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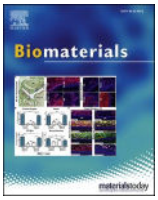

The plasticity of biocompatibility

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ABSTRACT

Biocompatibility concerns the phenomena that occur within the interactions between biomaterials and human patients, which ultimately control the performance of many facets of medical technology. It involves aspects of materials science, many different forms of engineering and nanotechnology, chemistry, biophysics, molecular and cellular biology, immunology, pathology and a myriad of clinical applications. It is not surprising that an overarching framework of mechanisms of biocompatibility has been difficult to elucidate and validate. This essay discusses one fundamental reason for this; we have tended to consider biocompatibility pathways as essentially linear sequences of events which follow well-understood processes of materials science and biology. The reality, however, is that the pathways may involve a great deal of plasticity, in which many additional idiosyncratic factors, including those of genetic, epigenetic and viral origin, exert influence, as do complex mechanical, physical and pharmacological variables. Plasticity is an inherent core feature of the performance of synthetic materials; here we follow the more recent biological applications of plasticity concepts into the sphere of biocompatibility pathways. A straightforward linear pathway may result in successful outcomes for many patients; we may describe this in terms of classic biocompatibility pathways. In other situations, which usually command much more attention because of their unsuccessful outcomes, these plasticity-driven processes follow alternative biocompatibility pathways; often, the variability in outcomes with identical technologies is due to biological plasticity rather than material or device deficiency.

1. Introduction

Trained as a metallurgist, I never thought I would use the term 'plasticity' in a biological context. After all, plasticity is defined as '*the ability of certain solids to change shape permanently when subjected to stresses*' [1], the emphasis being on 'permanently' to distinguish this deformation from elasticity, which is reversible, or non-permanent. After working in biomaterials science, and specifically the area of biocompatibility, for over 50 years, I thought even less of using plasticity in the description of biocompatibility phenomena. On moving from the engineering of implantable devices to the highly biologically-oriented arena of regenerative medicine, I witnessed with a detached perspective the use of this term to describe some aspects of stem cell behavior [2].

But, a few months ago, I was re-reading Darwin's '*The Origin of the Species*' [3], and there I encountered him using '*plastic*' and '*plasticity*' to explain some concepts of natural selection in living species, which had nothing to do with permanent changes of shape in solids. To add to my increasing confusion, I then read a biography [4] of Santiago Ramón y Cajal, the 1906 Nobel Laureate in Physiology or Medicine for his work in neuroscience, only to find him discussing neuronal plasticity, a term that was used to describe metamorphic phenomena in sensory neurons. Both men used these terms sparingly, but they had a profound influence on subsequent thinking.

Darwin referred to this concept in two ways. First, he noted that in many plants it is possible to see endless points of structure and constitution in which the varieties and sub-varieties differ slightly from each other; "*the whole organization seems to have become plastic, and departs in a slight degree from that of the parental type*". This has become the basis of developmental plasticity [5,6] which is the capacity of the same genotype to produce different phenotypic outcomes depending upon inputs during development. Secondly, he referred to modifications to breeds of animal where the animal's organization is considered '*as something plastic, which they (breeders) can model as they please*'. Here we see the combined concepts of irreversible change with the ability to model, or mold.

The situation with Cajal is a little different, and I am indebted to Stahnisch and Nitsch for explaining the ambiguity that arose with his work [7]. According to La Ros et al. [8], brain structural plasticity is a phenomenon that allows the mature brain to adapt to environmental

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changes, to repair itself after lesions or disease, and to slow aging. One of Cajal's major achievements was to transfer concepts of functions in the peripheral nervous system to those in the central nervous system, a step which was too far for many of his contemporaries in the 1890s. He had great difficulty with the dogma of immutable morphology in the adult brain, which led him to speculate that "*but the functional specialization of the brain imposed on the neurones two great lacunae: proliferative inability and irreversibility of intraprotoplasmatic differentiation. It is for this reason that, once the development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably*" [9]. Once I saw the reference to irreversibility, I started to appreciate the real concept of plasticity here. Without the possibility of both reversible and irreversible change, brain function is limited and unadaptable. In the material science context, it is equivalent to saying that deformation of solids is restricted to elastic deformation, at the limit of which there can be no permanent change of shape, just brittle fracture; the '*founts of adaptation and manipulation dry up irrevocably*'.

So how is this relevant to biocompatibility? This term arose in the biomaterials field after years of misunderstanding about the host response to biomaterials, and was eventually defined, through consensus [10], as '*the ability of a material to perform with an appropriate host response in a specific application*'; this was in 1987 and it was reaffirmed as the correct definition at a consensus conference in Chengdu, China in 2019 [11]. Nevertheless, there has been controversy over the mechanisms of biocompatibility, whatever this definition says, for several decades [12]. The main problem is that the definition is conceptual and does not help anyone to develop biomaterials with superior biocompatibility characteristics; moreover, it gives no guidance as to what is 'appropriate'. Such difficulties have been compounded by the significant increase in the number and variety of biomaterials applications. Back in the 1980s these were largely confined to implantable devices and artificial organs; now there are also tissue engineering constructs, imaging and *in vivo* diagnostic systems, and drug and gene delivery systems, where objectives may be different, and concepts of appropriateness vary considerably.

Each clinical application of a biomaterial needs to be embraced by its own biocompatibility sphere. That does not mean that we need a different definition of biocompatibility for each situation, but we do need an overarching framework. For most implantable devices, this framework must incorporate all factors that can influence the development of the so-called foreign body response. For a biomaterial-based tissue engineering construct, the framework has to encompass both the avoidance of adverse effects on cells together with proactive stimulation and direction of tissue regeneration. For nanoparticle-based imaging contrast agents, it needs to address the same type of ADME (absorption, distribution, metabolism and excretion) factors that are involved with pharmacokinetics of drugs, and so on.

I have recently tried to identify the main scientific characteristics of biomaterials and their devices that control clinically significant biocompatibility outcomes [13]. I have also correlated the features of so-called bioactive materials with that paradigm [14] and have drawn attention to the implicit conundrum that is encountered with tissue engineering scaffolds [15] but have struggled to identify that overarching framework. What has been missing is that thread, or perhaps network, that holds the pieces together. In this paper, I propose that we consider biocompatibility is associated with the concept of plasticity, just as Darwin and Cajal showed in their respective areas.

Why is this important? It seems that there has been a retrograde movement in our collective understanding of biocompatibility in recent years. In all the clinical applications I have alluded to above, it is inevitable that not all patients will be satisfied with the outcome. An inability to achieve universal satisfaction is frequently attributed to device or biomaterial 'failure', which is usually related to deficiencies in biocompatibility. This attribution is fueled, in the USA at least, by the power of both litigation and social media (themselves inextricably linked), which leads to public demands for absolute safety and for 'biocompatible' materials; I should add here that for many years I have pointed to the inappropriateness of the adjective 'biocompatible' since, as the definition explicitly states, biocompatibility has to be placed into the context of the specific application, so that there is no such thing as a universally 'biocompatible material' [16]. The ensuing controversies often lead advocates of the 'failed material' accusations to develop hypothetical mechanisms of adverse reactions, usually introducing their own pejorative language to emphasize where the fault lies; terms such as metallosis related to the use of metallic systems in joint replacement, bridging fibrosis and meshoma to characterize responses to surgical meshes, and BII or breast implant illness with silicone breast implants, have contributed to the non-scientific treatment of serious problems.

Implicit in the development of this myriad of failure mechanisms is the assumption that each situation is new and different to others and gives rise to symptoms and diagnoses of new classes of conditions, or indeed, of new diseases. The reality is that the juxtaposition of foreign materials and tissues of the body is not new and our bodies have generic mechanisms to deal with these situations. These mechanisms are based on the principles of inflammation and immunity, with contributions from both toxicity and tissue repair. Because there are so many specific circumstances in which this juxtaposition arises, there will be many variations in the precise biocompatibility pathways that can be identified; in some situations, the pathways are quite simple and the outcomes of the plasticity phenomena are binary in nature, while other are far more complex. However, there is sufficient plasticity in these pathways for them to be accommodated within one overarching framework, and within which we see variations in pathology and clinical conditions that are quite consistent with existing biological science, without implications of new diseases. We cannot, of course, consider only the biomaterial properties in these pathways since we must take into account individual patient variables, clinical skill factors and, in many cases, epigenetic factors.

2. Outline of overarching biocompatibility model

I would like to think that the days have long gone when biocompatibility, equated in many people's minds with biological safety, was simply characterized by the classical perturbation of wound healing, involving the combination of inflammation and fibrosis, giving variations of the foreign body reaction. Our ideas about this process were largely shaped both by observations of the host response to monolithic implants placed in relatively unstressed sites within, for example, the paraspinal musculature of in-bred rats, together with the lack of any effects on cells and cellular components in *in vitro* test environments. Scenarios consistent with this simple paradigm are shown in Fig. 1.

These pathways are essentially linear sequences of events, on which may be superimposed bursts of cascade phenomena, such as macrophage or complement activation, and the outcomes will either be clinically acceptable resolution or clinically unacceptable unresolved situations, including progressive chronic inflammation, hyperplasia or cell/tissue death. In the materials science analogy, these pathways are equivalent to elastic systems, perhaps with the interjection of some superelasticity, which end in a functionally stable equilibrium or brittle fracture.

Such simple biocompatibility models do not, generally, take into account the wide array of system variables that could possibly influence the real-time interactions between biomaterials and human hosts, such as.

- Biomechanical environments, including processes of mechanotransduction, and associated effects of Body Mass Index, physical activity etc.,
- Altered biophysical characteristics,
- Variations in individual responses in innate immunity,
- Variations in individual responses of adaptive immunity, including effects of immunomodulatory biomaterials,

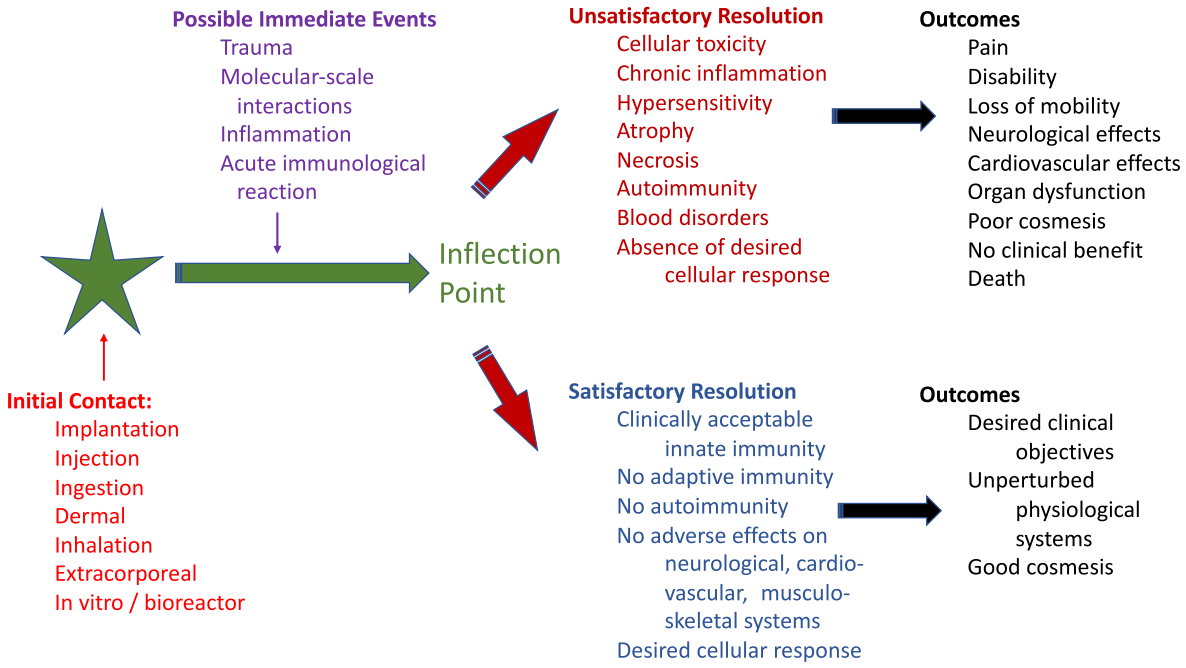

Fig. 1. The simple linear paradigm for biocompatibility pathways, based upon conventional ideas about the host response.

- Susceptibility to chronic inflammation,
- Effects of prior exposure to viruses, e.g., Epstein-Barr Virus,
- Genetic predisposition to autoimmunity,
- Variations in mechanisms of internalization of particles, especially nanoparticles,
- Effects of age, gender and diet,
- Effects of co-morbidities and accidental trauma,
- Effects of life-style factors such as smoking and recreational drugs,
- Influences of separate pharmacological agents,
- Iatrogenic effects associated with clinical technique,
- Biomaterial-induced epithelial-mesenchymal transition,
- Metal ion influence on downstream signaling pathways that control the equilibrium between osteoblast and osteoclast activity.

There may not seem to be much connectivity between these phenomena, but there are already some hints with the language, including 'transition', 'prior exposure' and 'predisposition', that are suggestive of idiosyncrasy and both genetic and epigenetic factors. In the following sections, many of these factors will be addressed within discussions about selected clinical scenarios in which the complexity of biocompatibility pathways significantly influences outcomes. This will allow the establishment of a framework that embraces the concepts of plasticity of these pathways. The selection of scenarios discussed here has been based on those areas that have substantial relevant data, and they cover areas with which I have, personally, some experience; many other applications, such as contact lenses and bioartificial organs, could well be considered within this context.

One thing will become clear from this analysis. For many patients there will be successful outcomes of procedures involving biomaterials technology (i.e., characterized by the lower right section of Fig. 1), and we can denote the events taking place as being of historically conventional biocompatibility pathways. For others, where the outcomes are, to a greater or lesser extent, unsatisfactory, (top right of Fig. 1), the events may be dependent on plasticity, following different biocompatibility pathways.

3. Clinical scenarios

In each of the exemplars described in this section, there is a summary of the background story, a discussion of the mechanisms (established or proposed) of the specific phenomena, and the identification of the plasticity characteristics.

3.1. BIA-ALCL; breast implant associated – anaplastic large cell lymphoma

I start with a biocompatibility (and, indeed, a biological safety) issue that has only arisen very recently. It is important since it relates to observations of tumors associated with a very popular type of medical device, that is the breast implant.

3.1.1. Background

For many years there have been the occasional claim that implants, including breast implants, can be the cause of tumors; there is a remarkable lack of evidence (epidemiological, pathological, clinical etc.), as I summarized a few years ago in relation to surgical meshes [17], but this new scenario is of significance since it concerns lymphomas occurring at sites remote from the implant. A lymphoma is the most common cause of blood cancer, affecting lymphocytes. Overall incidence is highly variable [18]; as an example, in the USA, about 100,000 individuals are diagnosed with lymphoma each year. Non-Hodgkin lymphoma is the most common form of hematological malignancy, and within this category is anaplastic large cell lymphoma (ALCL). There are several risk factors for lymphomas, including certain bacterial infections, prior exposure to some viruses, a lowered immune system, and autoimmune conditions. ALCL is an aggressive type of lymphoma that is usually of the T-cell type, which may become manifest in the lymph nodes, skin, lungs and elsewhere; there is no single cause of ALCL It has been recognized for decades, however, that one gene, anaplastic lymphoma kinase gene (ALK) plays a significant role in the development of ALCL [19] and that there are different outcomes with individuals who are ALK negative to those who are ALK positive [20]. All ALCL patients have large neoplastic cells of a cohesive growth pattern, with abundant cytoplasm, pleomorphic nuclei, and uniform strong expression of CD30. However, a greater proportion of ALK negative ALCL tumors are CD2 and CD3 positive, and ALK positive ALCL tumors are more often EMA (epithelial membrane antigen) positive with greater cytotoxic protein expression. The histopathological appearance of ALK negative

lymphoma is shown in Fig. 2.

Keech and Creech were the first to publish a report on anaplastic T-cell lymphoma in the proximity of a breast implant in 1997 [22]. This involved a patient who had been implanted with saline-filled products 6 years previously; a biopsy revealed ALCL, which was treated successfully with chemotherapy and radiation. No causality between the lymphoma and the implant was demonstrated. The next report was that of Sahoo et al., [23] who described an ALCL in a patient who had several types of implant over a period of 15 years.

A pathological study was published in 2008, Roden et al. reporting four women with neoplastic T-cell seroma in the vicinity of either saline or silicone gel-filled implants [24]. All were ALK negative, and the condition was described as an indolent T-cell lymphoproliferative disorder that was readily resolved by conventional cancer therapies. De Jong et al. reported a survey of women who had received breast implants, yielding 11 patients with ALCL. The report suggested that there was an association between implants and lymphomas but noted that the absolute risk was 'exceedingly low' [25]. Miranda et al. described 21 cases of ALCL, 15 of which, all ALK negative, were associated with breast implants, '*suggesting a pathogenic relationship*' [26]. Lipworth et al. reviewed five studies involving 43,000 women with cosmetic breast implants, for up to 37 years [27]. There were 48 observations of non--Hodgkin's lymphoma, which was less than the number expected on the basis of a statistical analysis of a control cohort group. They concluded that there was no credible evidence of an increase of non-Hodgkin's lymphoma originating in the breast among women with implants.

Kim et al. [28,29] concluded that there is a positive correlation between breast implants and ALCL, that it is usually clinically indolent with favorable prognosis. Miranda et al. published a follow up of 60 patients [30]. They suggested that there were two patient sub-sets, most presenting with an effusion around the implant, without a tumor mass, achieving complete remission with excellent disease-free survival. A smaller sub-set presented with a tumor mass associated with the fibrous capsule, which was more aggressive. Thompson and Prince confirmed the existence of these two sub-sets, stating again that women with effusions but no tumor masses had excellent long-term survival [31].

Several other epidemiological and literature review-based studies were published between 2017 and 2021 [32–37]. These suggested that the incidence of BIA-ALCL is between 1 in 1000 and 1 in 30,000 implant recipients, that there is little difference between saline and silicone gel filled products, that implants with textured surfaces tended to be associated with more cases, and that most cases were ALK negative and CD30 positive.

3.1.2. Mechanisms

The first comprehensive discussion about potential mechanisms of BIA-ALCL was published by Ye et al. [38], which confirmed that the typical patient was around 50 years old and had received a silicone shell implant a decade before. The most common symptoms were late seroma and the presence of a palpable mass. The authors suggested four possible mechanistic factors.

- Chronic inflammation and the inflammatory milieu; the response to the implant is a form of inflammation and states of inflammation exhibit higher incidences of cancer.
  - Inflammatory oncotaxis; this is the attraction to and activation of circulating neoplastic cells within a host by inflamed tissue space.
- Immunogenicity of implants; associated with the implant materials or surface texture.
- Subclinical infection: there is a substantial body of evidence that many incidences of cancers in general, but including lymphomas, are attributable to infections.

Montes-Mojarro et al. discussed the appearances of large cell lymphomas in general and those apparently associated with breast implants in particular [39]. They described this condition as a $CD30^{+}$ lymphoproliferative disease; epidemiological studies had not been able to demonstrate an increased risk of lymphoma in patients with breast implants. The women were diagnosed between the ages of 24 and 82 years, presenting with a mass or ~~a~~ periprosthetic fluid; one subgroup presented as an effusion around the implant, and a second presenting with a palpable indolent tumor. In the first group, the capsule is commonly thickened, showing a granular layer with adjacent fibrinoid material, but the implants usually are intact. The second subgroup of patients shows a wider morphological spectrum. The neoplastic cells grow in a cohesive manner within a fibrotic or chronic inflammatory background and show multinodular appearance with necrosis and abundant sclerosis. Some cases show a predominant chronic inflammatory infiltrate composed by lymphocytes, histiocytes, and eosinophils, masking the neoplastic cells, which themselves are strongly positive for CD30 and usually negative for ALK. T cell-associated antigens such as CD3, CD5, and CD7 are usually negative. Chromosomal abnormalities involving ALK, DUSP22, and TP63 genes are absent, but recurrent mutations in the JAK-STAT3 pathway have been reported.

These observations and their interpretation were consistent with those of Di Napoli et al., who referred to the '*inflammatory cytological patterns*' [40]. Kadin et al. reinforced the potential role of inflammation, especially allergic inflammation, through the observation of the

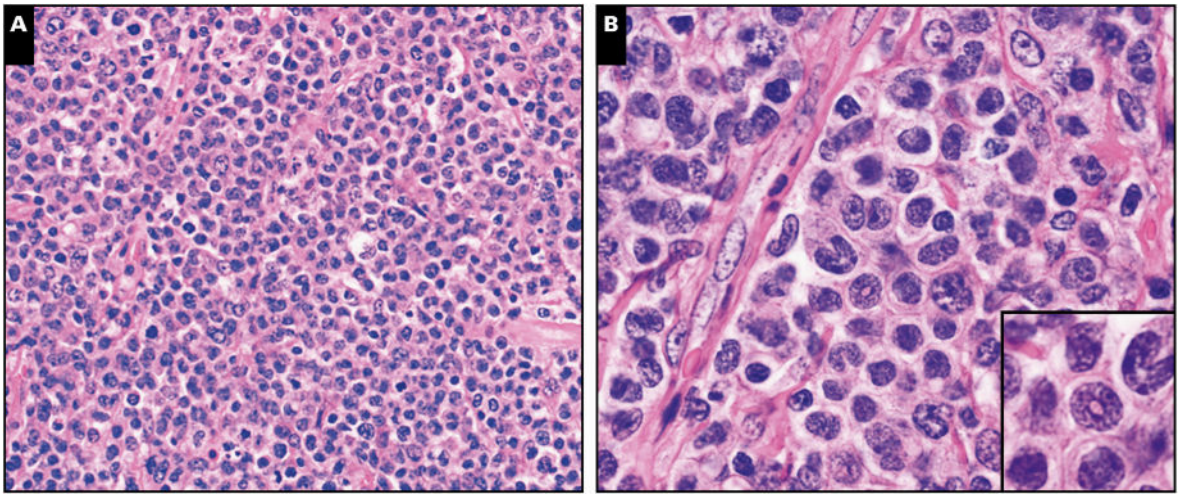

Fig. 2. Pathological features of ALK-negative anaplastic large cell lymphoma, showing sheets of medium-to-large size cells with reniform nuclei and doughnut cells (in inset), H&E x400. After Amador and Feldman [21], with permission.

cytokine IL-13 in the tumor cells in BIA-ALCL, which they describe as the '*signature cytokine of allergic inflammation*' [41]. The essential question then focuses on the agent to which the allergic inflammation is directed, these authors suggesting '*that BIA-ALCL is the end result of an amplified immune response, possibly to antigen(s) associated with bacteria in the biofilm surrounding breast implants*' and '*these findings suggest the hypothesis that an amplified immune response with features of a chronic allergic reaction in a susceptible patient underlies the pathogenesis of BIA-ALCL'*.

With respect to the comments in the previous paragraphs about mutations and chromosomal aberrations, attention has recently been directed towards genetic factors [42]; BIA-ALCL may have a unique pattern of genetic alterations. It is consistently negative for most ALCL-related gene rearrangements, but the JAK-STAT3 pathway is constitutively activated in BIA-ALCL In a 2020 study by Laurent et al., it is particularly important to recognize their main conclusion that '*the BIA-ALCL genomic landscape is characterized by not only JAK/STAT activating mutations but also loss-of-function alterations of epigenetic modifiers*' [43]. Although there are many possibilities here, the type of molecules released during some inflammatory conditions could cause genetic modifications within signaling pathways that lead to lymphoma production.

This broad conclusion was supported by the study of DeCoster et al., who concluded that an inflammatory microenvironment may facilitate malignant transformations through this JAK-STAT3 signaling pathway [44]. On the other hand, Blombery et al., pointed to the observation that some cases of BIA-ALCL occurred in patients with germline TP53 mutations, which is a rare genetic condition that predisposes the individuals to some forms of cancer, including breast cancer [45]. In a similar manner, de Boer et al., reported that women with a germline mutation in the BRAC1 or BRAC2 genes who had received breast implants were at higher risk of developing BIA-ALCL [46]. Tevis et al. also reported genetic susceptibility factors that are responsible for germline genetic variation in human leukocyte antigen in patients with BIA-ALCL [47].

As Rondon-Lagos et al. point out [48], there appear to be some unique genomic abnormalities leading to dysfunction of these biological pathways, especially the JAK1/STAT3 signaling pathway and the occurrence of BIA-ALCL, with a complexity of chromosomal aberrations, and genetic amplifications not seen elsewhere. One possible factor is that some rare lymphomas occur in situations where there is chronic inflammation but also decreased immune surveillance; some other forms of lymphoma have been found within the central nervous system and testes, both known to be immune-privilege sites, and such conditions could be present in the breasts of some patients [49].

