*(This article is "in embryo" and would need much new work and updating. It is "hung" on this web page to allow the reader to see how the "molecular" aspects of morphostasis were derived from a clinical perspective.)*

# Clinical Morphostasis


## Abstract

In a previous article, Morphostasis and Immunity (1), I presented `a whistle stop tour' of the clinical consequences of morphostasis. This paper expands this `tour'. The central concept revolves around the premise that auto-rejection is a standard housekeeping technique. It shows how the destructive effects of intensifying auto-rejection need to be counter-balanced by a fail safe inhibition of phagocyte aggression. This inhibition presents cell mediated immunity (CMI) with a dichotomy when it is searching for sick cells. At one extreme, surveillance by phagocytes for sick cells is impaired when CMI is "immature" and, at the other, impaired when CMI becomes too fierce. Surveillance is at its most effective when CMI, and any consequent auto-rejection, is modestly activated. In this article, I go on to consider the pathophysiologies of auto-rejective diseases, cancer and infections and show how these can be accomodated within the concept of morphostasis


## Introduction

Introduction here - may be added later

## Anergy

The fate of the individual cells that make up an animal are important only in that their death or survival should not endanger gene propagation. It is particularly important that they present no danger to the species gene pool. The logical way of housekeeping is to (auto)reject suspect cells. Cell loss can then be replenished by tissue regeneration - a resurgence of morphogenesis (2). Sometimes, when an inflammatory process is particularly strong and few if any clearly unusual epitopes are present, lymphocytes will mount an aggressive response to epitopes typical of the local sick tissues (eg, in burns (3) and adjuvant arthritis (4,5)). Whilst this concentrates phagocyte attention at particular tissue sites, it runs the risk of becoming an uncontrolled, yet focused, positive feedback. Without constraint, it will lead to catastrophic, localised auto-rejection. A fail safe feedback mechanism must exist. This will be brought into play where tissue destruction becomes excessive.

This may be controlled at any or all of the following points:-

- inhibition of phagocyte ingression (chemotaxis)
- inhibition of phagocyte aggression
- inhibition of further aggressive lymphocyte activation
- a tightening of endothelial cell junctions
- encapsulation in a fibrin sheath (fibrocytes later)
- promotion of lymphocytic tolerance to typical Ag
- production of auto-antibodies to the newly cloned, locally reactive lymphocytes (lymphocytotoxic Abs)

This fail safe is most necessary within and around the affected tissue so it is localised. However, some spill-over of the anergic state may also be anticipated. This will lead to a systemic depression of delayed type hypersensitivity (DTH is the immune mechanism dominantly responsible for tissue rejection). (General references (6,7,8,9,10,11,12)). This leads to a general depression of DTH - or anergy - and this is seen in diseases such as TB, sarcoidosis and cancer.

## Growth and Regeneration

Generation (growth) and regeneration (repair) are essentially similar. They are rate limited processes. Where regeneration is high, growth will be low and vice versa. So, auto-rejection causes a temporary suspension of growth. In a growing animal, auto-rejection must be prevented from reaching the intensity that can later be afforded in mature animals or growth will be stunted. The luxury of auto-rejection, as a morphostatic technique, can only be employed to its full in adult animals. The mechanisms that initiate and accelerate rejection need to be less fierce in growing animals than they are in adults. Lymphocytes must behave less aggressively. This is probably brought about by moderating the intensity with which inflammation and APCs are able to stimulate aggressive T-cells (13,14,15). Both cell mediated immunity and IgG activity must be dampened (for IgGs capable of reaching the extracellular spaces even when there is no inflammation). This results in the relative ease with which very young animals can be tolerised. This reduced capacity to reject (and so, auto-reject) is apparent in neonates in which the tolerance of grafts is much enhanced. They can tolerate a level of cerebral ischaemia that would cause extensive tissue death in adults. This relative incapacity to auto-reject also moderates the adverse sequelae of many virus infections. These are often more severe when the viruses first strike in adult life (eg, infectious mononucleosis (16), infectious hepatitis - both can be uncomplicated URTIs in young children - mumps, chicken pox, measles and lymphochoriomeningitis in mice (17)). Often, their sequelae (arthritis, jaundice, meningitis, orchitis & etc) can be prevented, or at least moderated, by immunosuppressive drugs or steroids. From this perspective, `immunological immaturity' is a misnomer. The infant's immune system is likely to be perfectly balanced for an optimal compromise (15).

