Version 4

Systemic lupus erythematosus in African-American Women: Immune cognitive modules, autoimmune disease, and pathogenic social hierarchy

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Abstract

Examining elevated rates of systemic lupus erythematosus in African-American women from the perspective of the emerging theory of immune cognition suggests the disease constitutes an internalized physiological image of external patterns of psychosocial stress, a 'pathogenic social hierarchy' involving the synergism of racism and gender discrimination. The disorder represents the punctuated resetting of 'normal' immune self-image to a self-attacking 'excited' state, a process formally analogous to models of punctuated equilibrium in evolutionary theory. We speculate that this punctuated onset takes place in the context of a particular immunological 'cognitive module' similar to what has been proposed by evolutionary psychologists for the human mind, and may be stratified by a relation to cyclic physiological responses

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which are long in comparison with heartbeat period: circadian, hormonal, and annual light/temperature cycles. The high rate of lupus in African-American women suggests existence of a larger dynamic which entrains powerful as well as subordinate population subgroups, implying that the wide ranging programs of social and economic reform required to cause declines in disease among African-American women will bring significant benefit to all.

Key words: chronic inflammation, circadian cycle, cognitive module, gender discrimination, immune cognition, information theory, lupus, racism, social hierarchy

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder which most frequently affects young women. Arthritis, skin rash, osteoporosis, cataracts, accelerated atherosclerotic vascular disease (ASVD), central nervous system dysfunction, and renal disease are the most common manifestations, whose severity may markedly fluctuate over time. The damage of the disease is of 'Type III', i.e. mediated by immune complexes which can range from just a few molecules to relatively huge structures involving whole cells coated or cross-linked by antibody, accounting for the great variety of pathology seen in this form of illness (Paul, 1999; Liang et al., 2002). The disease is characterized by polyclonal B-cell activation, elevated production of pathogenic autoantibodies, impaired immune complex clearance and inflammatory responses in multiple organs. Like asthma, the pathological cascade is marked by an imbalance between depressed Th1 cell cytokines, which promote cell-mediated immunity, and enhanced Th2 cell cytokines, which support humoral immunity. There increasingly strong evidence that the cytokine Interleukin-6 (IL-6) is central to this process. IL-6 is a B-cell differentiation factor that induces the final maturation of IL-4-preactivated B cells into immunoglobulin (Ig)-secreting plasma cells (e.g. Schotte et al., 2001; Linker-Israeli et al., 1991; Cross and Benton, 1999).

Kiecolt-Glaser et al. (2002) discuss how chronic inflammation involving IL-6 has been linked with a spectrum of conditions associated with aging, including cardiovascular disease, osteoporosis, arthritis, type II diabetes, certain cancers, and other conditions. In particular the association between cardiovascular disease and inflammation, as mediated by IL-6, is related to its central role in promoting the production of C-reactive protein (CRP),

an ancient and highly conserved protein secreted by the liver in response to trauma, inflammation, and infection. CRP is a pattern recognition molecule of the innate immune system keyed to surveillance for altered self and certain pathologies, providing early defense and activation of the humoral, adaptive, immune system. It is increasingly seen as a linkage between the two forms of immune response (Du Clos, 2000; Volanakis, 2001).

As Cross and Benton (1999) note, although IL-6 (and IL-10) have been most intensely studied for involvement in the pathogenesis of SLE, the cascade nature of cytokines means that all components of the cytokine network must, ultimately, be considered. We shall attempt to model this in a very general way below.

Within the US, SLE disproportionately affects African-American women, and accelerated ASVD occurs in subjects who are predominately premenopausal women at an age when ASVD is rare or unusual (Liang et al., 2002; Bongu et al., 2002). Between 1979 and 1998, SLE death rated have increased approximately 70 percent among African-American women aged 45-64 years (MMWR, 2002).

The basic disparity in disease occurrence is considerable, approximately four times higher in African-Americans than Caucasians (Bongu et al., 2002). Among Caucasian women, total SLE mortality has remained stable since the late 1970's at about 4.6 deaths per million with a decline in rates in younger and a rise in older women. Among African-American women, total SLE mortality rose 30 percent to a mean annual rate of 18.7 per million, with a constant rate in younger and a rising rate in older women. The rising disparity involves both increasing prevalence and worse disease in younger African-American women (Bongu et al., 2002).

Parks et al. (2002) find that the increased risk of SLE in African-Americans cannot be explained by hormonal or reproductive risk factors (i.e. breastfeeding, preeclamsia), occupational exposures (i.e. silica, mercury), medication allergy, herpes zoster, or similar factors. They suggest, rather, a central role for such "personal and social stressors" as racism and poverty in creating the disparity, a fundamental insight.

Here we will utilize Irun Cohen's theory of immune cognition (e.g. Cohen, 2000; Atlan and Cohen, 1998), particularly his concept of the 'immunological homunculus', a submodule representing the immune system's self-image of the body, instantiated through a mathematical model, to delineate the basic biology of what can be characterized as 'pathogenic social hierarchy' in the etiology of the disease. This is far from a trivial enterprise: we shall first

have to produce a detailed general treatment of autoimmune disease, which we then can apply specifically to SLE. Following Pielou (1977), however, we must be careful to understand the principal utility of the mathematical model is in raising questions for empirical study, rather than answering them.

We assume some familiarity with earlier work in this direction, using an information theory approach (e.g. Cohen, 2000; Atlan and Cohen, 1998; Wallace and Wallace, 2002; Wallace, 2002a).

We will express deviations from a 'zero-order reference state' of the immunological homunculus in terms of a relatively few 'nonorthogonal eigenmodes' representing complex systemic responses to applied perturbation – infection, tumorigenesis, tissue damage, and the like. These eigenmodes – autoimmune address of self-antigens – are a combination of innate and learned responses to such perturbation.

