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Comorbidity: 1. Autocognitive developmental disorders of structured psychosocial stress

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Abstract

We explore the regularities apparent in comorbid psychiatric and chronic inflammatory disorders from an extension of Irun Cohen's perspective on autoimmune disease, finding that structured psychosocial stress can literally write a distorted image of itself onto child development, resulting in a life course trajectory to characteristic forms of comorbid mind/body dysfunction. Extension of the approach appears possible for schizophrenia and associated conditions, although without such direct relation to structured stress.

Key words: American apartheid, chronic inflammation, comorbidity, developmental disorder, evolution, information theory, mental disorder, punctuated equilibrium, schizophrenia

I. Introduction

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Certain mental disorders, for example depression and substance abuse, and many conditions of chronic inflammation like lupus, coronary heart disease, breast and prostate cancers, diabetes, obesity, and asthma, are well known to show marked regularities at the community level of organization according to the social constructs of 'race', 'gender', 'ethnicity', and 'socioeconomic status'. Indeed, a virtual research industry has emerged in the United States to address the 'mystery' of such 'health disparities'. Population-level structure in disease permits profound insight into etiology because, to the extent these are 'environmental' disorders, the principal environment of humans is other humans, moderated by a uniquely characteristic embedding cultural context (e.g. Durham, 1991). Thus culturally-sculpted 'social exposures' are likely to be important at the individual, and critical at the population, levels of organization in the expression of certain mental disorders and the diseases of chronic inflammation.

Further, mental disorders are often comorbidly expressed, both among themselves and with certain kinds of chronic physical disorder: Picture the obese, diabetic, depressed, anxious patient suffering from high blood pressure, asthma, coronary heart disease, and so on. Such comorbidity is the rule rather than the exception for the seriously ill, and is the central focus of this work.

As Cohen (2000) describes for autoimmune disease, however, the appearance of comorbid conditions is, given the plethora of possibilities, rather surprisingly constrained to a relatively few often-recurring patterns. We will find this to be a central point.

Here we will examine how a long list of 'cognitive submodules' may become synergistically linked with embedding, culturally structured, psychosocial stress to produce comorbid patterns of illness associated with mental disorder and chronic disease. We will further suggest that many such disorders either have their roots in utero, as a stressed mother communicates environmental signals across the placenta, and programs her developing child's physiology, or else are initiated during early childhood. This pattern may affect underlying susceptibility to chronic infections or parasitic infestation as well as more 'systemic' disorders (e.g. Wallace and Wallace, 2002).

We are particularly interested in the effects of 'stress' on the interaction between mind and body over the life course. 'Stress', we aver, is not often random in human societies, but is itself usually a socially and culturally constructed artifact, a very highly structured, 'language', having both a grammar and a syntax, so that certain stressors are 'meaningful' in a particular

context, and others are not, having little or no long-term physiological effect. We first argue that rational thought, emotion, immune function and related physiological processes, and sociocultural network function are, in fact, cognitive systems each associated with a 'dual information source' which may also be expressed as a kind of language. It is the punctuated interpenetration of these 'languages' which we will find critical to an understanding of how structured psychosocial stress affects the mind-body interaction, and, ultimately, writes a literal image of that structure upon that interaction, beginning in utero or early childhood, and determining a trajectory to inherently comorbid disease.

We begin with a recitation of some 'cognitive submodules' of human psychology and physiology which we believe interact both with each other and with structured psychosocial stress. Next we explore cognition as 'language', infer the existence of a 'generalized cognitive homunculus' much like that proposed by Cohen (2000) as the basis of autoimmune disease, and, ultimately, propose a model based on autoimmune disease to account for a life trajectory of chronic comorbid psychiatric/inflammatory disorder as a pathologically and recurrently 'permanent' excited state of that cognitive homunculus. Extension of the model to include such social pathologies as systematic violent behavior is direct, following the arguments of Wallace et al. (1996) and Wallace and Fullilove (1999).

Although not falling strictly within our principal focus on the outcomes of structured psychosocial stress, schizophrenia seems nonetheless to broadly lie within our paradigm.

Some comment on our methodology is appropriate.

We adapt recent advances in understanding 'punctuated equilibrium' in evolutionary process (e.g. Wallace, 2002b; Wallace and Wallace, 1998, 1999) to the question of how embedding structured psychosocial stress affects the interaction of 'mind' and 'body', and specifically seek to determine how the synergism of stress and cognitive submodules might be constrained by certain of the asymptotic limit theorems of probability.

We know that, regardless of the probability distribution of a particular stochastic variate, the Central Limit Theorem ensures that long sums of independent realizations of that variate will follow a Normal distribution. Analogous constraints exist on the behavior of information sources – both independent and interacting – and these are described by the limit theorems of information theory. Imposition of phase transition formalism from statistical physics, in the spirit of the Large Deviations Program of applied probability,

permits concise and unified description of evolutionary and cognitive 'learning plateaus' which, in the evolutionary case, are interpreted as evolutionary punctuation (e.g. Wallace, 2002a, b). This approach provides a 'natural' means of exploring punctuated processes in the effects of structured stress on mind-body interaction.

