REVIEW

Reactive arthritis or chronic infectious arthritis?

J Sibilia, F-X Limbach

Microbes reach the synovial cavity either directly during bacteremia or by transport within lymphoid cells or monocytes. This may stimulate the immune system excessively, triggering arthritis. Some forms of ReA correspond to slow infectious arthritis due to the persistence of microbes and some to an infection triggered arthritis linked to an extra-articular site of infection.

Reactive arthritis (ReA) was first described in 1916 during the first world war by Fiessinger and Leroy in France and Reiter in Germany. It was, however, only in 1969 that a Scandinavian team rationalised the concept of ReA by defining it as a transient non-purulent (reactive) arthritis appearing in the weeks following a digestive infection. Actually, this notion of exclusively aseptic ReA has been repeatedly contradicted by different observations.

MICROBIOLOGICAL HISTORY OF REACTIVE ARTHRITIS: FROM MICROSCOPY TO MOLECULAR BIOLOGY

A study of the microbiological history of ReA is instructive as it illustrates well the influence of technological progress and, in particular, the impact of molecular biology on the evolution of such concepts.

• As early as the 1970s, the first studies disclosed microscopic intracellular inclusions in synovial tissues which could correspond to Chlamydia trachomatis, the principal arthritogenic microbe involved in ReA. Confirmation of this work was, however, hindered for many years by the fact that most of these bacteria are very difficult or almost impossible to cultivate from synovial samples.

• Since the beginning of the 1990s, the explosive development of new molecular biology techniques has led to the detection (by polymerase chain reaction methods) of small quantities of C trachomatis DNA in the articular cavity. These first results immediately raised a large number of questions. Did they indicate the presence of viable bacteria in the joint, or were these simply genomic vestiges of bacteria passively transported into the joint by macrophages? The reply was provided by the discovery of messenger and ribosomal RNA of C trachomatis using a reverse transcriptase-polymerase chain reaction (RT-PCR) method. The presence of these nucleic acids, which have a very short half life in tissues (some minutes), implies the occurrence of transcription and hence active multiplication of the bacteria. These findings thus suggest that microbes can survive in small numbers in the articular cavity in certain forms of ReA (table 1).

• The phenomenon has grown since 1995 with discovery of DNA of most other classical arthritogenic agents in synovial samples from patients with ReA. One must nevertheless take a fairly critical point of view because although the results are convincing for C trachomatis, they are much less so for enterobacteria. It is true that DNA of Versinia, Shigella, or Campylobacter has been identified in some studies, but these are few and include very few patients. Thus, Ekman et al identified DNA of Salmonella in synovial samples, but could not repeat their results. This might have been owing to technical artefacts, which lead to false positives, or to a very small amount of bacterial DNA in the synovium. Despite these reservations, the list of arthritogenic agents continues to grow from year to year, even if for many of them there is no confirmation of their intrasynovial persistence (table 2).

Chlamydia pneumoniae and Borrelia burgdorferi, for instance, have been associated with cases of monarthritiasis or oligoarthritis comparable with those seen in ReA. In this context, it is interesting to return to the case described by Reiter in 1916 and his publication entitled “Über eine bisher unerkannte Spirochäteninfection (Spirochaetosis arthritis)”. One might wonder, in view of the high prevalence of B burgdorferi infections in Central Europe, whether this spirochaete rheumatism was not one of the first reports of Lyme arthritis? Identical observations have been made in other situations quite closely related to ReA. Propionibacterium acnes, a microbe implicated in inflammatory outbreaks of acne, was recently identified in articular samples from SAPHO patients, suggesting an infectious origin of this syndrome often regarded as a form of spondyloarthropathy. Mycobacterium bovis, used in BCG (Bacille Calmette-Guérin) treatment, is known to cause, presumably aseptic, oligoarthritis and polyarthritiasis, but we have also detected bacterial DNA in synovial fluid from patients with arthropathy triggered by intravascular injection of BCG. In other situations, the

Abbreviations: IFN, interferon; IL, interleukin; LFA, leucocyte function associated antigen; LPS, lipopolysaccharide; MOMP, major outer membrane protein; Osp, outer surface protein; ReA, reactive arthritis; RT-PCR, reverse transcriptase-polymerase chain reaction; TNF, tumour necrosis factor
Reactive arthritis or chronic infectious arthritis?

