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A narrow range, medium molecular weight pentastarch reduces structural organ damage in a hyperdynamic porcine model of sepsis

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Abstract. *Objective:* to compare diafiltered 6% pentastarch (Pentafraction – PDP, MW_n 120000 and MW_w 280000) and native pentastarch (Pentaspan – PSP, MW_n 63000 and MW_w 264000 dalton) in a porcine model of faecal peritonitis. *Design:* Randomised prospective study in 12 adolescent pigs. *Interventions:* Prior to infection the study solution was infused to increase Q_t by 25%. Thereafter adjustments in infusion rate were made (up to 1 l/h) in an attempt to maintain Q_t at 25% above baseline values. *Measurements and results:* Animals were sacrificed at 8 h. Tissue was excised from the right lobe of liver and from the right lung and fixed for later electron microscopy and digital morphometric analysis. Patent sinusoidal lumen was significantly greater in group PDP compared to PSP (11.3% ± 2.3% of liver tissue versus 4.8% ± 1.1%, $p < 0.05$) and this was accounted for by a significantly lower proportion of sinusoidal lumen occluded with white cells (2.1% ± 0.6% versus 6.6% ± 1.9%, $p < 0.05$). Similarly, patent capillary represented a significantly higher proportion of lung tissue for group PDP versus PSP (26.2% ± 1.9% versus 18.5% ± 2.7%, $p < 0.05$). The arithmetic mean alveolar capillary barrier thickness was significantly greater in group PSP than in group PDP (4.3 ± 0.3 μm versus 2.5 ± 0.3 μm, $p < 0.01$). *Conclusions:* The molecular weight profile of Pentafraction was associated with less structural organ damage including less tissue oedema and less white cell occlusion.

Key words: Septic shock – Multiple organ dysfunction syndrome – ARDS – Liver damage – Leukostasis – Hydroxyethyl starch – Pentastarch

The sepsis syndrome is often associated with the multiple organ dysfunction syndrome (MODS), the mortality approaching 100% when there is failure of three or more organs [1]. The syndrome is associated with capillary leak and relative hypovolaemia [2]. There is pulmonary and hepatic leukostasis [3] and a reduction in oxygen uptake [4]. It is thought that hepatic and pulmonary damage are due, in part, to the action of activated, degranulating neutrophils [5, 6] releasing lysosomal enzymes and superoxide radicals. In addition, much emphasis has been placed on the role of cardiovascular dysfunction and an inability to maintain adequate tissue oxygen utilisation in the pathogenesis of MODS. This has led to recommendations to increase cardiac output (Q_t) and oxygen transport (DO_2) to greater than normal levels in order to ensure adequacy of supply in patients at risk of MODS [7, 8]. It is well established that increased capillary permeability, with the consequent loss of plasma volume [9–12] and myocardial depression [13, 14] are major contributing factors leading to cardiovascular dysfunction. Optimization of the stroke volume of a heart which is failing through sepsis requires a greater than normal blood volume to ensure an optimal preload [15].

Although there is no consensus as to the ideal solution to expand the plasma volume, the use of colloid solutions for fluid resuscitation requires less volume than crystalloid solutions [16], there is less tendency toward fluid overload and oedema formation [17] and resuscitation times are shorter [18]. There is laboratory evidence that the use of medium molecular weight colloids can impede the transport of water and smaller molecular weight proteins through capillary walls in states of capillary leak [19, 20]. We have studied a narrow range, medium molecular weight pentastarch in an adolescent porcine model of sepsis and multiple organ failure. The model was developed in our laboratory to assess the efficacy of therapeutic agents [21]. We previously compared diafiltered pentastarch (Pentafraction) with high molecular weight hetastarch [22]. Less Pentafraction was required to prevent haemoconcentration and there was less histological evidence of pulmonary damage. In the present study 6% Pentafraction (Du Pont Pharmaceuticals, Stevenage, UK–PDP) was compared with the native 6% pentastarch (Pentaspan, Du Pont Pharmaceuticals, Stevenage, UK–PSP) in a porcine model of faecal peritonitis. Hetastarch was not used as the comparative colloid to ensure that any differences found were related to differences in molecular weight profiles and not related to differences

in the degree of substitution of glucose units. We were particuraly interested in the effects of Pentafraction on the structural integrity of the lungs and liver when used to maintain a hyperdynamic circulation. We therefore used the solutions to maintain an increase of Q_t by at least 25% from baseline. The 25% increase was chosen to limit reductions in DO_2 caused by haemodilution.

