Letters

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Human albumin administration in critically ill patients

Editorial by McClelland

Evidence needs to be shown in paediatrics

EDITOR—We are concerned that the Cochrane Injuries Group's meta-analysis regarding administration of albumin[1] may alter the practice of resuscitating hypovolaemic hypotensive children, infants, and neonates. Although we are affiliated to the Institute of Child Health, we want to emphasise that this article does not reflect our own clinical practice, and at present we believe that it provides no compelling evidence to change our practice.

We reviewed the 32 articles in the three groups. We identified only one paediatric study (So et al) in the hypovolaemia group, in which 63 preterm infants received albumin for hypotension. In the burns group there is only one paediatric study (n = 70), in which albumin was given to maintain arbitrary serum concentrations (Greenhalgh et al). Finally, in the hypoproteinaemic group there are two studies of 64 neonates that addressed several hypotheses, including whether albumin was detrimental to respiratory status (Greenough et al) and was beneficial in weight gain (Kanarek et al). In a third study (n = 27) that assessed the use of bicarbonate in acidotic neonates only the control groups of 5% dextrose and albumin were compared (Bland et al).

We are now faced with concerns from parents about the "killer fluid," and our junior staff are confused about the appropriate fluid to use for resuscitation of critically ill children. Have we been put into a legally indefensible position by this report from the Cochrane Injuries Group?

We continue to use albumin for several reasons. To produce the same sustained increase in blood pressure as a 20 ml/kg bolus of albumin, up to five times as much volume of crystalloid would have to be given based on their relative oncotic pressures.[2] This increased volume of crystalloid may lead to problems with fluid overload, hyperchloraemia in renal dysfunction, and pulmonary oedema. One leading manufacturer supplies £11.5 million of albumin to British hospitals each year.[3] We must be certain that stopping the use of albumin is not a financially driven decision.

We would be prepared to accept that albumin may be detrimental on the basis of appropriate data. At present we do not think, however, that there is enough evidence for us to stop using albumin for resuscitation in this population. In an attempt to resolve this controversy in a responsible manner we are about to embark on a prospective study to assess the safety of albumin use in children. Would the authors of the meta-analysis be prepared to enrol patients into such a study or would they consider it unethical?

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1 Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998; 317: 225-40. (25 July.)
2 Shoemaker WC. Comparison of the relative effectiveness of whole blood transfusions and various types of fluid therapy in resuscitation. *Crit Care Med* 1976;4:71-8.
3 Mitchell P. Review sparks controversy over human albumin therapy. *Lancet* 1998;352:377.

Critical analysis of original studies has to take place

EDITOR—Members of the Cochrane Injuries Group have written a systematic review of the administration of albumin in the critically ill, the sole inclusion criterion being that trial subjects had to be prospectively randomised to one of two (or more) interventions.[1] Among a group of 20 trials in which albumin was used to treat hypovolaemia, however, there are five trials (totalling 26% of patients) where the controls were simply given no albumin, which implies no intervention at all. In these studies presumably either the control group was left underresuscitated or the intervention group suffered iatrogenic fluid overload. Either scenario raises questions about the ethical conduct of these studies and casts doubt on any conclusions drawn in relation to mortality.

I make the above point in order to show the problems that arise if critical analysis of the original studies is omitted. The list of contributors headed by Roberts seems to lack individuals capable of such analysis. No one in the list has expertise in adult intensive care. This lack of clinical insight was also identified as a problem by respondents to a forerunning article from the same group, a meta-analysis of fluid resuscitation with colloid or crystalloid.[2]

The authors have done more than merely publish a paper of dubious scientific merit—they have actively subverted the peer review process. The Cochrane Injuries Group is reported to have urged the health secretary to take "appropriate steps to protect the public,"[3] six weeks before the *BMJ* had even published the article. It then participated in a classic media circus that will have created anxiety for many patients and confusion for many clinicians. The group has made a mockery of its own call for use of albumin to be confined to the context of a rigorously conducted randomised controlled trial.[1] Such a trial will now be virtually impossible. The process in operation here has had nothing to do with evidence based medicine, and it is unfortunate that the potential of the Cochrane Collaboration is being misused in this way.

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1 Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998;317: 235-40. (25 July.)
2 Schierhout G. Roberts I. Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. *BMJ* 1998;316:961-4.
3 Mills H. 300 die as health chiefs dither. *Observer*, 26 July 1998:1.