In some tissues, extensive auto-destruction would be disastrous: it would seriously impair the ZDC's function and survivability. These tissues include the eye and the nervous system. These sites enjoy a so called "immunological privilege". This privilege is achieved, in part, by locking out inflammatory cells behind tight endothelial cell junctions (18). The sparse numbers of local APCs is probably a direct consequence of this.

## Auto-rejective disorders

Tissue rejection is dominantly the province of cell mediated mechanisms (19). Whilst antibodies can affect the course of organ rejection, they cannot on their own effect it (ie, precipitate it). In contrast, rejection can be provoked by injections of appropriately activated lymphocytes. Once we accept that disordered self cells are actively rejected, we are in a position to state the following:

*Every disease that leads to an inflammatory response will have an auto-rejective element even if this is limited to a mildly increased tissue turnover.*

There should, then, be a group of disorders that are largely auto-rejective and in which humoral auto-immunity plays little part - provided debris is efficiently removed. Since immune function changes through life, the intensity of auto-rejection is likely to vary with age. Because the initiation of auto-rejection is suppressed in the young (13,14,15) and its execution becomes progressively impaired in the elderly (20) its incidence should reach a zenith in the healthy young adult. Thus, a disease that is caused by extensive auto-rejection will be most likely to occur and also to be at its most severe in this central age range (Figure 1). One likely cause of such disease is deliberate interference with and mimicry of aspects of the host's identity machinery. Micro-organisms, with their capacity for rapid genetic adaptation, are the most likely offenders. Where micro-organisms acquire epitopes resembling some element of the host's identity machinery, they will mask their foreigness and so gain easier access to the host's tissues and cytoplasm. Cells that are damaged in consequence should still signal malfunction (shout "foul"). However, if there is a relative scarcity of clearly strange antigen (processed peptide), the resultant inflammatory reaction will become focused on self. Whenever these self antigens are re-encountered, an amplified inflammation will ensue. The auto-rejective attack that follows will not necessarily remain confined to the initiating site.

Adjuvant arthritis is characterised by a group of component disturbances with features reminiscent of the sero-negative arthritides and sarcoidosis. This experimentally provoked disease is probably caused because clearly foreign antigen is sparse and the immune response is, in consequence, forced to focus on local tissue

epitopes (Table 1). Whipple's disease may be an extreme example of this sort of disease - Nb, the idiosyncratic infection (21,22) and familial aggregation of cases (22,23).

## TABLE 1: the clinical pattern of adjuvant arthritis

| MANIFESTATION | ADJUVANT ARTHRITIS |
|---|---|
| **Joint lesions** | polyarthritis |
| | spondylitis |
| | tendinitis & tenosynovitis |
| **Nodules** | erythema nodosum like |
| **Muco-cutaneous** | pustules |
| | acanthosis |
| | parakeratosis & hyperkeratosis |
| | Urethritis |
| **Colon** | non-specific diarrhoea |
| | inflammatory infiltration of the submucosa |
| **Ocular** | uveitis |
| | keratitis |
| | Conjunctivitis |
| **Heart** | pericarditis |
| | Myocarditis |
| **Visceral** | granulomata in liver and lungs |
| **Neurological** | focal encephalitis |
| | meningitis |

The bacteria that colonise epithelial surfaces are a threat to the colony. They often have the ability to bind selectively to cells in particular epithelial sites (24). Since they have evolved this specificity it is likely that they have also managed to mimic and interfere with the host's identity machinery (especially tissue/site LIGANDs). The clinical pattern and incidence of auto-rejective disease can be anticipated from basic principle: the compatibility of organ transplants ranges from a relatively common slight compatibility to a rare complete compatibility (25). Extrapolating this observation to microbial mimicry, we might expect to find minor mimicry often and extreme mimicry rarely. The sero-negative arthritides and their component complications do, indeed, show this sort of structuring (Table 2). Their clinical pattern can be summed up by 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.'