Materials and methods

The study was authorized by the UK Secretary of State under the provisions of the Animals (Scientific Procedures) Act 1986. Twelve adolescent pigs weighing 26.8±0.5 kg (mean±SEM) were studied. Animals were assigned to fluid maintenance groups (PDP or PSP) according to a randomization code. The physical properties of the study colloids are characterised in Table 1. Animals were fasted overnight but allowed free access to water. Anaesthesia was induced with azaperone 2.0 mg/kg i.m. and metomidate 10 mg/kg i.p. and maintained with 50% oxygen, nitrous oxide and 1–2% halothane throughout the surgical procedure. A 9.0 mm cuffed endotracheal tube was inserted through a tracheostomy and a flow directed thermodilution pulmonary artery catheter (93A-301-7F, American Edwards Laboratories, Santa Ana, Calif.) was inserted via the right femoral vein. Cannulae were inserted into the right external jugular vein and the right femoral artery for sampling and administration of drugs or fluids. A catheter was advanced via the right internal jugular vein to the hepatic vein with ultrasound guidance. This catheter was used for sampling to allow calculation of hepatic oxygen consumption. Fluid maintenance for the surgical procedure was with 500 ml balanced electrolyte (Hartmann's) solution.

A laparotomy was performed and electromagnetic flow probes (SP7515, Spectramed Inc., Oxnard, Calif.) were placed around the portal vein (8.0 mm) and hepatic artery (3.0 mm). After completion of the surgical procedures, the lungs were ventilated with a tidal volume of 12–15 ml/kg adjusted to maintain $PaCO_2$ between 35 and 45 mmHg. Initially FiO_2 was 0.4 but adjustments were made as necessary up to 0.6 to maintain $SaO_2 > 95\%$. Anaesthesia was thereafter maintained with 80–100 mg/kg intravenous α-d-chloralose given when signs of lightening of anaesthesia appeared. The solution was prepared freshly in 0.9% saline at 80 °C and kept at 40 °C.

The mean oxygen consumption (VO_2) was measured by sampling inspired and expired gases with a Deltatrac metabolic monitor (Datex, Helsinki, Finland). Sampling was continuous for 15 min before other measurements. Arterial oxygen saturation and haemoglobin were measured with a co-oximeter (OSM-2, Radiometer, Copenhagen, Denmark). Blood gas and arterial lactate measurements were made (IL 1304, Instrumentation Laboratories Ltd, Warrington, UK and GM7 analyzer, Analox, London, UK). All vascular pressures were referenced to mid thoracic level and measurements were made at end expiration. Cardiac output (Q_t) was measured intermittently by thermodilution, each measurement being made in triplicate. Values lying within 10% of each other were accepted and indexed to body weight.

An infusion of the study colloid solution was started at 1000 ml/h and continued until a 25% increase in Q_t was measured or 1000 ml had been given. After volume loading a caecotomy was performed; 35 ml of caecal content were aspirated and diluted to 50 ml with tap water. After closure of the caecotomy the faeces were spread around the peritoneum to induce peritonitis and the laparotomy closed. After infection fluid infusion rates were adjusted to maintain Q_t at 25% greater than pre-treatment baseline or to a maximum of 1000 ml/h. Blood samples were withdrawn and haemodynamic and oxygen utilization measurements were recorded at baseline (b), pre-infection (x) and every 60 min (t1–t8) for 8 h in surviving animals. Q_t was measured at hourly intervals and more frequently immediately after any adjustment of the fluid infusion rate. After measurements at t8 surviving animals were sacrificed by the injection of pentobarbitone (30 mg/kg i.v.).

Table 1. Physical characteristics of the study solutions

	PSP	PDP
$MW_{number\ average}$	63000	120000 dalton
$MW_{weight\ average}$	264000	280000 dalton
Degree of substitution	0.45	0.45
Osmolality	326	320 mOsm/l

Source – Du Pont Pharmaceuticals, Stevenage, UK

Tissue samples were excised surgically from the liver (right lobe) and right lung, fixed in 3% glutaraldehyde in cacodylate buffer, post-fixed in 1% osmium tetroxide in buffer, dehydrated in ascending concentrations of ethanol and embedded in Spur's resin. Tissue samples were prepared for electron microscopy and digital morphometric analysis. These were coded and randomized by a person unfamiliar with the techniques or conditions of the experiment. Ten consecutive frames from each sample were analysed at a magnification of ×5500.

The relative volume densities of various components of lung and liver tissue were estimated from their relative area densities using a modification of the Delesse principle [23]. An image capture system (Sight Systems, Newbury, UK) linked to an Elonex microcomputer was used to store images captured from the electron microscope. Areas were measured by the technique of pixel counting using a commercial software package (Freelance, Foster Findlay Associates Ltd, Newcastle upon Tyne, UK). The following hepatic areas were measured and related to the area of hepatic tissue studied: total sinusoidal area (including endothelium); luminal red cells; luminal white cells; remaining luminal area and endothelium including Kupffer cells. The following lung tissue areas were measured and related to the area of lung tissue studied (i.e. excluding alveolae): total capillary area and capillary lumen excluding white cells. In addition the arithmetic mean thickness (τ) of the alveolar capillary barrier was estimated by the method of Weibel et al. [24].

