

Farming human pathogens

Here we examine examples of the farming of coevolutionary systems, focusing on the mutually amplifying roles of large-scale psychosocial stress, economic structure, and reductionist interventions in the ecology and evolution of highly adaptive disease organisms. We find, in general, that population-level socioeconomic and other stressors, in synergism with reductionist interventions, are precisely suited to trigger mesoscale resonance coevolutionary resilience domain shifts affecting rapidly evolving pathogens. In an ideal world these changes would be the deliberate alteration of socioeconomic structure aimed at decreasing rates of infection and/or virulence, perhaps extending the utility of reductionist intervention. These case histories examine exactly contrary patterns.

6.1 Culture and the infection phenotype: a modeling exercise

Taking the perspectives of the earlier chapters, we can begin to model how population-directed, structured, psychosocial stress imposes an image of itself on the coevolutionary conflict between a highly adaptive chronic infection and the immune response.

As population-level structured stress appears a fundamental part of the biology of disease in human populations, this suggests the possibility that simplistic individual-oriented magic-bullet drug treatments, vaccines, and risk-reduction programs that do not address the fundamental living and working conditions which underlie disease ecology will fail to control many current epidemics. In addition, such reductionist interventions may go so far as to select for more holistic pathogens characterized by processes operating at multiple levels of biocultural organization.

6.1.1 Introduction

Earlier work in this direction (Wallace and Wallace, 2002; Wallace, 2002a) examined culturally-driven variation in HIV transmission and malaria pathology. HIV responds to immune challenge as an evolution machine, generating copious variation and hiding from counterattack in refugia at multiple scales of space, time, and population. *P. falciparum* engages in analogous rapid clonal antigenic variation, and cyto-adherence and sequestration in the deep vasculature, primary mechanisms for escaping from antibody-mediated responses of the host's immune system (Alred, 1998). Something much like the mutator phenotype (Thaler, 1999) or second order selection (Tenallion et al., 2001), by which the mechanisms mutations come about are themselves subjected to selection, appears to generate antigenic variation in the face of immune attack for a large class of pathogens. This could well be another version of the Baldwin effect.

Concomitantly, DiNoia and Neuberger (2002) outline the mechanisms by which the immune system's own antibody-producing B-cells engage in a second-order fine tuning of antibody production through somatic hypermutation, allowing organisms to respond quickly and effectively to pathogens that they have been exposed to previously (Gearhart, 2002).

Many chronic infections, particularly pathogens that cloak themselves in antigenic coats of many colors, are very often marked by distinct stages over the course of disease. HIV infections typically involve an initial viremia triggering an immune response that drives the virus into refugia during an extended asymptomatic period which, with the collapse of the immune system, ends in AIDS. Malaria's most evident stages are expressed as explosive outbursts of rapid parasite replication that facilitate insect-mediated transmission between hosts. HIV, malaria, and a third disease, tuberculosis, account for over five million deaths a year worldwide and exemplify the evolutionary success of multiple-stage chronicity as a life history strategy (Ewald, 2000; Villarreal, et al., 2000).

Here we analyze how pathogen life history stages represent a kind of co-evolutionary punctuation for chronic infection in the face of relentless immune and other selection pressures. For HIV that punctuation may arise from the direct interactions between the virus and the immune system response. In the case of malaria, it may result by means of a second order punctuation through the mutator mechanism (Thaler, 1999) associated with rapid antigenic variation. Elsewhere we have studied clonal selection in tumorigenesis from such a second order perspective (Wallace et al., 2003).

How can we characterize the interpenetration between antagonistic adaptive processes that defines disease dynamics? As described earlier, Adami et al. (2000) applied an information theoretic approach to conclude that genomic complexity resulting from evolutionary adaptation can be identified with the amount of information a gene sequence stores about its environment. Lewontin (2000) suggested something of a reverse process, in which environmental

complexity represents the amount of information organisms introduce into their environment as a result of their collective actions and interactions. We propose modeling the interactions among information sources – generalized languages – provides a more faithful encapsulation of the interactive, multi-scale nature of pathogen-immune dynamics than does the common differential equation predator-prey paradigm (e.g., Nowak and May, 2000).

Characterizing information sources as able to reflect their own context, as Adami et al. mapped out, we have applied a rate distortion argument in the context of imposed renormalization symmetry to obtain evolutionary punctuated equilibrium, and can use the more general Joint Asymptotic Equipartition Theorem (JAEPT) to conclude that pathogenic adaptive response and coupled cognitive immune challenge will be jointly linked in chronic infection, and subject to a transient punctuated interpenetration very similar to evolutionary punctuation. Multiple punctuated transitions, perhaps of mixed order, may well constitute shifts to the different stages of chronic infection.

Examining paths in parameter space for the renormalization properties of such transitions – the universality class tuning of chapter 3 – produces a second order punctuation in the rate at which the selection pressure of the immune system imposes a distorted image of itself onto pathogen structure. This is our version of the mutator or Tenallion et al.’s second order selection.

Recognizably similar matters have long been under scrutiny: interactions between the central nervous system (CNS) and the immune system, and between genetic heritage and the immune system have become academically codified through journals with titles such as *Neuroimmunology* and *Immunogenetics*. Elsewhere (Wallace and Wallace, 2002) we introduced another complication by arguing that the culture in which humans are socially embedded also interacts with individual immune systems to form a composite entity that we labeled an *immunocultural condensation* (ICC). It is, we will argue here, the joint entity of immune, CNS, and embedding sociocultural cognition that engages in orders of punctuated interpenetration with an adaptive chronic infectious challenge. Similar arguments are already in the French literature (e.g., Combes, 2000).

Included among the most damaging cultural inputs on immune system function are the long-term psychosocial stresses of war, oppression, and discrimination imposed by one population on another. If valid, the paradigm has fundamental consequences for concepts of human biology. While Diamond (1997) and others (Crosby, 1986; Hughes, 2001) popularized ecological explanations of human history, the paradigm presented here suggests investigation in something of the other direction, at the means by which human history shapes biological ontogeny, often through punctuated processes of mesoscale resonance.

The paradigm would appear to have practical implications as well. Interpenetrations among pathogens, the immune system’s response, and the embedding culture in which individuals find themselves would greatly color the success of the kinds of individual-level disease interventions largely pursued

today. Reductionist interventions – drug regimens, vaccines, risk reduction programs – aimed at holistic diseases, defined by myriad processes operating at multiple scales of time and space both within and without individuals, are likely to fail. Furthermore, what successes reductionist interventions have had against reductionist diseases may very well select for holistic diseases able to dilute or deflect the effectiveness of interventions pursued at single scales alone.

There are some general considerations. First, the information theory approach we have adopted in this book is notorious for providing existence theorems whose representation, to use physics jargon, is arduous. For example, although the Shannon Coding Theorem implied the possibility of highly efficient coding schemes as early as 1949, it took more than forty years for practical turbo codes to be created. The program we propose is unlikely to be any less difficult.

Second, we are invoking information theory variants of the fundamental limit theorems of probability. These are independent of exact mechanisms, but, as necessary conditions, constrain the behavior of those mechanisms. For example, although not all processes involve long sums of independent stochastic variables, those that do, regardless of the individual variable distribution, collectively follow a Normal distribution as a consequence of the Central Limit Theorem. Similarly, the games of chance in a Las Vegas casino are all quite different, but nonetheless the success of strategies for playing them is strongly and systematically constrained by the Martingale Theorem, regardless of game details. Languages-on-networks and languages-that-interact, as a consequence of the limit theorems of information theory, will be subject to necessary-condition regularities of punctuation and generalized Onsager relations, regardless of detailed mechanisms, as important as the latter may be.

Finally, just as parametric statistics are imposed, at least as a first approximation, on sometimes questionable experimental situations, relying on the robustness of the Central Limit Theorem to carry us through, we will invoke here a similar heuristic approach for the information theory limit theorems we define.

We begin with a reiteration and reinterpretation of some results from chapter 3.

6.1.2 Universality class tuning

Here we again iterate the general argument of chapter 3 onto the process of phase transition itself, obtaining Tenallion's second order selection – the mutator – in a natural manner.

We suppose that a structured environment, which we take itself to be an appropriately regular information source \mathbf{Y} – e.g., the immune system, or more generally, for humans the immunocultural condensation (ICC) – engages a modifiable system – e.g., a pathogen – through selection pressure.

The ICC begins to write itself on the pathogen's genetic sequences or protein residues in a distorted manner permitting definition of a mutual information $I[K]$ splitting criterion according to the Rate Distortion or Joint Asymptotic Equipartition Theorems. K is an inverse coupling parameter between system and environment. According to our development, at punctuation – near some critical point K_C – the systems begin to interact very strongly indeed, and we may write, near K_C , taking as the starting point the simple physical model of section 3.4,

$$I[K] \approx I_0 \left[\frac{K_C - K}{K_C} \right]^\alpha.$$

For a physical system α is fixed, determined by the underlying universality class. Here we will allow α to vary, and to itself respond explicitly to selection pressure.

Normalizing K_C and I_0 to 1, we obtain,

$$I[K] \approx (1 - K)^\alpha.$$

(6.1)

To repeat, the horizontal line $I[K] = 1$ corresponds to $\alpha = 0$, while $\alpha = 1$ gives a declining straight line with unit slope which passes through 0 at $K = 1$. Consideration shows there are progressively sharper transitions between the necessary zero value at $K = 1$ and the values defined by this relation for $0 < K, \alpha < 1$. The rapidly rising slope of transition with declining α is, we assert, of considerable significance.

Again, the instability associated with the splitting criterion $I[K]$ is defined by

$$Q[K] \equiv -K dI[K]/dK = \alpha K (1 - K)^{\alpha-1},$$

(6.2)

and is singular at $K = K_C = 1$ for $0 < \alpha < 1$. And again we interpret this to mean that values of $0 < \alpha \ll 1$ are highly unlikely for real systems, since $Q[K]$, in this model, represents a kind of energy barrier for information systems.

On the other hand, smaller values of α mean that the system is far more efficient at responding to the adaptive demands imposed by the embedding structured ecosystem, since the mutual information which tracks the matching of internal response to external demands, $I[K]$, rises more and more quickly toward the maximum for smaller and smaller α as the inverse coupling parameter K declines below $K_C = 1$. That is, *systems able to attain smaller α are more adaptive than those characterized by larger values*, in this model, but smaller values will be hard to reach, and can probably be done so only at some considerable physiological or other cost, an energy argument similar to that of the previous chapter.

