

Review

Immune cognition and vaccine strategy: beyond genomics

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Abstract

I.R. Cohen's work on immune cognition has profound implications for vaccine strategies when simple elicitation of sterilizing immunity fails, given Nisbett's analysis showing that cognition by the central nervous system is culturally determined. We reinterpret West African cultural variation in immune response to malaria, and the US cultural variation in HIV transmission, from this perspective, which does not reify 'race'. © 2002 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

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1. Introduction

Malaria and HIV are the major causes of morbidity and mortality for which no vaccine strategy has produced sterilizing immunity. Malaria has a complicated parasite life cycle with multiple and often changing antigens, and HIV is an evolution machine. Indeed, many, if not most, infectious diseases and malignancies have basic ecological and life-cycle factors that obviate simple effective vaccination on the smallpox model.

Such complications are increasingly under scrutiny, for example, interactions between the central nervous system (CNS) and the immune system, and between the genetic heritage and the immune system have become officially recognized and academically codified through journals with titles such as *Neuroimmunology* and *Immunogenetics*. We introduce here another complication, arguing that the culture in which humans are socially embedded also interacts with individual immune systems to form a composite entity that might well be labeled an immunocultural condensation (ICC).

We first examine current visions of the interaction between genes and culture, and between the CNS and culture, and follow with a summary of Cohen's view of immune cognition [1–3]. We next argue that immune cognition and cognitive socioculture can become fused into

a composite entity, the ICC, following the arguments of Nisbett et al. [4]. In the light of the ICC we reinterpret recent observations of culturally specific immune response to malaria in West Africa, and to heterosexual AIDS in the US.

2. Genes, cognition, and culture

Increasingly, biologists excoriate simple genetic reductionism which neglects the role of environment. Lewontin [5], for example, explains that genomes are not 'blueprints', as genes do not 'encode' for phenotypes. Organisms are instead outgrowths of fluid, conditional interactions between genes and their environments, as well as developmental 'noise'. Organisms, in turn, shape their environments, generating what Lewontin terms a triple helix of cause and effect. Such interpenetration of causal factors may be embodied by an array of organismal phenomena, including, as we shall discuss, culture's relationships with the brain and the immune system. We propose reinterpreting immune function in this light, with profound implications for medical and public health interventions for infectious diseases where the smallpox model fails.

The current vision of human biology among evolutionary anthropologists is consistent with Lewontin's analysis and is summarized by Durham [6]. Durham 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

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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.

A goodly part of hominid evolution can be characterized as an interweaving of genetic and cultural systems. Genes came to encode increasing hypersociality, learning, and language skills. The most successful populations displayed increasingly complex structures that better aided in buffering the local environment [7].

Every successful human population seems to have a core of tool usage, sophisticated language, oral tradition, mythology and music, focused on relatively small family/extended family groupings of various forms. More complex social structures are built on the periphery of this basic genetic-cultural object [8].

At the level of the individual, the genetic-cultural object appears to be mediated by what evolutionary psychologists postulate are cognitive modules within the human mind [9]. Each module was shaped by natural selection in response to specific environmental and social conundrums Pleistocene hunter-gatherers faced. One set of such domain-specific cognitive adaptations addresses problems of social interchange [10]. The human species’ very identity may rest, in part, on its unique evolved capacities for social mediation and cultural transmission. Anthropologist Robert Boyd has remarked that culture is as much a part of human biology as the enamel on our teeth.

The brain-and-culture condensation has been adopted as a kind of new orthodoxy in recent studies of human cognition. For example, Nisbett et al. [4] review an extensive literature on empirical studies of basic cognitive differences between individuals raised in what they call ‘East Asian’ and ‘Western’ cultural heritages. They view Western-based pattern cognition as ‘analytic’ and East-Asian as ‘holistic’ Nisbett et al. [4] find the following. 1) Social organization directs attention to some aspects of the perceptual field at the expense of others. 2) What is attended to influences metaphysics. 3) Metaphysics guides tacit epistemology, that is, beliefs about the nature of the world and causality. 4) Epistemology dictates the development and application of some cognitive processes at the expense of others. 5) Social organization can directly affect the plausibility of metaphysical assumptions, such as whether causality should be regarded as residing in the field vs. in the object. 6) Social organization and social practices can directly influence the development and use of cognitive processes such as dialectical vs. logical ones.

