the British Pharmacopoeia for human albumin solution, even though until the mid 1980s it was termed 'plasma protein fraction'.²¹

The Kistler and Nitschmann variant of ethanol fractionation¹⁹ was introduced by BPL in 1964 and has remained the basis for production ever since, even though the scale has increased from a few tens of litres to over 6000 litres of plasma per batch. In the early days, the excess water and ethanol present in the albumin after cold ethanol fractionation were removed either by freeze-drying or, from the early 1980s, by thin-layer evaporative methods.⁴³ However, since 1987 this step has been carried out by the use of diafiltration technology, which is far less likely to result in protein denaturation than the previous methods.

Polishing improves purity

A chromatographic refining or 'polishing' step was also introduced into the BPL process in 1991 to further reduce concentrations of contaminant proteins and occasional high endotoxin concentrations. After diafiltration and adjustment to a suitable pH, the albumin solution is applied to a DEAE-Sepharose Fast Flow chromatography column, where impurities are bound and removed. The albumin, which is unretained, is then formulated, filled and pasteurized to produce the product known as Zenalb®, which has been in use for over 8 yr. The addition of this single anion-exchange chromatographic step produced marked improvements in the quality of the product. The purity of the albumin increased to $\geq 99\%$ and the monomer content to $>95\%$. At the same time, concentrations of endotoxin and aluminium were consistently lowered, as shown in Fig. 2.

Whereas the introduction of a chromatographic polishing step has resulted in a major improvement in the albumin product, several other process changes, instituted over the past 10 yr, have also influenced purity and quality. The addition in 1992 of bulk pasteurization of the albumin before filling (whilst retaining the post-filling pasteurization step) has helped to control PKA concentrations during storage. The treatment of the plasma pool with the diatomaceous filter aid Celite, introduced in 1995, promotes the removal of PKA during the early fractionation process. Also, since 1997, aluminium concentrations have been further reduced by changing the type of glass used for the product container, a change widely adopted by other manufacturers.¹⁷

The net result of these process changes is a chromatographically purified human albumin solution that meets or exceeds the specifications set by regulatory bodies. The albumin remains undamaged during processing, contamination with non-albumin proteins is reduced to negligible concentrations, and the concentrations of PKA, endotoxin and aluminium are well controlled. This increased purity has enabled the shelf-life at room temperature storage to be extended. At the same time, the process for this very high purity albumin delivers a high yield within an acceptable processing time.

Clinical implications

The clinical importance of these product improvements has been demonstrated in the evaluation of patients undergoing therapeutic plasma exchange. In one comparison,⁴⁶ the incidence of product-related adverse reactions (defined as untoward changes in pulse, blood pressure or temperature) was markedly reduced from 1 for every 83 units infused (500 ml, 4.5% albumin) with the old BPL product to 1 for every 374 units infused with Zenalb 4.5. Likewise, in an initial assessment of Celite-treated albumin,⁴ reduced numbers of febrile reactions were observed in comparison with the non-Celite-treated product (0.34 and 2.5%, respectively).

Albumin solution is generally well tolerated, especially in view of the size of the infusion volume. Adverse reactions have been reported in the scientific literature,^{11 34} most notably when albumin has been used in plasma exchange. The tolerability of modern human albumin solution is illustrated by the incidence of spontaneously reported adverse reactions. Although such reporting underestimates the true incidence of adverse events, it provides a useful indication of a product's overall safety profile. Spontaneous reports received by the BPL Medical Department from various indirect sources (such as publications) or directly from individuals using Zenalb® suggest that the reported incidence of adverse reactions may be as low as 1 in 17 200 infusions for 4.5% albumin and 1 in 78 200 infusions for 20% albumin. Based on the information received, the adverse reactions were assessed by the BPL Medical

Department in terms of the seriousness of the reaction and the body system (e.g. cardiac, vascular, respiratory, neurological) affected (Table 2). None of the adverse events classified as serious in Table 2 was fatal. This level of incidence compares favourably with the 1 in 6600 incidence of adverse reactions to albumin reported by McClelland in 1990.²⁶

Discussion

This review has concentrated on the methods of preparation and their relevance to the clinical use of albumin. Nevertheless, a number of papers have appeared over recent years which are critical of any significant role for albumin in therapeutic strategies, favouring other colloids or crystalloid solutions.^{24 42 47} However, whereas Tjoeng and colleagues⁴² recommend the use of synthetic colloidal supplements as an alternative to albumin, they do not discuss the adverse reactions which can occur to these alternatives, such as anaphylactoid reactions, problems with disordered coagulation and alterations in blood viscosity,^{5 26 37} or their frequency, which may exceed those for albumin.²⁶