The more biologically realistic renormalization strategies given in chapter 3 produce sets of several parameters defining the universality class, whose tuning gives behavior much like that of α in this simple example.

We can formally iterate the phase transition argument on this calculation to obtain our version of the mutator, focusing on paths of universality classes.

6.1.3 The adaptive mutator

Suppose the renormalization properties of a biological or social language-on-a-network system at some ‘time’ k are characterized by a set of parameters $A_k \equiv \alpha_1^k, \dots, \alpha_m^k$. Fixed parameter values define a particular universality class for the renormalization. We suppose that, over a sequence of ‘times’, the universality class properties can be characterized by a path $x_n = A_0, A_1, \dots, A_{n-1}$ having significant serial correlations which, in fact, permit definition of an adiabatically piecewise memoryless ergodic information source associated with the paths x_n . We call that source \mathbf{X} .

We further suppose, as described earlier, that external selection pressure is also highly structured – e.g., the cognitive immune system or, in humans, the ICC – and forms another information source \mathbf{Y} which interacts not only with the system of interest globally, but specifically with its universality class properties as characterized by \mathbf{X} . \mathbf{Y} is necessarily associated with a set of paths y_n .

We pair the two sets of paths into a joint path, $z_n \equiv (x_n, y_n)$ and invoke an inverse coupling parameter, K , between the information sources and their paths. This leads, by the arguments above, to phase transition punctuation of $I[K]$, the mutual information between \mathbf{X} and \mathbf{Y} , under either the Joint Asymptotic Equipartition Theorem or under limitation by a distortion measure, through the Rate Distortion Theorem (Cover and Thomas, 1991). The essential point is that $I[K]$ is a splitting criterion under these theorems, and thus partakes of the homology with free energy density which we have invoked above.

Activation of universality class tuning, our version of the mutator, then becomes itself a punctuated event in response to increasing linkage between organism – the pathogen – and externally imposed selection or other pressure – responses of the ICC. Mutation rates become a function of the relationship

between the ICC and the pathogen, above and beyond environmental insult alone.

Thaler (1999) has suggested that the mutagenic effects associated with a cell sensing its environment and history could be as exquisitely regulated as transcription. Our invocation of the Rate Distortion or Joint Asymptotic Equipartition Theorems in address of the mutator necessarily means that variation comes to significantly reflect the grammar, syntax, and higher order structures of the embedding processes. This involves far more than a simple colored noise – stochastic excursions about a deterministic spine – and most certainly implies the need for exquisite regulation. Our information theory argument here converges with Thaler’s speculation.

In the same paper Thaler further argues that the immune system provides an example of a biological system which ignores conceptual boundaries that separate development from evolution. While evolutionary phenomena are not cognitive in the sense of the immune system (Cohen, 2000), they may still partake of a significant interaction with development, in which the very reproductive mechanisms of a cell, organism, or organization become closely coupled with structured external selection pressure in a manner recognizably analogous to ‘ordinary’ punctuated evolution.

That is, we argue the staged nature of chronic infectious diseases like HIV and malaria represents a punctuated version of biological interpenetration, in the sense of Lewontin (2000), between a cognitive ‘immunocultural condensation’ and a highly adaptive pathogen. We further suggest that this punctuated interpenetration may have both first (i.e., direct) and second order characteristics, involving cross interactions between direct cognitive effects of the immune system or immunocultural condensation, or, more generally, of the ICC and the mutator mechanisms of both the immune system and its pathogen targets.

Another path to the mutator might be through a second order iteration similar to that just above, but focused on the parameters defining the universality class distributions of section 3.3.

6.1.4 Population stress and pathogen response

As we discuss elsewhere (Wallace and Wallace, 2002; Wallace, 2002a), structured psychosocial stress directed at populations, by policy choice or as unforeseen consequence, constitutes a determining context for immune cognition or, more generally, the immunocultural condensation. We wish to analyze the way structured stress affects the interaction between the cognitive ICC and an adaptive mutator, the principal line of defense against the ICC for a large class of highly successful pathogens. To do this we must extend our theory to three interacting information sources, briefly reiterating the argument of Section 2.4.

The Rate Distortion and Joint Asymptotic Equipartition Theorems are generalizations of the Shannon-McMillan Theorem which examine the inter-

action of two information sources, with and without the constraint of a fixed average distortion. We conduct one more iteration, and require a generalization of the SMT in terms of the splitting criterion for triplets as opposed to single or double stranded patterns. The tool for this is at the core of what is termed network information theory (Cover and Thomas, 1991, Theorem 14.2.3), leading to equations (2.1) and (2.2). We briefly review that development.

Suppose we have three (adiabatically piecewise stationary) ergodic information sources, Y_1, Y_2 and Y_3 . We assume Y_3 constitutes a critical embedding context for Y_1 and Y_2 so that, given three sequences of length n , the probability of a particular triplet of sequences is determined by *conditional probabilities with respect to Y_3* :

$$P(Y_1 = y_1, Y_2 = y_2, Y_3 = y_3) = \prod_{i=1}^n p(y_{1i}|y_{3i})p(y_{2i}|y_{3i})p(y_{3i}). \quad (6.3)$$

That is, Y_1 and Y_2 are, in some measure, driven by their interaction with Y_3

Then, as with previous 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),

$$N(n) \propto \exp[nI(Y_1; Y_2|Y_3)], \quad (6.4)$$

where splitting criterion is given by equation (2.1),

$$I(Y_1; Y_2|Y_3) \equiv H(Y_3) + H(Y_1|Y_3) + H(Y_2|Y_3) - H(Y_1, Y_2, Y_3).$$

We can then examine mixed cognitive/adaptive phase transitions analogous to learning plateaus (Wallace, 2002b) in the splitting criterion $I(Y_1, Y_2|Y_3)$, which characterizes the synergistic interaction between structured psychosocial stress, the ICC, and the pathogen's adaptive mutator. These transitions delineate the various stages of the chronic infection, which are embodied in the slowly varying APSE phase between transitions. Again, our results are closely analogous to the Eldredge-Gould treatment of evolutionary punctuated equilibrium in evolution.

We can, if necessary, extend this model to any number of interacting information sources, Y_1, Y_2, \dots, Y_s conditional on an external context Z in terms of a splitting criterion defined by equation (2.2):

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

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

6.1.5 The phenotype coevolution ratchet

We have so far focused this treatment on complex parasites such as malaria which may have mutator mechanisms determining behavior of their antigenic coat of many colors. A simplified analysis can also be applied directly to HIV, which, as a kind of evolution machine, seems to engage in endless, rapid, direct mutation, and, at broader temporal scales, recombination. The essential argument regarding RNA viruses is that the high error rate inherent to viral replication is very nearly the lowest possible energy state consonant with quasi-species survival, according to the rate distortion argument of chapter 5. Nonetheless, a virus does not exist alone. It functions in cooperation with, as well as in conflict with, the host organism. Some RNA viruses, for example poliomyelitis and measles, have high error rate replication, but a (nearly) fixed phenotype, permitting effective vaccination.

The development of Chapter 5 suggests that the coevolutionary ratchet between virus and immune system can be generalized to phenotype-phenotype interactions. That is, to the competition between the virus and the cognitive immune system. At the level of the pathogen-host system, the possible coevolutionary stable states are either a highly variable phenotype-phenotype conflict near a critical point, or else a fixed, phenotype-phenotype quasi-equilibrium point at the low variability end of the ratchet.

This dichotomy appears to be extended to structurally more complex pathogens, for example, malaria, which, although it is not near some evolutionary error catastrophe, has apparently nonetheless been ratcheted down to the high variability equilibrium point for phenotype coevolution.

The cognitive nature of the immune system may play an important role here. SIV, the simian version of HIV, in long-evolved relations with a host

species, exists at high blood titre without eliciting an inflammatory response (Gordon et al., 2005). In terms of the cognitive model of section (1.2), SIV antigen has been relegated to the ‘ B_0 ’ model of ‘not recognized’ rather than the ‘ B_1 ’ mode of immune attack. One speculates as to the possible importance of cognitive gene expression in determining more complex phenotypic coevolutionary processes. An example is perhaps found in the recent work of Ley et al. (2008) on the evolution of mammals and their gut microbes. They conclude that the tolerance of the immune system to gut microbes is a basal trait in mammal evolution.

As stated at the end of chapter 5, however, a large deviations argument suggests that external mesoscale ecosystem shifts might well drive a relatively stable host-pathogen relationship from low to high variability, not a good thing.

6.1.6 Implications of the model

Scientific enterprise encompasses the interaction of facts, tools, and theories, all embedded in a path-dependent political economy that seems as natural to us as air to a bird. Molecular biology, Central Limit Theorem statistics, and 19th century mathematics, presently provide the reductionist tool kit most popular in the study of immune function and disease process. Many essential matters related to the encompassing social, economic, and cultural matrix so fundamental to human biology are simply blindsided, and one is reminded, not very originally, of the joke about the drunk looking for his missing car keys under a street lamp, “because the light here is better.”

The asymptotic limit theorems of probability beyond the Central Limit Theorem, in concert with related formalism adapted from statistical physics, would seem to provide new tools. We think these can generate theoretical speculations of value in obtaining and interpreting empirical results about infection and immune process.

Our model explicitly invokes the possibility of synergistic interaction between the selection pressure of the immunocultural condensation (ICC) that characterizes human immune response and the variable antigenic coat of an established pathogen population, particularly in the context of embedding patterns of structured psychosocial stress which, to take a Rate Distortion perspective, can literally write an image of itself onto that interaction. The ICC, through immune hypermutation and the choice of immune response pursued, may engage in its own second order selection. What results are first, second, and possibly mixed, order interpenetrations, in which the ICC and pathogens constitute each other’s selection pressure and selected structure, an interaction that may become a distorted image of enfolding patterns of socioeconomically, historically, and politically determined psychosocial stress. As the evolutionary anthropologist Robert Boyd put succinctly, Culture is as much a part of human biology as the enamel on our teeth (Boyd and Richerson

1995; Richerson and Boyd, 2004). It follows that any efforts to characterize and respond to threats to human biology need account for culture's roles.