Haemodynamic data were compared with a two-factor repeated measures analysis of variance (ANOVA). Post-hoc analysis was by Fisher's protected least significant difference test where inter-group differences were found and the Dunnett test to compare interval data with pre-infection data within groups. An unpaired Student's *t*-test was used to compare inter-group data in the morphometric analysis. All data are presented as mean±SE.

Results

There were differences in the initial responses to the two study solutions in the animal model. The initial fluid infusion (up to 1000 ml) failed to increase Q_t by 25% in 2 animals of group PSP. In the remaining 4 animals of group PSP 10.0±1.1 ml/kg of colloid increased Q_t by 37±4%. In the 6 animals of group PDP a satisfactory increase of Q_t of 40±10% was achieved with 10.7±2.1 ml/kg colloid. The subsequent Q_t responses (indexed to body weight) are summarised in Fig. 1. All animals of group PSP survived for 8 h post-infection whereas 2 animals of group PDP died early (after 3h for one in which Q_t had failed to increase and after 5 h for another despite an initial satisfactory increase in Q_t). The fluid volumes required to maintain Q_t post-infection in the surviving animals were 224±16 ml/kg for group PDP and 247±26 ml/kg for group PSP. This difference was not statistically different. Oxygen transport and tissue respiration are represented in Fig. 2. There were no significant differences between the groups or within groups compared to pre-infection (point x). Although Q_t was generally increased from baseline (point b) it is worth noting that DO_2 was not increased due to haemodilution (haemoglobin fell from 9.8±0.4 [baseline] to

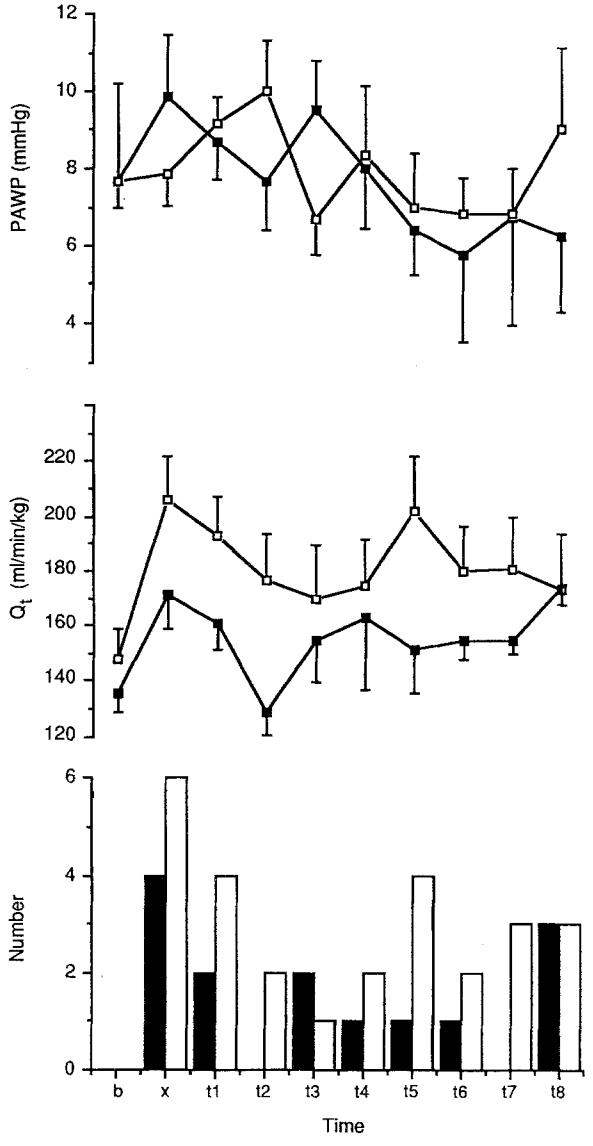


Fig. 1. PAWP (*top*), cardiac index (CI – *middle*) and number of animals achieving a 25% increase in cardiac index from baseline (*bottom*) at each measurement point. Line graph data are mean±SE. Point (*b*) is baseline, point (*x*) is pre-infection and points t1 – t8 are hourly intervals. *Solid points* represent group PSP and *open points* PDP