Nisbett et al. [4] conclude that tools of thought embody a culture’s intellectual history, that tools have theories built into them, and that users accept these theories, albeit unknowingly, when they use these tools.

We argue that the condensation between culture and both the gene and the brain described here may also be found for

the immune system. The next step is to show that the immune system is also cognitive.

3. Immune cognition

Recently Atlan and Cohen [3] have proposed an information-theoretic model of immune function and process, a paradigm incorporating pattern recognition behaviors analogous to those of the CNS.

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. As the meaning is defined by the type of response there is indeed a response repertoire, not merely a receptor repertoire.

To account for immune interpretation, Cohen [1] 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 is 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 func

tional ‘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.

4. Immune cognition and culture

As we show at length elsewhere [11–16], it is possible to give Atlan and Cohen’s language metaphor of meaning-from-response a precise information-theoretic characterization, and to place that characterization within a context of recent developments which propose the ‘coevolutionary’ mutual entrainment of different information sources to create larger metalanguages with the originals as subdialects. This work, a formalism based on the Large Deviations Program of applied probability, permits treating gene-culture and brain-culture condensations using a unified conceptual framework of information source ‘coevolutionary condensation’. Cohen’s immune cognition model suggests, then, the possibility that human culture and the human immune system may be jointly convoluted: that is, there would appear to be, in the sense of the gene-culture and brain-culture condensations of the previous section, an immune-culture condensation as well. To ‘neuroimmunology’ and ‘immunogenetics’ we add ‘immunocultural condensation’.

The evolutionary anthropologists’ vision of the world implies that language, culture, gene pool, and individual CNS and immune cognition are intrinsically melded and synergistic. We propose that where the smallpox vaccine model fails, culture and immune cognition may become a joint entity, determining, in considerable measure, the kind of vaccine strategy which may be effective. This effect may be ‘confounded’—and even masked—by the distinct population genetics often associated with linguistic and cultural isolation.

Africa contains great cultural and genetic diversity, suggesting the need for severe local refining and monitoring of any vaccine strategy. Traditional ‘case-control’ studies can, in fact, be profoundly compromised by linguistic and cultural differences which are convoluted with an associated genetic divergence that may be a simple marker of such difference rather than its cause. Similarly, the US, as a nation of immigrants, encompasses considerable cultural and genetic diversity, even in the context of both de-jure and de-facto deculturation.

In sum, population differences of immune function heretofore attributed to genetic factors alone may, rather, represent differences in immune cognition driven by, or through, the proposed ICC, synergistic with profound cultural differences.

We reinterpret recent observations on malaria in Burkina Faso and heterosexual AIDS in New Jersey from this perspective.

5. Malaria and the Fulani

Modiano et al. [17–20] have conducted comparative surveys on three roughly co-resident West African ethnic groups—which they describe as ‘sympatric’—exposed to the same strains of malaria. The Fulani, Mossi, and Rimaibe live in the same conditions of hyperendemic transmission in Sudan savanna area northeast of Ouagadougou, Burkina Faso. The Mossi and Rimaibe are Sudanese Negroid populations with a long tradition of sedentary farming, while the Fulani are nomadic pastoralists, partly settled and characterized by non-Negroid features of possible Caucasoid origin.

Parasitological, clinical, and immunological investigations showed consistent interethnic differences in *Plasmodium falciparum* infection rates, malaria morbidity, and prevalence and levels of antibodies to various *P. falciparum* antigens. The data point to a remarkably similar response to malaria in the Mossi and Rimaibe, while the Fulani are clearly less parasitized, less affected by the disease, and more responsive to all antigens tested. No difference in the use of malaria protective measures was demonstrated that could account for these findings. Known genetic factors of resistance to malaria showed markedly *lower* frequencies in the Fulani [19]. The differences in the immune response were not explained by the entomological observations, which indicated substantially uniform exposure to infective bites.

Modiano et al. [17] conclude that sociocultural factors do not seem to be involved, and that the available data support the existence of unknown genetic factors, possibly related to humoral immune responses, determining interethnic differences in the susceptibility to malaria. In spite of their later finding that the Fulani in their study region have significantly *reduced* frequencies of the classic malaria-resistance genes compared to the other ‘sympatric’ ethnic groups, Modiano et al. [19] again conclude that their evidence supports the existence in the Fulani of unknown genetic factor(s) of resistance to malaria.