Human chronic infection cannot, in particular, be simply abstracted as a matter of conflict between the pathogen and the immune system alone. Indeed, the concept of an immune system 'alone' has no meaning within our model, in stark contrast with, for example, the well-stirred Erlenmeyer flask predator-prey population dynamics of Nowak and May (2000). The cells of the immune system comprise only the point of a long biocultural sword aimed at the throats of most infections.

Individual and collective history, socioeconomic structure, psychosocial stress and the resulting emotional states, may not be mere adjuncts to what is termed basic science in the medical journals. Rather, they may be as much a part of basic human biology as T-cells. Magic bullet vaccines, therapeutic drugs, or highly-focused medicalized social interventions against HIV disease and other mutagenic parasites – approaches that inherently cannot reckon with socioeconomic, historical, and cultural determinants of health and illness – will likely largely fail as they are overwhelmed by a combination of relentless pathogen adaptation, cross-population variation in immune cognition, and a globalized travel network that increasingly confronts host populations with myriad pathogen variants. For chronic infections like HIV and malaria, individual level or limited social network intervention strategies which neglect larger embedding context, and the history of that context, embody a grossly unreal paradigm of basic human biology.

We know that some social systems have succeeded in controlling malaria through, for example, persistent and highly organized programs of insect vector control. For HIV, humans are both vector and host. The larger social context, then, plays a fundamental role in the individual- and population-level decisions that promote or decelerate the HIV epidemic (D. Wallace and R. Wallace 1998; Schoepf et al. 2000). The biological consequences of ignoring the larger context are devastating, above and beyond the awful human cost of the epidemic.

R.G. Wallace (2004) suggests that, alone, individual-level antiretroviral treatment of the HIV epidemic may constitute a selection pressure forcing evolutionary changes in HIV life history, including, in one albeit remote possibility, a more rapid onset of AIDS. A key result, however, is that increasing infection survivorship and decreasing the transition rate from the asymptomatic stage to AIDS, as drug regimens aim to do, may induce the greatest increase in infection population growth. Because infection survivorship is physiologically enmeshed with host survivorship the asymptomatic stage becomes under the drug regimens a demographic shield against epidemiological intervention. In other words, HIV may use processes at one level of biocultural organization to defend itself against cures directed at it at other levels. Any successful intervention, then, must display a comparable multidimensionality.

Cartesian reductionism internalizes causality by assuming the whole of any phenomenon is a sum of its parts. Despite its successes, many (Wimsatt, 1980;

Bignami, 1982; Levins and Lewontin, 1985; Mayr, 1996; Levins, 1998; Oyama et al., 2001; Van Regenmortel and Hull, 2002; Gould 2003) have pointed out the problems with the reductionist approach in the study of biological phenomena, including of disease. Reductionism's widespread application, even on problems that do not yield to its approaches, is in part an outgrowth of social decisions about the role and nature of science.

Our work, here and cited, suggests a further complication. The consequences of reductionism's failures do not merely include mischaracterizing epidemics. The nature of study itself can affect the evolution of pathogens. The reductionist approach may very well, through a mesoscale resonance-driven microbial ecosystem resilience domain shift, *select for* holistic or dialectical responses on the part of pathogens. Reductionism's wholesale application, while succeeding against diseases such as polio and smallpox, welcome developments notwithstanding, may select for diseases that are characterized by complex sociogeographies, multiple hosts, and multidimensional interactions across scale. The HIV, malaria, and tuberculosis epidemics, as we have discussed, are obvious examples of holistic pathogens. In industrial countries, heart disease, cancer, and obesity take their toll; so-called diseases of affluence the poorest and most marginalized typically suffer the worst (Wallace et al., 2003; Wallace, 2005a). The ecology literature tells us sources of mortality compete. While pharmaceuticals, surgery, and individual-level risk reduction interventions control reductionist threats – additive sources of mortality both within individuals and populations – the pathogenic playing field appears now tilted towards holistic diseases we are largely unable to address because of the restricted scientific and medical practices pursued.

Our model raises the possibility of effective integrated pathogen management (IPM) programs through synergistic combinations of social, ecological, and medical interventions. IPM far transcends 'medical' strategies that amount to little more than a kind of pesticide application, an approach increasingly abandoned in agriculture as simply inadequate to address pathogen evolutionary strategies.

Prospects for studying immunocultural condensation and implementing a related IPM appear both exciting and difficult. New modes of intervention need involve new means of modeling basic biology. While we can model the interaction of first and second order phenomena in the context of structured stress using network information theory, it is difficult to envision interaction between second order 'tuning' processes, or the mechanics of even higher order effects: can we continue to 'tune the tuners' in a kind of idiosyncratic hall of mirrors? The mathematics would be straightforward, but the corresponding molecular biology would have to be subtle indeed. Higher order interpenetration – mutating the mutator – may be observable in certain isolated circumstances, for example in the interplay between B-cell somatic hypermutation and a pathogen's hypervariable membrane proteins. More likely some version of rate distortion manifold retina-like focus operates. Clearly much work is needed to trace the connections among the culture-specific and cognitive na-

ture of the immune system, pathogen adaptation, the information dynamics of their interaction, the molecular manifestations of those dynamics, and the particularities of intervention.

As a first effort toward testing the proposed relations among the ICC and disease, we next qualitatively apply our paradigm to characterizing specific pathogens and the socioecological contexts in which they evolve.

6.2 Culture and the infection phenotype: case histories

6.2.1 Introduction

Following closely Wallace and Wallace (2002), we begin with a reconsideration of some implications of the Atlan-Cohen perspective on immune cognition (Cohen, 1992, 2000; Atlan and Cohen, 1998) for understanding the role of culture in the phenotypic expression of infectious disease, and the implications for vaccine strategies when simple elicitation of sterilizing immunity fails. This will provide an introduction to more complicated circumstances in which culture, and the policies which derive organically from it, can actually drive pathogen evolution.

The Atlan-Cohen view takes on special importance in the context of recent work by Nisbett et al. (2001) showing clearly that cognition in the central nervous system (CNS) is not universal, but rather differs fundamentally for populations with different cultural systems. We propose the immune system too may be a culture-specific condensation of sociocultural and biological cognition, in the same sense that neuroimmunology and immunogenetics describe the condensation of CNS and genetic ‘languages’ with immune function. Modifying Boyd’s aphorism about culture described previously, we propose that culture is as much a part of the human immune system as T-cells. It follows that successful vaccine strategies where the smallpox model fails most likely must take such immunocultural condensation into account. In this introductory section we reinterpret recent studies of West African cultural variation in immune response to malaria, and in the efficacy of interventions against it. We also review similar US cultural variation in HIV transmission. The approach neither reifies ‘race’ nor, as in much of the biomedical literature, denies the burdens of social and political histories.

Malaria and HIV are 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*. Another complication, described in the previous section, recognizes 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).

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.

6.2.2 Genes, cognition, and culture

Increasingly, biologists excoriate simple genetic reductionism which neglects the role of environment. Lewontin (2000), 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, a fourth branch to the Lewontin helix, that is, culture’s relationships with the brain, the immune system, and the ecology of infectious disease. 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 (1991). 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 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 (Bonner, 1980). 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 (Richerson and Boyd, 2004).

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 (Barkow et al., 1992). At the risk of reifying a preformationist ontology, 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 (Cosmides and Tooby, 1992). Regardless of the exact origins of the human mind, the human species' very identity may rest, in part, on its unique evolved capacities for social mediation and cultural transmission.

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. (2001) 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. (2001) find that

[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. (2001) 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. Next we briefly review some implications of the Atlan-Cohen arguments regarding immune cognition.

6.2.3 Immune cognition and culture

Section 1.2.1 examined the Atlan/Cohen view of immune cognition at some length. As we have shown earlier, 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 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.

6.2.4 Malaria and the Fulani

Modiano et al. (1996, 1998, 2001) 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 a 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 *P. 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 (Modiano et al., 2001). The differences in the immune response were not explained by the entomological observations, which indicated substantially uniform exposure to infective bites.

Modiano et al. (1996) 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 later finding 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. (2001) 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. (1998) 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:

“ 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 two-fold 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. (1998) 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 (2000) we beg to differ with the ad hoc presumptions of genetic causality, which paper over alternatives involving environment and development consistent with these observations.

The medical anthropologist Andrew Gordon has published a remarkable study of Fulani cultural identity and illness (Gordon, 2000):

“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. Though sickly, Fulani men only reluctantly give into malaria and forgo work. To give into 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., Schapiro et al., 1998) 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., Crofton, 1971) 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 the 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.

6.2.5 'Heterosexual AIDS' in Northern New Jersey

Studies by Skurnick et al. (1998) and Rohowsky-Kochan et al. (1998), 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 (MHC)-encoded class I and class II antigens.

Couples were characterized by 'ethnicity' as 'Black, Non-Hispanic', 'White, non-Hispanic', and 'Hispanic'.

Skurnick et al. (1998) 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 (OR) 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. (1998) 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. (1998) examined 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 subpopulations...

[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 Skurnick et al. (1998) 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 two hundred years of sexual exploitation in slavery and under American Apartheid, 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 (Massey and Denton, 1993; Acevedo-Garcia, 2000), 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 (1993) 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 (1993) put it, comparing African-Americans and Hispanics,

“No other group in the contemporary United States comes close to this level of isolation within urban society. 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 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.

6.2.6 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 (1996, 1998, 2000), 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 1β . 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. (1998) 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., de Groot et al., 2001; Gryazeva

et al., 2001; Stefanski et al, 2001). Elenkov and Chrousos (1999) 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 now 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 of 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 and evolutionary biologists 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. Crosssectional marginalization and deprivation are synergistic with longitudinal path dependent, 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 culture, environment and development in the production of the ‘quadruple helix’ generating susceptibility to, and expression of, infection by pathogens. 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 bear the burdens, however, as the experiment with insecticide-treated curtains in Burkina Faso implies, circumstances may be difficult indeed.

Many of these matters should be directly testable, using immune system adaptations of Nisbett’s (2001) experimental techniques.

In the next section, we add the effects of HIV’s spatial economy on the virus’ holistic evolution – a sociogeographic mode of farming pathogens.

