flexibility with the new electrophoretic ink. In the near term, the electronic ink should allow innovations in low-resolution, low-content reflective displays such as street signs and electronic badges. In the long term, it could serve in more demanding applications — in disposable TV screens, or in active camouflage, or as electronic wallpaper, perhaps. Jacobson's long-term goal[4] is to build complete electronic books, which can be electronically changed into any book that the reader wants. □

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Autoimmunity

The pathogen connection

Christophe Benoist and Diane Mathis

Several indirect arguments support the idea that microbial agents influence the occurrence or course of certain autoimmune diseases. These include the fact that migrant populations acquire the disease prevalence of the geographical area to which they move, a prevalence correlated with latitude; that the incidence or frequency of autoimmune diseases has dramatically changed in the last two centuries; and that non-obese-diabetic (NOD) mice are protected from diabetes by bacterial infections. The nature of the agents involved and their mechanism of action remain unclear. Is there immunological cross-reactivity between anti-pathogen and anti-self responses — molecular mimicry? Or do the pathogens upset the metastable equilibrium of self-tolerance by disrupting immunoregulation — bystander activation? Recent papers[1–3], the latest by Horwitz *et al.*[1] in this month's *Nature Medicine*, bring interesting evidence to the debate.

Immune tolerance to self is not absolute. Given the breadth of protein epitopes in higher eukaryotes, an immune system from which all potential self-reactivity had been deleted would probably not respond to anything. Thus, clonal deletion in the thymus and peripheral lymphoid organs seems to spare a large number of T lymphocytes that are potentially reactive against self-components. These T cells essentially ignore the self-antigens because they are seen with low affinity, they occur at low abundance, or because they hide behind tissue or processing barriers.

The currently fashionable concept of molecular mimicry[4] (Fig. 1a) proposes that pathogens express a stretch of protein that is related — in sequence or structure — to a particular self-component. This pathogen-encoded epitope can be presented by the major histocompatibility complex and activate self-reactive T cells. Activation could occur because the T cell's antigen receptor has a higher affinity for the pathogen protein than for the self-component, or because T cells are more readily primed in the inflammatory context of an infection. Because primed and amplified T lymphocytes have a lower threshold for activation, they can now attack self-antigens that they previously ignored.

The alternative concept of bystander activation (Fig. 1b) proposes that pathogens disturb self-tolerance without antigenic specificity coming into play. They can do this in several ways: by provoking cell death and thus the release of cellular antigens, increasing their visibility or abundance; by attracting and potentiating antigen-presenting cells; or by perturbing the cytokine balance (either locally or over long distances) through the inflammation that is associated with infection. In a sense, bystander autoimmunity falls within the broader idea of parasite or virus-associated immunopathology — that the immune response is most deleterious to the host, not the intrinsic toxicity of the pathogen.

There is good evidence that molecular mimicry *could* operate. Relevant homologies between mammalian and pathogen sequences have been found (albeit in the midst of much chaff from statistically or structurally undiscriminating database searches). Experimental support has come from animals immunized with peptides containing such homologous motifs[5], and transgenic mice in which a viral epitope is expressed on particular organs[6,7]. But how relevant is such evidence to real-life situations in human pathology? This is a thorny issue for complex, multi-factorial diseases, because it will be particularly arduous to identify the culprit microbe if the autoimmune manifestation is a low-frequency complication of infection by common pathogens.

One case in point is Coxsackie B virus, which has been linked to autoimmune diabetes (insulin-dependent diabetes mellitus; IDDM). Sero-epidemiological evidence for such an association is sketchy[8], but