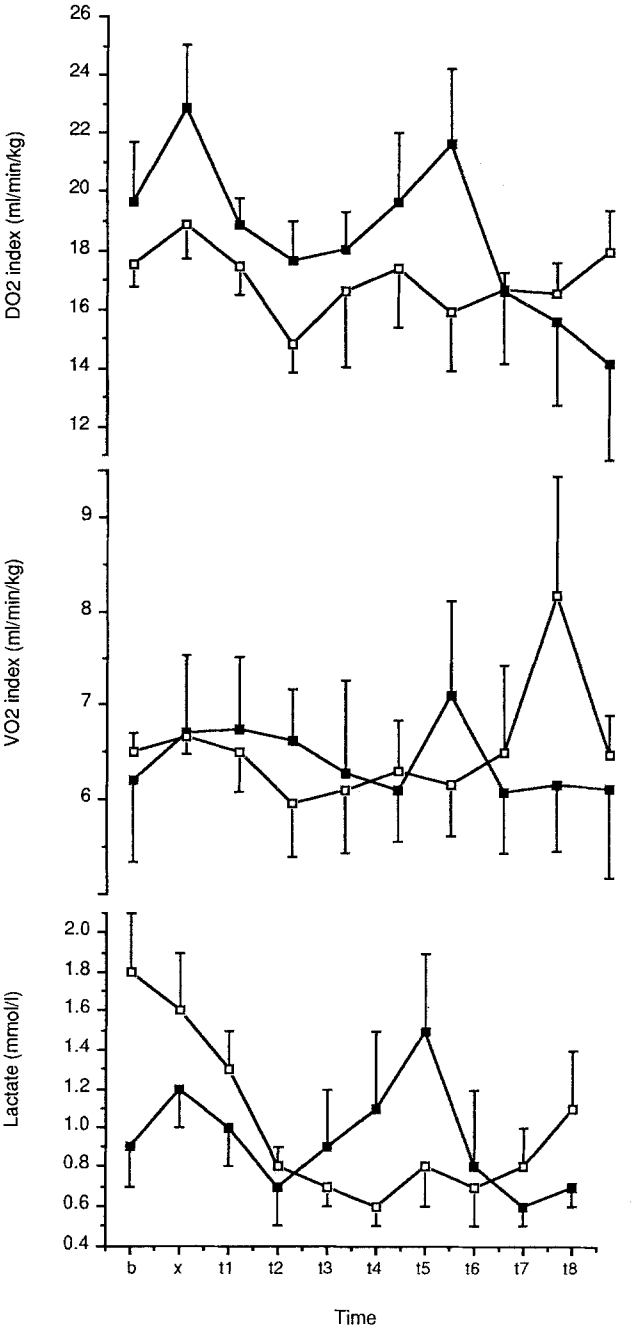


Fig. 2. DO_2 (top), VO_2 (*middle*) and arterial lactate concentration (bottom) at each measurement point. Data are mean±SE. Oxygen transport data are indexed to body weight. Point (*b*) is baseline, point (*x*) is pre-infection and points t1–t8 are hourly intervals. *Solid points* represent group PSP and *open points* PDP

8.0±0.7 g/dl [t8] in surviving animals of group PSP and from 10.1±0.6 to 7.4±0.6 g/dl in group PDP). Figure 3 demonstrates total blood flow into the liver along with hepatic oxygen transport and consumption. Once again there were no significant differences detected between the colloids or within groups compared to pre-infection (point x).

Pulmonary histology of both groups of animals showed evidence of capillary occlusion with cell debris and white cells, particularly degranulating neutrophils. There was swelling and disruption of the capillary endothelium and the alveolar epithelium (Fig. 4). These changes were generally more severe in group PSP than in group PDP. Hepatic histology revealed occlusion of sinusoids by degranulating neutrophils, lymphocytes and stagnant red cells. In addition there was endothelial and

Table 2. Capillary area, capillary lumen and alveolar capillary barrier thickness after 8 h of faecal peritonitis. Data are presented as mean±SE. The tissue area (i.e. excluding alveolar air space) is related to the measurement frame. All other areas are related to the tissue area

	Group PSP	Group PDP	*p*-value
Tissue area (%)	62.4±2.1	62.2±3.8	NS
Total capillary area (%)	36.2±1.1	41.2±2.3	NS
Capillary lumen (%)	18.5±2.7	26.2±2.0	<0.05
Mean alveolar capillary barrier thickness (τ) (μm)	4.3±0.3	2.5±0.3	<0.005

