Medical Hypotheses (1999) 52(3), 213-219 © http://dx.doi.org/10.1054/mehy.1997.0645

Received 23 May 1997 Accepted 8 September 1997

From terra firma to terra plana - danger is shaking the foundations: deconstructing the 'immune system'

SUMMARY

The paradigm of an immune system presumes that a system arose specifically to combat infection - hence its name. This paradigm gained credibility with the discovery of antibodies and anamnestic immunity, even though these are relatively late arrivals in evolution. Another presumption has been that thymus-dependent T cells are responsible for discriminating self from non-self. Subsequent opinion has crystallized around these presumptions. This paradigm is flawed. Transforming it into a morphostatic system resolves the problems. There is, arguably, no such thing as an immune system.

PREAMBLE

(All that follows is opinion)

The conventional view of the adaptive immune system is that it arose to combat infection, to identify pathogens and to discriminate self from non-self antigens. These presumptions were based on the discovery of antibodies. Antibodies protect the animal from infective disease; immune deficiencies result in infective crises. So it was natural and obvious to make these presumptions - just as it was obvious to presume that the earth was flat, that it was placed at the centre of the universe and that time is rigidly fixed throughout it. Such self-evident truths only need challenging when observations no longer hang well on the presumed framework. Then it is time for a revolution.

Langman and Cohn *(1)* recently published a 'Cutting Edge' article in which (I contend) they patch up the decaying fabric of a failing perspective. They entitled it 'Terra firma: a retreat from danger'. Well, was this view firm earth or flat earth? We have learnt that 'stale paradigms are held like religious beliefs.' Their article was provoked by polly Matzinger's hypothesis of a danger-driven, adaptive immune system *(2)* and a bevy of articles in Science (cited in *(3)*) leading to the claim that the old order is close to collapse *(4)*. Others *(3,5,6)* have expressed their doubt that this portends a real revolution in immunology. I hope to show you that it does - and, further, that this may be the first Kuhnian revolution in biology *(7)*.

I could begin with a detailed dissection of conventional beliefs but these are, to my mind, Heath Robinson (Rube Goldberg for North Americans) and it would require a tortuous exploration even before touching on the grand plan. So, I will just reiterate the central tenets and leave the reader to discover, in the following text, how a perceptual revolution can deal with each in turn.

- The immune system arose specifically to combat invasion by foreign organisms.
- In the thymus, any T lymphocytes that might attack self antigens are eliminated in utero; mammals use this fetal period to establish an immune definition of self.
- All discrimination is based on the categorization of antigens into self (S) or non-self (NS). The process whereby this is achieved is still uncertain but it involves Signal 1 and Signal 2.
- Foreign organisms have to be discriminated from the host. This fact led to the concepts of discrimination of S from NS by antigens and of a horror autotoxicus (to self antigens).
- The immune system responds to a foreign organism by mounting a lethal, lymphocyte led attack on its antigens. This rids the host of the organism without killing the host.

This conventional perspective misses important points. It is stalled on the idea that antigens are used to discriminate S from NS. Here, I argue that this emphasis on antigens is a quagmire conviction, bogged down in an outmoded perception. I have previously proposed that the critical function of the immune (or

morphostatic) system is the discrimination of healthy-self cells from other-than-healthy-self cells *(8,9)*. The immune systems of countless invertebrates carry out this discrimination without anamnestic lymphocytes: our distant ancestors did so long before they evolved into vertebrates and acquired Tc or Th cells. Imagine being a primitive metazoan. You have just learnt to use gap junctions to expand your body plan beyond the cell membrane so that it now spans a population of zygote derived cells. You will need to break off communication with any cells that become irreversibly sick; you would prefer that such sick cells commit suicide; you will want to replace the lost cells; and, when elective suicide fails and sick cells spill their contents, you will need to clear away the debris quickly. This is the grand plan and, as you will discover, little may have changed in mammals.