The model, as in the relation of the Central Limit Theorem to parametric statistical inference, is almost independent of the detailed structure of the interacting information sources inevitably associated with cognitive process, important as such structure may be in other contexts. This finesses the profound ambiguities associated with 'dynamic systems theory' and 'deterministic chaos' treatments in which the existence of 'dynamic attractors' depends on very specific kinds of differential equation models akin to those used to describe ecological population dynamics, chemical processes, or physical systems of weights-on-springs. Cognitive phenomena are neither well-stirred Erlenmeyer flasks of reacting agents, nor distorted mechanical clocks, and the application of 'dynamic systems theory' to cognition will likely be found to involve little more than hopeful metaphor.

In contrast, it seems actually possible to uncover the grammar and syntax of structured psychosocial stress and the function of cognitive submodules, and to express their relations in terms of empirically observed regression models relating measurable biomarkers, behaviors, beliefs, and so on. Our analysis will focus on the eigenstructure of those models, constrained by the ergodic and other properties of information sources.

Clearly our approach takes much from parametric statistics, and, while idiosyncratic 'nonparametric' models may be required in special cases, we may well capture the essence of the most common relevant phenomena.

II. The cognitive modules

1. Immune function Atlan and Cohen (1998) have proposed an information-theoretic model of immune function and process, a paradigm incorporating cognitive pattern recognition-and-response behaviors analogous to those of the central nervous system.

From this perspective, the meaning of an antigen can be reduced to the type of response the antigen generates. That is, the meaning of an antigen is functionally defined by the response of the immune system. The meaning of an antigen to the system is discernible in the type of immune response produced, not merely whether or not the antigen is perceived by the receptor

repertoire. Because the meaning is defined by the type of response there is indeed a response repertoire and not only a receptor repertoire.

To account for immune interpretation Cohen (1992, 2000) has proposed a cognitive paradigm for the immune system. The immune system can respond to a given antigen in various ways, it has 'options.' Thus the particular response we observe is the outcome of internal processes of weighing and integrating information about the antigen.

In contrast to Burnet's view of the immune response as a simple reflex, it is seen to exercise cognition by the interpolation of a level of information processing between the antigen stimulus and the immune response. A cognitive immune system organizes the information borne by the antigen stimulus within a given context and creates a format suitable for internal processing; the antigen and its context are transcribed internally into the 'chemical language' of the immune system.

The cognitive paradigm suggests a language metaphor to describe immune communication by a string of chemical signals. This metaphor is apt because the human and immune languages can be seen to manifest several similarities such as syntax and abstraction. Syntax, for example, enhances both linguistic and immune meaning.

Although individual words and even letters can have their own meanings, an unconnected subject or an unconnected predicate will tend to mean less than does the sentence generated by their connection.

The immune system creates a 'language' by linking two ontogenetically different classes of molecules in a syntactical fashion. One class of molecules are the T and B cell receptors for antigens. These molecules are not inherited, but are somatically generated in each individual. The other class of molecules responsible for internal information processing is encoded in the individual's germline.

Meaning, the chosen type of immune response, is the outcome of the concrete connection between the antigen subject and the germline predicate signals.

The transcription of the antigens into processed peptides embedded in a context of germline ancillary signals constitutes the functional 'language' of the immune system. Despite the logic of clonal selection, the immune system does not respond to antigens as they are, but to abstractions of antigens-in-context.

2. Tumor control We propose that the next cognitive submodule after the immune system is a tumor control mechanism which may include 'immune

surveillance', but clearly transcends it. Nunney (1999) has explored cancer occurrence as a function of animal size, suggesting that in larger animals, whose lifespan grows as about the 4/10 power of their cell count, prevention of cancer in rapidly proliferating tissues becomes more difficult in proportion to size. Cancer control requires the development of additional mechanisms and systems to address tumorigenesis as body size increases – a synergistic effect of cell number and organism longevity. Nunney concludes

> "This pattern may represent a real barrier to the evolution of large, long-lived animals and predicts that those that do evolve ... have recruited additional controls [over those of smaller animals] to prevent cancer."

In particular, different tissues may have evolved markedly different tumor control strategies. All of these, however, are likely to be energetically expensive, permeated with different complex signaling strategies, and subject to a multiplicity of reactions to signals, including those related to psychosocial stress. Forlenza and Baum (2000) explore the effects of stress on the full spectrum of tumor control, ranging from DNA damage and control, to apoptosis, immune surveillance, and mutation rate. Elsewhere (R. Wallace et al., 2003) we argue that this elaborate tumor control strategy, at least in large animals, must be at least as cognitive as the immune system itself, which is one of its components: some comparison must be made with an internal picture of a 'healthy' cell, and a choice made as to response: none, attempt DNA repair, trigger programmed cell death, engage in full-blown immune attack. This is, from the Atlan/Cohen perspective, the essence of cognition.