The essence of the argument is recognition that the immunological homunculus, the immune system's image of the self, is not a simple physical structure whose zero-order reference mode is a minimum energy state to which the system will automatically return, like a collection of weights on springs left to itself: all states of the immune system are, relatively speaking, rather active high energy states. We infer, then, the necessity of a *cognitive* decision by the immune system as to which of the possible nonorthogonal eigenmodes of the immunological homunculus is to be taken as the zero-order-reference mode to which the system is reset, i.e. the 'normal' pattern of self-recognizing maintenance activities of the immune system. This line of reasoning seems analogous to Nunney's (1999) argument regarding the necessity of an elaborate tumor control strategy for large animals, since the probability of tumorigenesis grows synergistically as the 0.4 power of cell count times animal lifetime, itself dependent on animal size. Some similar power law calculation can probably be done comparing the number of possible 'eigenmodes' of the immune homunculus vs. the 'murunculus' for mouse models of autoimmune diseases.

We are, then, proposing that the immune system has evolved a number of interlocking 'cognitive modules' in a manner analogous to that proposed by evolutionary psychologists for the human mind (e.g. Barkow et al. , 1992). Cohen's immunological homunculus self-image of the body is clearly one such module. We will infer the necessity of others.

Cognitive processes have dual information sources which, through Rate Distortion Theorem (RDT) or Joint Asymptotic Equipartition Theorem (JAEPT) arguments, can become linked across levels of organization with external

structured 'signals' of one kind or another in a punctuated or 'phase transition' manner. Thus an appropriate signal – an infection, chemical exposure, or pattern of psychosocial stress – can, if strong enough, suddenly reset the zero-order of the immunological homunculus to a mode different from the learned zero-order maintenance mode, i.e. an actively self-attacking mode, in a manner recognizably analogous to the Eldredge/Gould model of evolutionary punctuation (e.g. Eldredge, 1985; Gould, 2002; Wallace, 2002b). The (relatively) limited number of possible high probability activated states – nonorthogonal eigenmodes – then, accounts for the limited number possible autoimmune diseases. Different excited eigenmodes will generally be triggered by different patterns of external signals through the cognitive reset-to-zero process.

We shall be particularly interested in the possible role of pathogenic social hierarchy as such a signal in the onset of SLE.

The model

1. Cognition as language. Atlan and Cohen (1998) and Cohen (2000) argue that the essence of immune cognition is comparison of a perceived antigenic signal with an internal, learned picture of the world, and then, upon that comparison, the choice of one response from a large repertoire of possible responses. Following the approach of Wallace (2000, 2002a), we make a 'weak', and hence very general, model of that process.

Pattern recognition-and-response, as we characterize it, proceeds by convoluting (i.e. comparing) an incoming external 'sensory' antigenic signal with an internal 'ongoing activity' – the 'learned picture of the world' – and, at some point, triggering an appropriate action based on a decision that the pattern of sensory activity requires a response. We need not model how the pattern recognition system is 'trained', and hence we adopt a weak model, regardless of learning paradigm, which can itself be more formally described by the Rate Distortion Theorem. We will, fulfilling Atlan and Cohen's (1998) criterion of meaning-from-response, define a language's contextual meaning entirely in terms of system output.

The model is as follows.

A pattern of sensory input is convoluted (compared) with internal 'ongoing' activity to create a path of convoluted signal $x = (a_0, a_1, ..., a_n, ...)$. This path is fed into a highly nonlinear 'decision oscillator' which generates an output $h(x)$ that is an element of one of two (presumably) disjoint sets B_0 and B_1. We take

$$B_0 \equiv b_0, ..., b_k,$$

$$B_1 \equiv b_{k+1}, ..., b_m.$$

Thus we permit a graded response, supposing that if

$$h(x) \in B_0$$

the pattern is not recognized, and if

$$h(x) \in B_1$$

the pattern is recognized and some action $b_j, k+1 \leq j \leq m$ takes place.

We are interested in paths x which trigger pattern recognition-and-response exactly once. That is, given a fixed initial state a_0, such that $h(a_0) \in B_0$, we examine all possible subsequent paths x beginning with a_0 and leading exactly once to the event $h(x) \in B_1$. Thus $h(a_0, ..., a_j) \in B_0$ for all $j < m$, but $h(a_0, ..., a_m) \in B_1$.

For each positive integer n let $N(n)$ be the number of paths of length n which begin with some particular a_0 having $h(a_0) \in B_0$ and lead to the condition $h(x) \in B_1$. We shall call such paths 'meaningful' and assume $N(n)$ to be considerably less than the number of all possible paths of length n – pattern recognition-and-response is comparatively rare. We further assume that the finite limit

$$H \equiv \lim_{n \to \infty} \frac{\log[N(n)]}{n}$$

both exists and is independent of the path x. We will – not surprisingly – call such a pattern recognition-and-response cognitive process *ergodic*.

We may thus define an ergodic information source $\mathbf{X}$ associated with stochastic variates X_j having joint and conditional probabilities $P(a_0, ..., a_n)$ and $P(a_n|a_0, ..., a_{n-1})$ such that appropriate joint and conditional Shannon uncertainties may be defined which satisfy the relations

$$H[\mathbf{X}] = \lim_{n\to\infty} \frac{\log[N(n)]}{n} =$$

$$\lim_{n\to\infty} H(X_n|X_0, ..., X_{n-1}) =$$

$$\lim_{n\to\infty} \frac{H(X_0, ..., X_n)}{n}.$$

(1)

We say this information source is *dual* to the ergodic cognitive process.

Different 'languages' will, of course, be defined by different divisions of the total universe of possible responses into different pairs of sets B_0 and B_1, or by requiring more than one response in B_1 along a path. Like the use of different distortion measures in the Rate Distortion Theorem (e.g. Cover and Thomas, 1991), however, it seems obvious that the underlying dynamics will all be qualitatively similar. Dividing the full set of possible responses into the sets B_0 and B_1 may itself require 'higher order' cognitive decisions by other modules.

Meaningful paths – creating an inherent grammar and syntax – are defined entirely in terms of system response, as Atlan and Cohen (1998) propose. See figure 1 for a schematic.

