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Host defences in continuous ambulatory peritoneal dialysis and the genesis of peritonitis*

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Abstract. Continuous ambulatory peritoneal dialysis (CAPD) has come to be extensively used for the treatment of end-stage renal failure in children, and especially infants, such that now more than half of children on dialysis worldwide receive treatment by this means. Peritonitis, however, is commoner in children than in adults receiving treatment, and is a major source of morbidity and treatment failure in children started on CAPD. Only recently has the immunology of the normal peritoneum been studied extensively, with the need to assess the impact of the installation of large volumes of fluid into the peritoneal sac during dialysis. The main phagocytic defences of the peritoneum depend upon a unique set of macrophages which are present free in the peritoneal fluid but also in the submesothelium and in perivascular collections together with B lymphocytes in the submesothelial area. Both the number of macrophages per unit volume and the concentration of opsonic proteins, such as IgG, complement and fibronectin, are reduced to between only 1% and 5% when dialysis fluid is continuously present in the peritoneal sac. In addition, the fluids used for CAPD are toxic to both macrophages and to mesothelial cells. Thus minor degrees of contamination frequently lead to peritonitis and in addition the majority of patients have catheters inserted in their peritoneum which become colonised with organisms capable of producing exopolysaccharide (slime), which promotes adhesion of the organism to the plastic and protects them against phagocytic attack and the penetration of antibiotics. Thus the peritoneum is in a state of continual inflammation, as well as being a markedly more vulnerable site than the normal peritoneum to the entry of organisms. Whether clinical peritonitis appears in this state of chronic contamination probably depends on perturbation in the balance between host defences and the organism. Whilst *Staphylococcus epidermidis* is the commonest cause of peritonitis, *Staphylococcus aureus* and Gram-negative organisms are much more serious and more frequently lead either to temporary catheter removal or discontinuation of dialysis altogether. This review describes the peritoneal defences in relation to the genesis of peritonitis.

Key words: Continuous ambulatory peritoneal dialysis – Peritonitis – Peritoneal macrophages – Lymphocytes – Opsonins – Complement – Fibronectin – Immunoglobulin – Biofilm

Introduction

Continuous ambulatory peritoneal dialysis (CAPD) [1] was first introduced almost 20 years ago, and since the early 1980s has formed a major part of the repertoire for the treatment of end-stage renal disease in children and infants [2–5]. It has proved especially useful and attractive in younger children and infants, in whom haemodialysis presents extra problems, and more extensive use of cycling machines has been made than in adult populations [3–5]. Now, more than one-half of children undergoing dialysis receive treatment using this technology [3, 4]. A particular problem in dialysing small children is the high proportion who have urinary tract anomalies in this age-group, so that urinary diversion is relatively common and may make CAPD difficult or impossible.

However, CAPD has major problems, the greatest of which is the tendency of the irrigated peritoneum to develop peritonitis [6–11], usually bacterial, less commonly from yeast and rarely fungal. This is the major complication of the technique and accounts for the greatest proportion of treatment failures in both adults and children [3, 4]. The incidence of peritonitis is almost uniformly higher in children than in adults [6–11], which makes the problem of especial importance in paediatric nephrology.

Most paediatricians and nephrologists looking after patients maintained on CAPD are aware that a few of their

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patients give rise to the majority of the episodes of peritonitis recorded, whilst others seem never to have episodes of infection. Since recurrent peritonitis is the main cause of peritoneal thickening [12], technique failure and transfer to haemodialysis, from early in the history of CAPD a search has been conducted for reasons why some patients are apparently so peculiarly susceptible to peritonitis. The great majority of studies on host defences in the dialysed peritoneum have been performed on adults, and here I extrapolate these results to children. However, we must not forget that the development of peritoneal immunity during childhood has scarcely been studied, expecially in relation to the higher incidence of peritonitis just mentioned.

Dirt or defect?

Obviously acute infectious peritonitis implies the entry and multiplication of pathogenic organisms within the peritoneal cavity. In some instances poor technique, poor training and poor hygiene are clearly at fault; but in the majority of patients with recurrent peritonitis, there is no record of more frequent prior technique failure than in periods without peritonitis. Thus attention has turned towards host factors which might determine poor resistance to the micro-organisms involved. This in turn has led to studies of normal peritoneal immunology, and especially in patients instilling large volumes of CAPD fluid several times a day into their peritoneum.

The normal peritoneum

The peritoneal lining

The peritoneal cavity is lined with a layer of cells, the *mesothelium* [12–16]. These are cells of mesodermal origin, which form an unbroken cobblestone layer (seen en face) with close junctions between four and seven other mesothelial cells. They show many surface microvilli, with a prominent rough endoplasmic reticulum, and are capable of ingesting particles or organisms by pinocytosis, but not of forming phagosomes and digesting/killing these. Apart from containing cytokeratin, vimentin and secreting laminin, as might be expected, they also secrete fibronectin [17] and express the leucocyte adhesion molecule intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (but not endothelial cell leukocyte adhesion molecule ELAM-1) [18, 19]. A prominent Golgi apparatus and ribosomes, and many mitochondria, suggest considerable synthetic activity, which is borne out by recent studies showing a capability to synthesise and release prostaglandins (PGI_2, PGE_2, but not thromboxane A_2 (TxA_2) or leukotrienes [20], together with cytokines and chemokines [interleukin-1 (IL-1), IL-6 [21], IL-8 [22] and macrophage chemotactic protein-1 (MCP-1)] [19, 23] and a variety of other molecules including tissue-type plasminogen activator [24]. Prominent lamellar lipid bodies are present which form the origin of phosphatidylcholine in peritoneal fluid, in which mesothelial cells resemble type II pneumocytes. It should not be forgotten that one of the peritoneal mesothelium's main functions is lubrication. Finally, mechanical integrity of the mesothelial layer protects the submesothelium from exposure and invasion by micro-organisms during peritonitis. In CAPD peritonitis, in contrast to surgical peritonitis, recovery of organisms from the blood is the exception rather than the rule.