Review did not provide recommendations for alternative treatment

EDITOR—The Cochrane Injuries Group's systematic review of the use of albumin in critically ill patients raises important issues.[1] The group concluded that use of albumin was associated with a 6% excess mortality and should be reviewed. On closer analysis the aim of many of the studies included was comparison of haemodynamic variables or effects of albumin in hyperalimentation rather than mortality. The concentration of albumin used varied (2.5-50%). Only one study evaluated use of albumin in cases of sepsis, and no study evaluated it in children. While the authors of the review concluded that risk of death after use of albumin depended on the underlying condition, the suggestion that use of albumin should be halted was incomprehensible on the basis of the available data. We have treated 410 children with meningococcal disease in the past six years. Meningococcal septicaemia causes capillary leakage, together with myocardial dysfunction and multisystem failure.[2] Our patients required fluid resuscitation of 80 ml/kg (range 20-300 ml/kg) during the first 12 hours of admission to restore circulating volume. Most of this was 4.5% albumin. Laboratory and clinical data suggest that 4.5% albumin is the optimal resuscitation fluid currently available for

these patients. Sepsis causes leakage of proteins along with water from plasma. This leak may be precipitated by dysfunction of endothelial cells.[3] The degree of leakage seems to depend on molecular size and charge: small molecules leak more; negatively charged molecules are preferentially retained. As endothelial dysfunction progresses, all molecules leak, which leads to hypovolaemia and oedema.[4] Pulmonary oedema is often present even before fluid resuscitation and develops in about a fifth of children with meningococcal sepsis. The choice of resuscitation fluid for sepsis includes crystalloids and colloids. Crystalloids leak rapidly through damaged endothelium, whereas colloids will, in theory, be preferentially retained. Apart from albumin, the available colloids are manufactured substances. The use of large volumes of these substances in children with sepsis has not been subjected to controlled trials.

Where large volumes of albumin were used in children with meningococcal disease, the case fatality ratio was lower than predicted.[5] Until an alternative fluid has proved to be more effective, 4.5% albumin will continue to be our recommended resuscitation fluid for children with septic shock.

The recommendation that albumin use be halted was based on irrelevant data and has already had effect. Several district general hospitals have now made albumin unavailable. The care of children with septic shock may be compromised by the ongoing confusion generated by this review, which did not suggest any alternative treatment that has been subjected to the controlled trials recommended for albumin.

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1 Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998;317: 235-40. (25 July.)
2 Nadel S, Levin M, Habibi P. Treatment of meningococcal disease in childhood. In: Cartwright K, ed. *Meningococcal disease.* Chichester: John Wiley, 1995:207-43.
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4 Nadel S, Kydd P, Hughes C, Levin M. *Proteinuria in meningococcal infection: a clue to the capillary leak. Proceedings of the British Paediatric Association.* Warwick: British Paediatric Association, 1995.
5 Levin M, Galassini R, De Munter C, Nadel S, Habibi P, Britto J, et al. *Improved survival in children admitted to intensive care with meningococcal disease. Proceedings of the 2nd Annual Meeting of the Royal College of Paediatrics and Child Health.* York: Royal College of Paediatrics and Child Health, 1998.

More research into proper use of albumin is needed

EDITOR—The Cochrane Injuries Group's report shows that there is no evidence from randomised trials to support the use of albumin.[1] The argument in favour of albumin in case of massive loss of blood during extensive surgery, however, is strong. Replacement with red cells and crystalloid or artificial colloids dilutes serum components, albumin among them. Initially the losses will be made up from the tissue pool. When a certain threshold is exceeded, however, serum albumin concentrations drop and the tissue pool gets depleted. The studies show that once this situation has occurred infusion of albumin no longer prevents the slide into multiple organ failure and death.

Experience in the Netherlands Cancer Institute suggests that timely replacement with albumin during extensive surgery can prevent this. Since 1996 we have treated 21 patients with pseudomyxoma peritonei by aggressive cytoreduction and hyperthermic intraperitoneal mitomycin. During these long procedures (mean 12 hours), massive loss of blood and plasma occurs (mean 20 litres). We maintain serum albumin concentration above 35 g/l by infusion of albumin 20% throughout the procedure.

Peripheral or lung oedema was rarely seen. Spontaneous respiration could be resumed directly after operation in all patients. No patient developed multiple organ failure or adult respiratory distress syndrome. Important decreases in albumin bound electrolytes (calcium and magnesium) were observed, necessitating frequent monitoring and correction.

In a subset of patients, radioactively labelled albumin was given one week before the procedure, to label the tissue albumin pool. Tissue samples taken during the procedure showed no depletion of the tissue albumin pool. This seems to show that infusion of albumin can be effective if adequate plasma concentrations of albumin are maintained, depletion of the tissue pool is prevented, and changes in electrolyte concentrationss are promptly corrected. Few of the reviewed studies have used albumin in this way.

We hope that this Cochrane overview will stimulate well designed studies to assess the proper use of albumin and not be the end of research into this potentially powerful drug.

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Albumin has been used in meningococcal disease

EDITOR—We were concerned by the findings of the Cochrane Injuries Group Albumin Reviewers, who suggest the use of human albumin may increase mortality in critically ill patients.[1] Albumin has been one of the main fluids recommended for resuscitating children with meningococcal disease in the United Kingdom.[2 3 4] We have found that its use for this condition was widespread.

During 1992-4 we studied 126 children with meningococcal disease who had been admitted to four Merseyside hospitals. Human albumin was given to 106 (84%) children, including 45 of the 46 with severe disease. Nine of these 106 children had a skin core temperature difference of less than 3°C, which suggested that they were not in shock.