We can apply this formalism to the stochastic neuron in a neural network: A series of inputs $y_i^j, i = 1, ...m$ from m nearby neurons at time j to the neuron of interest is convoluted with 'weights' $w_i^j, i = 1, ..., m$, using an inner product

$$a_j = \mathbf{y}^j \cdot \mathbf{w}^j \equiv \sum_{i=1}^{m} y_i^j w_i^j$$

(2)

in the context of a 'transfer function' $f(\mathbf{y}^j \cdot \mathbf{w}^j)$ such that the probability of the neuron firing and having a discrete output $z^j = 1$ is $P(z^j = 1) = f(\mathbf{y}^j \cdot \mathbf{w}^j)$.

Thus the probability that the neuron does not fire at time j is just $1 - P$. In the usual terminology the m values y_i^j constitute the 'sensory activity' and the m weights w_i^j the 'ongoing activity' at time j, with $a_j = \mathbf{y}^j \cdot \mathbf{w}^j$ and the path $x \equiv a_0, a_1, ..., a_n, ...$ A little more work leads to a standard neural network model in which the network is trained by appropriately varying $\mathbf{w}$ through least squares or other error minimization feedback. This can be shown to replicate rate distortion arguments, as we can use the error definition to define a distortion function which measures the difference between the training pattern y and the network output $\hat{y}$ as a function, for example, of the inverse number of training cycles, K. As we will discuss in another context, 'learning plateau' behavior emerges naturally as a phase transition in the parameter K in the mutual information $I(Y, \hat{Y})$.

Thus we will eventually parametize the information source uncertainty of the dual information source to a cognitive pattern recognition-and-response with respect to one or more variates, writing, e.g. $H[\mathbf{K}]$, where $\mathbf{K} \equiv (K_1, ..., K_s)$ represents a vector in a parameter space. Let the vector $\mathbf{K}$ follow some path in time, i.e. trace out a generalized line or surface $\mathbf{K}(t)$. We will, following the argument of Wallace (2002b), assume that the probabilities defining H, for the most part, closely track changes in $\mathbf{K}(t)$, so that along a particular 'piece' of a path in parameter space the information source remains as close to memoryless and ergodic as is needed for the mathematics to work. Between pieces we impose phase transition characterized by a renormalization symmetry, in the sense of Wilson (1971). See Binney, et al. (1986) for a more complete discussion.

We will call such an information source 'piecewise memoryless ergodic'.

2. Nonorthogonal eigenmodes of the immunological homunculus. Cohen (2000) defines the immunological homunculus as the immune system's image of the self, i.e. its characteristic pattern of response to self-antigens through autoantibodies, as regulated by a set of anti-autoantibodies. The immune system can monitor the self through examination of fluctuations in the immunological homunculus, and respond accordingly in a coherent, programmatic manner. Infection or injury will perturb the immune system's image of the self, which, after successful address, will return to the 'zero order state'. To anticipate the argument, an essential problem, for the immune system, is to recognize what that state is, among all possible pictures of the self

represented by the possible states of the immune homunculus: There is no 'energy minimization' strategy which permits a simple identification of such a state, since all states of the dynamic immunological homunculus are, effectively, high energy states. We argue that such recognition requires, in fact, a fairly sophisticated 'second order' cognitive decision. That is, identifying a baseline states is itself a cognitive process.

We are arguing, essentially, for the immunological equivalent of the 'mental modules' which evolutionary psychologists argue must have evolved in the human mind to efficiently process particular sets of sensory data, especially those related to human social interactions – recognition of facial expression, language, perhaps pheromone detection (e.g. Barkow et al. , 1992). Elsewhere (Wallace et al., 2002), following Nunney (1999), we have already argued that the body's 'tumor control strategy' must, in effect, be such a cognitive module, made increasingly complicated for large animals by the interaction of cell number with organism longevity. Here we extend that argument to autoimmunity.

We assume that the immune homunculus can be represented by some elaborate system of nonlinear equations, possibly involving cytokine, self-antibody, and anti-self-antibody concentrations and their spatial distributions. Our principal assumption is that the 'zero order state' is learned, and that changes about that state induced by external perturbations are relatively small.

We further assume that, expanding about the 'reference state', all variables, x_i depend on all others 'nearly linearly', so that we can write, to first order at time t, a system of empirical regression equations describing the cascade of cytokines:

$$x_i(t) = \sum_{j \neq i}^{s} b_{i,j} x_j(t) + \epsilon_i(t, x_1(t), ..., x_s(t)).$$

(3)

At reference, the x_i are defined to be zero, as are the ϵ_i. Most critically, we will assume the $b_{i,j}$ *have been determined from empirical regression relations.* This assumption provides the mathematical foundation for our analysis.

Here the $x_j, j = 1, ..., s$ are both 'independent' and 'dependent' variables involved in the inevitable cytokine feedback cascade about the 'reference configuration', and the ϵ_i represent 'error terms' which are not necessarily small in this approximation. s may be fairly large, depending, presumably, on the size of the animal according to some power law. Note that the ϵ terms will become external perturbations in the subsequent analysis.

In matrix notation this set of equations becomes

$$X(t) = \mathbf{B}X(t) + U(t)$$

(4)

where $X(t)$ is an s-dimensional vector, $\mathbf{B}$ is an $s \times s$ matrix of regression coefficients having a zero diagonal, and U is an s-dimensional vector containing 'error' terms which are not necessarily small. We suggest that, on the timescale of applied perturbations and initial responses, the $\mathbf{B}$-matrix remains relatively constant.

This structure, by virtue of its determination through least squares linear regression, has a number of interesting properties which permit estimation of the effects of a perturbation. Rewriting, we obtain

$$[\mathbf{I} - \mathbf{B}]X(t) = U(t)$$

(5)

where $\mathbf{I}$ is the $s \times s$ identity matrix and, to reiterate, $\mathbf{B}$ has a zero diagonal.

We next *reexpress matters in terms of the eigenstructure of* $\mathbf{B}$.