6.3 Multiple Drug Resistant HIV in New York

6.3.1 Introduction

Human immunodeficiency virus (HIV) displays the strongest positive selection of any known organism. The virus, then, should be expected to successfully adapt to selection pressures generated by antiretrovirals, other microbicides, and vaccines. HIV can respond not only by developing multiple drug resistance, but also by significant alterations in life history strategy – increased virulence. Effective control of such a pathogen requires sophisticated multifactorial ecosystem intervention, including a return to traditional public health approaches aimed squarely at improving living and working conditions among the marginalized populations which are the keystones of pandemic infection.

Here we examine the likely impacts of a stunning counter strategy, the coevolutionary farming of the virus by a systematic program of forced displacement affecting poor African-Americans living in New York City's most heavily infected neighborhoods. The particular context is that the city is both the principal driving epicenter for the hierarchical spatial diffusion of emerging infections in the US and its economic partners, and is a central focus of HIV itself.

A conference held in 1993 by the Office of the High Commissioner for Human Rights of the United Nations characterized forced displacement in these terms (UNHCHR, 1993):

“The practice of forced displacement involves involuntary removal of persons from their homes or land, directly or indirectly attributable to the State... The causes of forced evictions are very diverse. The practice can be carried out in connection with development and infrastructure projects... housing or land reclamation measures, prestigious international events, unrestrained land or housing speculation, housing renovation, urban redevelopment or city beautification initiatives, and mass relocation or resettlement programmes...

The practice of forced displacement shares many characteristics with related phenomena such as population transfer, internal displacement of persons, forced removals during or as a result or object of armed conflict, ‘ethnic cleansing’, mass exodus, refugee movements, etc....”

Here we examine a decades-long process of forced displacement affecting African-Americans in New York City, with a special focus on the Harlem section of the Borough of Manhattan. We study the possible impacts of continuing displacement policies on the emerging scourge of multiply-drug resistant, or other evolutionarily transformed variants, of HIV.

A well-known report by Freeman and McCord (1990) examined excess mortality in Harlem, finding that, at the time, men in Bangladesh had a higher probability of survival after age 35 than men in Harlem. They noted, almost in

passing, that Harlem's population had declined from 233,000 in 1960 to only 122,000 by 1980, with most of the population loss concentrated in the group living in substandard housing, much of it abandoned or partially occupied buildings. In that period the death rate from homicide increased from 25.3 to 90.8 per 100,000, with cirrhosis and homicide together accounting for some 33% of Harlem's excess deaths between 1979 and 1981. By 1990 AIDS became the most common cause of death for persons between 25 and 44 years of age in Harlem.

The policy-driven process inducing that depopulation has been described in some detail elsewhere (Wallace, 1990; R. Wallace and D. Wallace, 1997c; D. Wallace and R. Wallace, 1998, 2003; D. Wallace, 2001, and references therein). Withdrawal of essential housing-related municipal services, including fire extinguishment resources, from minority voting blocks in the 1970's triggered processes of large-scale contagious urban decay and forced migration involving a devastating synergism of fire, housing abandonment, and pathology (Wallace, 1988). The process was described by the New York State Assembly Republican Task Force on Urban Fire Protection (Task Force, 1978) as follows:

“There is mounting evidence that the lack of fire protection which has plagued communities in the South Bronx, Central Harlem, Brownsville and Bushwick is assuming city-wide dimensions as it spreads to [other neighborhoods]... there are indications the City Planning Commission and other agencies condoned [fire service] reductions in the context of a ‘planned shrinkage’ policy... there is strong evidence that these actions have resulted in unwarranted loss of life and destruction of city neighborhoods...”

After examining the consequences Wallace (1990) wrote:

“...[T]he... origins of public health and public order are much the same and deeply embedded in the security and stability of personal, domestic and community social networks and other institutions... [D]isruptions of such networks, from any cause, will express themselves in exacerbation of a nexus of behavior, including violence, substance abuse and general criminality. These in turn have the most severe implications for...[many pathologies including the] evolution and spread of AIDS.”

The policy-driven displacement of population affecting Harlem between 1970 and 1980 created a massive de-facto refugee camp environment for emerging and re-emerging infection. By 1990 Harlem was an epicenter of both AIDS and tuberculosis, and of their interaction (D. Wallace and R. Wallace, 1998, 2003; R. Wallace and D. Wallace, 1997a; D. Wallace, 2001).

By 2005 Harlem and East Harlem rivaled the Gay center of New York City, Manhattan's Chelsea-Clinton neighborhood, in rates of HIV diagnoses per 100,000 population, respectively 132.4, and 108.2, vs 135.0. Age-adjusted

death rates per 1000 persons with AIDS were, however, quite different: 31.9 and 32.6 vs. 11.4 (NYCDOH, 2006). This divergence represents not only a contrast in the effective availability of antiretroviral drugs, but also obvious population differences in patterns of burden and affordance between African-Americans, other minorities, and middle-class Whites, in spite of similarly draconian pressures enforcing the social and spatial segregation of ethnic and sexual minorities in the United States (R.G. Wallace, 2003; Massey and Denton, 1992).

The planned shrinkage program, which exacerbated the spread of AIDS and tuberculosis (Wallace and Wallace, 1998), had, by 1990, set the stage for a subsequent round of displacement. The loss of economic, social, and political capital consequent on the induced contagious urban decay of the 1970's left Harlem without effective means of resisting 'gentrification' by majority populations, that is, the ongoing reduction of Harlem to a largely-White 'Central Park North'.

Newman and Wyly (2006) describe this as follows:

"Central Harlem received an influx of middle-class residents throughout the 1970s and 1980s but the changes during the late 1990s and early 2000s are different. Harlem's residents report a solid flow of SUV's (sports utility vehicles) of people driving through the neighborhood scouting for homes. One resident described the housing demand: 'People are coming up while you're on the street asking who owns the building. It's a daily thing'. The neighborhood also appeals to renters seeking livable space with manageable commutes. In less than 15 minutes, residents are whisked to midtown on a 2 or A train; in 30 minutes, they can reach jobs on Wall Street. A 20-minute cab ride gets you to LaGuardia Airport and every highway intersects with Harlem. Rents for floor-through apartments in brownstones are capturing \$1,700 a month."

They conclude:

"According to neighborhood informants, many [of those displaced by the rise in rents] are moving out of the city to upstate New York, New Jersey and Long Island... Those who are forced to leave gentrifying neighborhoods are torn from rich local social networks of information and cooperation (the 'social capital' much beloved by policy-makers); they are thrown into an ever more competitive housing market shaped by increasingly difficult trade-offs between affordability, overcrowding and commuting accessibility to jobs and services. All of the pressures of gentrification are deeply enmeshed with broader inequalities of class, race and ethnicity, and gender... As affordable housing protections are dismantled in the current wave of neo-liberal policy-making, we are likely to see the end-game of gentrification as the last remaining barriers to complete neighborhood transformation

are torn down... Low-income residents who manage to resist displacement may enjoy a few benefits from the changes brought by gentrification., but these bittersweet fruits are quickly rotting as the supports for low-income renters are steadily dismantled.”

The forced displacement of New York City’s African-American population to a suburban/exurban ring around New York City, much like the Black townships surrounding Capetown, can be expected to induce a new round of refugee camp behavioral syndromes which will further exacerbate the spread of HIV among African-Americans. At present African-Americans account for 15% of the US population, but constitute over half of new HIV infections.

Katrina-like dispersal of New York City’s communities of color can be expected to fatally compromise:

[1] ongoing antiretroviral drug treatment of those already infected with HIV,

[2] the effectiveness of treating new cases with antiretrovirals, and

[3] virtually all possible infection prevention strategies.

This will, in all likelihood, markedly accelerate the development and spread of drug resistant viral strains.

Mathematical analysis of contagious process in a commuting field (Wallace et al., 1997, 1999; Wallace, 1999) suggests that, for national hierarchical diffusion, Metropolitan Regions are the systems of fundamental interest. From that perspective, a disease epicenter has much the same large-scale force of infection whether it is concentrated in the center, or dispersed around the periphery, of a particular large city: urban-suburban linkages are strong enough to create a functional equivalence (Wallace, 1997).

Given the powerful central role of New York City and its metropolitan region in the economic and political function of the American Empire, as we have come to know it, larger scale, that is, international, hierarchical diffusion of infection from it can be expected to occur. Recent elegant, and very disturbing, phylogeographic analysis by Gilbert et al. (2007) clearly confirms that the first wave of international spread of HIV was driven by incubation within the United States. Their work demonstrates convincingly that, for HIV-1 group M subtype B, the predominant variant in most countries outside of sub-Saharan Africa, while the virus had an initial transfer event from Africa to Haiti around 1966, the key to subsequent geographic diffusion was what then happened in the United States:

“...[A]ll..subtype B infections from across the world emanated from a single founder event linked to Haiti. This most likely occurred when the ancestral pandemic clade virus crossed from the Haitian community in the United States to the non-Haitian population there.... HIV-1 was circulating in one of the most medically sophisticated settings in the world for more than a decade before AIDS was recognized... [That is],[o]ur results suggest that HIV-1 circulated cryptically in the United states for \approx 12 years before the recognition of AIDS in 1981.”

The essential inference is not that ‘AIDS originated in Haiti’, but rather that HIV-1 group M subtype B became entrained into the US social and spatial system, strongly dominated by New York City and its metropolitan region, where it circulated for over a decade, and then spread hierarchically from the US to its trading partners. This is the pattern which may be expected for drug resistant or other evolutionarily transformed variants of the virus which are now incubating in the vast marginalized subpopulations of the United States.

A recent comprehensive review by Jones et al. (2008), which examined the pattern of emerging infections from 1940 to 2004, not just AIDS, broadly confirms this analysis. They found that two developed regions strongly dominated the expression of all new diseases in that period: the Northeast Corridor of the U.S, including Boston, New York, Philadelphia, Baltimore, and Washington D.C., each of which has a vast marginalized subpopulation, and the Greater London metro region.

We recapitulate something of the evolutionary biology of HIV and of the canonical pattern of hierarchical disease diffusion within the US, and end with the implications of African-American forced displacement for both national and international spread of evolutionarily transformed HIV.

6.3.2 Evolutionary biology of HIV

Affluent populations in the US have, at least in the short term, benefited greatly from the introduction of highly active antiretroviral therapy (HAART) against HIV. From 1995 to 1997, for example, HIV/AIDS deaths declined 63% in New York City, primarily among middle-class, and highly organized, Gay males (Chiasson et al., 1999). Declines in AIDS deaths have otherwise been quite heterogeneous, depending critically on both the economic resources and community stability of affected populations (e.g., R.G. Wallace, 2003).