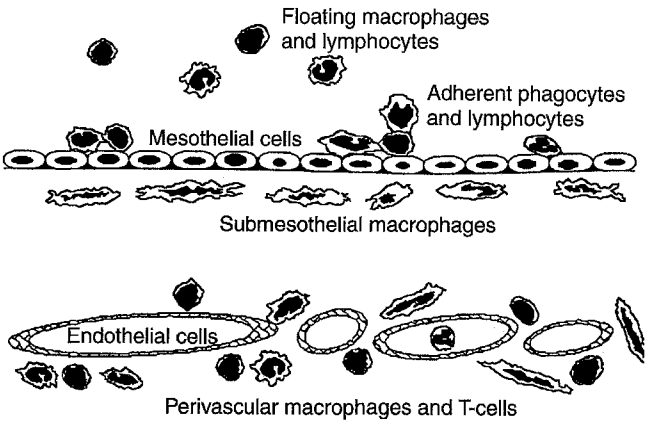

Fig. 1. The spatial distribution of resident peritoneal cells which provide a first line of defence against invading micro-organisms. Four populations of resident cells can be identified: an intraperitoneal population, predominantly macrophages but also containing CD4+ T lymphocytes, neutrophils, a few eosinophils and B lymphocytes; cells adherent to the peritoneal mesothelium, normally few in number but increased during peritonitis, consisting of macrophages and a few neutrophils in the resting peritoneum; a submesothelial layer of macrophages; and finally submesothelial perivascular aggregates of T lymphocytes and macrophages. Within 1 h of microbial invasion these populations change, the predominant cell within the peritoneal fluid and adherent to the mesothelium becoming the polymorphonuclear leucocyte. From Suassuna et al. [25], with permission

This layer of mesothelial cells lies upon a *basement membrane*, which in turn lies over a *submesothelial stroma* of areolar tissue 1–2 mm in depth. This contains collagen fibres in a matrix of ground substance with an organisation depending upon the visceral or parietal origin of the peritoneum. Normally there are rather few cells in this region, but mast cells are present and recently we have shown [25] that there is a layer of *submesothelial macrophages* which obviously are in a position to form an important defence barrier (Fig. 1). In addition, *submesothelial vessels* are surrounded by lymphocytes and dendritic cells [22], forming a perivascular unit analogous to that already known to be present in the skin. Thus there are four populations of defensive cells in the peritoneum: those free in the peritoneal fluid, those adherent to the peritoneum (normally rather small in number, but increased in peritonitis), the submesothelial layer of macrophages and the submesothelial perivascular units.

The peritoneal microcirculation

This provides the site of the physiological interactions between the circulating plasma and the peritoneal cavity [26]. Unfortunately, the effective blood flow to the peritoneal surface is inaccessible to measurement, although calculations suggest that for small solutes blood flow is unlikely to

Table 1. Peritoneal fluid in health and continuous ambulatory peritoneal dialysis (CAPD)

	Normal	CAPD
Volume (ml)	50	2,000
Cell count (/ml)	10^6-10^7	10^3-10^4
Opsonins (IgG, C3, fibronectin) (% plasma level)	100	1–3

be rate limiting. There are many arcades in the perietal peritoneum, which will equalise both pressures and flows over wide areas, with few if any arteriovenous anastomoses, as observed at many other sites. The overall permeability of the peritoneal vessels is about the same as most other capillary beds. Constriction and dilatation of the capillary bed can take place, affecting exchange during dialysis, which is clearly a point of importance. The dynamics of fluid exchange across peritoneal capillaries obey Starling forces as elsewhere. The endothelium of the peritoneum displays tight junctions as elsewhere, and probably forms the main filtration barrier. The perivascular immune cells have been discussed in the previous section.

Peritoneal defences

How does the peritoneum defend itself against microbial invasion in health? Apart from the mechanical integrity of the mesothelial layer and the submesothelium, the peritoneum has a number of humoral, mechanical and cellular defences. These have been reviewed extensively during the past 5 or 10 years [27–35].

First, the peritoneal cavity contains a small amount of fluid, in which are found both opsonins and phagocytic cells. This fluid has been studied in health, principally by study of normal adult women at laparoscopy, or in adults during abdominal surgery, and its composition and contents are shown in Table 1. The volume is probably only about 50–100 ml in adults. The principal cell population is made up of monocytes/macrophages (90%) and lymphocytes (5%), and there is good evidence that the main phagocyte of the normal peritoneal cavity is not the polymorphonuclear leucocyte (present as only 5% of cells), but the monocyte/macrophage [36–41]. These are found normally in concentrations of 10^6-10^7/ml and show markers of activation and maturation. They are not identical to tissue macrophages, however, forming a population of cells unique to the peritoneal cavity. This means that studies of peripheral blood cells, or those derived from other sites, have little relevance. For purposes of this review, however, we will refer to them simply as "macrophages".

Plasma proteins (including immunologically relevant molecules such as antibodies, complement components and fibronectin) are present at approximately equal concentrations to those found normally in plasma. These are the principal opsonins of plasma and tissue. Opsonins are proteins which coat the bacteria making them more readily phagocytosable, and the principal molecules involved are IgG, complement-generated C3b and C3bi and fibronectin. The bacteria coated with IgG are recognised by the Fcreceptors and the C3b by the CR-1 receptor of the phagocyte. In the case of *Staphylococcus aureus*, the protein A of the organism binds fibronectin. However, non-opsonic phagocytosis is important also, particularly for *Pseudomonas* and *Escherichia coli*, through the medium of *lectinophagocytosis*. *E. coli* are phagocytosed following binding of their type 1 fimbriae to macrophage-borne carbohydrate residues [42]. Carbohydrate residues bound in this way include components of CD11/CD18 molecules and Fcγ receptors expressed by the cells. In addition, mature macrophages themselves express lectins known as mannose or β-glucan receptors. These bind sugar residues on a variety of micro-organisms, which leads to internalization and killing in the absence of any opsonins. The possible importance of these mechanisms in peritoneal defence has yet to be established, however.

Thus the model of normal peritoneal defence suggests that when bacteria enter the peritoneal cavity they are phagocytosed, with or without opsonisation, by macrophages and polymorphs and then killed by oxidative and non-oxidative mechanisms. Both free and phagocytosed organisms are removed by transit of peritoneal fluid through the peritoneal lymphatics, principally across the diaphragm.

The effect of instilling CAPD fluid into the peritoneum

Obviously these normal defences are profoundly disturbed by the unphysiological intervention of CAPD, during which large volumes of toxic fluid are instilled into the peritoneum. CAPD fluid contains a low but detectable count of microparticulate matter (plastic and glass), has a pH of about 5–5.5, an osmolality of 300–500 mmol/l, a very high glucose concentration of 35 mmol/l of lactate.

Toxic effects on cells

In vitro and ex vivo, raw CAPD fluid inhibits the respiratory burst, phagocytosis and bacterial killing by peritoneal macrophages [35, 43–54], and is cytotoxic to lymphocytes [55]. During the dwell time within the peritoneum (4–12 h), the pH of the fluid rapidly equilibrates (within 1–2 h), but the hypersomolality remains present throughout – as it must to effect ultrafiltration. Naturally there have been attempts to analyse the means by which dialysate exerts its toxicity, and the most popular view is that this is the result of the hyperosmolarity [53]; however, in some studies a fall in intracellular pH seemed to correlate best [54], and products of glucose sterilisation have been suggested rather than glucose itself [56]. Heating glucose results in a variety of products, including 3-acetyl acrylic acid (which gives the yellow-brown colour to bags improperly sterilised) and formic acid, which may be responsible for the pain when such bags are infused into the peritoneum. Unfortunately, glucose polymer solutions seem to share toxicity with simple glucose [52]. As well as the toxic effects of dialysate on the peritoneal macrophages, the constant removal of large numbers in the dialysate results in a younger popu-

lation of cells showing fewer marks of maturation [57]. This may be in part why the performance of the intraperitoneal cells is different in patients undergoing CAPD compared with normals.