One of us (AW) studied the initial management of 27 children with suspected meningococcal septicaemia in Birmingham during 1997. Fluid boluses were given during the first hour to 25 children. Two children received normal saline boluses, 23 were given 4.5% albumin (median volume 20 ml/kg; range 10-140 ml/kg). Albumin was given to all 18 with prolonged capillary refill (>3 seconds), but volumes of 10-30 ml/kg were also given to seven without poor perfusion.

Our findings suggest that albumin boluses are commonly given in meningococcal septicaemia, even in the absence of shock. Halting such widespread use will require firm evidence. None of the studies in the Cochrane Injuries Group's meta-analysis included children with meningococcal sepsis. More data are therefore needed before evidence based guidelines about the initial fluid for resuscitation of children with meningococcal sepsis can be drawn up. A randomised controlled trial will be required to answer this difficult question, but at present there is little evidence on which to base clinical practice.

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1 Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998;317:235-40. (25 July.)
2 Advanced Paediatric Life Support Group, ed. *Advanced paediatric life support—the practical approach.* 2nd ed. London: BMJ Publishing Group, 1997.
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Validity of review methods must be assessed

EDITOR—I was asked to review the Cochrane Injuries Group's paper for the *BMJ*.[1] I quote from my covering letter: "It should not be published." Altogether 30 randomised studies with population sizes ranging from 12 to 219 (over half had fewer than 30 patients) were assessed, with a total of 1419 patients. No account taken of the purpose, design, or specific end points of the studies. The end point of the review—mortality—was not an end point in most studies, many of which were over less than five days. Most deaths occurred outside the study times. Variables ignored included age, medical conditions, severity of disease, dose of albumin, mode of

administration, and attributable mortality of the states of disease that were treated.

The evolution of fluid management between the 1970s and now was also dismissed. Common factors were randomised controlled trials that compared administration of albumin with no administration or administration of crystalloid, and, of course, the term "critically ill."

The message, presented with the combined weight of Cochrane and the *BMJ*, is that albumin, whether used in neonates or adults, whether for volume replacement or the support of biochemical variables, whether given intraoperatively as a single dose or long term over days or weeks, is potentially hazardous. Practice is already changing. Change, with its potential hazards, is entirely justifiable if the evidence is powerful enough to decree change but it is not. The review is a tribute to an association of key words and modern computer technology, and the results are serendipitous and amount to evidence that is at best circumstantial. The authors talk of totality of available evidence, but is that totality synonymous with adequacy?

Evidence should lead to change, but surely there is a responsibility to ensure that the weight of evidence published by august bodies is adequate to justify that change. Does the responsibility lie with the researcher, the reviewer, or the journal? When does a strongly negative peer review become negative? Surely negative reviews should be acknowledged by the journal, otherwise publication fraudulently implies positive peer review. Finally, are these review methods valid? It is time to define their value because I believe that otherwise such studies will damage the credibility of not only the methods used, which are potentially powerful and useful, but also of the journals that carry them.

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1 Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998;317:235-40. (25 July.)

Paper failed to mention earlier review

Editor—The systematic review by the members of the Cochrane Injuries Group suggests that they were the first to doubt whether albumin is being properly used.[1] An editorial made that point in 1995.[2] Soni wrote that there was no convincing evidence for using albumin either to replace volume or to treat low concentrations of serum albumin, and that the widespread use of albumin has more to do with word association and the treatment of items that are marked on the pathology form with an asterisk than with scientific medical management. He should have been cited as the first reference in the introduction to the Cochrane Injuries Group's review. He is cited at reference 44, as if he supports the physiological basis of the use of albumin, and as an authority for albumin's supposed anticoagulant properties. This is unfair on Soni, and on the people who actually did the work on anticoagulation.

The Cochrane review failed to cite the earlier systematic review on a similar subject which shared a lead author.[3] Salami slicingof research work is frowned on—are systematic reviews to be treated differently?

Finally, it is curious that a 6% excess mortality from albumin is shouted from the rooftops to condemn the clinicians who use it, while in the same issue of the *BMJ* a possible 11% increase in deaths associated with selegeline is dismissed as a small excess risk,[4] and the media take no notice.

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1 Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998;317:235-40. (25 July.)
2 Soni N. Wonderful albumin? *BMJ* 1995;310:887-8.
3 Schierhout G, Roberts I. Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. *BMJ* 1998;316:961-4.
4 Thorogood M, Armstrong B, Nichols T, Hollowell J. Mortality in people taking selegeline: observational study. *BMJ* 1998;317:252-4. (25 July.)

Analysis is superficial and conclusions exaggerated

Editor—In their meta-analysis of the use of human albumin solutions in critically ill patients members of the Cochrane Injuries Group conclude that administration of albumin in patients with hypovolaemia, burns, or hypoalbuminaemia may increase mortality and should not be used outside controlled trials.[1] In his editorial Offringa calls for the use of albumin to be halted until the results of such trials are available.[2]

As the authors themselves admit, their review should be interpreted with caution. It is a summation of predominantly small trials, and the validity of the assumption that preterm neonates, adults after major surgery or trauma, patients in general intensive care, and patients with hypoalbuminaemia constitute a population sufficiently similar to be treated as homogeneous is questionable. It is therefore surprising that the fixed effects model for meta-analysis was preferred, as opposed to the more conservative random effects approach. Making no allowance for the time between giving albumin and subsequent death is also misleading, since many factors other than the initial resuscitation fluid may be relevant to the ultimate outcome of a critically ill patient during a prolonged stay in an intensive care unit and hospital. A further methodological point relates to the decision to exclude 215 patients in studies where there were no deaths, since this exaggerates the detrimental effect of albumin in the analysis overall.