Recent original work has confirmed the simultaneous presence of RNA of numerous bacterial species in synovial samples from patients with rheumatoid arthritis, unexplained arthritis, and osteoarthritis, but not in samples taken during meniscectomy from presumably healthy subjects. In this study employing RT-PCR, respectively 92 and 50 different bacterial species were identified by sequencing in the synovial fluid of rheumatoid arthritis and osteoarthritis. Only six species (Corynebacterium, Escherichia coli, Streplococcus, Pseudomonas, Leptospira, and Methylobacterium) were detected exclusively in rheumatoid arthritis, although without proof of this being an argument in favour of their pathogenic role. These astounding results, apparently obtained by reliable methods, demonstrate that the synovium is not a sterile structure, but more probably an interfaz zone which can be colonised by bacteria originating from the environment and the endogenous flora.

“The synovium is not sterile but can be colonised by bacteria from the environment”

Recently, a description was given of arthritogenic microbes detectable in synovial samples not only in cases of presumably ReA but also in other forms of inflammatory rheumatism. In fact, C trachomatis and pneumonafiae are present in the synovial fluid of patients with rheumatoid polyarthri in respectively 30% and 15% of cases; identical observations have been reported for Mycoplasma pneumoniae and fermentans. Sometimes several microbes may be found together in the same joint, as suggested by the RT-PCR study described above. This unusual association was observed for C trachomatis and pneumonafiae for C trachomatis and B burgdorferi in synovial samples from patients with spondyloarthropathy, unexplained arthritis, and even rheumatoid arthritis. One should nevertheless maintain a critical attitude until these results have been confirmed by other studies. Thus, one report published only in abstract form suggests that the presence of intrasynovial bacterial DNA might after all be an exceptional phenomenon. In this work, a search by PCR analysis for the bacterial 16S and 23S ribosomal RNA genes proved negative in the synovium of 81 patients (42 rheumatoid arthritis, 8 other cases of inflammatory rheumatism, 31 osteoarthritis) when using drastic conditions of sterility.

THE PATHOGENIC MECHANISMS OF REACTIVE ARTHRITIS

The most original microbiological observations described in the previous section raise a number of questions which require an answer to help to understand the pathogenesis of reactive arthritis.

How do these bacteria persist in the articlar cavity and escape from the immune system of the host?

Role of antigenic modulation

Several recent studies have shown that C trachomatis can survive in a particular form whereby it down regulates the expression of membrane antigens (MOMP), while continuing to synthesise immunomodulatory proteins like heat shock proteins. It has further been shown that these modifications can be induced in vitro by prolonged antibiotic treatment (ciprofloxacin), which might have important practical implications for future therapeutic strategies.

B burgdorferi can likewise modulate its expression of surface antigens. On entering the host, this bacterium in fact down regulates expression of the principal membrane outer surface protein A (Ospa) and expresses larger quantities of another membrane protein OspC. Such antigenic modifications may permit these bacteria to escape from the immune system of the host.

Table 1 The principal detectable microbes in reactive arthritis and undifferentiated arthritis: analysis of the different methods of identification

<table>
<thead>
<tr>
<th>Antigens</th>
<th>DNA</th>
<th>RNA</th>
<th>Culture</th>
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<tbody>
<tr>
<td>C trachomatis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Y enterocolitica</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Y pseudotuberculosis</td>
<td>+</td>
<td>+</td>
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<tr>
<td>S flexneri and sonnei</td>
<td>+</td>
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<tr>
<td>S typhimurium and enteritidis</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>C jejuni</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>U urealyticum</td>
<td>+</td>
<td>+</td>
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<tr>
<td>C pneumoniae</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>B burgdorferi</td>
<td>+</td>
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<td>T whipelli</td>
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Table 2 List of the “classical” and “new” arthritogenic agents implicated in reactive arthritis