THE MEMBERSHIP RULES

Each zygote-derived cell is charged with monitoring and maintaining its own health. The overwhelming majority of all sick (dysfunctional) somatic cells are identified in house, within and by the disordered cell itself, using internal checkpoint controls. Sick cells (infected, aging, ectopic etc.) elect to apoptose on this internal realization of dysfunction: first they try to resolve the problem but when this fails they trash their contents. Resident intracellular pathogens will also be trashed in the process, particularly those that have not developed strategies to circumvent apoptosis. The conventional view is that aggressive immune activity (Tc/Th-cells) is focused primarily on NS antigens. I propose that it is focused primarily on a subset of other than healthy self cells and their debris. Immune aggression acts as a backstop - or mop up - mechanism that is poised to remember some caricature of sick cells that previously failed to successfully trash (and so sanitize) themselves. These cells and their debris are a danger. Organisms that invade the extracellular spaces disrupt extracellular structures (connective tissues and intercellular junctions). This sets off an inflammatory reaction. Those that cannot hide within a cell are, generally, easy meat for the innate immune system. Most of them are recognized - then eliminated - on the basis of absent self, surface ligands and characteristic bacterial features. Antigen-presenting cells (APCs) - these include dendritic cells, macrophages and other phagocytes - are professional trashers. Debris is initially attacked in lysozymes but then phagocytes trash their own contents, destroying all but the most resistant cell contents. Phagocytes are not re-circulated. Once they enter somatic tissues, they are destined for apoptosis - either in the soma or, by default, after migration to the draining lymph nodes.

WHY IS CELL-MEDIATED AUTO-AGGRESSION SO COMMON?

Why have I not used the term auto-immunity? We need to establish what we mean by this term. Its invention was an etymological disaster. Immunity to self seems to be implied rather than the intended undesirable aggression to self Perhaps, at that time, all anamnestic activity was perceived to be aggressive. The classical auto-immune disorders include a pot-pourri of humoral (immunoglobulin) reactions that appear to have gone wild and so disrupt normal functions. In the paper 'Morphostasis and immunity' *(7)* I developed the concept that the anamnestic immune system originally evolved to classify sick cells into those that die in a controlled fashion (trashing their contents whilst ensuring that this trash remains confined in convenient, phagocytosable bilipid membrane packets) and those that die in a more catastrophic fashion (spilling their inflammatory contents into the surrounding extracellular tissues). This implies that the origin of anamnesis is rooted in the classification of whole cell death into safe or dangerous: the next time that similar cells are encountered, they can be left to get on with it themselves (for safely trashed cells) or encouraged to adopt a lowered threshold to apoptosis (for dangerous, non-trashed, spilt cells). Tc cells (class I presentation) look for cells resembling somatic cells that died catastrophically last time (dangerous) and Thl cells (class II) look for APCs resembling APCs that previously picked up and then presented cell debris during an inflammatory reaction. When this debris contains living organisms, the APCs themselves may become diseased and provoke Tc activation should they die catastrophically rather than by electively trashing their (dangerous) contents.

This implies that the cell-mediated anamnestic immune system is engineered to recognize and encourage the elimination of sick and suspect self cells. Internal turmoil leads to the accumulation of intra-cytoplasmic protein junk. This junk may be repaired (by HSPs) or chopped up (by proteosomes) and escorted off the premises (by ubiquitins). Class I Mhc molecules hang this peptide junk, flag like, off the external cell

membrane, ready for classification into safe or dangerous. NK cells regard cells as safe when they display safe peptide debris in combination with self Mhc molecules. Vertebrate Tc cells evolved as a functional inversion of NK cells. In mammals, cell dysfunction that leads to leakage of cytoplasm or perturbs membranes will provoke an element of T cell-mediated auto-rejection. Tissue rejection is dominantly a cell-mediated event. Antibodies are largely bystanders - 'complicandees' - generally incapable of inducing rejection but able to gum up the works.

So, where are all these auto-rejective diseases that are dominantly cell mediated and that have minimal Ig auto-reactivity? They are there! They are those disorders that the experimental model, adjuvant arthritis, mimics. They include ankylosing spondylitis, Reiter's syndrome, Behçet's syndrome, psoriatic arthropathy, inflammatory bowel disease, Whipple's disease and sarcoidosis. The structure of these disorders suggests that they occupy an iceberg tip of rare, severe and extensive disease; but there is also a large iceberg base of mild, common, single-component disorders. The sero-negative arthritides are composed of component disorders that are more prevalent as milder, isolated diseases. Behçet's is a good example. Recurrent aphthous ulceration (RAU) occurs in 5% of the population, RAU + female genital ulcers in 0.5% of the population, RAU + male genital ulcers in 0.05% and Behçet's syndrome in 0.0005% (ballpark figures). Much as the aphthoses seem to be part of a clinical continuum - from the mild aphthosis of RAU, through RAU + genital ulceration to the severe multisystem Behçet's syndrome - so the meningo-encephalo-myelitis of Behçet's syndrome seems to be in clinical continuum with Eale's disease, Devic's disease, other transitional scleroses and these, in turn, in continuum with multiple sclerosis (MS) (which represents the isolated and mildest, meningo-encephalo-myelitic component). The visual metamorphosis, from the plaques of MS to the necrotic foci of Behçet's, can be traced in a similar continuum (of severity) through these diseases and their experimental counterparts, experimental allergic encephalitis (EAE) and hyperacute EAE. And, it goes further, because benign MS is more common still - in my practice four to one. I have a detailed argument for this, 'The neurological complications of Behçet's syndrome', awaiting revision and completion.