What are the implications if there is some truth in these results? How might administration of albumin be responsible for an increased mortality in critically ill patients? Since the albumin is derived from human blood, any detrimental effect is presumably a result of the amount and manner of administration rather than direct toxicity. Both Offringa and Berger discuss some of the possible mechanisms by which this might occur.[2 3] As a consequence of the current concerns surrounding the use of the pulmonary artery catheter, conventional approaches to fluid resuscitation in critically ill patients are being reassessed. Appropriate end points for administration of fluid may be as important as the type of fluid, particularly as any biologically active substance is likely to be harmful in excess. The Cochrane Injuries Group and Offringa have conducted superficial analyses and produced exaggerated conclusions rather than confronting these issues and admitting the true complexity of the question they have addressed. As a result, an opportunity to provide the detailed and sophisticated insights on which to base future studies has been missed.

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1 Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998;317:235-40. (25 July.)
2 Offringa M. Excess mortality after human albumin administration in critically ill patients. *BMJ* 1998;317:223-4. (25 July.)
3 Berger A. Why albumin may not work. *BMJ* 1998;317:240. (25 July.)

Statisticians not trained in burns care should not evaluate data

Editor—We believe that the paper by the Cochrane Injuries Group shows ignorance and incomprehension on the part of statisticians untrained in burns care.[1] Statistics are only as good as the data fed into them, and the data are inadequate and misinterpreted. The feeding frenzy in the press that followed this publication is appropriate, but the hurt to relatives of all of those who have died in burns units must be tremendous.

Albumin is given in virtually all of the best units in the world at some stage during resuscitation. If four out of every five paediatric patients with burns to over 95% of the body surface area can survive in the United States with this regimen, then clearly albumin is not the problem. To reduce mortality in Britain we need smaller numbers of more highly specialised, staffed, and equipped units, with the minor burns treated in smaller units. In this way, properly conducted randomised controlled trials can take place, but until then it will be difficult properly to conduct the trials that the Cochrane Group suggest.

The Cochrane Group seems to have reviewed only three, totally dissimilar, papers, with fewer than 150 patients in total. Albumin was hypo-osmotic in one paper and only lung water was measured; in another paper albumin was given in paediatric patients only for low serum concentrations of albumin. The outcome was not morbidity, and the regimens are not standard treatment policies on burns units. The third paper was hardly worth reviewing with respect to the collection of data. I presume that two investigators

independently sought and analysed the data (by telephone calls to authors from over 30 years ago) as mortality was not the end point of the papers. Disagreements were then "resolved by discussion."

I suspect that the Cochrane Group was driven by a need to show that there are cheaper options to albumin. Our unit recognised this, together with the risks of transmissible disease, 18 months ago. We have used a regimen of crystalloid in the first eight hours and albumin thereafter, with crystalloid replacement for insensible loss. We admitted over 400 patients with burns last year and expect about 600 patients to be admitted this year, about 15% of whom will need fluid resuscitation. We cannot confirm the mortality given statistically by the Cochrane Group from this inadequate and dangerous study.

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I would not want an albumin transfusion

Editor—Reactions to the systematic reviews of controlled trials of colloids[1] and albumin[2] by the Cochrane Injuries Group have been fascinating and disturbing. The Committee on Safety of Medicines advised that "patients should be reassured if they have received albumin treatment and recovered from their illness (sic)." The blood transfusion service in Scotland advised that the albumin review provides convincing evidence that infusion of albumin is associated with higher mortality in the circumstances studied in the trials, and warned that other colloids cannot be assumed to be safer. The secretary of state for health, Frank Dobson, deemed the *Observer* newspaper "hysterical" for suggesting that people should worry about evidence implying that albumin might be killing hundreds of people at an annual cost to the NHS of £12 million[3]; yet he said that it was worth investing £70 million a year on leucodepletion, given the theoretical risks of transmitting new variant Creutzfeldt-Jakob disease through blood products.

Some clinicians have described the reviews as inadequate; others, reflecting the lack of evidence that albumin reduces mortality, say that there may well be situations in which albumin or synthetic colloids are the most effective treatment but at the present time they do not know what these are.

What would I want if I or someone I cared for was critically ill? If I survived, I would attempt to sue anyone who had given me an infusion of albumin; and I would not give my informed consent to take part in a randomised trial. I am not aware of any instance in which a systematic review of controlled trials suggesting that a form of care increases mortality has been followed by a controlled trial showing that the intervention concerned actually reduces mortality.