Hu et al., in 2015, were among the first to suggest that bacteria were associated with large cell lymphoma [50]. Their conclusions were derived from a study in pigs, and from some observations in human patients, where there was a significant correlation between the number of bacteria and the number of lymphocytes in tissue fluid. The microbiome of breast implants and the periprosthetic tissues of patients was recently reported by Walker et al. [51]. The microbiome showed commonly cultured microbes in both BIA-ALCL and control samples, with no significant differences between them. Swanson has argued persuasively that there is unlikely to be a significant infectious etiology [52].

Two papers were published in 2020 that drew attention to the potential association of the Epstein-Barr virus (EBV) with susceptibility to BIA-ALCL. Rodriguez-Pinilla et al. described three cases of EBV positive large cell B lymphomas in patients with breast implants [53] and Mescam et al. reported a similar number of cases [54]. Medeiros et al. [55] noted here that the EBV is a member of the herpes virus family; it is very common, most cases of infection being mild. The virus usually becomes inactive for long periods of time, potentially reactivating under certain conditions, where stressors such as surgery, accidents, a depleted immune system or emotional stress are present. The cases typically had $CD30^+$ EBV-infected B-cells. Lymphomas were usually inside the tissue capsule, with varying amounts of inflammatory cells. There was a distinct overlap between the morphologies of these EBV-associated lymphomas and the usual non-EBV-associated ones, but there are clearly some differences. It has been postulated that these EBV-positive diffuse large-B-cell lymphomas arise at the site of chronic inflammation, driven by a local immunosuppression [56]; as such they have been labelled DLBCL-CI, Diffuse Large B Cell Lymphoma – Chronic Inflammation.

These possibilities created by an apparent association of EBV and BIA-ALCL raise several questions. First, as noted by Mansy et al. [57], the spectrum of breast implant large cell lymphomas extends beyond BIA-ALCL, rendering diagnosis less certain. Secondly, since the true incidence of EBV involvement in all BIA-ALCL cases is not known, and since EBV itself is a known risk factor for multiple forms of cancer [58], including Hodgkin's lymphoma, it is possible that this virus is the main driver of BIA-ALCL. As Mansy et al. point out, '*the etiology of EBV-associated cancers likely results from a complex intersection of genetic, clinical, environmental and dietary factors*'.

There has been an increasing interest in the role of surface topography of breast implants (discussed as texture or roughness, see Fig. 3) in BIA-ALCL and its relationship to the degree and type of inflammation within the host response and capsule formation. Most epidemiological studies have pointed to the significant preponderance of incidences of BIA-ALCL with textured implants, but there has been considerable speculation as to why this should be so. In 2012, Britez et al. showed a statistically significant higher level of lymphocytes and histiocytes with textured breast implants compared to smooth walled implants, with a dominance of T lymphocytes over B cells [60].

A major review of large cell lymphomas associated with breast implants, concluded that these cases were site- and material-specific lymphomas [61]; out of 173 cases, none were found in patients with smooth devices, while they were unrelated to the implant fill material (silicone gel or saline). The evidence suggested that there was a chronic inflammatory cause, and the demographics and associated skin lesions suggested a genetic predisposition. A similar paper by Loch-Wilkinson et al. [62] confirmed the increased risk with '*high surface-area textured implants*', suggesting that the high surface area leads to greater colonization by bacteria. They correctly point to the multi-factorial nature of the phenomenon, speculating that these surfaces lead to chronic antigen stimulation in genetically susceptible hosts over a prolonged period of time, a view reinforced by Clemens when commenting on this paper [63]. Doloff et al. have shown that topography influences the immune response to silicone implants, suggesting that a roughness of 4 μm is ideal since it is associated with a lower foreign body response, and the production of immunosuppressive regulatory cells [64].

Although the evidence that BIA-ALCL is more associated with textured rather than smooth wall implants is incontrovertible, even though some authors now question the strength of the association [65], there is still no universally accepted explanation. It is most likely that the textured implants generate a stronger chronic inflammatory response, which mutates in some way to a lymphoma in genetically susceptible patients, but efforts to identify differences with responses to different surfaces have failed to produce significant outcomes [66]. The situation may be even more complex following observations of both B-cell and T-cell lymphomas in the same implant capsule, with indications that autoimmunity is involved [67].

Any attempt to specifically and uniquely link anaplastic large cell lymphomas to breast implants, and especially textured breast implants, with demonstrable evidence of causation, has to consider whether similar lymphomas are found in situations involving other type of implanted device. Cheuk et al. [68] identified eight cases in the clinical literature where lymphomas had been reported around metallic implants. These implants routinely showed osteomyelitis associated lymphoma, with long-standing chronic inflammation or irritation, with a long latency period and histological features of $CD20^+$ large B cell lymphoma, and association with EBV. Palraj et al. have reported a case

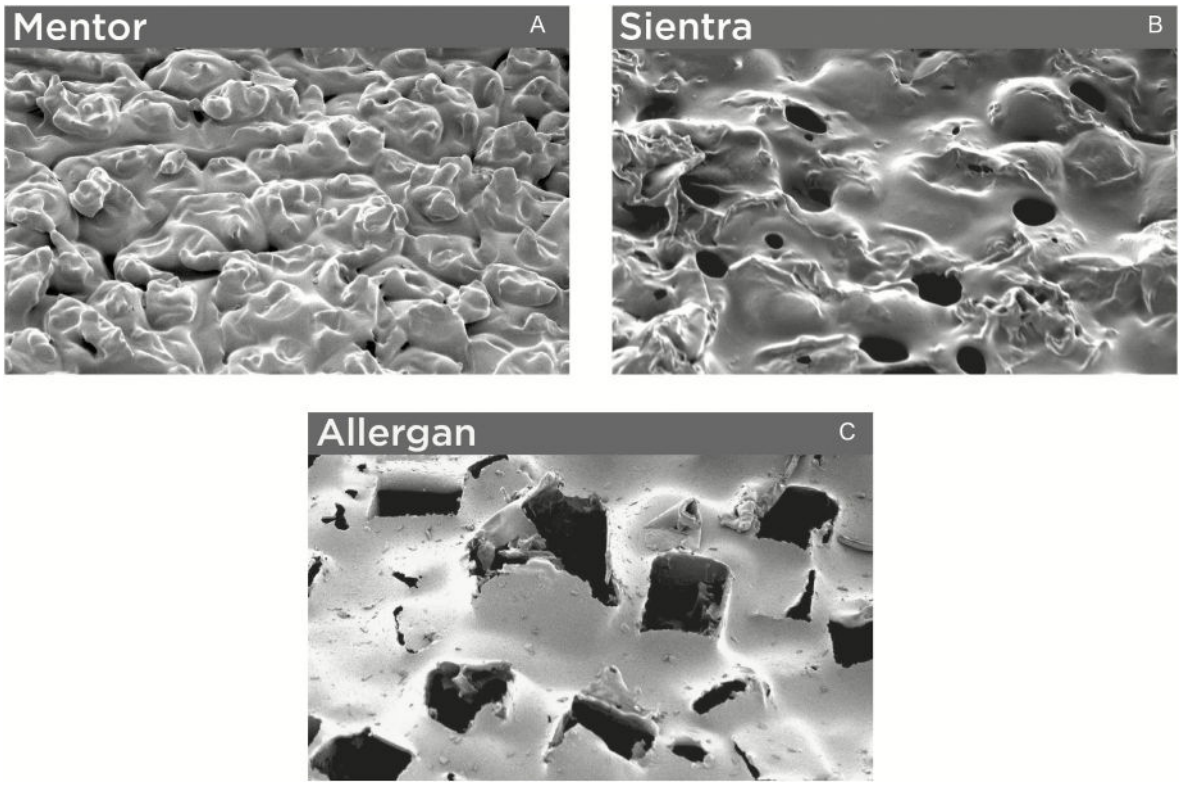

Fig. 3. Scanning Electron Micrographs of textured surfaces of some commercial breast implants, After Calobrace et al. [59], with permission.

of soft tissue large T-cell lymphoma around a stainless steel fixation plate implanted in the tibia for 7 years, inferring that the mechanism involved a chronic inflammatory reaction to the implant-derived antigenic stimulus which evolved to lymphoma through clonal transformation and/or genetic mutation to a particular subset of lymphocytes [69]. Sanchez-Gonzales et al. reported a case of a diffuse large B-cell lymphoma in a knee replacement patient, with proliferation of EBV transformed B cells induced by chronic inflammation [70]. Wang et al. reported a similar pathology associated with metallic screws and rods used in lumbar spinal fusion surgery [71]. An EBV- associated diffuse large B-cell lymphoma has been reported in the chest wall 20 years after reconstruction with polyethylene terephthalate mesh [72]. The same type of material, in the form of a Dacron aortic prosthesis, was reported to be associated with an ALK-negative anaplastic large cell lymphoma in a patient who had been treated with endovascular aortic aneurysm repair 7 years previously [73].

A controversial aspect in this context is the apparent occurrence of large cell lymphomas associated with space-filling gluteal prostheses, Mosquera-Zamudio et al. reporting one case of diffuse large B-cell lymphoma in a patient with necrotizing fasciitis in the region of silicone implants in the buttock [74], Shauly et al. reporting a similar, but more aggressive, case [75]. Mendez et al. discussed a case in which a woman with gluteal augmentation by silicone implants experienced increasing volume and distortion of the left buttock, which was shown to be infected and later explantation revealed large cells positive for CD30 and CD4 and negative for ALK [76]. However, both Senderoff [77] and Piubelli et al. [78] believe that it is premature to draw analogies between the gluteal and breast implant experiences.

Whether or not it is premature to draw precise analogies cannot negate the fact that lymphomas do occur in patients with prostheses other than breast implants [79]. Two reports in pathology journals, one [80] appearing before all of the attention given to BIA-ALCL, and one [81] just last year, present balanced, unbiased views on this matter. Descriptions of these lesions according to the first of these papers included '*aggregates of large lymphoma cells with definite cytologic atypia, aberrant immunophenotype, immunoglobulin light chain restriction and gene rearrangement, a very high proliferation index and uniform labelling of cells for Epstein Barr Virus*', with a clear indication of diffuse large B-cell lymphoma with long-standing or slow-growing chronic inflammation, occurring in enclosed environments and in association with the EBV.

3.1.3. Plasticity

The conventional biocompatibility pathway for breast implants involves acceptable degrees of inflammation and fibrosis, leading to the formation of a fibrous capsule around the device. The extent of fibrosis varies, and in some cases may be excessive and painful, giving the clinical condition of capsular contracture.

The plasticity of breast implant biocompatibility, specifically related to BIA-ALCL, is shown schematically in Fig. 4. Inevitably, there will be an inflammatory response to the implant, associated with the surgical procedure and possibly influenced by implant characteristics, including surface texture, and bacterial biofilms. The inflammatory cells release cytokines, the profile of this release, both temporally and molecularly, controlling cellular responses. Thus, inflammation activated cytokine generation is the driver for BIA-ALCL, while the consequences are dependent on the susceptibility of the host, where major risk factors are ALK negativity, certain genetic pathway mutations, some germline mutations, mutations in epigenetic regulators and prior exposure to certain viruses including EBV. Depending on a variety of processes which are not yet clear, the magnitude of the effects of these biological factors, and interactivity between them, determine whether, as in the majority of cases, the proliferation of T lymphocytes leads to an indolent and manageable effusion, or, in rare cases, it leads to malignancy.

The metallurgical analogy is that of deformation, where the driver is mechanical stress and where the consequences of that applied stress are determined by inherent material characteristics, such as grain boundaries and precipitates (analogous to genetic factors and viruses) and by environmental factors such as temperature (analogous to epigenetic factors).

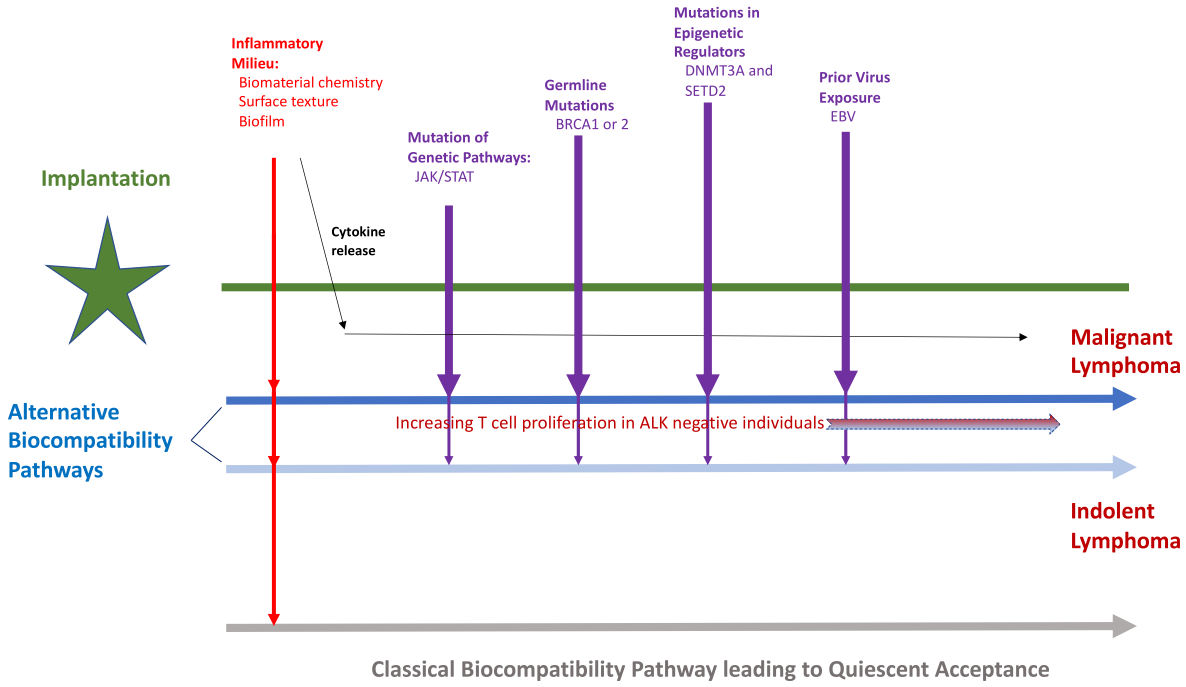

Fig. 4. Plasticity in breast Implant biocompatibility - The genesis of alternative biocompatibility pathways in BIA-ALCL. The starting point is the creation of an inflammatory milieu, associated with the surgical intervention and the possible accentuating factors of implant texture and biofilms. The inflammation involves cytokine release from cells. In patients who do not have pre-disposing characteristics, the classical pathway is followed, leading to fibrous encapsulation of the implant. When pre-disposing factors are present, there may be increasing proliferation of T cells in ALK negative individuals. Depending on a number of factors, this proliferation may yield indolent (and easily treatable) lymphomas or malignancy. Thus we have at least two-subsets of BIA-ALCL, arising from variations in the highly plastic alternative biocompatibility pathways.

3.2. Intraocular lens opacification and epithelial – mesenchymal transition

Intraocular lenses are highly successful implanted devices, but some patients do suffer from one significant complication, posterior capsular opacification (PCO). This arises from the proliferation, migration and abnormal differentiation of residual lens epithelial cells and fibers in the capsular bag.

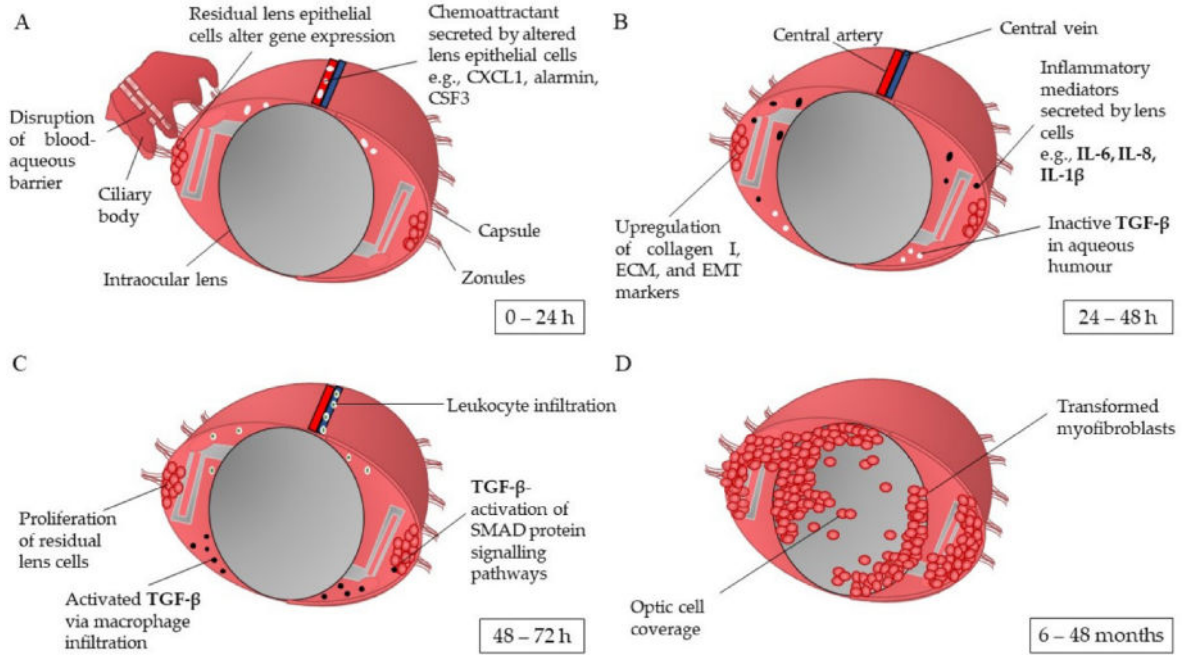

Fig. 5. One interpretation of posterior capsule opacification, after Cooksley et al. [85]. In (A) residual lens epithelial cells are stimulated by surgical trauma, resulting (B) in upregulation of inflammatory mediators followed by epithelial-mesenchymal transition, proliferation and infiltration of leukocytes and activation of SMAD signaling pathways (C) and migration of transdifferentiated lens cells over the IOL optic (D).

3.2.1. Background

This is not widespread problem but is a good example of how one type of biological event can trigger an unusual biocompatibility pathway. The effects are obvious to the patient and can be readily monitored by physicians; moreover, the process may take place slowly over a few years in the absence of significant mechanical forces or significant release of chemical substances from the biomaterials. There have been references in the literature to the role of the biomaterial's surfaces and protein adsorption in the pathogenesis of PCO.

3.2.2. Mechanisms

Nibourg et al. have recently discussed the pathogenesis and prevention of PCO [82]. Lens epithelial cells (LECs) are normally situated in a single layer on the inner side of the anterior lens capsule; they are mostly removed during cataract surgery, but some remain in the capsular bag afterward and they are able to proliferate and migrate to the posterior capsule. Moreover, LECs are able to transdifferentiate, especially to myofibroblasts, which are primarily responsible for the PCO (Fig. 5). This epithelial to mesenchymal transformation, EMT, can cause the lens capsule surface to become wrinkled, because the myofibroblasts contain α-smooth muscle actin and therefore have contractile properties; when in the visual axis, these wrinkles give rise to visual disturbances.

EMT is a biological process in which epithelial cells lose their characteristics (e.g., cell-cell junctions, apical-basal polarity, epithelial markers) and acquire mesenchymal features such as cell motility and a spindle cell shape [83]. Originally discussed in terms of defining important cell changes in embryogenesis, it is now well accepted that it plays a significant role in cancer progression and tissue fibrosis. Of relevance to this essay, EMT has been determined to '*display highly plastic and dynamic manners during cell fate transitions*' [84]. The transition is regulated at different levels by multiple factors, including cell-signaling, transcriptional control, epigenetic modification and post-translational modifications. It has been demonstrated that EMT and metastatic cancer cascades are inextricably linked, with clear relationships between EMT and cancer stem cells. Of relevance is the fact that cancer cells are observed exhibiting a plasticity that demonstrates the ability to switch between cancer stem cells and non-cancer stem cells in different situations.

In the context of IOLs, EMT is triggered within inflammatory responses, induced in this case by the surgery itself, where the damaged ocular tissue releases chemokines. Also the family of TGF-β growth factors has been implicated in the EMT process. A latent form of TGF- β is present in aqueous humor and is activated by trauma. Signaling by TGF-β starts with its binding to serine/threonine kinases on the cell surface, eventually resulting in cell signaling by phosphorylation of Smad proteins. Clearly, there are well-established signaling pathways that translate ocular tissue damage in the region of, but not caused by, the IOL implant into important clinical outcomes. Nibourg et al. did state that the IOL materials and design do influence the extent of PCO, one of the citations used to support this [86] specifically states that it is the IOL design and not the material that influences PCO. Other studies support the importance of design [87,88], whereas others are equivocal [89]. It should be noted, as pointed out by Bozukova et al., the design issue largely concerns the role of the IOL optic acting as a barrier to cell migration rather than being involved in causation of migration and EMT [90]. Evidence concerning surface properties, protein adsorption and cell behavior on IOL surfaces is very confusing. In the paper of Bozukova et al. mentioned above, it is stated on one page that "*implants exhibiting hydrophilicity associated with strong cell adhesion*", while on the next page report "*biomaterials with a hydrophilic surface are known for effective reduction of protein deposition and cell adhesion*". They do refer to published data that suggest that low aqueous contact angles (<40) and those of high angles (>75) have low cell attachment, whereas maximum attachment is seen at intermediate angles. The work of Awasthi et al. [91] confirm this confusing situation through the comments: "*Comparison of hydrophobic and hydrophilic materials showed that the type might influence PCO development … although it is well recognized that a hydrophilic acrylic material is more biocompatible, IOLs made of this material have been shown to* support *LEC adhesion, migration, and proliferation and thus PCO development compared with an IOL made of PMMA or hydrophobic acrylic materials*".

3.2.3. Plasticity

There are several key factors that control the development of PCO (Fig. 6). The first, which is considered to be the driver of the phenomenon, is the effect of local trauma associated with the surgical removal of the cloudy lens which leaves behind some epithelial cells. Above a certain level of residual lens epithelial cells, a series of events involving upregulation of inflammatory mediators is activated. It is unclear exactly what is that critical level of residual cells; indeed, a central point in the plasticity of the opacification pathway is that this critical level is likely to be dependent on individual characteristics. These include genetic factors; for example, decorin is believed to be involved in these processes, the expression of which appears to be significantly elevated in situations that lead to opacification [92]. Over time, the residual lens epithelial cells proliferate, which is influenced by signaling pathways and mediators such as TGF β.

In susceptible individuals, this process may lead to EMT. Lamouille et al. recently reviewed molecular mechanisms of EMT [93]. A critical sentence in the introduction to this paper reads:"

The ability of epithelial cells to transform into mesenchymal cells, and back, either partially or fully, illustrates an inherent plasticity in the epithelial phenotype". The switch in cell differentiation is mediated by key transcription factors, the functions of which are finely regulated at the transcriptional, translational, and post-translational levels. As noted above, the EMT here may lead to the formation of myofibroblasts, which are responsible for the opacification.

3.3. Surgical meshes

A surgical mesh implantable device is a piece of a textile or tissue fabric that is used to support weakened or damaged internal soft tissues. There are several conditions in which meshes are commonly used, two important applications being hernias (especially ventral, inguinal and incisional hernias) and pelvic organ prolapse, in which certain pelvic organs, such as uterus, bladder and rectum descend through the vagina (or possibly the anus in the latter case). Millions of patients suffer from one or other of these conditions annually and globally. The materials of which the meshes are made, which can be synthetic or natural, are accurately described as 'biomaterials' and their performance has become a major concern in recent years. I discuss here the features of this performance within the concepts of disease causation and mesh biocompatibility, especially focusing on the widely pronounced putative causes of mesh failure.

3.3.1. Background

Although there are other clinical applications of meshes, I deal only with hernia and prolapse issues here; meshes are widely used in the treatment of urinary incontinence in women, but additional factors are involved, especially infection, and it is better to leave those aside in the present discussion. I consider the hernia and prolapse meshes together for although there are differences there is much commonality, which allows a broader and more comprehensive assessment.

