MORPHOSTASIS & IMMUNITY

PART 1: THE BASIC PHILOSOPHY

INTRODUCTION

As I look back to my textbook introduction to immunology, I can now analyse some of the impressions I absorbed concerning its presentation. There was always an obligatory section in the text referring to Metchnikov and paying lip service to the fundamental importance of phagocytes and non-specific immunity. Then, with an almost indecent haste, the text would return to the real "meat" of immunology, the function of the immunoglobulins and lymphocytes. Now life without lymphocytes may be very awkward but without phagocytes it's impossible. So why were the sections on phagocytic recognition and discrimination so disproportionately sparse in contrast to this cell's importance? The answers probably lie in the differences between immunity and immunology. Immunology is the science of immunity: that is, it concerns what is known of it. The best understood areas are either those that are relatively easy to investigate or those that attract most interest. Inevitably, immunology could cast a distorting perspective on immunity and we need to accept that this distortion could be severe.

The term immunity doesn't help to clear distortion. We know, for sure, that protection from re-infection is but a single facet of that subject we continue to regard under the title "immunology". Jan Klein has titled his recent textbook "Immunology: the science of self/non-self discrimination" and I regard this as an important improvement in definition. But I would, nevertheless, take his definition one step further and describe it as "the science of healthy self (HS)/other than healthy self (OTHS) discrimination": but now I am referring to HS/OTHS cells. To accept this redefinition we need to assume that an individual cell has mechanisms to monitor its own continuing good health and, whilst this remains good, to present clear indication of this healthy self status at its surface. A corollary of this assumption is that the immune system observes a relative horror autotoxicus to HS cells. By combining this surveillance for OTHS (and its subsequent demolition) with tissue regeneration we can now promote the concept of immunity to morphostasis.

To restate a fundamental point, life without lymphocytes is awkward but without phagocytes it's impossible. Lymphocytes are, therefore, both functionally and phylogenetically "icing for the phagocytic cake". They serve only to sharpen phagocyte based discrimination of OTHS from HS. It is, thus, with morphostasis (and regeneration related morphogenesis) that I shall begin my discussion. This looks back to the evolutionary origins of those systems designed to maintain animal form in spite of its hostile environment. My style will be unashamedly conclusory. Discussion in any depth will have to be presented elsewhere.

To understand the following arguments, let's look at some basic metazoan requirements. The first mechanistic hurdles for multi-cellularity must have been the twin problems of morphostasis and morphogenesis.

Morphogenesis: the generation of animal form beginning with the zygote and culminating in the complex organisation of the fully developed zygote derived clone.

Morphostasis: the maintenance of animal form despite environmental insults and despite the onset of disorder in a varying proportion of the zygote derived clone.

The cells of all multicellulates co-operate with each other and will either ignore or attack non-self: it is clear that some form of cell to cell recognition is occurring. I have envisaged three basic forms of recognition that I consider to be essential: the recognition of:-

1. species gametes by each other (sexual recognition)
2. zygote derived cells by dedicated surveillance cells (personal recognition: the horror autotoxicus principle)
3. organ cells by each other (tissue and site recognition)

Now it's important that HS cells should be distinguishable from both unhealthy self and clearly non-self cells/organisms (collectively OTHS). This can be most easily achieved by displaying markers of self on healthy cells and either evolving mechanisms that encourage their withdrawal on malfunction or that deliberately display unhealthy self markers - or both. I will argue that much evidence points towards the cell's use of surface markers or "flags" (forthwith ligands) for this sort of recognition and this implies there are also dedicated receptors.

IDENTITY

There are many examples of cell recognition. For instance, it is reported in bacterial agglutination and conjugation *(1)*, in slime moulds *(2)*, in sponges *(3)*, in other primitive multicellulates *(4)*, in plants *(5)*, in vertebrates and (the thoroughly investigated example) in homeotherms *(6)*. Recognition is a basic biological function occurring in enzymes, restriction endonucleases and in protozoans (in which organelle transplants are rejected when foreign *(7)*) . In embryogenesis there is a continuing recognition of cell position and destination whilst the experiments on organ cell reaggregation point clearly to tissue site recognition *(8)*. Cell homing is another instance of specific recognition: it is seen when injected marrow cells search out the host marrow and when plasma cells from gut associated lymphoid tissue home back to the gut wall *(9)*.