Let $\mathbf{Q}$ be the matrix of eigenvectors which diagonalizes $\mathbf{B}$ (or at least reduces it to block-diagonal Jordan canonical form). Take $\mathbf{Q}Y(t) = X(t)$ and $\mathbf{Q}W(t) = U(t)$. Let $\mathbf{J}$ be the diagonal matrix of eigenvalues of $\mathbf{B}$ so that $\mathbf{B} = \mathbf{Q}\mathbf{J}\mathbf{Q}^{-1}$. The eigenvalues of $\mathbf{B}$ can be shown to all be real (D. Wallace

and R. Wallace, 2000). Then, for the eigenvectors Y_k of $\mathbf{B}$, corresponding to eigenvalues λ_k,

$$Y_k(t) = \mathbf{J}Y_k(t) + W_k(t).$$

(6)

Using a term-by-term shorthand for the components of Y_k, this becomes

$$y_k(t) = \lambda_k y_k(t) + w_k(t).$$

Define the mean of a time dependent function $f(t)$ over the time interval $[0, \Delta T]$ as

$$E[f] \equiv \frac{1}{\Delta T} \int_0^{\Delta T} f(t)dt.$$

(7)

We assume an appropriately rational structure as $\Delta T \rightarrow \infty$. The variance $V[f]$ over the same time interval is defined as $E[(f - E[f])^2]$. Taking matters again term-by-term, we obtain

$$V[(1 - \lambda_k)y_k] = V[w_k]$$

so that

$$V[y_k] = \frac{V[w_k]}{(1 - \lambda_k)^2}$$

or

$$\sigma(y_k) = \frac{\sigma(w_k)}{|1 - \lambda_k|},$$

(8)

where σ represents the standard deviation.

The y_k are the components of the eigentransformed immune system variates, and the w_k are the similarly transformed variates of the driving externalities of infection, injury, or stress, as perceived by the immune homunculus.

The eigenvectors Y_k are characteristic but non-orthogonal combinations of the original variates X_k whose standard deviation is that of the transformed externalities *amplified by the term* $1/|1 - \lambda|$. Characteristic patterns of perturbation w can therefore trigger characteristic, but nonorthogonal, amplified patterns of general response Y_k in the immune homunculus, which must, among other things, instantiate the immune system's perception of the self. Although there may be s of these 'excited eigenmodes' – in addition to the zero reference state – relatively few of them will be highly probable. It is these highly probable Y_k which we propose form the possible set of defined zero states of the immune homunculus, one of which, including the initial '$Y_0 = 0$' state, must be chosen by a cognitive reset-to-zero module.

Note in particular that the nonorthogonal nature of the eigenstructure of **B** implies plieotropy, i.e. that a single input signal may have multiple possible outputs, here in proportion to the magnitude of the excitation.

Extension of the model to include rates of change of cytokine concentrations and the like, in addition to their magnitudes, is algebraically complicated but seems fairly direct. Intuitively, such extension must give a first order matrix relation much like equation (4), but now in terms of both the x_j and their time rates of change $\dot{x}_j$. Such matrix equations typically have eigenmodes with *complex* eigenvalues representing linked patterns of dynamical limit cycles, rather than simple fixed eigenstructures. Thus the problem becomes one of perturbation from a reference pattern of limit cycles, and of characterizing the behavior of a cognitive submodule permitting identification of that reference pattern.

3. Circadian and other cycles. If the immunological homunculus could be entirely described by a simple system of first order differential equa-

tions, expanded near a zero-state, then under perturbation we would have something like

$$\dot{X}(t) = \mathbf{R}X(t) + \epsilon(t)$$

(9)

where $X(t)$ is the vector of displacements from the zero state, $\epsilon(t)$ the vector of perturbations, and $\mathbf{R}$ an appropriate fixed matrix of real numbers, here having purely imaginary eigenvalues. Thus the trace of $\mathbf{R}$, the sum of the real parts of the eigenvalues, is zero, analogous to the condition on the B-matrix above. This is a simple version of the famous Langevin equation, with a full solution in terms of the Fokker-Planck equation if $\epsilon(t)$ has appropriately random 'white noise' properties, an analysis which moves rapidly into the realm of stochastic differential equations. Unfortunately, $\epsilon(t)$ is unlikely to be random in the sense necessary for such an approach, which requires the covariance of ϵ between different times to be proportional to a delta function. We would, on the contrary, generally expect $\epsilon(t)$ to be the output of an appropriately regular information source, with elaborate covariance structure.

We can, however, make a simplified treatment quite like the previous development, provided the system is asymptotically bounded in the sense that, for all time t, there is a fixed, positive real number c such that, for all components of the vector X,

$$|x_j(t)| \leq c.$$

(10)

That is, the system cannot move arbitrarily far from its 'zero state'. Then, taking the time average of equation (9) in the sense of the previous development gives

$$E[\dot{X}] = \mathbf{R}E[X] + E[\epsilon],$$

(11)

where we very explicitly do not assume the perturbations are random with zero mean. Implicitly, then, we are assigning a grammar and syntax to the perturbing structures.

Writing out the left hand side of the equation gives, component by component

$$E[\dot{x_j}] = \lim_{\Delta T \to \infty} \frac{1}{\Delta T} \int_0^{\Delta T} [dx_j/dt]dt$$

$$= \lim_{\Delta T \to \infty} \frac{1}{\Delta T}[x_j(\Delta T) - x_j(0)].$$

This expression is bounded both above and below by

$$\lim_{\Delta T \to \infty} \frac{2c}{\Delta T} = 0,$$

and is thus itself zero.

We obtain, then,

$$\mathbf{R}E[X] = -E[\epsilon].$$

(12)

Somewhat heuristically, to first order an eigentransformation in terms of $\mathbf{R}$ gives a result analogous to equation (8), again component-by-component:

$$E[y_k] = -\frac{E[w_k]}{\omega_k}.$$

(13)

Y_k is the k-th eigenvector of $\mathbf{R}$, W_k is the *eigentransformed* perturbation, and ω_k is the frequency of the cyclic eigenmode Y_k.

The equation states that cyclic eigenmode amplification by nonrandom structured external perturbation is inversely proportional to eigenmode frequency. That is, slower cycles are amplified by perturbation more than rapid ones, in proportion to their period. Again, there is no orthogonality constraint on the eigenvectors of $\mathbf{R}$, suggesting the possibility of plieotropic response.