3. Emotion Thayer and Lane (2000) summarize the case for what can be described as a cognitive emotional process. Emotions, in their view, are an integrative index of individual adjustment to changing environmental demands, an organismal response to an environmental event that allows rapid mobilization of multiple subsystems. Emotions are the moment-to-moment output of a continuous sequence of behavior, organized around biologically important functions. These 'lawful' sequences have been termed 'behavioral systems' by Timberlake (1994).

Emotions are self-regulatory responses that allow the efficient coordination of the organism for goal-directed behavior. Specific emotions imply specific eliciting stimuli, specific action tendencies including selective attention to relevant stimuli, and specific reinforcers. When the system works properly,

it allows for flexible adaptation of the organism to changing environmental demands, so that an emotional response represents a *selection* of an appropriate response and the inhibition of other less appropriate responses from a more or less broad behavioral repertoire of possible responses. Such 'choice', we will show, leads directly to something closely analogous to the Atlan and Cohen language metaphor.

Damasio (1998) concludes that emotion is the most complex expression of homeostatic regulatory systems. The results of emotion serve the purpose of survival even in nonminded organisms, operating along dimensions of approach or aversion, of appetition or withdrawal. Emotions protect the subject organism by avoiding predators or scaring them away, or by leading the organism to food and sex. Emotions often operate as a basic mechanism for making decisions without the labors of reason, that is, without resorting to deliberated considerations of facts, options, outcomes, and rules of logic. In humans learning can pair emotion with facts which describe the premises of a situation, the option taken relative to solving the problems inherent in a situation, and perhaps most importantly, the outcomes of choosing a certain option, both immediately and in the future. The pairing of emotion and fact remains in memory in such a way that when the facts are considered in deliberate reasoning when a similar situation is revisited, the paired emotion or some aspect of it can be reactivated. The recall, according to Damasio, allows emotion to exert its pairwise qualification effect, either as a conscious signal or as nonconscious bias, or both, In both types of action the emotions and the machinery underlying them play an important regulatory role in the life of the organism. This higher order role for emotion is still related to the needs of survival, albeit less apparently.

Thayer and Friedman (2002) argue, from a dynamic systems perspective, that failure of what they term 'inhibitory processes' which, among other things, direct emotional responses to environmental signals, is an important aspect of psychological and other disorder. Sensitization and inhibition, they claim, 'sculpt' the behavior of an organism to meet changing environmental demands. When these inhibitory processes are dysfunctional – choice fails – pathology appears at numerous levels of system function, from the cellular to the cognitive.

Thayer and Lane (2000) also take a dynamic systems perspective on emotion and behavioral subsystems which, in the service of goal-directed behavior and in the context of a behavioral system, they see organized into coordinated assemblages that can be described by a small number of control parameters,

like the factors of factor analysis, revealing the latent structure among a set of questionnaire items thereby reducing or mapping the higher dimensional item space into a lower dimensional factor space. In their view, emotions may represent preferred configurations in a larger 'state-space' of a possible behavioral repertoire of the organism. From their perspective, disorders of affect represent a condition in which the individual is unable to select the appropriate response, or to inhibit the inappropriate response, so that the response selection mechanism is somehow corrupted.

Gilbert (2001) suggests that a canonical form of such 'corruption' is the excitation of modes that, in other circumstances, represent 'normal' evolutionary adaptations, a matter to which we will return at some length below.

4. 'Rational thought' Although the Cartesian dichotomy between 'rational thought' and 'emotion' may be increasingly suspect, nonetheless humans, like many other animals, do indeed conduct individual rational cognitive decision-making as most of us would commonly understand it. Various forms of dementia involve characteristic patterns of degradation in that ability.

5. Sociocultural network Humans, however, are particularly noted for a hypersociality which inevitably enmeshes us all in group processes of decision, i.e. collective cognitive behavior within a social network, tinged by an embedding shared culture. For humans, culture is truly fundamental. Durham (1991) argues that genes and culture are two distinct but interacting systems of inheritance within human populations. Information of both kinds has influence, actual or potential, over behaviors, which creates a real and unambiguous symmetry between genes and phenotypes on the one hand, and culture and phenotypes, on the other. Genes and culture are best represented as two parallel lines or tracks of hereditary influence on phenotypes.

Much of hominid evolution can be characterized as an interweaving of genetic and cultural systems. Genes came to encode for increasing hypersociality, learning, and language skills. The most successful populations displayed increasingly complex structures that better aided in buffering the local environment (e.g. Bonner, 1980).

Successful human populations seem to have a core of tool usage, sophisticated language, oral tradition, mythology, music, and decision making skills focused on relatively small family/extended family social network groupings. More complex social structures are built on the periphery of this basic object (e.g. Richerson and Boyd, 1995). The human species' very identity may rest on its unique evolved capacities for social mediation and cultural transmis-

sion. These are particularly expressed through the cognitive decision making of small groups facing changing patterns of threat and opportunity, processes in which we are all embedded and all participate.