THE GROUND RULES

All this leads to a number of conclusions:-

1. To maintain tissue homeostasis (morphostasis) the zygote derived colony must distinguish HS from all else. Unhealthy self cells and clearly non-self cells must be identifiable. There are two ways to approach this problem: the first is to mark all HS cells with a set of membrane ligands that are peculiar to the individual and/or the species; the second, is to evolve a mechanism of remembering all possible unhealthy self and non-self (ie, OTHS) components. Clearly, the second way is too complex to be a reasonable solution in simple animals though, as I will observe later, it may become a useful adjunct to (or substitute for) phagocytic OTHS identification in more complex animals. Thus, even in the earliest multicellulates, we should expect to see a horror autotoxicus to HS cells.
2. Pathogens, virtually by definition, are specialised for invasion of their chosen host. An obvious ruse for gaining entry into the host is to interfere with the normal methods of discrimination and one way of achieving this is by mimicry of identity. By doing this, these pathogens ensure a preferential entry into the host's zygote derived colony. As an example, antibodies raised to plant tissues cross react with their pathogens *(rf)* suggesting that mimicry may be operating.
3. For morphogenesis to be regularly reproducible, it must use a standard and invariable set of identities and many of these are likely to be ligands. However, this opens the way for the evolution of pathogen mimicry so, in evolving metazoans, a system was needed that could create an independent set of differing (pleomorphic) personal identities within a population. These could then be used as a second reference, particularly in areas where tissue inflammation occurred in the wake of cell malfunction.
4. Cell malfunction needs to be identified within and by the cell in which it originates or, at least, by this cell's immediate neighbours. This could be done with both an active (internal) surveillance system and a failsafe mechanism. Thus, damaged, infected, mutated, ectopic and inappropriately behaved cells should all be declared by the release of inflammatory mediators and the subsequent withdrawal of HS ligands (or the expression of unhealthy self ligands). We require no large mechanistic jumps to explain all this for it is already generally assumed that other cells of identical genetic origin make a similar decision (phagocytes and lymphocytes).
5. The obvious cells to act as "law enforcers" are the phagocytes and the obvious source of the zygote derived cell's HS ligands are major histocompatibility complex (Mhc) products. Phagocytes have as their brief, the task of ridding the body of OTHS whilst still observing a relative horror autotoxicus to HS. It seems to me that polymorphs rely (almost?) exclusively on class III ligands for their discriminatory ability whilst macrophages will probably prove able to use more sophisticated methods: in the first place they will be most aggressive to cells failing to display class III ligands and

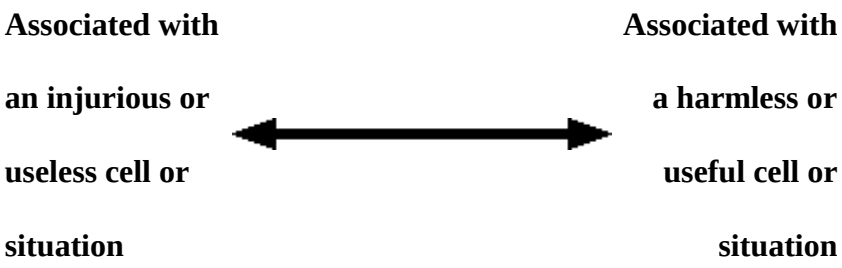
then as the macrophages become progressively angrier, to cells also failing to display appropriate class I ligands. (I have ascribed class III products a ligand function here: this will be clarified later.)

6. So, I have developed the concept that there are two broad groups of cells, somatic and phagocytic. The somatic cells organise tissue generation and regeneration around a standard set of ligands: phagocytes, once invited in amongst somatic cells, will preferentially attack cells failing to display HS ligands. The latter are based on a pleomorphic set of Mhc encoded ligands. Note that phagocytes are not required to scurry around searching for all OTHS events. It is the somatic cells that "report" offences by releasing chemotaxins. Then phagocytes, like policemen, are summoned to the scene of the crime.