## Table 2: The clinical components of the sero-negative arthritides

| The SERO-NEGATIVE ARTHRITIDES and COMPONENT DISORDERS | | | | | | | |
|---|---|---|---|---|---|---|---|
| **COMPONENT DISORDER** | **MULTI-SYSTEM DISORDER** | | | | | | |
| | SLE | PsA | RS | BS | UCA | CDA | Sa |
| Acneiform lesions | | | | + | + | | |
| Ankylosing spondylitis | R | + | + | R | + | + | R |
| Aphthous ulceration | + | | + | + | + | + | |
| Arthritis | + | + | + | + | + | + | + |
| Atopy | + | + | | | + | + | + |
| Encephalomelitis ± meningitis | + | | + | + | + | | + |
| Epididymo-orchitis | | | | + | | | + |
| Erythema nodosum | | | + | + | + | + | + |
| Neurosis and/or psychosis | + | | + | + | + | + | + |
| Ophthalmitis | + | + | + | + | + | + | + |
| ***Conjunctivitis*** | **+** | **+** | **+** | **+** | **+** | **+** | **+** |
| ***Anterior uveitis*** | | | **+** | **+** | **+** | **+** | **+** |
| ***Posterior uveitis*** | | | **+** | **+** | **R** | **R** | **+** |
| ***Periphlebitis retinae/retinitis*** | | | | **+** | | | **+** |
| ***Optic neuritis*** | | | **+** | **+** | **+** | | **+** |
| Peri-/myo-carditis | + | | + | + | + | | + |
| Psoriasis | | + | | R | + | + | |
| Pustules | | + | + | + | + | | |
| Tenosynovotis | | | + | + | | | |
| Terminal ileitis/colitis | | | | + | + | + | |
| Thrombophlebitis | | | + | + | + | + | |
| Urethritis (Non-specific) | | | + | + | | | |

+ = clinical association
**R = recorded though significance of association unclear**

SLE=SystemicLupus: PsA=PsoriaticArthropathy: RS=Reiter'sSyndrome:
BS=Behcet'sSyndrome UCA=UlcColitis+Arthritis:
CDA=Crohn'sDisease+Arthritis:Sa=Sarcoisosis

For example, recurrent aphthous ulceration occurs in about 5% of the population, oro-genital ulceration in about 0.5% or less and Behçet's syndrome (BS) (in Britain) in about 0.0001%. It is clear that an expanding clinical overlap with the other sero-negative arthritides is paralleled by the increasing severity of the disorder as it rises through this spectrum: more of the constituent components coincide in an individual (Table 2). The pathogenesis of these disorders, like non-acute graft rejection (19), should be dominated by cell mediated immune aggression. Circulating antibodies tend to be bystanders in the process. The pathological tempo of the constituent components often increases along with the severity of the syndrome disorder. Thus, in psoriasis, the prevalence of arthritis and iritis increases greatly in patients who have the

exfoliative and the pustular forms of the disease (26). On the basis of an extensive study, I believe that the meningo-encephalitis of multiple sclerosis should be regarded as an isolated component. It becomes expressed more severely in the meningo-encephalitis that is encountered in BS (unpublished) - nb, MS is a meningo-encephalitis (27).

The age incidences of these disorders are typical (28). The population incidences of the commoner conditions show that they begin and peak earlier than in the rarer disorders. The majority of components are consistently modulated by certain events, eg, menstrual exacerbation, second and third trimester quiescence, puerperal exacerbation, stress precipitation and, finally, amelioration of symptoms with steroid and immunosuppressive therapy. Note that NK cell activity and quantity directly matches this pattern (29).

Two other disorders have features to suggest that they might also be included amongst the (predominantly) auto-rejective disorders. These are sarcoidosis and systemic lupus erythematosis. Both have areas of clinical overlap with the sero-negative arthritides and SLE has a similar component structuring. Note that high turnover granulomas are a recognised consequence of many cell mediated immune reactions (30).

## Cancer

Broadly speaking it can be surmised that cancer follows:-

- an instantaneous triggering event (induction).
- changes in cell behaviour (promotion).
- a breakdown in surveillance (progression).

The events that lead affected cells into loss of growth control need not concern us in this article other than to point out that there is a final trigger, a `last straw' event frequently revolving around the protein p53 (31). This occurs in a single cell from which the cancer then `explodes'. A unifying early step is that a growth control gene is inappropriately transcribed (induction). But leave all this to one side for now. I will, instead, focus attention on the reasons for the body's failure to identify the miscreant cell and its progeny (progression). Before proceeding, note the stark contrast there is between the Hayflick limit of about 50 doublings (in cultures of healthy cells) and the apparent immortalisation of cell lines derived from many cancers. GJ communication is clearly important in the development of a cancer (32,33).