Some clinicians dismissed a systematic review of controlled trials that suggested that prophylactic antiarrhythmic drugs might increase mortality after myocardial infarction. Nearly a decade passed before this adverse effect was confirmed in a large trial, and it has been estimated that continued use of these drugs during the interim resulted in more premature deaths in the United States than the Vietnam war.[4]

The research evidence supporting many elements of critical care is rather thin, when one considers how much funding this sector of the health service needs.[5] The opinions and attitudes reflected in most responses to the albumin and colloid reviews do not inspire confidence that those working in intensive care have yet acknowledged sufficiently the need for reliable evidence about the effects of their care on outcomes that matter to patients.

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1 Schierhout G, Roberts I, Alderson P. Colloids compared to crystalloids in fluid resuscitation of critically ill patients (Cochrane Review). In: *The Cochrane Library*, Issue 3. Oxford: Update Software, 1998. Updated quarterly.
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Modified editorial might have restrained media response

Editor—As has occurred in the past with other sensational stories, doctors using human albumin solution were taken unawares by the press response to Offringa's editorial and the Cochrane Injuries Group's systematic review.[1 2] The advice from the Committee on Safety of Medicines ("Human albumin therapy in critically ill patients," CEM/CMO/98/11), faxed to the profession, did not begin to cascade until 8 am, 24 July—several hours after press coverage was well established. Critically ill patients were given albumin during the media coverage. It is possible that their relatives received the information about the potential hazards before the medical professionals who were treating the patient. Since relatives would know the critical nature of the patient's illness, they might be expected to be even more shaken than is usual when medical mishaps or blunders are brought to light: television and radio sets are abundant in intensive care units and their waiting areas.

The last sentence of the editorial stated that use of human albumin solution "should be halted" (sic). It seems, however, that this was not what the editorial meant, because an author's addendum was published on the same day in the internet edition of the *BMJ* and later as a letter. This was not noticed by many doctors or the press—for example, the *Observer*, published two days later—but modified the published view, suggesting instead that use of human albumin solution should be carefully reviewed but not halted. "Pause for thought" was the new message.

The media handling of this editorial was predictable. The difficulties placed on medical practitioners looking after critically ill patients were considerable. The editorial has probably done little to change the way practitioners will prescribe human albumin solution, because, if they wish to use a colloid (or a crystalloid), one set of problems has merely been replaced by a different one.

The editorial policy may have done more to damage the standing of the *BMJ*, the systematic review process, and the Cochrane Collaboration, than it has advanced the longstanding debate on crystalloid versus colloid resuscitation.

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1 Offringa M. Excess mortality after human albumin administration in critically ill patients. *BMJ* 1998;317:223-4. (25 July.)
2 Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998;317: 235-40. (25 July.)

Some patients may benefit

Editor—The Cochrane Injuries Group concluded that human albumin should not be given to critically ill patients outside rigorously conducted randomised controlled trials, and so did Offringa in his accompanying editorial.[1 2] The Cochrane group has found that giving albumin to critically ill patients with hypovolaemia, burns, or hypoalbuminaemia may increase mortality.

In early 1997 we carried out an audit on the use of human albumin solution (4.5% and 20%) after the use of it had increased in our trust. Our audit showed that 4.5% human albumin solution was used non-specifically in patients with low serum concentrations of albumin in a variety of clinical conditions (including an occasional request for only 500 ml), and 20% human albumin solution was used mainly in patients with chronic liver disease.

During this audit we did a literature search on the indication for the use of human albumin solution.[3–5] We found little conformity and often conflicting advice given on clinical indications in all the literature reviewed. A comparison between four European countries that had agreed national indications for the use of human albumin solution also showed considerable variation, with only two indications in country A but 12 indications in country D. The amount of albumin used per 1000 population also varied widely (109-810 g a year).[5]

Our literature search has shown an ineffective use of human albumin solution as nutritional supplementation; as volume replacement if blood loss is less than 30% of total blood volume; for early treatment (less than 48 hours) of burns and thermal injuries; for albumin replacement in chronic protein loss as a result of enteropathy, cirrhosis, and nephrosis; and in low volume paracentesis. We have established local clinical indications for the use of human albumin solution for

both 4.5% and 20%, taking into consideration the non-indications identified above.

The inappropriate use of this product may be a result of the lack of universal and specific clinical indications. Although albumin administration may be harmful in certain categories of patients, favourable effects in others may have been obscured in the Cochrane analysis, and the use of albumin solution should not be stopped. A concerted effort must be made to identify those patients who may benefit from albumin administration.

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1 Offringa M. Excess mortality after human albumin administration in critically ill patients. *BMJ* 1998;317:223-4. (25 July.)
2 Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systemic review of randomised controlled trials. *BMJ* 1998;317:235-40. (25 July.)
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Authors' response

Editor—On the basis of our systematic review of randomised trials we concluded that "there is no evidence that albumin administration reduces mortality in critically ill patients, and a strong suggestion that it may increase mortality." We read with anticipation the letters in response to our review, but note with concern that none of the correspondents provide any evidence that albumin is beneficial in critically ill patients, in which case our conclusions stand.