As well as these effects upon intraperitoneal macrophages, dialysate is toxic to cultured mesothelial cells in vitro [58, 59], with increased release of ^{51}chromium label. Instillation of CAPD leads to a brisk efflux of mesothelial cells in the effluent [60], presumably as a result of loss of cells from the mesothelial layer. Mesothelial cell production of cytokines is also inhibited strongly [61], together with leukotriene production [62]. Within weeks of beginning CAPD, morphological changes occur in the peritoneal lining [63, 64], even in the absence of peritonitis. The rough endoplasmic reticulum increases in amount, the surface villi become more sparse, micropinocytotic vacuoles become less frequent and there is an increase in submesothelial collagen. In the rat, however, there was an increase in cell density and in number of villi, pinocytotic vacuoles and rough endoplasmic reticulum [65].

Dilution of cells and opsonins

The other obvious effect of instilling CAPD intraperitoneally is that both cells and proteins are diluted, initially to almost zero concentrations, the exact level depending upon residual fluid (usually about 200–400 ml). Thereafter, the cell count and concentrations rise [66–68], but by the end of the dwell the cell concentration is only about 10^4–10^5/ml (10–100/μl, 1%–10% of normal) and the concentration of plasma proteins only 2%–4% of plasma levels. The peritoneal membrane is poorly selective for proteins [69], so that there is little difference in the penetration of large and small molecular weight species into the peritoneal cavity during equilibration. Other effects of the large volume of intraperitoneal fluid on lymphatic removal of organisms have been noted already.

Thus the peritoneum in CAPD patients is an immunocompromised site, with semi-sterile access several times a day to an external world teeming with organisms; under these circumstances it is perhaps surprising that peritonitis is not *more* common than it actually is in patients practising CAPD!

The organisms causing CAPD peritonitis

The first important fact to be noted is that the organisms responsible for peritonitis in patients on CAPD are completely different from those causing surgical peritonitis, in nephrotic children and (to a lesser extent) patients with cirrhosis. In all published series [70, 71], including our own, the list of organisms responsible for peritonitis is similar and has changed little during the past decade, although the proportion of cases attributed to *S. epidermidis* has fallen a little under the impact of disconnect systems. The organisms in children are much the same as in adults. An analysis of 646 published cases in children [10] showed 44% Gram-positive organisms principally *S. epidermidis* and *S. aureus*, 21% Gram-negative organisms, 2% of cases with fungi or yeasts and 8% with a variety of unusual organisms. In these collected series, there was no growth in 25% of patients. Although many of these represent cases of *S. epidermidis*, a recent study of 37 adult patients using reculture found that there were cases of both Gram-negative and fungal peritonitis amongst this initially culture-negative group [72]. The rate of positive cultures may be promoted by lysis of the cells which have ingested organisms [73], and intracellular sequestration without killing may be a factor in relapse and persistence of infections [73, 74]. Many units use techniques similar to those applied to blood cultures to isolate organisms from CAPD fluid [75], and with care the proportion of negative cultures can be as low as 2%–3%.

The most common single infecting organism is *S. epidermidis*. *S. aureus* (about 20%) is the next most common organism, with Gram-negative organisms (occasionally in mixed growth) forming the majority of the remainder. A zoo of rare species may be found, but particular mention must be made of peritonitis arising from yeasts such as *Candida* or fungi. That intraperitoneal defences are important is suggested by the observation that fugal and pseudomonal infections are commoner in patients with the acquired immunodeficiency syndrome (AIDS) on CAPD [76] – although other observers have noted the usual mix of organisms in this context [77].

The route of entry of the various common organisms into the peritoneum is almost certainly different: *S. epidermidis* mostly comes in externally contaminated dialysate, then, once the indwelling catheter is colonised with biofilm, escapes into the general peritoneal cavity; this suggestion is supported by the fact that "flush before fill" Y connector systems cut the incidence of peritonitis almost exclusively in the group arising from *S. epidermidis*, both in adults [78–81] and in children [82]. However, when Brown et al. [83] compared the strains of *S. epidermidis* present on the hands and at the exit site with those from the peritoneum during peritonitis, they failed to find any concordance. These important observations deserve to be repeated.

S. aureus is strongly associated with exit site or tunnel infections with the same organism [84–90], which are both associated with chronic nasal carriage of this organism [68, 73]. Gram-negative organisms [91] may enter either by contamination or translocate across the bowel wall, especially if diverticular or inflammatory bowel disease is present, as in many older adults. In children, this route is of course less likely. We have shown that the residual volume within the peritoneum may be important in determining the appearance of peritonitis, since there is a "washout" of organisms at every exchange [92]. This is most important for rapidly dividing, virulent organisms such as *S. aureus*, whereas with more slowly dividing organisms the likelihood of multiplication exceeding washout is relatively independent of residual volume; similar considerations apply in the bladder, of course. An important clinical point is that need to remove the catheter is strongly associated with the presence of either *S. aureus* [85–87], Gram-negative organisms or fungi, reflecting the greater clinical severity of peritonitis resulting from these organisms.

Table 2. Anti-microbial function of peritoneal macrophages from peritoneal dialysis patients

Function	Result	Control	Target	Author	Year	Reference
Phagocytosis	Normal	NPMPH	*S. epidermidis/E. coli*	Peterson et al.	1985	[38]
			S. epidermidis	McGregor et al.	1987	[39]
				Lamperi	1990	[99]
	Normal	NPMPH	*S. epidermidis/E. coli*	Verbrugh et al.	1983	[36]
	Depressed	UPMO		Brando et al.	1988	[97]
	Increased	NP cells		Betjes et al.	1993	[110]
	Depressed	NPMPH	Latex	Sulowicz et al.	1991	[103]
	Depressed	NPMO	*E. coli*	Lewis et al.	1995	[106]
Oxidative metabolism						
Peroxidase	Normal	NPMPH	–	Peterson et al.	1985	[38]
Hydrogen peroxide generation	Depressed	NPMPH	Zymosan	McGregor et al.	1990	[101]
	Normal	NPMPH		Bos et al.	1988	[57]
Chemiluminescence	Increased	UPMH	Zymosan	Davies et al.	1989	[40]
	Depressed	NPMPH	Zymosan	Verbrugh et al.	1983	[36]
	Increased	NPMPH	Zymosan, PMA	Peterson et al.	1985	[38]
Bacterial killing	Normal	NPMPH	*Candida*	Verbrugh et al.	1983	[36]
	Normal	NPMPH/NPMO	*S. aureus*	Goldstein et al.	1984	[37]
	Depressed	NPMPH	*S. epidermidis*	McGregor et al.	1987	[39]

NPMPH, Normal peritoneal macrophages; UPMO, uraemic peripheral blood monocytes; NP cells, normal peritoneal cells (unseparated); NPMO, normal peripheral blood monocytes; UPMH, uraemic peritoneal macrophages; PMA, phorbol myristate acetate

The defences of the peritoneum during CAPD

It has been an abvious goal to examine the performance of the peritoneal defences during CAPD, both to see whether individuals vulnerable to peritonitis could be identified and also to see if improving peritoneal immunity is possible and might lead to a fall in the high incidence of peritonitis. Thus both peritoneal macrophage function and, to a lesser extent, intraperitoneal opsonins have been the subject of intense study in patients undergoing CAPD. Obviously any data obtained must be interpreted in the light of the fact that these patients are all to varying degrees uraemic and also in some cases less than optimally nourished, both factors well known to influence immune responses in general [93, 94].