<table>
<thead>
<tr>
<th>“Classical” candidates</th>
<th>“New” candidates</th>
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<tr>
<td>Chlamydia trachomatis</td>
<td>Chlamydia pneumoniae</td>
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<tr>
<td>Ureaplasma urealyticum</td>
<td>Mycoplasma hominis and fermentans</td>
</tr>
<tr>
<td>Yersinia enterocolitica and pseudotuberculosis</td>
<td>Neisseria gonorrhoeae</td>
</tr>
<tr>
<td>Shigella flexneri and sonnei</td>
<td>Borrelia burgdorferi</td>
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<tr>
<td>Salmonella typhimurium, enteritidis and others</td>
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<td>Helicobacter pylori</td>
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<td>Campylobacter jejuni</td>
<td>Brucella abortus</td>
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<tr>
<td>C trachomatis</td>
<td>Calmette – Guerin Bacillus</td>
</tr>
<tr>
<td>C pneumoniae</td>
<td>-Haemolytic streptococci</td>
</tr>
<tr>
<td>S typhimurium</td>
<td>Propionibacterium acne</td>
</tr>
<tr>
<td>S flexneri</td>
<td>Escherichia coli</td>
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<tr>
<td>B burgdorferi</td>
<td>Helicobacter pylori</td>
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ND, not done.

*The detection of nucleic acid of enterobacteria in the synovium is subject to caution for reasons related to the different techniques employed and the very small numbers of patients studied; 1RNA has only been detected in one case.

discovery of inflammatory articular manifestations, sometimes of unexplained recurrent arthritis following documented infection, suggests the possibility of reactive arthritis “in the wide sense of the term.” However, in the majority of these cases, the proof is not tangible, although sufficient for one to keep in mind the hypothesis.

Recently, in 1998, new observations came to light which complicated the picture: the joint is not a sterile medium, as shown by the discovery of DNA of C trachomatis (by PCR) in synovial samples from healthy volunteers and patients with osteoarthritis (in respectively 9% and 20% of cases). In this study, only PCR amplifications using primers hybridising with 16S RNA or plasmid genes were positive, while attempts to amplify the major outer membrane protein (MOMP) gene were always negative. This suggests, assuming these results to be pertinent, that the bacteria persist in a “particular” form. It should nevertheless be noted that the variability of the PCR results can equally be explained by differences in sensitivity related to the amplification target. Similarly, use of the “generic” technique known as “universal” bacterial gene amplification has allowed the detection of a certain number of unexpected intrasynovial microbes, the pathogenic significance of which remains to be confirmed, because this type of method carries the risk of amplifying a commensal bacterium or contaminant gene of no particular importance.

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Role of intracellular localisation of the bacterium
As pointed out by Zinkernagel, numerous circumstances exist in which microorganisms (especially viruses) escape from the immune system by persisting in non-lymphoid cells (papillomavirus in keratinocytes, Epstein-Barr virus in epithelial cells). Similarly, certain arthritogenic bacteria can enter and persist in the synoviocytes (or other cells such as endothelial cells), sometimes despite use of antibiotics, as has been shown for *C. trachomatis* and *B. burgdorferi*.57–42

“Arthritogenic bacteria can persist in synoviocytes despite antibiotic treatment”

The situation is less clear in the case of enterobacteria and differs according to the microbe. *Versinia* and *Salmonella* can persistently infect the mucosa of the intestine and the digestive ganglia but not the synovium. These microbes are also present in monocytes, which serve perhaps as a reservoir but above all as “transporters” from extra-articular sites into the joint.43–45 *Shigella*, conversely, only infects digestive epithelial cells and cannot survive in monocytes and its mechanisms of persistence and transport are less well known.

Role of molecular mimicry
Certain bacteria have constituents which display strong homology with proteins of the host (YopH of *Y. pseudotuberculosis* and CD45, *M. fermentans* and CD4). This molecular mimicry can give rise to a tolerance to some microbes, which may thus escape from the immune system of the host. One recently described example is the case of Lyme borreliosis. It has been shown that a dominant epitope of OspA of *B. burgdorferi* (usually presented by HLA-DRB1*0401*) has close sequence homology with leucocyte function antigen-1 (LFA-1), which is a β2-integrin expressed at the surface of lymphocytes, polynuclear granulocytes, and monocytes.8 As a result, OspA can bind to intracellular adhesion molecule-1 (ICAM-1), a ligand of LFA-1 expressed by synoviocytes, enabling the bacterium to persist in the synovium. On the other hand, the mimicry may also be differently interpreted by the host because the homology between this bacterial constituent and an antigen of the articular cavity can induce an “autoimmune” synovitis, as will be discussed later.