At present, AIDS deaths in the US are, largely, another marker of long-standing patterns of racism and socioeconomic inequity (e.g., Wallace and McCarthy, 2006; R. Wallace et al., 2007). Those who have economic resources, or reside in stable communities not subject to various forms of redlining and/or de-facto ethnic cleansing, have effective access to HAART. Others, without resources, do not have such access.

HIV is, as indeed are most retroviruses, however, an evolution machine (Rambaut et al., 2004) which, at the individual level, almost always develops multiple drug resistance, resulting in overt AIDS and subsequent premature fatality. Such response to chemical pesticides, as has been the case with myriad other biological pests, is now becoming manifest at the population level. By 2001, in the US some 50% of patients receiving antiretroviral therapy were infected with viruses that express resistance to at least one of the available retroviral drugs, and transmission of drug-resistant strains is a growing concern (Clavel and Hance, 2004; Grant et al., 2002). Multiple drug resistant (MDR) HIV is, in fact, rapidly becoming the norm, and the virus may even

develop a far more virulent life history strategy in response to the evolutionary challenges presented by HAART, its successor microbicide strategies, or planned vaccines (R.G. Wallace, 2004; Wallace and Wallace, 2004), a circumstance which may have already been observed (e.g., Simon et al., 2003).

The review by Rambaut et al. (2004) puts the matter thus:

“HIV shows stronger positive selection than any other organism studied so far... [its viral] recombination rate... is one of the highest of all organisms... Within individual hosts, recombination interacts with selection and drift to produce complex population dynamics, and perhaps provide an efficient mechanism for the virus to escape from the accumulation of deleterious mutations or to jump between adaptive peaks. Specifically, recombination might accelerate progression to AIDS and provide an effective mechanism (coupled with mutation) to evade drug therapy, vaccine treatment or immune pressure... More worryingly, there is evidence that some drug-resistant mutants show a greater infectivity, and in some cases a higher replication rate, compared with viruses without drug resistant mutations.”

R.G. Wallace (2004) finds that

“...HAART may select for... an HIV with a semelparous life history and a precocious senescence... [which] may be embodied by an accelerated time to AIDS or related pathogenesis... Because infection survivorship is physiologically enmeshed with host survivorship the asymptomatic stage becomes under HAART a demographic shield against epidemiological intervention. The results appear to exemplify how pathogens use processes at one level of biological organization to defend themselves against impediments directed at them at another.”

Above we have suggested that as population-level structured stress appears a fundamental part of the biology of many chronic infectious diseases including AIDS. This raises the possibility that simplistic individual-oriented magic bullet drug treatments, vaccines, and risk-reduction programs that do not address the fundamental living and working conditions which underlie disease ecology will fail to control many current epidemics. In addition, such reductionist interventions may go so far as to select for more holistic pathogens characterized by processes operating at multiple levels of biocultural organization.

MDR-HIV is already emerging in the very epicenters and epicenter populations where HIV itself first appeared (Clavel and Hance, 2004), since these were the first to benefit from HAART, and thus seems likely to follow diffusion patterns similar to those of the earlier stage of the AIDS epidemic. More general ET-HIV's can be expected to follow a similar pattern. We reconsider the initial period.

6.3.3 Hierarchical diffusion

Infectious disease is often seen as a marker for underlying urban structure. For example, Gould and Tornqvist (1971, p. 160) write:

“As the urban lattice hardens, and the links between the major centers strengthen, the dominant process is apt to change from a [spatially] contagious to a hierarchical one.

We have few examples of this dramatic change in innovation diffusion, but one particularly striking one comes from the early history of the United States (Pyle, 1969). The disease cholera is hardly an innovation we would like to spread around, but it does form a useful geographical tracer in a spatial system, rather like a radioactive isotope for many systems studied by the biological sciences. The first great epidemic struck in 1832 at New York and Montreal, and then diffused slowly along the river systems of the Ohio and Great Lakes. A graphical plot of the time the disease was first reported against distance shows a clear distance effect, indicating that basically processes of spatial contagion were operating. A plot of time against city size shows no relationship whatsoever. However, by 1849, the rudimentary urban hierarchy of the United States was just beginning to emerge. The second epidemic struck at New York and New Orleans in the south, and a plot of first reporting times against city size, indicates that a hierarchical effect was beginning to structure innovation flows at this time. Finally, in 1865, when the third epidemic struck, the railways were already strengthening the structure of America’s urban space. The disease jumped rapidly down the urban hierarchy, and a plot of reporting time against city size shows that a very clear hierarchical process was at work.”

The first stages of the AIDS pandemic in the US provide a modern example. The cover of Gould’s 1993 book *The Slow Plague*, with more detail in Gould (1999), presents a time sequence of maps showing the number of AIDS cases in the US on a logarithmic scale. Cases first appear in the largest US port cities: New York, Los Angeles, San Francisco, Miami and Washington DC. Subsequent spread is by hierarchical hopscotch to smaller urban centers, followed by a spatially contagious winestain-on-a-tablecloth diffusion from city center into the surrounding suburban counties.

Figure 6.1, from Wallace et al. (1999), gives a detailed analytic treatment of the hierarchical hopscotch. Using multivariate analysis of covariance, it shows the log of the number of AIDS cases in each of the 25 largest US metropolitan regions for two periods, [1] through April, 1991 and [2] from April 1991 through June 1995, as functions of a composite index defined in terms of a region’s local pattern of susceptibility and its position in the US urban hierarchy. The local indices are (i) the log of the number of violent crimes in the region for 1991, and (ii) an index of ‘rust belt’ deindustrialization, the log of the ratio

of manufacturing employment in 1987 to that in 1972. The global index, of position on the US urban hierarchy, is the log of the probability of contact with the New York City metro region, the nation's largest, determined from a county-by-county analysis of migration carried out by the US Census for the period 1985-1990.

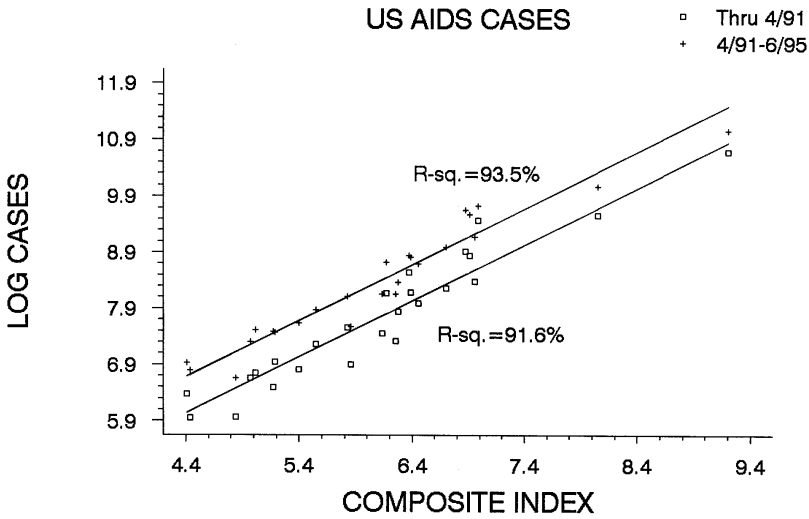


Fig. 6.1. Log number of AIDS cases in the 25 largest US metropolitan regions, through 4/91 and 4/91-6/95. The composite index is $X = .764 \text{ Log(USVC91)} + .827 \text{ Log(USME87/USME72)} + .299 \text{ Log(Prob. NY)}$. USVC91 is the number of violent crimes, USME_n the number of manufacturing jobs in year *nm*, and (Prob. NY) the probability of contact with New York City according to Census migration data for 1985-1990. Applying multivariate analysis of covariance, the two lines are parallel with different intercepts: The second is obtained simply by raising the first. The New York Metropolitan Region (NYMR) is at the upper right of the graph. The pattern is consistent with the assumption that the NYMR drives the hierarchical diffusion of HIV nationally. This suggests a powerful, coherent, national-scale, spatiotemporal hierarchical diffusion strongly linking marginalized communities in the NYMR, the Apartheid policies which marginalize them, and the epidemic outbreak within them, to the rest of the country.

Locally, high levels of violence and industrial displacement represent bust-town and boom-town social dynamics leading to the loosening of social control. Nationally, the probability of contact with New York represents inverse socio-spatial distance from the principal epicenter of the US AIDS epidemic. Multivariate analysis of covariance finds the lines for the two time periods

are parallel and each accounts for over 90 % of the variance in the dependent variate. Thus later times are obtained from the earlier simply by raising the graph in parallel. This means that processes within the New York Metropolitan Region, the upper right point of the graph, drive the national hierarchical diffusion of AIDS during this time span, the pre-HAART period of AIDS spread. We take this as representing a propagating, spatio-temporally coherent epidemic process which has linked disparate, marginalized ‘core group’ neighborhoods of Gay males, intravenous drug users, and ethnic minority populations across time and space with the rest of the urbanized US, ultimately placing some 3/4 of the nation’s population at increasing risk: as go the New York Metropolitan Region’s segregated communities, so goes the Nation. See Wallace, Wallace et. al (1999) for details, and Ablner et al. (1971) or Gould (1993, 1999) for more general background.

The results of Gilbert et al. (2007) prove conclusively that a similar pattern affects the hierarchical spread of HIV variants from the US to its principal trading partners. The US, and by inference its dominant conurbation, the New York Metropolitan Region, served as the primary source for diffusion of HIV-1 group M subtype B to the industrialized world, and will almost certainly continue to do so for its evolutionary transformed variants.

The social and geographic spread of infectious disease within a polity is constrained by, and must be consistent with, an underlying sociogeography in which segregated and oppressed subgroups traditionally constitute ecological keystone populations. Acutely marginalized communities within and surrounding the largest cities are particularly central.

In contrast to the conclusions of Jones et al., (2008), who inferred a ‘mismatch’ in global resources currently allocated to emerging infectious disease surveillance and control, with developed countries receiving, in their view, an unneeded preponderance of resources, we see a two-fold, synergistic process affecting diffusion of HIV and other emerging infections, which may be summarized as:

- [1] All roads lead to Rome.
- [2] All roads lead from Rome.

