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New Perspectives on the Pathogenesis of Rheumatoid Arthritis

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In the pathogenesis of rheumatoid arthritis, locally produced antibodies complex with an inciting antigen, yet to be identified, within the joint and activate the complement system, resulting in articular inflammation mediated primarily by polymorphonuclear leukocytes and their products. Chronic inflammatory cells then produce soluble factors that induce both tissue destruction and inflammation. A major issue is how and why apparently normal immune responses in the acute stage progress to chronic inflammation in subsequent months to years. Although it is often assumed that the initial etiologic agent, persisting in the joint or at an extra-articular site, is responsible for continued synovitis, this need not be the case. It is possible that once the inciting agent is cleared from the joint through a normal immune response, the presence of activated cells rich in surface class II histocompatibility (Ia) antigens could, under the influence of multiple genetic or environmental factors, become the target of autoimmune attack. Alternatively, the process might result from the interactions of synovial lining cells and their products with T cells assuming a secondary role. Further research into the relative contributions of soluble products, T helper and suppressor subsets, synoviocytes, and antigen determine which model is correct.

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Rheumatoid arthritis is a complex disease of unknown origin in which genetic, hormonal, and immunologic factors interact to produce joint and systemic manifestations. Both the humoral and cellular arms of the immune response appear to participate [1]. The former is responsible for the exudative phase of the arthritis. Antibodies made within the joint space, particularly rheumatoid factors (anti-immunoglobulins), complex with antigens and engage the complement system. The resultant articular inflammation is mediated primarily by polymorphonuclear leukocytes and their products. Cellular immunity is represented by the chronic inflammatory cells (e.g., lymphocytes and macrophages) that infiltrate the synovium and produce soluble factors that induce both tissue destruction and inflammation [2]. In this article, I will consider some of the factors that are known or suspected to contribute to the initiation and perpetuation of rheumatoid arthritis, focusing especially on the notion that pathways other than conventional T cell-mediated immune responses may be involved in the pathogenesis of chronic rheumatoid synovitis.

A proper understanding of the pathogenesis of rheumatoid arthritis requires an appreciation of the distortion of the joint architecture that is produced by the disease. Normal diarthrodial joints are lined by a fine membrane comprised of differentiated connective tissue cells (synoviocytes) sitting on a loose acelluar stroma, interspersed with a rich network of small capillaries. Two types of synoviocyte that differ in function and morphology have been identified. The first ("type A" synoviocyte) is phagocytic and has morphologic and phenotypic characteristics of a histiocytic cell derived from the monocyte/macrophage lineage. The other ("type B" synoviocyte) resembles a fibroblast. The phagocytic cells are constantly replaced by precursors from the bone marrow; the origin of the synovial fibroblast is less clear [3].

The earliest recorded change in the joint during the days to weeks following the first symptoms of rheumatoid arthritis is damage to the endothelium of the microvasculature [4,5]. At about the same time, a sparse infiltration of the edematous subsynovial space with acute inflammatory cells (polymorphonuclear leukocytes) occurs and fibrin is deposited along the synovium. A modest increase in the number of lining cells can be seen, but the lymphocytes and plasma cells that are so conspicuous in established disease are virtually absent (**Figure 1**). In the subsequent weeks, segmental obliteration of the microvasculature by inflammatory cells and thrombi develops, and lining cell hyperplasia and perivascular accumulation of lymphocytes becomes evident (**Figure 2**).

As the disease becomes more chronic and well-established, the characteristic morphologic features of rheumatoid arthritis can be recognized [3]. These include a great increase in the number and size of lining

cells, synovial villous hypertrophy, massive subintimal infiltration by lymphocytes and plasma cells (often associated with large lymphocytic nodules), in-growth of a chronic granulation tissue, and proliferation of subchondral connective tissue (pannus) that erodes cartilage, bone, ligaments, and tendons. Phenotypic and functional analyses of the infiltrating lymphocytes show them to be primarily CD4 cells of the helper subclass. This is especially notable for CD4 cells located in proximity to macrophages that express large amounts of glycoproteins coded for by the class II genes of the major histocompatibility complex (hereafter referred to as immune activation or Ia antigens) [6–10]. This picture is analogous to that seen in antigen-presenting regions in lymphatic tissues where B lymphocytes and plasma cells are scattered in and about the T cells [2,7,8]. A proportion produce immunoglobulins, some with specificities similar to the rheumatoid factors found in the circulation.