Now it should be clear that the auto-rejective diseases occupy a spectrum where there are mild component disorders through to severe syndrome disorders. The components include RAU, acneiform lesions, erythema nodosum, psoriasis, thrombophlebitis, tenosynovitis, polyarthritis, ankylosing spondylitis, epididymo-orchitis, pan-opththalmitis, meningo-encephalomyelitis and, perhaps, even irritable bowel syndrome as a mild, common representative of inflammatory bowel disease. Even in the severe disorders, the addition of extra components increases the lethality (severity) of the patient's disease.

This can all be summed up in an axiom: *'The severity of any single patient's disease - whether it is an isolated component or a syndrome complex of more than one component - is inversely proportional to its incidence in the population and directly proportional to the number of components found in association with one another.'*

So, the anamnestic immune system, far from observing a rigorous aversion to attacking self tissues, uses the auto-rejective process as a mechanism to clear pockets of disordered cells. This suggests that a likely precipitant of these disorders is an agent that makes a substantial proportion of cells sick. To survive elimination, the agent (probably an intracellular infection) needs to present little that is distinctly novel at the cell's surface or when it migrates from one cell to another. So, rather like graft compatibility, there will be a fair proportion of organisms that evolve a low level of (mimicking) compatibility with the host (i.e. of processed epitopes) enabling them to gain a survival advantage (see *(10)* and also look back to a 1968 book by Burch *(11)*). But only a small proportion of organisms will develop a high degree of compatibility - this will give them a high degree of protection from detection and elimination. In the absence of clearly novel epitopes to typify these sick cells, other (self) epitopes will be chosen to be used as the pegs on which to hang an accelerated inflammation on re-encounter.

SYNTHESIS

To recap, precursor Tc cells are designed to recognize the mode of a cell's death (apoptotic - safe, and lytic - dangerous). Precursor Thl cells are designed to recognize peptide debris processed by APCs. Debris presented following ingestion of apoptotic, membrane packaged, cell fragments will be tolerated (safe) and

spilled cell debris, once ingested and presented by APCs in an 'angry', inflammatory presentation, will induce aggression. Subsequently, when new APCs ingest new debris and present it at their surface, these (now committed) Th precursor cells will either encourage peace and quiet (safe epitopes - T suppression) or let all hell loose (dangerous epitopes - Thl activation) to accelerate and accentuate the current inflammatory response. This gives inflammation a memory. This poses a new problem, for it could get out of hand and lead to catastrophic tissue destruction should self-epitopes be the dominant peg on which the accelerated inflammatory response is hung. This leads to a need to paralyse phagocytes when the response gets too intense - read *(12)*. In turn, this leads to a requirement to mop up debris when focal phagocyte anergy gets going. Hence, IgM evolved. A recent article supports this presumption *(13)*.

Some organisms provoke phagocyte anergy (by excessive Th 1 stimulation to self epitopes) as a ruse to develop an encapsulated, phagocyte-incompetent culture medium (staphylococcus boils, TB, syphilis). TB and syphilis (in the middle years of life) are dominantly auto-rejective disorders! They mimic the sero-negative arthritides. The result is a large uniform auto-rejective response over which is superimposed a more idiosyncratic response, unique to the organism. Syphilis has many features in common with the Reiter's/Behçet's pattern and TB has many features in common with the ankylosing spondylitis/ sarcoidosis/inflammatory bowel disease pattern. This parallelism is most marked in the middle years of life, tracking the age incidence profile of the sero-negative arthritides. Outside of these years, they tend to be diffuse and disseminated infections - more semblant of miliary cancer than the intensely destructive caseating lesions seen in the middle years.