Pelvic floor dysfunction, which includes prolapse, is a very serious issue, being described as a hidden epidemic in the USA in 2005 [94], accounting for some 300,000 women requiring treatment annually. However, according to Weber and Richter [95], virtually all women with prolapse can be treated and their symptoms improved, if not completely resolved. Anatomically and functionally, support for pelvic organs in women is provided by the vagina, which is itself supported by complex interactions between the levator ani muscles and their fascial

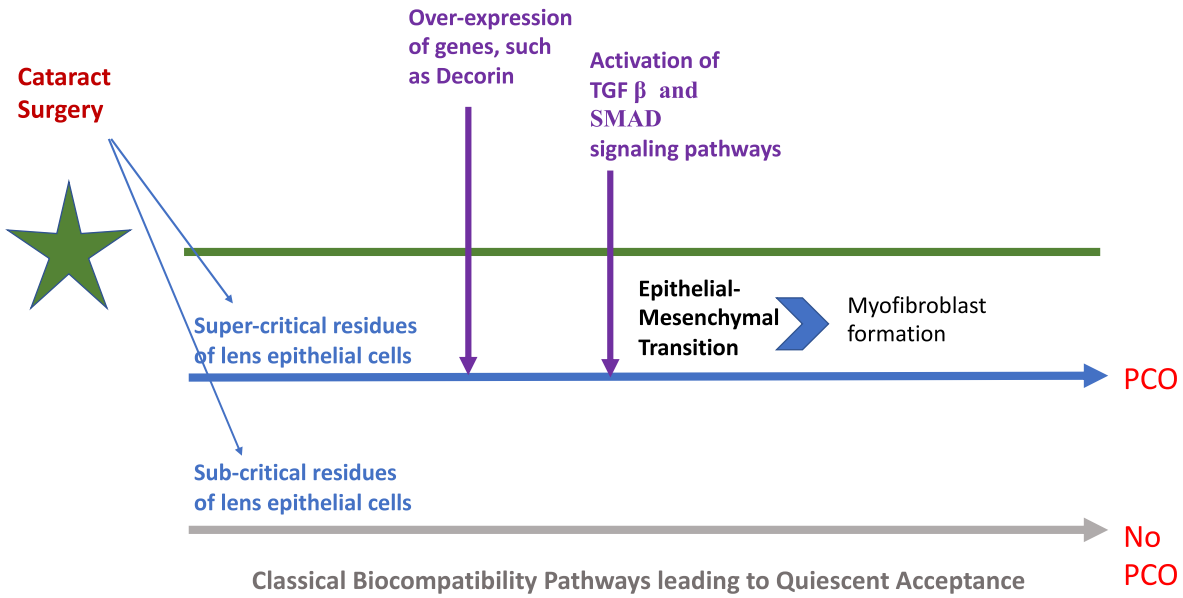

Fig. 6. Plasticity in IOL posterior capsule opacification pathway. See text for explanation.

coverings, and by connective tissue attachment of the vagina to the bony pelvis, including the uterosacral ligaments, the arcus tendinous fascia pelvis, and the perineal body and membrane. The levator ani complex consists of three sections, the pubococcygeus, puborectalis and iliococcygeus, which are separated to allow passage of the urethra, vagina and rectum. The sphincteric and support systems within this complex control functions during normal activity, for example maintaining urethral closing pressure to counteract increasing bladder pressure [96]; decreases in the number of striated muscle fibers occurring with age can profoundly influence this balance. Damage to, or deficiencies in, any part of the vaginal connective tissue system can change the vaginal axis so that the vagina may no longer be compressed against the levator muscles, predisposing to incontinence and/or prolapse.

When considering the pathophysiology of prolapse, it is necessary to consider predisposing, inciting and promoting factors [97]. With predisposing factors, there is good evidence that increasing parity (i.e., number of vaginal births), advancing age and obesity are principal factors, with an increasing amount of evidence to indicate the role of genetic predisposition. The inciting events mostly center around pregnancy and delivery, but with previous surgeries, especially hysterectomy, also potentially involved. Promoting factors include pulmonary diseases, especially those with significant coughing, physical activity and chronic constipation.

The reason why the pathophysiology of prolapse is mentioned here is that these factors may indirectly control biocompatibility of meshes used in treatment. Put simply, in the majority of cases, there are predisposing factors which involve either weakened supporting tissue and altered anatomy, that, coupled with several difficult vaginal deliveries and maybe individual factors such as obesity and lifestyle issues, result in diminishing resistance to the abdominal pressure, and the tendency to prolapse. This may be controlled non-surgically, but in many cases, surgical reconstruction is necessary. It might seem rather naïve to assume that successful reconstruction can be achieved by placing a simple mesh into the affected area, which is already compromised biomechanically and physiologically, hoping that the normal 'rules' of biocompatibility apply.

With hernias, there are several different situations, but the etiology can be understood by reference to abdominal wall hernias (with or without the involvement of prior surgery and failure of incisional healing) and the special case of inguinal hernias. The abdominal wall is a complex laminated cylinder of muscle and fascia, which provides protection for the viscera and support for both respiratory mechanics and musculoskeletal posturing [98]. The interplay between the dynamic muscle layers and static fascial framework allows for the maintenance of a constant intraabdominal pressure to support normal physiologic functions. If the wall is in a weakened state, the pressure will be focused on that point, increasing susceptibility to a hernia, which is the progressive penetration of the wall by internal tissues (Fig. 7). Not surprisingly, one source of such weakening is prior surgery, leading to incisional hernias [99]. Inguinal hernias are very common; the inguinal canal starts at the internal inguinal ring, ending at the superficial ring, and contains the spermatic cord in men and the round ligament in women [100]. The integrity of the abdominal wall here depends on the orientation of the inguinal canal; herniation can proceed laterally from the internal inguinal ring, or medially from a weakened transversalis fascia. Once again, meshes are used to repair and support the abdominal wall tissues that have been, and probably remain, compromised.

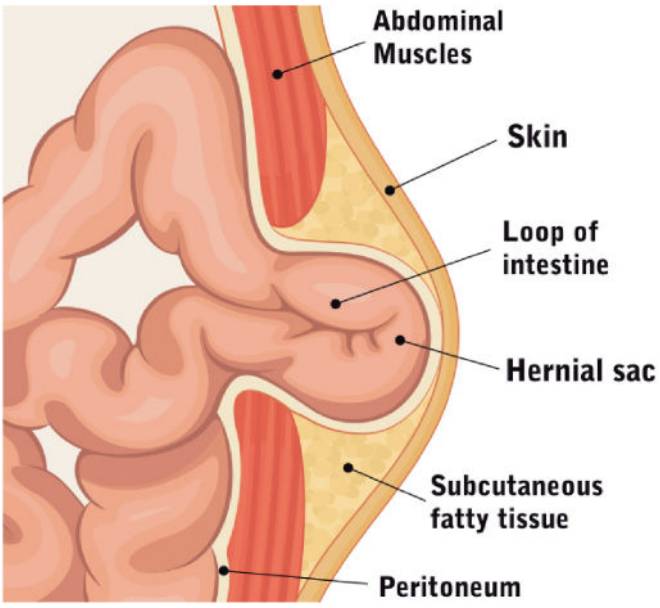

Fig. 7. Gross anatomy of abdominal hernia.

3.3.2. Mechanisms

In this section, I deal with the pathophysiology of the underlying tissue conditions that lead to hernia or prolapse alongside the mechanisms of biocompatibility associated with meshes used in their treatment. For purposes of clarity, I only discuss synthetic meshes (rather than biological meshes) and I refrain from discussing technical details such as methods of mesh fixation since, although very important from a practical clinical perspective, it is difficult to rationalize their specific effects.

In terms of pathophysiology, the following are the principal contributing factors.

3.3.2.1. Connective tissue changes. Henriksen et al. [101] discussed the role of altered collagen metabolism in the causation of hernias, finding that there are alterations at three levels; the type I to III ratio is decreased, collagen quality is poorer (primarily based on cross-linking characteristics) and collagen breakdown is increased. The collagen fibers and fibrils are thinner and more evenly distributed in the rectus sheath of hernia patients compared to controls. Klinge et al. confirmed the presence of decreased collagen I/III ratios and altered levels of matrix metalloproteinases (MMPs) in incisional hernia patients, indicative of collagen disorders [102]. This point was amplified by Thankam et al. [103] who described disturbances in collagen homeostasis in some patients following surgery, including alterations in expression of collagen subtypes and impairment in the transdifferentiation of fibroblasts to myofibroblasts, increasing susceptibility to incisional hernia. Pans et al. [104] concluded that molecular alterations in collagen are associated with groin hernias, while Chen and Yeh [105] showed increased turnover involving matrix metalloproteinases and serine proteases in pelvic tissue predisposed to incontinence and prolapse, while Jackson et al. found that reduction in total collagen content and increases in intermediate intermolecular cross-links and advanced glycation cross-links were seen in prolapsed tissue [106].

3.3.2.2. Biomechanics. Consistent with these observations of connective tissue changes, Moali et al. found that tissues in patients who experience prolapse undergo remodeling as a result of the biomechanical stresses induced by pelvic organs on the vaginal wall [107]. Mei et al. [108] considered the smooth muscle cell content of the vaginal wall, noting that in the posterior vaginal wall this was much lower in women with prolapse than those without, suggesting that biomechanically controlled smooth muscle contractility changes are involved in prolapse. Concerning susceptibility to herniation, it is recognized that the human abdominal wall is a complex composite structure, the layers of which vary considerably in mechanical characteristics [109]; the linea alba, a midline band of connective tissue that separates the two parallel portions of the rectus abdominis muscle, is composed primarily of type I collagen and has considerable anisotropy. Along with the aponeuroses, this performs most work in the abdomen, and variations in their characteristics control mechanical stability and resistance to hernia [110].

3.3.2.3. Genetics and hereditary factors. There is good evidence that there are genetic and hereditary associations for both prolapse and hernia. Cartwright and colleagues [111,112] have indicated that there are at least four biologically plausible polymorphisms associated with prolapse, primarily including the *COL1A1* gene, but also in *ESR1*, *FBLN5* and *PGR* genes. Matrix metalloproteinase-9 (MMP-9) is also a candidate gene for prolapse [113]. Family history of prolapse among first-degree relatives in an established risk factor [114]. According to Barnett et al., inguinal hernia is associated with several genetic syndromes and related disorders in some ECM components [115]. More specifically, and in relation to adult-onset inguinal hernia, Jorgensen et al. identified four inguinal hernia susceptibility loci near the genes WT1, EFEMP1, EBF2 and ADAMTS6, which suggests a role in collagen homeostasis and elastin maintenance [116].

3.3.3. Plasticity

As implied above, situations in which surgical meshes are used in patients are far more dependent on the patient's conditions that necessitate their use than most other medical device applications. The factors involved are shown on the left-hand side of Fig. 8. These factors reflect the compromised state of the connective tissue and most of them continue to influence the process of wound healing in tissue repair.

Dealing specifically with hernia repair, many patients progress through the wound healing phase, involving classical biocompatibility pathways, and there is no need to invoke mechanisms of plasticity. There are two phenomena that can adversely interfere with early stages of repair, neither of which are significantly related to the device design or materials, and which can necessitate re-intervention. These are adhesions and infection, being prominent causes of device failure; they are not considered here. However, there are two drivers of poor wound healing, the first being related to the condition of the tissue that has to be repaired; the second is associated with the biomechanical environment within which the repair process takes place.

The plasticity of biocompatibility is clearly seen here. In most cases, there is no single, well-defined event that demarcates failure of the process. There is an interplay between the natural mechanisms of soft tissue repair (involving those of inflammation and fibrosis in all of their complexities) and those of resistance, including the application of mechanical forces which are inconsistent with the mechanisms of mechanotransduction within in a reparative environment, and the presence of connective tissue disorders that interfere with repair. The influences of obesity [117] and diabetes mellitus [118] as co-morbidity factors are especially important.

If the natural processes are in the ascendency, after a few weeks, the patient may be unaware of the original conditions and, while taking good care of his or her body, never have a recurrence. To the contrary, the repair process may be less than ideal, in which case the patient will have to live with the consequences, such as chronic pain, the inflexibility of scar tissue, and the psychological aspects of not knowing if the abdominal wall will herniate or rupture again. Put simply, the tissue is always in a state of metastability, the plasticity being associated with the balance between reversibility and irreversibility of the connective tissue characteristics. That this is a characteristic of the hernia mesh biocompatibility is seen by the variable influences of different meshes on the stimulation of chronic inflammation, and of the role of elasticity and anisotropy of meshes on the stress distribution in the mesh – abdominal wall complex. The plasticity associated with inflammatory responses, especially involving transition between cellular (especially macrophage) phenotypes, is likely to be a major factor.

3.4. Metal-on-metal hip replacement prostheses

3.4.1. Background

The history of total hip replacement is well-known and there is little need to rehearse that here. Notwithstanding considerable clinical success over several decades, failures did occur, especially with loosening of components in cemented polyethylene – metal combinations. In 1995, Harris analyzed the situation and concluded that '*many acetabular components become loose because of the ingress of particulate debris that leads to linear bone loss at the interface with the pelvis, a process that is biologically akin to the more florid forms of osteolysis*' [119]. The particulate debris referred to was that of ultra-high molecular weight polyethylene, released through the wear process; the particles were typically 0.40–1.15 μm in size, appearing in numbers that depended on many factors but usually between 10^8 and 10^{10}/gram tissue [120]. The occurrence of osteolysis, with implications for the role of the bone-resorbing cell, the osteoclast, led to studies of potential molecular pathways for the phenomenon. The discovery that the TNF receptor family member, RANK, played a major role in osteoclast differentiation [121] led to observations of a correlation of RANK, RANKL and TNFα expression with bone loss and wear debris around hip replacements

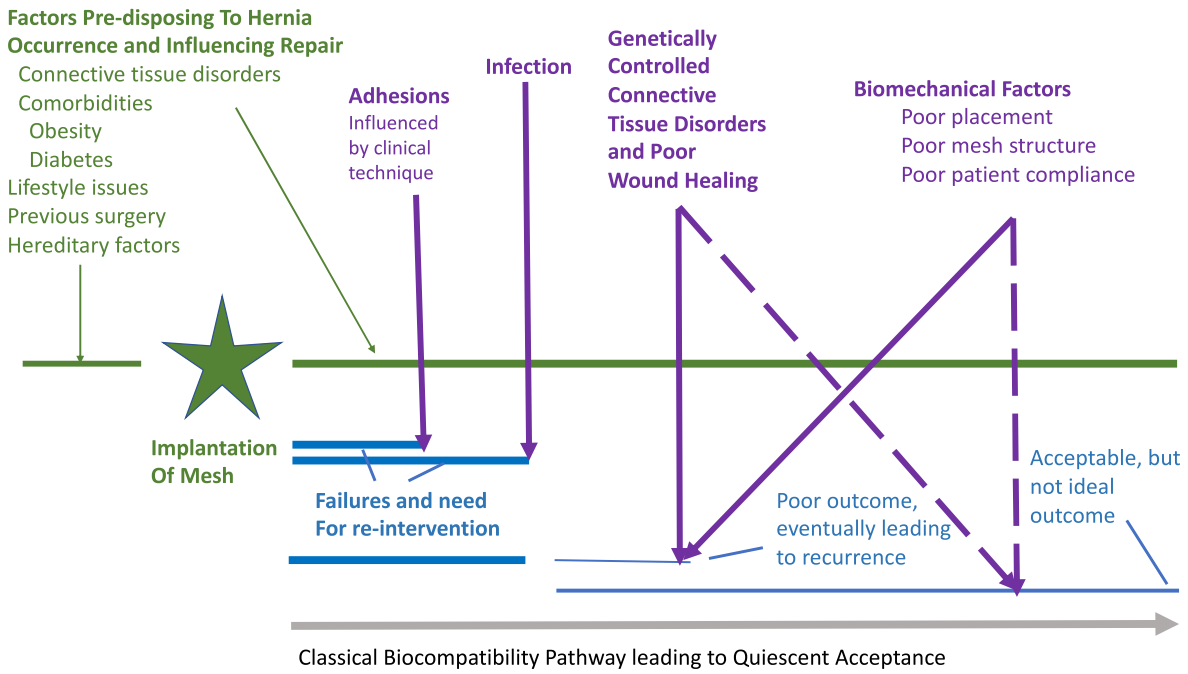

Fig. 8. Plasticity in hernia mesh biocompatibility pathways. Several factors control the susceptibility to both hernia formation and the ability of the damaged tissue to be repaired. Some factors, such as adhesion formation and infection, both of which can occur in most abdominal surgical procedures (for example as a consequence of clinical technique) cause early failure, essentially unrelated to biocompatibility. In susceptible patients, the drivers of different biocompatibility pathways, involving genetically-determined deficiencies in connective tissues and inappropriate biomechanical environments, cause variations in the repair processes, often leading to recurrence of the hernia.

[122]. It has also become clear that multinucleated giant cells play a role in bone-related diseases, especially concerning osteoclasts and macrophage-derived foreign body giant cells [123]. It has been known for some time that the macrophage dominated the response to wear debris, of any kind [124], and their fusion into foreign body giant cells is a major factor in inflammation and bone resorption. The interaction between osteoclasts and foreign body giant cells in this context [125] is an intriguing aspect of osteolysis; indeed, this interaction provides an insight into the plasticity of biocompatibility with respect to joint replacement biomaterials. However, this is not the focus of this section, since far greater clinical significance has been attached to an alternative material combination, involving an interface of two metallic components, with quite different wear characteristics and pathological responses.

Metal-on-metal hip replacements were first used not long after Charnley's introduction of the metal-on-plastic device, McKee and Watson-Farrar describing this alternative system in 1966 [126]. The device was reported to give excellent results [127], but occasional failures associated with pain and joint effusions were noted. Willert et al. carried out a histomorphological study and concluded that this was most likely a lymphocyte dominated immunological response [128]. These implants went out of favor as the Charnley-type became very popular. However, the attraction of the far greater engineering performance of alloy systems compared to plastics, led to their re-emergence in the first decade of the 21st century, especially for hip re-surfacing techniques which involved much less bone sacrifice. Advantages and disadvantages were described by Jacobs et al. in 2009 [129]. The disadvantages soon became very obvious, with significant number of early failures [130], which led to extensive litigation, and the introduction of new terminology, including ALVAL (aseptic lymphocyte-dominated vasculitis-associated lesion, ARMD (adverse reactions to metal debris), metallosis and pseudotumors.

3.4.2. *Mechanisms*

Clinical patterns of failures were quite soon established, although hypotheses for the exact mechanisms varied. Typically, notable effusions were found at revision surgery, with a '*creamy, milk-stained fluid*', usually with apparent tissue necrosis [131]. It was becoming clear that the host response to metal debris from these prostheses was different to that from other material combinations, including metal – on - polyethylene, ceramic – on – ceramic and ceramic – on – polyethylene. The reasons were not definitively obvious, but among the facts were the following.

- The size of metal debris particles was much lower than that of polyethylene particles and also varied quite considerably depending on the precise type of device and the biomechanical circumstances associated with any one patient [132]; the mean particle size under 'normal' wear conditions was 35 nm compared to 95 nm under edge-loading conditions, so that the latter particles, which were more elongated, had 630 times more cobalt than the former.
- The majority of metal-on-metal devices used cobalt-chromium-molybdenum alloys. Although intrinsically very corrosion-resistant, these very small particles, with their enormous surface area/volume ratio, could release metal ions into their environment. Polyethylene particles are essentially insoluble in aqueous media.
- Under certain conditions, these metal ions, especially the cobalt, may exert direct toxic effects and stimulate hypersensitivity in susceptible patients.

This combination of factors means that it is possible that different biological pathways could be superimposed upon those that have been determined for the metal-on-polyethylene systems. This leads to the scenario of a combined macrophage/foreign body giant cell driven innate response and lymphocyte driven adaptive immune response, a perfect situation in which to witness plasticity in the host response, especially where it is strongly influenced by idiosyncratic hypersensitivity and, to some extent, by clinical techniques which result in the disadvantageous edge wear.

Many papers have been published on this scenario, but just a few of

the most significant will be cited here. First, there is no doubt that cobalt, as released from prostheses, can exert toxic effects [133], both locally and systemically; these ions, which are released intracellularly from internalized particles because of the highly acidic environment within phagosomes, impair functions of macrophages, fibroblasts and osteoblasts, the soluble cobalt ions activating extrinsic and intrinsic apoptotic pathways. This process is entirely consistent with the concept of DAMPS, (Damage Associated Molecular Pathways) which can be used to explain non-pathogenic innate immune responses, the central component of which is the inflammasome, and which involves recognition of danger signals, lysosomal destabilization, an increase in NADPH and significant generation of reactive oxygen species [134]; the authors of this paper referred to the substantial plasticity between the key cell types associated with implant-related osteolysis. In many ways, this process is qualitatively similar to that associated with any other wear debris generated by orthopedic devices (Fig. 9), where the macrophages activated in this way secrete chemokines and proinflammatory cytokines, increasing osteoclastogenesis and suppression of osteoblast function, essentially a variant of the innate immune response [136].

Landgraeber et al. [134] also state that lymphocytes can also play a crucial role in the peri-implant debris-reactivity environment, both T and B lymphocytes frequently being present in the tissue. Interestingly it is the T-helper, TH1 subtypes that predominate, which are known to recruit and activate macrophages. Again, it is noted that macrophages and lymphocytes seem to interact with each other, *via* lesser-reported receptors and cytokines, such as IL-15. This is characteristic of a type IV delayed hypersensitivity response, that is an adaptive slow cell mediated response. The mutually interactive recruitment of these cells can lead to runaway inflammation, which is the cause of the effusions alongside the osteolysis.

A major question arises as to whether the delayed hypersensitivity responses are seen in patients who are sensitized to one of the metals involved. This has been difficult to resolve because of uncertainty of the diagnosis of hypersensitivity, but there is sufficient evidence to show a strong possibility of such causation [137,138], which would explain the significant individual variations in responses. This idiosyncratic response is also a factor that partially explains the frequently observed poor correlation between whole blood, synovial fluid and periprosthetic tissue levels of metals and histological findings [139].

The current state of knowledge has been summarized by two recent papers. Paukkeri et al. [140] found high blood cobalt and chromium concentrations are associated with macrophage dominated inflammatory response in tissues around failed implants, with tissue damage and necrosis. There is an increased production of proinflammatory cytokines IL-6 and TNFα, which amplifies the reaction. In addition, there may be perivascular reaction which is T-cell dominated; in about half of the cases examined, this response predominated over the macrophage response. Here the metal ions released from metal-protein complexes (haptens) that may be recognized by the immune system as foreign antigens, resulting in the activation of the adaptive immune system.

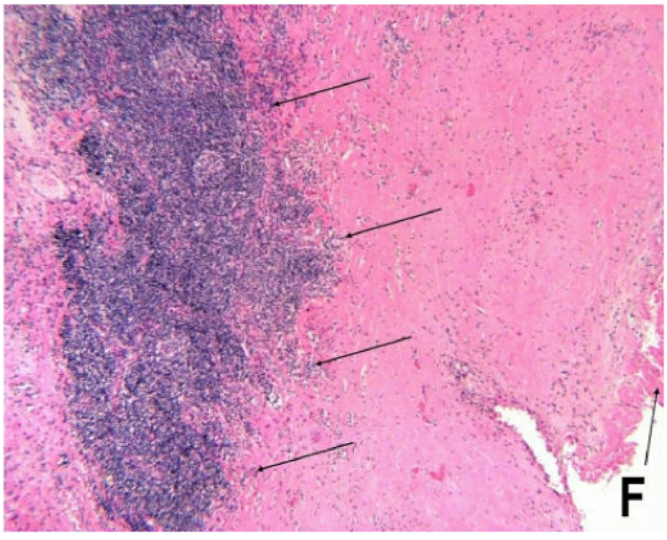

Fig. 9. Histological appearance of tissues around metal-on-metal hip replacement, showing dense aggregates of lymphocytes (arrowed) and acellular zone (F) of fibrin. After Campbell et al. [135] with permission.

Perhaps the best position on this matter, and one that emphasizes the plasticity nature of the biocompatibility of metal-on-metal hip replacements, was that provided by Samelko et al. [141] in 2019. In their model, the processes of DAMPs/inflammasome activation and delayed hypersensitivity to metals are inextricably linked. They found that NLRP3 inflammasome and its main effector caspase 1, along with the cytokine IL-1β promote adaptive IL-17 production by $CD4^+$ T cells, which drive metal-delayed hypersensitivity responses to prostheses-derived metal. The interaction of caspase-1 and NLRP2 inflammasome has very recently been shown to be responsible for bone resorption under some conditions [142]. The critical point here is that, it is hypothesized, '*implant debris induced inflammasome activation tips the balance toward inflammatory IL*-17 A/F *producing* $CD4^+$ *T cells that drive metal hypersensitivity responses*'. In effect, there may be a transition from metal-delayed hypersensitivity resistance to susceptibility, which is facilitated by active danger signaling (i.e., inflammasome-caspase-1 signaling) and the resulting production of IL-17; the local release of various cytokines, together, promote the effector T cell immune reactivity that elicits the delayed hypersensitivity. This transition will be governed by the characteristics of the implant debris and of the patient.

3.4.3. Plasticity

The driver of biocompatibility pathways for joint replacements is the release of wear debris. The characteristics of the debris (particle size and shape, rate of release etc.) depends primarily on the nature of the articulating surfaces, not just metal-on-polyethylene and metal-on-metal, but also ceramic-on-ceramic, ceramic-on-polyethylene and others, but also on the biomechanical environment. The consequences of this release, and the plasticity of the subsequent biocompatibility pathways, are controlled by the interactions between the released particles and the cells that are attracted to, and activated within, the tissue (Fig. 10). With the micron-sized, biologically inert, polyethylene particles, the dominant inflammatory cell is the macrophage, often accompanied by foreign body giant cells, which respond to the released cytokines. The consequences vary from patient to patient, and, indeed, between different regions within the joint capsule, the plasticity being evident by the transitioning between pro- and anti-inflammatory phenotypes [143,144]. With metallic particles, which may be of size below 20 nm and that are both soluble and toxic within cells, although macrophages are involved in the inflammatory response, there is likely to be a greater polarization towards the pro-inflammatory M1 phenotype, which will stimulate the involvement of T-lymphocytes. The extent of cytotoxic and genotoxic responses will vary from one situation to another, with considerable plasticity in the overall cellular profile. Genetic factors will be partly responsible for the activation of delayed hypersensitivity in susceptible patients.