Two sorts of cancer are discernible:

- The first type is where inappropriate CAMs are used by the malignant cells to make junctional communication. Adjacent, healthy cells find it hard to communicate with them but the malignant cells make good communication with one other.
- The second type is where the cell becomes `immortalised'. This process depends on cell growth breaking free, by mutation, from a dependency on GJ communication. Normally, as the number of cell doublings approaches 50, GJ communication is progressively inhibited and cell reduplication is eventually abolished (34). Immortalisation coincides with freeing 50+doublings from this dependance on GJs but the cells now behave independently rather than as a tightly controlled colony. Malignancies that form distant metastases by haematogenous dissemination are almost invariably of this sort. They communicate little with each other through GJs.

Morphostatic surveillance fails when local conditions impair its efficiency. One cause is probably anergy. This leads to local depression of phagocyte surveillance. Anergy is necessary to limit the intense auto-rejection that the lymphocytic system could otherwise unleash (particulalry TH1 cells). Malignant cells that communicate with each other will probably not be identified as UHS by phagocytes that invade the substance of the tumour. Only at the interface between normal and malignant tissue will they identify the non-communicators. Normal cells will be attacked if the uropod attaches to a malignant cell or vice versa if the uropod attaches to a healthy cell. Where immortalised malignant cells escape detection it is probably because focal surveillance has been suppressed by anergy. This is originally induced by unrelated focal auto-rejection but has then become self perpetuating as attempted rejection of the tumour takes over. Phorbol

esters stabilise cells that break communication. They inhibit apoptosis by preventing a prolonged rise in intracellular calcium (35). In so doing, they may allow an otherwise correctly identified miscreant cell to survive where it should have been eliminated.

Cancer and infection with non-pathogenic or opportunistic organisms should be most prevalent when morphostatic surveillance is least effective. The cells making up an animal are highly regimented (there are around 10 to the 13th of them in man!). There must be intense cell co-operation to maintain such order within the ZDC's tissues. By implication alone, disruptive cells (dead, damaged, dying, mutated and those with disordered growth control) must be almost universally rejected and, indeed, it has long been clear that phagocytes do recognise malignant cells and remove them (36,37). The main attention here should be directed at those events that lead to the impairment and subsequent failure of this final phagocytic surveillance. Focal anergy is likely to be one of these events and may well be a major factor in the escape of malignant cells from surveillance.

In mammals, this impairment of surveillance should occur either at the extremes of life or following prolonged focal auto-rejection and its consequent anergy. In the elderly, the increasing impairment of immunity coupled with the heightened susceptibility of epithelium to various noxiae (and thus auto-rejection) may predispose to a high incidence of carcinomas. Focal anergy on its own (consequent upon intense auto-rejection) may be a major cause of the predilection that certain cancers have to strike young adult to middle aged patients (eg, lymphomas, focal cancers like colonic cancer in ulcerative colitis and testicular tumours following mumps (38,39)). In the very young there is a relative incapacity to reject tissue. It is worth noting, then, that the predisposition for epithelial cancers found in the elderly is not mirrored in the young. Cancers are relatively common in the very young and there is evidence to suggest that many regress before they reach clinical significance (40). Note that carcinoma-in-situ occurs more often than overt cancer, the abnormal cells tend either to be kept in check or are eliminated by lympho-monocytic cells.

Cancer is characterised by a failure of growth control. The affected cells revert to a form of behaviour more typical of embryonic cells - retrodifferentiation (41) - and they display various CAMs (integrins) that promote this invasive behaviour (42). Using a `reductio ad absurdam' argument these changes are more likely to happen when regeneration and/or proliferation are exuberant (eg, T-cells in lymphomas) rather than quiescent (eg, cartilage, neurones, macrophages). Note that lymphomas are relatively common in the years in which auto-rejection is most intense (16-45yrs) and also note that, in granulomatous disorders, lymphomas predominate over other cancers, perhaps because local tissue regeneration is impaired (43,44).