Physiological auto-rejection invokes the need for re-generation. Regeneration is resurgent morphogenesis. In a rapidly growing animal, extensive auto-rejection and subsequent regeneration could (and do!) stunt growth. The luxury of extensive auto-rejection as a morphostatic technique can only be afforded to its maximum in fully grown animals. So, immunological immaturity is an illusion. The aggressive, anamnestic immune system is deliberately downregulated in newly born animals to avoid undesirable tissue rejection *(14)*. Pockets of such down-regulation persist into adulthood in immunologically privileged sites (e.g. eye and brain) where extensive auto-rejection would (and does! - NB Behçet's) seriously disadvantage the colony. These points are reflected in the age incidences of the auto-rejective disorders.

Previously *(8,9)* I proposed that it was apoptosis that induces immune tolerance and that viral peptides, when presented by apoptosing inflammatory cells, would induce tolerance. A recent article lends support to this presumption *(15)*. Reference *(14)* demonstrates that immunological immaturity is due to down regulation of aggressive anamnesis rather that an intrinsic inability to respond. Indeed, in immunological immaturity, the anamnestic response is strong - but deliberately channelled into tolerance.

Immune networks are like the feedback round an audio amplifier. The open amplifier has massive gain: much of this gain is fed back to the input as negative feedback. The advantage is that the output faithfully follows the input - but at substantial gain. Remove the input (response to sick cells here) and the output clamps down to zero again. Hence the experimentally induced auto-rejective disorders (e.g. simple EAE and adjuvant arthritis) are short-lived unless the irritating input is maintained. Here is the purpose of immune networks. High gain and negative feedback allows auto-rejection to be used as a fast, focused, morphostatic technique. Minor levels of local sickness will provoke an exaggerated focal response. This will be clamped back to base levels (after a brief hysteresis) once the insult passes. For me, the idea that immune networks act as a template of self is both Heath Robinson (Rube Goldberg) and unstable.

The original purpose of thymic tolerance may have been to protect lymphocyte peptides from being the focus of auto-rejection. The function of these cells requires that they migrate into areas where there is a high risk of lysis/necrosis. A pre-emptive tolerance of their typical epitopes is desirable - and many of these epitopes are expressed by other somatic cells.

Phagocyte anergy (which inhibits runaway Th1 induced auto-rejection) may result in the escape of malignant cells from elimination by macrophages and NK cells - read *(12)*. Logic dictates that there will be a narrow, temporal window of risk. Macrophages paralysed by anergy will be unable to destroy cells that have a malfunction of identity and/or gap-junctional communication. So, when strong anergy and the onset of a

p53-related abnormality coincide, a tumour colony may gain a chance to grow to a critical mass, beyond which control becomes difficult.

These various conclusions led to my first article *(8)*. A second article advances the argument *(9)*. By arguing dominantly from an evolutionary viewpoint, this clarifies the raision d'etre of the morphostatic (tissue homeostatic) system. This hypothesis paints a clear picture of the fanning evolution of defence mechanisms - ranging from plants *(16)* to mammals - and it highlights the evolutionary steps that lead to the mammalian anamnestic immune system.

ROUND UP

It is fatuous to argue that the immune system does or does not discriminate S from NS - except as a provocative means of forcing us to rethink a paradigm. For most day-to-day tasks, it is appropriate and effective that an individual works on the assumption that the universe is centred around him or her self. But this perspective is confusing when trying to understand planetary paths, when navigating space probes or when trying to form a universal view of what is happening. This is analogous to the lymphocentric (anamnestic) immune universe. Everything is relative. To gain a better understanding, we need to adopt a different perspective. It is beyond dispute that the anamnestic immune system tends to tolerate self and attack foreign but, what needs to be said - with force - is that this is not its primary raison d'etre. Indeed, the absolute adherence to a lymphocentric perspective has been gradually falling from favour. A phagocentric immune system is closer to reality but this does not go deep enough. Morphostasis is rooted in the process of intracellular surveillance for dysfunction within each individual cell of the zygote-derived colony. All immune activity stems from the success or failure of intracellular surveillance for dysfunction in order to avert danger. Only when the danger signals (IL-1 and eicosanoids are contenders) break free from their containment within the affected cell membrane do they need to stimulate the aggressive anamnestic immune system.

I believe there will be rapid advances once immunologists accept that immunity is the passive consequence of the cell colony's morphostatic process. To re-emphasize, the system revolves around intracellular surveillance, within individual cells, for dysfunction. Dysfunction is identified by and within each and every nucleated cell of the colony. Danger is signalled when such cells cannot complete a successful and controlled shutdown as things go wrong. My ideas have focused on cell lysis as the dominant danger signal though any lesser manifestation of failed, controlled shutdown might suffice. The value of this concept becomes clear when considering the roles of Class I and Class II presentation of antigen.