III. Cognition as 'language'

Atlan and Cohen (1998), as we have paraphrased them, argue that the essence of cognition is comparison of a perceived external signal with an internal, learned picture of the world, and then, upon that comparison, the choice of one response from a much larger repertoire of possible responses. Clearly, from this perspective, the Thayer and Lane vision of the emotional process is cognitive. Upon recognition of a new perturbation in the surrounding environment, emotional cognition evaluates and choose from several possible responses: no action necessary, or one or a few succinct emotions elicited. Upon appropriate conditioning, the emotional response is able to accelerate the decision process as to what large-scale, general response may be needed, much as the immune system has a more efficient response to second pathogenic challenge once the initial infection has become encoded in immune memory. Similar considerations apply to individual rational thought and to culturally-sculpted group processes.

Following the approach of Wallace (2000, 2002a), we make a very general model of this process.

Pattern recognition-and-response, as we characterize it, proceeds by convoluting (i.e. comparing) an incoming external 'sensory' 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 (Cover and Thomas, 1991; Ash, 1990)

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

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

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

(1)

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

The Shannon-McMillan Theorem provides a kind of 'law of large numbers' and permits definition of the Shannon uncertainties in terms of cross-sectional sums of the form

$$H = -\sum P_k \log[P_k],$$

where the P_k are taken from a probability distribution, so that $\sum P_k = 1$. Again, Cover and Thomas (1991) or Ash (1990) provide algebraic details.

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.

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 'adiabatically piecewise memoryless ergodic' (APME). The ergodic nature of the information sources is a

generalization of the 'law of large numbers' and implies that the long-time averages we will need to calculate can, in fact, be closely approximated by averages across the probability spaces of those sources. This is no small matter.

IV. Interacting information sources: 'sociocultural psychoneuroimmunology'

We suppose that the behavior of a cognitive subsystem 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 'structured psychosocial stress' can also be 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 cognitive process and 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

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

(3)

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) or Ash (1990) for mathematical details. As stated above, the Shannon-McMillan Theorem and its variants permit expression of the various uncertainties in terms of cross sectional sums of terms of the form $-P_k \log[P_k]$ where the P_k are appropriate direct or conditional probabilities. 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, according to the Shannon-McMillan Theorem and its 'joint' variants,

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

(4)

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 cognitive system of interest and the structured 'language' 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

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

(5)

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; Wallace, 2000; 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 cognitive mechanism and external perturbation. An extensive mathematical treatment of these ideas is presented elsewhere (e.g. Wallace, 2000, 2002a,b; Wallace et al., 2003).

Elaborate developments are possible. From a the more limited perspective of the Rate Distortion Theorem, a selective corollary of the Shannon-McMillan Theorem, we can view the onset of a punctuated interaction between the cognitive mechanism and external stressors as the literal writing of distorted image of those stressors upon cognition:

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, Y_1, Y_2, Z, for which one in particular, here Z, is the 'embedding context' affecting the other two, can also be divided by a splitting criterion into two sets, having high and low probabilities respectively. The probability of a particular triplet of sequences is then determined by the conditional probabilities

$$P(Y_1 = y^1, Y_2 = y^2, Z = z) = \Pi_{j=1}^{n} p(y_j^1|z_j)p(y_j^2|z_j)p(z_j).$$

(6)

That is, Y_1 and Y_2 are, in some measure, driven by their interaction with Z.

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)

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

(7)

where splitting criterion is given by

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

$$H(Z) + H(Y_1|Z) + H(Y_2|Z) - H(Y_1, Y_2, Z).$$

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

We can, for the purposes of this work, extend this model to any number of interacting information sources, $Y_1, Y_2, ..., Y_s$ conditional on an external context Z in terms of a splitting criterion defined by

$$I(Y_1; ...; Y_s|Z) = H(Z) + \sum_{j=1}^{s} H(Y_j|Z) - H(Y_1, ..., Y_s, Z),$$

(8)

where the conditional Shannon uncertainties $H(Y_j|Z)$ are determined by the appropriate direct and conditional probabilities.

V. The simplest model of cognition and stress

Stress, as we envision it, is not a random sequence of perturbations, and is not independent of its perception. Rather, it involves a highly correlated, grammatical, syntactical process by which an embedding psychosocial environment communicates with an individual, particularly with that individual's multiple cognitive modules, typically in the context of social hierarchy. We first view the structured stress experienced by an individual as APME information source, interacting with a similar dual information source defined by some cognitive submodule or, more typically, an interacting 'splitting criterion' defined by the interaction of several such modules.

Again, the ergodic nature of the 'language' of stress is essentially a generalization of the law of large numbers, so that long-time averages can be well approximated by cross-sectional expectations. Languages do not have simple autocorrelation patterns, in distinct contrast with the usual assumption of random perturbations by 'white noise' in the standard formulation of stochastic differential equations.