The rate at which malfunctional cells arise (for any reason) probably increases with age. The net effect of this will be to cause a diffuse increase in the multiple foci of auto-rejection and, consequently, a gradual summation of focal anergy. This will eventually lead to a systemic spill over of focal anergy - a saturation effect. Epithelium is the tissue most exposed to infection, noxiae, regeneration and, in consequence, an increased probability of genetic divergence. Foci of anergy will be very frequent in this tissue form and carcinomas should, consequently, be more prevalent than sarcomas. Once initiated, cancer will itself lead to auto-rejection and, in turn, increased focal anergy. Thus, it is likely that there exists a critical mass and growth rate above which surveillance is irreparably impaired and the cancerous process becomes self perpetuating (45). Progression may, therefore, occupy only a narrow interval, that occurs in the brief period immediately following the full transformation of cells into malignancy (the p53 "last straw"). Efficient surveillance is critical during this time "window". Note that macrophages observed in vitro are clearly able to recognise malignant cells as abnormal (36,37).

Now it is instructive to compare the age incidence profiles of various cancers with those of the auto-rejective disorders. However, before doing so it is important to establish which cancers are likely to flourish in the wake of intense auto-rejection (probable examples are lymphomas and testicular tumours (38,39,46)). These must be recognised as distinct from the commonest form of cancer (carcinoma) which seems to occur most frequently in the wake of an impairment in immune surveillance associated with aging. In general, these cancers have a steadily increasing incidence with age. Some cancers, particularly mesodermal malignancies, follow an incidence pattern showing a nadir in the middle years. It is interesting to note that the age

incidence pattern of acute leukaemia is an inversion of the age incidence pattern of the auto-rejective disorders (Figure 1). (See (46)).

It should now be clear that the lymphocytic system can have a dichotomous influence on cancer surveillance. While it may enhance the focal accumulation of phagocytic cells and thus aid the (auto-)rejection of aberrant cells, the more aggressively it does this, the more likely it is to precipitate the suppression of focal rejection in order to avert piecemeal self destruction. Indeed, in those animals that have evolved them, the possession of lymphocytes may have incurred an increased risk of cancer: cancer is relatively uncommon in invertebrates (47,48) and is relatively scarce in congenitally athymic mice (49,50) that have abundant aggressive phagocytes (51) and natural killer cells (52). It is interesting to note that in the animal kingdom there is an inverse relationship between the capacity to regenerate body form and the prevalence of cancer (53,54): and that carcinogens may induce supernumerary structures in lower phylae (eg, limbs) (55,56) .

Napolitano et al (57) report that tumour cells generally display less class I Mhc Ag at their surface than normal cells. They draw attention to the fact that, the more malignant the tumour is, the less class I Ag it expresses. They interpret this as a cause of the malignant behaviour. However, this could be interpreted as the cells expressing UHS status. Macrophages in vitro have little trouble in identifying malignant cells (36,37). It seems that some chance event is allowing the lymphocytic amplification system to become preoccupied with an inappropriately strong response to the "wrong" tissue Ags (macrophages latching their uropods onto cancerous cells seems a good bet). This, in turn, has intensified focal auto-aggression and focal anergy. The phagocytes' capacity to eliminate UHS (tumour) cells is thus impaired, permitting a (so far) dormant carcinoma-in-situ to grow to a critical mass where focal anergy will never subside: at this point, the focal impairment of phagocyte activity becomes irreversible and uncontrolled growth of the tumour takes over. This is consistent with the finding that tumour cells towards the centre of the tumour have a lower expression of class I Ags than tumour cells towards the outside (57). At the edges of the tumour, macrophage activity is likely to be much more active and successful in eliminating abnormal cells.

## Infection

Infection can be defined as the survival and proliferation of an organism, not descended from the originating zygote, within the tissue of the ZDC. The colony need only remove these cells if they interfere with its structure or function (though the only ones that don't interfere will probably be highly specialised commensals or symbionts).