This is an interesting result: Many physiological cycles are characterized by several relatively slow processes, in comparison with the 'standard physiological clock' of the heartbeat: daily circadian, monthly hormonal, and annual light/temperature cycles. Pathologically amplified (nonorthogonal) eigenmodes – displacements from zero related to autoimmune disease – according to this argument, may well be intimately associated with these cycles. The monthly hormonal cycle of non-menopausal women might then be related to a particular form of 'non-zero offset', i.e. an excited mode representing a particular autoimmune disease. Similarly, tropical populations could suffer less from excited modes associated with annual cycles of light and temperature (and their ecological sequelae), perhaps accounting for the 'tropical gradient' in multiple sclerosis, an autoimmune disease of the central nervous system. That is, autoimmune disease might well be classifiable by associated cycle or cycles, as well as by perturbation-of-onset.

Most autoimmune diseases would seem, of necessity, to be particularly related to the circadian cycle, which is universal, very powerful, and always fairly long compared to the heartbeat. Thus autoimmune diseases may, from this development, be especially stratified by their disturbance in various circadian rhythms (e.g. Lechner et al., 2000; Hilty et al., 2000).

4. Plieotropy: the retina of the immunological homunculus. A slight variation of the model above leads to further interesting speculations. Rather than taking a differential equation approach, we suppose that the

daily circadian or some other cycle imposes a temporal structure on the immunological homunculus, in the sense that its 'state' at some time $t+1$, which we write X_{t+1}, is a function of its state at time t:

$$X_{t+1} = \mathbf{R}_{t+1} X_t. \tag{14}$$

If X_t, the simplified, internal picture of the body at time t, is of dimension m, then $\mathbf{R}_t$, the manner in which that picture changes in time (from time t to $t+1$), has m^2 components. If the state of the homunculus at time $t=0$ is X_0, then iterating the relation above gives the state at time t as

$$X_t = \mathbf{R}_t \mathbf{R}_{t-1} \mathbf{R}_{t-2} ... \mathbf{R}_1 X_0. \tag{15}$$

The state of the body is, in this picture, essentially represented by an information-theoretic path defined by the stochastic sequence in $\mathbf{R}_t$, each member having m^2 components: the grammar and syntax of how things change tells us much about how we are. That sequence is mapped onto a parallel path in the states of the immunological homunculus, the set $X_0, X_1, ..., X_t$, each having m components.

If the state of the body can, in fact, be characterized as an information source – a generalized language – so that the paths of $\mathbf{R}_t$ are autocorrelated, then the autocorrelated paths in X represent the output of a parallel information source which is, Rate Distortion arguments to the contrary, apparently a greatly simplified, and thus grossly distorted, picture of that body.

This may not necessarily be the case.

Let us examine a single iteration in more detail, assuming now that there is a zero reference state, $\mathbf{R}_0$, for the sequence in $\mathbf{R}_t$, and that

$$X_{t+1} = (\mathbf{R}_0 + \delta\mathbf{R}_{t+1})X_t,$$

(16)

where $\delta\mathbf{R}_t$ is 'small' in some sense compared to $\mathbf{R}_0$.

We again invoke a diagonalization in terms of $\mathbf{R}_0$. Let $\mathbf{Q}$ be the matrix of eigenvectors which (Jordan) diagonalizes $\mathbf{R}_0$. Then we can write

$$\mathbf{Q}X_{t+1} = (\mathbf{Q}\mathbf{R}_0\mathbf{Q}^{-1} + \mathbf{Q}\delta\mathbf{R}_{t+1}\mathbf{Q}^{-1})\mathbf{Q}X_t.$$

If we take $\mathbf{Q}X_t$ to be an eigenvector of $\mathbf{R}_0$, say Y_k, with eigenvalue λ_k, we can rewrite this equation as a spectral expansion,

$$Y_{t+1} = (\mathbf{J} + \delta\mathbf{J}_{t+1})Y_k \equiv \lambda_k Y_k + \delta Y_{t+1} =$$

$$\lambda_k Y_k + \sum_{j=1}^{n} a_j Y_j,$$

(17)

where $\mathbf{J}$ is a (block) diagonal matrix, $\delta\mathbf{J}_{t+1} \equiv \mathbf{Q}\mathbf{R}_{t+1}\mathbf{Q}^{-1}$, and δY_{t+1} *has been expanded in terms of a spectrum of the eigenvectors of* $\mathbf{R}_0$, with

$$|a_j| \ll |\lambda_k|, |a_{j+1}| \ll |a_j|.$$

(18)

The essential point is that, provided $\mathbf{R}_0$ is chosen or 'tuned' so that this condition is true, the first few terms in the spectrum of the plieotropic iteration of the eigenstate will contain most of the essential information about the perturbation. We envision this as similar to the detection of color in the retina, where three overlapping non-orthogonal 'eigenmodes' of response suffice to characterize a vast plethora of color sensation. Here, if such a spectral analysis is possible, a very small number of eigenmodes of the immunological homunculus would suffice to permit identification of a vast range of perturbed bodily states: the rate-distortion constraints become very manageable indeed. This is necessarily a significantly more complex process than color detection since the immune system has both innate and learned components, and genetic programming is of limited value. The key to the problem, we believe, would lie in the proper rate-distortion tuning of the system, i.e. the choice of zero-mode, $\mathbf{R}_0$. Such choice, we suspect, would be very complicated and require a cognitive submodule of immune cognition.

Next we examine how the information source dual to the cognitive reset-to-zero process for fixed eigenmodes, eigenpatterns of limit cycles, or tuned spectra, can become linked in a punctuated manner with structured systems of external perturbation, a highly nontrivial development.