CURRENT MODEL: A CONVENTIONAL T CELL-DRIVEN IMMUNE RESPONSE

Although the actual events leading to the established rheumatoid arthritis lesion are not entirely understood, it is generally thought to begin when an antigen, arguably a joint-seeking ("arthrotropic") pathogen, comes to the joint from an extra-articular location. The responsible factor is unknown, but viruses harbored in macrophages or lymphocytes, non-biodegradable products of bacteria, or antibodies directed against intra-articular structures have all been implicated as potential candidates. At some point, the initial microvascular insult and inflammation becomes a chronic inflammatory process. In the generally accepted scenario, this switch results from a T cell-mediated immune reaction directed at the persisting pathogen (**Figure 3**).

Much evidence has been advanced to support this sequence of events [11]. The histology of rheumatoid arthritis synovitis is reminiscent of chronic immunologic reactions in laboratory animals. The joint lesions of Lyme arthritis (caused by minute amounts of spirochetal antigens), are similar to those of rheumatoid arthritis [12]. The T cells from synovial effusions, and to a lesser extent from subintimal tissues, display cell surface molecules that are associated with an "activated state," such as Ia antigen [6,8,9]. Large amounts of Ia antigens are also seen on synovial lining cells and interdigitating macrophages. Ia antigen induction is generally due to gamma-interferon, a classic lymphokine secreted by stimulated T cells [9,13]. Lymphocytes intimately associated with Ia-rich accessory cells produce a variety of other lymphokines that, along with macrophage-derived factors, can promote synovial proliferation and the growth and differentiation of B lymphocytes into antibody-secreting cells [11]. Finally, several new or exotic therapies for rheumatoid arthritis (thoracic duct drainage, total lymphoid irradiation, and cyclosporin) are targeted at T lymphocytes. Thus, the paradigm that rheumatoid arthritis synovitis results from a typical T cell-driven immune response can explain: (1) synovial lining cell hyperplasia and increased cell surface class II gene-encoded molecules (i.e., Ia antigen induction); (2) the accumulation of large numbers of T lymphocytes in the region beneath the intimal lining; and (3) B cell hyperactivity as reflected by local antibody production. Indeed no alternative view would be acceptable unless it could account for these three hallmarks of synovitis.

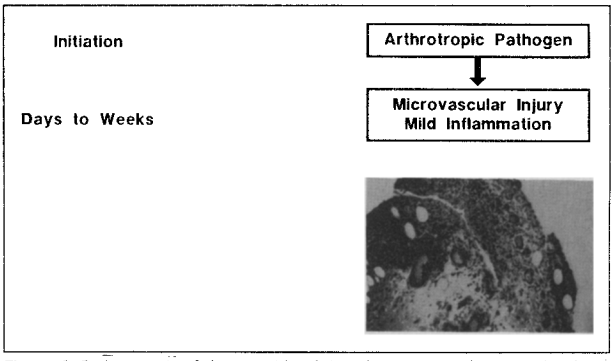

Figure 1. Pathogenesis of rheumatoid arthritis: the events in rheumatoid arthritis during the first days to weeks following the initial joint symptoms. A synovial biopsy specimen taken in the third week shows primarily microvascular injury, minimal synovial intimal cell changes, and cellular infiltration (photomicrograph kindly provided by R. Schumacher).

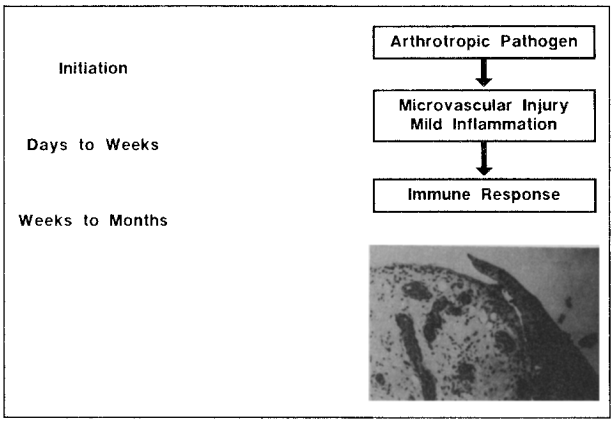

Figure 2. After the first several weeks the inflammation in rheumatoid arthritis resembles an early immune response. A synovial biopsy specimen taken in the third month following in the onset of symptoms shows microvascular injury, early hypertrophy, and hyperplasia of synovial intimal cells, and collections of mononuclear cells in the subintimal layer, particularly in a perivascular distribution (photomicrograph kindly provided by R. Schumacher).