Phagocytosis by peritoneal macrophages during CAPD

The cells within the dialysed, but peritonitis-free peritoneum [95–121] differ not only in number but also activity from those present in the normal peritoneum [36–40]. There is much greater variability in both the cell count and the proportion of the various cells making up the population between individuals. Macrophages are usually predominant, as in the normal state, but may vary from only 20% up to 90% of cells; lymphocytes likewise may predominate, rather than being a minority population. The proportion of polymorphonuclear leucocytes varies also, from 10% to 30% or more. Eosinophils are prominent during the first weeks after catheter insertion, but become scaree thereafter, possibly representing an allergic reaction to the catheter material, which is supported by higher IgE concentrations in the plasma of these patients [95].

Numerous studies have tried to determine whether cell respiration and bacterial phagocytosis and/or killing are normal in macrophages from CAPD drainage fluid taken after various dwell times [36–41, 96–107]. Serial studies have also been performed [108–110], and the study of Betjes et al. [111] is particularly important in that they examined events immediately prior to an attack of peritonitis and suggested that some macrophage functions were depressed at this time. Almost all these data come from adults, but at least one study in children has been performed [112].

We have already noted that *fresh* CAPD effluent inhibits phagocytosis almost completely, but at the end of the dwell time of 4–12 h the results obtained have been diverse and contradictory (Table 2), even when opsonin concentrations have been allowed for. Some workers (including ourselves) have found defective phagocytosis, others normal phagocytic behaviour but defective killing; in contrast, in a few studies dialysis-elicited macrophages even showed a greater respiratory burst and greater killing capacity for *Candida* than resident laparoscopy macrophages [38].

The divergence in these results has been discussed in detail by Lewis and van Epps [96] and Holmes [34], and arises at least in part from the facts that: (1) different target organisms were used – usually *E. coli* or *S. epidermidis* – sometimes zymosan or *Candida*, or even inert particles; (2) the unique nature in terms of activation and maturation makes peripheral blood monocytes poor controls; in some studies, therefore, peritoneal macrophages obtained at laparoscopy in normal women were used; (3) the method of separating the macrophages has differed; some studies employed removal of plastic adherent cells (which alters cell function profoundly) [82], others gradient centrifugation and re-suspension and yet others flow cytometry; (4) although some studies were performed in standard solutions, in some the host's own effluent was used, which must contain a very variable quantity of opsonins; (5) in one study [109], which has not been repeated, the phagocytic capacity as well as the number of peritoneal macro-

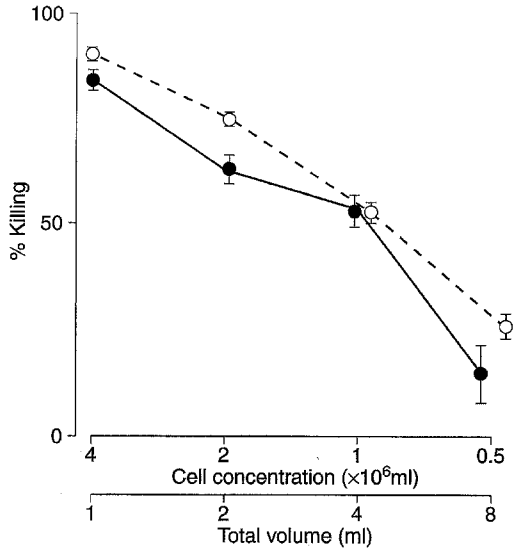

Fig. 2. Interactions between peripheral blood leucocytes and organisms (*Escherichia coli* E/2/64) in peritoneal dialysate in the presence of normal serum (for opsonisation). Both when the number of cells was held constant (4×10^6/tube) and the volume varied from 1 to 8 ml, or the volume kept constant and the number of organisms varied from 0.5 to 4×10^6, bacterial killing ceased below a concentration of 0.5×10^6/ml, 10 times that present is the resting peritoneum during peritoneal dialysis. From Duwe et al. [43], with permission

phages decreased with time following the initiation of dialysis, becoming stable after the 1st year or so, a variable which has not be controlled for in most other studies; (6) Antonsen et al. [104] have pointed out that the viable cells in effluent, especially after long dwell times, represent only a small fraction of the total cell population and may not be representative.

In general, a summary of all these results suggests that even after equilibration the phagocytic and killing capacity of the very diluted concentration of monocytes within the peritoneal fluid is reduced, although not dramatically. In fact, the phagocytic capacity may not be crucial in the fluid phase during *initiation* of peritonitis, since if a 1:1 mixture of organisms and phagocytic cells is taken and diluted in vitro, when the concentration of phagocytes falls below about 5×10^5/ml (500/μl) killing almost ceases (Fig. 2) [43]. "Normal" peritonitis-free CAPD fluid nearly always contains less than 50 cells/μl, although this level may rise a 100-fold or more in peritonitis. The most convincing evidence that peritoneal macrophage phagocytic capacity may be important was presented by Betjes et al. [111] who found a reduction in phagocytic capacity preceded attacks of clinical peritonitis. Other serial studies [108, 109] showed that in the year following the initiation of dialysis the number of peritoneal macrophages fell one or two orders of magnitude, whilst the number of lymphocytes increased [108].

Nevertheless, in the period immediately following the infusion of dialysate into the peritoneum – when fresh organisms are most likely to be introduced – phagocytosis is almost eliminated for a period of 1–2 h, and obviously this could be important. Also, in the control and resolution of established peritonitis phagocytic capacity could be crucial. In many instances, phagocytosis is not followed by killing, and sequestration of an organism within the macrophage may even protect it [73, 74]. In summary, despite a large body of evidence it remains unclear whether macrophage phagocytic capacity is a crucial factor or not in determining the appearance of peritonitis; if it is crucial, then the encounter between phagocyte and organism is much more likely to occur on the surface of a mesothelial cell or the dialysis catheter, rather than free in the vast litres of peritoneal dialysis fluid.

Other intraperitoneal cell populations during CAPD

We have concentrated upon macrophages because they form the majority of the cells (about 40%–50%) in the "resting" peritoneum during CAPD and because they form the initial population of cells which must resist bacterial invasion. In addition, in experimental animals there is clear evidence of transport of bacteria through the lymphatics [114]. However, some 5%–10% of intraperitoneal cells are *polymorphonuclear leucocytes* [115, 116] and after bacterial invasion the count of macrophages changes little, whilst enormous numbers of polymorphs are recruited after about 1 h [116], leading in most cases to a visible turbidity of the peritoneal fluid ("cloudy bag").