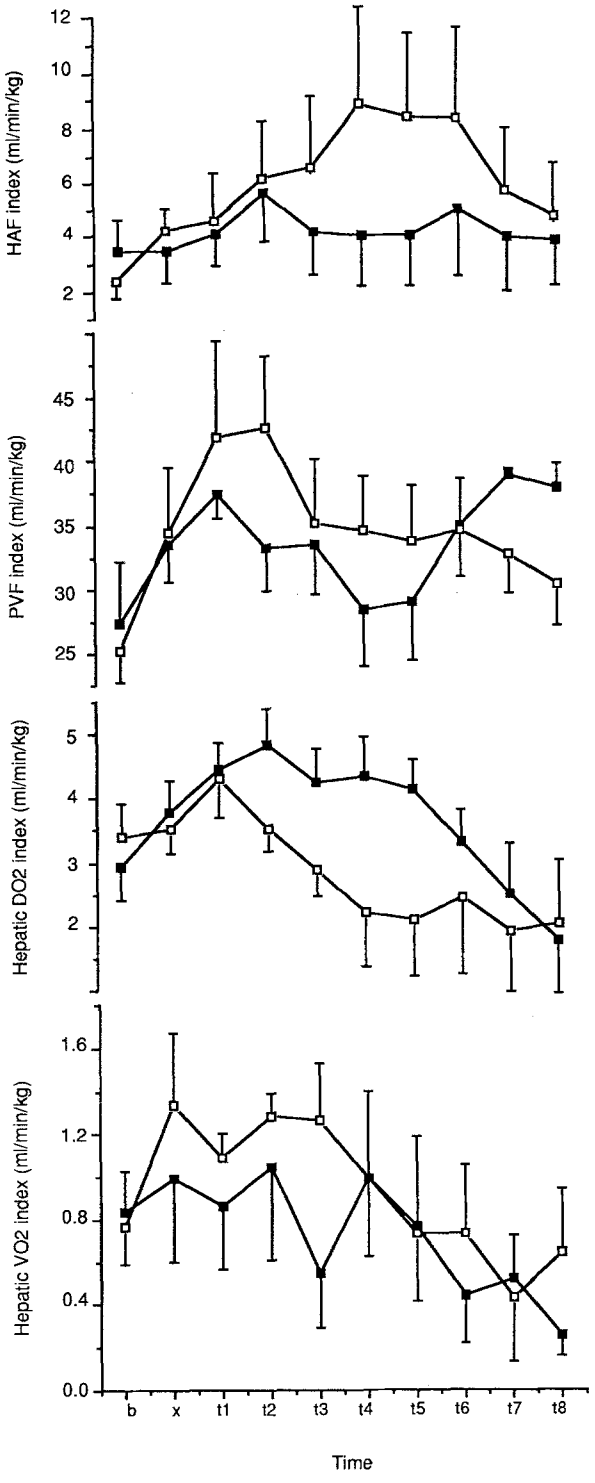


Fig. 3. Hepatic artery flow (*top*), portal venous flow (*upper middle*), hepatic DO_2 (*lower middle*) and hepatic VO_2 (*bottom*) at each measurement point. Data are indexed to body weight and are presented as mean ± SE. Point (*b*) is baseline, point (*x*) is pre-infection and points t1–t8 are hourly intervals. *Solid points* represent group PSP and *open points* PDP

Kupffer cell swelling and in some areas endothelial stripping with loss of the space of Disse (Fig. 5). These changes were more pronounced in group PSP than group PDP. The results of morphometric analysis are documented in Tables 2 and 3.

Table 3. Sinusoidal area, lumen, stagnant red cells, white cells and endothelial thickness after 8 h of faecal peritonitis. Data are presented as mean ± SE. All areas are related to the measurement frame which was equal to the total tissue area analysed in all cases

	Group PSP	Group PDP	*p*-value
Sinusoidal area (%)	28.6 ± 2.8	24.9 ± 2.0	NS
Sinusoidal lumen (%)	4.8 ± 1.1	11.3 ± 2.3	< 0.05
Stagnant sinusoidal red cells (%)	3.9 ± 1.3	2.1 ± 0.4	NS
Sinusoidal leukocytes (%)	6.6 ± 1.9	2.1 ± 0.6	< 0.05
Endothelium (%)	13.2 ± 1.5	9.4 ± 0.9	NS