That is, at first, de-facto colonial exploitation of economically peripheral zones by the American Empire and its more developed client states, creates circumstances ripe for the emergence of new infectious disease by a variety of mechanisms. These pathogens are then entrained by economically determined travel patterns into the largest urban centers of the US and its allies (in particular the Northeast Corridor of the US, and the London Metro Region), which serve as the New Rome of the current imperial system.

Second, the domestic version of the US colonial enterprise, in particular the fatal legacy of slavery, which developed into the present system of American Apartheid (*sensu* Massey and Denton, 1992), has created vast marginalized populations within the nation’s largest metropolitan regions, particularly the Northeast Corridor. Newly-imported emerging infections then incubate largely unnoticed within these huge permanent de-facto refugee camps, and

subsequently blow back down the US urban hierarchy, and across to its more developed client states, in particular the European Union.

There are several implications of this model for HIV. Most simply, the find-the-cure 'Treatment Culture' which has dominated both official and non-governmental organizations' AIDS policy in the US for some time, and particularly since the development of HAART, is ending as HIV evolves resistance to drug regimens or alters its life history (R.G. Wallace, 2004; Simon et al., 2003; Wallace and Wallace, 2004). Possible vaccines seem similarly challenged by HIV's protean evolutionary nature, which allows the virus rapidly evolve out from under immune suppression. Indeed, a consensus is now emerging that the twenty-year search for a vaccine against HIV has made no progress, with little hope for future results (Baltimore, 2008).

As the AIDS Treatment and Vaccine subcultures disintegrate under the relentless pressure of pathogen evolution new social organizations must emerge to confront the disease. Traditional public health approaches, which address underlying structural factors responsible for disease incubation and spread at the population level – primarily the power relations between groups – have largely been abandoned in the US for reasons of political expediency. The field is now dominated by a kind of neo-liberal, rightist intellectual analog to the Stalinist sophistry of the fallen Soviet Union, effectively a Center-Right Lysenkoism strongly driven by funding biases.

Controlling MDR, vaccine-resistant and other ET-HIV's will require resurrection of traditional public health, but this will be difficult because, in the US, so much of the discipline's history has been lost in favor of the blame-the-victim, medicalized, and individual-oriented perspectives now popular with the current crop of major AIDS funding agencies and their client organizations. Many resulting projects are characterized as 'fundable trivialities' or 'planting a tree in a desert' even by foundation staff administering financial support.

ET-HIV's are now poised to spread from the main US AIDS epicenters, particularly the New York Metropolitan Region, following much the same patterns as the pre-HAART pandemic. In contrast, evidence exists that, for at least one more egalitarian social system – Amsterdam – there is a declining trend in transmission of drug-resistant HIV (Bezemer et al., 2004).

What is also clear, at least in the New York Metropolitan Area which drives the hierarchical diffusion of all emerging infection (Gould, 1993, 1999), and thus a keystone in the international spread of HIV variants from the US to its trading partners (Gilbert et al., 2007; Jones, et al., 2008), is that rebuilding of housing lost to prior policies of ethnic cleansing and stabilizing remaining low income housing, is necessary for both regional and national control of ET-HIV's. The current gentrification of Central Harlem and other communities of color, given the region's recent history, will simply further tighten the contact probability field which links metropolitan counties (e.g. Wallace and McCarthy, 2007 and references therein), and thus hasten the diffusion of the new virus within the New York Metropolitan Region. As a result of

its dominance and sociogeographic centrality in humanity's ecosystem, New York HIV will be catapulted throughout the United States and the rest of the world.

In sum, displacing African-American and other poor populations from Harlem and East Harlem into the lower-rent suburban periphery will create refugee camp conditions in the outlying New York Metropolitan Region for the development and international spread of evolutionarily-transformed HIVs, including multiple-drug-resistant strains of the virus. Urban-suburban linkages are strong in and near New York City, and can be expected to link periphery and center in a new, virulent ecology of ET-HIV which will then diffuse down the urban hierarchy, then from city center to suburban ring, effectively placing at increased risk some 3/4 of the US population. Subsequent spread of ET-HIV's to other industrialized countries will likely follow the pattern uncovered by Gilbert et al. (2007).

At present, with condominiums presently selling for an average of well over US \$1.2 million each in Manhattan, assembling a package of only a dozen or so 100 unit apartment houses in Harlem represents a potential profit of nearly US \$1 billion. For a billion dollars most developers, and their clients among public officials and the leaders of non-governmental organizations, are unlikely to give much thought to the national and international diffusion of multiple-drug-resistant HIV. Pushing poor people out offers too much opportunity for profit. The results seem likely to establish the New York Metropolitan Region as the global source of MDR-HIV in much the same manner that China's Guangdong Province has, for deep structural reasons, become the epicenter for worldwide transmission of highly pathogenic influenza A H5N1. the avian influenza virus.

6.4 Avian influenza

6.4.1 Panic in the city

Hong Kong, March 1997. An outbreak of deadly avian influenza sweeps through poultry on two farms (Davis, 2005; Greger, 2006). The outbreak subsides, but two months later a three-year-old boy dies of the same strain, identified as a highly pathogenic version of influenza A (H5N1). Officials are shocked. This appears the first time such a strain has jumped the species barrier and infected a human. Shocking too, the outbreak proves persistent. In November a six-year-old is infected, recovering. Two weeks later, a teenager and two adults are infected. Two of the three die. Fourteen additional infections rapidly follow.

The deaths spur panic in the city and, with the onset of the regular flu season, send many patients to the hospital worried their symptoms might be those of the new flu. By mid-December poultry begin to die in droves in the city's markets and it now seems most humans infected had handled birds. Hong

Kong acts decisively on that information. Authorities order the destruction of all of Hong Kong's 1.5 million poultry and block new imports from Guangdong, the mainland province across the Shenzhen River from which some of the infected birds had been transported. Despite another human death in January, the outbreak is broken.

The poultry infected with this version of the virus suffer more than the gastrointestinal condition typical of avian influenza. The clinical manifestations include swelling of the wattles and infraorbital sinuses, congestion and blood spots on the skin of the hocks and shanks, and a blue discoloration of the comb and legs (Yuen and Wong, 2005). The latter is characteristic of the cyanosis and oxygen deprivation suffered by many human victims of the 1918 pandemic. Internally, infected poultry are marked by lesions and hemorrhaging in the intestinal tract and the trachea, with blood discharge from the beak and cloaca. Many birds also suffer infection in other organs, including the liver, spleen, kidney, and the brain, the last infection leading to ataxia and convulsion.

Most worrisome for human health is this strain's capacity for broad xenospecific transmission. The Hong Kong outbreak, first alerting the world to H5N1, infected humans with an influenza much more pathogenic than the relatively mild infections of other avian outbreaks that have intermittently crossed over into human populations. These patients presented with high fever, later developing some combination of acute pneumonia, influenza-like illness, upper respiratory infections, conjunctivitis, pharyngitis, and a gastrointestinal syndrome that included diarrhea, vomiting, vomiting blood, and intestinal pain (Bridges et al., 2000; de Jong et al. 2006). Patients also suffered multiple-organ dysfunction, including that of the liver, kidney, and bone marrow. The respiratory attacks involved extensive infiltration of both lungs, diffuse consolidation of multiple infected loci, and lung collapse.

If much of H5N1's morbidity is distressing, its associated mortality is alarming. Once infected, the lungs' vasculature becomes porous and fibrinogen—a protein involved in blood clotting—leaks into the lungs (de Jong et al., 2006). The resulting fibroblast exudates clog the lungs' alveolar sacs, where gas exchange takes place, and an acute respiratory disease syndrome results. In a desperate effort to save its charge, the immune system recruits such a storm of cytokines that the lungs suffer oedema. In effect, patients drown in their own fluid only days after infection.

After Hong Kong, H5N1 slipped somewhat underground with local outbreaks largely limited to birds in southern China. During this time the virus underwent the first of a series of reassortment events, in which several genomic segments were replaced with those from other serotypes, reemerging as a human infection in Hong Kong in 2002 (Li et al., 2004; Webster et al., 2006). The following year H5N1 again reemerged, this time with a vengeance. The Z genotype that surfaced as the dominant recombinant spread across China, into Vietnam, Thailand, Indonesia, Cambodia, Laos, Korea, Japan, and Malaysia. Two additional strains would subsequently materialize. Since

2005 the Qinghai-like strain has spread across Eurasia, as far west as England, and into Africa (Salzberg et al. 2007). The Fujian-like strain, emerging from its eponymous southern China province, has spread regionally across Southeast Asia and, more recently, into Korea and Japan (Smith et al., 2006).

Since 2003 H5N1 has infected 387 humans, killing 245 (WHO, September, 2008). Most of these infections have been poultry related; often the children of small farmers playing with a favorite bird. But an increasing number of documented cases of human-to-human transmission have accumulated—in Hong Kong, Thailand, Vietnam, Indonesia, Egypt, China, Turkey, Iraq, India, and Pakistan (Kandan et al., 2006; Yang et al., 2007). The short chains of transmission have largely consisted of relatives living with or tending a patient. The worry, well publicized, is that H5N1 will improve upon these first infections, evolving a human-to-human phenotype that ignites a worldwide pandemic.

The geographic diffusion of the virus is intimately related to the emergence of such a phenotype. As are other pathogens, H5N1 is finding the regions of the world where animal health surveillance remains underdeveloped or degraded by national structural adjustment programs associated with international loans (Rweyemamu et al., 2000). There is now too a greater integration of aquaculture and horticulture, a burgeoning live-bird market system, and widespread proximity to backyard fowl (Gilbert et al., 2007; Cristalli and Capua, 2007). Rural landscapes of many of the poorest countries are now characterized by unregulated agribusiness pressed against periurban slums (Guldin, 1993; Fasina et al., 2007). Unchecked transmission in vulnerable areas increases the genetic variation with which H5N1 can evolve human-specific characteristics. In spreading over three continents fast-evolving H5N1 also contacts an increasing variety of socioecological environments, including locale-specific combinations of prevalent host types, modes of poultry farming, and animal health measures.

In this way, by a type of escalating demic selection, H5N1 can better explore its evolutionary options (Wallace and Wallace, 2003). A series of fit variants, each more transmissible than the next, can evolve in response to local conditions and subsequently spread. The Z reassortant, the Qinghai-like strain, and the Fujian-like strain all outcompeted other local H5N1 strains to emerge to regional and, for the Qinghai-like strain, continental dominance. The more genetic and phenotypic variation produced across geographic space, the more compressed the time until a human infection evolves.