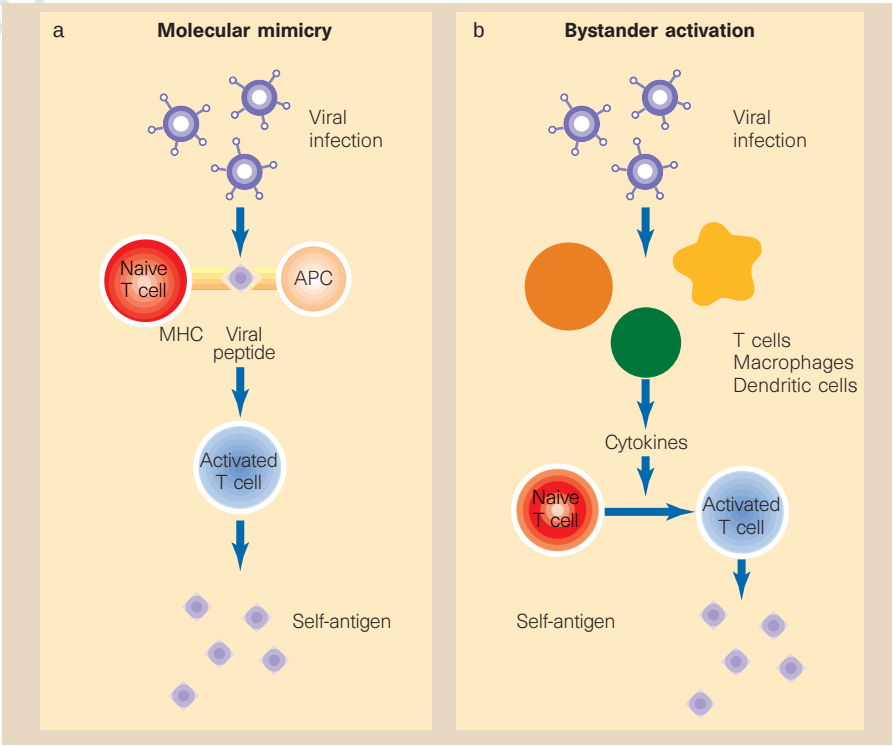

Figure 1 **Two ways in which pathogens might trick the immune system into attacking its own cells.** a, **Molecular mimicry. Naïve T cells recognize, and are activated by, viral antigen that is related to a self protein. When these T cells subsequently encounter that protein, they mount a cytotoxic response.** b, **Bystander activation. The virus induces an inflammatory response resulting in, among other things, the release of cytokines. Dormant T cells in close proximity are woken up, and have a lower threshold for activation, meaning that they can now attack self-antigens that they may previously have ignored. The studies of Horwitz *et al.*[1] indicate that, for Coxsackie-virus-induced diabetes at least, bystander activation may be an important mechanism.**

attention has been drawn to the homology between determinants of the Coxsackie P2-C protein and glutamate decarboxylase (GAD), one of the autoantigens recognized in IDDM (for review see ref. 9). Could Coxsackie infection unleash autoreactivity to GAD and thereby provoke IDDM?

If viruses activate pathogenic autoimmunity through molecular mimicry, they should not be able to do so if the immune repertoire is blind to cross-reactive epitopes. Horwitz *et al.*[1] tested this possibility — and the potential importance of virus-induced bystander activation — by studying the BDC2.5 mouse model of diabetes. Most of the T cells in these transgenic mice are reactive against a naturally expressed pancreatic antigen that is distinct from GAD. When carried on the NOD genetic background, BDC2.5 mice show heavy infiltration of the pancreas by T cells; the local lesion is active, as shown by lymphocyte activation, division and programmed cell death, but a balance is somehow maintained such that complete destruction of insulin-producing cells is avoided for a long time[10].

Horwitz and colleagues found that infection by Coxsackie B4 rapidly provoked diabetes in the transgenic mice, but not in non-transgenic littermates or in NOD animals, which show a less extensive pancreatic infiltration. This effect was at least to some degree virus specific, because it did not occur after infection by lymphocytic choriomeningitis virus. Coxsackie B4 infects pancreatic cells[11], so the local inflammation that it provokes probably disturbs the immunoregulatory balance of autoreactive T cells in the vicinity (increased levels of antigen and pro-inflammatory cytokines).

This interpretation is consistent with a previous analysis from the Zinkernagel group[2], using another transgenic system. They found that functional cytotoxic T cells could be elicited through bystander activation, but could not home to and destroy the pancreas — unlike T cells activated, in higher numbers, by recognition of cognate viral antigen. The results of Zhao *et al.*[3], although interpreted in the context of molecular mimicry, also underscore the importance of local effects of pathogens. These authors found that T cells activated by a mimic from Herpes simplex virus could not provoke corneal keratitis without a local, virus-induced lesion.