Let us suppose we cannot measure either stress or cognitive submodule function directly, but can determine the concentrations of hormones, neurotransmitters, certain cytokines, and other biomarkers, or else macroscopic behaviors, beliefs, and other responses associated with the function of cognitive submodules according to some 'natural' time frame inherent to the system. This would typically be the circadian cycle in both men and women, and the hormonal cycle in premenopausal women. Suppose, in the absence of extraordinary 'meaningful' psychosocial stress, we measure a series of n biomarker concentrations, behavioral characteristics, other indices at time t which we represent as an n-dimensional vector X_t. Suppose we conduct a number of experiments, and create a regression model so that we can, in the absence of perturbation, write, to first order, the markers at time $t+1$ in terms of that at time t using a matrix equation of the form

$$X_{t+1} \approx \mathbf{R} X_t + b_0, \tag{9}$$

where $\mathbf{R}$ is the matrix of regression coefficients and b_0 a (possibly zero) vector of constant terms.

We then suppose that, in the presence of a perturbation by structured stress

$$X_{t+1} = (\mathbf{R} + \delta\mathbf{R}_{t+1})X_t + b_0$$

$$\equiv \mathbf{R}X_t + \epsilon_{t+1},$$

(10)

where we have absorbed both b_0 and $\delta\mathbf{R}_{t+1}X_t$ into a vector ϵ_{t+1} of 'error' terms which are not necessarily small in this formulation. In addition it is important to realize that this is not a population process whose continuous analog is exponential growth. Rather what we examine is more akin to the passage of a signal – structured psychosocial stress – through a distorting physiological, psychological, or sociocultural filter.

If the matrix of regression coefficients $\mathbf{R}$ is sufficiently regular, we can (Jordan block) diagonalize it using the matrix of its column eigenvectors $\mathbf{Q}$, writing

$$\mathbf{Q}X_{t+1} = (\mathbf{Q}\mathbf{R}\mathbf{Q}^{-1})\mathbf{Q}X_t + \mathbf{Q}\epsilon_{t+1},$$

(11)

or equivalently as

$$Y_{t+1} = \mathbf{J}Y_t + W_{t+1},$$

(12)

where $Y_t \equiv \mathbf{Q}X_t, W_{t+1} \equiv \mathbf{Q}\epsilon_{t+1}$, and $\mathbf{J} \equiv \mathbf{QRQ}^{-1}$ is a (block) diagonal matrix in terms of the eigenvalues of $\mathbf{R}$.

Thus the (rate distorted) writing of structured stress onto cognitive response through $\delta\mathbf{R}_{t+1}$ is reexpressed in terms of the vector W_{t+1}.

It is important to note that, in general, the eigenvectors of $\mathbf{R}$ are not orthogonal, suggesting the possibility that excitation of a single eigenvector will result in 'overtones' of 'mixed cognitive responses' in our model. We will return to the importance of nonorthogonality below.

The sequence of W_{t+1} is the rate-distorted image of the information source defined by the system of external structured psychosocial stress. This formulation permits estimation of the long-term steady-state effects of that image on emotional state. The essential trick is to recognize that because everything is (APM) ergodic, we can either time or ensemble average both sides of equation (12), so that the one-period offset is absorbed in the averaging, giving an 'equilibrium' relation

$$< Y >= \mathbf{J} < Y > + < W >$$

or

$$< Y >= (\mathbf{I} - \mathbf{J})^{-1} < W >,$$

(13)

where $\mathbf{I}$ is the $n \times n$ identity matrix.

Now we reverse the argument: Suppose that Y_k is chosen to be some fixed eigenvector of $\mathbf{R}$. Using the diagonalization of $\mathbf{J}$ in terms of its eigenvalues, we obtain the average 'cognitive excitation' in terms of some eigentransformed pattern of exciting perturbations as

$$< Y_k >= \frac{1}{1-\lambda_k} < W_k >$$

(14)

where λ_k is the eigenvalue of $< Y_k >$, and $< W_k >$ is some appropriately transformed set of ongoing perturbations by structured psychosocial stress.

The essence of this result is that *there will be a characteristic form of perturbation by structured psychosocial stress – the W_k – which will resonantly excite a particular 'mixed cognitive eigenmode'.* Conversely, by 'tuning' the eigenmodes of **R**, output can be trained to galvanized response in the presence of particular forms of long-lasting perturbation.

This is because, if **R** has been appropriately determined from regression relations, then the λ_k will be a kind of multiple correlation coefficient (e.g. Wallace and Wallace, 2000), so that particular eigenpatterns of perturbation will have greatly amplified impact. If $\lambda = 0$ then perturbation has no more effect than its own magnitude. If, however, $\lambda \to 1$, then the written image of a perturbing psychosocial stressor will have very great effect. Following Ives (1995), we call a system with $\lambda \approx 0$ *resilient* since its response is no greater than the perturbation itself.