This vision of the world carries consequences, seriously constraining interpretation of the efficacy of interventions. Modiano et al. [20] recently conducted an experiment in their Burkina Faso study zone involving the distribution of permethrin-impregnated curtains (PIC) to the three populations, with markedly different results. They relate as follows:

“The PIC were distributed in June 1996 and their impact on malaria infection was evaluated in [the three] groups whose baseline levels of immunity to malaria differed because of their age and ethnic group. Age- and ethnic-dependent efficacy of the PIC was observed. Among Mossi and Rimaibe, the impact (parasite rate reduction after PIC installation with respect to the pre-intervention surveys) was 18.8% and 18.5%, respectively. A more than twofold general impact (42.8%) was recorded in the Fulani. The

impact of the intervention on infection rates appears positively correlated with the levels of anti-malaria immunity...”

Most critically, Modiano et al. [20] conclude from this experiment that the expected complementary role of a hypothetical vaccine is stressed by these results, which also emphasize the importance of the genetic background of the population in the evaluation and application of malaria control strategies.

While we fully agree with the importance of the results for a hypothetical vaccine, much in the spirit of Lewontin [5] we beg to differ with the ad hoc presumptions of genetic causality, which paper over alternatives involving environment and development consistent with these observations. Recently the medical anthropologist Andrew Gordon published a remarkable study of Fulani cultural identity and illness [21]. He remarks the following:

“Cultural identity—who the Fulani think they are—informs thinking on illnesses they suffer. Conversely, illness, so very prevalent in sub-Saharan Africa, provides Fulani with a consistent reminder of their distinctive condition... How they approach being ill also tells Fulani about themselves. The manner in which Fulani think they are sick expresses their sense of difference from other ethnic groups. Schemas of [individual] illness and of collective identity draw deeply from the same well and web of thoughts... As individuals disclose or conceal illness, as they discuss illness and the problem of others, they reflect standards of Fulani life—being strong of character not necessarily of body, being disciplined, rigorously Moslem, and leaders among lessors... to be in step with others and with cultural norms is to have pride in the self and the foundations of Fulani life.”

The Fulani carried the Islamic invasion of Africa into the sub-Sahara, enslaving and deculturating a number of ethnic groups, and replacing the native languages with their own. This is much the way African Americans were enslaved, deculturated, and taught English. As Gordon puts it:

“‘True Fulani’ see themselves as distinguished by their aristocratic descent, religious commitments, and personal qualities that clearly differ from lowland cultivators. Those in the lowland are, historically, Fulani subjects who came to act like and speak Fulani, but they are thought to be without the right genealogical descent. The separation between pastoralists and agriculturists repeats itself in settlements across Africa. The terms vary from place to place in Guinea, the terms are Fulbhe for the nobles and the agriculturalist Bhalebhe or Maatyubhee; in Burkina Faso, Fulbhe and the agricultural Rimaybhe; and in Nigeria, the Red Fulani and the agricultural Black Fulani... The schemas for the Fulani body describe the differences between them and others. These are differences that justify pride in being Fulani and not Bhalebhe, Maatyubhe, Rimaybhe, or Black Fulani. In Guinea, the word ‘Bhalebhe’ means ‘the black one’. The term ‘Bhalebhe’ carries the same meaning as ‘Negro’ did for Africans brought to North America. It effaces any tribal identity...”

The control a Fulani exercises over the body is an essential feature of ‘the Fulani way’. Being out of control is shameful and not at all Fulani-like... To act without restraint is to be what is traditionally thought of as Bhalebhe...

Being afflicted with malaria—and handling it well—is a significant proof of ethnicity. How Fulani handle malaria may be telling. What they lack in physical resistance to disease they make up in persistence. Although sickly, Fulani men only reluctantly give in to malaria and forgo work. To give in to physical discomfort is not *dimo*. When malaria is severe for a man he is likely not to succumb to bed, but instead to sit outside of his home socializing.”

Parenthetically, many primate studies (e.g. [22]) show that dominance rank, an important psychosocial factor, strongly and positively affects immune response in a stable social setting, while a vast body of parasitological observation and theory (e.g. [23]) shows the ‘overdispersion’ of parasites within affected populations—i.e. relative concentration—is closely but inversely related to social dominance.

Our Occam’s razor hypothesis, then, is that the observed significant difference in both malarial parasitization and efficacy of intervention between the dominant Fulani and co-resident ethnic groups in the Ouagadougou region of Burkina Faso is largely accounted for by factors of immunocultural condensation, particularly in view of the *lower* frequencies of classic malaria-resistance genes found in the Fulani.

