Spallation of dialysis materials. Problems and perspectives *

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Exposure of dialysis patients to foreign material has been a source of constant concern to nephrologists. Past experience shows that the clinical implications of exposure to foreign materials tend to be understimated for a long period even after the potential risks have been appreciated; this is exemplified by the history of aluminum intoxication [1-4]. It is obvious that the safety of many components used for dialysis has not been rigorously established, e.g. of phthlate plasticizers in dialysis tubing, of polyhydroxyethyl starch as plasma expanders etc.

In uremic patients clinical pathology relating to introduction of foreign material particles may not be unique in hemodialysis. For instance, particulate material in peritoneal dialysis solution has been shown to cause peritoneal reaction [5], and this may or may not be related to chronic sclerosing peritonitis [6], one of the most devastating consequences of continous ambulatory peritoneal dialysis. Furthermore, although no related pathology has been documented to date, the acceptability of current safety standards for particulate material in infusion fluids [7] may need reconsideration for patients on hemofiltration given the enormous volumes infused per hemofiltration session.

Spallation of silicone dialysis tubing and deposition of silicone filings in viscera of hemodialysed patients has recently been described by several authors [8-12].

The following editorial will be restricted to hemodialysis. We shall summarize what is known with respect to particle related pathology, discuss recent evidence concerning pathogenic mechanisms involved and consider bioengineering aspects of the problem.

Particle Introduction. A General Risk of Procedures Involving Access to the Vascular System

Although some biodegradable particles may be present in the circulation without harm, e.g. particulate starch entering by persorption through intestinal mucosa [13-15], most particles consisting of nonbiodegradable material pose potential or definite hazards.

The demonstration of particles, i.e. rubber, bast, cellulose fibers etc. in infusion fluid led to the introduction of rigorous standards for particle content in intravenous fluids [16]. Injection of particles, especially cellulose fibers, into experimental animals caused pulmonary granuloma [16]. Although dialyzers are not free of debris and cellulosic extractables in the 40-90 kD range [17], no related pathology has been recognized in dialysis patients.

During bypass surgery, emboli may enter the brain from various sources —debris from the circuit and the prime, flakes coming off plastic from the pump, silicone antifoam and precipitates from abded drugs as discussed by Wildevuur [18]. Brain dysfunction after open heart surgery was related to particle microembolism [19]. Taylor et al. [20] noted an increase of cerebrospinal fluid creatinine kinase after open heart surgery; such increase was prevented when a micropore filter was added to the extracorporeal circuit to prevent microembolism.

Other authors noted that the difficulty to resuscitate hearts after cardiac standstill was related to particle content in the perfusion fluid [21]; micropore filtration eliminated this problem.

The above examples of pulmonary, cerebral or cardiac microembolism with microvascular occlusion demonstrate the hazards of introducing particulate material into the circulation.

A different type of particle-related pathology, i.e. particle deposition in macrophages of various viscera, has recently been demonstrated in dialysis patients. To date, it is not entirely clear whether these particles enter the circulation by microembolism of after ingestion by circulating monocytes.

Evidence for Silicone Particles in Dialysis Patients

Both we [8] and Leong et al. [9] noted refractile material in macrophages or foreign-body giant cells within various organs, e.g. lung, liver, spleen, bone marrow, skin and lymph nodes. With the use of energy-dispersive X-ray fluorescence microanalysis, it has been established that such material contains the element

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silicon (Si) which is normally absent in biological tissue. Silicon dioxide (SiO_2) has been used for the pretreatment of cellulosic dialysis membranes to prevent caking during the manufacturing process. However, we could clearly establish that the refractile particles are not composed of SiO_2, but of silicone, i.e. the inorganic polymer polydimethylsiloxane.

Identification is based on laser activation micromass analysis (LAMMA) which unequivocally showed fragment masses indicative of polydimethylsoloxane. In brief, the LAMMA technique involves evaporation of the sample in microscopically defined regions, ionisation with pulsed laser beams and subsequent analysis with mass spectrometry. Material other than silicone, particularly PVC, has not been demonstrated to date in organs of dialysis patients. However, available electron microprobe of LAMMA techniques do not permit to reliably detect PVC or polyurethane in microparticulate form within biological tissue.

Silicone is not biologically degradable. Despite some claims to the contrary [22] the Si-O-Si bonds are not hydrolyzed in eukaryotic cells, although some prokaryotes may degrade silicone polymers. Indeed, because it is virtually nondestructible, silicone is used as a marker for contamination by contemporaneous material in archeological studies or environmental research [48].

In hemodialysis patients, the following features have been related to silicone particles: hepatomegaly [8, 9], granulomatous hepatitis [8-10] and elevation of transaminases presenting as non-A, non-B hepatitis [8-10]. Another syndrome presumably related to silicone particles is spenomegaly [23] with splenogenic pancytopenia [24] which is reversed by splenectomy.

One would anticipate that interference with macrophage function shoud cause impairment of immune reactions and antimicrobial resistance. No definite evidence for this has been reported, but our anecdotal observations would be compatible with this possibility. We have noted severe recurrent fatal Yersinia infection refractory to antibiotic treatment, and spontaneous peritonitis by bacterial permeation in the two patients with most severe silicone deposition. No silicone related malignoma formation (see below) has been reported in dialysis patients.

Silicone Causes Clinical Pathology in Nonrenal Patients

The clinical consequences of silicone largely depend on the physical nature of the polymer. Technically available silicone is provided in different consistencies which vary from that of oil to hard rubber.

Silicone oil is used paramedically for cosmetic purposes, e.g. for augmentation mammoplasty [25-32] or hip augmentation in trasvestites or homosexuals [33, 34].