In this model learning, is, most obviously, the process of tuning response to perturbation. That is, we envision the regression matrix **R** as itself a tunable set of variables.

Suppose we require that λ itself be a function of the magnitude of excitation, i.e.

$$\lambda = f(| < W > |)$$

where $| < W > |$ is the vector length of $< W >$. We can, for example, require the amplification factor $1/(1-\lambda)$ to have a signal transduction form, an inverted-U-shaped curve, for example the signal-to-noise ratio of a stochastic resonance, so that

$$\frac{1}{1-\lambda} = \frac{1/| < W > |^2}{1 + b \exp[1/(2| < W > |)]}.$$

(15)

This places particular constraints on the behavior of $\mathbf{R}$, and gives a pattern of initial generalized hypersensitization, followed by anergy or 'burnout' with increasing average stress, a behavior that might well be characterized as 'pathological resilience', and may also have evolutionary significance.

VI. The generalized cognitive homunculus and its retina: responding to sudden change

Cohen (2000) argues at some length for the existence of an 'immunological homunculus', i.e. the immune system's own perception of the body as a whole. The particular utility of such a homunculus, in his view, is that sensing perturbations in such a self-image can serve as an early warning sign of pending necessary inflammatory response – expressions of tumorigenesis, acute or chronic infection, parasitization, and the like. Thayer and Lane (2000) argue something analogous for emotional response as a quick internal index of larger patterns of threat or opportunity.

It seems obvious that the collection of interacting cognitive submodules we have explored above must also have a coherent internal self-image of the state of the mind-and-body and its social relationships. This inferred picture, at the individual level, we term the 'generalized cognitive homunculus', (GCH).

Suppose we write a GCH response to short-term perturbation – not the effects of long-lasting structured psychosocial stress – as

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

Again we impose a (Jordan block) diagonalization in terms of the matrix of (generally nonorthogonal) eigenvectors $\mathbf{Q}_0$ of some 'zero reference state' $\mathbf{R}_0$, obtaining, for an initial condition which is an eigenvector $Y_t \equiv Y_k$ of $\mathbf{R}_0$,

$$Y_{t+1} = (\mathbf{J}_0 + \delta\mathbf{J}_{t+1})Y_k = \lambda_k Y_k + \delta Y_{t+1} =$$

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

(16)

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

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

(17)

The essential point is that, provided $\mathbf{R}_0$ has been properly 'tuned', so that this condition is true, the first few terms in the spectrum of the plieotropic iteration of the eigenstate will contain almost all of the essential information about the perturbation, i.e. most of the variance. We envision this as similar to the detection of color in the optical retina, where three overlapping non-orthogonal 'eigenmodes' of response suffice to characterize a vast array of color sensations. Here, if a concise spectral expansion is possible, a very small number of (typically nonorthogonal) 'generalized cognitive eigenmodes' permit characterization of a vast range of external perturbations, and rate distortion constraints become very manageable indeed. Thus GCH responses – the spectrum of excited eigenmodes of $\mathbf{R}_0$, provided it is properly tuned – can be a very accurate and precise gauge of environmental perturbation.

The choice of zero reference state $\mathbf{R}_0$, i.e. the 'base state' from which perturbations are measured, is, we will claim, a highly nontrivial task, necessitating a specialized apparatus.

This is a critical point. 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). Here we have postulated the necessity of other physiological and social cognitive modules. 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 our generalized 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.

We argue that identification of the 'normal' state of the GCH – generalized cognition's self-image of the body and its social relationships – is a difficult matter requiring a dedicated cognitive submodule within overall generalized cognition. This is essentially because, for the vast majority of information systems, unlike mechanical systems, there are no 'restoring springs' whose low energy state automatically identifies equilibrium: relatively speaking, all states of the GCH are 'high energy' states. That is, active comparison must be made of the state of the GCH with some stored internal reference picture, and a decision made about whether to reset to zero, which is 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 generalized cognition and its image of the self, become increasingly complicated with rising number of cells and levels of linked cognition.

Failure of that cognitive submodule results in identification of an 'excited' state of the GCH as 'normal', triggering the collective patterns of systemic activation which constitute certain comorbid mental and chronic physical disorders. This would result in a relatively small number of characteristic 'eigenforms' of comorbidity, which would typically become more mixed with increasing disorder.

In sum, since such 'zero mode identification' (ZMI) is a (presumed) cognitive submodule of overall generalized cognition, it involves convoluting incoming 'sensory' with 'ongoing' internal memory data in choosing the zero state, i.e. defining $\mathbf{R}_0$. 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 and related arguments above. From a RDT perspective, then, those external information sources literally write a distorted image of themselves onto the ZMI, often in a punctuated manner: (relatively) sudden onset of a developmental trajectory to comorbid mental disorders and chronic inflammatory disease.

Different systems of external signals – including but not limited to structured psychosocial stress – will, presumably, write different characteristic

images of themselves onto the ZMI cognitive submodule, i.e. trigger different patterns of comorbid mental disorder and chronic diseases.