At this point, it is important to recognize that not all the available information supports the notion that rheumatoid synovitis results from a conventional T cell-mediated immune response. First, the classic findings of rheumatoid arthritis synovial histopathology are not always present [14,15]. Although biopsy specimens from many patients have lymphoid aggregation and immunoreactive regions containing interdigitating antigen-presenting cells and T helper lymphocytes, others from patients with an identical clinical picture show a diffuse infiltration of the synovium with equal numbers of T cells of the CD4 and CD8 phenotype. In a minority of patients, the interstitial region contain primarily fibroblasts and only a few lymphocytes.

Even more disquieting is the paucity of data supporting the paradigm that T cell activation actually occurs in the rheumatoid arthritis synovium. Ordinarily, when appropriately stimulated, T lymphocytes will sequentially display activation antigens (Ia, interleukin-2 receptor, and transferrin) on their surface, elaborate lymphokines, such as interleukin-2 and gamma-interferon, and enlarge and divide [9]. Most

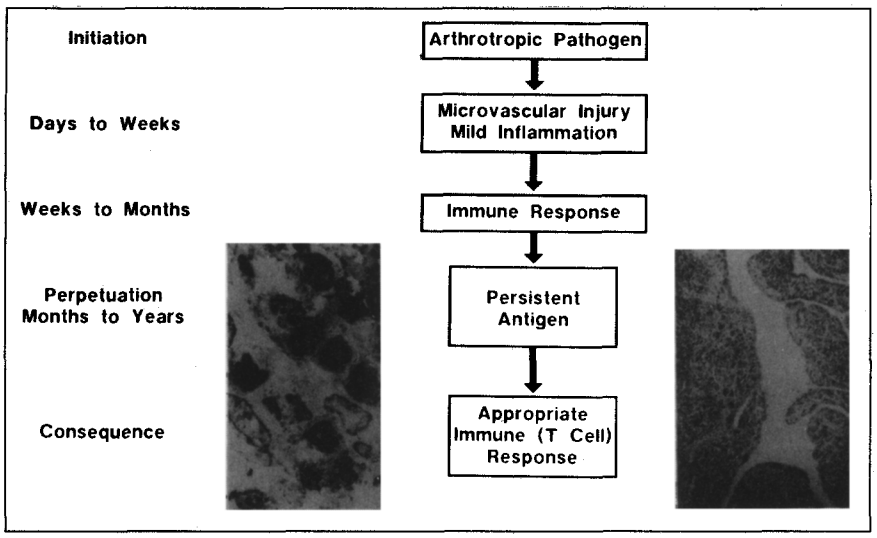

Figure 3. Conventional model of established rheumatoid arthritis. The micrograph (**right**) shows typical changes of synovial villous formation, hypertrophy and hyperplasia of synovial lining cells, and widespread infiltration with mononuclear cells. The immunoelectron micrograph (**left**; kindly provided by M. Ziff) shows that the cells accumulating in the transitional zone are primarily CD4 lymphocytes.

rheumatoid arthritis synovial T cells are small and quiescent in appearance, and have only small amounts of surface Ia antigens [16]. Although interleukin-2 receptors are present on some cells, the degree of expression at the mRNA level is little more than that of resting peripheral blood T cells, rather than that found in mitogen-stimulated cells. T cell mitosis and blast transformation are rare [16], and only a minority of the cells in a typical synovial lymphoid follicle stain with an antibody that identifies nuclear antigens present in all stages of the cell cycle apart from G_0 [17]. Taken together, these findings suggest that although the T lymphocyte is the dominant cell *in situ*, few of them have passed through the G_0-G_1 interface and only a minority are truly activated.

When lymphocytes from synovial tissue and fluid are studied in culture they proliferate weakly when stimulated and produce diminished amounts of interleukin-2 and gamma-interferon as compared with normal peripheral blood cells [15,18]. These defective responses appear to result from specific inhibitors of interleukin-1, and perhaps interleukin-2 [18,19]. The inhibitor(s) is likely derived from synovial fluid monocytes, perhaps reflecting an attempt to control the chronic immunologically mediated inflammation. A failure to demonstrate lymphokines of T cell origin in the rheumatoid arthritis joint is also consistent with this notion of T cell arrest. Interleukin-2, gamma-interferon, and human interleukin-3 have each been looked for in synovial tissues and exudates without success [20,21]; whereas macrophage-derived factors are present in abundance (see next section). The absence of gamma-interferon is particularly noteworthy, since it is the conventional explanation for the abundant Ia surface molecules present on macrophages and intimal lining cells. Thus, the classic T cell model may require modification. At the very least, the information about T cell inhibitors must be incorporated, and perhaps alternative models need to be considered.