The abundant *lymphocytes* (20%–40%) within the peritoneum have been little investigated [49, 117–123], compared with the many studies of intraperitoneal monocytes. All studies concur that the majority of lymphocytes are T cells, the majority CD4 positive and are in general a population showing both activation and maturation markers, such as class II major histocompatibility complex antigens. Thus they are capable of secreting γ-interferon and IL-2. Little is known about the B cells of the peritoneum [40, 117, 121]. In one of our studies [40], they appeared incapable of responding in vitro with antibody production to non-specific stimuli, whilst peripheral blood B cells from the same patient could do so. It seems unlikely therefore that the make much contribution, if any, to antibody concentrations within the peritoneum. Finally eosinophils are present, usually in small numbers, but in a few episodes of serositis are the predominant cell within the peritoneum [95]. These episodes are not usually associated with positive bacterial culture.

Opsonins within the peritoneum during CAPD

Functional opsonic activity and concentrations of individual opsonins have been studied in dialysis effluent [122–132]. As noted above, concentrations of all plasma proteins within the dialysed peritoneum rise from nearly zero immediately after inflow of dialysate to 2%–4% of plasma concentrations during the dwell period. This is still far below that normally present or present in tissues elsewhere. In general, functional opsonic activity increases in parallel with the increase in protein concentrations (Fig. 3) during dwell within the peritoneum. However, Coles [126] reported that, like the concentration of cells, IgG concentrations fall with time in patients on CAPD for several months or more.

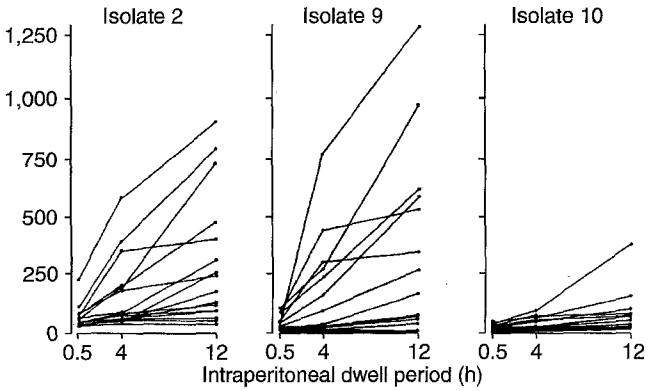

Fig. 3. Opsonisation (chemiluminescence) of different strains of *Staphylococcus epidermidis* by peritoneal dialysate macrophages from 16 individuals on peritoneal dialysis at various times following instillation of dialysate. Opsonisation immediately after instillation of dialysate is, not surprisingly, negligible because of dilution. However, both the opsonic susceptibility of different organisms varies greatly in the same patient and opsonic recovery during the dwell period varies greatly between patients. Data of Bennett-Jones et al. [67] redrawn

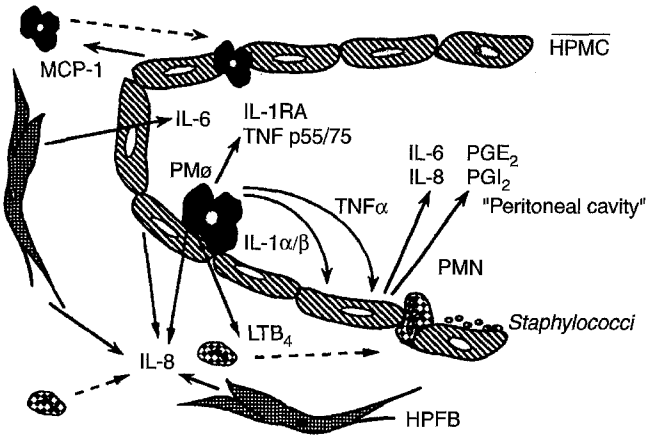

Fig. 4. Interactions between mesothelium, intraperitoneal cells and bacteria, *IL-1*, Interleukin-1; *TNF*, tumour necrosis factor; *MCP-1*, monocyte chemotactic protein-1; *PGE_2*, prostaglandin E_2; *PMN*, polymorphonuclear leucocytes; *LTB_4*, leukotriene B_4; *HPMC*, human peritoneal mesothelial cell; *HPFB*, human peritoneal fibroflast. [From Topley and Williams (1994) with permission]

Schroeder et al. [133] noted that young children completely lacked IgG2 (important in activity against capsular polysaccharides) in their peritoneal fluid; this intriguing observation has not been re-studied, but Fivush et al. [134] noted global hypogammaglobulinaemia in children on CAPD, an observation confirmed by Hisano et al. [135] and Katz et al. [136].

It has been suggested that intraperitoneal macrophages secrete some complement components, including C2 and C3, together with fibronectin [131], although others could not confirm these observations [132]; but again washout suggests that this will not contribute in the dialysed peritoneum – although it could be important in the normal, non-dialysed peritoneum.

The addition of IgG to CAPD fluid increases opsonic activity for *S. epidermidis* in vitro [122] and addition of complement that for *E. coli* [122], whilst heating (which destroys complement activity) reduces it; we showed that some clinical strains of *S. epidermidis* also require complement for optimal opsonisation [67] and that some strains are poorly or not all opsonised by the protein concentrations in CAPD fluid, even at the end of the dwell (Fig. 3). *E. coli* display lectins on their fimbriae and are susceptible to phagocytosis without the intervention of opsonins (lectinophagocytosis) [42]. To begin with there was hope that adding IgG to CAPD fluids might improve opsonisation and decrease peritonitis rates, but the practical problems, cost and fugitive increase in concentration of IgG [137] led to this idea being abandoned. Specific opsonic activity in CAPD effluent dependent on anti-staphyloccus antibodies does not correlate with peritonitis [138].

Until recently there were almost no studies on the opsonisation of *S. aureus*. We have shown [98] that, as well as complement and IgG, fibronectin is also an important opsonin for this organism; this is not surprising, since the complex molecule of fibronectin includes a domain which binds to the A protein of the staphylococcus [139].

Interactions between mesothelium, intraperitoneal cells and bacteria

We are now in a position to put these observations together and try to deduce what happens when bacteria gain access to the peritoneum, first in numbers that can be coped with by the defences outlined above and then in quantities that permit multiplication faster than opposing factors and washout. The players in this game are the invading bacteria, the resident mesothelial cells, the macrophages, lymphocytes and opsonins of the peritoneal fluid. The cellular elements communicate, as do cells throughout the body, by signals involving paracrine and autocrine mediators: eicosanoids and other lipid mediators, cytokines and growth factors. It is not surprising that during peritonitis the concentrations of IL-1β [120], IL-6 [140–142], IL-8 [141–143], tumour necrosis factor-α (TNF-α) [144] and γ-interferon [145], as well as PGE_2 [146] and other prostaglandins, are all increased in the dialysate, relative to dialysed patients without peritonitis. However, it is worth noting that these concentrations, in turn, are higher than those in the few observations of normal peritoneal fluid. This tells us only that inflammatory events are underway, but from in vitro studies of the various origins of these cytokines [147–150] a picture of the cross-talk between cells has been constructed by the Cardiff group (Fig. 4) [149–151].