6.4.2 Farming deadly influenza

Despite its impacts epidemiological and psychological, Hong Kong's H5N1 represented no first outbreak of avian influenza. In fact, within the United States alone, where the southern Chinese H5N1 has yet to reach, there have been a series of outbreaks the past decade. These outbreaks were typically low pathogenic, causing lesser damage to poultry. There was, however, an outbreak of highly pathogenic H5N2 in Texas in 2002. A low pathogenic H5N2 outbreak

in California, beginning in farms outside of San Diego, evolved greater virulence as it spread through California's Central Valley (Davis, 2005). Another outbreak worthy of note is that of a low pathogenic strain of H5N1 in Michigan in 2002. H5N1, then, has already invaded the United States in a less deadly form, telling us that the molecular identity of a strain is insufficient for defining the danger of any single outbreak. Low and high pathogenic strains must be distinguished otherwise. Some mechanism must transform low pathogenic strains into more virulent ones (and, we should hope, back again).

The nastiness of the southern Chinese H5N1 may be in part due to an antigenic shift to which we presently have no immunity. Humans have this past century been infected almost exclusively by H1, H2, and H3 strains to which we have developed antibody memory. When many of us are confronted by another strain of these same types we can slow down the infection. We have partial immunity at the individual level and herd immunity at the population level. Since we have never been exposed to H5 infections *en masse* we have nothing to slow down infection within each person and nothing to keep it damped down across the population. What cannot be slowed down arrives earlier. It is likely then that, as was the case for the 1957 and 1968 pandemics, the main wave of the next new human-to-human influenza will sweep the planet earlier than the typical seasonal flu, perhaps even as early as August some terrible year in the near future (Cliff et al. 1986).

But how are we to account for an increase in virulence *within* a particular flu subtype? Recall the low pathogenic strain of H5N1 in Michigan. Another explanation leans on a large modeling literature (reviewed by Dieckmann et al., 2002; Ebert and Bull, 2008) that hypothesizes a relationship between the rate of transmission and the evolution of virulence, the amount of damage a strain causes its host. Simply put, to start, there is a cap on pathogen virulence. Pathogens must avoid evolving the capacity to incur such damage to their hosts that they are unable to transmit themselves. If a pathogen kills its host before it infects the next host it destroys its own chain of transmission. But what happens when the pathogen 'knows' that the next host is coming along much sooner? The pathogen can get away with being virulent because it can successfully infect the next susceptible in the chain before it kills its host. The faster the transmission rate, the lower the cost of virulence.

A key to the evolution of virulence is the supply of susceptibles (Lipsitch and Nowak, 1995). As long as there are enough susceptibles to infect, a virulent phenotype can work as an evolutionary strategy. When the supply runs out it does not matter what virulence a pathogen has evolved. Time is no longer on the particular strain's side. A failed supply of susceptibles, drained by high mortality or rebound immunity, forces all influenza epidemics to ultimately burn out at some point. That's cold comfort, of course, if millions of people are left dead in a pandemic's wake.

What caused southern China's H5N1 to evolve its breathtaking virulence? The circumstantial evidence points overwhelmingly to factory farming (Shortridge, 2003; FAO, 2004; Greger 2006). Growing genetic monocultures removes

whatever immune firebreaks may be available to slow down transmission (Garrett and Cox, 2008). Larger poultry population sizes and densities facilitate greater transmission. Such crowded conditions depress immune response. High turnover, a part of any industrial production, provides a continually renewed supply of susceptibles, the fuel for the evolution of virulence.

There are additional pressures on influenza virulence on such farms. As soon as industrial poultry reach the right bulk they are killed. Think ‘No Factory for Old Chickens,’ with Javier Bardem as the plant manager. Resident influenza infections must reach their transmission threshold quickly in any given bird, before the chicken or duck or goose is sacrificed. The quicker viruses are produced, the greater the damage to the chicken. Increasing age-specific mortality in factory chickens should select for greater virulence. With innovations in production the age at which chickens are processed has been reduced from 60 days to 40 days (Striffler, 2005), increasing pressure on viruses to reach their transmission threshold – and virulence load – that much faster.

Along with hosting experiments in mounting virulence, industrial production has also increased the diversity of human-friendly influenza. Over the past 15 years an unprecedented variety of influenzas capable of infecting humans has emerged across the global archipelago of factory farms. Along with H5N1 there are H7N1, H7N3, H7N7, H9N2, in all likelihood H5N2, and perhaps even some of the H6 serotypes (WHO 2005, Puzelli et al. 2005, Meyers et al., 2007; Ogata et al., 2008). Something of a positive loop appears to have emerged in kind: the very efforts pursued to control pathogenic avian influenza may in passing increase viral diversification. In late 2006, virologist Guan Yi and his colleagues at the University of Hong Kong identified the previously uncharacterized Fujian-like H5N1 lineage (Smith et al., 2006). The team ascribed the emergence of the strain as a viral evolutionary reaction to the Chinese government’s campaign to vaccinate poultry. As in the case of other influenza serotypes (Suarez et al., 2006; Escorcia et al., 2008), the virus appeared to evolve out from underneath the pressure of vaccine coverage.

Factory farms provide what seems to be an ideal environment for the evolution of a variety of virulent influenzas. And that seems to be a cost agribusiness is willing to incur for the cheaper manufacture of its product.

6.4.3 The political virology of offshore farming

In Israel recently researchers selected for a lineage of featherless chickens (Yaron et al., 2004). The birds look like walking groceries, ready to hop up into the meats freezer in aisle 6 of your local supermarket. These chickens, able to survive in warm climes alone, were developed in the interests of the producer, not the consumer. Consumers have long avoided plucking feathers. That’s typically done at the factory. A featherless poultry will allow producers, on the other hand, to scratch off plucking feathers from production. The bald bird offers the anatomical equivalent of the factory epidemiology agribusiness is imposing on poultry-generating artificial chicken ecologies that could never

persist in nature because of the epidemiological costs they incur, but that allow more poultry to be processed faster. The resulting costs are shifted to consumers and taxpayers alike.

The lengths to which agribusiness has changed poultry production are remarkable, including, more recently, in the present avian influenza zone. Southern China serves as a regional incubator for new methods in poultry breeding (Luo et al., 2003); Sun et al., (2007), for instance, describe a Guangdong program in which geese were exposed to a counter-seasonal lighting schedule that induced out-of-season egg-laying. The innovation helped double profits for local goose production and expanded the market, and Chinese appetite, for goose meat. The resulting market advantages forced smaller farms out of business and led to a consolidation of the province's agribusiness. The structural shift marks a perverse turn back toward the farm collectivization the Chinese government abandoned in 1980, this time, though, under the control of far fewer hands.

Karl Marx (1867/1990) traced many of the fundamentals of such efforts at commodification. In the first chapter of the first volume of *Capital* Marx wrote that human-made objects have multiple characteristics. They have use value – a hammer can be used to beat down nails. In all human economies objects also have an exchange value-how many other objects (say, screwdrivers) for which a hammer can be exchanged. A capitalist economy adds a third characteristic, turning objects into commodities. Surplus value is that part of the object's worth that accrues to capitalists as profit. Marx's contribution was showing that capitalists expropriate the surplus value by taking it out of the value that workers added to the commodity when they make it, usually by paying workers lower wages or increasing worker productivity, paying them the same or less for more work.

In our efforts to better understand how influenza evolves we need only address here Marx's point that capitalists produce commodities not because commodities are useful – have use value – but because they accrue surplus value, to capitalists the most important characteristic of the object. Changing the color or style of a hammer to attract more consumers may not seem such a big deal, but for other objects changes in use value can have far-reaching, even dangerous, consequences. In this case, agribusiness has changed its commodity – living, breathing organisms-to maximize productivity. But what does it mean to change the use value of the creatures we eat? What happens when changing use value turns our poultry into plague carriers? Does out-of-season goose production, for instance, allow influenza strains to avoid seasonal extirpation, typically a natural interruption in the evolution of virulence? Are the resulting profits defensible at such a cost to the rest of us?

Mass commodification of poultry emerged in what is now called the 'Live-stock Revolution.' Before the great shift, poultry was largely a backyard operation. In Boyd and Watts' (1997) map of poultry across the United States in 1929, each dot represents 50,000 chickens. We see wide dispersion across the country-300 million poultry total at an average flock size of only 70 chick-

ens. The production filiere of that era shows local hatcheries sold eggs to backyard poultry producers and independent farmers, who in turn contracted independent truckers to bring live poultry to city markets.

That changed after WWII. Tyson, Holly Farms, Perdue, and other companies vertically integrated the broiler filiere, buying up other local producers and putting all nodes of production under one company's roof (Manning and Baines, 2004; Striffler, 2005). Boyd and Watts show by 1992 US poultry production is largely concentrated in the South and parts of a few other states. Each dot now represents 1 million broilers, 6 billion in total, with average flock size of 30,000 birds.

By the 1970s, the new production model was so successful it was producing more poultry than people typically ate. How many roasted chickens were families prepared to eat a week? With the assistance of food science and marketing the poultry industry repackaged chicken in a mind-boggling array of new products, including chicken nuggets, strips of chicken for salads, and cat food. Multiple markets were developed large enough to absorb the production.

Industrial poultry also spread geographically. With production widespread, world poultry meat increased from 13 million tons in the late 1960s to about 62 million by the late 1990s, with the greatest future growth projected in Asia (FAO, 2003). In the 1970s Asian-based companies such as Charoen Pokphand set up vertical filieres in Thailand and, soon after, elsewhere in the region. Indeed, CP was the very first foreign company allowed to set up production in Guangdong under Deng Xiaoping's economic reforms. China has since hosted a veritable explosion in annual chickens and ducks produced (Gilbert et al., 2007). Increases in poultry have also occurred throughout Southeast Asia, though not nearly at the magnitude of China.