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Effects of the Heartbeat Wales programme

Effects of government policies on health behaviour must be studied

Editor—The Heartbeat Wales programme,[1] in common with several other community health promotion projects that aim to reduce the risk of cardiovascular diseases,[2] has reported no net changes in intervention compared with control regions. Tudor-Smith et al report these negative findings in an exemplary way, using a straightforward analysis.[1] Their study concludes that more debate on the most appropriate methods of assessing the effectiveness of such programmes is needed.

The investigators suggest that lack of power and contamination of the control region explain their failure to detect effects of the programme. The study had sufficient power to detect a 5% difference in prevalence between intervention and control regions. If the other community based interventions that were previously reviewed[2] were included in a meta-analysis, the power would increase, but the lack of effect would still be apparent as these other programmes also had essentially negative results.

Contamination of the control region is a possible explanation for the findings. Similar community health promotion programmes conducted from the 1970s to the 1990s have, however, reported consistent findings—no net difference in risk factors or clinical events attributable to the intervention. Moreover, the downward secular trends in mortality from cardiovascular disease in countries with diverging practices in health promotion suggests that these programmes are ineffective.

The notion that alternative study designs can be found that will produce the right answer is fallacious. Quasi-experiments at community level and randomised controlled trials at the workplace, among families, or individual people show a consistency of small changes to the risk factor in effect only and no significant reduction in mortality.[3] Similar interventions applied to populations at high risk (such as people with hypertension or pre-existing cardiovascular disease) are, however, effective.[2] Consequently, health promotion programmes in their current form have only a limited potential for improving the health of the population.

The response to rigorous evaluations that showed little or no added value of health promotion programmes for cardiovascular disease has been that either the design and execution of potentially misleading and methodologically flawed studies,[4] for which exorbitant claims are made,[5] or the methods are not appropriate in this situation.

If more money is to be spent on research into health promotion an understanding of the effects of employment (changing socioeconomic position), food (pricing and availability), and transport (travel concessions) policies on health behaviours and risk factors would be a better investment than an attempt to shift the goalposts.

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Market researchers are not suitable for collecting health data

Editor—Tudor-Smith et al admit that they underestimated the difficulties they would encounter in evaluating their health promotion programme.[1] When they first put their project forward, many of us predicted this result, but the project fitted the political fashions and public relations requirements of that time, in the only place that mattered—the then unelected and unaccountable Welsh Office.

We already had the experience of the multiple risk factor intervention trial in the United States, which prevented 12 coronary deaths at a cost of $115m (£72m) and produced no significant difference between reference and control populations, because it was not possible to isolate controls from media information.[2] The suggestion that contamination of the Yorkshire reference group might be attributed to the Heartbeat Wales programme, more than the many other initiatives pursued at all levels throughout the United Kingdom at that time,[3] is as unconvincing as were the expectations that Heartbeat Wales raised at its launch.

There are two lessons to be learnt from the failed programme. The first is to remain sceptical when governments offer to pay for inquiries into questions for which they are already sure they know the answers. The second is never to do epidemiology on the cheap by farming out data collection to market research companies, instead of developing and maintaining dedicated research teams in house. To apply questionnaires to a random sample of the population and measure blood cholesterol concentrations and arterial pressure in a subset is not demanding.

There were reasons to think that non-respondents would be at highest risk, and high response rates were therefore especially important. Response rates in this study ranged from 61% to 88%, far below the standards established by Cochrane, Elwood, and other researchers in the tradition of South Wales epidemiology.[4] High response rates and good data depend on generally unrecognised, underpaid women (rarely men), who are honest, persistent, patient, and friendly even when they feel they could scream. Market researchers who have just come off detergents and will move on to vacuum cleaners will never be the same.

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Health promotion is a waste of time and money

EDITOR—Tudor-Smith et al admit that the efficacy of the Heartbeat Wales programme in attempting to change behavioural risks associated with cardiovascular disease in Wales could not be concluded definitely.[1] Does this admission hide a more serious conclusion—namely, that most health promotion is expensive and a wasted effort?

The 1990 contract forced disinterested general practitioners to collect meaningless data and to hold health promotion clinics. Only worried well patients attended—never those who drank, smoked or ate chips and whose habits might endanger their health. The only reason for general practitioners to hold a health promotion clinic was the £45 fee. Any doctor who said publicly that the emperor had no clothes was considered not politically correct. General practitioners were diverted from their main task of treating ever more patients with diminishing resources.

The "self" (sic) promotion units were amazing self publicists, preaching to the converted with humourless, messianic zeal. Patients do not, however, listen to general practitioners or heed health promotion campaigns. They copy the behaviour of soap and pop stars, follow fashions, teen magazines, and the current media scare (until it is superseded by the next one)—and may finally modify their behaviour after the government intervenes by banning advertising or inflating prices. Schools, a key influence on children, have abandoned home economics (teaching hygiene, nutrition, cooking, home care, etc). No wonder fats and convenience food flourish among the groups perceived to be most at risk.

Should this sacred cow now be investigated to determine if most health promotion is cost effective and evidence based? Instead of employing expensively trained staff issuing pamphlets, health promotion units could be replaced by shelves. Patients can then pick up the leaflets themselves.