FUNCTIONAL ASPECTS

Neither HS identity nor phagocyte aggressiveness are likely to be absolute "all" or "nothing" qualities. This is already evident in phagocytes where aggression is increased by lymphokines, the Fc fragments of Ab/Ag complexes and various complement components. Healthy self identity is also likely to be graded: it should be strongest in young and healthy cells whilst weaker in aging or malfunctioning cells. Thus, whilst the fate of a cell may depend upon its own (or its neighbours) perception of its health, the threshold at which such rejection occurs will ultimately depend upon phagocyte aggressiveness. So, cell destruction will increase with rising phagocyte aggression and decrease with the intensity of healthy self identity.

So how are lymphocytes functioning as the "icing" for the phagocytic "cake"? They are being used as a means of enhancing the efficiency of phagocytic discrimination of OTHS from HS. They do this in both an aggressive (Th - helper) and a horror autotoxicus (Ts - suppressor) mode. Precursor lymphocytes seem to acquire their paratope (Ag recognition site) spontaneously. On meeting their appropriate epitope (the Ag itself) they are expanded into clones of aggressor or suppressor T cells. Epitopes are thus categorised into a spectrum that lies somewhere along the following scale:



This categorisation is made on the basis of the context in which the epitope is commonly met. If encountered predominantly in a HS context, tolerance will be favoured, and if encountered predominantly in an OTHS (inflammatory) context then aggression will be favoured. Freshly occurring OTHS events that have been previously encountered and have already provoked an aggressive T-cell response will lead to a greatly accelerated phagocytic attack. Most self antigens will be well tolerated, though, if they are normally "hidden" behind tight endothelial cell junctions (immunologically privileged sites), they may provoke an aggressive response more readily than other self antigens when they are exposed during periods of unusually intense inflammation (eg, sympathetic ophthalmia). On the other hand, foreign Ag is most likely to be met in an OTHS context and the first encounter will nearly always provoke an aggressive response.

Note that phagocytes (and APCs) are ideally placed to act as generals commanding all other immune cell troops. When these cells aren't priming T-cells by presenting Ag in the context of class II Mhc products, they are still active in delivering T-cells with their aggressive "kick" through IL-1 and IL-2.

When aggressive lymphocytes or immunoglobulins meet their epitope, they release factors that speed up and focus phagocyte accumulation and then switch these cells into an "angry" state. Except in the case of Tc cells, the final decision as to whether to attack or leave cells that are marked with this epitope is (usually) still a phagocytic decision and this may remain influenced by the HS status of the cells. However, the angrification of phagocytes means that the threshold of acceptable HS is raised: so as macrophages become angrier, progressively fewer HS cells will escape attack. Tc cells are capable of delivering an independent

cell attack but, as will be seen later, such aggressors are recognising cells that are indisputable undesirables anyway.

Now every animal is a zygote derived colony of highly co-operating cells that is intent upon gene propagation to ensure its immortality. Genetic exchanges between individuals is a more or less universal prerequisite for the rejuvenation of co-operating cell lines. It probably represents a form of genetic repair (fidelity conservation). Whatever, it is clear that clonal expansion of cell cultures from animals is limited (50 doublings in man *(rf)*). This restriction is only placed on co-operating cell lines *(rf)* as longevity is dramatically extended in cell cultures that no longer observe contact inhibition *(rf)*.

The fates of individual cells in an animal are only important in that neither their death nor their survival should endanger reproduction. So, auto-rejection of aberrant cells is a logical method of housekeeping and cell deficits are, self evidently, renewable by tissue regeneration (a resurgence of morphogenesis). However, if an inflammatory process is particularly strong and clearly foreign antigen is sparse, an aggressive lymphocyte mediated response may be induced against Ags peculiar to the affected tissues (eg, in burns *(rf)* and adjuvant arthritis*(rf)*). The acceleration in tissue turnover may get out of hand leading to excessive auto-rejection (see below). Auto-rejection may be of use in focusing phagocyte attention into requisite areas pending the emergence of a more specific response to foreign Ag (eg, say, pharyngeal antigen in a viral pharyngitis).