3.5. Bone bioactivity

3.5.1. Background

A recent essay written by the present author addressed the controversial topic of bioactive materials [14], which, if used in a medical technology application, should '*beneficially and appropriately direct interactions between a device and a host system through the modulation of biological activity*'. It is implicit that this process should be intentional (that is, by design and not accident) and that there should be satisfactory empirical evidence of the biocompatibility pathways that are involved.

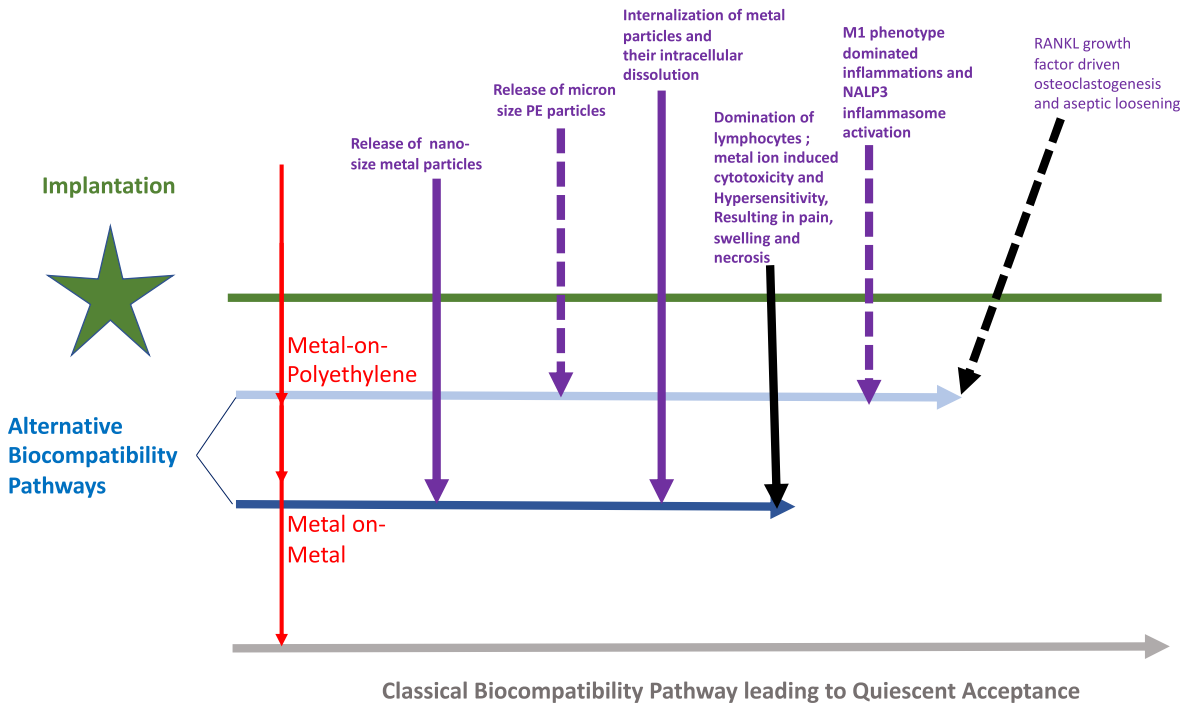

Fig. 10. Biocompatibility pathways for metal-on-polyethylene and metal-on-metal hip replacements. See text for explanation.

With respect to bone bioactivity, this presents a conundrum since there are so many materials that have been characterized as having bone-inducing, or bone-bonding properties, but which have little in common and, usually, with little connectivity to bone formation mechanisms. These materials include calcium phosphates, certain glasses, calcium carbonate systems, graphene and other nanostructured carbon derivatives, collagen-based materials, chitosan and other biopolymer-based hydrogels, bisphosphonate-functionalized materials, magnesium-based alloys, and nanoscale modified titanium. It has become necessary to rationalize the behavior of these materials if we are to understand the phenomenon of bone bioactivity, and this has to start with a discussion of the mechanisms of bone formation.

3.5.2. *Mechanisms*

It should be noted at the outset that it is insufficient for a material to solely induce hydroxyapatite deposition on its surface, since that does not result in functioning bone; functional bone is a mineralized connective tissue, the properties of which critically depend on its cellular components and the ECM, and the interaction between these [145]. When a biomaterial is placed within a site that has been surgically prepared, the response to the material must be considered in the context of bone repair, alongside the normal host response to an implanted device. As noted previously, this host response involves both inflammation and fibrosis. With non-bioactive materials, the default position is the formation of an interfacial zone of fibrous tissue: for bioactivity to become a reality, the bone repair process has to dominate fibrosis.

Throughout human life, there is a constant turnover of bone as it is resorbed and re-formed. Resorption takes place by the activity of osteoclasts, while formation is determined by osteoblasts. There is a wide range in the kinetics and balance of this remodeling, caused by genetic variation involving genes that encode regulators of bone homeostasis, and by diseases such as osteoporosis. During bone remodeling, there is significant cross-talk between osteoclasts and osteoblasts [146], which allows bi-directional transduction of activation signals and the regulation and survival of both types of cell. Bone marrow-derived macrophages also influence osteoblast activity through cytokines secretion [147]. The ECM components contribute a network of signaling mechanisms that influence bone metabolism and affect proliferation, differentiation and migration of the cells.

Bone formation in normal remodeling is highly regulated [148], with activation, resorption, reversal, formation and termination phases in the cycle, the process being orchestrated by osteocytes, which are long-living cells that are formed when osteoblasts are buried in the mineralized matrix of bone. They form dendritic processes within the bone canaliculi, providing networks that are able to sense local and systemic environmental changes. Local regulation is critical to this sequence, such regulation being dominated by two signaling pathways, the RANKL/RANK/OPG and Wnt pathways.

The RANKL/RANK/OPG system is extremely important in bone physiology [149] and is the basis for several clinical therapies for osteoporosis and bone cancers. Cytokines and hormones that promote osteoclast formation first act on the osteoblast lineage, promoting the regulation of osteoclastogenesis; this regulator is the receptor activator of the NF-κB ligand, RANKL, which acts upon its receptor in the hematopoietic lineage, giving a dual RANKL-RANK signaling interaction that influences both osteoclast and osteoblast functions. There have been suggestions that bioactive materials influence this system by inhibiting osteoclastogenesis, promoting bone formation rather than resorption; the role of biomaterial-derived cations may be important here. Strontium-substituted bioactive glasses appear to inhibit osteoclastogenesis by suppression of the RANKL-induced signaling pathway [150], the strontium ion possibly inhibiting osteoclast differentiation by disruption of the RANKL activated p38 signaling and NF-κB pathways.

Wnt pathways are also important [151,152]; Wnt proteins transit across cells through the secretory pathway, associating with several proteins in the endoplasmic reticulum and the Golgi apparatus, with prominent glycosylation and acetylation modifications. They act as ligands, binding to co-receptors of the LRP family (low density lipoprotein receptor-related proteins) and to the signaling receptors Frizzleds. When the heterotrimeric Wnt-LRP-Frizzled complex is activated, Frizzled signaling takes place in the cell cytosol, activating the protein β-catenin, which translocates to the nucleus, where it is able to regulate many cell-cell adhesion and gene expression processes. There is a causal relationship between Wnt signaling and bone formation, the β-catenin being involved in the regulation of both osteoblasts and osteoclasts. There have been several suggestions that bioactive biomaterials

influence the Wnt pathway, with some evidence to support such effects with nanostructured titanium [153], lithium-doped surfaces [154] and some calcium phosphates [155].

When considering how putative bioactive materials can influence any of these bone formation pathways in clinical practice, it seems clear that the direct chemical interaction between the biomaterial and any signaling molecule is, with one exception mentioned below, highly unlikely; this would have to involve the release of some active entity from the surface, but the specific targeting of such entities to one, and only one, part of complex signaling pathways would be a very difficult challenge. The one exception involves metal ions, it being noted above that both strontium and lithium can, at least under *in vitro* conditions, affect some pathways. There is also some experimental evidence that Mn, Ca, Zn, Si, Cu and B ions are able to regulate cell function and influence bone remodeling [156]. Because many so-called bioactive materials release multiple types of ions, evidence of causation is only qualitative and phenomenological.

With respect to calcium phosphate – based materials, the mere fact that the mineral phase of bone is a calcium phosphate does not mean that these materials are automatically bioactive. It is true that Ca^{2+} transport in the extracellular space is an important regulator of cell phenotype [157], but this is a complex process that is dependent on ion concentration in the tissue and the presence of downstream signaling molecules. It is possible that ions released from a material surface could activate Ca^{2+} channel transporters and some downstream pathways, including MAPK and P13K-AKT pathways, causing activation of transcription factors in the nucleus and osteoblast differentiation. Even then, the bioactivity of calcium phosphate glasses and ceramics is not guaranteed since many factors are involved, including those of kinetics, concentration and equilibrium.

Alternative mechanisms of bone bioactivity involve mechanotransduction and the role of surface topography; cells are constantly interacting with their environment such that engagement with other cells and the ECM involves the formation of dynamic adhesions and the application of cellularly generated forces by means of these adhesions [158]. Active materials may be able to recapitulate the dynamic microenvironment of living tissues at their surface. For example, microstructured topographies may influence osteogenic differentiation of mesenchymal stem cells through mechanotransduction induced upstream expression of integrin subunits, focal adhesion complexes and the upregulation of FAK/MAPK and ILK/β-catenin signaling cascades [159].

3.5.3. Plasticity

Possible pathways are shown in Fig. 11. It is not surprising that there is considerable plasticity in the biological pathways that may be followed after contact is made between a biomaterial and bone or periosteal tissue. These pathways are controlled by the balance between osteoblasts and fibroblasts (i.e., bone forming or fibrous tissue forming cells) and between the osteoblasts and osteoclasts (i.e., bone forming and bone resorption cells). In the former case, fibrous tissue will naturally develop first unless there is a specific mechanism that favors bone formation. In relation to osteoblasts and osteoclasts, there is continual cross-talk between these cells, which can lead to a variable bone-forming scenario, influenced by local factors, for example mechanotransduction factors within the changing biomechanical environment. Metal ions are also a source of variable responses, especially as many biomaterials contain several metallic components, which may be released at different rates, and which may have opposite effects on cellular components and pathways. The main factors that control the ultimate fate of the osteoblast/osteoclast balance are the numerous signaling pathways, especially RANKL/RANK/OPG and Wnt, which can be influenced by the biomaterial, and push the bone formation-resorption equilibrium in different directions. The resulting plasticity can produce variable bone bioactivity profiles with ostensibly very similar biomaterials, for example within the ranges of 'bioactive' glasses and calcium phosphate materials.

3.6. Imaging contrast agents

3.6.1. Background

Contrast agents have been used for many years to enhance anatomical visualization of tissues during imaging processes, of either functional or molecular variety. In recent years, attention has been focused on suspensions of nanoparticles that are capable of intravenous injection. Such nanoparticle-based contrast agents, however, have not been extensively used clinically because of the potential for adverse effects in the human body. These adverse events are usually seen within the kidneys of some patients, for example the contrast induced nephropathy following the use of some iodinated agents [160], or the nephrogenic systemic fibrosis seen with some gadolinium-based MRI agents [161]. Considerations of biocompatibility are complicated by the fact that the agents are not classical solids, but injectable chelates or particles, where the host response is better discussed in terms of biodistribution, pharmacokinetics and toxicity rather than conventional tissue responses

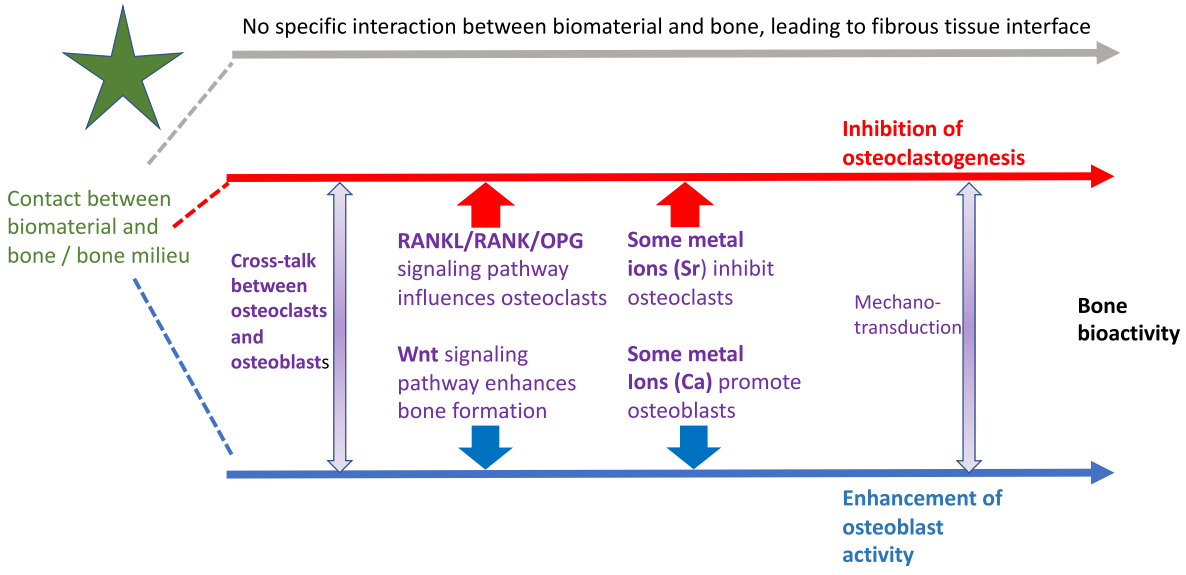

Fig. 11. Plasticity of biocompatibility pathways in bone bioactivity, see text for explanation.

[162]. As revealed by a retrospective analysis of over 10,000 MRI cases, acute adverse reactions are quite rare [163] but there are uncertainties over long-term immunotoxicity and neurotoxicity, and, therefore, on the overall biocompatibility of these imaging nanoparticulate or chelated agents [164].

3.6.2. Mechanisms

There may be some features in common between different forms of contrast agent, but there are some significant differences in the way they interact with the human body. It is also relevant to note that there are several other biomedical applications of nanoparticles, such as in drug and gene delivery, where the interactions with the body are different, and have different consequences. In addition, nanoparticles can be introduced into the body, either intentionally or inadvertently, with a whole array of potential biological effects. This section is solely concerned with the biological consequences (including biocompatibility) of contrast agents in imaging applications.

It is appropriate to consider iron oxide and gadolinium systems in this context. With iron oxide, there are several different forms depending on particle size [165]; ultrasmall superparamagnetic particles (USPIOs) are in the range 5–50 nm, superparamagnetic particles (SPIOs) are 50–150 nm and some are in the microscale rather than nanoscale regions (MPIOs) at around 1 μm. Both the size and polydispersity affect *in vivo* performance, as does the surface charge [166]. Of critical importance is the fact that most iron oxide nanoparticle formulations have surface coatings, such as polyethylene glycol (PEG) and polyethylenimine (PEI) or dopamine-based systems [167], which influence functionality and biocompatibility.

The major factors that determine biocompatibility of these particles are the following.

- Iron is an element essential for life but can also be hazardous to tissues under some circumstances. Upon entering the bloodstream, iron oxide nanoparticles are phagocytosed within the reticuloendothelial system, where macrophages and monocytes internalize them by receptor-mediated endocytosis and transported to sites such as the liver, bone marrow and spleen; the blood pool half-life of the particles is measured in minutes or hours.
- Iron oxide nanoparticles are biodegradable, degradation times being dependent on size and coating. Shapiro [168] discusses elimination times of around 100 days for PLGA coated particles *in vitro*, but much faster when injected intravenously and phagocytosed and transported to the liver. Within macrophages, the nanoparticles are degraded, and the iron is ultimately incorporated within the body's iron store.
- However, as ferrous ions are released, they can generate excessive amounts of reactive oxide species (ROS), *via* Fenton and Haber-Weiss reactions [169], the products of which include the very reactive hydroxyl radical ($OH^{\cdot}$). According to Wu et al. [170], USPIOs, of size <5 nm, can directly penetrate the cell cytoplasm, promoting robust ROS generation and activation of the NLRP3 inflammasome. There is increasing evidence that the specific toxicity characteristic associated with this iron accumulation is ferroptosis, a type of programmed cell death accompanied by the accumulation of lipid peroxides [171]. There are also possible genotoxic effects associated with the over-expression of inflammatory mediators following the endogenous production of ROS [172]. Importantly, these effects are not seen with larger SPIOs, nor are they seen with most other metal oxide particles.
- The clearance of nanoparticles is also of importance since many biomedical applications depend on their retention at the site of interest for an appropriate length of time. Iron oxide particles >100 nm appear to be trapped in the liver and spleen through macrophage phagocytosis, but those <10 nm are eliminated quickly through renal clearance [166]. Positively charged nanoparticles tend to be cleared faster than neutral ones.

Greater biocompatibility and toxicity concerns have arisen over gadolinium-based agents [173]. The significance of gadolinium, which is a rare earth metal, is that the proton relaxation times, which are critically important in MRI performance, are influenced by paramagnetic ions, and Gd^{3+} possesses the most unpaired electrons of any stable ion, creating a high magnetic moment and enhanced proton relaxation [174]. Because of this, the first specifically designed MRI contrast agent, introduced into clinical practice in 1988, was a gadolinium compound, gadopentetate dimeglumine, Magnevist® [175]. However, gadolinium compounds do have some toxicity characteristics, much depending on the chelation components and routes of administration [176]. The gadopentetate dimeglumine has a linear structure in which a polyamino-carboxylic acid backbone wraps around the Gd^{3+} ion but does not fully enclose it. This structure can release substantial amounts of Gd^{3+} under some conditions [177]. Specifically, it became apparent that patients with end-stage renal failure could suffer severe systemic disease, as noted earlier. The nature of the chelate used clinically was changed from a linear to a macrocyclic structure, which much reduces the gadolinium release. Nevertheless, problems still exist [178], including immunotoxicity [179] and neurotoxicity [180].

3.6.3. Plasticity

Plasticity is not so obvious with imaging contrast agents, partly due to the lack of clinical evidence and the narrow range of applications. The possibilities may be examined with two popular groups of agents, as outlined above and features in Fig. 12, bearing in mind that the main application is MRI, where functionality depends on magnetic properties.

The drivers of biocompatibility here (in many situations equated with toxicity) are the immediate biodistribution of the agent and its interactions with cellular and non-cellular biological components. Because of the magnetic property requirements, the critical chemical components are based on metallic elements which, because of inherent toxicity, have to be shielded in some way from the *in vivo* environment, by polymer coatings or by chelation with non-metallic compounds. The plasticity represents the balance between agent biodistribution, the release of metal ions from the agent and their speciation, retention or excretion and the host susceptibility to the cytotoxic and genotoxic effects of the ions. Thus, while a macrocyclic gadolinium chelate may avoid release of Gd^{3+} ions and provide good MRI functionality without adverse effects, linear chelates may release such ions, which may result in retention in the kidney and necrosis or apoptosis in renal tubular cells. Some recent papers on gadolinium toxicity, concerning general mechanisms [181], retention [182], nephrotoxicity [183] and effects on astrocytes [184] tend to confirm these general principles of plasticity.

3.7. Degradable tissue engineering scaffolds

3.7.1. Background

Specifications for biomaterial scaffolds have been controversial for many years, and the present author has discussed this matter on several occasions recently [15,185]. In terms of biocompatibility, there are two generic requirements, which may seem contradictory. First, the material itself, including any degradation products, should have no significant adverse effects on the patient in whom the scaffold is placed. Secondly, however, since tissue engineering may be defined as *'the creation of new tissues for the therapeutic reconstruction of the human body by the deliberate and controlled stimulation of selected target cells through a systematic combination of molecular and mechanical signals'* [186], there is an absolute necessity for the biomaterial to pro-actively and selectively influence the tissue-expressing capacity of those target cells. The first of these requirements has dominated material selection in tissue engineering for several decades, where those scaffolds intended for commercial products have been largely based on synthetic biodegradable polymers, or a few degradable natural biopolymers, for which biological safety has been determined through prior use in implantable medical devices. It should be of no surprise that scaffold materials based on these

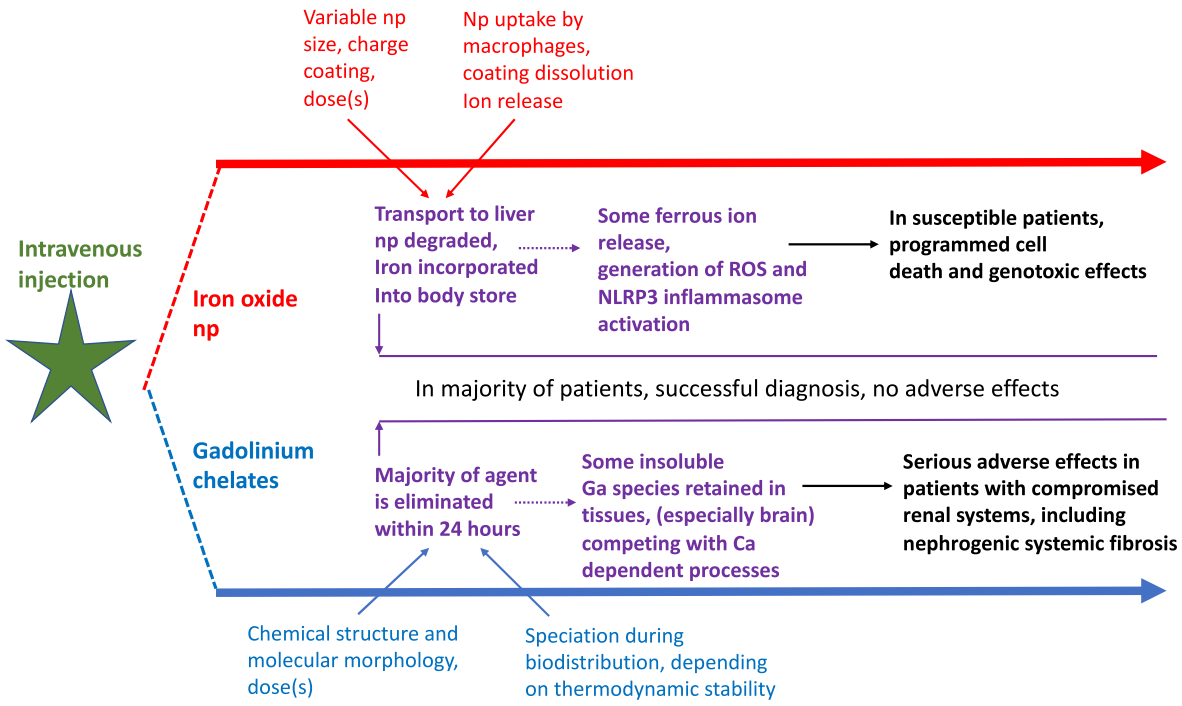

Fig. 12. Exemplars of biocompatibility/toxicity pathways with contrast agents.

concepts have had little success in facilitating tissue regeneration. The situation is even more complex when the architecture and microstructure of scaffolds are taken into account as well as chemistry. Scaffolds are usually microporous solids (as in Fig. 13) or hydrogels. It is highly unlikely that a porous polymer will have a structure that resembles the microenvironment of the target cells of the tissue engineering process. For such a cell (for example, a stem cell) to optimally perform under the applied mechanical and molecular signaling, it should occupy the appropriate space, or niche, and this will not occur in the vast majority of situations. Thus, conventional scaffolds have neither the desired chemical nor structural characteristics to effectively facilitate tissue regeneration.