This model postulates that the primary event may be the activation of intraperitoneal macrophages when they encounter and phagocytose opsonised organisms. This results in secretion of both prostaglandins (TXB_2 and PGE_2) and cytokines IL-1β and IL-1α, TNF-α and IL-8. Under the influence of these agents the mesothelial cells synthesise prostaglandins and cytokines in turn, in particular PGE_2 and PGI_2, together with IL-1β and IL-8. This last is a powerful chemoattractant for polymorphonuclear leucocytes, which enter the peritoneal cavity in large numbers on a time-scale consistent with this postulated. Mesothelial

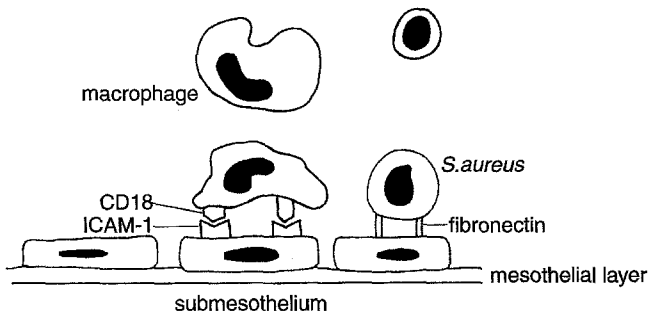

Fig. 5. Adherence of *S. aureus* and peritoneal phagocytes to the peritoneal mesothelium. The adherence of *S. aureus* is dependent upon fibronectin (Glancey et al. [18]) whilst the long-term adherence of leucocytes is mediated by intercellular adhesion molecule-1 (*ICAM-1*) on the mesothelial cells and its ligand lymphocyte function associated molecule LFA-1 on the leucocytes [156]. However, before this firm adhesion is established, initial "rolling" contact mediated by P- and E-selectins is needed [158], similar to leucocyte adhesion to vascular endothelial cells

cells can also secrete MCP-1 [19, 23] in a fashion inducible with IL-1β and TNF-α. MCP-1 is an attractant for macrophage/monocytes, as is RANTES, normally produced by T lymphocytes, but also by mesothelial cells [23]. It is worth noting that the migration of the polymorphs and monocytes is from basal to apical across the mesothelium, the opposite to the migration of these cells from the plasma through endothelial cell layers.

In addition, we must consider the direct cell-cell interactions between bacteria, mesothelial cells and peritoneal macrophages (Fig. 5). Adherence to surfaces facilitates phagocytosis [152]. Organisms have a varied capacity to adhere to mesothelial layers in vitro, *S. aureus* being much more capable in this respect than *S. epidermidis* [153]. Studies in our laboratory have shown that one of the critical molecules in the adherence of *S. aureus* is mesothelial fibronectin [18]: adherence is inhibited by anti-fibronectin antibody treatment of the cells or by soluble fibronectin treatment of the organism, and only strains expressing staphylococcal protein A will adhere. Adhesion mediated by lipoteichoic acid is also important [153]. In our experiments [20] cytokine pre-treatment of the mesothelial cells gave varied results: IL-1 and lipopolysaccharide stimulated adherence, whilst γ-interferon inhibited it. Thus a major feature of virulence is ability to adhere, and pinocytosis of the organism without killing by the mesothelial cell, which occurs in vitro, will only serve to protect the organism from phagocytosis and antibiotics. *S. epidermidis* adherence to mesothelial cells has been shown to inhibit PGE_2 production, but in macrophages leukotriene B_4 (LTB_4) and LTC_4 production is increased [149]. Muijsken et al. [74] point out that after endocytosis *S. epidermidis* remains viable within the cells and may be protected in this environment from antibiotics other than those which penetrate well into cells. Detached mesothelial cells are shed into the dialysate [154] even in the absence of peritonitis, and large areas of basement membrane may be denuded of mesothelial cells during peritonitis. Mesothelial cells are capable also of secreting autocrine growth factors [155] which may be important in the rapid re-mesothelialisation after injury.

In addition, macrophages and neutrophils [156, 157] can adhere to mesothelial cells, which process is ICAM-1 [156], as well as L- and P-selectin [158] dependent. This adhesion stimulates PGE_2 production, as does treatment with IL-1 and TNF-α [147], both produced in quantity by activated macrophages. Surprisingly, in peritoneal biopsies macrophages adherent to the mesothelium are only rarely seen. However, almost certainly in peritonitis-free patients, encounters between macrophages and cells take place predominantly on the *surfaces* of mesothelium, and particularly the catheter biofilm; the phagocytic capacity of the peritoneal macrophages could play a crucial role in the outcome of these encounters, but in the only study to address this important point [159] macrophages proved incapable of phagocytosing organisms on the surface of mesothelial cells, although polymorphonuclear leucocytes had this capacity. This important observation needs to be repeated.

Exit site and tunnel infections; catheter biofilm

Exit site infections. One major unsolved problem in patients performing CAPD is the long-term presence of a silastic catheter from the skin surface into and within the peritoneal cavity. The subcutaneous tunnel and exit site, however carefully placed, often becomes the site of chronic contamination, with or without actual suppuration [84–90]. Exit site infections are more common in children than in adults on CAPD [3]. In a single-centre study of children [160], 46% of infections were with *S. aureus*, both with and without pus, and 11% showed *Pseudomonas aeruginosa*. Gram-positive infections were commonest even in infants.

Exit site infection is in turn is strongly associated with peritonitis [84–90], especially when the organism involved is *S. aureus* (38 of 132 episodes in the series of Levy et al. [160] developed peritonitis). In adults there is a strong host influence, since a major factor in the appearance of *S. aureus* exit site infection is prior nasal carriage of the organism [84–90], although reports to the contrary have appeared [161]. In contrast to the incidence in actual peritonitis, *S. epidermidis* accounts for only about 10% of exit site infections.

Catheter biofilm. As well as exit site and tunnel infections, the catheter within the tunnel and within the peritoneum is almost invariably coated with a *biofilm* [162–165], consisting of adherent *S. epidermidis* embedded in a slime secreted by the organism, under the stimulus of the catheter, plus host protein (particularly fibrin) and cellular debris. This exopolysaccharide ("slime") may be found on many plastics in several sites within the body and was in fact first noted on jugulo-atrial shunts used for the treatment of hydrocephalus – although it was noted on catheters quite early in the history of CAPD [166]. It is produced in varying quantities by different strains of staphylococci [167] and is present on 80%–100% of catheters removed electively, as well as in those patients with recurrent peritonitis.

Table 3. Patients with high and low peritonitis rates: immunological differences?