This proposed mechanism for concentrating phagocyte attention is a positive feedback and, without constraint, it could lead to catastrophic auto-rejection. Failsafe mechanisms must exist that can be brought into play if tissue destruction becomes excessive. This could happen at any or all of the following points:-

(a) inhibition of phagocyte ingression (chemotaxis)

(b) inhibition of phagocyte aggression

(c) inhibition of further aggressive lymphocyte activation

(d) a tightening of endothelial cell junctions.

This failsafe must be primarily focal though a systemic spill-over of its effects may be expected. This is possibly, in part, the reason for the many observations of anergy noted in such diseases as TB and sarcoidosis. There is certainly some evidence that anergy is expressed more intensely at the local rather than a systemic level *(rf)*.

It seems likely that the rate at which generation and regeneration can proceed will be limited. Since these are essentially similar (morphogenetic) processes, auto-rejection must be relatively curtailed in fast growing animals so that growth retardation is avoided. Put another way, the luxury of extensive auto-rejection, as part of a morphostatic technique, can only be fully afforded in adult animals. Thus, in growing animals, those mechanisms that initiate and accelerate rejection (of all kinds) need to be less fierce than in adults. Thus there should be a moderation of aggressive instructions to lymphocytes leading to a reduced intensity of cell mediated immunity and a reduced production of those IgGs that would be capable of reaching the extracellular spaces even when there is no inflammation. The result of all this is to enhance immunological tolerance in the very young animal. This impairment of rejection is apparent in the neonate in which the tolerance of grafts is much enhanced: the neonate can also tolerate severe cerebral ischaemia that, in adults, would cause extensive tissue necrosis (an auto-rejective event). This relative incapacity to auto-reject is also a protection against certain dangerous sequelae to virus infections. The latter often produce their most severe effects in adults [eg, infectious mononucleosis, infectious hepatitis (both often mere URTIs in young children), mumps, chicken pox and measles; and an example from the mouse, lymphochoriomeningitis *(rf)*] . The sequelae (arthritis, jaundice, meningitis, orchitis etc.) can be prevented or ameliorated by immunosuppressives or steroids. Immunological immaturity, by this view, is a misnomer for the infants immune system is likely to be perfectly adapted for optimal function.

The age incidence patterns of many disorders have been shown, by Burch *(rf)*, to be mathematically predictable. He used a stochastic approach and the same principles may be adapted to the present hypothesis though we must now assume that the proportion of cells that are, at any moment, becoming malfunctional tends to increase as the animal ages. This acceleration may be fuelled by infection and by genetic divergence occurring in the course of successive cell divisions. Epithelium is the tissue most exposed to infection and damage so it should also be subject to the greatest amount of auto-rejection and anergy and also have the highest cell turnover. The consequence of these assumptions is that there will be a progressive impairment of immune functions as the animal ages; especially those concerned with tissue rejection (predominantly cell mediated immune reactions) *(rf)*.

SUMMARY

In summary, the concept of horror autotoxicus has been rejuvenated but redefined and so, incidentally, has the concept of immunological surveillance: but it is for all malfunctioning cells and not just for neoplasia. Indeed, the evolution of the lymphocytic system may have occurred at the expense of a heightened prevalence of cancer (see below).

The remainder of this article will be concerned with the way that these principles can be extrapolated into the pathophysiology of a number of disease states.

PART 2: THE CLINICAL CONSEQUENCES

AUTO-REJECTIVE DISORDERS

A consequence of the preceding observations is that the intensity of auto-rejection is going to be dependant upon age. It will be at its most aggressive in the 16 to 45 age range. Initiation of auto-rejection is suppressed in the very young *(rf)* and its execution becomes impaired in the elderly *(rf)*. Thus, a disease manifesting itself by extensive auto-rejection will be most likely to occur in this age range (figure 2). One likely cause of such a disorder is the mimicry, by micro-organisms, of the host's identity profiles since this will allow them easier access to the tissues and the cytoplasm. Damaged cells should signal malfunction but, in the absence of clearly foreign antigen, auto-rejection based on self Ags will ensue and this will not necessarily remain confined to the initiating site. Whipple's disease may be an extreme example of this sort of disease (nb, the idiosyncratic infection *(rf)* and familial aggregation of cases *(rf)*).