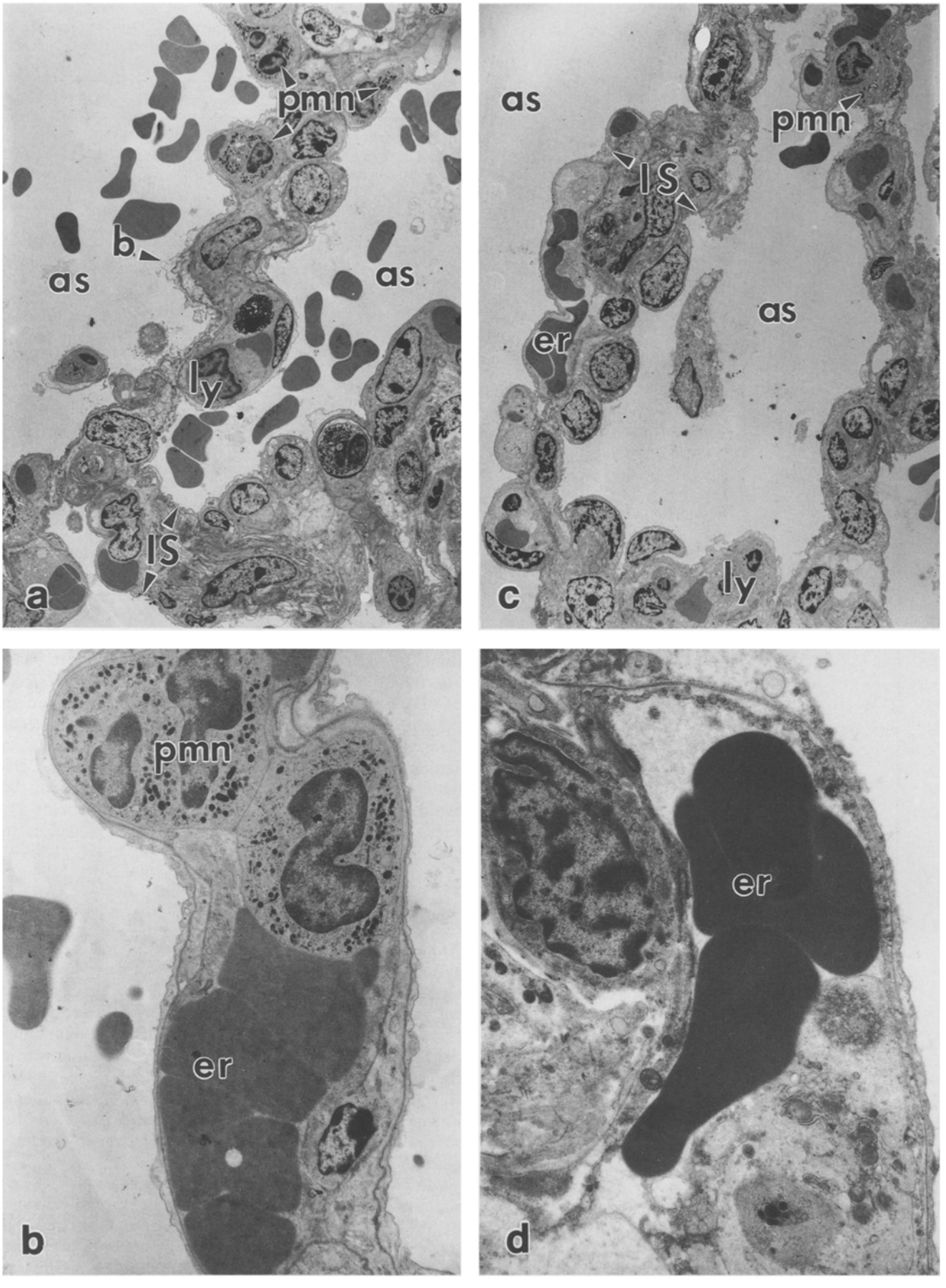
Discussion

The primary aim of this study was to assess the histological effects of a diafiltered pentastarch (PDP) with a narrow range of medium molecular weights in an animal model of MODS. This was based on the recognition that plasma volume expansion assumes an important part of the support of critically ill patients with multiple organ failure and its associated capillary leak. The physical properties of PDP approach the ideals suggested for states of capillary leak [25, 26]. In our previous study with PDP in the faecal peritonitis model we titrated fluid to avoid haemoconcentration [22]. In the present study, recognising the common clinical approach to sepsis of maintaining a hyperdynamic circulation, we have titrated fluids in an attempt to maintain Q_t at 25% above baseline values. We were particularly interested in the effects of PDP on structural organ changes compared to a more polydisperse pentastarch which contains smaller molecular weight fractions, both solutions being used to treat to similar haemodynamic goals. We did not compare PDP with other colloid solutions since we were anxious to avoid the difference in degree of substitution or differences in molecular structure as confounding factors in the analysis.

The animal model

Animal models have been used extensively for the investigation of therapeutic interventions in septic shock and multiple organ failure [6, 27–29]. The major problem with the interpretation of such animal data is that the septic shock produced has often been hypodynamic unlike the hyperdynamic state associated with human septic shock. Furthermore, animal models are often used to study single interventions in a controlled environment. Plasma volume expansion is a fundamental part of the resuscitation of human septic shock but has often been neglected in animal models.

In previous studies with the adolescent pig model [21] we have demonstrated reproducible histological evidence of MSOF after faecal peritonitis. Histology of the lungs showed reduced alveolar capillary patency with occlusion by degranulating neutrophils and lymphocytes. There was disruption of the capillary endothelium and alveolar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epithelium, and the type II pneumocytes showed loss of their lamellar bodies. Histology of the liver showed occlusion of the sinusoids by degranulating neutrophils and lymphocytes; there was Kupffer cell and endothelial cell hypertrophy with consequent narrowing of the sinusoidal lumina. These histological appearances are similar to those found in primate models of sepsis and multiple organ failure [3].