Given their protective ICC, the Fulani simply may not need those classic genes. It is not that the Fulani are not parasitized, or that the ‘Fulani way’ prevents disease, but that the population-level burdens of environment are modulated by historical development, and these are profoundly different for the (former) masters and the (former) slaves.

6. ‘Heterosexual AIDS’ in northern New Jersey

Studies by Skurnick et al. [24] and Rohowsky-Kochan et al. [25], under the general rubric of the Heterosexual Transmission Study (HATS), have examined 224 heterosexual couples discordant for HIV type 1 infection (one partner HIV infected) and for 78 HIV-concordant couples (both partners HIV-infected) to identify demographic and behavioral risk factors for HIV transmission. A large subset of this cohort was subsequently studied for differences in major histocompatibility complex-encoded class I and class II antigens.

Couples were characterized by ‘ethnicity’ as ‘Black, non-Hispanic’, ‘white, non-Hispanic’, and ‘Hispanic’. Skurnick et al. [24] state:

“In New Jersey, heterosexual transmission has played nearly as large a role in the AIDS epidemic as has injection drug use. Heterosexual contact was the category of transmission associated with the greatest increase in reported AIDS cases from 1994 to 1995. The severity of the

epidemic and the frequency of heterosexual transmission in northern New Jersey motivated us... to evaluate the importance of behavioral and biological factors that facilitate or impede heterosexual transmission of HIV...

Risk factors that had significant bivariate associations with concordance were included in a multiple logistic regression model to evaluate their relative importance in their simultaneous effects on concordance... Ethnicity was the strongest correlate. Black and Hispanic couples were both more likely to be concordant [in HIV infection] than were whites or others."

This was no small effect. The odds ratio for concordance associated with 'Hispanic' ethnicity was 4.9 (1.9–12.7, $P = 0.001$), that for 'Black' a whopping 8.6 (2.9–25.3, $P = 0.0001$). The numbers in parenthesis are the 95% confidence limits and the associated P -value.

A principal conclusion of Skurnick et al. [24] was that ethnicity may relate to genetic differences in susceptibility of the uninfected partner or infectiousness of the infected partner. That is, genetic factors *entirely internal* to the couples themselves primarily determine their concordant or discordant status.

The subsequent paper by Rohowsky-Kochan et al. [25] examines the genetic hypothesis in more detail:

"Our results suggest that there may be different HLA alleles involved in the susceptibility and/or resistance to HIV infection in individuals of different ethnic backgrounds. It is possible that an as yet unidentified susceptibility/resistance genetic factor for HIV infection may be linked with different HLA alleles in different ethnic backgrounds...

The American Caucasians... are a very heterogeneous group comprised of a mixture of [identifiable] ethnic sub-populations...

[S]ignificant HLA associations with HIV resistance/susceptibility were detected in both Black and Hispanic cohorts but not in Caucasians... suggest[ing] that genetic factors may play a role in the finding of [24] that Black and Hispanic heterosexual couples have a greater risk for HIV-1 concordance than Caucasian couples."

Again, alternative explanations consistent with the results are left unexplored in favor of a simplistic genetic reductionism.

European colonialism in the Americas parallels, in critical respects, that of the Fulani in sub-Saharan Africa. 'Black' populations now speak English, and 'Hispanic' populations Spanish, and these terms efface tribal identity. Although white ethnics can usually trace their past to some European homeland, African-Americans—'Negroes', 'Blacks'—many of whom are, after 200 years of sexual exploitation in slavery, more than a little 'white', usually cannot. Intermediate are the Hispanics in the US, who are, in spite of Spanish colonialism, more recognizably diverse. In Northern New Jersey they include self-identified Cubans, Puerto Ricans, Mexicans, Garafuna, Aymara, etc. etc., many of whom travel regularly to the homeland.

Northern New Jersey is, however, according to many studies [26,27], one of the most heavily segregated regions of the US. Newark, the largest city in Northern New Jersey, in terms of what Massey and Denton [26] call statistical measures of unevenness, isolation, clustering, centralization and concentration, is even more segregated than nearby New York City, one of the world's most segregated cities. As Massey and Denton [26] put it, comparing African-Americans and Hispanics:

"No other group in the contemporary US comes close to this level of isolation within urban society. The US Hispanics, for example, are also poor and disadvantaged; yet in no metropolitan area are they hypersegregated. Indeed, Hispanics are never highly segregated on more than three [of our five study factors] simultaneously... Despite their immigrant origins, Spanish language, and high poverty rates, Hispanics are considerably more integrated in the US society than are blacks."