Note that virtually all disease should have an autorejective element even if this is clinically limited to an increased tissue turnover.

The microbial flora colonising epithelial surfaces present a special hazard. It is recognised that bacteria have evolved the ability to selectively bind to cells in particular sites *(rf)*. Having achieved this it is very likely that they will also have evolved closer mimicry of the host's identity profiles (especially tissue and site ligands). Access to tissues during periods of surveillance depression should, in consequence, be easier (eg, after virus infections, burns and other tissue damage). The clinical pattern and incidence of such auto-rejective disease should be definable from basic principle: compatibility of organ transplants ranges from a common slight compatibility to a rare complete compatibility *(rf)*. When this principle is extrapolated to microbial mimicry, one would expect to find minor mimicry often and extreme mimicry rarely. The seronegative arthritides and their component complications show just this sort of structuring (table 1). Their clinical pattern can be summed up in an axiom:-

The severity of disease in any one patient (isolated component through to syndrome complex) is inversely proportional to its incidence in the population and directly proportional to the number of components found in association with one another.

For example, recurrent aphthous ulceration (RAU) occurs in 5% of the population, oro-genital ulceration in 0.5% or less and Behçet’s syndrome in 0.0001%. With increasing severity of the disorders there is increasing clinical overlap as more of the components occur together. Such autorejection will be dominated

by cell mediated immune aggression as it is in non-acute graft rejection *(rf)*. The pathological tempo of the components also increases with severity of the syndrome disorder. Thus, in psoriasis, the incidence of arthritis and iritis increases greatly in the exfoliative and the pustular forms of the disease *(rf)*. On the basis of a personal study of the world literature on neurological Behçet's syndrome (BS) (unpublished) I believe that multiple sclerosis should be regarded as the component form of the meningo-encephalitis seen with BS (nb, MS is a meningo-encephalitis *(rf)*).

The age incidences of these disorders are typical *(rf)*. The commoner conditions begin and peak earlier than the rarer disorders. In the majority of components there is evidence of constant modulation by specific factors: menstrual exacerbation, second and third trimester quiescence, puerperal exacerbation, stress precipitation and, finally, amelioration of disease activity with steroid and immunosuppressive therapy.

At least two further disorders have features that suggest that they should be included amongst the predominantly auto-rejective disorders: sarcoidosis and systemic lupus erythematosis. Both of these have areas of clinical overlap with the sero-negative arthritides and SLE shows similar component structuring. (nb, high turnover granulomas are probably the result of a cell mediated immune reaction *(rf)*).

CANCER

Broadly speaking it can be stated that cancer follows:-

(a) a triggering event (induction)

(b) a breakdown in surveillance (promotion)

Opportunistic infections and cancer should be most prevalent when surveillance is least effective. In mammals, this will (generally) be at the extremes of life. Focal anergy consequent upon intense auto-rejective disorders may contribute to a raised incidence of cancers in the middle years (eg, lymphomas and focal cancers like colonic cancer in ulcerative colitis). In the elderly, increasing impairment of immunity coupled with the heightened susceptibility of epithelium to various noxiae, and thus auto-rejection, will predispose to a high incidence of carcinomas. In the very young, in whom auto-aggression is tardily initiated, there should be no comparable predisposition to epithelial cancers. Cancers are relatively common in the very young and there is evidence to suggest that many regress before reaching clinical significance *(rf)*.

Cancer is characterised by disturbed growth control and a reversion to an embryonic cell behaviour (retrodifferentiation *(rf)*). These conditions seem most likely to occur when regeneration and/or proliferation (eg, T-cells in 1ymphomas) are exuberant. There is an inverse relationship between, regenerative capacity and cancer in the animal kingdom *(rf,rf)* and it is worth noting that carcinogens may induce supernumerary structures (eg, limbs) in lower phylae *(rf,rf)*. Note that lymphomas will be relatively common in the years in which auto-rejection can become intense (16-45yrs) and also note that lymphomas will predominate over other cancers in granulomatous disorders since local regeneration is impaired *(rf,rf)*.