Haemodynamic and oxygen transport responses

The haemodynamic responses to plasma volume expansion were not significantly different between the groups. It is of interest that a 25% increase in Q_t could not be achieved pre-infection in 2 animals of group PSP, including one which subsequently died. Although the initial infusion of colloid was prior to the faecal peritonitis there may have been some inflammation related to surgical trauma in the peritoneal cavity and therefore more rapid loss of the smaller molecules of PSP. It is difficult to comment on the abilities of the solutions to achieve the desired therapeutic goals in the absence of statistical significance, but PDP was more frequently associated with a satisfactory increase in Q_t throughout the study period. The infusion rates required to achieve and maintain the therapeutic goals were high (up to 1000 ml/h). This was due, in part, to the systemic capillary leak associated with multiple organ failure although the majority of the fluid loss was via the local site of inflammation in the peritoneal cavity.

The oxygen transport and VO_2 responses to fluid loading in the model were similar in the two groups. The trend towards a decrease in oxygen transport was primarily due to haemodilution. VO_2 was maintained in both groups and there was no increase in blood lactate levels. These responses are different to those obtained in our previous study [22] where there was a late fall in VO_2 and a late rise in lactate in both colloid groups. This suggests that attempts at maintaining a hyperdynamic circulation avoided the critically low levels of DO_2 below which VO_2 would fall [30].

We must conclude that the haemodynamic and oxygen transport measurements made in this study revealed little difference between the two colloid solutions. This is perhaps not surprising since the therapeutic goal was the maintenance of a high Q_t. However, a criticism of our attempts to mimic modern therapeutic goals for sepsis syndrome [7, 8] must be that we failed to increase DO_2. Thus we cannot exclude an inadequate DO_2 as a factor contributing to the severity of the histological changes seen, even though VO_2 was maintained.

Histological responses

There were considerable differences between the morphological appearances of lung biopsies in the two groups. The greater capillary patency in group PDP was suggestive of better capillary blood flow due to reduced white cell occlusion and possibly due to reduced leakage to the pulmonary interstitium since there was also an increased mean alveolar-capillary barrier thickness in group PSP. These findings are in agreement with the findings of our previous study [22].

The hepatic sinusoidal changes demonstrated in this study of porcine faecal peritonitis were similar to those seen previously in a similar model in untreated rabbits [6] and in rats [31] or monkeys [3] infused with live *E. coli*. Thus the maintenance of Q_t and hepatic blood flow after the induction of faecal peritonitis was not enough to prevent organ damage in the liver. The reduction in white cell occlusion of the sinusoidal lumen in group PDP was similar to that seen for pulmonary capillaries. It is not yet clear why pentafraction should be associated with reduced white cell occlusion in this model. The question is the subject of current laboratory research. However, we know from other studies of pentafraction in animal models that there is a reduction in capillary leak [20, 22]. It is unlikely that a reduction in capillary leak is related to different effects on Starling forces. Haemodynamic responses were similar and since colloid osmotic pressure (COP) is a function of the number of molecules in solution [26] and the concentrations of the study solutions were equal, PSP had a higher COP than PDP by virtue of its smaller molecular weight fractions. The question of the effect of COP on capillary leak has been addressed previously. Zikria et al. demonstrated that a high COP associated with smaller molecules and a lower COP associated with larger molecules of 6% dextran solutions did not produce differences in capillary permeability [20]. We showed that the intravascular COP response was similar despite differences in the COP of study solutions when comparing hetastarch to PDP in our previous study in porcine faecal peritonitis [22]. Thus a reduction in capillary leak is presumed to be due to a pentafraction-endothelium interaction [32]. Although we believe that the medium molecular size is critical for such an interaction we do not know whether it is something that is peculiar to hydroxyethyl starches. The nature of this interaction remains speculative but it is of course possible that it may reduce the interaction between endothelium and activated white cells. Whatever the mechanisms, both a reduction in capillary leak and a reduction in white cell capillary occlusion are useful features of a colloid that is capable of providing plasma volume expansion in the sepsis syndrome.

Fig. 4. a, b Pentaspan lung biopsies show thickened inter-alveolar septal walls (*IS*) with capillary patency much reduced by occluding neutrophils (*pmn*), lymphocytes (*Ly*) and packed erythrocytes (*er*). The alveolar epithelium shows areas of bleb formation (*b*) and extra-vascular red cells are in the alveolar space (*as*). **c, d** Pentafraction lung biopsies show the inter-alveolar septal wall (*IS*) contains many thin walled capillaries with better patency and reduced occlusion by neutrophils (*pmn*) and lymphocytes (*Ly*). The alveolar epithelium shows less bleb formation and there are fewer extra vascular red erythrocytes in the alveolar space (*as*). Magnifications (**a**) ×900, **b** ×3500, **c** ×900, **d** ×7000