5. Phase transitions of interacting information systems. We suppose that the reset-to-zero cognitive module of the immune system devoted to the immunological homunculus can be represented by a sequence of 'states' in time, the 'path' $x \equiv x_0, x_1, ...$ Similarly, we assume an external signal of infection, tissue damage, chemical exposure, or 'psychosocial stress' can be similarly represented by a path $y \equiv y_0, y_1, ...$ These paths are, however, both very highly structured and, within themselves, are serially correlated and can, in fact, be represented by 'information sources' $\mathbf{X}$ and $\mathbf{Y}$. We assume the reset-to-zero cognitive process of the immunological homunculus and the external stressors interact, so that these sequences of states are not independent, but are jointly serially correlated. We can, then, define a path of sequential pairs as $z \equiv (x_0, y_0), (x_1, y_1), ...$ The essential content of the Joint Asymptotic Equipartition Theorem, one of the fundamental limit theorems of 20th Century mathematics, is that the set of joint paths z can be partitioned into a relatively small set of high probability which is termed *jointly typical*, and a much larger set of vanishingly small probability. Further, according to the JAEPT, the *splitting criterion* between high and low probability sets of pairs is the mutual information

$$I(X,Y) = H(X) - H(X|Y) = H(X) + H(Y) - H(X,Y)$$

(19)

where $H(X), H(Y), H(X|Y)$ and $H(X,Y)$ are, respectively, the Shannon uncertainties of X and Y, their conditional uncertainty, and their joint uncertainty. See Cover and Thomas (1991) for mathematical details. Similar approaches to neural process have been recently adopted by Dimitrov and Miller (2001).

The high probability pairs of paths are, in this formulation, all equiprobable, and if $N(n)$ is the number of jointly typical pairs of length n, then

$$I(X,Y) = \lim_{n\to\infty} \frac{\log[N(n)]}{n}.$$

(20)

Generalizing the earlier language-on-a-network models of Wallace and Wallace (1998, 1999), we suppose there is a 'coupling parameter' P representing the degree of linkage between the immune system's reset cognition and the system of external signals and stressors, and set $K = 1/P$, following the development of those earlier studies. Then we have

$$I[K] = \lim_{n\to\infty} \frac{\log[N(K,n)]}{n}.$$

The essential 'homology' between information theory and statistical mechanics lies in the similarity of this expression with the infinite volume limit of the free energy density. If $Z(K)$ is the statistical mechanics partition function derived from the system's Hamiltonian, then the free energy density is determined by the relation

$$F[K] = \lim_{V \to \infty} \frac{\log[Z(K)]}{V}.$$

(21)

F is the free energy density, V the system volume and $K = 1/T$, where T is the system temperature.

We and others argue at some length (e.g. Wallace and Wallace, 1998, 1999; Rojdestvensky and Cottam, 2000; Feynman, 1996) that this is indeed a systematic mathematical homology which, we contend, permits importation of renormalization symmetry into information theory. Imposition of invariance under renormalization on the mutual information splitting criterion $I(X, Y)$ implies the existence of phase transitions analogous to learning plateaus or punctuated evolutionary equilibria in the relations between the cognitive reset mechanism and the system of external perturbations. An extensive mathematical treatment of these ideas is presented elsewhere (e.g. Wallace, 2000, 2002a,b; Wallace et al., 2002a).

Elaborate developments are possible. From a the more limited perspective of the Rate Distortion Theorem we can view the onset of a punctuated interaction between the cognitive reset-to-zero mechanism of the immune homunculus and external stressors as a distorted image of those stressors within the homunculus:

Suppose that two (piecewise, adiabatically memoryless) ergodic information sources $\mathbf{Y}$ and $\mathbf{B}$ begin to interact, to 'talk' to each other, i.e. to influence each other in some way so that it is possible, for example, to look at the output of $\mathbf{B}$ – strings b – and infer something about the behavior of $\mathbf{Y}$ from it – strings y. We suppose it possible to define a retranslation from the B-language into the Y-language through a deterministic code book, and call $\hat{\mathbf{Y}}$ the translated information source, as mirrored by $\mathbf{B}$.

Define some distortion measure comparing paths y to paths $\hat{y}$, $d(y, \hat{y})$ (Cover and Thomas, 1991). We invoke the Rate Distortion Theorem's mutual information $I(Y, \hat{Y})$, which is the splitting criterion between high and low probability pairs of paths. Impose, now, a parametization by an inverse

coupling strength K, and a renormalization symmetry representing the global structure of the system coupling.

Extending the analyses, triplets of sequences can be divided by a splitting criterion into two sets, having high and low probabilities respectively. For large n the number of triplet sequences in the high probability set will be determined by the relation (Cover and Thomas, 1992, p. 387)

$$N(n) \propto \exp[nI(Y_1; Y_2|Y_3)],$$

(22)

where splitting criterion is given by

$$I(Y_1; Y_2|Y_3) \equiv$$

$$H(Y_3) + H(Y_1|Y_3) + H(Y_2|Y_3) - H(Y_1, Y_2, Y_3)$$

We can then examine mixed cognitive/adaptive phase transitions analogous to learning plateaus (Wallace, 2002b) in the splitting criterion $I(Y_1, Y_2|Y_3)$. Note that our results are almost exactly parallel to the Eldredge/Gould model of evolutionary punctuated equilibrium (Eldredge, 1985; Gould, 2002).

Autoimmune disease

According to current theory, the adapted human mind functions through the action and interaction of distinct mental modules which evolved fairly rapidly to help address special problems of environmental and social selection pressure faced by our Pleistocene ancestors (e.g. Barkow et al., 1992). As is well known in computer engineering, calculation by specialized submodules – e.g. numeric processor chips – can be a far more efficient means of solving particular well-defined classes of problems than direct computation by a generalized system. We suggest, then, that immune cognition has evolved specialized submodules to speed the address of certain commonly recurring challenges. Nunney (1999) has argued that, as a power law of cell count,

specialized subsystems are increasingly required to recognize and redress tumorigenesis, mechanisms ranging from molecular error-correcting codes, to programmed cell death, and finally full-blown immune attack.

Here we argue that identification of the 'normal' state of the immunological homunculus – the immune system's self-image-module of the body – is a highly nontrivial task requiring a separate, specialized cognitive submodule within overall immune cognition. This is essentially because, for the vast majority of information systems, unlike a mechanical system, there are no 'restoring springs' whose low energy state automatically identifies equilibrium. That is, active comparison must be made of the state of the immunological homunculus with some stored internal reference picture, and a decision made about whether to reset to zero, a cognitive process. We further speculate that the complexity of such a submodule must also follow something like Nunney's power law with animal size, as the overall immune system and the immune image of the self, become increasingly complicated with rising number of cells.