Since the rate at which cells become malfunctional probably increases with age, the net effect will be to cause a diffuse increase in the foci of auto-rejection and, consequently, a gradual summation of the systemic spill-over of focal anergy. Epithelial tissue will be most exposed to infection, noxiae, regeneration and an increased probability of genetic divergence so foci of anergy will be very frequent in these tissues and cancers consequently more prevalent than sarcomas. Once initiated, cancers will themselves lead to auto-rejection and, in turn, increased focal anergy *(rf)*. Thus, it is likely that there exists a critical mass and growth rate above which surveillance is irreparably impaired and cancer becomes self perpetuating.

The age incidence of cancer can now be compared to that of the auto-rejective disorders. Before doing so it is important to distinguish those cancers likely to occur in the wake of intense auto-rejection (as examples, lymphomas and, perhaps, testicular tumours *(rf,rf)*) from those occurring due to age related changes in immune function. Those due to the latter can now be seen to occur least frequently in the middle years and follow an incidence pattern similar to acute leukaemia (figure 2).

It should now be apparent that lymphocytes can have a dichotomous effect on cancer surveillance: whilst they may improve phagocyte accumulation and the auto-rejection of aberrant cells, the efficiency with which they do this also demands a protective negation of focal surveillance to avoid self destruction. Indeed, the evolution of lymphocytes may have occurred at the expense of an increased risk of cancer. The latter is relatively uncommon in primitive animals *(rf,rf)* and is scarce in congenitally athymic mice *(rf,rf)* that have abundant aggressive phagocytes *(rf)* and natural killer cells *(rf)*.

INFECTION

Infection occurs when an organism, not descended from the host's zygote, survives and proliferates within the host's cell colony. I have categorised four distinct ways in which surveillance could be overcome:-

1. The first form of infection occurs when an organism acquires some mimicry of its host's identity. Species and tissue site identity can be cultured throughout the whole mass (surface actually!) of a species and over its entire duration as a discrete species. Such specificity is clearly evident in a variety of infections (eg, streptococcal infections *(rf)*, mycobacterium TB, bovine TB, avian TB etc, and in plant infections *(rf)*). Personal identity can only be mimicked in a short span of time (about 60-70yrs in man) and in a small mass (60-70kg). If mimicry does develop, it will permit an easier access to the tissues and there will be a relative paucity of clearly foreign antigen. Tissue antigens common to both the organism and the host will be utilised leading to increased rejection of self tissues. Such self destruction is seen in adjuvant arthritis *(rf)* that produces clinical features similar to the sero-negative arthritides and sarcoidosis (table 2). (This first form of infection has already been considered under the title "auto-rejective disorders".)
2. A second group of organisms manage to foil surveillance by virtue of their small size and obligate intracellular existence. The organisms of this group are the viruses. As soon as an infected cell is sufficiently compromised it should signal a malfunction, so triggering inflammation and phagocyte attention (particularly macrophages) and this will lead to activation of an appropriate precursor lymphocyte clone. After an interval of 10-14 days a strong anamnestic response to viral antigen will have developed. In the meantime, selected auto-antibodies may be used to enhance phagocyte accumulation at the affected site until the specific anti-viral Ab response is established.
3. The third group are the opportunistic infections. These may also use mimicry but now rely almost exclusively on the mimicry of site and species identity *(rf)*. Their ploy is to use the depressions of focal surveillance that follow virus infections, burns, surgical incisions and trauma (etc.). Each of these leads to auto-rejection of damaged and malfunctioning tissue with consequent focal anergy *(rf)*. Examples of such opportunistic infections include tonsillitis, otitis, sinusitis, bronchitis and various wound infections.
4. The last group are those organisms that can deliberately induce their own field of surveillance depression by maximally stimulating focal auto-rejection. Mycobacterium TB is the prime example and will be considered here though syphilis is another. The properties of such an organism should include:- (i) poor foreign antigenicity; (ii) a strong attraction for macrophages (adjuvant attraction); (iii) a good resistance to initial destruction as evidenced by prolonged survival within macrophages. The result will be intense focal auto-rejection (like the adjuvant arthritis response) and, in consequence, focal anergy. This will lead to a field of surveillance impairment in which the bacterium may flourish upon the cell debris evoked by the auto-rejection. Clinical mimicry of the autorejective disorders should be apparent: this does occur and is most noticeable in the middle years, in keeping with the auto-rejective disorders (table 3). When tuberculosis occurs outside these middle years, it is accordingly different in its clinical expression. The lesions tend to be miliary and disseminated without intense tissue destruction. Instead, the pattern resembles miliary cancer. Therefore, at these ages, it appears to be acting more like an opportunistic infection. The overall age incidence of TB can now be regarded as a combination of the auto-rejective and the cancer type age incidence (figure 2).