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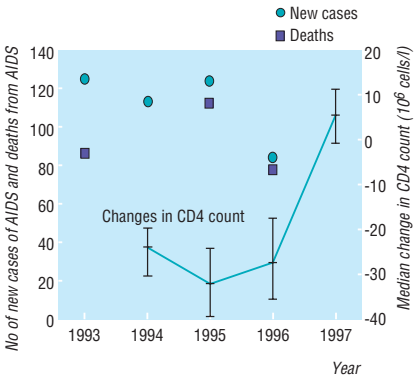
Antiretroviral combination therapy and HIV infection

Such treatment improved CD4 counts in Scottish patients

EDITOR—Egger et al describe the positive impact of antiretroviral combination treatment of people with HIV infection in Switzerland.[1] We analysed data from Scotland's national CD4 lymphocyte monitoring scheme to describe the effect of antiretroviral combination therapies on progression of HIV disease among infected people in Scotland.[2]



No of new cases of AIDS and death from AIDS, with median changes (and 95% confidence intervals) in CD4 cell counts in Scotland, by year

We divided people undergoing monitoring of CD4 counts over two consecutive years in 1993-7 into four cohorts. Altogether 770 patients underwent CD4 cell count monitoring during 1993 and 1994, 731 during 1994 and 1995, 706 during 1995 and 1996, and 708 during 1996 and 1997. Median differences in CD4 cell counts were calculated by comparing the patients' first CD4 cell counts in years one and two. In each cohort the median first CD4 cell count in year one (baseline) was similar, ranging between 247 and 290 $\times$ 10^6 cells/l. For each of the three cohorts spanning 1993-6, the median loss of CD4 lymphocytes over consecutive years ranged between 24 and 32. For the 1996-7 cohort, however, there was a median gain of six CD4 cells (95% confidence interval 0 to 12) (figure).

It is well recognised that progression of HIV disease is associated with the loss of CD4 lymphocytes in the peripheral circulation. The dramatic change from median losses of around 30 cells per year during 1993-6 to a median gain of 6 cells between 1996 and 1997 suggests that giving combination therapy regimens during this time has had a major impact on preventing CD4 count depletion and has possibly contributed to cell gain.

The extent of the change in therapeutic practice in Scotland is difficult to gauge because surveillance data from the Scottish Centre for Infection and Environmental Health on treatment are incomplete. A minimum of 34% of cases in the 1996-7 cohort, however, were taking dual and a further 23% triple regimens at some stage during 1997, compared with 17% and 6% during 1996. Furthermore, most clinicians who manage patients with HIV infection in Scotland indicated that they have been giving combination therapies where possible since the latter part of 1996. In keeping with these findings, the figure shows that the annual numbers of cases of diagnosed AIDS and deaths from AIDS have decreased since 1995.

The local difficulties in funding treatment described in England[3] are equally applicable in Scotland. Despite these difficulties it seems that the benefits of combination therapy that were observed in randomised controlled trials are now being successfully translated into clinical practice.

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Long term follow up of patients under triple therapy is necessary

EDITOR—Egger et al reported reduced progression of and mortality from HIV disease with the new antiretroviral combination therapies in a Swiss HIV cohort during 1988-96.[1] They were not, however, able to assess the contribution of triple therapy with protease inhibitors, which is an important recent development in combination therapy.[2] We attempted to do so in the Aquitaine cohort in France.[3]

At enrolment our cohort (n = 3550) was comparable with the Swiss cohort in age and HIV transmission group after stratification for the inclusion calendar period. There was an increasing proportion of men in the Aquitaine cohort in 1995-6. Clinical stage differed in each inclusion period, the Aquitaine cohort having consistently more patients with C stage disease at inclusion. The follow up per period was 20% longer in our group on average.

We distinguished five groups of antiretroviral treatment: monotherapy alone with a nucleoside analogue; dual therapy alone with two nucleoside analogues; triple therapy alone including one protease inhibitor; monotherapy followed by dual therapy; and monotherapy or dual therapy followed by triple therapy. The few patients who were treated with protease inhibitors but were not having triple therapy were excluded from the analysis.

A multivariate analysis of the risk of progression to a first diagnosis of AIDS or death was performed with a Cox proportional hazards regression model; the five groups were compared with patients who had never been treated, on the basis of intention to treat. The model was adjusted for CD4 cell count, age, sex, disease stage, history of intravenous drug use, use of prophylaxis against opportunistic infections, and period of enrolment (table). Time was measured from the date of first CD4 cell count under 200 $\times$ 10^6 cells/l.