Failure of that cognitive submodule results in identification of an 'excited' state of the immunological homunculus as 'normal', triggering the systematic patterns of self-antibody attack which constitute autoimmune disease, and which our analysis suggests may often be related to particular physiological cycles or signals which are long compared to heartbeat rate.

In sum, since such 'zero mode identification' (ZMI) is a (presumed) cognitive submodule of overall immune cognition, it involves the process of figure 1, convoluting incoming 'sensory' with 'ongoing' internal memory data in choosing the zero state. The dual information source defined by this cognitive process can then interact in a punctuated manner with 'external information sources' according to the Rate Distortion arguments above. From a RDT perspective, then, those external information sources literally write a distorted image of themselves onto the ZMI in a punctuated manner: (relatively) sudden onset of autoimmune disease.

Different systems of structured external signals – infections, chemical exposures, systems of 'psychosocial stress' – will, presumably, write different characteristic images of themselves onto the ZMI cognitive submodule, i.e. trigger different autoimmune diseases, perhaps stratified by their relation to circadian, hormonal, or annual cycles.

Discussion and conclusions

Recent theories of coronary heart disease – CHD – (e.g. Ridker 2002; Libbey et al., 2002) identify a dynamic and progressive chronic vascular inflammation as the basic pathogenic biological mechanism, a process in which the cytokine IL-6 and C-reactive protein (CRP) play central roles. We have reviewed something of the "IL-6" hypothesis regarding the etiology SLE. An earlier analysis along these lines identified social structures of 'pathogenic social hierarchy' (PSH) in the US as critical in determining population-level patterns of CHD among African-American males (Wallace et al., 2002b). In that paper, historical cultural patterns of racism and discrimination were viewed as directly writing themselves onto the 'language' of immune cognition in a punctuated Rate Distortion manner to produce chronic vascular inflammation among subordinate populations.

Female hormones are known to be generally protective against CHD. Where, then, does the stress of PSH express itself in women? Figure 2 is taken from material on health and hierarchy in Singh-Manoux et al. (2002). It displays, for men and women separately, self-reported health as a function of self-reported status rank, where 1 is high and 10 low rank, among some 7,000 male and 3,400 female London-based office staff, aged 35-55 working in 20 Civil Service departments in the late 1990's. Self-reported health is a highly significant predictor of future morbidity and mortality.

Remarkably, the results for men and women are virtually indistinguishable in what is clearly a kind of toxicological dose-response curve, displaying physiological response against a 'dosage' of hierarchy which may include measures of both stress and real availability of resources (Link and Phelan, 2000).

We propose that PSH can also write itself onto a particular internal module of the cognitive immune system, what we have called 'zero mode identification' which defines the 'inactive' state of the immunological homunculus. The (relatively) protective role of female hormones against CHD, given the indistinguishability of men and women in figure 2, implies existence of a plastic, pleiotropic, response of the immune system to PSH. In essence, one has a sex-based choice of death by hanging or by firing squad, i.e. CHD induced by chronic vascular inflammation for African-American men, or a particular induced autoimmune disease for African-American women, SLE. A roughly similar story can probably be told regarding the increased rate of aggressively fatal breast cancer, diabetes, and other disorders in African-American women.

That is, the 'message' of PSH in the US is written onto the bodies of

African-American men and women as, respectively, elevated rates of coronary heart disease, systemic lupus erythematosus, and allied disorders of chronic inflammation.

The rise in SLE among African-American women appears to parallel the rise of asthma among US minority urban children, which has increased 50 percent since 1980 (CDC,, 1996; NCHS, 1996). As we and others have described, (Wallace, Wallace and Fullilove, 2002; Carr et al., 1992) the geography of asthma in places like New York City closely matches the geography of public policy-driven urban burnout, contagious urban decay, and 'urban renewal' which has left most US urban minority neighborhoods looking like Dresden after the firebombing. Elsewhere (Wallace, Wallace and Fullilove, 2002) we have interpreted the rise of asthma among urban minority children as the writing of a kind of deliberate community lynching upon the developing immune system. Geographic analysis might well show that rising rates of SLE among African-American women represent the writing of that practice upon the developed immune system of women of reproductive age. In both cases a Th2 phenotype appears to be imposed. These are questions for future research.

As many have argued, health disparities are inevitably only the tip of an iceberg which can enmesh powerful or majority populations into dynamics affecting the marginalized. Relative raised rates of autoimmune disease among African-American women are a red flag: Pathogenic social hierarchy may place a severe biological limit on the ultimate effectiveness of traditional medical behavioral and drug approaches to immune-related disease across all US subgroups, not merely for African-Americans.

This suggests in particular that 'magic bullet' medical interventions against lupus, to be effective at the population level, must be integrated as part of a larger 'ecosystem' strategy addressing the more basic problems of pathogenic social hierarchy and gender discrimination in the US. African-American women are, however, doubly burdened through the synergism of historical patterns of racism with a traditional gender discrimination which may, in fact, reflect that racism within African-American communities, and should be among the first to benefit from such reforms.

The remarkable rise of both lupus and asthma in US minority communities after 1980 seems to indicate, from this perspective, the tightening of discrimination rather than any efforts at reform. Our own studies (e.g. D. Wallace and R. Wallace, 1998) suggest that the inevitable failure of American Apartheid to effectively shield the powerful from the forces and impacts

of marginalization means that the dominant population is being brought into a dynamic of increasing pathology as well. Nobody is more entrained into systems like figure 2 than the white majority in the US, which holds itself within the same structure it holds others, and would thus benefit by reform. Such, indeed, was the message of the Rev. Dr. Martin Luther King Jr., a message which appears to have a very basic biological reality.