SEX ORGAN MORPHOSTASIS

Immune surveillance, auto-rejection and tissue regeneration combine to maintain general tissue homeostasis (morphostasis). The rates of tissue destruction and regeneration are modulated by corticosteroids. Sex hormones may, therefore, be regarded as modulators of morphostasis in sexual organs. As these hormones are varyingly active at different ages, they probably alter the age incidence patterns of sex organ cancers from those of general cancers. So, it should not be assumed that the former are typically affected by age related changes in general surveillance efficiency.

AUTO-IMMUNE DISORDERS

Several articles discussing immune surveillance have suggested that cancer and auto-immunity should represent opposite poles of surveillance efficiency. However, the auto-immune title does not imply auto-rejection. These disorders, rather than being primarily auto-rejective, result in one of two basic functional disturbances. The first is a disturbance of membrane function by the attachment of autoantibodies (eg, Graves disease, myaesthenia gravis) and the second is a tissue destruction that is apparently centred predominantly around (non-cellular) connective tissues (the "collagenoses"). Here, cell destruction is possibly secondary to the activation of macrophages in the locality of this connective tissue. The extent of damage and the clinical prevalence of the "collagenoses" is, perhaps, understandable when it is remembered that connective tissues constitute a quarter of all body protein. Auto-immune disorders are relatively common towards the end of life and their incidence here is possibly exacerbated by the gradual decline in the efficiency of phagocytes in clearing tissue debris.

CONCLUSION

This hypothesis has re-examined the perception of immune function and suggested its major function is morphostasis. The lymphocyte's perceived role has been relegated to one of subservience with the phagocytes acting as the main orchestrators of morphostasis. Morphostasis has evolved to prevent the degradation of animal form as a consequence of its incessant bombardment from a hostile environment.

To summarise; morphostasis begins with the location of Other Than Healthy Self. Phagocytes are particularly concerned with identifying this condition: lymphocytes and their antibodies are so organised as to accelerate the rejection of OTHS. Auto-rejection is extensively used to restore tissue homeostasis and can range from the simple elimination of aging cells (basal tissue turnover) to the kind of accelerated auto-rejection such as is seen in the sero-negative arthritides and certain infections (like TB). Organism aging probably occurs because gradual genetic divergence makes it progressively more difficult to hold the zygote derived colony together.

Whilst the argument presented may be simplistic, I believe that it provides a good framework for refinement.

Endnote:

Apart from replacing many "which"s with "that"s and fixing the spelling mistakes, this is the same as a printout dated November 1984. The references were not completed.

Figure 1	Not included
Figure 2	combination of the Sero Negative Arthritides and cancer age incidences
Table 1	Sero Negative Arthritides and components
Table 2	Adjuvant arthritis components
Table 3	Clinical mimicry SNAs and TB

These Figures and tables were probably similar to those used in Clinical morphostasis and it is these diagrams and tables that are included below.