3.7.2. *Mechanisms*

It is difficult to describe knowledge of mechanisms of biocompatibility, including biocompatibility pathways, in the context of tissue engineering scaffolds since these are rarely discussed in any meaningful way in the literature. Certainly there are many papers published, perhaps thousands per year, which allude to the apparent biocompatibility of scaffold materials, but the vast majority of these refer to yet

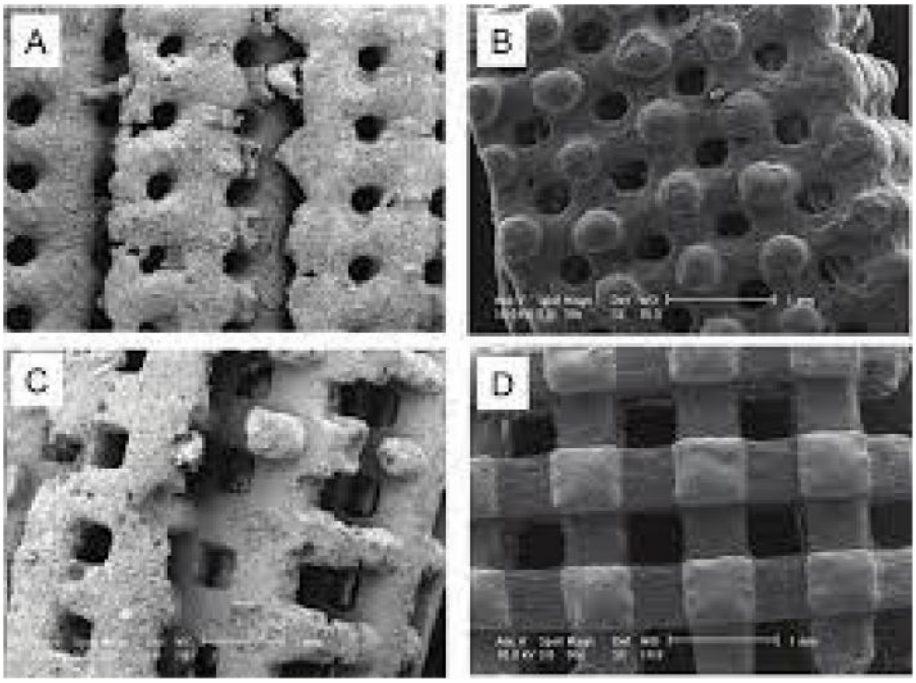

Fig. 13. Images of 90/10 polycaprolactone-hydroxyapatite scaffolds with (A) 200 μm pores, (B) 300 μm pores, (C) 400 μm pores, (D) 600 μm pores, After Lu et al. [187] with permission.

another variation in material composition, structure, fabrication and so on in relation to so-called innovative scaffolds, and describe a simple *in vitro* or *in vivo* test, usually short-term cytotoxicity, the results of which are then used to justify a statement that the scaffold is 'biocompatible', without any attempt to define mechanisms.

If we consider the variations in scaffold types and therapeutic procedures, ranging from 3D-printed hydrogel scaffolds that incorporate stem cells within a printable gel, along with appropriate growth factors and nutrients, where the resulting construct is placed at the relevant tissue site, to the manufactured porous solid that is cultured with relevant cells within a bioreactor before implantation, a number of key determinants of the resulting biocompatibility can be identified, such as.

- scaffold material [188],
- scaffold hierarchical architecture [189],
- scaffold mechanical characteristics [190],
- scaffold surface properties [191],
- material degradation rate [192],
- material degradation product characteristics [193],
- ability to distribute degradation products away from site,
- cell adhesion to material surface [194],
- mechanical interactions between material and host tissues [195],
- effect of material on inflammation and immune responses [196],
- ability of scaffold to stimulate tissue matrix expression [197],
- ability of scaffold to facilitate innervation and vascularization [198].

These, and other, variables may have synergistic or antagonistic character, and the interactions will vary with time. This situation is obviously fertile ground for variability in biocompatibility pathways and, therefore, for plasticity in biocompatibility mechanisms.

3.7.3. Plasticity

These plasticity factors become obvious when the determinants of whether a tissue engineering strategy can lead to new tissue regeneration or not (Fig. 14). Those determinants are grouped into six different categories for an *in vitro* bioreactor system, and it will be recognized that in each case, the effect of any characteristics has to be considered quantitatively. For example, with the first category, that of the stimulus to inflammation, it may be the extent and biological nature of the stimulus, that will contribute to the overall chance of success. Each of these factors is likely to change over time, and indeed with the spatial position within the scaffold-bioreactor system. The plasticity is also likely to be predominantly directional. If the early tissue formation is largely that of functionally irrelevant fibrous scar tissue, it is unlikely to be reversed by any changes in subsequent characteristics. If, however, the early tissue formation is of good relevant quality and characteristics, that could change, for example, if the late stage of scaffold degradation is pro-inflammatory, replacing the desirable regenerated tissue with macrophages, or if the angiogenic factors are not maintained such that vascularization diminishes.

3.8. Degradable intravascular stents

3.8.1. Background

The coronary arteries are derived from the aortic arch and deliver oxygenated blood to the muscles of the heart. They have a small diameter, around 3 mm, and are tortuous. They are prone to plaque deposition, risk factors being smoking, high blood pressure and high levels of fat and/or sugar in the blood. The plaque may be continuous or irregular and may be susceptible to fragmentation. The plaque can significantly narrow the arterial lumen or cause blood clots that completely block the vessel, resulting in a heart attack. This coronary artery disease is the leading cause of mortality and morbidity in the world [199] so that methods of prevention and treatment are extremely important. Several drugs are available to treat the symptoms and reduce the progress of the disease, but in many patients some form of therapeutic intervention becomes necessary; the two main forms of treatment are the surgical implantation of a device to by-pass the blockage and the use of minimally invasive procedures to remove or counteract the plaque deposition. A series of developments took place over several decades with the latter possibility, resulting in the introduction of the intravascular stent [200].

The success of any therapeutic intervention for coronary artery disease depends (as with many other situations described in this essay) on the pathophysiological details of the disease itself, in this case being well-defined in 2005 by Libby and Theroux [201]. The formation of fatty plaques in arteries, referred to as atherogenesis, involves complex interactions between many features of blood and the vessel wall, the center of attention being inflammation. When stimulated by one or more factors, for example pro-inflammatory cytokines derived from excess

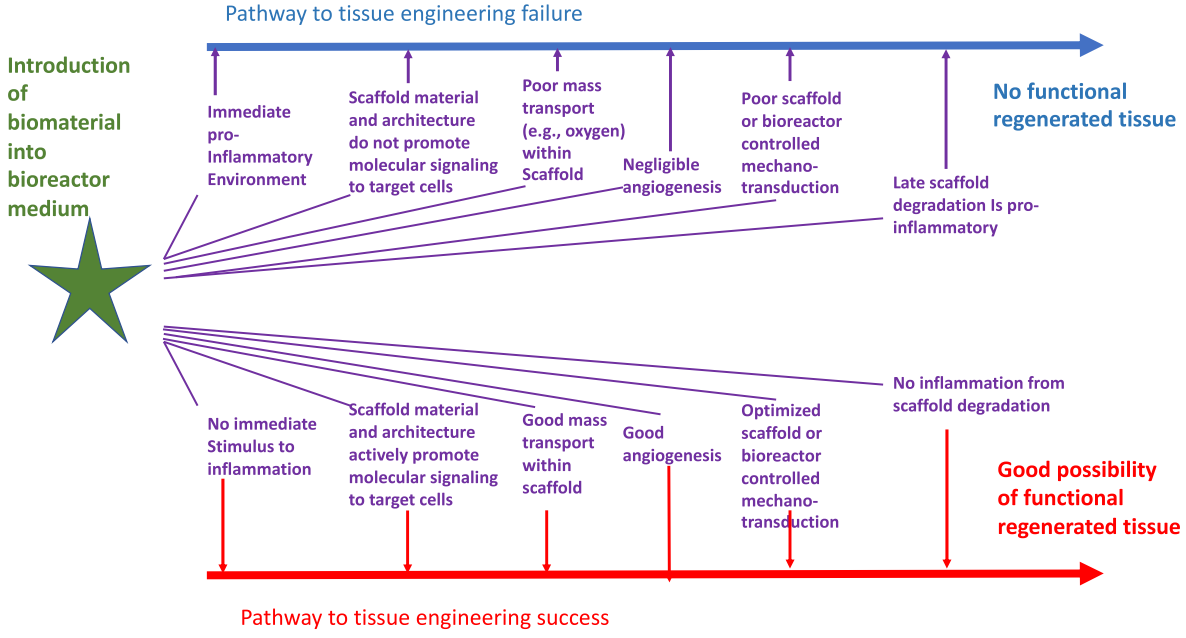

Fig. 14. Plasticity of biocompatibility pathways in bioreactor/scaffold based tissue engineering, See text for explanation.

adipose tissue, arterial endothelial cells promote the expression of adhesion molecules and the consequential sticking of leukocytes to the inner surface of the vessel wall. There is then communication between these leucocytes (mainly macrophages and T-lymphocytes) and smooth muscle cells, the latter migrating from the tunica media into the intima. The cells proliferate and generate a complex extracellular matrix, causing a remodeling of the arterial wall (arterial stenosis), with subsequent lipoprotein modification and glycation, often resulting in calcification, leading to the development of lipid-rich necrotic core of the atherosclerotic plaque.

The first attempts to address the hemodynamic consequences of this plaque involved its removal or compression, for example using the balloon expansion technique of angioplasty, but these usually were temporary rather than permanent solutions as further plaque accumulation and endothelial remodeling, known as re-stenosis, often occurred [202]. As described by Udriste et al. [203], the preferred answer was to use the minimally invasive balloon technology to expand the lumen diameter and deliver a tubular device, the stent, to maintain that expanded configuration. These mesh-like metallic structures, were either expanded by the action of the balloon itself or were made of shape memory materials such as the nickel-titanium alloy Nitinol and would expand to a pre-determined diameter upon deployment in the vessel. A major problem then emerged when the process of stenosis re-emerged in the months and years that followed, this being referred to as in-stent restenosis [204].

This restenosis should be considered in the context of stent biocompatibility. The intervention itself is injurious to the vascular endothelium, which responds with a profound activation of platelets, leading to a platelet - fibrin thrombus. An intense cellular infiltration occurs, involving the subendothelial space, especially with macrophages and lymphocytes. Smooth muscle cell proliferation and migration into the thrombus increases neointimal volume and allows progressive restenosis. This problem was substantially addressed by the introduction of drug-eluting stents in 2001 [205]; the concept here was to incorporate a pharmacological agent into the stent (or stent coating) that had potent antiproliferative effects, while preserving vascular healing. Ideally, such a drug should contain hydrophobic elements to ensure high local concentrations, as well as hydrophilic properties for homogeneous drug diffusion, having a wide therapeutic to toxic ratio with no pro-thrombotic or inflammatory effects. Drugs that interfere early in the cell cycle were preferred to agents that affect the cell cycle in a later stage. Drug-eluting stents were developed on the basis of immunosuppressive, antiproliferative, anti-inflammatory or antithrombotic properties, some, such as sirolimus, affecting multiple targets in the restenotic process.

Several drug-eluting stents have been successful clinically, although not without problems. Arguments have been presented over many years that the benefit of stents are achieved over the first few months, but later problems with proliferation, hyperplasia and restenosis arise because of the chronic irritation associated with the persistence of the stent. If this were the case, then one solution could lie with degradable/absorbable stents (Fig. 15).

3.8.2. Mechanisms

Although several biodegradable polymers and metallic systems have been used, most clinical experience with absorbable stents has been obtained with a small group of polymers, and only these will be discussed here. The major example here is the 'Absorb bioresorbable vascular scaffold', (BVS or BRS), of Abbott Vascular. This device has a 150 μm thick poly (L-lactide) scaffold, with a 7 μm thick poly (D,L-lactide) coating which contains the drug everolimus; this is an immunosuppressive drug, which blocks growth-driven transduction signals in the T-cell response to alloantigen [206]. According to Otsuka et al. [207], the mean cumulative percentage of everolimus released during the first 28 days was 79%, with 35% being released during the first 24 h; 96% had been released at 90 days. The maximum everolimus

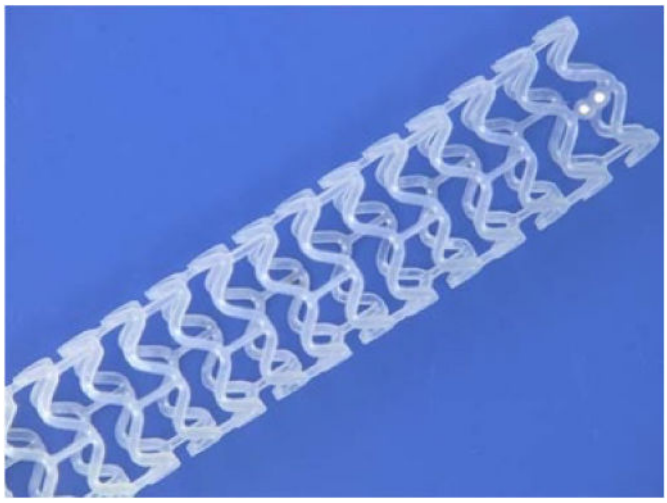

Fig. 15. The Absorb bioresorbable vascular scaffold system.

concentration in scaffold-contacting arterial segments occurred at 3 h (16.2 ng/mg), decreasing to 2.3–4.6 ng/mg at 28 days and 0.6 ng/mg at 90 days. It is important to note that this drug inhibits growth factor-driven cell proliferation at sub-nanomolar concentrations [208]. Otsuka et al. also reported that the polymer molecular weight decreased slowly, by about 18% during the first 6 months, with full resorption by 36 months, and that, in a porcine model, inflammation progressively decreased over this period, the scaffold being replaced by collagen.

First clinical studies of the Absorb stent were carried out in Europe and New Zealand and results, at 1 year, appeared to be good [209]; no late thromboses occurred and there was only mild reduction in stent area. The first large, multicenter randomized trial in the USA, however, showed that target-lesion failure occurred in 7.8% of patients at 1 year, compared to 6.1% with a non-absorbable drug-eluting stent [210]; the performance was described as being within '*the prespecified margin for noninferiority with respect to target lesion failure at 1 year*'. A couple of years later, a systematic review and meta-analysis of randomized trials reported that Absorb had higher 2-year relative risks of the device-oriented composite endpoint than did a non-absorbable everolimus-eluting device, with increased rates of target vessel related myocardial infarction (5.8% vs 3.2%) and ischemia driven target lesion revascularization (5.3% vs 3.9%). There were non-significant differences in cardiac mortality but the cumulative 2-year incidence of device thrombosis of 2.3% compared to 0.7% [211].

At three years, Absorb had a higher rate of target lesion failure compared to the non-absorbable control (11.7% vs 8.1%), mostly driven by a greater target vessel myocardial infarction rate (7.8% vs 4.2%) and ischemia-driven target lesion revascularization (6.6% vs 4.4%); device-related thrombosis rates were also significantly higher [212]. Madanchi et al. have reported data up to five years post-implantation [213], showing '*device-oriented composite endpoint*' of 17% at one year, 27% at two years and 40% at five years, with an 8.4% incidence of scaffold thrombosis by 5 years.

Clinical data largely support these observations, and the device is no longer commercially available. The broad opinion is that the theoretical advantages of a stent that totally resorbs over a 3-year period (i.e., is no longer present within the vessel after that time) have not been fulfilled in practice. The papers referred to above, and others, suggest that the following factors are collectively responsible; it will be obvious that these encompass a series of biocompatibility mechanisms.

- The more aggressive vessel preparation required for implantation, particularly in complex lesions,

- Sub-optimal scaffold expansion and strut embedding in vessel wall, with resulting mal-apposition; poor use of post-dilatation techniques and inadvertent scaffold overlap when multiple devices are used,
- The larger footprint of the device, leading to occlusion of small side branches,
- The thicker, wider, scaffold struts that result in non-laminar flow and altered shear stresses, with enhanced medial layer injury and inflammation and neo-intimal hyperplasia,
- The irregular process of erosion of the polymer, sometimes resulting in a significant loss of radial strength and vessel recoil, with possible disintegration rather than dissolution, yielding scaffold discontinuities,
- The dysregulation of macrophage and endothelial cell functions by the polymer and its degradation products,
- The intraluminal presence of the collagen/proteoglycan provisional matrix may serve as a nidus for thrombus formation,
- Insufficient duration of dual antiplatelet therapy,
- Possible confounding effects of pharmacokinetic of everolimus release and early degradation of the polymer; this could also be affected by surface cracking of the polymer during deployment.

Clearly, multiple biological events take place, both simultaneously and consecutively, and these are influenced by multiple parameters associated with the polymer, the drug, the clinical technique and patient-related idiosyncratic factors. This is a classical scenario for involvement of the plasticity of biocompatibility.

3.8.3. Plasticity

The recent revelations about the role of smooth muscle cell phenotypic plasticity in various vascular diseases [214] provide firm evidence of the significance of plasticity in the biocompatibility of coronary artery stents, including the performance of completely degradable stents. The significant factor here is that vascular smooth muscle cells are different from skeletal and cardiac myocytes since they do not terminally differentiate, retaining a high degree of cellular plasticity. They are able to dramatically alter their phenotype in response to extracellular signals and environmental cues. This allows them to play very significant, and variable, roles in disease states such as atherosclerosis, calcification and aneurysms as well as in intimal hyperplasia, stenosis and re-stenosis. The vascular smooth muscle cell phenotype is influenced by many signals, including those of contractility and both fluid and structural stresses, and cytokines, integrins and growth factors. It is no wonder that within the complex biomechanical and biochemical milieu of the stent/intimal tissue, especially with time-dependent drug release kinetics and polymer degradation profiles, the smooth muscle cells can orchestrate the control of stenosis and re-stenosis.

There are several players in this orchestrated response, including those of a biological nature and those that are biomaterial related (Fig. 16). On the biological side, the endothelial cells are well-known to exhibit plasticity themselves and can adopt pro- and anti-inflammatory phenotypes depending on the specific environment. As noted above, the degradation profile will influence the regulation of both macrophage and endothelial cell function and the complexity of mechano-transduction factors contributes to the overall plasticity characteristics. As with several other examples in this essay, but perhaps seen especially in the context of coronary arteries, both diet and exercise can act as fulcrums of plasticity as they influence arterial shear stresses and plaque build-up.

3.9. Implantable contraceptive devices

3.9.1. Background

This section is concerned with the changing landscape of contraceptive methods at the end of the last century, as discussed by Rowlands [215], focusing on reversible contraception and permanent birth control. For many years, the only commonly available method of female sterilization was laparoscopic tubal ligation, in which the fallopian tubes were clamped and sealed. This was performed under general anesthesia and included risks of entering the peritoneal cavity. An alternative technology was developed that could be delivered hysteroscopically, (i.e., an endoscopic transcervical approach to the uterine cavity) which avoided abdominal incisions and the need for general anesthesia [216]. The one device used for this procedure, Essure, was introduced two decades ago [217]; it is based on the hypothesis that placement of a flexible tubular shaped device within the proximal lumen of a fallopian tube could induce, within its structure, new benign fibrous tissue. One device would have to be placed within each fallopian tube, which would require a method of expansion once released from the delivery system; the patient would have to rely on other contraceptive methods during the period of new tissue growth.

The principal components of the device are an outer and inner coil, these being soldered together at their ends (Fig. 17). The outer coil is made of the nickel-titanium alloy Nitinol, and the inner one is stainless steel The space between these coils contains polyethylene terephthalate

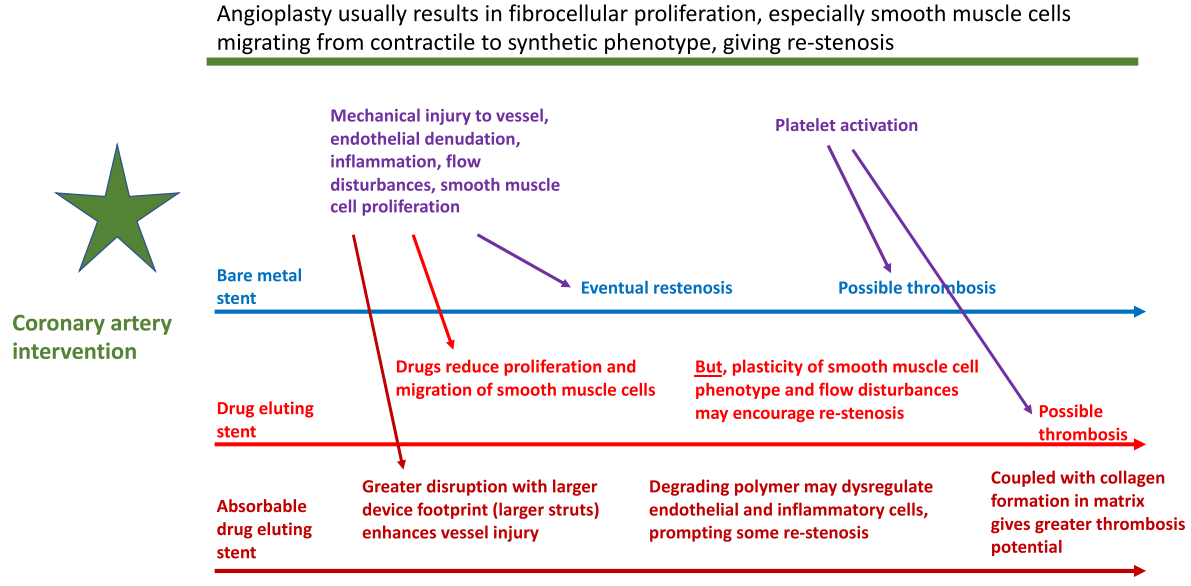

Fig. 16. Plasticity of biocompatibility pathways with different types of coronary artery stent, compared to angioplasty. See text for explanation.

Fig. 17. The Essure contraceptive device.

fibers, winding in and around the stainless steel coil. The implant is intended to span the utero-tubal junction, where the fallopian tube connects to the uterus; here it is far enough into the tube to resist expulsion through uterine contractions, but still proximal enough to allow a portion to trail into the uterus. The shape-memory properties of the Nitinol allow this coil to instantaneously expand its diameter so that it anchors itself to the fallopian tube wall.

Several papers in the years following first clinical use, showing good acceptance of, and confidence in, the Essure device [218]. Over the next ten or so years, several studies, including single-center series [219] and systematic reviews [220], continued to show good outcomes. However, in 2012 Povodano et al. reported on minor complications with the procedure [221]; during the next few years, several single case studies of possible hypersensitivity to the nickel in Nitinol were published [e.g., 222, 223]. The matter became very controversial, and marketing of the device was discontinued.

3.9.2. Mechanisms

The controversy mentioned above centered around the putative adverse effects associated with the device and the impression that its biocompatibility was questionable. Several studies continued to support the safety and effectiveness of Essure. Franchini et al. reported on an 11-year survey of patients fitted with Essure, showing significant satisfaction and an absence of long-term complications [224]. Camara et al. concluded, from a 5-year single-center study [225], that patient satisfaction was at 98%, with very low failure rates. Questions were still raised about nickel sensitivity, but Siemons et al. showed that there were no statistically significant changes in nickel patch tests results and allergy related symptoms after Essure sterilization [226], and Raison-Peyron *et a*l determined that nickel sensitization *via* a classical delayed hypersensitivity pathway did not seem to be responsible for any adverse events attributed to Essure [227].

On the other hand, the incidence of acute pelvic pain after hysteroscopic sterilization was reported to be 8.1%, and of persistent pain after 3 months at 4.2% [228]. It was noted that patients with diagnosis of preexisting chronic pain may be at increased risk of developing pelvic pain after the procedure. Mao et al. showed great levels of adverse effects [229]. Patients undergoing hysteroscopic sterilization had a 10-fold higher risk of undergoing reoperation than those treated with laparoscopic sterilization; the hysteroscopic patients were older and more likely to have has a history of pelvic inflammatory disease, major abdominal surgery and cesarian section deliveries. Kamencic et al. confirmed the existence of both *de novo* and recurring pain, but at low rates, it being assumed that some were associated with device migration [230]. Bouillon et al. showed that among women undergoing first sterilization, the use of hysteroscopic procedures was significantly associated with higher risk of gynecological complications up to three years later than with laparoscopic procedures [231]. The presence of pre-existing pain and abnormal uterine bleeding were associated with higher rates of chronic pelvic pain and post-procedure uterine bleeding according to Carney et al. [232].

There is no doubt that the reporting of dissatisfaction and 'negative experiences' with Essure increased after 2015. Siemons et al. showed that after a follow-up of 144 months, approximately 50% of women reported having symptoms and 16% underwent device removal [233]. Symptoms included menstrual disorders, fatigue, abdominal pain, lower back pain and amnesia; there was no evidence about the device and causation. Similar findings were reported by Stirum et al. [234]. Both of these latter two papers drew attention to the role of social media in the spreading of 'information' about experiences with Essure, and the increased demand for device removal. This was the subject of the editorial in 2019 [235].

3.9.3. Plasticity

This is not a straightforward example, partly because of the lack of significant reliable data, and the multiplicity of so-called adverse outcomes.

As indicated in Fig. 18, there are several device-related factors, such as mechanical irritation, corrosion products [236] and the release of metal ions [237] that could enhance the risks of significant local host responses, although there is scant evidence that any of these by themselves, including the potential of nickel to induce hypersensitivity responses, are of profound importance; the effects may be accumulative or synergistic, but that has not been demonstrated. What is more important is the nature of the host tissues. The female genital tract microbiome is known to be an important determinant of women's health and reproduction [238]. Of significance is the recently recognized influence of the immune cell profile on the fallopian tubes themselves on tubal pathologies and fertility [239]; the lymphocyte and macrophage populations are susceptible to changes on the concentration of reproductive hormones, for example. Variations in inflammatory cell profiles, including lymphocytes and plasma cells have been associated with the presence of pain [240], one of the main 'adverse effects' with Essure. Of course, the possibility of confounding gynecologic conditions makes a rational assessment of causation quite difficult [241], but the accumulating evidence is suggestive that the plasticity of biocompatibility in this very sensitive area is driven by host susceptibility rather than device-related mechanisms.