ALTERNATIVE MODEL: THE AUTOREACTIVE T CELL

Although it is usually assumed that the initiating agent in rheumatoid arthritis is responsible for both the early changes and the perpetuation of chronic inflammation, this need not be the case. Indeed there is reason to believe that the chronic rheumatoid lesion may be perpetuated in the absence of the inciting agent by immune responses to antigens quite distinct from those responsible for starting the process (**Figure 4**, *right*). Such a scenario has been used to explain other chronic inflammatory processes, like chronic thyroiditis, during which it appears that an initial viral insult results in an appropriate localized immune response [22]. This response is characterized by infiltration into the lesion of T lymphocytes that elaborate lymphokines, especially interferon-gamma. Interferon-gamma induces Ia antigens on the surface of thyroid cells and these alone, or in combination with other surface molecules, are the antigens that become the target of autoimmune attack. The reaction between stimulator cells rich in surface Ia antigens and autologous T lymphocyte has been termed the autologous mixed leukocyte reaction (AMLR). It has been studied extensively as an *in vitro* correlate of autoimmunity. In addition, factors produced in the culture specimens can induce B cell proliferation and antibody formation [23]. Of interest are recent data in mice and humans suggesting that the cytokine milieu produced in the AMLR is nearly identical to that seen in rheumatoid synovitis. In contrast to allogeneic mixed leukocyte reactions, in which the culture supernatants contain a number of lymphokines, including interleukin-2 and interferon-gamma, very little of these lymphokines are found in the AMLR [24]. Although T helper cells proliferate, the responsible soluble factor has yet to be defined.

A number of other observations favor the notion that rheumatoid arthritis represents a localized AMLR. The low level of Ia antigens on T cells in the synovium is consistent with this model insofar as *in vitro* autologous stimulation produces a relatively weak T cell response. The cytotoxic cells present in rheumatoid arthritis joint effusions are identical to the natural killer-like cells produced in the *in vitro* AMLR [25,26]. But most important is the fact that the articular cavity and synovium contain a variety of potential stimulator cells. These include synoviocytes and synovial tissue macrophages that express high levels of surface class II antigens and Ia-rich dendritic cells, which constitute 5 to 10 percent of the mononuclear

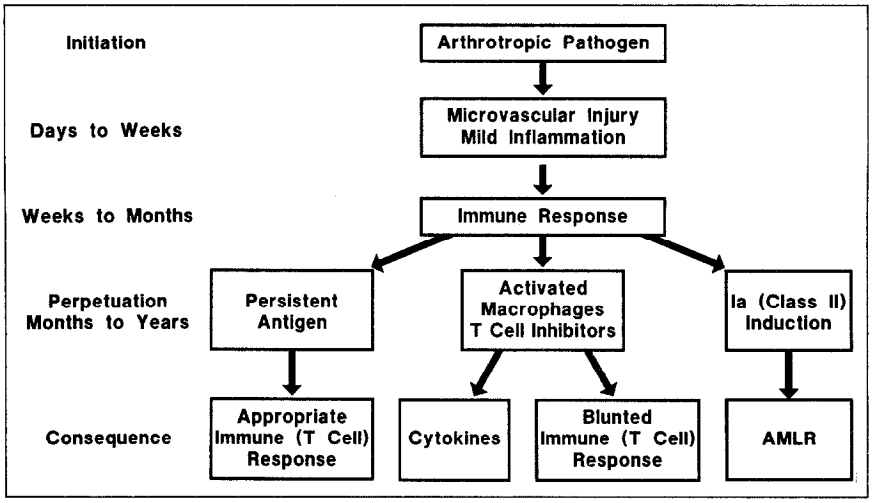

Figure 4. Schematic representation of the several pathways that may be involved in the perpetuation of rheumatoid arthritis.

cells in synovial fluid and are reported to be the most potent stimulators of mixed leukocyte reactions with blood cells [27].