Role of interactions with the immunogenetic characteristics of the host
To resolve an infection, especially with intracellular bacteria, cytokines such as interferon γ (IFNγ) produced by T cells play a major part.86 It has been shown that in ReA the antibacterial Th1 cytokine response (production of IFNγ, interleukin 2 (IL2) and IL12) is impaired in favour of a Th2 response (IL4 and IL10).87–89 Thus, in the absence of a “good” antibacterial reaction, the microbes can survive. Little is known about the pathogenesis of this Th1/Th2 imbalance, but it is likely that genetic factors of the host are causally involved. Among these factors, the polymorphism of cytokine genes is probably implied. For instance, in Finnish patients, the microsatellites IL10.G10 and IL10.G12 from the promoter region of the IL10 gene seem to be protective against the development of ReA.90

In a German study, it has been demonstrated that the level of tumour necrosis factor α (TNFα) secretion by T cells at ReA onset is inversely proportional to the disease duration and severity.77 However, ReA cannot be explained merely by cytokine production or polymorphism and other susceptibility factors certainly play a part. One of them is that arthritogenic bacteria like *Versinia* or *Salmonella* can modulate HLA-B27 (modification of the messenger RNA splicing, peptide modification) and, possibly, the lymphocyte response.4 These interferences may facilitate the persistence of the bacteria within cells or tissues.

How can these bacteria, which seem to escape from the immune system of the host, cause arthritis?
An analysis of the microbiological and immunological data suggests the existence of two forms of reactive arthritis.

Reactive arthritis of the type chronic infectious arthritis
Certain forms of ReA may represent authentic chronic infectious arthritis caused by slow growing organisms which are very difficult to cultivate and hence impossible to identify by the usual microbiological methods. In the light of current knowledge, this hypothesis would appear to hold for *Chlamydia*, *Mycoplasma*, and *Borrelia*, although not for enterobacteria. Such microbes enter the articular cavity during bacteremia or within monocytes 27–31 and can survive in small numbers in a “vegetative” state, probably with intermittent periods of replication triggered by still unknown phenomena.27–29 This has been clearly demonstrated for *C. trachomatis*, which persists in the form of “atypical” reticulated bodies.32–34

These microbes have an attenuated virulence, unlike those responsible for septic arthritis. Such forms of ReA are thus related to a “slow” intrasynovial infection, a condition also called “slow infectious arthritis” or “infection reactive arthritis”40–42. Similarly, it is by invoking the same mechanisms that one explains today the arthritis of Whipple’s disease, whereas for many years it was not possible to identify or cultivate this slow growing organism.29–31

Reactive arthritis of the type infection triggered aseptic arthritis
Some forms of ReA are probably aseptic and if so it is the persistence of bacterial antigens (lipopolysaccharides, heat shock proteins) which may explain the appearance of an inflammatory reaction in the synovium. This hypothesis applies above all to enterobacteria (*Versinia*, *Salmonella*, . . .), microbes not found in the joint except possibly in authentic (but rare) cases of acute septic arthritis.34–39 In chronic forms, it is unlikely that viable and active bacteria persist in the synovium, although it has occasionally been possible to detect bacterial DNA40–43 and even recently intrasynovial RNA in a case of ReA caused by *Versinia pseudotuberculosis*.44 Conversely, it is likely that these bacteria survive at an extra-articular site, in particular in the mucosal membranes of the digestive system for the lymphatic ganglia, and are carried to the joint by synoviocytes, probably in recurrent fashion.44–45 In support of this theory, there is some evidence indicating that a preferential connection exists between gut and joints. It has been observed that mucosal leucocytes collected from patients with an inflammatory bowel disease can bind well to synovial vessels.46 This homing implies many receptors and their ligands, which differ according to the leucocyte subset, and mononuclear cells from peripheral blood do not share the binding characteristics of gut derived cells. Although these results only concern inflammatory bowel diseases, the concept can probably be applied to enteric ReA. After the homing, the bacterial antigens can subsequently persist sometimes for a long time in the synovium, in certain cases in the form of bacterial “ghosts” without nucleic acid.44–45 This type of arthritis, triggered by bacterial antigens originating from an extra-articular site in the absence of any viable intra-articular microbe, may be called “infection triggered reactive arthritis”.