Silicone rubber is used medically for dialysis tubing [8-11], cardiac ball valves [35-37], or joint prostheses [38-41].

After subcutaneous injection of silicone oil, Ellenbogen et al. [34] noted a chronic syndrome characterized by granulomatous hepatitis with elevated transaminases. Similar observations were made with «bleeding silicone bags», i.e. when silicone bags used for augmentation mammoplasty leaked silicone. An acute fatal syndrome with fever, respiratory distress and acute renal failure was observed by several authors after accidental intravenous injection of silicone oil [32]. Furthermore, acute respiratory distress resulting from alveolitis was noted in homosexuals who had injected huge amounts of silicone oil into the subcutaneous fat of the pelvic region [33]. The alveolar lavage fluid revealed numerous macrophages studded with silicone oil granules. The presence of fever and macrophage-related organ pathology may give a clue to the pathogenic mechanisms involved as will be discussed below.

Several complications of the medical use of silicone rubber have been reported. Systemic dispersion of silicone particles is a known hazard of aortic ball valves. As described by Fiegenberg et al. [36] and Ridilfi et al. [35], silicone debris may come off defective aortic ball valves when the surface is roughened by fatigue and fissures. Associated pathology included abnormal transaminases and granuloma formation in the liver [36].

Whether silicone particles are related to malignoma formation has not been established. However, we had the opportunity to study a patient previously described by Digby and Wells [38] who had lymphoma in the regional lymph nodes of an arm bearing silicone articular prostheses of the fingers. The lymphoma was identified as malignant lymphoblastoma. In the lymph nodes bearing the malignancy, silicone deposits could be demonstrated by electron microscopy and X-ray fluorescence microanalysis. Silicone lymphadenopathy is a well known complication of silicone elastomer finger joint prosthesis [39, 40]. One further case of immunoblastoma in regional lymph nodes of an articular silicone prosthesis has meanwhile been reported by Benjamin et al. [41].

Mechanism of Particle-Induced Clinical Pathology

In our histological studies [8] we noted that silicone particles were uniformly present in macrophages and were never seen as microemboli in capillary lumina. This observation led to experimental studies on macrophage function in rats chronically exposed to intravenous or intraperitoneal administration of silicone particles. It could be shown that prostaglandine E_2 and thromboxane B_2 release from peritoneal macrophages was increased both under basal conditions and after stimulation, e.g. with bacterial lipopolysaccharide, zymosan particles or conca-

navalin A. These abnormalities of arachidonic acid metabolism are indicative of macrophage activation [42].

As reported in this issue anecdotal observations in dialysed patients point to similar abnormalities of spleen cell (and presumably macrophage) arachidonic acid metabolism in humans. The mechanisms by which activated macrophages induce organ damage are unknown, but several possibilities exist, e.g. enzyme release, oxygen radical generation etc. These possibilities must be examined in future studies.

The observation of high fever in patients exposed to great amounts of silicone oil [33, 34], as discussed above, would be compatible with the notion that macrophages activated by silicone produce interleukin-1. The longterm consequences of such interleukin-1 production are of some concern. It has recently been suggested that interleukin-1 is produced by monocyttes of dialysis patients after contact with dialysis membranes [43]. Whether such interleukin-1 production is potentiated by the simultaneous influences of particle loading and membrane contact must be clarified in future studies.

A further interaction may be of clinical importance. When examining tissues of dialysis patients with electron microprobe analysis, we were struck by the simultaneous presence of refractile silicone particles on the one hand and aluminum and iron deposits on the other hand within lysosomes of the same macrophages [44]. Whether simultaneous aluminum and iron overload potentiates the action of silicone particles on macrophage function deserves further studies.

Bioengineering Aspects of Spallation

As reported elsewhere [45], scanning electron microscopy demonstrated extensive damage to the luminal surface of dialysis tubing after exposure to a roller pump for 5 h. After such exposure, the surface was covered by debris consisting of large 100 µm flakes and small ground-up powder of 1-10 µm grain size. Similar luminal destruction by pumps is also found in tubing used for cardiac pulmonary bypass surgery [46] and subcutaneous insulin pumps [47].

To further quantitate the number of particles and total amount of silicone filing generated during individual dialysis sessions, we analyzed fragmentation for silicone tubing in an in vitro system imitating the conditions used during dialysis [45]. Particle counts were done by microscopy after quick filtration of the recirculation fluid on a millipore filter; silicone was quantitated using flameless atomic absorption spectrophotometry.

The results show that approximately 1.6 mg silicone per session, corresponding to approximately 250 mg per year, can be released by the roller pump. The amount of silicone released and the number of silicone particles generated can be decreased considerably, i.e. to approximately one eighth and one fourth respectively, when the occlusion force is reduced.

Perspectives

Given the above evidence for silicone-particle-related pathology, the question must be addressed whether such evidence necessarily justifies costly and laborious modifications of today's dialysis techniques.

Substitution of other plastic material for silicone does not appear to be a promising approach since our experimental studies [42] showed similar macrophage abnormalities when animals were exposed to polyvinylchloride or polyurethane particles.

Our experiments [45] show that careful adjustment of occlusion pressure and controlling the distance between rolls and abutment will cause effective reduction of the silicone load. Occlusion pressure in the pump segment has been shown to be the major determinant for silicone debris generation.

Only future can tell whether better handling of existing technologies is sufficient to avoid particle-related problems, or whether more radical changes of the pump system (e.g. introduction of membrane pumps) will be required to control spallation.

Once loading with silicone particles is established, what approaches for patient management are available? Pancytopenia resulting from hypersplenism has been shown to respond satisfactorily to splenectomy [24]. Other complications known today do not necessitate therapeutic intervention. Whether pharmacological modulation of macrophage function will be indicated is unknown.

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