Correspondence

Does particle disease really exist?

Sir,—The hypothesis of wear particles causing foreign-body reaction, periprosthetic osteolysis and eventually prosthetic loosening was already put forward in the 1970s (Brinkmann and Heilmann 1974, Willert et al. 1974). The term cement disease was coined in the 1980s (Jones and Hungerford 1987), generalized to particle disease in the 1990s (Harris 1994), and wear particles are still widely considered to cause prosthetic loosening by a foreign-body reaction, i.e. through a complex series of inflammatory responses to the wear particles. However, the results of some studies contradict this hypothesis of wear-particle-induced loosening. Hence, it seems justified to review the evidence and the counter-evidence for this hypothesis.

Histological evidence from periprosthetic tissue samples
The hypothesis of wear-particle-induced loosening was proposed on the basis of histological findings in periprosthetic tissue samples. Wear particles and numerous macrophages and giant cells were observed in the periprosthetic tissue of failed hip prostheses, and a correlation between the quantity of wear particles and this foreign-body reaction was (and has later repeatedly been) demonstrated. As wear particles were found to be transported to the lymph nodes draining the hip, a wear product transportation equilibrium was suggested: if the quantity of wear products exceeds the transportation capacity, wear products should accumulate in the joint cavity and cause cellular reactions resulting in infiltrating granulomas, periprosthetic osteolysis and eventually prosthetic loosening. Later, in many histological, histochemical and immunohistochemical studies and reviews, attempts have been made to evaluate the impact of various immunological factors in the complex series of inflammatory responses to wear particles in periprosthetic tissue samples from failed prosthetic components (Goodman et al. 2014, Steinbeck et al. 2014, Singh et al. 2015, Wang et al. 2015, Athanasou 2016, Kandahari et al. 2016, Sukur et al. 2016, Jämsen et al. 2017, including numerous references in these papers). These investigations assume, explicitly or implicitly, that the correlation between the quantity of wear particles and the foreign-body reaction represents a causal relationship, and that it is the wear debris that triggers the inflammatory response.

Histological counter-evidence from periprosthetic tissue samples
Histological studies cannot always distinguish between inflammatory responses to wear particles and inflammatory reactions for other reasons in the periprosthetic tissue samples. A few exceptions are cited below.

Linder et al. (1983), who examined the periprosthetic tissue from failed cemented hip prostheses, noticed that wear particles were not always present in granulomatous tissue and that they seemed to play no part in initiating the loosening. The authors concluded that the tissue reaction was caused by prosthetic instability.

Lennox et al. (1987), who examined the interface membrane from failed cemented hip prostheses, found that the implant membranes were abundant in macrophages and giant cells in areas adjacent to the bone surface as opposed to the cement surface. These cells were obviously focused on breaking down dead bone, not on consuming cement particles.

Betts et al. (1992) studied the periprosthetic tissue of failed cemented hip prostheses and found polymethylmethacrylate (PMMA) and polyethylene particles in only half of the periprosthetic tissue sections. The authors concluded that much of the debris seen at revision was generated after the prosthesis became significantly loose.

Rock and coworkers (Rock and Kono 2008, Rock et al. 2011) described in their reviews how the inflammatory response to necrotic cell death (as opposed to apoptotic cell death) develops and they emphasized the fact that when the necrotic tissue is resorbed, the tissue site is rapidly invaded by granulation tissue through a complex series of inflammatory responses to the damage-associated molecular patterns of the necrotic cells. Thus, the wear particles, so often associated with the periprosthetic osteolysis, may actually be innocent passengers in this inflammatory process.

Wear-induced loosening or loosening-induced wear?
The increased wear rate in patients with periprosthetic osteolysis (Dumbleton et al. 2002, Wilkinson et al. 2005) may at first glance be interpreted as support for the hypothesis of wear-particle-induced osteolysis, i.e. that the osteolysis is caused by a foreign-body reaction to an increased amount of wear particles.
formed a series of animal experiments on particles and fluid lesions (Figure 1). Wear debris transported to the site, may cause the osteolytic thesis and suggested that this high pressure, in addition to the 200 mmHg) in an osteolytic cavity adjacent to a loose hip pros-

cavity and cause increased acetabular wear (McKellop et al. 1994, Nieuwenhuijse et al. 2012, Pijs et al. 2012, Klerken et al. 2015, van der Voort et al. 2015, Johanson et al. 2016). These findings strongly indicate that wear particles do not initiate prosthetic loosening (wear particles cannot be expected to have their major influence during the early period of rapid migration).