Below I suggest four ways in which surveillance can be overcome:-

- The first form of infection occurs when an organism acquires the ability to interfere, agonistically or antagonistically, with the host's machinery for establishing intracellular sickness and/or cell identity. In dedicated pathogens, this interference will be an intrinsic feature of their pathogenicity (58). However, interference can evolve in the lifetime of an individual ZDC, leading to an idiosyncratic infection. Strategies based on species and tissue site identity can be cultured throughout the whole mass (surface mostly!) of a species and over its entire duration as a discrete species. The way in which foetal cells reaggregate into tissues rather than species (59,60) and the survival of skin transplants, from distant species, in nude mice (61) suggest that tissue site identities may remain similar in widely separated species. A variety of infectious organisms may be interfering with this tissue site identity (eg, streptococci (62) and staphylococci). Many organisms have a clear species specificity (eg, mycobacterium TB, bovine TB, avian TB etc, various plant infections (63)). Interference with individual (Mhc) identities (in homo sapiens) can only be evolved in a relatively short time (about 60-70yrs) and in a small mass (about 60-70kg) of which only a small proportion is epithelium. Should mimicry of personal identity develop, this will facilitate that organism's access to the ZDC's tissues and, once there, there will be a relative lack of "strange" processed peptide to attack. The resulting inflammatory response will, therefore, tend to concentrate its attention on tissue peptides common to both the organism and the host or just to the host. These self Ags will be selected as anchors for the subsequent lymphocyte accentuated inflammation, so leading to an

accelerated rejection of self tissues: Th1 cells will be mostly responsible. This kind of destructive attention to self is probably occurring in adjuvant arthritis (4,5). This disorder has clinical features closely reminiscent of the sero-negative arthritides and sarcoidosis (Table 1). It is likely, therefore, that a highly idiosyncratic interference, by an organism, with the personal identity mechanism is a common factor in the pathophysiology of the "auto-rejective disorders". Such disease will be precipitated by interference by the microbe with the host's identity machinery and this will probably evolve in the lifetime of the animal. In biological systems, things are rarely "black or white" so the relative blend of the common/consensus and the idiosyncratic/individual response to infection will probably vary in a spectral manner (Fig 2 in ref (1)). Note that bacteria that manage to invade and survive within the cytoplasm are the most likely to lead to auto-rejective disease (particularly microbes in macrophages - Th1 activation).

- Rejection will always be aimed at whatever is most clearly OTHS (strange). The amount of auto-rejection will increase with the angrification of phagocytes, especially when foreign (strange) OTHS is sparse. With the angrification of phagocytes, the level of HS identity that a cell must express to avoid attack will need to be raised. In consequence, many mildly compromised self cells will no longer remain immune from self attack.
- A second group of organisms, the viruses, foil surveillance by virtue of their small size, their sophisticated pathogenicity (there may be little spread across species) and their obligate intracellular niche. However, animal cells have ancient mechanisms, dating back to their unicellular origins, to survey and repair their own internal malfunction. As soon as an infected cell is sufficiently compromised it should register a malfunction and trigger apoptosis. (Pathogenic viruses frequently block apoptosis.) Failing this, infection will lead to uncontrolled cell death, inflammation and phagocyte interest. This will lead on to the aggressive activation of appropriate precursor lymphocyte clones. After an interval of 10-14 days an aggressive anamnestic response to various viral-peptide+Mhc-antigens will have developed. In the meantime, selected self Ags may be used to anchor a Tc and Th1 accelerated accumulation of phagocytes at the affected site whilst waiting for the emergence of a more specific anti-viral activity. Viruses are mostly "hit and run" infections: they are soon suppressed or cleared from the system and those that persist do so by remaining dormant within cells.)
- The third group are the opportunistic infections. Whilst these may interfere with the mechanics of tissue and species identification (64) most of their success is dependent on the depressions of focal surveillance that follow virus infections, burns, surgical incisions and trauma (& etc). Each of these noxiae lead to the auto-rejection of damaged and malfunctioning tissue with subsequent focal anergy (12). Probable examples of such opportunistic infections include bacterial tonsillitis, otitis, sinusitis, bronchitis, boils (65) and various wound infections.
- The last group are organisms that set out to subvert the immune response by creating a field of intense focal anergy. They do so by maximally stimulating focal inflammation with the object of inducing focal auto-rejection. Mycobacterium tuberculosis is the example that will be considered here though syphilis is certainly another.