4. The collective assessment of plasticity in biocompatibility pathways

Foreign materials and agents have been used within or on human patients in clinical therapies (and some diagnostic procedures) for a long time. Many of these perform their tasks with adequate functionality and 'safety' in most of these patients, and some of the associated technologies can be considered as remarkable advances in medical practice. However, success cannot be guaranteed, nor can performance be reliably predicted in advance of a biomaterial being introduced to a host. Even if a biomaterial-related procedure gives patient satisfaction in 90% of cases, the 10% where satisfaction is not obtained (for whatever reason), can cause that procedure to be withdrawn from clinical practice, because of litigation, regulatory action or market downturn, often fueled these days by social media promoted opinion; this means, obviously, that large numbers of prospective patients will be denied access to certain technologies.

This essay is intended to address the fundamental problem that lies at the heart of this conundrum. In each type of technology, there is, or are, an interface(s) between the biomaterial and the host. On one side of that interface will be the biomaterial, usually (although not always) thoroughly characterized and tested according to government and industry recognized standards. On the other side of the interface will be the patient; each patient is unique, there is no such thing as a standard patient when it comes to the performance of these technologies. The uniqueness

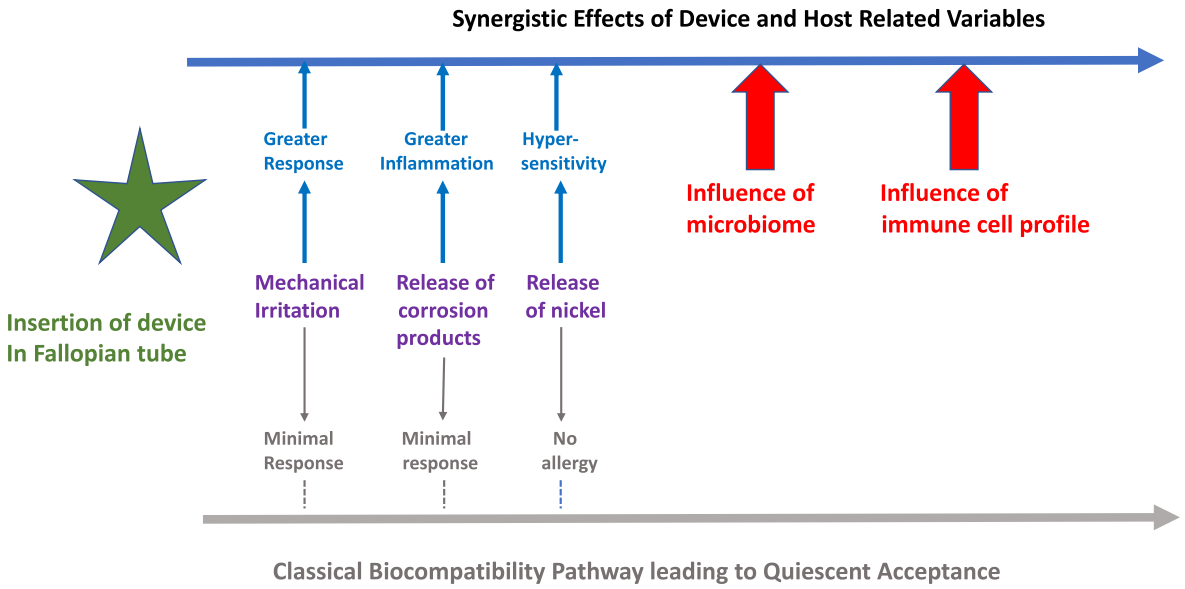

Fig. 18. Plasticity of biocompatibility pathways in contraceptive device.

is governed by genetic, epigenetic, viral, bacterial, biochemical, immunological, cellular, anatomical, biomechanical, biophysical, and other factors. These are compounded by the variable effects of clinical technique, while co-morbidities, nutrition and lifestyle play their part.

While it has been recognized for some time that different biocompatibility pathways operate in different clinical settings, they have largely been considered as linear sequences of events, as identified in section I of the essay, (with occasional cascade amplification), the majority of which are determined by device and biomaterial characteristics. This cannot possibly reflect the actual situation if the pathways are not linear but can change direction and character. This can be seen from the few examples in Fig. 19, involving macrophage phenotype polarization, genetic, viral and microbiome influences on signaling pathways, mechanotransduction, epithelial-mesenchymal transitions and material degradation induced chronic inflammation. The changes in direction are circles in the diagram, and it should be noted that some changes can be reversed at a later stage.

It is perhaps serendipitous that my thoughts of comparing biological to metallurgical plasticity came with examination of the works of Charles Darwin and Santiago Ramón y Cajal and my own recollections of training over 50 years ago. It is not intuitively obvious that we can compare the elastic to plastic transition in a steel rod that is subject to mechanical stress with the phenotypic transition of inflammatory cells in host tissues that are subject to biological stress. It is the concept of reversibility that is at the heart of this comparison.

In considering the steel rod, there are many structural features that control how the material responds to the stress, including grain boundaries, precipitates, dislocations and twins, and a plurality of phases. At a critical value of applied stress, plastic yielding takes place, leading to deformation. Although there have been irreversible atomic movements, however, the internal structure can be subsequently altered to relieve stress fields, by thermal treatments such as annealing and tempering, causing an effective reverse of structural change. Metallurgists refer to the processes as time-temperature-transformations, which control the properties of these alloys. This emphasizes the reversibility of plasticity. In biocompatibility processes, there are also features that control the host response, including those of immunity and cell signaling, which are influenced by genetic, epigenetic, viral and other

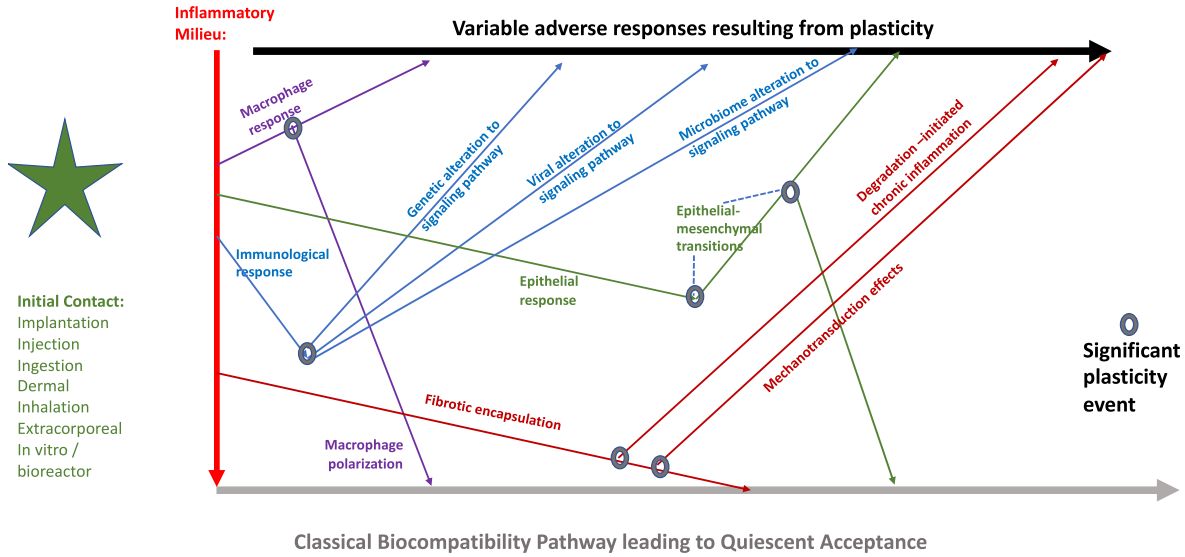

Fig. 19. Representation of some biocompatibility pathways influenced by plasticity.

factors, all of these contributing to the overall biocompatibility pathway that is followed. The reversibility here is produced not by thermally-induced atomic movements, but by phenotypic changes and cellular transformations; the effect could be considered as time-cell signaling-transformations.

Obviously not all the plasticity phenomena discussed in the examples given in this essay can be included in a diagram such as Fig. 19; this schematic can be considered as a template for others to populate in the future. Of generic significance, however, are the following features of biocompatibility plasticity.

- Signaling pathways are influenced by genetic modifications, which lead to variations in host responses to biomaterials,
- The polarization of macrophage phenotype is multidirectional and reversible, being influenced by many factors,
- There is cross-talk between different cellular phenotypes, for example between macrophages and lymphocytes, and between osteoblasts and osteoclasts, which can direct tissue changes,
- There are also transitions from one cell type to another, for example the epithelial – mesenchymal transition that can profoundly alter outcomes,
- The quality of tissues that come into contact with biomaterials is variable, often being determined by genetic factors, which can seriously impact subsequent repair or regeneration,
- Stressors experienced through tissue – biomaterial contact can reactivate viruses, which then impact on subsequent events,
- The biomaterial may affect the tissue by the well-known DAMPS processes, but these effects have spatio-temporal character, for example following late-stage material degradation,
- The biomaterial may act as a chronic antigen stimulus, generating effects in genetically susceptible hosts,
- Since immune surveillance varies between tissues and organs, some sites (possibly fallopian tubes, for example) may be uniquely susceptible to unusual innate immune responses,
- Unsurprisingly, there may be synergy or antagonism between the controllers of plasticity; indeed, it may be the intersection of factors that ultimately decides fate and outcomes.

It should be obvious that there is no intention here to imply that there is just one uniform set of plasticity mechanisms in biocompatibility; there is a general framework into which different mechanisms may be subsumed. Nor should we believe that this concept of plasticity implies that there are old, long-established pathways alongside new pathways. There are both qualitative and quantitative differences between different pathways and there are likely to be simultaneous or competing effects. Plasticity represents a continuum, both temporally and spatially, in the development of a host response.

While this reassessment of biocompatibility pathways should allow a far better understanding of the phenomena themselves, the implications of plasticity have some fundamental consequences related to how the performance and safety of biomaterials and medical technologies are evaluated and determined. The vast majority of regulatory standards assume that the material and device characteristics are the main, if not the sole, drivers of biocompatibility. Test procedures in most jurisdictions now substantially reply on increasingly sophisticated chemical characterization of the biomaterials coupled with toxicological risk assessments and simple, indeed, trivial, *in vitro* and small animal procedures, none of which can detect or determine plasticity or the effects of significant variations in the eventual human patients. The potential for using alternative methods, for example organoid or other tissue-engineered constructs, is attractive here, but only if they can replicate the totality of the biomaterial – host environment, which seems unlikely at this point in their development.

Biocompatibility phenomena are classic examples of metastability; if we do not understand the significance of the conditions which evoke plasticity and directional changes in the host response, we will never improve upon that 10% failure rate. We cannot assume that all patients are the same, or indeed that all clinicians have the same skills and it is becoming necessary to develop algorithms that allow better matching of patients to the technologies. That this can be done is evidenced by those few cases where simple algorithms exist, for example deciding which heart valve replacement to use based on patient age and susceptibility to calcification and thrombosis.

Perhaps of equal significance is the possibility of developing therapeutic strategies that could be used alongside biomaterials applications to minimize undesirable response changes related to the plasticity. In the heart valve situation mentioned above, this can be partly achieved by the use of certain anti-platelet therapies; it may be envisaged that immunomodulatory agents could be used to avoid some excesses of immunological responses, or some agents to modulate unwanted signaling pathways in repair or regenerative processes.

It is a fascinating observation that, after surveying the spectrum of biocompatibility phenomena seen with these clinical scenarios, the plasticity is far more obvious on the patient side of the interface than the material side. That does not mean, however, that biomaterials do not influence, or more importantly are not influenced by, the biological plasticity. If we consider the degradation profile of intentionally degradable polymeric biomaterials, the changes that are observed, for example in molecular weight, polydispersity and oligomer generation, are very much dependent on water diffusion, the activity of phagocytic cells at the interface, the pH in the microenvironment, the generation of reactive oxygen species and so on. These factors have to be taken into account is assessing the overall biocompatibility phenomena.

As noted earlier, it is extremely important to avoid the connotation that biomaterials can be 'biocompatible'; this concept is clearly nonsense, and we have known that for some time. This should now be taken a step further to avoid the concept that a biomaterial can be considered 'biocompatible' as long as the application is specified. If the determinants of biocompatibility, and to most in this industry this is equated with safety, are patient driven, we cannot contemplate the outcome in any individual patient solely on the basis of the materials-oriented database of biocompatibility properties.

Credit author statement

David Williams is the sole author of the submission "The Plasticity of Biocompatibility".

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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References

[1] S.P. Parker, Editor-in-Chief, McGraw-Hill Dictionary of Engineering, McGraw-Hill, New York, 1994.
[2] A.J. Wagers, I.L. Weissman, Plasticity of adult stem cells, Cell 116 (5) (2004) 639–648, https://doi.org/10.1016/s0092-8674(04)00208-9.
[3] C. Darwin, The Origin of the Species, sixth ed., Grolier Enterprises, Connecticut, 1872.

[4] B. Ehrlich, The Brain in Search of Itself: Santiago Ramon Y Cajal and the Story of the Neuron, Farrar, Strauss & Giroux, New York, 2022.
[5] M.J. West-Eberhard, Developmental plasticity and the origin of species differences, Proc. Natl. Acad. Sci. USA 102 (Suppl1) (2005) 6543–6549, https://doi.org/10.1073/pnas.0501844102.
[6] A.J. Lea, J. Tung, E.A. Archie, et al., Developmental plasticity, Evol. Med. Public Health (2017) 162–175, https://doi.org/10.1093/emph/eox019.
[7] F.W. Stahnisch, R. Nitsch, y Santiago Ramon, Cajal's concept of neuroplasticity: the ambiguity lives on, Trends Neurosci. 25 (11) (2002) 589–591.
[8] C. La Rosa, R. Parolisi, L. Bonfanti, Brain structural plasticity: from adult neurogenesis to immature neurons, Front. Neurosci. (2020), https://doi.org/10.3389/fnins.2020.00075.
[9] S. Ramon y Cajal, The Croonian Lecture, - La fine structure des centres nerveux, Proc. Roy. Soc. Lond. 55 (1894) 331–335.
[10] D.F. Williams, Definitions in Biomaterials, Elsevier Scientific, Amsterdam, 1987, p. 72.
[11] X.D. Zhang, D.F. Williams, Definition in Biomaterials for the Twenty-First Century, Elsevier, Oxford, 2019, p. 280.
[12] D.F. Williams, On the mechanisms of biocompatibility, Biomaterials 29 (20) (2008) 2941–2953, https://doi.org/10.1016/j.biomaterials.2008.04.023.
[13] D.F. Williams, Biocompatibility pathways: biomaterials-induced sterile inflammation, mechanotransduction and principles of biocompatibility control, ACS Biomater. Sci. Eng. 3 (1) (2017) 2–35, https://doi.org/10.1021/acsbiomaterials.6b00607.
[14] D.F. Williams, Biocompatibility pathways and mechanisms for bioactive materials; the, bioactivity zone, Bioact. Mater. 10 (2022) 306–322, https://doi.org/10.1016/jbioaactmat.2021.08.014.
[15] D.F. Williams, The biomaterials conundrum in tissue engineering, Tissue Eng. 20 (7–8) (2014) 1129–1131, https://doi.org/10.1089/ten.tea.2013.1769.
[16] D.F. Williams, There is no such thing as a biocompatible material, Biomaterials 35 (38) (2014) 10009–10014, https://doi.org/10.1016/j.biomaterials.2014.08.035.
[17] D.F. Williams, Carcinogenicity of implantable materials; the experimental and epidemiological evidence, Int. Urogynecol. J 25 (2014) 577–580, https://doi.org/10.1007/s00192-014-2346-5.
[18] A. Smith, S. Crouch, S. Lax, et al., Lymphoma incidence, survival and prevalence 2004-2014: sub-type analysis from the UK's Hematological Malignancy Research Network, Brit. Cancer J. 112 (2015) 1575–1584, https://doi.org/10.1038/bjc.2015.94.
[19] S.W. Morris, M.N. Kirsten, M.B. Valentine, et al., Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in Non-Hodgins's lymphoma, Science 263 (5151) (1994) 1281–1284, https://doi.org/10.1126/science8122112.
[20] K.J. Savage, N.L. Harris, J.M. Vose, et al., ALK^{-} anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK^{+} ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project, Blood 111 (12) (2008) 5496–5504, https://doi.org/10.1082/blood-2008-01-134270.
[21] C. Amador, A.L. Feldmann, How I diagnose anaplastic large cell lymphoma, Am. J. Clin. Pathol. 155 (40) (2021) 479–497, https://doi.org/10.1093/ajcp/aqab012.
[22] J.A. Keech, B.J. Creech, Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant (Letter), Plast. Reconstr. Surg. 100 (2) (1997) 554–555, https://doi.org/10.1007/00006534-199708000-00065.
[23] S. Sahoo, P.P. Rosen, R.M. Feddersen, et al., Anaplastic large cell lymphoma arising in a silicone breast implant capsule: a case report and review of the literature, Arch. Pathol. Lab Med. 127 (2003) e115–e118, https://doi.org/10.5858/2003-127-e115-ALCLAI.
[24] A.C. Roden, W.R. Macon, G.L. Keeney, et al., Seroma-associated primary anaplastic large-cell lymphoma adjacent to breast implants: an indolent T-cell lymphoproliferative disorder, Mod. Pathol. 21 (2008) 455–463, https://doi.org/10.1038/modpathol.3801024.
[25] D. De Jong, W.L.E. Vasmel, J.P. de Boer, et al., Anaplastic large-cell lymphoma in women with breast implants, JAMA 300 (17) (2008) 2030–2035, https://doi.org/10.1001/jama.2008.585.
[26] R.N. Miranda, L. Lin, S.S. Talwalkar, et al., Anaplastic large cell lymphoma involving the breast: a clinicopathologic study of 6 cases and review of the literature, Arch. Pathol. Lab Med. 133 (9) (2009) 1383–1390, https://doi.org/10.5858/138.9.1383.
[27] L. Lipworth, R.E. Tarone, J.K. McLaughlin, Breast implants and lymphoma risk: a review of the epidemiologic evidence through 2008, Plast. Reconstr. Surg. 123 (2009) 790–796, https://doi.org/10.1097/PRS.0b013e318199edeb.
[28] B. Kim, C. Roth, K.C. Chung, et al., Anaplastic large cell lymphoma and breast implants: a systematic review, Plast. Reconstr. Surg. 127 (2011) 2141–2148, https://doi.org/10.1097/PRS.0b013e3182172418.
[29] B. Kim, C. Roth, V.L. Young, et al., Anaplastic large cell lymphoma and breast implants: results from a structured expert consultation process, Plast. Reconstr. Surg. 128 (2011) 629–635, https://doi.org/10.1097/PRS.0b013e31821f9f23.
[30] R.N. Miranda, T.N. Aladily, H.M. Prince, et al., Breast implant-associated anaplastic large-cell lymphoma: long-term follow up of 60 patients, J. Clin. Oncol. 32 (2) (2014) 114–120, https://doi.org/10.1200/JCO.2013.82.7911.
[31] P.A. Thompson, H.M. Prince, Brest implant-associated anaplastic large cell lymphoma: a systematic review of the literature and mini-meta analysis, Curr. Hematol. Malig. Rep. 8 (2013), 1960210, https://doi.org/10.1007/s11899-013-0164-3.
[32] A.N. Leberfinger, B.J. Behar, N.C. Williams, et al., Breast implant -associated anaplastic large cell lymphoma – a systematic review, JAMA – Surg 152 (12) (2017) 1161–1168, https://doi.org/10.1001/jamasurg.2017.4026.
[33] B.E. Becherer, M. de Boer, P.E.R. Spronk, et al., The Dutch Breast Implant Registry: registration of breast implant-associated anaplastic large cell lymphoma – a proof of concept, Plast. Reconstr. Surg. 143 (2019) 1298–1305, https://doi.org/10.1097/PRS0000000000005501.
[34] M. Magnusson, K. Beath, R. Cooter, et al., The epidemiology of breast implant-associated anaplastic large cell lymphoma in Australia and New Zealand confirms the highest risk for grade 4 surface breast implants, Plast. Reconstr. Surg. 143 (2019) 1285–1297, https://doi.org/10.1097/PRS0000000000005500.
[35] F.S. Di Pompeo, M. Sorotos, M.W. Clemens, et al., Breast implant associated anaplastic large cell lymphoma (BIA-ALCL): review of epidemiology and prevalence assessment in Europe, Aesthetic Surg. J. 41 (9) (2021) 1014–1025, https://doi.org/10.1093/asj/sjaa285.
[36] D.R. Mackay, Commentary on: breast implant associated anaplastic large cell lymphoma (BIA-ALCL): review of epidemiology and prevalence assessment in Europe, Aesthetic Surg. J. 41 (9) (2021) 1026–1028, https://doi.org/10.1093/asj/sjab038.
[37] M. Camp, Breast implant-associated anaplastic large cell lymphoma, Adv. Surg. 55 (2021) 299–306, https://doi.org/10.1016/jyasu.2021.05.019.
[38] X. Ye, K. Shokrollahi, W.M. Rozen, et al., Anaplastic large cell lymphoma (ALCL) and breast implants: breaking down the evidence, Mutat. Res., Rev. Mutat. Res. 762 (2014) 121–132, https://doi.org/10.1016/jmrrev.2014.08.002.
[39] I.A. Montes-Mojarro, J. Steinhilber, I. Bonzheim, et al., The pathological spectrum of systemic anaplastic large cell lymphoma (ALCL), Cancers 10 (4) (2018) 107, https://doi.org/10.3390/cancers10040107.
[40] A. Di Napoli, G. Pepe, E. Giarnieri, et al., Cytological diagnostic features of late breast implant seromas: from reactive to anaplastic large cell lymphoma, PLoS One 12 (7) (2017), e0181097, https://doi.org/10.1371/journal.pone.0181097.
[41] M.E. Kadin, J. Morgan, H. Xu, et al., IL-13 is produced by tumor cells in breast implant-associated anaplastic lymphoma; implications for pathogenesis, Hum. Pathol. 78 (2018) 54–62, https://doi.org/10.1016/j.humpath.2018.04.007.
[42] N. Oishi, R.N. Miranda, A.L. Feldman, Genetics of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), Aesthetic Surg. J. 39 (S1) (2019) S14–S20, https://doi.org/10.1093/asj/sjy311.
[43] C. Laurent, A. Nicolae, C. Laurent, et al., Gene alterations in epigenetic modifiers and JAK-STAT signaling are frequent in breast implant-associated ALCL, Blood 135 (5) (2020) 360–370.
[44] R.C. DeCoster, M.W. Clemens, A. Di Napoli, et al., Cellular and molecular mechanisms of breast implant associated anaplastic large cell lymphoma, Plast. Reconstr. Surg. 147 (2021) 30e, https://doi.org/10.1097/PRS0000000000007423.
[45] P. Blombery, E.R. Thompson, H.M. Prince, Molecular drivers of breast implant-associated anaplastic large cell lymphoma, Plast. Reconstr. Surg. 143 (2019), https://doi.org/10.1097/PRS0000000000005570, 59S:30e.
[46] M. De Boer, M. Hauptmann, N.J. Hijmering, et al., Increased prevalence of BRCA ½ mutations in women with macrotexture breast implants and anaplastic large cell lymphoma of the breast, Blood 136 (11) (2020) 1368–1371, https://doi.org/10.1082/blood-2019004498.
[47] S.E. Tevis, K.K. Hunt, R.N. Miranda, et al., Differences in Human Leukocyte Antigen expression between breast implant-associated anaplastic large cell lymphoma patients and the general population, Aesthetic Surg. J. 39 (10) (2019) 1065–1070, https://doi.org/10.1093/asj/sjz021.
[48] M. Rondon-Lagos, N. Rangel, G. Camargo-Villalba, et al., Biologic and genetic landscape of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), Eur. J. Surg. Oncol. 47 (2011) 942–951, https://doi.org/10.1016/ejso.2020.10.029.
[49] R.L. King, J.R. Goodlad, M. Calaminici, et al., Lymphomas arising in immune-privileged sites: insights into biology, diagnosis, and pathogenesis, Virchows Arch. 476 (2020) 647–665, https://doi.org/10.1007/s00428-019-02698-3.
[50] H. Hu, A. Jacombs, K. Vickery, et al., Chronic biofilm infection in breast implants is associated with an increased T-cell lymphocytic infiltrate: implications for breast implant-associated lymphoma, Plast. Reconstr. Surg. 135 (2015) 319–329, https://doi.org/10.1097/PRS000000000000886.
[51] J.N. Walker, B.M. Hanson, C.L. Pinkner, et al., Insights into the microbiome of breast implants and periprosthetic tissue in breast implant-associated anaplastic large cell lymphoma, Sci. Rep. 9 (2019), 10393, https://doi.org/10.1038/s41598-019-46535-8.
[52] E. Swanson, Breast implant-associated anaplastic large cell lymphoma (BIA_ALCL): why the search for an infectious etiology may be irrelevant, Aesthetic Surg. J. 37 (9) (2017) NP118–NP121, https://doi.org/10.1093/asj/sjx108.
[53] S.M. Rodriguez-Pinilla, F.J.S. Garcia, O. Balague, et al., Breast implant associated Epstein-Barr virus-positive large B-cell lymphomas: a report of three cases, Haematologica 105 (2020) e412, https://doi.org/10.3324/haematol.2019.232355 (letter to the editor).
[54] L. Mescam, V. Camus, J.-M. Schiano, et al., EBV^{+} diffuse large B-cell lymphoma associated with chronic inflammation expands the spectrum of breast-implant related lymphomas, Blood 135 (22) (2020) 204–208 (letter to the editor, May 28th).
[55] L.J. Medeiros, M.L. Marques-Piubelli, V.F.I. Sangiorgio, et al., Epstein-Barr virus-positive large B cell lymphoma associated with breast implants: an analysis of eight patients suggesting a possible pathogenic relationship, Mod. Pathol. (2021), https://doi.org/10.1038/s41379-021-00863-1. Published on-line July 5th.
[56] C. Khoo, C. McTigue, D.J. Hunter-Smith, et al., EBV positive fibrin/chronic inflammation associated diffuse large B-cell lymphoma: an incidental finding associated with a breast implant, Pathology 53 (5) (2021) 673–675, https://doi.org/10.1016/j.pathology.2020.09.022 (letter to the editor).