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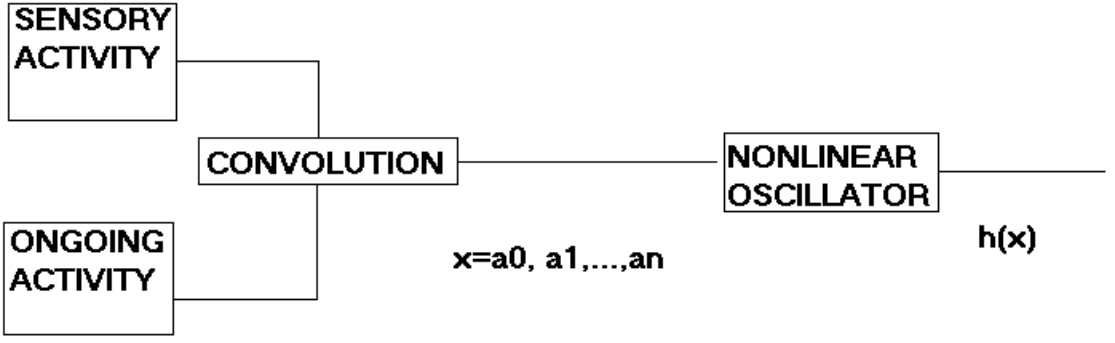
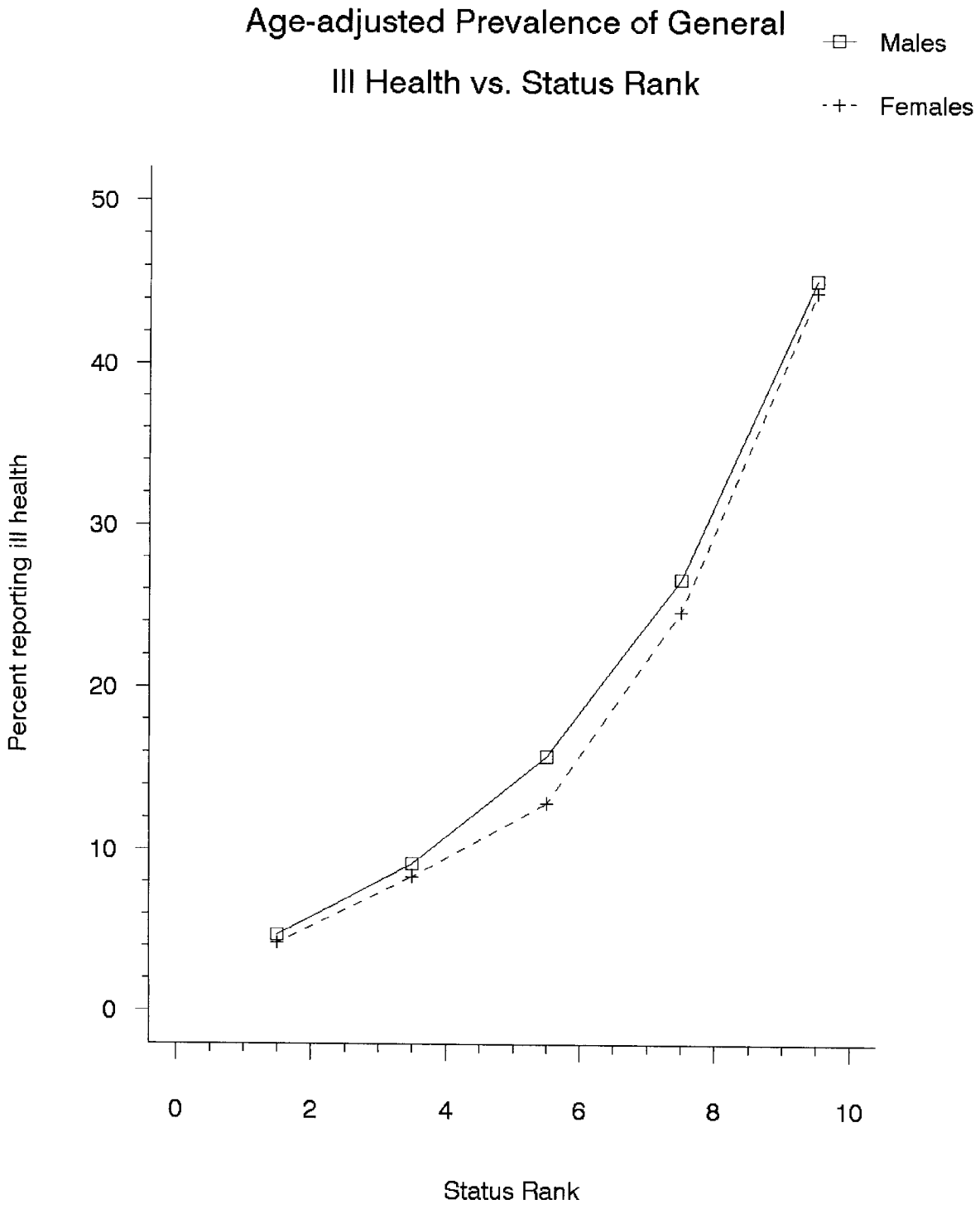
Figure captions

Figure 1. Schematic of a generalized cognitive process. This is a two-fold system involving, first, a generally complicated convolution of an external 'sensory' signal with an internal 'ongoing activity' memory to produce the path $x_m = a_0, a_1, ..., a_m$. We are interested in those paths which trigger the 'oscillator' $h(x)$ once, so that $h(x_{m-j}) \in B_0$ for all $j \geq 1$, but $h(x_m) \in B_1$. We call such paths *meaningful*. Let $N(n)$ be the number of meaningful paths of length n, and assume it to be very much less than the number of all possible paths of length n. If the limit $H = lim_{n\to\infty} \log[N(n))]/n$ is finite and independent of path, we say H represents an ergodic information source *dual* to the cognitive process.

Figure 2. Redisplay of data from Singh-Manoux et al. (2002). Sex-specific dose-response curves of age-adjusted prevalence of self-reported ill-health vs. self-reported status rank, Whitehall II cohort, 1997 and 1999. 1 is high and 10 is low status. Note that the curves are virtually identical, and that the upper point is very near the EC-50 level in this population. Self-reported health is a highly significant predictor of later morbidity and mortality.


SENSORY ACTIVITY
ONGOING ACTIVITY
CONVOLUTION
x=a0, a1,...,an
NONLINEAR OSCILLATOR
h(x)


Age-adjusted Prevalence of General
Ill Health vs. Status Rank
Males
Females
Percent reporting ill health
50
40
30
20
10
0
0
2
4
6
8
10
Status Rank