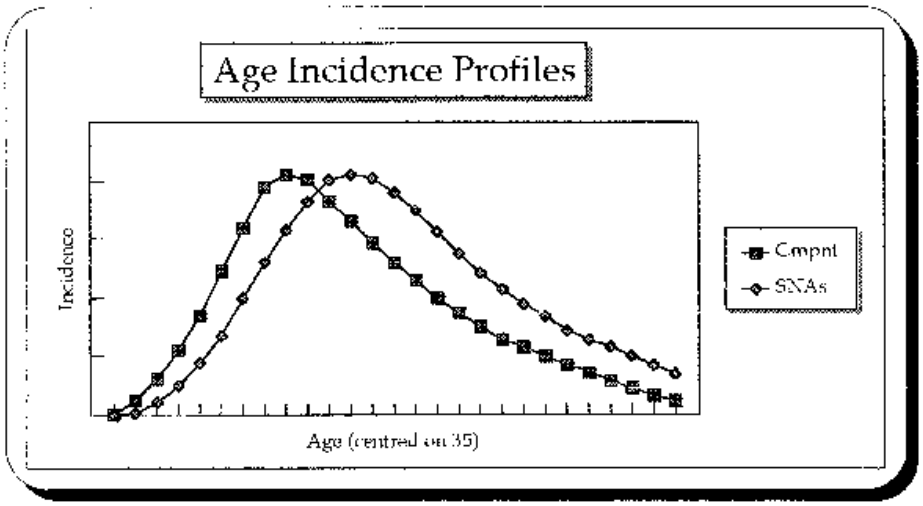
The properties of such an organism should include:
**poor** initial foreign antigenicity
**strong** attraction for macrophages (adjuvant attraction)
**good** resistance to initial destruction as evidenced by prolonged survival within macrophages

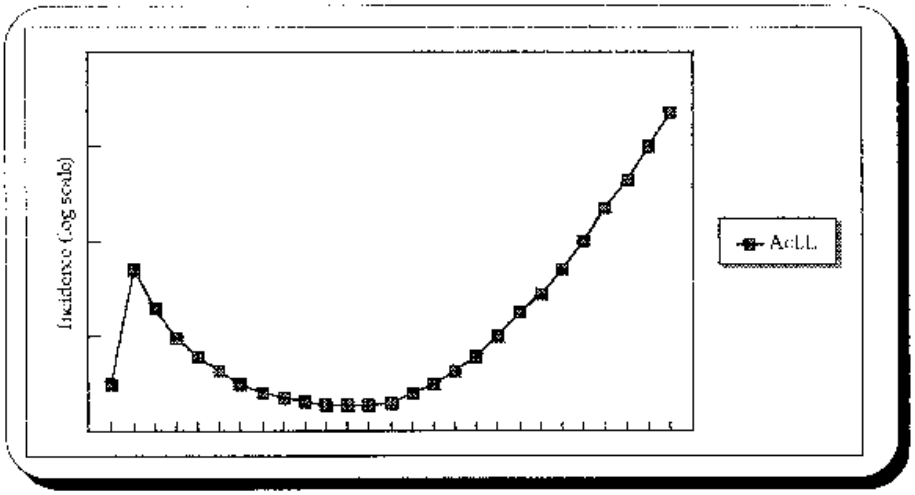
The result of these properties is that they lead to uncontrolled cell death in macrophages. Inflammation is provoked and Th1 cells are switched into aggression. This is followed by local auto-rejection and focal anergy. This leads to a field of surveillance impairment in which the bacterium flourishes, feeding upon the cell debris that is left in the wake of auto-destruction (66,67). Clinical mimicry of the auto-rejective disorders should be discernible. This, in fact, can be seen and is most noticeable in the middle years, an observation that is in keeping with the auto-rejective disorders (Table 3). When tuberculosis occurs outside these middle years it is different in its clinical expression. The lesions now tend to be miliary and disseminated and occur without the same intense tissue destruction. The pattern now resembles miliary cancer. So, at the extremes of life TB appears

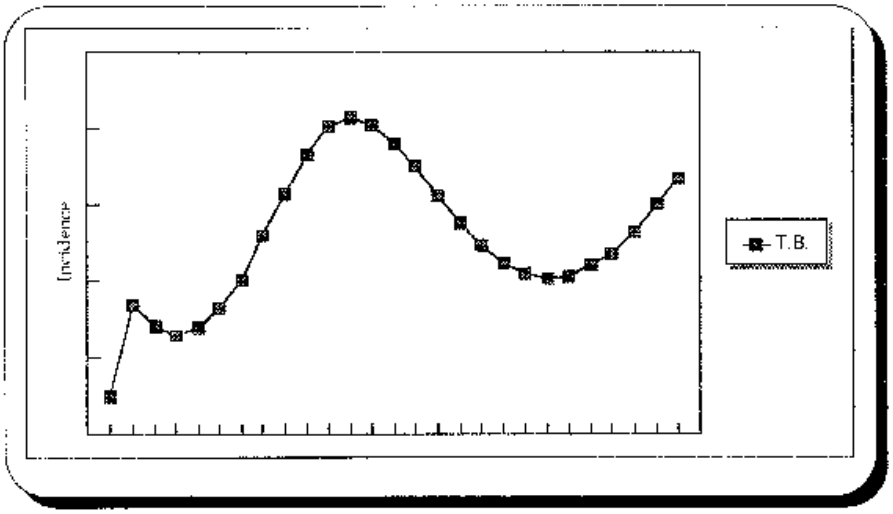
to be acting more like an opportunistic infection. The overall age incidence pattern of TB can be regarded as a combination of the auto-rejective and the cancer type age incidence (Figure 1) (*Nb, components and SNAs at the top, acute lymphatic leukaemia in middle and TB at the bottom.*)