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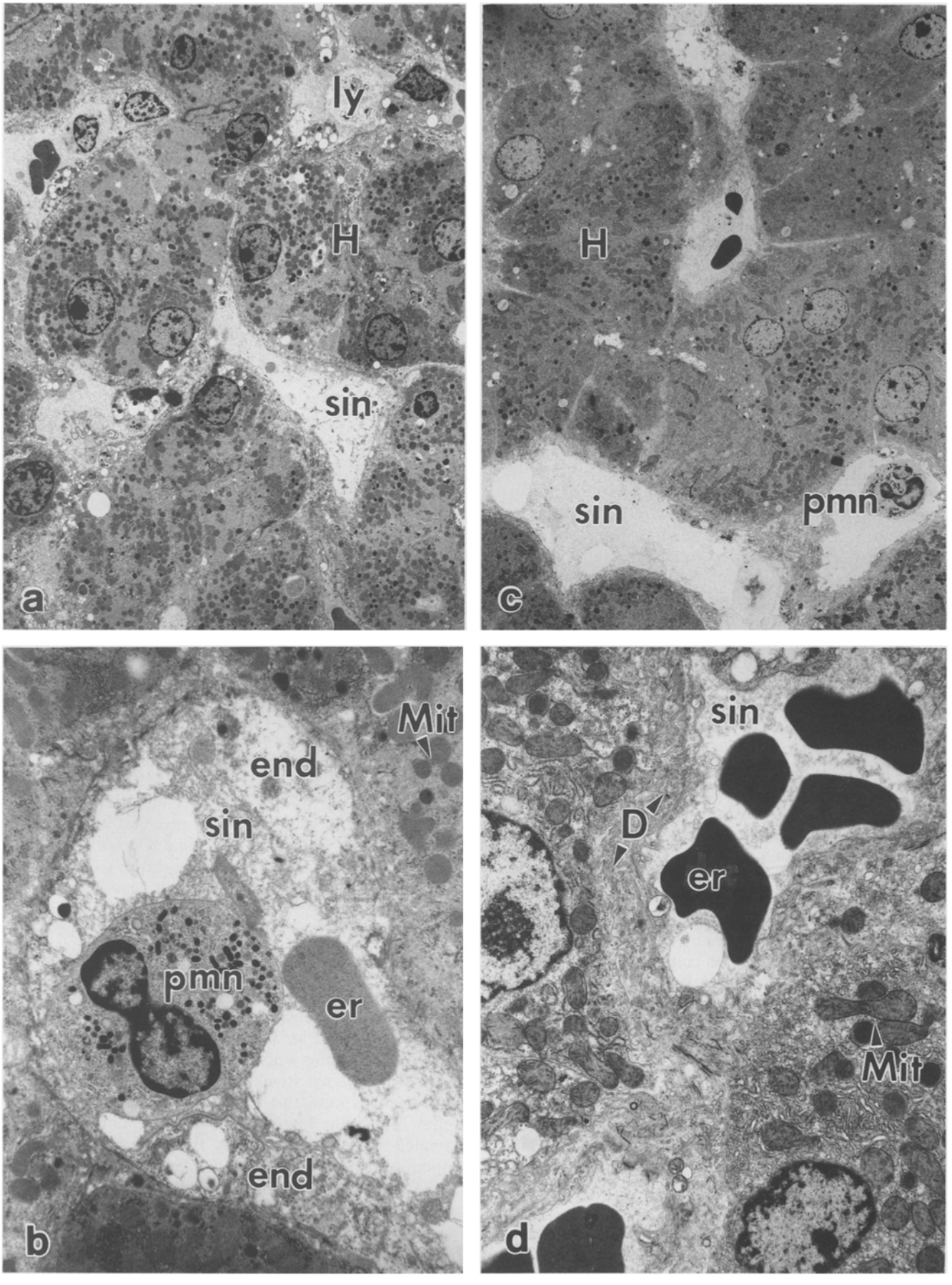
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Fig. 5. a, b Pentaspan liver biopsies show hepatocytes (*H*) and many sinusoid lumens (*Sin*) occluded by cell debris, leukcocytes (*Ly*), erythrocytes (*er*) and neutrophils (*pmn*). The subendothelial space of Disse has become indistinct where the endothelium (*end*) has swollen. The hepatocyte mitochondria (*mit*) are swollen with indistinct cristae and a granular matrix. **c, d** Pentafraction liver biopsies show many patent sinusoid lumens (*Sin*) with erythrocytes (*er*) and neutrophils (*pmn*). The subendothelial space of Disse (*D*) is distinct with a thin endothelium. The hepatocyte mitochondria (*mit*) show distinct cristae and a clear matrix. Magnifications **a** ×900, **b** ×3500, **c** ×900, **d** ×3500

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