What are the bacterial factors and the immunogenetic factors of the host which are important to explain the appearance of arthritis?
Although the above description of the two forms of reactive arthritis gives a fairly simple picture, it is possible that the future will reveal a more “heterogeneous” reality. In any case, the appearance of arthritis is a consequence of the encounter between an arthritogenic bacterium and a predisposed host. Thus the key to the mystery of ReA will undoubtedly lie in a
Table 3  Arthritogenic microbes implicated in reactive arthritis: role of HLA-B27

<table>
<thead>
<tr>
<th>Arthritogenic bacteria dependent on HLA-B27: the “classical” candidates</th>
<th>Arthritogenic bacteria independent of HLA-B27: the “new” candidates</th>
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</thead>
<tbody>
<tr>
<td>• Chlamydia trachomatis</td>
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<td>• Clostridium difficile</td>
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Detailed study of these host-bacterium interactions, of which we already know some of the subtleties.

- All bacteria do not have the same arthritogenic potential. As an example, certain strains of *Shigella flexneri* contain a plasmid with a gene coding for a peptide sequence homologous to the HLA-B27 molecule, which could confer particular arthritogenic properties. The arthritogenic strains of *yersinia* also possess plasmid and chromosome virulence factors which can modulate the processes of cellular adhesion and invasion. Other examples may exist, like for instance Lyme arthritis in Europe, which would seem to be preferentially related to *B burgdorferi* sensu stricto, although the virulence factors of this species are not yet known.

- The immunogenetic characteristics of the host likewise have an important role, especially HLA-B27, but not necessarily as an antigen presenting molecule because studies based on this mechanism remain inconclusive. Indeed, it has been shown that the adhesion molecules of certain bacteria (*yersinia, Salmonella*) use HLA-B27 as a ligand to attach to cells of the synovial environment. Moreover, in some genetically predisposed subjects, HLA-B27 appears to lack the ability to eliminate infected macrophages normally, thus facilitating the intra-articular persistence of the microbe (*Salmonella*). Recently, a new attractive hypothesis was proposed by Colbert’s group about the role of HLA-B27 in ReA. This team has shown that during the antigen processing and assembly pathway into the endoplasmic reticulum, HLA-B27 has a tendency to misfold even without any β2m or peptide deficiency. This misfolding implicates the β pocket of the molecule and may, at least partially, explain the link between HLA-B27 and arthrogenicity. Misfolding can lead to a stress response which could increase the production of proinflammatory cytokines by an activation of NF-xB. Moreover, accumulation of HLA-B27 heavy chains might induce the formation of abnormal homodimers at the cell surface and in this way activate the immune system. However, some types of reactive arthritis are not linked to HLA-B27 but probably to other immunogenetic factors and one can distinguish at present the forms dependent on and independent of HLA-B27 (table 3).

What are the mechanisms leading to the development of synovitis during reactive arthritis?
The mechanisms inducing an inflammatory reaction of the synovium are basically the same in the two types of reactive arthritis.

**Bacterial lipopolysaccharides (LPS): mechanism of action**
Bacterial products, and in particular LPS, are powerful macrophagic stimulators which can trigger the synthesis of proinflammatory cytokines (TNFα, IL1, IL6) through CD14, Toll-like receptor activation. This mechanism plays a part in ReA induced by *Chlamydia* and in the forms involving enterobacteria.

**Bacterial antigens**
Bacterial antigens, whether produced by a viable intrasynovial bacterium or brought into the articular cavity by monocytes, have an immunomimetic action. These antigens can most likely persist in the joint either “stuck” to the extracellular matrix or within antigen presenting cells and by the various mechanisms described below can trigger a lymphocyte reaction potentially responsible for arthritis. It remains to be explained why this antibacterial response can in certain subjects exceed its physiological protective role and induce synovitis:

- Either the bacterial antigens are simple polyclonal lymphocyte activators which can stimulate multiple B or T clones in a non-selective manner, as has been demonstrated for *Mycoplasma*
- Or some antigens may behave as superantigens which can stimulate whole families of T lymphocytes characterised by a particular T receptor, as has been demonstrated for *Yersinia* and *Mycoplasma*
- Or some bacterial antigens display close homology with a “self” antigen (molecular mimicry), which as already mentioned can induce a form of tolerance enabling the bacterium to avoid elimination. However, this mimicry can likewise trigger veritable “autoimmune” intra-articular inflammatory reactions in predisposed subjects. There are many known examples of microbial homology: some epitopes of *Shigella* and *Ureaplasma* display strong homology with HLA-B27, *M fermentans* has an epitope sharing sequence homology with CD4, and one of the best examples is probably the recently discovered sequence homology between OspA and LFA-1 described in a preceding section. This induces in certain subjects a strong intra-articular anti-OspA/LFA-1 lymphocyte response, which could participate in the pathogenesis of Lyme arthritis. Nevertheless, there are several reasons (modification of the expression of OspA, species diversity of OspA) for thinking that this mechanism is of no major importance, even if it may exist in some chronic forms of the disease.

A new immunostimulator: bacterial DNA
A new, most attractive hypothesis just put forward recently suggests another candidate immunostimulator. Bacterial DNA, which differs from that of eukaryotes by the presence of non-methylated CpG motifs, can stimulate intensely monocytes-macrophages. It has been shown that experimental intra-articular injection of bacterial DNA (*Escherichia coli, Staphylococcus aureus*) or simply of non-methylated CpG motifs is sufficient to trigger arthritis in mice. The hypothesis is that bacterial DNA may be directly responsible for part of the naive inflammatory reaction. This merits further investigations in man, particularly to assess whether the quantity of bacterial DNA required to induce arthritis is comparable with the “inoculum” observed in vitro in reactive arthritis.

**SUMMARY: THE IMPORTANCE OF HOST-BACTERIA INTERACTION**
All these points illustrate well the fundamental importance of host-bacterium interactions in the pathogenesis of inflammatory arthropathy. The important facts may be summarised as follows:

- The synovial cavity is not as previously believed a sterile environment and banality of these infections explains the presence of “bystander” bacterial constituents in synovial samples from patients with osteoarthritis and healthy volunteers. Such intra-articular microbes may then be eliminated, or may trigger a sterile inflammatory reaction, or provoke a
slow synovial infection, depending on the characteristics of the host and different factors controlling the synovial micro-environment (figs 1 and 2 and box 1).

- Certain forms of presumably ReA thus sometimes correspond to authentic slow infectious arthritis (C trachomatis, Mycoplasma, B burgdorferi ...), while “reactive” arthritis of the type infection triggered aseptic arthritis certainly exists. Moreover, there is nothing to indicate that the two mechanisms are exclusive, notably for Borrelia and perhaps for some enterobacteria. At the present stage of our knowledge, one may continue to use the term ReA provided that one distinguishes clearly between the chronic infectious forms related to the intrasynovial persistence of viable microbes and the infection triggered forms linked to an extra-articular site of infection (figs 1 and 2).

CONCLUSION

The concept of inflammatory rheumatism is probably going to be transformed by study of these slow growing bacteria which have the particular ability of entering the host easily (by binding to mucosal adhesion molecules) and persisting there by “hiding” in certain cells and/or by inducing a specific immune tolerance through molecular mimicry.

It is perhaps these “parasite” bacteria, perfectly adapted to their host, which have been selected in the course of the parallel evolution of the bacterial world and the human species.

Figure 1  The spectrum of arthritis induced by a bacterial infection. The host-bacterium interactions and, in particular, the bacterial virulence factors lead to different forms of arthritis. In some cases there may be no more than a simple “bystander” bacterial presence in the synovium.

Figure 2  Natural history of arthritogenic infections in reactive arthritis. See also Box 1.
This cohabitation results from a subtle equilibrium between the immune system of an immunocompetent host and the virulence of the bac-


terium. Any modification of one of these factors may lead to the appearance of inflammatory arthropathy of the type ReA and probably also of other forms of peripheral inflammatory rheumatism. However, numerous questions still remain to be answered (box 2).

ACKNOWLEDGEMENTS

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Authors’ affiliations

J Sibilia, F-X Limbach, Rheumatology Department, University Hospital of Strasbourg, France

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