The AMLR model has a serious shortcoming, however, namely the requirement for the continuous expression of high levels of immune activation antigen on the cell surface of the stimulator population. The relative deficiency in the rheumatoid joint of interferon-gamma, the most potent inducer of Ia antigen, presents a problem. Unusual sensitivity of patients with rheumatoid arthritis to low levels of interferon-gamma has been excluded as an explanation [28]. Although synergy with other factors, like tumor necrosis factor or IL-4 is still possible, the most likely explanation is an alternative Ia antigen inducer (see next section). Another interesting, but unproven, possibility is that high levels of surface MHC molecules could be maintained through the action of an infectious agent that specifically induces Ia antigens on the surface of antigen-presenting cells [29]. Thus, a viral infection could act indirectly as an adjuvant to autologous stimulation without actually inducing a primary response toward itself.

ALTERNATIVE MODEL: TRANSFORMED SYNOVIAL LINING CELLS

In all the models proposed up to this point, T lymphocytes have been assigned the major role for the perpetuation of the rheumatoid inflammatory process. Presumably, the by-products of these cells spreading in a centrifugal fashion alter the endothelium of adjacent blood vessels, cause the proliferation and differentiation of nearby B cells, and directly influence the macrophages and synoviocytes in the lining above them. This scenario, however, is not consistent with the fact that most of the soluble products measured in synovial fluid or tissue supernatants appear to be produced by non-T cells [2,21,30–32]. Thus, a third pathway needs to be considered, namely, that rheumatoid synovitis is driven by factors produced by neighboring macrophages and synovial fibroblasts in the joint lining that can influence one another in a resonating or paracrine manner (Figure 4, *middle*). For instance, synovial fibroblasts, transformed to a "rheumatoid phenotype" might secrete factors that activate adjacent macrophages and induce increased amounts of Ia molecules on their surface membranes. Alternatively, macrophages activated in the periphery might enter the joint, home to the intimal lining, and stimulate adjacent synovial fibroblasts to proliferate and secrete deleterious products such as collagenase and prostaglandins [33]. Consistent with this third pathway is the demonstration that synoviocytes from rats given injections of complete Freund's adjuvant show biochemical and morphologic evidence of activation, including a fourfold increase in surface Ia antigen expression before the onset of arthritis or the appearance of mononuclear cells in the synovial membrane [34].

Factors such as granulocyte-macrophage colony-stimulating factor, colony-stimulating factor-1, platelet-derived growth factor, and interleukin-6 are examples of potentially important factors made by fibroblasts, whereas interleukin-1 and tumor necrosis factor might be responsible for the macrophage-driven events. Each of these cytokines and growth factors has been identified within the rheumatoid joint. Granulocyte-macrophage colony-stimulating factor is particularly relevant. It alone among a number of mediators (including interleukin-1, -2, -3, -4, and -6, and colony-stimulating factor-1 and tumor necrosis factor) consistently increases surface Ia antigen expression on normal blood monocytes. This effect of granulocyte-macrophage colony-stimulating factor is additive with low concentrations of interferon-gamma and synergistic with tumor necrosis factor [35]. Granulocyte-macrophage colony-stimulating factor is produced constitutively by rheumatoid synovial tissue cells, and the Ia antigen-inducing activity present in supernatants of cultured synovial tissue explants is neutralized by specific antibody to this cytokine [35]. Thus, granulocyte-macrophage colony-stimulating factor is probably the illusive, non-interferon macrophage-activating factor responsible for the high levels of Ia antigens in the intimal lining cells.

A prediction of the transformed synoviocyte model is that T lymphocytes are not sequestered in the joint in response to a specific antigen; rather, they accumulate under the influence of factors made in the lining. Thus, there is no requirement that the T cells be anything more than innocent bystanders attracted by the inflammatory process, much like spectators at a fire.

This would account for the minimal T cell activation and proliferation. Likewise, the abundant antibody production by B cells in the synovium would have to come about through T cell-independent mechanisms, perhaps under the influence of molecules such as interleukin-6, or polyclonal activators. Furthermore, this model implies that the analysis of locally produced antibody or studies of the T cell antigen receptor are unlikely to provide clues to the origin of rheumatoid arthritis.

Obviously, these three schemes do not encompass all of the pathogenetic mechanisms possible in rheumatoid arthritis; nor are they mutually exclusive. The ability of vascular endothelium and B lymphocytes to act as antigen-presenting cells or the interactions of mast cells and fibroblasts are examples of other potentially important interactions that have not been included. Likewise, it is an oversimplification to think that any of these pathways would operate in isolation. Products of synoviocyte/macrophage activation could well be responsible for down-regulating an appropriate immune response to a persistent antigen or switching the T cells in the interstitium to an autoreactive pathway against induced Ia antigens.