The component ideas developed in my earlier articles have gradually born fruit. Many have already been vindicated. The fulcral importance of gap junctions is a contentious deduction, still only supported by a feeling for what ought to be there and observational rumour. But it is much stronger now than when first adopted. Recent revelations about the involvement of N-CAM and gap junctions in the development of the nervous system are adding weight to the argument *(17).* Assumptions made when this hypothesis was in embryo are proving to require minimal revision: this adds support to the hypothesis.

AND SO TOWARDS THE APOTHEOSIS

So, is the morphostasis hypothesis secure?

A simple exercise provides support. Wherever I have used danger or dangerous" these terms can be (respectively) replaced with mess or messy. Similarly, safe and safely can be replaced by tidy and tidily. Now, even the danger analogy becomes outmoded. This tautology *(9)* - the last and the most significant - is simplicity itself. It brings us to a realization of what we have always known but never quite verbalized. The thymus-dependent immune system is a mess/non-mess discriminator and the whole morphostatic system is dedicated to maintaining a tidy household! All cytoplasm has to remain membrane packaged, and preferably communicating, for it to be tolerated in the zygote-derived colony (ZDC): it is exquisitely simple.

Virtually by definition, pathogens make a mess; but, there are many viruses and bacteria that don't make a mess. Anything is welcome in the ZDC provided it doesn't make a mess or get in the (inter- or intra-cellular) way. Succinctly:

- The system is a morphostatic, not an immune system.
- Metazoans never developed an immune system specifically dedicated to identifying foreign organisms.
- NK lymphocytes are dominantly interested in cells that are disconnected. Furthermore, cells that are connected need not raise any alarm. They are - like Kärre' s submarines *(18)* - the 'don't bother to call us if you see one of these' variety.
- APCs also take a particular interest in disconnected cells. My original presumption was that disconnection led to an attack by APCs. It probably only leads to enhanced APC attention ((i.e. 'let's take a closer look'), whereas connected cells can be safely ignored (again - the 'don't bother to call us if you see one of these' variety) .

Most current textbooks of immunology make the presumption that the immune system arose to combat infection and distinguish S from NS. Now, these statements might be justified if, when we talked of the immune system, we encompassed all the mechanisms that lead to the protection of the colony of cells (that constitute an animal) from infection. However, it has been a peculiarity of modern immunology that the immune system is largely seen as the anamnestic (memorizing) lymphocytic system. The substantive belief is that T-cells of the Tc and Th lineage have, as their raison d'être, the job of distinguishing S from NS and, in particular, S cells from NS organisms. What is more, there is a belief, based on the crises that occur in the absence of anamnestic immune cells, that these cells are necessary for identifying and eliminating micro-organisms.

So why are countless invertebrates so successful when they don't have such an immune system?

I believe that the conventional view has got it drastically wrong. The anamnestic T-cell system never was an immune system. It is a morphostatic system. Should there be a system specifically designed to recognize and fight foreign organisms, then it is a more basic and universal property that is manifest in and by each and every living cell. S/NS discrimination is a fundamental capability possessed by all cellular organisms. It is based on a series of physical barriers, internal checkpoint controls (internal surveillance), restriction endonucleases and factors that join the individual cells of a colony into a unitary animal (CAMs, SAMs and ICJs) *(19)*. The anamnestic immune system (dominated by thymus-dependent lymphocytes) is only involved when controlled shutdown fails and the colony is left to dispose of a mess of lysed cells and their debris. Thymus dependent lymphocytes do not concern themselves one jot in the classification of epitopes into S or NS - even though the result of their primary raison d'être has lead us to believe that they do.

FINALLY

Remember this point. When NS organisms make a mess (lyse self cells and spill cellular debris), the Tc and Thl cells will 'memorize' a caricature of this mess (preferring the most unusual epitopes). On any fresh encounter, they can identify similarly caricatured cells and their resultant debris.

Even down to the cellular level, I suspect that the system will turn out to be, dominantly, a morphostatic rather than an immune system. The fact that infection is one of the greatest threats to morphostasis is of no consequence to the system. Morphostasis blindly crashes on in its attempt to restore the morphostatic status quo - even when this becomes manifestly directed towards self-damaging epitopes (as in the auto-rejective and auto-immune disorders).

In converting the analogy to a mess/non-mess discriminator, the whole morphostasis hypothesis has been strengthened. In particular, the fulcral role of gap junctions has become much more secure. Once we chart the problems faced by an immune system and show how a morphostatic system resolves them, there is - I submit - no contest.