Macrophage function		Author	Year	Reference
Phagocytosis	No	Lamperi and Carozzi	1990	[99]
	No	Lewis and van Epps	1987	[96]
Staphylococcus killing	No	McGregor et al.	1987	[39]
Expression of DR/RFD7	Yes	Davies et al.	1989	[40]
Secretion of interleukin-1	Yes	Lamperi et al. and Carozzi	1990	[99]
Secretion of prostaglandin E_2	Yes	Lamperi and Carozzi	1990	[99]
Fc receptor expression	Yes	Lamperi and Carozzi	1990	[99]
	No	Lewis and van Epps	1987	[96]
Fibronectin secretion	Yes	Goldstein et al.	1984	[37]
	No	Khan et al.	1987	[125]

This slime will inhibit both lymphocyte blastogenesis [168] and phagocytosis by peritoneal macrophages in vitro [169], and of course provides a privileged environment for the organism away from phagocytosis and antibiotics [170], and obviously could play a role in recurrent peritonitis.

In agreement with this, *S. epidermidis* can be cultured from peritoneal effluent in 5%–10% of healthy patients at any time [171]. In contrast, *S. aureus* is virtually only cultured in the presence of clinical peritonitis. Patients in whom a catheter is placed for CAPD rapidly develop antibodies directed against *S. epidermidis* even in the absence of peritonitis or positive cultures [172], again suggesting that colonisation is near universal.

Continuous intraperitoneal contamination and inflammation

These observations, plus the evidence already alluded to which suggests complement activation [69, 130] and increased cytokine release in the dialysed peritoneum even in the absence of clinical peritonitis [140], has led to a new concept of the pathogenesis of peritonitis in CAPD patients. In contrast to the "classical" model of CAPD peritonitis, in which the peritoneum was pictured as a sterile cavity until bacterial contamination sufficient to overwhelm host defences took place, in almost all healthy patients on CAPD there is a *continued* low-*grade intraperitoneal inflammation* as a result of the localised "pericatheteritis" maintained within the catheter biofilm, possibly also from organisms within peritoneal macrophages or mesothelial cells. Only when the balance in this host-parasite relationship is disturbed does clinical peritonitis appear. This model holds only for *S. epidermidis*, however. If *S. aureus* or Gram-negative organisms are cultured from dialysate, it is almost always in the context of clinical peritonitis, perhaps reflecting the greater virulence and faster replication of this organism.

Table 4. Patients with high and low peritonitis incidences: immunological differences?

		Author	Year	Reference
Opsonisation	Yes	Keanel et al.	1984	[122]
	Yes	Steen et al.	1986	[203]
	Yes	Bennett-Jones	1987	[66]
	Yes	Coles	1990	[126]
	Yes	McGregor et al.	1987	[39]
	Yes	Lamperi and Carozzi	1986	[123]
	No	de Vecchi et al.	1990	[180]
	No	Bennett-Jones	(unpublished)	
	No	Gordon et al.	1990	[152]
IgG concentration	Yes	Keane et al.	1984	[122]
	Yes	Bennett-Jones	1987	[66]
	Yes	Goodship et al.	1986	[124]
	Yes	Coles	1990	[126]
	Yes	Olivas et al.	1990	[179]
	Yes	Kuroda et al.	1992	[182]
	No	Steen et al.	1986	[203]
	No	Anwar et al.	1992	[177]
	No	Zemel et al.	1989	[176]
	No	Nagano et al.	1992	[181]
C3 concentration	Yes	Coles	1990	[126]
	No	Steen et al.	1986	[203]
	No	Anwar et al.	1992	[177]
	No	Kuroda et al.	1992	[182]
Fibronectin	Yes	Goldstein et al.	1986	[131]
	No	Khan et al.	1987	[125]

Studies of patients with high and low peritonitis incidences

Given the variety of host factors, factors intrinsic to the organism, plus the possibility of a triple inter-relationship between organism, macrophage and mesothelial cell, one obvious way to assess the importance of host immune defences is to compare these in patients who have frequent peritonitis and/or lose their catheters with their peers, who enjoy almost indefinite trouble-free dialysis [173–177], with the object of determining whether any host factors can be identified which predict frequent peritonitis (Tables 3, 4). Unfortunately the data are conflicting in many areas, perhaps because of the difficulty of defining new episodes of peritonitis from recurrences in those with frequent attacks and the overall low incidence of peritonitis in most units today. These data are discussed extensively by Holmes and Lewis [34, 113, 127].

Peritonitis and activity of peritoneal monocytes

Numerous studies have been made of macrophage activity, including phagocytosis, oxidative burst, bacterial killing and release of immune mediators on the one hand and susceptibility to develop peritonitis on the other [173–176]. The results are confusing (Table 3), which is not surprising in view of the disagreement about whether these functions are normal overall in dialysis-elicited macrophages from CAPD patients. Most authors have come to the conclusion that there is no difference between

monocytes from those patients with repeated peritonitis and others. However, Carozzi [119] and Lamperi and Carozzi [123] have described several functions of peritoneal macrophages, including decreased IL-1 production, increased PGE_2 secretion and decreased expression of complement receptors in patients as associated with regular peritonitis; some of these observations have not been confirmed, others have not been re-studied as yet. On balance the role of functional macrophage deficiency does not appear to be very important, if it operates at all. Again the importance of macrophage phagocytic capacity, if it exists, probably relates to encounters between organism and macrophage on *surfaces* of the peritoneum or catheter, and not free in the large volume of intraperitoneal fluid.

Peritonitis incidence and opsonic activity of CAPD fluid

Several studies have been conducted to see if either concentrations of particular opsonins (IgG has been studied most frequently) or total opsonic activity correlates with high peritonitis incidence [176–182]. Some data are summarised in Table 4. From this it appears that despite the difficulties and variability there is some relationship between poor opsonisation and frequent peritonitis. However, even in those studies in which a correlation between levels of IgG and/or poor opsonisation and peritonitis rates was found, the overlap in the data is such that it is impossible to predict those who will suffer peritonitis. In addition, the usual effect of negative studies not being published formally is evident: for example, although in an initial study we were able to relate dialysate IgG concentrations to peritonitis rates [66], later work which failed to show any relation of opsonisation to peritonitis has never been presented (Bennett-Jones et al., unpublished observations). However, in sum these data do suggest that varying dilution of opsonins *may* be a weak factor in the genesis of repeated peritonitis.

Peritonitis incidence and presence or extent of biofilm

Although a convincing case can be made that biofilm *should* be important, one immediate obstacle to this idea is that biofilm is almost universally present in patients, whatever their peritonitis histories [162]. Even the extent of the biofilm did not correlate in this best prospective analysis of the subject. Thus, at the moment the presence or extent of biofilm does not seem to be an important issue in determining *which* patients get recurrent peritonitis; however it is almost certainly of crucial importance in determining the continued presence of at least *S. epidermidis* within the peritoneum.

What can we do to minimise the incidence of peritonitis?