To explain the rapid early migration, the theory of early loosening was suggested (Mjöberg 1994, 1997), which not only postulates that loosening is initiated at an early stage, but also that the progression of loosening (if initiated) depends on the degree of early instability, on the bone quality, and on the magnitude of the mechanical stresses to which the prosthetic components are exposed: these stresses vary according factors such as body weight, level of physical activity, prosthetic neck length, varus/valgus position, impingement, friction and acetabular component eccentricity (due to design or wear). For example, a femoral component with a long neck or in a varus position is exposed to extra high torque during walking and, especially, when climbing stairs and rising from a chair. After initiation of loosening, all else equal, such a femoral component can be expected to increase the micromovements faster and thus to result in an earlier clinical failure than a femoral component with a short neck or in a valgus position. The theory of early loosening proved able to largely explain the epidemiology of clinical failure of hip prostheses—without any need for the hypothesis of wear-particle-induced osteolysis.

Conclusion

Does particle disease really exist? Probably not. This hypothesis of wear-particle-induced loosening seems to have originally been suggested because the inflammatory responses to necrotic cells in periprosthetic tissue samples were misinterpreted as inflammatory responses to wear particles. Multiple studies have now consistently demonstrated that loosening

Fluid pressure can cause osteolysis, particles hardly can!

Anthony et al. (1990) measured high pressure (up to 200 mmHg) in an osteolytic cavity adjacent to a loose hip prosthesis and suggested that this high pressure, in addition to the wear debris transported to the site, may cause the osteolytic lesion (Figure 1).

Inspired by this observation, Aspenberg and coworkers performed a series of animal experiments on particles and fluid pressures. They found no evidence of polyethylene particle-induced bone resorption at a stable interface (Aspenberg and Herbertsson 1996), but they found that polyethylene particles may inhibit new bone formation (bone ingrowth) and thus possibly modulate the later stages of the loosening process (Aspenberg and Herbertsson 1996, Goodman et al. 1996). Above all, they proved that increased local fluid pressure may cause massive osteolysis and granuloma formation (Aspenberg and van der Vis 1998), that “the effect of a moderately increased hydrostatic pressure outshines any effect of PMMA particles” (Skoglund and Aspenberg 2003), and that short bursts of high fluid pressure or high fluid velocity are enough to induce osteolysis (Fahlgren et al. 2010).

Radiostereometric analysis (RSA)

RSA enables highly accurate in vivo measurements of displacements of the prosthetic components after surgery, which means that some issues concerning prosthetic loosening that previously have given rise to various hypothetical explanations can now be decided.

The migration pattern of hip prosthetic components has been evaluated by RSA measurements in multiple studies. A consistent observation is the rapid early migration of some prosthetic components (Figure 2), which has been found to predict an increased risk of clinical failure several years later, whereas prosthetic components without significant early migration have been found to remain stable (Kärrholm et al. 1994, Nieuwenhuijse et al. 2012, Pijs et al. 2012, Klerken et al. 2015, van der Voort et al. 2015, Johanson et al. 2016). These findings strongly indicate that wear particles do not initiate prosthetic loosening (wear particles cannot be expected to have their major influence during the early period of rapid migration).

However, this causal relationship may well be the opposite, i.e. an unstable prosthetic component can cause excessive wear: when prosthetic micromovements have caused cement fragmentation, cement particles are pumped into the joint cavity and cause increased acetabular wear (McKellop et al. 1990, Wang et al. 2001)—which then in turn accelerate the progression of loosening of a loose eccentric acetabular component due to the mechanical stresses caused by the increased torque (Ramadier et al. 1980).

Conclusion
is initiated at an early stage, i.e. long before any significant amounts of wear particles have been produced.

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