Elsewhere (R. Wallace, 2003) we speculate that patterns of autoimmune disease are likely to be related to both circadian and hormonal cycles, factors which may come into play in comorbidity of more general mental and chronic physical disorder.

Further theoretical development would introduce the 'generalized Onsager relation' analysis of gradient effects in driving parameters which affects system behavior between phase transitions (e.g. Wallace, 2002a). All these extensions remain to be done, and are not trivial.

VII. Generalized autocognitive disorder as a developmental disease

To reiterate, if Y represents the information source dual to 'zero mode identification' in generalized cognition, and if Z is the information source characterizing structured psychosocial stress, which serves as an embedding context, the 'mutual information' between them

$$I(Y;Z) = H(Y) - H(Y|Z)$$

(18)

serves as a splitting criterion for pairs of linked paths of states.

We suppose it possible to parametize the coupling between these interacting information sources by some 'inverse temperature', K, writing

$$I(Y;Z) = I[K],$$

(19)

with structured psychosocial stress as the embedding context.

Invocation of the mathematical homology between equations (4) and (5) permits imposition of renormalization formalism (Wallace, 2000; Wallace et al., 2003a) resulting in punctuated phase transition depending on K.

Socioculturally constructed and structured psychosocial stress, in this model having both 'grammar' and 'syntax', can be viewed as entraining the function of zero mode identification when the coupling with stress exceeds a threshold. More than one threshold appears likely, accounting in a sense for the typically staged nature of 'environmentally caused' disorders. These should result in a synergistic – i.e. comorbidly excited – mixed affective, 'rationally cognitive', psychosocial, and inflammatory 'excited state' of otherwise 'normal' response, and represent the effect of stress on the linked decision processes of various cognitive functions, in particular through the identification of a false 'zero mode' of the GCH. This is a collective, but highly systematic, 'tuning failure' which, in the Rate Distortion sense, represents a literal image of the structure of imposed psychosocial stress written upon the ability of the GCH to characterize a 'normal' mode of excitation, causing a mixed 'excited state' representing comorbid mental and chronic physical disorder.

Coronary heart disease (CHD) is already understood as a disease of development, which begins *in utero*. Work by Barker and colleagues, which we cited above, suggests that those who develop CHD grow differently from others, both in utero and during childhood. Slow growth during fetal life and infancy is followed by accelerated weight gain in childhood, setting a life history trajectory for CHD, type II diabetes, hypertension, and, of course, obesity. Barker (2002) concludes that slow fetal growth might also heighten the body's stress responses and increase vulnerability to poor living conditions later in life. Thus, in his view, CHD is a developmental disorder that originates through two widespread biological phenomena, developmental plasticity and compensatory growth, a conclusion consistent with the work of Smith et al. (1998), who found that deprivation in childhood influences risk of mortality from CHD in adulthood, although an additive influence of adult circumstances is seen in such cases.

With regard to asthma, Wright et al. (1998) find prospective epidemiological studies showing that the newborn period is dominated by Th2 reactivity in response to allergens, and it is also evident that Th1 memory cells selectively develop shortly after birth, and persist into adulthood in non-atopic subjects. For most children who become allergic or asthmatic, the polar-

ization of their immune systems into an atopic phenotype probably occurs during early childhood. There is evidence that parental reports of life stress are associated with subsequent onset of wheezing in children between birth and one year. It has been speculated that stress triggers hormones in the early months of life which may influence Th2 cell predominance, perhaps through a direct influence of stress hormones on the production of cytokines that are thought to modulate the direction of immune cell differentiation.

We are led to suggest that these two case histories represent a far more general phenomenon in the etiology of the larger spectrum of chronic and comorbid mental and physical disorders, in the sense that structured psychosocial stress can literally write an image of itself upon the developing child, and if acute enough, on the adult, initiating trajectories to comorbid mental and chronic physical disorder.

VIII. Remarks on schizophrenia

Schizophrenia, as it does not fully display the 'health disparities' pattern which is the central focus of this work, seems nonetheless to fall broadly within the paradigm of a developmental, generalized autocognitive disorder. As Gaughran et al. (2002) note, there is good evidence of immune activation in schizophrenia. Up to a third of patients has an autoimmune condition clinically unrelated to their psychiatric illness, and first degree relatives of people with schizophrenia also have increased incidence of autoimmune disease.

Torrey and Yolken (2001) note the similarities and contrasts between schizophrenia and rheumatoid arthritis. Both are chronic, persistent diseases displaying lifelong prevalence and a relapsing and remitting course. Both are felt to involve environmental insults occurring in genetically susceptible individuals, and their diagnosis depends upon syndromal diagnostic criteria which have been developed by committees and have changed over time. Many studies, however, have observed a striking inverse correlation between the two diseases, although both are believed to run in families, with a population prevalence of about one percent. That is, people with schizophrenia seem less likely to suffer from rheumatoid arthritis, although perhaps more likely to suffer autoimmune disease in general.