[57] M. Mansy, A.C. Wotherspoon, D. El-Sharkawi, et al., Fibrin-associated diffuse large B-cell lymphoma misdiagnosed as breast-implant associated anaplastic large-cell lymphoma, Histopathology 79 (2021) 269–271, https://doi.org/10.1111/his.14372.

[58] D. Bakkalci, Y. Jia, J.R. Winter, et al., Risk factors for Epstein Barr virus associated cancers: a systematic review, critical appraisal, and mapping of the epidemiological evidence, J. Glob. Health 10 (1) (2020), 010405.

[59] M.B. Calobrace, M.B. Schwartz, K.R. Zeidler, et al., Long-term safety of textured and smooth breast implants, Aesthetic Surg. J. 38 (1) (2018) 38–48, https://doi.org/10.1093/asj/sjx157.

[60] M.E.M. Britez, C.C. Llano, A. Chaux, Periprosthetic breast capsules and immunophenotypes of inflammatory cells, Eur. J. Plast. Surg. 35 (2012) 647–651, https://doi.org/10.1007/s002238-012-0728-9.

[61] G.S. Brody, D. Deapen, C.R. Taylor, et al., Anaplastic large-cell lymphoma occurring in women with breast implants: analysis if 173 cases, Plast. Reconstr. Surg. 135 (3) (2015) 695–707, https://doi.org/10.1097/PRS.0000000000001033.

[62] A. Loch-Wilkinson, K.J. Beath, R.J.W. Knight, et al., Breast implant-associated anaplastic large cell lymphoma in Australia and New Zealand: high surface area textured implants are associated with increased risk, Plast. Reconstr. Surg. 140 (2017) 645–654, https://doi.org/10.1097/PRS.0000000000003654.

[63] M. Clemens, Discussion: breast implant-associated anaplastic large cell lymphoma in Australia and New Zealand: high surface area textured implants are associated with increased risk, Plast. Reconstr. Surg. 140 (2017) 660–662, https://doi.org/10.1097/PRS.0000000000003714.

[64] J.C. Doloff, O. Veiseh, R. de Mezerville, et al., The surface topography of silicone breast implants mediates the foreign body response in mice, rabbits and humans, Nature Biomed. Eng. 5 (2021) 1115–1130, https://doi.org/10.1038/s41551-021-00739-4.

[65] M.B. Nava, P. Chiodini, G. Catanuto, et al., Is breast implant associated – anaplastic large cell lymphoma linked to texture implants, Aesthetic Plast. Surg. 45 (6) (2021) 2593–2601, https://doi.org/10.1007/s00266-021-02260-0.

[66] M. Orciani, M. Caffarini, M. Torresetti, et al., Breast implant texturization does not affect the crosstalk between MSC and ALCL cells, Inflammation 42 (2) (2019), 72130, https://doi.org/10.1007/s10753-018-0930-4.

[67] L. Har-Shai, Y. Har-Shai, I. Metanes, et al., Composite breast implant associated anaplastic large cell lymphoma (BIA-ALCL) and extra-nodal marginal zone lymphoma (MZL) in the capsule of a silicone breast implant, Autoimmun. Rev. 18 (5) (2019) 556–557, https://doi.org/10.1016/j.autrev.2019.03.014.

[68] W. Cheuk, A.C.L. Chan, J.K.C. Chan, et al., Metallic implant-associated lymphoma: a distinct subgroup of large B-cell lymphoma related to pyothorax-associated lymphoma? J. Surg. Pathol. 29 (6) (2005) 832–836, https://doi.org/10.1097/01.pas.0000157747.10967.f4.

[69] B. Palraj, A. Paturi, R.G. Stone, et al., Soft tissue anaplastic large T-cell lymphoma associated with a metallic orthopedic implant: case report and review of the current literature, J. Foot Ankle Surg. 49 (2010) 561–564, https://doi.org/10.1053/j.jfas.2010.08.009.

[70] B. Sanchez-Gonzales, M. Garcia, F. Montserrat, et al., Diffuse large B-cell lymphoma associated with chronic inflammation in metallic implant, J. Clin. Oncol. 31 (10) (2013) e148, https://doi.org/10.1200/JCO.2012.42.8250.

[71] S.-J. Wang, D.-L. Cao, H.-W. Xu, et al., Development of primary diffuse large B cell lymphoma around an internal fixation implant after lumbar fusion surgery" A case report and review of the literature, World Neurosurg 137 (2020) 140–145, https://doi.org/10.1016/wneu.2020.01.227.

[72] M. Fujimoto, H. Haga, M. Okamoto, et al., EBV-associated diffuse large B-cell lymphoma arising in the chest wall with surgical mesh implant, Pathol. Int. 58 (2008) 668–671, https://doi.org/10.1111/j.1440-1827.2008.02288.x.

[73] T. Menter, V. Ballova, C. Caspar, et al., ALK-negative anaplastic large cell lymphoma arising in the thrombus of an aortic prosthesis preceded by clonally related lymphomatoid papulosis, Virchows Arch. 474 (2019) 763–767, https://doi.org/10.1007/s00428.019-02531-x.

[74] A. Mosquera-Zamudio, R. Parra-Medina, L. Moreno, et al., Diffuse large B-cell lymphoma in a patient with necrotizing fasciitis secondary to silicone biopolymer implants in the buttock, Int. J. Surg. Pathol. 25 (7) (2017) 606–607, https://doi.org/10.1177/1066896917704900.

[75] O. Shauly, D.J. Gould, I. Siddiqi, et al., The first reported case of gluteal implant-associated anaplastic large cell lymphoma (ALCL), Aesthetic Surg. J. 39 (7) (2019) NP253–N258, https://doi.org/10.1093/asj/sjz044.

[76] J. Mendes, V.A. Mendes Maykeh, L.F. Frascino, et al., Gluteal implant-associated anaplastic large cell lymphoma, Plast. Reconstr. Surg. 144 (2019) 610–613, https://doi.org/10.1097/PRS.0000000000005910.

[77] D.M. Senderoff, No proven association between anaplastic large cell lymphoma (ALCL) and textured buttock implants, Aesthetic Surg. J. 39 (8) (2019) NP366–N367, https://doi.org/10.1093/asj/sjz133.

[78] M.L.M. Piubelli, M.C. Ferrufino-Schmidt, R.N. Miranda, Gluteal implant associated anaplastic large cell lymphoma (ALCL) is distinct from systemic ALCL ALK negative in a patient with gluteal implants, Aesthetic Surg. J. 39 (8) (2019) NP366–N367, https://doi.org/10.1093/asj/sjz133.

[79] G. Ramos-Gallardo, A.A. Carballo-Zarate, J. Cuenca-Pardo, et al., What is the evidence of lymphoma in patients with prostheses other than breast implants? Aesthetic Plast. Surg. 44 (2020) 286–294, https://doi.org/10.1007/s00266-019-01569-1.

[80] F. Loong, A.C.L. Chan, B.C.S. Ho, et al., Diffuse large B-cell lymphoma with chronic inflammation as an incidental finding and new clinical scenarios, Mod. Pathol. 23 (2010) 493–501, https://doi.org/10.1038/modpathol.2009.168.

[81] M. Parkhi, C. Singh, P. Malhotra, et al., Non-mammary implant associated anaplastic large cell lymphoma, Pathology 53 (2) (2021) 282–285, https://doi.org/10.1016/j.pathol.2020.06.022.

[82] L.M. Nibourg, E. Gelens, R. Kuijer, et al., Prevention of posterior capsular opacification, Exp. Eye Res. 136 (2015) 100–115, https://doi.org/10.1016/j.exer.2015.03.011.

[83] X. Lai, Q. Li, F. Wu, et al., Epithelial-mesenchymal transition and metabolic switching in cancer: lessons from somatic cell reprogramming, Front. Cell Dev. Biol. 8 (2020) 760, https://doi.org/10.3389/fcell.2020.00760.

[84] A.P. Thankamony, K. Saxena, R. Murali, et al., Cancer stem cell plasticity - a deadly deal, Front. Mol. Biosci. 7 (2020) 79, https://doi.org/10.3389/fmolb.2020.00079.

[85] G. Cooksley, J. Lacey, M.K. Dymond, et al., Factors affecting posterior capsule opacification in the development of intraocular lens materials, Pharmaceutics 13 (6) (2021) 860, https://doi.org/10.3390/pharmaceutics13060860.

[86] S. Hazra, H. Palui, G.K. Vemuganti, Comparison of design of intraocular lens versus the material for PCO prevention, Int. J. Ophthalmol. 5 (2012) 59–63, https://doi.org/10.3980/j.issn.2222-3959.2012.01.12.

[87] L. Leishman, L. Werner, Z. Bodnar, et al., Prevention of capsular bag opacification with a modified hydrophilic acrylic disk-shaped intraocular lens, J. Cataract Refract. Surg. 38 (2012) 1664–1670, https://doi.org/10.1016/j.jcrs.2012.04.040.

[88] A. Ollerton, L. Werner, S.R. Fuller, et al., Evaluation of a new single-piece 4% water content hydrophobic lens in the rabbit model, J. Cataract Refract. Surg. 38 (2012) 1827–1832, https://doi.org/10.1016/j.jcrs.2012.05.039.

[89] G. Kahraman, H. Schrittwieser, M. Walch, et al., Anterior and posterior capsular opacification with the Tecnis ZCB00 and AcrySof SA60AT IOLs: a randomized intraindividual comparison, Br. J. Ophthalmol. 98 (2014) 905–909, https://doi.org/10.1136/bjophthalmol-2013-303841.

[90] D. Bozukova, C. Pagnoulle, R. Jerome, et al., Polymers in modern ophthalmic implants – historical background and recent advances, Mater. Sci. Eng. R Rep. 69 (2010) 63–83, https://doi.org/10.1016/mser.2010.05.002.

[91] N. Awasthi, S. Guo, B.J. Wagner, Posterior capsular opacification; A problem reduced but not yet eradicated, Arch. Ophthalmol. 127 (2009) 555–562, https://doi.org/10.1001/archophthalmol.2009.3.

[92] S. Shibata, N. Shibate, S. Ohtsuka, et al., Role of Decorin in posterior capsule opacification and eye lens development, Cells 10 (2021) 863, https://doi.org/10.3390/cells10040863.

[93] S. Lamouille, J. Xu, R. Derynck, Molecular mechanisms of epithelial-mesenchymal transition, Nat. Rev. Mol. Cell Biol. 15 (3) (2014) 178–196, https://doi.org/10.1038/nrm3758.

[94] J.O.L. DeLancey, The hidden epidemic of pelvic floor dysfunction: achievable goals for improved prevention and treatment, Am. J. Obstet. Gynecol. 192 (2005) 1488–1495, https://doi.org/10.1016/j.ajog.2005.02.028.

[95] A.M. Weber, H.E. Richer, Pelvic organ prolapse, Obstet. Gynecol. 106 (3) (2005) 615–634, https://doi.org/10.1097/01.AOG.0000175832.13266.bb.

[96] J.A. Ashton-Miller, J.O.L. DeLancey, Functional anatomy of the pelvic floor, Ann. NY Acad. Sci. 1101 (2007) 266–296, https://doi.org/10.1196/annals.1389.034.

[97] K.A. Jones, P.A. Moalli, Pathophysiology of pelvic organ prolapse, Female Pelvic Med. Reconstr. Surg. 16 (2) (2010) 79–89, https://doi.org/10.1097/SPV.0b013e3181d6ff65.

[98] B. Ghazi, O. Deigni, M. Yezhelyev, et al., Current options in the management of complex abdominal wall defects, Ann. Plast. Surg. 66 (5) (2011) 488–492, https://doi.org/10.1097/SAP.06013e31820d18db.

[99] E. Yahchoucht-Chouillard, T. Aura, O. Picone, et al., Incisional hernia: related risk factors, Dig. Surg. 20 (2003) 3–9, https://doi.org/10.1159/000068850.

[100] S. Oberg, K. Andresen, J. Rosenberg, Etiology of inguinal hernias: a comprehensive review, Front. Surg. 4 (2017) 52, https://doi.org/10.3389/fsurg.2017.00052.

[101] N.A. Henriksen, D.H. Yadete, L.T. Sorensen, et al., Connective tissue alteration in abdominal wall hernia, Br. J. Surg. 98 (2011) 210–219, https://doi.org/10.1002/bjs.7339.

[102] U. Klinge, Z.Y. Si, H. Zheng, et al., Collagen I/III and matrix metalloproteinases (MMP)1 and 13 in the fascia of patients with incisional hernias, J. Invest. Surg. 14 (1) (2002) 47–54, https://doi.org/10.1080/089419301750072202.

[103] F.G. Thankam, G. Palanikumar, R.J. Fitzgibbons, et al., Molecular mechanisms and potential therapeutic targets in incisional hernia, J. Surg. Res. 236 (2019) 134–143, https://doi.org/10.1016/j.jss.2018.11.037.

[104] A. Pans, A. Albert, C.M. Lapiere, et al., Biochemical study of collagen in adult groin hernias, J. Surg. Res. 95 (2001) 107–113, https://doi.org/10.1006/jsre.2000.6024.

[105] B. Chen, J. Yeh, Alterations in connective tissue metabolism in stress incontinence and prolapse, J. Urol. 186 (5) (2011) 1768–1772, https://doi.org/10.1016/juro.2011.06.054.

[106] S.R. Jackson, S.D. Eckford, P. Abrams, et al., Changes in metabolism of collagen in genitourinary prolapse, Lancet 347 (9016) (1996) 1658–1661, https://doi.org/10.1016/S0140-6736996)91489-0.

[107] P.A. Moali, S.H. Shand, H.M. Zyczynski, et al., Remodeling of vaginal connective tissue in patients with prolapse, Obstet. Gynecol. 106 (5–1) (2005) 953–963, https://doi.org/10.1097/01.AOG.0000182584.15087.dd.

[108] S. Mei, M. Ye, L. Gil, et al., The role of smooth muscle cells in the pathophysiology of pelvic organ prolapse, Female Pelvic Med. Reconstr. Surg. 19 (5) (2013) 254–259, https://doi.org/10.1097/SPV.0b013e31829ff74d.

[109] C.R. Deeken, S.P. Lake, Mechanical properties of the abdominal wall and biomaterials utilized for hernia repair, J. Mech. Behav. Biomed. Mater. 74 (2017) 411–427, https://doi.org/10.1016/.j.mbbm.2017.05.008.

[110] B. Hernandez-Gascon, A. Mena, E. Pena, et al., Understanding the passive mechanical behavior of the human abdominal wall, *Ann. Biomed. Eng.* 41 (2013) 433–444, https://doi.org/10.1007/s10439-012-0672-7.

[111] R. Cartwright, A.C. Kirby, K.A.O. Tikkine, et al., Systematic review and meta-analysis of genetic association studies of urinary symptoms and prolapse in women, Am. J. Obstet. Gynecol. 212 (199) (2015), https://doi.org/10.1016/j.ajog.2014.08.005 e1-24.

[112] K. Allen-Brady, J.W.F. Chua, R. Cuffolo, et al., Systematic review and meta-analysis of genetic association studies of pelvic organ prolapse, Int. Urogynecol. J. 33 (2022) 67–82, https://doi.org/10.1007/s00192-021-04782-2.

[113] J.M. Wu, A.G. Visco, E.A. Grass, et al., Matrix metalloproteinase-9 genetic polymorphisms and the risk for advanced pelvic organ prolapse, Obstet. Gynecol. 120 (3) (2012) 587–593, https://doi.org/10.1097/AOG.0b013e318262234b.

[114] K. Allen-Brady, P.A. Norton, A. Jolyn Hill, et al., Risk of pelvic organ prolapse treatment based on extended family history, Am. J. Obstet. Gynecol. 223 (2020) 105,e108, https://doi.org/10.1016/j.ajog.2019.12.271.

[115] C. Barnett, J.C. Langer, A. Hinek, et al., Looking past the lump: genetic aspects of inguinal hernia in children, J. Pediatr. Surg. 44 (7) (2009) 1423–1431, https://doi.org/10.1016/j.jpedsurg.2008.12.022.

[116] E. Jorgenson, N. Makki, L. Shen, et al., A genome-wide association study identifies four novel susceptibility loci underlying inguinal hernia, Nat. Commun. (2015), 610130, https://doi.org/10.1038/ncomms10130.

[117] S. Sauerland, T. Korenkov, M. Kleinen, et al., Obesity is a risk factor for recurrence after incisional hernia repair, Hernia 8 (2004) 42–46, https://doi.org/10.1007/s100029-003-0161-x.

[118] G. Hellspong, U. Gunnarsson, U. Dahlstrand, et al., Diabetes as a risk factor in patients undergoing groin hernia surgery, Langenbeck's Arch. Surg. 402 (2) (2017) 219–225, https://doi.org/10.1007/s00423-016-1519-8.

[119] W.H. Harris, The problem is osteolysis, Clin. Orthop. Relat. Res. 311 (1995) 46–53.

[120] A. Kobayashi, W. Bonfield, Y. Kadoya, et al., The size and shape of particulate polyethylene wear debris in total joint replacements, Proc. Inst. Mech. Eng. H 211 (1) (1997) 11–16, https://doi.org/10.1243/0954411971534638.

[121] W.C. Dougall, M. Glaccum, K. Charrier, et al., RANK is essential for osteoclast and lymph node development, Genes Dev. 13 (180) (1999) 2412–2424, https://doi.org/10.1101/gad.13.18.2412.

[122] C.A. Holding, D.M. Findlay, R. Stamenkov, et al., The correlation of RANK, RANKL and TNFα expression with bone loss volume and polyethylene wear debris around hip implants, Biomaterials 27 (2006) 5212–5219, https://doi.org/10.1016/j.biomaterials.2006.05.054.

[123] P.J. Brooks, M. Glogauer, C.A. McCulloch, An overview of the derivation and function of multinucleated giant cells and their role in pathologic processes, Am. J. Pathol. 189 (6) (2019) 1148–1158, https://doi.org/10.1016/j.japath.2019.02.006.

[124] P.E. Purdue, P. Koulouvaris, B.J. Nestor, et al., The central role of wear debris in periprosthetic osteolysis, HSS J. 2 (2006) 102–113, https://doi.org/10.1007/s11420-006-9003-6.

[125] G.J. Ahmed, E. Tatsukawa, K. Murishita, et al., Regulation and biological significance of formation of osteoclasts and foreign body giant cells in an extraskeletal implantation model, Acta Histochem. Cytoc. 49 (3) (2016) 97–107, https://doi.org/10.1267/ahc.16007.

[126] G.K. McKee, J. Watson-Farrar, Replacement of arthritic hip by the McKee-Farrar prosthesis, J. Bone Jt. Surg. 48B (1966) 245–259.

[127] G.P. Arden, A.R. Taylor, B.M. Ansell, Total hip replacement using the McKee-Farrar prosthesis, Ann. Rheum. Dis. 29 (1970) 1–4.

[128] H.-G. Willert, G.H. Buchhorn, A. Fayyazi, et al., Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study, J. Bone Jt. Surg. Am. 87 (1) (2005) 28–36, https://doi.org/10.2106/JBJS.A.02039pp.

[129] J.J. Jacobs, R.M. Urban, N.J. Hallab, et al., Metal-on-metal bearing surfaces, J. Am. Acad. Orthop. Surg. 17 (2) (2009) 69–76, https://doi.org/10.5435/00124635-200902000-00003.

[130] D.J. Langton, S.S. Jameson, T.J. Joyce, et al., Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement, J Bone Jt. Surg. Brit. 92 (2010) 38–46, https://doi.org/10.1302/0301-620X.92B1.

[131] J.A. Browne, C.D. Bechtold, D.J. Berry, et al., Failed metal-on-metal hip arthroplasties: a spectrum of clinical presentations and operative findings, Clin. Orthop. Relat. Res. 468 (2010) 2313–2320, https://doi.org/10.1007/s11999-010-1419-0.

[132] M. Kovochich, E.S. Fung, E. Donovan, et al., Characterization of wear debris from metal-on-metal hip implants during normal wear versus edge-loading conditions, J. Biomed. Mater. Res. B 106 (30) (2018) 989–996, https://doi.org/10.1002/jbm.b.33902.

[133] A.C. Cheung, S. Banerjee, J.J. Cherian, et al., Systemic cobalt toxicity from total hip arthroplasties, Bone Joint Lett. J 98 (8) (2016) 6–13, https://doi.org/10.1302/0301-620X.98B1.36374.

[134] S. Landgraeber, M. Jager, J.J. Jacobs, et al., The pathology of orthopedic implant failure is mediated by innate immune systems cytokines, Mediat. Inflamm. (2014), https://doi.org/10.1155/2014/185150. ID 185150.

[135] P. Campbell, E. Ebramzadeh, S. Nelson, et al., Histological features of pseudotumor-like tissues from metal-on-metal hips, *Clin. Orthop. Relat. Res.* 468 (9) (2010) 2321–2327.

[136] J. Pajarinen, E. Jamsen, Y.T. Konttinen, et al., Innate immune reactions in septic and aseptic osteolysis, J. Long Term Eff. Med. Implants 24 (4) (2014) 283–296, https://doi.org/10.1615/jlongtermeffmedimplants.2014010564.

[137] C.H. Lohmann, R. Hameister, G. Singh, Allergies in orthopedic and trauma surgery, Orthop. Traumatol. Surg. Res. 103 (2017) 575–581, https://doi.org/10.1016/j.otsr.2016.06.021.

[138] J.G. Galbraith, J.S. Butler, T.-J. Browne, et al., Infection or metal hypersensitivity? The diagnostic challenge of failure in metal-on-metal bearings, Acta Orthop. Belg. 77 (2) (2011) 145–151.

[139] L. Lehtovirat, A. Reito, J. Parkkinen, et al., Association between periprosthetic tissue metal content, whole blood and synovial fluid metal ion levels and histopathological findings in patients with failed metal-on-metal hip replacement, PLoS One 13 (5) (2018), e0197614, https://doi.org/10.1371/journal.pone.0197614.

[140] E.-L. Paukkeri, R. Korhonen, M. Hamaiainen, et al., The inflammatory phenotype in failed metal-on-metal arthroplasty correlates with blood metal concentration, PLoS One 11 (5) (2016), e0155121, https://doi.org/10.1371/journal.pone.0155121.

[141] L. Samelko, M.S. Caicedo, J. Jacobs, et al., Transition from metal-DTH resistance to susceptibility is facilitated by NLRP3 inflammasome signaling induced Th17 reactivity; Implications for orthopedic implants, PLoS One 14 (1) (2019), e0210336, https://doi.org/10.1371/journal.pone.0210336.

[142] F.R.G. Rocha, A.E. Delitto, J.A. Chaves de Souza, et al., Relevance of caspase-1 and Nlrp3 inflammasome in inflammatory bone resorption in a murine model of periodontitis, Sci. Rep. 10 (2020) 7823, https://doi.org/10.1038/s41598-020-6465-y.

[143] M. Couto, D.P. Vasconcelos, D.M. Sousa, et al., The mechanisms underlying the biological response to wear debris in periprosthetic inflammation, Front Mater 7 (2020) 274, https://doi.org/10.3389/fmats.2020.00274.

[144] A.J. Rao, E. Gibon, T. Ma, et al., Revision joint replacement, wear particles and macrophage polarization, Acta Biomater. 8 (7) (2012) 2815–2823, https://doi.org/10.1016/j.actbio.2012.03.042.