## Table 3: the parallels between TB and the sero-negative arthritides

| TUBERCULOSIS | SERO-NEGATIVE ARTHRITIDES |
|---|---|
| **ORAL ULCERS (up to 20% affected at autopsy)** | **RAU** |
| **EPIDIDYMO-ORCHITIS** | **BS Sa** |
| **ERYTHEMA-NODOSUM** | **BS RS UC CD Sa** |
| **INTESTINAL DISEASE with fistulation, resembling CD** | **BS Crohn's disease [78]** |
| **ARTHROPATHY**<br>**a) mild non-bacterial**<br>**b) bacterial involving SI joints, hips, knees, shoulders in descending order of prevalence**<br>**c) Pott's disease of the spine**<br>**d) TB tenosynovitis** | <br>**All**<br>**All have the same predilection for joints but no bacterial infection**<br>**AS may masquerade as Pott's disease [79]**<br>**RS BS** |
| **PLEURO-PERICARDO-PERITONITIS** | **SLE (all) & heart only in BS UC and Sa** |
| **ENCEPHALO-MYELITIS[80]** | **RS BS Sa SLE MS UC** |
| **APICAL PULMONARY CAVITATION** | **AS produces a clinically identical picture without TB bacillus infection [81]** |
| **LUPUS VULGARIS** | **Sa Discoid Lupus** |
| **OPHTHALMITIS**<br>**a) phlyctenular conjunctivitis**<br>**b) periphlebitis retinae** | <br>**All associated with conjunctivitis**<br>**BS Sa** |
| **ADDISON'S DISEASE** | **Idiopathic (auto-rejective) Addison's** |
| **FAMILIAL AGGREGATION of cases and genetic** | **All predisposed** |
| **STRESS PRECIPITATION and emotional factors [82]** | **Most** |
| **STEROID REPONSE Paradoxical initial improvement. Steroids and immunosuppressives lead to improvement of X-rays and amelioration of the acute features** | **All respond** |




## Auto-immune disorders

In previous articles, where immune surveillance has been discussed, it has been suggested that cancer and auto-immunity might be expected to represent opposite poles of surveillance efficiency (68). However, this auto-immune title does not automatically imply auto-rejection. These disorders tend to result in one of two disturbances. The first is an interference with functional membrane molecules by the attachment of auto-antibodies (eg, Graves disease, myaesthenia gravis). The second is tissue destruction but this is often centred predominantly around (non-cellular) connective tissues (the "collagenoses") and is apparently exacerbated,

if not caused, by an excessive auto-antibody production and the widespread deposition of Ab/Ag immune complexes. Here, cell destruction may be partly secondary to the activation of macrophages in the locality of this connective tissue. Towards the end of life auto-immune disorders are relatively more common than the sero-negative arthritides. Their prevalence at these older ages may possibly be exacerbated by a parallel decline in the efficiency with which phagocytes clear tissue debris. This, in turn, could lead to enhanced auto-antibody (immunoglobulin) production. The latter certainly appears to be a feature of many diseases causing widespread anergy, eg, sarcoidosis (69).

## Summary

This article has expanded the explanation of the `Clinical Consequences' section in `Morphostasis and Immunity' (1). It augments and strengthens the arguments proposed in both this article and its sequel, `Morphostasis: an evolving perspective'. It also paves the way for a further article, `The neurology of Behçet's syndrome' that expands the idea that MS represents the component form of the meningo-encephalomeyelitis that is seen, in severer form, in Behçet's syndrome. This, in its turn, augments and strengthens the arguments presented in the three preceding articles.

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