Immune evolution	An immaculate conception of anamnesis at the origin of the jawed vertebrates. It springs, Minerva like, out of nothing, in full armour. Sparse links with invertebrate immunity. Plants considered rank outsiders.	A clear gradual progression through evolutionary shells. These shells sequentially incorporate all the fundamental components of the morphostatic system. It even shows how plants use the inner shells.
Selection of antigen for aggressive attention	Complex and uncertain. Currently described in terms of associative recognition. Cytokine activity invoked as the cause of selection for tolerance or aggression. No real feel for how aggression is favored over tolerance.	Simple, permissive. No need to regard antigens as S or NS. Widespread apoptosis of effete S cells ensure that common S peptides are unlikely to be the first choice for aggression. Cytokine activity is clearly the consequence of controlled shutdown or catastrophic death. Mess/non-mess discrimination.
Origin of IgM	Author not aware of any clear consensus.	Clearly seen to be a debris 'mop'.
Auto-immunity	By definition it should not be allowed. The immune system paradigm has been bending over backwards to find excuses for its existence.	Automatically permitted (consider the experimental auto-immune disorders).
Horror autotoxicus	Clearly does not work as originally defined. Self antigens are, at best, loosely avoided.	Redefined to be the nurture of healthy, non-ectopic, communicating, self cells.
Immune surveillance for tumours	Much disagreement and argument over whether this is a real entity - let alone how it works	A logical translation of the immune surveillance theory into a sick-self surveillance mechanism
Cancer	A hazy picture of what is happening and why. Does not integrate gap junctions, p53 and the immune system into a simple-to-understand concept.	Fully incorporated into the basic paradigm. It even suggests that a window of p53 mutation, coincident with macrophage anergy, is the likely final common event leading to the overgrowth of an anarchic clone. Gap junction studies strongly support the paradigm.
Gap junctions	Rank outsiders. Not, to author's knowledge, mentioned by anything other than a tiny minority of immunologists.	Fundamental participants. GJs can act in a way that allows bystander cells to induce survival or apoptosis in their neighbours (compare this to T-cells and perforin). Note that GJ disconnection has now been noted to be an early accompaniment of subsequent auto-immune disease Clearly involved in morphostasis.
Integration with CAMs SA Ms and ICJs	Author not aware of any clear explanation of why the IgSF family is so central to the immune system.	A clear appreciation of why IgSFs gave rise to the Mhc system, the T-cell receptor and its evolvent families. It stems from enhancing membrane hole assembly by a seeding, multiplier mechanism.
TB/syphilis	The pathogenesis of' TB and syphilis are still ill understood.	A convincing explanation of the likely way that these organisms gain a survival niche in the ZDC. They mimic the sero-negative arthritides in the middle years of life. (See text for a brief' explanation.)
Auto-rejective disorders	In concept, non-existent as far as the author is aware.	At the component level, they are so abundant as to be ubiquitous. At the level of component syndromes, they form a matrix of overlapping disorders. Behçet's syndrome and MS are one of the overlapping groups.
Experimentally induced auto-immune disease	There is a strange double think here. It is so easy to induce and yet, still, there is faith in the horror autotoxicus principle.	It is plainly obvious that, in the absence of some strange epitope that will focus attention on the affected cells, self epitopes will be chosen as targets for autorejection/auto-immunity.
Innate immunity	Till recently, it was regarded as a separate system but now there is a suspicion that it may be closely linked.	It is fundamentally integral. There is seamless integration of the innate and the anamnestic systems.
Class I, II and III Mhc	There is no obvious explanation of why the Mhc Class I, II and III genes are grouped together.	Many of the Mhc Class I, II and III genes are clearly involved in Healthy Self/ OTHS discrimination.

ACKNOWLEDGEMENTS

Thanks to the Wessex Medical Library who made this synthesis possible. Thanks to Olwen, Steve, David, Rachel, James and to my colleagues for their support and tolerance. Thanks to Ray for his keen interest and prayers. This synthesis may have come together at my fingertips but it is overwhelmingly the product of multiple minds. I apologize to anyone who has done relevant work that I have neither identified nor quoted. I am indebted to Inspec Group PLC (now a Laporte company) for sponsoring this publication.

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5. http://www.morphostasis.org.uk/letters.htm
6. http://cig.salk.edu/bicd_140_W99/debate/ and then follow *day1p1.htm* and etc. I also have a copy of this debate.

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