Other workers have tried to critically assess the basis for the use of albumin in a variety of clinical conditions, and have classified albumin usage as being appropriate, unproven or inappropriate.^{5 9 44 45} Whereas usage for certain clinical conditions has fallen, for others (e.g. meningococcal disease) albumin therapy is still the preferred treatment.³¹ Other clinicians are unwilling to move away from the use of albumin in fluid replacement until the case has been proven by thorough clinical trials.^{12 29} A recent study in cirrhotic patients with spontaneous bacterial peritonitis showed that antibiotic plus albumin had a significant benefit on conserving renal function and survival compared with antibiotic alone,³⁹ although whether synthetic plasma expanders would have been equally effective was not studied.

A number of adverse events have been reported to be associated with albumin therapy, including allergic (anaphylactoid) reactions, impairment of renal function, hypotensive reactions, cardiac problems and pulmonary oedema.^{11 26 34} Anaphylactoid reactions to albumin occur relatively infrequently; they are likely to be due to a combination of subtle factors, including the sensitivity of the individual, the rate of infusion, and product characteristics. Problems with renal function and hypotensive reactions are thought to result from the presence of contaminants. Pulmonary oedema, resulting from the leakage of albumin into the extravascular space with its consequent osmotic effect on fluid accumulation, may be a result of inappropriate use. Rather than adhering to strict dosage regimens for albumin therapy, fluid and haemodynamic variables should be monitored carefully and therapy adjusted accordingly. In one report of pulmonary oedema occurring in children with nephrotic syndrome, the problem was assigned to too high an albumin dosage or too rapid

infusion.³⁴ Indeed, the study of Lucas and colleagues,²² who reported the greatest relative risk from albumin therapy, employed an extremely large 'fixed' dose of salt-poor albumin: 150 g during the operation and 150 g day⁻¹ for the first five postoperative days. Margaron and Soni²⁴ have pointed out the error of chasing strict plasma albumin concentrations rather than using the amount of protein required to restore the colloidal osmotic balance. Some practitioners have distinguished, in their acceptance of albumin therapy, between high- and low-concentration preparations.¹⁶ The tragic consequences of the inappropriate dilution of 25% human albumin have also been reported.³³

After the publication of the Cochrane meta-analysis,⁶ the use of albumin in the UK fell markedly.³⁶ Several authors have raised criticisms of the Cochrane meta-analysis itself, highlighting weaknesses in the performance of the review, failure to discriminate between data derived from patients with markedly different clinical conditions, and the grouping of data from trials with different clinical endpoints.^{10 31 35 38} Indeed, Horsey¹⁶ commented that there were only two explanations for the increased risk: that albumin had been given in excessive amounts or that it had become toxic as a result of commercial processing.

Some workers have suggested that the purity of the albumin preparations used may have influenced the results observed in clinical use, highlighting especially the toxicity of metal ions, in particular aluminium, which can be present in the products.^{6 24} The aim of albumin processing is to provide a safe product whose properties mirror as closely as possible those of albumin found in plasma. This review has shown that, far from remaining unchanged over half a century, the process by which albumin is extracted from plasma and purified has undergone continuous improvement. As a result, albumin solutions for clinical use have been improved markedly, particularly in the past 20 yr. Modern processing technology ensures that damaged protein is removed and that concentrations of impurities such as PKA and aluminium are minimized. Such significant changes to the manufacture of human albumin call into question the validity of clinical studies performed over 20 yr ago. When making realistic assessments of the risks and benefits of albumin therapy to patients in intensive care, it is important to base such judgements upon experience with modern-generation products.⁴¹ Some of the adverse reactions observed in the past may have been attributable to impurities that have since been eliminated or minimized by improved manufacturing technology.

It is also important to administer an appropriate dose of albumin, at a suitable rate, with careful monitoring of the patient's cardiovascular and pulmonary status. Although modern albumin solutions are closer than ever to the native substance, as with all therapeutic interventions there are inherent risks. With modern management techniques, such risks from albumin can be minimized and therapeutic gain achieved. Albumin is not just a fluid for hypovolaemia—

harnessing its carrier functions³² is a positive challenge for the future.

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Conflict of interest

The authors are employed by Bio Products Laboratory (BPL), a unit of the National Blood Authority, a special Health Authority within the UK National Health Service. BPL manufactures a range of plasma-derived products, including human albumin solutions under the registered trade names Zenalb 4.5 and Zenalb 20.

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