**Introduction**

Peritoneal dialysis (PD) is now an established and acceptable mode of treatment for end-stage renal failure. Whilst in short-term studies PD (3–5 years) has been shown to have a comparable outcome in terms of patient survival on haemodialysis [1–3], there are still concerns as to whether this mode of therapy can provide adequate treatment for end-stage renal disease in the longer term. Within the first 3–5 years, however, there is a considerable dropout rate from PD. This is principally due to episodes of peritonitis, loss of ultrafiltration or inadequate solute clearance [2–5].

Over the past decade, hand in hand with improvements in solution delivery systems and better understanding of the physiology of peritoneal transport, has been an increased awareness of the need to understand the basic biology of the peritoneal membrane and how this changes during PD. Investigations in several centres have revealed information about the peritoneum’s response to inflammation, as well as some insight into the changes that occur in the structure of this membrane during PD therapy. Peritoneal host defence appears to involve a complex interplay between the resident cells of the peritoneal membrane, infiltrating inflammatory cells and their secreted products in mediating the host’s response to PD itself, as well as to episodes of acute inflammation. This increase in our understanding of the cell biology of the peritoneum has enabled us to begin to address two key questions regarding this therapy:

1. Given that clinical data clearly show a deterioration of peritoneal ‘function’ with time on PD what are the causative factors? Is it related to (a) uraemia, (b) episodes of peritonitis, (c) structural changes in the peritoneal membrane, (d) continuous exposure to dialysis solution components, or (e) any combination of (a)–(d)?

2. If changes in peritoneal structure occur in PD patients, what form do they take and is their development related to the above factors?

The purpose of this review is to provide an overview of our current understanding of peritoneal membrane structure and function, and how this is impacted upon by inflammation and PD solutions over time. Initially we will attempt, based on published literature, to give an overview of the structure of the membrane and subsequently, using recent data from the ‘Peritoneal Biopsy Registry’, update this to give a more contemporary view of the changes that occur with time on PD. We will then examine the processes by which inflammation is activated and controlled, and investigate the potential link between this and peritoneal dysfunction. Subsequently we will discuss the potential impact of solution biocompatibility on peritoneal membrane structure and function. Finally, we will examine what measures might be taken to preserve the long-term function of the peritoneal membrane and discuss which ‘markers’ might be of prognostic value in monitoring the status of the peritoneum, as well as predicting adverse changes that might compromise PD therapy.

**Peritoneal structure and function: changes over time**

**The peritoneal cavity**

The peritoneum is a continuous, translucent serous membrane that consists of a monolayer of mesothelium resting on a basal lamina. Below this there is a compact zone at the margin of which are discontinuous bands of elastin fibres which give the membrane its normal elasticity. Within this ‘compact’ zone are interwoven numerous bundles of collagen fibres embedded in a connective tissue stroma. This
interstitium appears to be largely composed of glyco-proteins and proteoglycans [6–9], although this precise composition remains to be defined. Within the submesothelial interstitium there are visible occasional fibroblasts and mast cells, and interspersed within it are the lymphatics. At the margin of the compact zone reside the majority of small blood vessels. Beneath this layer is largely areolar connective tissue containing some blood vessels.

The peritoneum with its mesothelial monolayer is divided into two parts: the parietal peritoneum which bounds the outer surface of the body cavity and the visceral peritoneum which covers the abdominal organs. The space between these layers forms the peritoneal cavity. In addition, the greater omentum is a mesenteric apron that is continuous with the peritoneum and hangs freely into the peritoneal cavity, extending from the lower border of the stomach and covering the intestines. This consists of a trabecular loose fibrous connective tissue framework covered on its surface by a continuous mesothelial monolayer. It contains fibroblasts, blood and lymphatic vessels. In the visceral peritoneum the compact zone is significantly thinner and contains numerous blood vessels at its margins.

The mesothelium

The mesothelial layer consists of a single layer of squamous epithelial cells of mesodermal origin. In addition to the peritoneal cavity, mesothelial cell monolayers also line the pleural cavity and pericardium [10, 11]. The serosal surface of the mesothelium contains numerous microvilli. These serve to increase the peritoneal surface area, thereby facilitating absorption of materials and reducing friction and facilitating intestinal movement. The mesothelial surface is also covered by a microscopic electronegative ‘glycocalyx’ composed primarily of proteoglycans [12, 13]. These highly glycosylated molecules are hydrophilic, and this may aid the movement of closely opposed surfaces. This movement is also facilitated by the ability of the mesothelial cell to secrete specific phospholipid species possibly derived from the large number of lamellar bodies easily identifiable within the cytoplasm of these cells [14–16]. The mesothelial monolayer consists of a single layer of cells tightly opposed to each other with desmosomes and tight and gap junctions readily identifiable. In common with endothelium the mesothelial cell has a well-developed system of micropinocytotic vesicles and larger membrane-bound vacuoles.

Following the introduction of PD in the early 1970s interest in understanding the biology of the peritoneal cavity inevitably led to the isolation and culture of the cells lining it. Once it was clear (in common with all other tissue cells) that the mesothelium was more than an inert bystander in tissue homeostasis, investigation of the biology of these cells identified their potential role in peritoneal homeostasis and host defence against infection [17–21]. Subsequently, numerous studies, using cultured animal or human mesothelium, have identified that these cells have a vast biosynthetic capacity. Through their expression or secretion of various mediators they have the potential to contribute to peritoneal homeostasis as well as to its response to bacterial contamination. In this respect mesothelial secretion of inflammatory mediators (prostaglandins, cytokines, chemokines and nitric oxide), mediators of fibrinolysis (tissue plasminogen activator, its inhibitor and tissue factor), growth factors, phospholipids and proteoglycan species has been demonstrated [15, 16, 18–43]. In addition they express on their surface adhesion molecules important in their interaction with migrating leukocyte populations (ICAM-1 and VCAM-1). The list of activities secreted or expressed by mesothelium continues to expand.

The submesothelial interstitium

Ongoing research has clearly identified the contribution of the mesothelium to peritoneal homeostasis. More recently our understanding of the function of the cells that reside within the submesothelial interstitium (fibroblasts and capillary endothelium) and changes that occur in the acellular portions of the peritoneal membrane has also increased. The isolation and characterization of peritoneal fibroblasts (that reside within the peritoneal tissue) have demonstrated that these cells also have significant biosynthetic capacity [44, 45], and probably in common with mesothelium contribute to the peritoneum’s response to inflammation. In addition, given the importance of interstitial cells in controlling extracellular matrix turnover, these fibroblasts may be important controllers of structural ‘fibrotic’ changes that have been demonstrated in the dialysed peritoneal cavity. As we will describe later, further investigation will expand our understanding of the contribution of these and other ‘interstitial’ cells to peritoneal homeostasis, and to normal and abnormal extracellular matrix turnover in the dialysed peritoneal cavity.