The observation that infection can precipitate an autoimmune disease dates back more than a century. The first human autoimmune disease described, paroxysmal cold hemoglobulinuria, was thought of as a late consequence of syphilis, and rheumatic fever is still associated with preceding streptococcal infection. In modern times, these associations have been attributed to molecular mimicry. In its simplest form, the concept of molecular mimicry states that antigenic determinants of infectious microorganisms resemble structures in the tissues of the host but differ enough to be recognized as foreign by the host’s immune system. It is now clear that mimicry on the molecular level is a common phenomenon; that is, many sequential and structural determinants of infectious agents simulate epitopes of host tissues (1). But, as Mackay and I remarked recently, “There are, as yet, no firm instances of molecular mimicry by microorganisms serving as initiating agents of human autoimmune disease…” (2).

Molecular mimicry in Chagas’ disease
There is probably no better candidate for investigating mimicry than the cardiomyopathy of chronic Chagas’ disease. It afflicts about 30% of the 20 million individuals infected with the protozoan Trypanosoma cruzi in the Americas. The presence of a cardiac inflammatory infiltrate in apparent absence of parasites suggests that the trypanosome initiates an autoimmune response. Indeed, a number of cross-reactive human antigens have been implicated by their reaction with sera of Chagas patients. They include, for example, a 23 kDa ribosomal protein (3), a functional epitope on the β adrenergic receptor (4), a 48 kDa protein found in neuronal axons (5), and a heptapeptide of cardiac myosin heavy chain (6). In this issue of the JCI, Gironès and colleagues have identified another cross-reactive antigen (Cha), a novel peptide from human cells (7).

This peptide, which reacts with the sera of patients with chronic Chagas’ disease and of mice infected with T. cruzi, was found in abundance in human and mouse hearts. Cross-reaction between the mammalian and trypanosomal peptides was documented for both T and B cells. The finding that this peptide bears both B- and T-cell epitopes makes it a leading candidate for the induction of the cardiomegaly of Chagas’ disease through molecular mimicry, since it would facilitate T/B-cell cooperation (8).

This work leaves critical questions unanswered. Some patients with Chagas’ disease develop megacolon and megaesophagus due to destruction of parasympathetic ganglia, but Cha is not found in nervous tissue. No functional changes were associated with Cha-specific antibodies. On the other hand, mice immunized with a 13 amino acid ribosomal peptide of T. cruzi produced antibodies that caused functional changes in the heart without evidence of mononuclear infiltration (9). Finally, living trypanosomes induce Chagas-like lesions in the hearts of mice, but recombinant Cha does not. Thus, the question of whether molecular mimicry using a single, defined antigen of the parasite in the absence of infection actually mirrors clinical autoimmune disease remains unaddressed.

Molecular mimicry abounds
Recent insights into T-cell recognition have greatly broadened the original concept of molecular mimicry. A number of studies have shown that there is a fair measure of flexibility in the amino acid sequence acceptable for both MHC...
enhances the nonclonal costimulatory signals necessary to mount an immune response. Lack of appropriate costimulatory signals may account for the difference between a pathogenic and a nonpathogenic autoimmune response following infection. Our own studies with Coxackie B3–induced (CB3-induced) myocarditis exemplify such a situation. In genetically susceptible A/J mice, infection with CB3 induces autoimmune myocarditis (16). Injection of killed virus does not, suggesting that inflammation elicited by live virus provides costimulatory signals that influence subsequent immune responses. Evidence expanding this view came from experiments using less susceptible B10.A mice. If cotreated with bacterial LPS, as well as virus or cardiac myosin, the animals develop typical myocarditis. LPS acts through toll-like receptor 4 (TLR-4) and potently activates the innate immune response; particularly, it upregulates production of inflammatory cytokines such as IL-1 and TNF-α. Administration of either of these two cytokines converts a less susceptible to a more susceptible mouse. Furthermore, the production of autoimmune myocarditis in the susceptible mouse strain could be delayed or abrogated by administration of inhibitors of either of these two cytokines.

These results point to the importance of the inflammatory response itself in the generation of an autoimmune disease. They emphasize that an infectious microorganism may play two roles in the induction of disease (Figure 1). The first is to provide the requisite antigenic signal. This may come through molecular mimicry or through the release of excessive amounts of self-antigen from tissue cells during the infectious process. The second role of the infectious agent is to provide the adjuvant milieu in the form of upregulation of costimulatory molecules and other products of inflammation. The activation of antigen-presenting cells during microbial infection upregulates costimulatory molecules and secretion of inflammatory cytokines (17), thereby reducing the threshold needed for activation of T cells by the antigenic signal. This effect, which may promote protective immunity and thus benefit the host, may also prove be detrimental when it increases susceptibility to damaging autoimmune responses.