A clear understanding of rheumatoid arthritis awaits identification of the initiating pathogen. Hopefully that will happen soon. Until that time, however, it will be necessary to expand our concepts beyond an analysis of T helper and suppressor subsets and their products if we wish to clarify the means by which various kinds of arthritis, with different clinical presentations, are perpetuated. Re-examination of classic notions about the pathogenesis of rheumatoid arthritis may also prove helpful in designing new therapeutic interventions.

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DISCUSSION

Dr. Mackenzie: How do you assess the shreds of evidence suggesting that the inciting antigen might, indeed, persist in rheumatoid joints?

Dr. Zvaifler: There certainly are animal models in which a rheumatoid arthritis-like condition is produced by persistent antigen. I have no objection to the notion that such a situation might prevail in rheumatoid arthritis. However, good evidence for this simply doesn't exist.

Dr. Carsons: Would you comment on why the rheumatoid joint is so active in producing rheumatoid factors and other antibodies?

Dr. Zvaifler: People are looking very hard at this question, and there are two general approaches. The conventional explanation is that T helper cells interact with B cells, causing them to elaborate immunoglobulin, but in such a scheme rheumatoid factors would be less likely to be produced in abundance. In terms of the Th1-Th2 paradigm derived from murine studies, this conventional explanation is in accord with activities of the Th1 subset. A newer approach focuses on the Th2 subset, which on the basis of very incomplete evidence seems to drive B cells through a non-antigen-specific route, directly causing them to express their potential. This would seem to fit better with what we see in the rheumatoid joint.

Dr. Fox: Are individual lymphokines necessary and sufficient as opposed to necessary or sufficient in promoting immune responses?

Dr. Zvaifler: I'm afraid that as we clone more lymphokines we are facing the complexities that we saw with complement 20 years ago, namely, the problem of synergy. For example, interleukin-1 and interleukin-2 may be active only when you put them together. Interleukin-5 and interleukin-6 do things to B cells that neither one alone will do. Gamma interferon's effect on Ia antigen induction is increased synergistically by tumor necrosis factor. There are many other examples.

Dr. Paulus: Do you think that the lymphocytes in the synovium are driving the macrophages or that the macrophages are motoring on their own?

Dr. Zvaifler: My own belief is that macrophages are motoring on their own.

Dr. Paulus: Are all of these lymphocytes just bystanders, then?

Dr. Zvaifler: They are not necessarily bystanders. I think that they have been summoned into the joint but are not allowed to express their potential because if they did, they would blow the joint away. We see in rheumatoid arthritis the body's ongoing attempts to control what could be a fiercely destructive process.

Dr. Loudon: Is there any evidence that one can down-regulate Ia antigen induction by using any of the disease-modifying antirheumatic agents?

Dr. Zvaifler: Corticosteroids' effects on immune activation have been studied in mice. Dexamethasone has the ability to block interferon-gamma up-regulation of Ia antigens on the resting macrophage that already has some Ia.

Dr. Fox: Prostaglandin E can be shown to down-regulate interleukin-1 production by macrophages, which, in turn, would down-regulate interferon-gamma production. I might also mention that physiologic doses of chloroquine have been shown to interfere with the assemblage of the beta-chain and the alpha-chain in HLA-DR, preventing the transport of HLA-DR to the cell surface. So, chloroquine offers an extremely rapid and physiologic way of interfering with any HLA-DR-related process, and the same should be true of hydroxychloroquine.

Since both gold and hydroxychloroquine have been shown to accumulate in platelets and monocytes, this may be an important basic mechanism for reducing immune processing by the macrophage.

Dr. Rynes: Dr. Zvaifler, how does your model fit in with the prevalence of the HLA-DR4 marker in patients with rheumatoid arthritis?

Dr. Zvaifler: I cannot relate the two. At the same time, however, I don't doubt that the DR status is relevant to rheumatoid arthritis. It's unclear at this time, though, whether this has anything to do with susceptibility. I would point out that susceptibility to rheumatoid arthritis is influenced by more than one gene, and whether HLA-DR may influence the initiation or the perpetuation of rheumatoid arthritis is unknown. We have examined the notion that susceptibility to rheumatoid arthritis and other arthritides may be due to ease of Ia antigen induction. Although there is a 2-log difference among normal persons in terms of the ability of interferon-gamma to induce Ia, so far there is no evidence that patients with rheumatoid arthritis show an unusual pattern in this respect; they are right down the middle, most responding, like 80 percent of normal people, to 1 to 10 units of interferon-gamma.