[145] P.H. Schlesinger, H.C. Blair, D.B. Stolz, et al., Cellular and extracellular matrix of bone, with principles of synthesis and dependency of mineral deposition on cell membrane transport, Am. J. Physiol. Cell Physiol. 318 (2020) C11–C124, https://doi.org/10.1152/ajpcell.00120.2019.

[146] J.-M. Kim, C. Lin, Z. Stavre, et al., Osteoblast – _osteoclast communication and bone homeostasis, Cells 9 (2020) 2073, https://doi.org/10.3390/cells9092073.

[147] K. Chen, Y. Jiao, L. Liu, et al., Communications between bone marrow macrophages and bone cells in bone remodeling, Front. Cell Dev. Biol. 8 (2020), 598263, https://doi.org/10.3389/fcell.2020.598262.

[148] J.S. Kenkre, J.H.D. Bassett, The bone remodeling cycle, Ann. Clin. Biochem. 55 (2018) 308–327, https://doi.org/10.1177/0004563218759371.

[149] T.J. Martin, N.A. Sims, RANKL/OPG; Critical role in bone physiology, Rev. Endocr. Metab. Disord. 16 (2015) 131–139, https://doi.org/10.1007/s11154-014-9308-6.

[150] D. Huang, F. Zhao, W. Gao, et al., Strontium substituted sub-micron bioactive glasses inhibit osteoclastogenesis through suppression of RANKL-induced signaling pathway, Regen. Biomater. 7 (2020) 303–311, https://doi.org/10.1093/rb/rbaa004.

[151] C.M. Karner, F. Long, Wnt signaling and cellular metabolism in osteoblasts, Cell. Mol. Life Sci. 74 (2017) 1649–1657, https://doi.org/10.10007/s00018-016-2424-5.

[152] D. Grigorie, U.H. Lerner, The crucial role of the WNT system in bone remodeling, Acta Endocrinol. XIV (2018) 90–101, https://doi.org/10.4183/aeb.2018.90.

[153] R.P.F. Abuna, F.S. Oliveira, H.B. Lopes, et al., The Wnt/β-catenin signaling pathway is regulated by titanium with nanotopography to induce osteoblast differentiation, Colloids Surf.. B Interface 184 (2019), 110513, https://doi.org/10.1016/j.colsurfb.2019.110513.

[154] W. Liu, D. Chen, G. Jiang, et al., A lithium-containing nanoporous coating on entangled titanium scaffold can enhance osseointegration through Wnt/β-catenin pathway, Nanomedicine 14 (2018) 153–164, https://doi.org/10.1016/j.nano.2017.09.006.

[155] J.O. Abaricia, A.H. Shah, M. Chaubal, et al., Wnt signaling modulates macrophage polarization and is regulated by biomaterial surface properties, Biomaterials 243 (2020), 119920, https://doi.org/10.1016/j.biomaterials.2020.119920.

[156] Y. Zhou, C. Wu, J. Chang, Bioceramics to regulate stem cells and their microenvironment for tissue regeneration, Mater. Today 24 (2019) 41–56, https://doi.org/10.1016/j.mattod.2018.07.016.

[157] S. An, The emerging role of extracellular Ca2+ in osteo/odontogenic differentiation and the involvement of intracellular Ca2+ signaling: from osteoblastic cells to dental pulp cells and odontoblasts, J. Cell. Physiol. 234 (2019) 2169–2193, https://doi.org/10.1002/jcp27068.

[158] H. Niu, D. Lin, W. Tang, et al., Surface topography regulates osteogenic differentiation of MSCs via crosstalk between FAK/MAPK and ILK/β-catenin pathways in a hierarchically porous environment, ACS Biomater. Sci. Eng. 3 (2017) 3161–3175, https://doi.org/10.1021/acsbiomaterials.7b00315.

[159] P. Tian, Y. Wang, D.D. Bikle, IGF-1 signaling mediated cell-specific mechanotransduction, J. Orthop. Res. 36 (2018) 576–583, https://doi.org/10.1002/jor.23767.

[160] N.M.A. Mohammed, A. Mahfouz, K. Achkar, et al., Contrast-induced nephropathy, Heart Views 14 (2013) 106–116, https://doi.org/10.4103/1995-705X.125926.

[161] H. Ersoy, F.J. Rybicki, Biochemical safety profiles of gadolinium- based extracellular contrast agents and nephrogenic systemic fibrosis, J. Magn. Reson. Imag. 26 (5) (2007) 1190–1197, https://doi.org/10.1002/jmri.21135.

[162] D.F. Williams, Assessing the triad of biocompatibility, medical device, functionality and biological safety, Med. Devices Sens. 4 (2021), e10150, https://doi.org/10.1002/mds3.10150.

[163] V. Granata, M. Cascella, R. Fusco, et al., Immediate adverse reactions to gadolinium-based MR contrast media: a retrospective analysis on 10,608 examinations, BioMed Res. Int. (2016) 1–6, https://doi.org/10.1155/2016/3918292.

[164] B.Y.W. Hsu, G. Kirby, A. Tan, Relaxivity and toxicological properties of manganese oxide nanoparticles for MRI applications, RSC Adv. 6 (2019) 45462–45474, https://doi.org/10.1039/C6RA04421B.

[165] D.J. Korchinski, M. Taha, R. Yang, et al., Iron oxide as an MRI contract agent for cell tracking, Magn. Reson. Insights 8 (S1) (2015) 15–29, https://doi.org/10.4137/MRI.S23567.

[166] Q. Feng, T. Liu, J. Huang, et al., Uptake, distribution, clearance and toxicity of iron oxide nanoparticles with different sizes and coatings, Sci. Rep. 8 (2018) 2082, https://doi.org/10.1038/s41598-018-19628-z.

[167] F. Ahmadpoor, A. Masood, N. Feliu, et al., The effect of surface coating of iron oxide nanoparticles on magnetic resonance imaging relaxivity, Front. Nanotechnol. (2021), 644734, https://doi.org/10.3389/fnano.2021.644734.

[168] E.M. Shapiro, Biodegradable, polymer encapsulated, metal oxide particles for MRI-based cell tracking, Magn. Reson. Med. 73 (1) (2015) 376–389, https://doi.org/10.1002/mrm.25263.

[169] M. Geppert, M. Himly, Iron oxide nanoparticles in bioimaging – an immune perspective, Front. Immunol. 12 (2021), 688927, https://doi.org/10.3389/fimmu.2021.688927.

[170] L. Wu, W. Wen, X. Wang, et al., Ultrasmall iron oxide nanoparticles cause significant toxicity by specifically inducing acute oxidative stress to multiple organs, Part. Fibre Toxicol. 19 (2022) 24, https://doi.org/10.1186/s12989-022-00465-y.

[171] C. Han, Y. Liu, R. Dai, et al., Ferroptosis and its potential role in human diseases, Front. Pharmacol. 11 (2020) 239, https://doi.org/10.3389/fphar.2020.00239.

[172] K. Mortezaee, M. Najafi, H. Samadian, et al., Redox interactions and genotoxicity of metal-based nanoparticles: a comprehensive review, Chem. Biol. Interact. 312 (2019), 108814, https://doi.org/10.1016/j.cbi.2019.108814.

[173] A. Fatima, M.W. Ahmad, A.K.A. Al Saidi, et al., Recent advances in gadolinium based contrast agents for bioimaging applications, Nanomaterials 11 (2021) 2449, https://doi.org/10.3390/nano11092449.

[174] H.J. Weinmann, R.C. Brasch, W.R. Press, et al., Characteristics of gadolinium-DTPA complex: a potential NMR contrast agent, Am. J. Roentgenol. 142 (1984) 619–624, https://doi.org/10.2214/ajr.142.3.619.

[175] J. Lohrke, T. Frenzel, J. Endrikat, et al., 25 Years of contrast-enhanced MRI: developments, current challenges and future perspectives, Adv. Ther. 33 (2016) 1–28, https://doi.org/10.1007/s12325-015-0275-4.

[176] S. Hirano, K.T. Suzuki, Exposure, metabolism and toxicity of rare earths and related compounds, Environ. Health Perspect. 104 (1996) 85–95, https://doi.org/10.1289/ehp.96104s185.

[177] T. Frenzel, P. Lengsfeld, H. Schirmer, et al., Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37 degrees C, Invest. Radiol. 43 (2008) 817–828.

[178] M. Markowicz-Piasecka, A. Skupien, E. Mikiciuk-Olasik, et al., Biocompatibility studies of gadolinium complexes with iminodiacetic acid derivatives, Biol. Trace Elem. Res. 189 (2019) 426–436, https://doi.org/10.1007/s12011-018-1496-6.

[179] X. Tian, Z. Liu, L. Zeng, et al., Evaluation of *in vivo* immunotoxicity for Ho3+ doped Gd_2O_3 nanoparticles as dual-modality nanoprobes, Mater. Today Commun. 23 (2020), 100899, https://doi.org/10.1016/j.mtcomm.2020.100899.

[180] C.A. Mallio, A. Rovira, P.M. Parizel, et al., Exposure to gadolinium and neurotoxicity: current status of pre-clinical and clinical studies, Neuroradiology 62 (2020) 925–934, https://doi.org/10.1007/s00234-020-02434-8.

[181] M. Rogosnitzky, S. Branch, Gadolinium-based contrast agent toxicity: a review of known and proposed mechanisms, Biometals 29 (2016) 365–376, https://doi.org/10.1007/s10534-016-9931-7.

[182] R.J. McDonald, D. Levine, J. Weinreb, et al., Gadolinium retention: a research roadmap from the 2018 NIH/ACR/RSNA workshop on gadolinium chelates, Radiology 289 (2018) 517–534, https://doi.org/10.1148/radiol.2018181151.

[183] F. Martino, G. Amici, M. Rosner, et al., Gadolinium-based contrast media nephrotoxicity in kidney impairment: the physio-pathological conditions for the perfect murder, J. Clin. Med. (2021) 10.271, https://doi.org/10.3390/jcm10020271.

[184] W. Ariyani, W. Miyazaki, Y. Tsuhima, et al., Gadolinium-based contrast agent accelerates the migration of astrocyte via integrin αVβ3 signaling pathway, Sci. Rep. 12 (2022) 5850, https://doi.org/10.1038/s41598-022-09882-7.

[185] D.F. Williams, Challenges with the development of biomaterials for sustainable tissue engineering, Front. Bioeng. Biotechnol. 7 (2019) 127, https://doi.org/10.3389/fbioe.2019.00127.

[186] D.F. Williams, Essential Biomaterials Science, Cambridge University Press, Cambridge, UK, 2014.

[187] L. Lu, Q. Zhang, D.M. Wootton, et al., Mechanical study of polycaprolactone-hydroxyapatite porous scaffolds created by porogen-based freeform fabrication methos, *J. Appl. Biomater. Funct. Mater.* 12 (3) (2014) 145–154, https://doi.org/10.5301/JABFM.5000163.

[188] X. Zhao, D.A. Hu, D. Wu, et al., Applications of biocompatible scaffold materials in stem cell-based cartilage tissue engineering, Front. Bioeng. Biotechnol. 9 (2021), 603444, https://doi.org/10.3389/fbioe.2021.603444.

[189] K. Kim, D. Dean, J. Wallace, et al., The influence of stereolithographic scaffold architecture and composition on osteogenic signal expression with rat bone marrow stromal cells, Biomaterials 32 (15) (2011) 3750–3763, https://doi.org/10.1016/j.biomaterials.2011.01.016.

[190] R.E. Rivero, V. Capella, A. Cecilia Llaudat, et al., Mechanical and physicochemical behavior of a 3D hydrogel scaffold during cell growth and proliferation, RSC Adv. 10 (2020) 5827–5837, https://doi.org/10.1039/C9RA08162C.

[191] B. Majhy, P. Priyadarshini, A.K. Sen, Effect of surface energy and roughness on cell adhesion and growth – facile surface modification for enhanced cell culture, RSC Adv. 11 (2021) 15467–15476, https://doi.org/10.1039/D1RA02402G.

[192] H.-J. Sung, C. Meredith, C. Johnson, et al., The effect of scaffold degradation rate on three-dimensional cell growth and angiogenesis, Biomaterials 25 (26) (2004) 5735–5742, https://doi.org/10.1016/j.biomaterials.2004.01.066.

[193] J.E. Reing, L. Zhang, J. Myers-Irvin, et al., Degradation products of extracellular matrix affect cell migration and proliferation, Tissue Eng. 15 (3) (2009) 605–614, https://doi.org/10.1089/ten.tea.2007.0425.

[194] J. Nikolovski, D.J. Mooney, Smooth muscle cell adhesion to tissue engineering scaffolds, Biomaterials 21 (260) (2000) 2025–2032, https://doi.org/10.1016/S0142-9612(00)0079-X.

[195] K.K. Parker, D.E. Ingber, Extracellular matrix, mechanotransduction and structural hierarchies in heart tissue engineering, Philos. Trans. R. Soc. Lond. B Biol. Sci. 362 (1484) (2007) 1267–1279, https://doi.org/10.1098/rstb.2007.2114.

[196] L. Mao, Y. Yin, L. Zhang, et al., Regulation of inflammatory response and osteogenesis to citrate-based biomaterials through incorporation of alkaline fragments, Adv. Healthcare Mater. 11 (2022), 2101590, https://doi.org/10.1002/adhm.202101590.

[197] M. Zhu, W. Li, X. Dong, et al., *In vivo* engineered extracellular matrix scaffolds with instructive niches for oriented tissue regeneration, Nat. Commun. 10 (2019) 4620, https://doi.org/10.1038/s-41467-019-12545-3.

[198] J. Rouwkema, N.C. Rivon, van Blitterswijk, Vascularization in tissue engineering, Trends Biotechnol. 26 (8) (2008) 434–441, https://doi.org/10.1016/j.tibtech.2008.04.009.

[199] J. Iqbal, J. Gunn, P.W. Serruys, Coronary stents: historical development, current status and future directions, Br. Med. Bull. 106 (2013) 193–211, https://doi.org/10.1093/bmb/ldt009.

[200] U. Sigwart, J. Puel, V. Mirkovitch, et al., Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty, *N. Engl. J. Me*d. 316 (1987) 701–706, https://doi.org/10.1056/NEJM198703193161201.

[201] P. Libby, P. Theroux, Pathophysiology of coronary artery disease, Circulation 111 (2005) 3481–3488, https://doi.org/10.1161/CIRCULATIONAHA.105.537878.

[202] T. Meurice, B. Vallet, C. Bauters, et al., Role of endothelial cells in restenosis after coronary angioplasty, Fund. Clin. Pharmacol. 10 (3) (1996) 234–242.

[203] A.S. Udriste, A.-G. Niculescu, A.M. Grumezescu, et al., Cardiovascular stents: a review of past, current and emerging devices, Materials 14 (2021) 2498, https://doi.org/10.3390/ma14102498.

[204] R.S. Schwartz, T.D. Henry, Pathophysiology of coronary artery restenosis, Rev. Cardiovasc. Med. 3 (S5) (2002) S4–S9.

[205] J.E. Sousa, M.A. Costa, A.C. Abizaid, et al., Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one year angiographic and intravascular ultrasound follow up, Circulation 104 (17) (2001) 2007–2011, https://doi.org/10.1161/hc4201.098056.

[206] G.I. Kirchner, I. Meier-Wiedenbach, M. Manns, Clinical pharmacokinetics of everolimus, Clin. Pharmacokinet. 43 (2) (2004) 83–95, https://doi.org/10.2165/00003088-200443020-00002.

[207] F. Otsuka, E. Pacheco, L.E.I. Perkins, et al., Long-term safety of an everolimis-eluting bioresorbable vascular scaffold and the cobalt-chromium XIENCE V stent in a porcine coronary artery model, Circ. Cardiovasc. Interv. 7 (2014) 330–342, https://doi.org/10.1161/CIRCINTERVENTIONS.113.000990.

[208] W. Schuler, R. Sedrani, S. Cottens, et al., SDZ RAD A new rapamycin derivative, Transplantation 64 (10) (1997) 36–42.

[209] J.A. Ormiston, P.W. Serruys, E. Regar, et al., A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSSORB); a prospective open-label trial, Lancet 371 (2008) 899–907, https://doi.org/10.1016/S0140-6136(08)60415-8.

[210] S.G. Ellis, D.J. Kereiakes, C. Metzger, et al., Everolimus-eluting bioresorbable scaffolds for coronary artery disease, N. Engl. J. Med. 373 (20) (2015) 1905–1915, https://doi.org/10.1056/NEJMoa1509038.

[211] Z.A. Ali, P.W. Serruys, T. Kimura, et al., 2-year outcomes with the Absorb bioresorbable scaffold for treatment of coronary artery disease: a systematic review and meta-analysis of seven randomized trials with individual patient data substudy, Lancet 390 (10016) (2017) 760–772, https://doi.org/10.1016/S0140-6736(17)31470-8.

[212] Z.A. Ali, R. Gao, T. Kiura, et al., Three-year outcomes with the Absorb bioresorbable scaffold, Circulation 137 (2018) 464–479, https://doi.org/10.1161/CIRCULATIONAHA.117.031843.

[213] M. Madanchi, G.M. Cioffi, A. Attinger-Toller, et al., Long-term outcomes after treatment of in-stent restenosis using Absorb everolimus-eluting bioresorbable scaffold, Open Heart 8 (2021), e001776, https://doi.org/10.1136/openhrt-2021-001776.

[214] R. Chakraborty, P. Chatterjee, J.M. Dave, et al., Targeting smooth muscle cell phenotypic switching in vascular disease, JVS-Vascular Science 2 (2021) 79–94, https://doi.org/10.1016/jvssci2021.04001.

[215] S. Rowlands, New technologies in contraception, Brit. J. Obstet. Gynecol. 116 (2009) 230–239, https://doi.org/10.1111/j.1471-0528.2008.01985.x.

[216] R.D. Smith, Contemporary hysteroscopic methods for female sterilization, Int. J. Gynecol. Obstet. 108 (2010) 79–84, https://doi.org/10.1016/j.ijgo.2009.07.026.

[217] J.F. Kerin, C.S. Carignan, D. Cher, The safety and effectiveness of a new hysteroscopic method for permanent birth control: results of the first Essure

clinical study, Aust. NZ J. Obstet. Gynecol. 41 (2001) 364–370, https://doi.org/10.1111/j.1479-828x.2001.tb01311.x.
[218] J.M. Cooper, C.S. Carignan, D. Cher, et al., Microinsert nonincisional hysteroscopic sterilization, Obstet. Gynecol. 102 (2003) 59–67, https://doi.org/10.1016/s0029-7844(03)00313-9.
[219] V.F. Connor, Essure, A review six years later, J. Minim. Invasive Gynecol. 16 (2009) 282–290, https://doi.org/10.1016/j.jmig.2009.02.009.
[220] R. Hurskainen, S.-L. Hovi, M. Gissler, et al., Hysteroscopic tuba sterilization: a systematic review of the Essure system, Fertil. Steril. 94 (2010) 16–22, https://doi.org/10.1016/j.fertstert.2009.02.080.
[221] B. Povedano, J.E. Arjone, E. Velasco, et al., Complications of hysteroscopic Essure sterilization; report on 4306 procedures performed in a single center, Brit. J. Obstet. Gynecol. 119 (2012) 795–799, https://doi.org/10.1111/j.1471-0526.2012.03292.x.
[222] Al-Safi Z, Shavell VI, Hobson MD, et al., Nickel hypersensitivity associated with an intratubal microinsert system, Obstet. Gynecol. 2100;117:461-462, doi: 10.1097/AOG.0b013e3181f73021.
[223] N. Bibas, J. Lassere, C. Paul, et al., Nickel-induced systemic contact dermatitis and intratubal implants: the baboon syndrome revisited, *Dermatitis* 24 (1) (2013) 35–36, https://doi.org/10.1097/DER.0b013e31827cd32e.
[224] M. Franchini, B. Zizolfi, C. Coppola, et al., Essure permanent birth control, effectiveness and safety: an Italian 11-year survey, J. Minim. Invasive Gynecol. 24 (4) (2017) 640–645, https://doi.org/10.1016/j.jmig.2017.02.004.
[225] S. Camara, F. de C. Coelho, C. Freitas, et al., Essure present controversies and 5 year's learned lessons: a retrospective study with short- and long-term follow-up, Gynecol. Surg. 14 (2017) 20, https://doi.org/10.1186/s10397-017-1023-3.
[226] S. Siemons, M. Vieugels, H. van Eijnhoven, Evaluation of nickel allergic reactions to the Essure microinsert: theoretical risk or daily practice, J. Minim. Invasive Gynecol. 24 (1) (2017) 140–144, https://doi.org/10.1016/j.jmig.2016.09.001.
[227] N. Raison-Peyron, A. Du-Thanh, C. Compan, et al., Are adverse events attributed to Essure associated with nickel sensitization? Dermatitis 31 (2) (2020) 122–127, https://doi.org/10.1097/DER.0000000000000489.
[228] A.C. Yunker, J.M.B. Ritch, E.F. Robinson, et al., Incidence and risk factors for chronic pelvic pain after hysteroscopic sterilization, J. Minim. Invasive Gynecol. 22 (3) (2015) 390–394, https://doi.org/10.1016/j.jmig.2014.06.007.
[229] J. Mao, S. Pfeifer, P. Schlegel, et al., Safety and efficacy of hysteroscopic sterilization compared with laparoscopic sterilization: an observational cohort study, BMJ 351 (2015) h5162, https://doi.org/10.1136/bmj.h5162.
[230] H. Kamencic, L. Thiel, E. Karreman, et al., Does Essure cause significant de novo pain? A retrospective review of indications for second surgeries after Essure placement, J. Minim. Invasive Gynecol. 23 (7) (2016) 1158–1162, https://doi.org/10.1016/j.jmig.2016.08.823.
[231] K. Bouillon, M. Bertrand, G. Bade, et al., Association of hysteroscopic vs laparoscopic sterilization with procedural, gynecological and medical outcomes, *JAMA* 319 (4) (2018) 376–387, https://doi.org/10.1001/jama.2017.21269.
[232] P.I. Carney, J. Yao, J. Lin, et al., Occurrence of chronic pelvic pain, abnormal uterine bleeding and hysterectomy post-procedure among women who have undergone female sterilization procedures: a retrospective claims analysis of commercially insured women in the US, J. Minim. Invasive Gynecol. 25 (4) (2018) 651–660, https://doi.org/10.1016/j.jmig.2017.10.029.
[233] S.E. Siemona, M.P.H. Vleugels, S. Veersema, et al., Long-term follow-up after successful Essure sterilization: evaluation of patient satisfaction, symptoms and the influence of negative publicity, Fertil. Steril. 112 (2019) 1144–1149, https://doi.org/10.1016/j.fertnstert.2019.08.008.
[234] E.V.J. Von Limburg Stirum, N.V. Clark, A. Lindsey, et al., Factors associated with negative patient experiences with Essure sterilization, J. Soc. Laparoendosc. Surg. 24 (1) (2020), https://doi.org/10.4293/JSLS.2019.00065 e2019.00065.
[235] S.R. Lindheim, J.L. Madeira, B. Bagavath, et al., Social media and Essure hysteroscopic sterilization: a perfect storm, Fertil. Steril. 111 (2019) 1105, https://doi.org/10.1016/j.fertnstert.2019.03.009.
[236] M. Catinon, E. Roux, A. Auroux, et al., Identification of inorganic particles from degradation of Essure implants: study of 10 cases, Eur. J. Obstet. Gynecol. Reprod. Biol. 250 (2020) 162–170, https://doi.org/10.1016/j.ejogrb.2020.04.036.
[237] F. Parant, M. Bost, E. Nohuz, et al., Release of metal elements from the Essure implants: a prospective cohort study, Eur. J. Obstet. Gynecol. Reprod. Biol. 273 (2022) 20–25, https://doi.org/10.1016/j.ejogrb.2022.04.014.
[238] P. Punzon-Jimenez, P. Labarta, The impact of the female genital tract microbiome in women and reproduction: a review, J. Assist. Reprod. Genet. 18 (100) (2021) 2519–2541, https://doi.org/10.1007/s10815-021-02247-5.
[239] C.H. Rigby, F. Aljassim, S.G. Powell, et al., The immune cell profile of human fallopian tubes in health and benign pathology: a systematic review, J. Reprod. Immunol. 152 (2022) 1036–1046, https://doi.org/10.1016/j.jri.2022.103646.
[240] A.C. Yunker, J.M.B. Ritch, E.F. Robinson, et al., Incidence and risk factors for chronic pelvic pai after hysteroscopic sterilization, J. Minim. Invasive Gynecol. 22 (3) (2015) 390–394, https://doi.org/10.1016/j.jmig.2014.06.007.
[241] A. Rubin, J.-F. Chen, A. Veade, et al., Pathologic findings in fallopian tubes of women with chronic pain after Essure placement, Contraception 102 (2) (2020) 133–136, https://doi.org/10.1016/j.contraception.2020.04.010.