Flush before fill systems

Obviously at a clinical level the goal is to achieve a reduction in peritonitis rates. Obviously this starts with effective teaching of good practice, but a substantial reduction in peritonitis rates – mainly from *S. epidermidis* – has already been demonstrated by "flush before fill" systems of the Y connector type in two prospective controlled trials [78, 79] and registry data [80, 81], including children [82], which makes it more difficult to perceive any effects of host factors and minimises their overall importance. Now, however, the challenge is to try and help those patients who still have major problems with recurrent peritonitis despite careful use of disconnect and flush systems.

Treatment of S. aureus carriers

One area for attention is clearly the *S. aureus* skin and nasal carrier [85–90]. Identification of such patients before they have their catheter placed can help by eliminating or inhibiting the nasal carriage by local antiseptics such as mupirocin, chlorhexidine and vancomycin ointment, chlorhexidine baths etc. [183, 184]. The use of prophylactic antibiotics, including co-trimoxazole [185] and rifampicin [186], including impregnation of the catheter or flushing its lumen, has been recommended also. None of these manoeuvres is proven to reduce the incidence of peritonitis.

New styles of catheter placement

For some time it has been clear that details of the catheter placement, and especially the direction of the emergent catheter (downwards is preferable), have a major effect on the incidence of catheter track infections. A radical suggestion by the inventors of the technique of CAPD has been to make the initial placement of the catheter entirely subcutaneous, only allowing access to the outside world after the catheter track has healed in place [187]. This approach is under evaluation at the moment.

Immunisation against S. epidermidis and S. aureus

Is specific immunity against *S. epidermidis* important and can it be boosted? We have already noted that almost all patients bearing CAPD catheters develop antibodies against *S. epidermidis*, and that this bears no relationship either way to episodes of clinical peritonitis [162]. In addition, there is no relationship between intraperitoneal specific antibody in CAPD effluent and peritonitis [138]. Therefore it is not surprising that despite some initial good reports [188], a controlled trial of immunisation against *Staphylococcus* (Staphypan Berna, Swiss Serum and Vaccine Institute, Bern, Switzerland) has not shown it to be effective [189], perhaps because no good antibody response was obtained. However, given new vaccines and modern bioimmunotechnology, this approach deserves to be kept under review. This is illustrated by work with *S. aureus*, showing that it is possible, using conjugate antigens to enhance immunogenicity, to induce antibodies directed against the common types 5 and 8 capsular polysaccharides [190], including in uraemic patients on haemodialysis [191].

Increasing the opsonic activity of CAPD fluid

If opsonic activity of the CAPD fluid is important, then could it be increased? One obvious strategy is to add IgG to the dialysate, and this has been done [192, 193] with apparently beneficial effects. Although there have been claims that a single intraperitoneal instillation leads to persistent increases in levels of IgG, opsonisation and a reduction in peritonitis rates [193], we and others have been unable to replicate the results with regard to the IgG concentrations, finding an immediate washout of the preparation [137]. The high cost makes daily administration impractical on a routine basis, but the use of donor serum – which would add all opsonins – as suggested for surgical peritonitis [194] has yet to be applied in CAPD. It is difficult to see how this could be used prophylactically, although it might have a role in treating resistent peritonitis.

Stimulating phagocytic activity and peritoneal macrophage function

The division of opinion on the importance of macrophage activity and the low likelihood of free fluid encounter between macrophage and organism have been outlined above. However, Lamperi and Carozzi [195] have reported that intraperitoneal instillation of γ-interferon induces a sustained increase in phagocytic capacity of intraperitoneal macrophages. These studies have yet to be repeated. Likewise the use of 1,25′-dihydroxy vitamin D to stimulate macrophages has been suggested by the same group [196], but not confirmed by others [197].

"Resting" the peritoneum

If intraperitoneal macrophages and opsonins are very important, then the logical management of patients on CAPD would be to "rest" the peritoneum, and during an acute episode of peritonitis to haemodialyse the patient temporarily, thus allowing the concentration of phagocytic cells and opsonins to accumulate back to normal levels within the peritoneum [68]. Although the lack of washout could also allow rapid multiplication of any organism present, which might vitiate any advantage, the approach has been tried in patients with repeated attacks of peritonitis and seems to be of benefit [31].

As far as patients without peritonitis are concerned, "resting" the peritoneum can be achieved by schedules of automated peritoneal dialysis, and there is good (although not unanimous) evidence that the incidence of peritonitis using this technology is lower [198], even though immune responses within the peritoneum are similar; Brunkhorst et al. [199], however, found that macrophages were more responsive after a "rest" of 10 h. Thus repeated peritonitis might be one indication for employing this technique. In those with recurrent attacks of peritonitis, a regular "dry" or "rest" period might be introduced to allow the phagocytic defences of the peritoneum to recuperate. Both approaches cost a good deal more than standard CAPD, however, although savings of treatment of peritonitis and possibly catheter removal would made.

The dubious role of catheter biofilm in determining whether or not "pericatheteritis" turns into peritonitis has been outlined above. Two approaches have been used to remove biofilm. The first is the obvious one of removing the catheter, with immediate rather than delayed replacement. This has been done and proved effective [200], although long-term effects on repeated peritonitis are less secure.

Use of fibrinolytic agents

Another approach is to use urokinase or another fibrinolytic agent to digest off the intraperitoneal biofilm. One disadvantage is that this approach does not get rid of that along the catheter track, which could then re-extend into the peritoneum. Nevertheless, several groups have reported favourably on this approach [30, 201]. We have shown that fibrinogen is important for clumping of *S. aureus*, which protects the organism against opsonisation and phagocytosis [98]. In addition, in vitro urokinase treatment of effluent CAPD fluid improved opsonisation of *S. aureus*, but not *S. epidermidis*.

Conclusions

Do host factors matter, then, in determining repeated attacks of peritonitis? The answer, in a typical adult patient, is not much. One suggestive piece of evidence is the radically different pattern of peritonitis in AIDS patients found by some investigators [76]. Manipulation of host factors is unlikely ever to achieve as much in terms of a reduction in peritonitis rates as attention to details of catheter placement, careful instruction in meticulous technique and the introduction of "flush before fill" systems, such as the Y connector, have done. However, in some patients host defences are likely to be critical, an example being what can be achieved by simple measures, such as good positioning of the catheter outlet and identifying carriers of *S. aureus* and treating them appropriately.

One aspect which I have not mentioned so far is the question of nutrition, which is well known to have a profound effect on immune responses [94]. Most of us have the impression that our patients with recurrent peritonitis are the most "flaky" in the clinic – but this may well be the result of the recurrent peritonitis rather than its cause. However, despite promising early results, no clear data emerged from a multi-centre study relating any parameter of general nutrition, such as serum albumin concentration, to the incidence of peritonitis, but this may reflect the imprecision of the nutritional indices [202].

What is certain is that recurrent peritonitis remains a clinical challenge in a group of patients, both adults and above all children, whose best treatment would otherwise be CAPD; we owe it to them to pursue the solution of their problems by whatever means possible. We have very little information on the systemic or peritoneal immune responses of children on dialysis, especially infants, and in view of the higher incidence of peritonitis in young children this information is urgently needed.

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