This begins to resemble the 'eigenmode' patterns discussed above.

Grossman et al. (2003) describe how the recent emphasis on schizophrenia as a developmental disorder has focused on characterizing the role of non-genetic factors in the development of symptom patterns. Certain prenatal and perinatal environmental exposures, including maternal stress and

malnourishment, and obstetric complications such as low birth weight, have been reported to be associated with increased susceptibility to the disorder. Increased incidence has also been reported in children born to mothers who experienced infection from influenza or rubella during the second trimester of pregnancy. Thus early neurodevelopmental processes may be compromised, laying groundwork for disorder when taxed by later developmental demands, for example those associated with the stressful periods of social development in childhood and adolescence.

Rothermundt et al. (2001) further summarize at some length the case for both the infection and autoimmune hypotheses regarding onset of schizophrenia.

Torrey and Yolken (2001) conclude that the negative association between schizophrenia and rheumatoid arthritis may depend on the timing of some critical exposure, e.g. that exposure in utero or childhood produces schizophrenia, while exposure in adulthood produces rheumatoid arthritis. A slightly different hypothesis, consistent with the mathematical exercises above, is that rheumatoid arthritis and schizophrenia characterize different excited mixed eigenmodes falsely and recurrently identified as zero states by the progressive failure of the ZMI module discussed above. Such would tend to be mutually exclusive, although not absolutely so since the eigenmodes are not orthogonal.

The central focus of our analysis, however, remains the effects of structured psychosocial stress on the failure of the ZMI cognitive module, and further discussion of schizophrenia from our perspective will be the subject of a subsequent paper.

IX. Discussion and conclusions

Much of our reasoning has been based on a fairly elaborate mathematical model. Mathematical models of physiological, social, and other ecosystems – like those we present here – are notorious for their unreliability, instability, and oversimplification. As it is said, "all models are wrong, but some models are useful". The mathematical ecologist E.C. Pielou (1977, p. 106) puts the matter thus:

> "...[Mathematical] models are easy to devise; even though the assumptions of which they are constructed may be hard to justify, the magic phrase 'let us assume that...' overrides objections

> temporarily. One is then confronted with a much harder task: How is such a model to be tested? The correspondence between a model's predictions and observed events is sometimes gratifyingly close but this cannot be taken to imply the model's simplifying assumptions are reasonable in the sense that neglected complications are indeed negligible in their effects...
>
> In my opinion the usefulness of models is great... [however] it consists *not in answering questions but in raising them.* Models can be used to inspire new field investigations and these are the only source of new knowledge as opposed to new speculation."

The speculations arising from our analysis are of some interest. In particular our speculation that comorbid mental and chronic physical disorder represents a pathological 'excited' state is consistent with theorizing in both autoimmune disease and mental disorder. Gilbert (2001), for example, uses an evolutionary approach to conclude that the relatively small number of evolved adaptive defense mechanisms, for example the flight-or-fight hypothalamic-pituitary-adrenal (HPA) axis, may become pathologically activated to produce mental disorder. He suggests that such evolved defenses, of which there is a limited number, can become pathological when they are too easily aroused or prolonged, are arrested (i.e. aroused but not expressed), or are ineffective. These might involve depression, anxious arousal, or heightened vigilance to threat, with the type of defense (e.g. flight, fight, submit, help seeking) being mirrored in particular symptom presentations.

Jones and Blackshaw (2000) likewise argue that behavioral similarities between humans and animals show that many psychiatric states are distortions of evolved behavior, a perspective which provides, in their view, a new etiological approach to psychiatry transcending current mainstream empirical and phenomenological approaches which are principally forms of symptom classification.

Our work here attempts to extend this perspective to include chronic diseases of inflammation, in the context of local sociocultural network function so important in humans, and to incorporate the particular effects of structured psychosocial stress in the development of symptoms over the life course.

The model which emerged focuses on the 'eigenstructure' of a generalized cognitive homunculus, and particularly on failure of a higher cognitive module which permits identification of the 'zero mode' of such a homunculus. For

certain classes of comorbid mind/body symptomatology, early experiences of exposure to structured psychosocial stress can trigger identification of an 'excited mode' as the zero-reference state, and initiate a life course of comorbid psychiatric/inflammatory disorders. The typical pattern we have in mind would involve individual and population-level comorbidity among obesity, diabetes, hypertension, depression/anxiety, substance abuse, violent behaviors, coronary heart disease, breast/prostate cancer, and asthma or lupus – what might well be characterized as 'oppression disorder' at the individual level.

Our analysis suggests that historical patterns of discrimination, deprivation, and injustice – for example the evolved system of slavery which has been characterized as 'American Apartheid' – are a determining feature in population-level expression of comorbid psychiatric and chronic inflammatory disorder, patterns which are literally an image of that system imposed upon children, beginning in their mothers' wombs.

The more dubious aspects of the history of the United States are alive and well and being rewritten daily upon the developing bodies of its children.

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