Figure 2

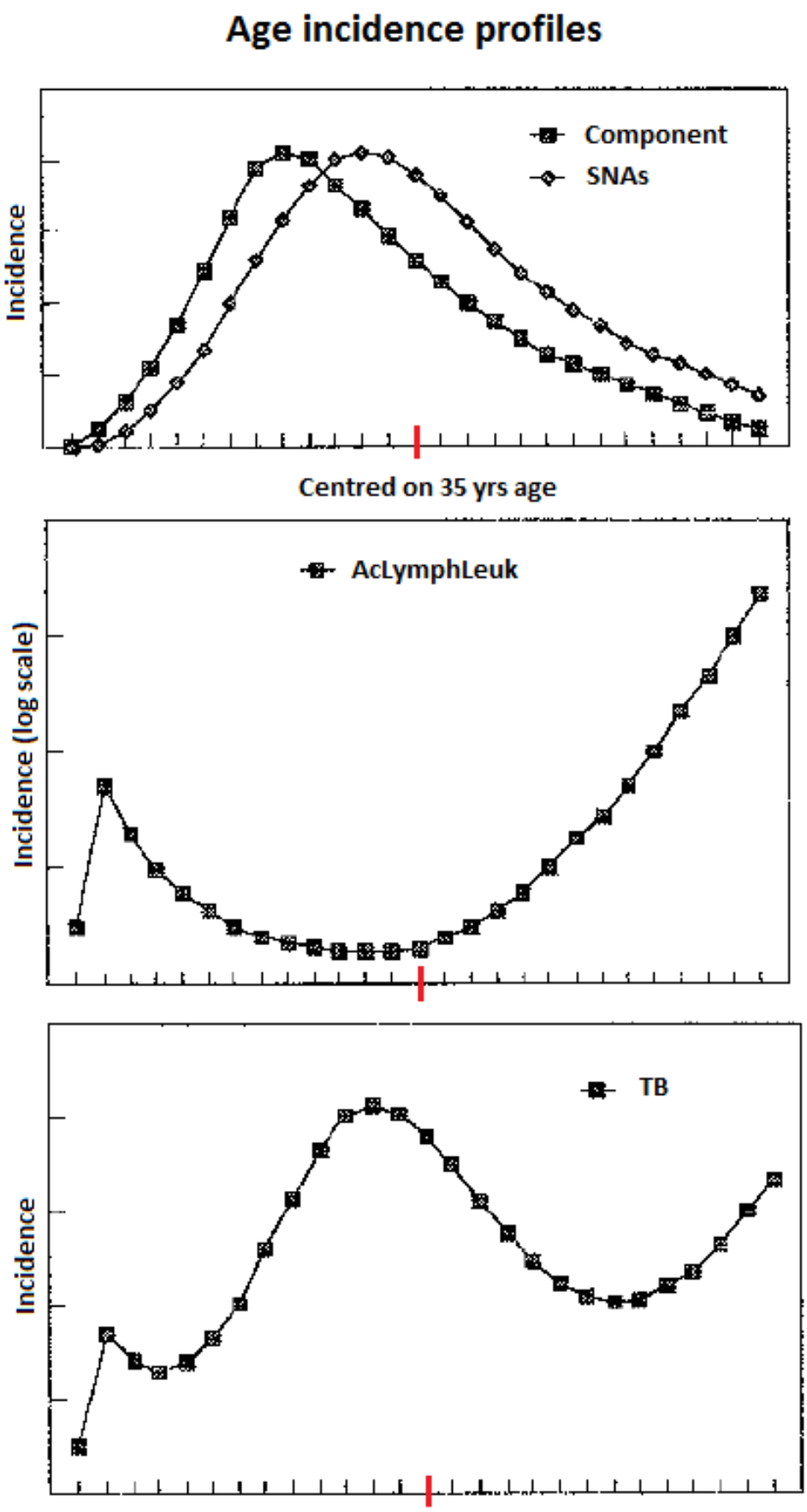

Age incidence profiles
Component
SNAs
Incidence
Centred on 35 yrs age
AcLymphLeuk
Incidence (log scale)
TB
Incidence

Table 1

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

Table 2 Components 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

Table 3 Parallels between SNAs and TB

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 a) mild non-bacterial b) bacterial involving SI joints, hips, knees, shoulders in descending order of prevalence c) Pott's disease of the spine d) TB tenosynovitis	 All All have the same predilection for joints but no bacterial infection AS may masquerade as Pott's disease [79] 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 a) phlyctenular conjunctivitis b) periphlebitis retinae	 All associated with conjunctivitis 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