Given these circumstances, and taking malaria in Burkina Faso as a template, it seems evident that effects of the ICC in the context of the US system of Apartheid ensure that Caucasian couples would show fewer genetic markers of HIV than others, and that Blacks would show greater susceptibility to HIV transmission than Hispanics, and Blacks and Hispanics together, greater susceptibility than Caucasians.

7. Conclusions and speculations

At the individual level, as opposed to community scales of space, time and population, these matters are fairly well understood. Recent work by Kiecolt-Glaser and Glaser [28–30], for example, has examined the effect of 'chronic stress' on the efficacy of influenza, hepatitis B, and pneumococcal pneumonia vaccine among elderly caregivers of dementia patients, and among medical students.

They found, for influenza, that the caregivers showed a poorer antibody response following vaccination relative to control subjects, as assessed by ELISA and hemagglutination inhibition. Caregivers also had lower levels of in vivo virus-specific-induced interleukin 2 levels and interleukin 1-beta. The data demonstrate that down-regulation of the immune response to influenza virus vaccination is associated with a chronic stressor in the elderly.

Similar effects were found among the elderly caregivers for response to pneumococcal pneumonia vaccination, leading to the conclusion that chronic stress can inhibit the stability of the IgG antibody response to a bacterial vaccine. Medical students who reported greater social support and lower anxiety and stress demonstrated a higher antibody response to HEP-B surface antigen at the end of the study period.

Glaser et al. [29] conclude that the differences in antibody and T-cell responses to HEP-B and influenza virus vaccinations provide a demonstration of how stress may be

able to alter both the cellular and humoral immune responses to vaccines and novel pathogens in both younger and older adults.

We reiterate that a vast body of animal model studies involving socially structured populations shows clear impacts of acute and chronic social and other stressors on immune competence (e.g. [31–33]). Elenkov and Chrousos [34] in particular suggest that glucocorticoids and catecholamines, the end-products of the stress system at the individual level, might selectively suppress cellular immunity, Th1 phenotype, in favor of humoral response—again at the individual level.

We suggest, however, that the essential role of culture in human biology takes matters considerably beyond such individual-level stress models, and into realms for which, to paraphrase Robert Boyd's aphorism, culture is as much a part of the human immune system as are T cells. We have characterized the interaction between immune and sociocultural cognition as an immunocultural condensation, and use the concept to provide an Occam's razor explanation of observed differences in patterns of malarial parasitization and response to intervention among co-resident ethnic groups in a section of Burkina Faso, and rates of heterosexual transmission of AIDS within different ethnic groups in Northern New Jersey.

The relation between the Fulani and the Rimaibe mirrors the relation between 'white' and 'Black' residents of the US. Thus we suspect that differences in ICC may play a large role in the health disparities evident between those groups, an effect which persists even in the face of adjustment for socioeconomic factors. This suggests the continuing burden of history—what organizational ecologists have come to call path dependence—written upon the individual level ICC.

AIDS is a disease of marginalization and poverty, spreading along the structural flaws of a society like water through cracks in ice. Cross-sectional marginalization and deprivation are synergistic with longitudinal path dependent, i.e. historically driven, structures of ICC to define the ecology of the infection. This perspective, unlike current simplistic geneticism, does not reify 'race', but rather focuses on the central roles of environment and development in the production of susceptibility to pathology and related phenotypes [5]. The analysis directly incorporates path dependence in a natural manner, making explicit the often-enduring effects of historical patterns of social, political, and economic exploitation. It goes well beyond cross-sectional socioeconomic status analyses.

To the degree that factors of ICC dominate a disease ecology, there is unlikely to be an effective, single, one-size-fits-all vaccine strategy. On the other hand, a more flexible attack, which makes appropriate use of ICC mechanisms may enjoy a synergistic boost in effectiveness, at least among those who do not bear the burdens of history. For those who do, however, as the experiment with insecticide-treated curtains in Burkina Faso implies, matters may be

difficult indeed. Many of these matters should be directly testable, using immune system adaptations of Nisbett's [4] experimental techniques.

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