Ultimately, the conclusion is that the suspected connection between Coxsackie B virus and IDDM is linked to viral infection of the pancreas and bystander activation of a pre-existing, but controlled, autoimmune state — homology to GAD would be a red herring. Although this would be overstating the case that can be made from the available data, it will be important to keep in mind these demonstrations of viral bystander effects. For example, therapeutic immunointervention focused on cross-reactive epitopes would be misguided if a pathogen's main contribution were bystander activation of dormant autoreactive cells. □

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Oceanography

Eddies make ocean deserts bloom

Richard G. Williams and Michael J. Follows

Phytoplankton require nutrients for growth and reproduction, and they need to have them in the euphotic zone, the sunlit 'skin' of the ocean where photosynthesis can take place. Traditionally, nutrient supply to the euphotic zone has been explained in terms of large-scale circulation over entire ocean basins. However, three papers[1–3], two of them[2,3] in this issue, invoke a complementary explanation — that energetic eddies, analogous to atmospheric weather systems, are a source of nutrients on a much smaller horizontal scale of several tens to hundreds of kilometres.

The central question to be answered is as follows. How is phytoplankton primary production sustained at observed levels in nutrient-poor parts of the ocean? Satellite observations[4] show that primary production is greatest at high latitudes and near coastal boundaries (Fig. 1). These areas broadly correspond with regions where winds induce upwelling of deep, nutrient-rich waters. Primary productivity is still observed over the comparatively nutrient-depleted subtropical gyre — the 'ocean desert' at mid-latitudes, which is characterized by downwelling (shown by the negative contours in Fig. 1). That in itself is no surprise because much of primary production uses recycled nutrients. But a fraction of primary production — new production — is sustained by newly supplied nutrients balancing a loss from sinking organic particles.

So where do these nutrients come from? Traditional explanations are unconvincing. Vertical diffusion is not the answer — estimates of vertical mixing rates[5] in the upper thermocline, where there are strong vertical gradients, are an order of magnitude too small to balance the nutrient budget. Atmospheric input of nitrogen is significant near the coast, but relatively small over the centre of the subtropical gyre. Lateral input of nitrate (one of the principal nutrients used by phytoplankton) from neighbouring upwelling regions occurs along the flanks of the gyre, but this contribution peters out towards the centre[6].

Last year, McGillicuddy and Robinson[1] proposed that in the Sargasso Sea, a subregion of the North Atlantic subtropical gyre, the time-varying eddy field might supply the required nutrients. They argued that geostrophic eddies cause nutrients to be 'upwelled' and 'downwelled' through the base of the euphotic zone. Upwelled nutrients are partly consumed by phytoplankton in the euphotic zone and converted into organic matter, whereas there is no equivalent conversion for downwelled nutrients. So eddies result in a rectified transport of nutrients into the euphotic zone because of the asymmetry in the ecosystem response; this process is analogous to how a combination of atmospheric eddy transport and photochemistry results in a maximum in total ozone at mid- to high latitudes in the atmosphere.

In the first of the papers in this issue (page 263), McGillicuddy *et al.*[2] extend this work — they discuss how new production levels of up

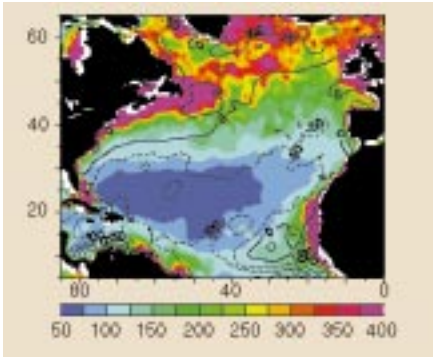

Figure 1 **Annual primary productivity (coloured values in g C $m^{-2} yr^{-1}$), and upwards vertical velocity of water (contoured in m yr^{-1}) in the North Atlantic. Productivity reaches maximum values of 400 g C $m^{-2} yr^{-1}$ where there are high levels of nutrient input from upwelling; and it has minimum values of 50 g C $m^{-2} yr^{-1}$ within the subtropical gyre where there is downwelling (negative contours) and comparative nutrient depletion. Previous estimates of nutrient supply seem inadequate to account for even these low values, hence the proposal[1–3] that eddy circulation may be responsible for supplying them. (Figure derived from satellite estimates of surface chlorophyll from ref. 4, and calculations of vertical velocity at the base of the surface wind-forced boundary (Ekman) layer[6].)**