Characteristics and use of antiretroviral treatment for participants enrolled in different time periods at first CD4 cell count <200 cells ($\times 10^6$/l). 1988-96

	1988-90 (n=774)	1991-2 (n=667)	1993-4 (n=474)	1995-6 (n=331)	P value
Mean (SD) age (years)	35.5 (9.9)	36.1 (9.7)	37.0 (10.0)	38.8 (9.6)	0.0001
No (%) male	587 (75.8)	525 (78.7)	368 (77.6)	267 (80.7)	0.306
Transmission group No (%):					
Men who have sex with men	310 (40.0)	259 (38.8)	177 (37.3)	129 (39.0)	0.001
Intravenous drug users	301 (38.9)	259 (38.8)	154 (32.5)	129 (39.0)	
Heterosexual transmission	139 (18.0)	118 (17.7)	113 (23.9)	82 (24.8)	
Other/unknown	24 (3.1)	31 (4.7)	30 (6.3)	26 (7.8)	
Median (90% range) CD4 lymphocyte count ($\times 10^6$/l)	122 (8-193)	128 (8-195)	116 (6-194)	74 (4-190)	0.0001
Clinical stage No (%):					
A	326 (37.3)	273 (33.8)	191 (42.5)	39 (35.1)	0.001
B	170 (1.5)	277 (34.3)	123 (27.4)	26 (23.4)	
C	378 (43.2)	257 (31.9)	135 (30.1)	46 (41.4)	
Mean (SD) follow up (years)	2.7 (2.1)	2.5 (1.6)	1.9 (1.2)	1.1 (0.7)	
Antiretroviral treatment:					
None	88 (11.4)	55 (8.2)	51 (10.8)	27 (8.2)	0.141
Monotherapy	447 (57.7)	364 (54.6)	165 (34.8)	30 (9.0)	0.001
Dual therapy	18 (2.3)	26 (3.9)	32 (6.7)	56 (16.9)	0.001
Triple therapy	13 (1.7)	4 (0.6)	6 (1.3)	44 (13.3)	0.001
Mono+dual therapy	86 (11.1)	98 (14.7)	100 (21.1)	33 (10.0)	0.001
Other+triple therapy	122 (15.8)	120 (18.0)	120 (25.3)	141 (42.6)	0.001

Dual therapy with (relative hazard 0.19 (95% confidence interval 0.14 to 0.25)) or without (0.29 (0.17 to 0.49)) previous antiretroviral treatment and triple therapy with (0.04 (0.03 to 0.06)) or without (0.07 (0.02 to 0.29)) previous antiretroviral treatment were independent protective factors of the risk of death compared with the absence of the antiretroviral treatment. Monotherapy alone did not change the vital prognosis (relative hazard 0.91 (0.75 to 1.1)). Triple therapy was more efficient than dual therapy, with a stronger protective effect regardless of history of previous treatment. Those results were comparable for the progression to AIDS except for monotherapy, which increased the risk of reaching the AIDS stage (relative hazard 2.00 (1.41 to 2.82)).

Like Egger et al's our results confirm the reduction in disease progression and mortality with introduction of antiretroviral combination therapies. We detailed the role of protease inhibitors in this risk reduction, confirming through an observational cohort the results of clinical trials.[2] A possible bias in our findings was that the first patients treated by triple therapy without previous treatment were more likely to be patients with C clinical stage disease. This implies that the protective effect of this new class of drugs in combination therapy is likely to be more important than observed so far. Long term follow up of patients receiving triple therapy such as in the Swiss or Aquitaine cohorts is necessary to confirm the efficacy of protease inhibitors under routine clinical circumstances.

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Technical ability to treat male factor infertility must not overtake academic knowledge

EDITOR—We were alarmed by Kurinczuk et al's findings that infants born after intracytoplasmic sperm injection are twice as likely as other infants to have a major birth defect and nearly 50% more likely to have a minor defect.[1] Our unit has been concerned about the safety of intracytoplasmic sperm injection,[2] and this concern has been voiced by other units. We previously suggested that routine karyotyping should be carried out, at least for the male partner, before intracytoplasmic sperm injection is used. It is not clear whether routine karyotyping was carried out in any of the populations reviewed in Kurinczuk et al's study and if so what the incidence of abnormalities was.

Infertile men have an increased incidence of chromosomal aberrations in their sperm compared with healthy sperm donors.[3 4] Furthermore, in a pilot study carried out in our unit in which fluorescence in situ hybridisation was used, infertile men seem to have a significantly higher incidence of X and Y aberrations in their peripheral leucocytes compared with healthy donors (1.3% (95% confidence interval 1.2% to 1.8%) and 0.25% (0.2% to 0.4%) respectively (P = 0.0006)). These findings suggest the existence of an inherent mitotic instability, similar to that inferred by Hsu et al,[5] that affects cell division in somatic cells of infertile men rather than a problem confined to spermatogenesis alone. Mitotic instability could predispose the chromosomes to non-disjunction. This group of infertile men could have "acquired" mitotic instability from an exogenous or endogenous source.

Rapidly improving new technology is creating exciting possibilities in the management of infertile couples. Intracytoplasmic sperm injection has revolutionised the treatment of male factor infertility, but we must question whether our technical ability in the treatment of male factor infertility has overtaken our academic knowledge of the subject. We should consider further the safety of intracytoplasmic sperm injection. We must be cautious in adapting this new technology without adequately assessing its safety. We need more robust tests to assess the chromosomal make up of the sperm used for intracytoplasmic sperm injection.

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