According to geographer David Burch (2005), the shift in the geography of poultry production has some very interesting consequences. Yes, agribusinesses are moving company operations to the Global South to take advantage of cheap labor, cheap land, weak regulation, and domestic production hobbled in favor of heavily subsidized agro-exporting (Manning and Baines, 2004; McMichael, 2006). But companies are also engaging in sophisticated corporate strategy. Agribusinesses are spreading their production line across much of the world. For example, the CP Group, now the world's fourth largest poultry producer, has poultry facilities in Turkey, China, Malaysia, Indonesia, and the US. It has feed operations across India, China, Indonesia, and Vietnam. It owns a variety of fast food chain restaurants throughout Southeast Asia.

Such rearrangements falsify the widely promulgated assumption that the market corrects corporate inefficiencies. On the contrary, vertical multinationalism cushions companies from the consequences of their own mistakes. First, multinationals producing at scale can price unprotected local companies out of business – the Wal-Mart effect. Consumers have nowhere else to go to punish subsequent corporate blunders. Secondly, by threatening to move operations abroad multinationals can control local labor markets; hobbling unions, blocking organization drives, and setting wages and working conditions. Unions are

an important check on production practices that affect not only workers and consumers, but both directly and by proxy the animals involved in production. Thirdly, vertical agribusiness acts as both poultry supplier and retailer. The CP Group, for instance, owns a number of fast-food chains in a number of countries selling, what else, CP chicken. In short, fewer independent chains exist to play suppliers off each other by demanding the food be prepared in a way healthy to animals and humans alike.

In operating factories across multiple countries multinationals can hedge their bets in a variant of David Harvey's (1982/2006) spatial fix. The CP Group operates joint-venture poultry facilities across China, producing 600 million of China's 2.2 billion chickens annually sold (Burch, 2005). When an outbreak of avian influenza occurred in a farm operated by the CP Group in Heilongjiang Province, Japan banned poultry from China. CP factories in Thailand were able to take up the slack and increase exports to Japan. With the price per poultry ton increasing in the wake of an avian influenza crisis it helped create, the CP Group grossed greater profits. A supply chain arrayed across multiple countries increases the risk of avian influenza spread even as it allows some companies the means by which to compensate for the resulting interruptions in business (Sanders, 1999; Manning et al., 2007).

To protect the interests of agribusiness even as its operations struggle or fail, multinationals also fund politicians or field their own candidates. Thaksin Shinawatra, the Prime Minister of Thailand during the country's first avian influenza outbreaks, came to power on the backs of the telecommunications and livestock industries. Shinawatra played a prime role in blocking Thai efforts to control avian influenza. As Mike Davis (2005) describes it, when outbreaks began in Thailand, corporate chicken-processing plants accelerated production. According to trade unionists processing increased at one factory from 90,000 to 130,000 poultry daily, even as it was obvious many of the chickens were sick. As word got out about the illness, Thailand's Deputy Minister of Agriculture made vague allusions to an 'avian cholera' and Shinawatra and his ministers publicly ate chicken in a show of confidence.

It later emerged that the CP Group and other large producers were colluding with government officials to pay off contract farmers to keep quiet about their infected flocks. In turn, livestock officials secretly provided corporate farmers vaccines. Independent farmers, on the other hand, were kept in the dark about the epidemic, and they and their flocks suffered for it. Once the cover-up was blown open, the Thai government called for a complete modernization of the industry, including requiring all open-air flocks exposed to migratory birds be culled in favor of new biosecure buildings only wealthier farmers could afford.

Attempts to proactively change poultry production in the interests of stopping avian influenza can be met with severe resistance by governments beholden to corporate sponsors. In effect, H5N1, by virtue of its association with agribusiness, has some of the most powerful representatives available

defending its interests in the halls of government. The very biology of avian influenza is enmeshed with the political economy of the business of food.

If multinational agribusinesses can parlay the geography of production into huge profits, regardless of the outbreaks that may accrue, who pays the costs? The costs of factory farms have long been externalized. As Peter Singer (2005) explains, the state has been forced to pick up the tab for the problems these factories cause; among them, health problems for its workers, pollution released into the surrounding land, food poisoning, and damage to transportation infrastructure. A breach in a poultry lagoon, releasing a pool of poultry shit into a Cape Fear tributary that causes a massive fish kill, is left to local governments to clean up.

With the specter of avian influenza the state is again prepared to pick up the bill so that farm factories can continue to operate without interruption, this time in the face of a worldwide pandemic agribusiness helped cause in the first place. The economics are startling. The world's governments are prepared to subsidize agribusiness billions upon billions for damage control in the form of animal and human vaccines, Tamiflu, and body bags. Along with the lives of millions of people, the establishment appears willing to gamble much of the world's economic productivity, which stands to suffer catastrophically if a pandemic were to erupt.

6.4.4 Why Guangdong? Why 1997?

In reorganizing its poultry industry under the American model of vertically integrated farming, Chinese farming helped accelerate a phase change in influenza ecology, selecting for strains of greater virulence, wider host range, and greater diversity. For decades a variety of influenza subtypes have been discovered emanating from southern China, Guangdong included (Chang, 1969; Shortridge and Stuart-Harris, 1982; Xu et al., 2007; Cheung et al., 2007). In the early 1980s, with poultry intensification under way, University of Hong Kong microbiologist Kennedy Shortridge (1982) identified 46 of the 108 different possible combinations of hemagglutinin and neuraminidase subtypes circulating worldwide at that time in a single Hong Kong poultry factory.

Shortridge detailed the likely reasons southern China would serve as ground zero for the next influenza pandemic:

[1] Southern China hosts mass production of ducks on innumerable ponds, facilitating fecal-oral transmission of multiple influenza subtypes.

[2] The greater mix of influenza serotypes in southern China increases the possibility the correct combination of gene segments would arise by genetic reassortment, selecting for a newly emergent human strain.

[3] Influenza circulates year-round there, surviving the interepidemic period by transmitting by the fecal-oral mode of infection.

[4] The proximity of human habitation in southern China provides an ideal interface across which a human-specific strain may emerge.

The conditions Shortridge outlined twenty-five years ago have since only intensified with China's liberalizing economy. Millions of people have moved into Guangdong the past decade, a part of one of the greatest migration events in human history, from rural China into cities of the coastal provinces (Fan, 2005). Shenzhen, one of Guangdong's Special Economic Zones for open trade, grew from a small city of 337,000 in 1979 to a metropolis of 8.5 million by 2006. As discussed earlier, concomitant changes in agricultural technology and ownership structure have put hundreds of millions more poultry into production (Luo et al., 2003; Burch, 2005; Sun et al., 2007). Poultry output increased in China from 1.6 million tons in 1985 to nearly 13 million tons by 2000.

As Mike Davis (2005) summarizes it, by the onset of pathogenic H5N1, only the latest pathogen to emerge under such socioecological conditions,

“[S]everal subtypes of influenza were traveling on the path toward pandemic potential. The industrialization of south China, perhaps, had altered crucial parameters in the already very complex ecological system, exponentially expanding the surface area of contact between avian and nonavian influenzas. As the rate of interspecies transmission of influenza accelerated, so too did the evolution of protopandemic strains.”

Pathogenic H5N1's hemagglutinin protein was first identified by Chinese scientists from a 1996 outbreak on a goose farm in Guangdong (Tang et al., 1998). News reports during the initial H5N1 outbreak in Hong Kong detailed local health officials' decision to ban poultry imports from Guangdong from where several batches of infected chickens originated (Kang-Chung, 1997). Phylogeographic analyses of H5N1's genetic code have pointed to Guangdong's role in the emergence of the first and subsequent strains of pathogenic H5N1 (Wallace et al., 2007). Scientists from Guangdong's own South China Agricultural University contributed to a 2005 report showing that a new H5N1 genotype arose in western Guangdong in 2003-4 (Wan et al., 2005).

Subsequent work has complicated the picture. With additional H5N1 samples from around southern China, Wang et al. (2008) showed virus from the first outbreaks in Thailand, Vietnam and Malaysia appeared most related to isolates from Yunnan, another southern Chinese province. Indonesia's outbreaks were likely seeded by strains isolated from the province of Hunan. These are important results, showing the complexity of influenza's landscape. At the same time they need not absolve Guangdong. Even if some H5N1 strains emerged elsewhere in the region, Guangdong's socioeconomic centrality may have acted as an epidemiological attractant, drawing in novel poultry trade-borne strains from around southern China before dispersing them again back out across China and beyond.

Mukhtar et al. (2007) meanwhile traced the origins of the genomic segments from the original 1996 outbreak in Guangdong. Most of the internal proteins (encoding for proteins other than surface proteins hemagglutinin and

neuraminidase) appeared phylogenetically closest to those of H3N8 and H7N1 isolates sampled from Nanchang in nearby Jiangxi Province. The 1996 hemagglutinin and neuraminidase appeared closest to those of H5N3 and H1N1 isolates from Japan. In the months before the outbreak in Hong Kong several of the proteins were again replaced by way of recombination, this time via strains of H9N2 and H6N1 (Guan et al., 1999; Hoffmann et al., 2000). H5N1 outbreaks in the years that followed Hong Kong emerged by still more recombination (Li et al., 2004). The sociogeographic mechanisms by which the various segments first converged (and were repeatedly shuffled) in Guangdong remain to be better outlined. The results so far do indicate the spatial expanse over which reassortants originate may be greater than Kennedy Shortridge, or anyone else, previously outlined. But genomic origins tell us little how this particular complement led to a virus that *locally evolved* such virulence other than showing the genetic variation upon which the virus can draw.

A closer look at Guangdong's drastically shifting socioeconomic circumstances, then, appears necessary in better illuminating the local conditions that selected for such deadly pathogens so easily spread; not only H5N1, but a diverse viral portfolio, including influenza A (H9N2) (Liu et al., 2003), H6N1 (Cheung et al., 2007), and SARS (Poon et al., 2004). What exactly are the 'crucial parameters' for the area's disease ecosystem? What are the mechanisms by which changes in southern China's human-animal composite lead to regular viral pulses emanating out to the rest of China and the world? Why Guangdong? Why 1997 and thereafter?

6.4.5 700 million chickens

We begin with the death of Mao and the rehabilitation of Deng Xiaoping. In the late 1970s, China began to move away from a Cultural Revolution policy of self-sufficiency, in which each province was expected to produce most foods and goods for its own use. In its place, the central government began an experiment centered about a reengagement with international trade in Special Economic Zones set up in parts of Guangdong (near Hong Kong) and Fujian (across from Taiwan), and later the whole of Hainan Province. In 1984, 14 coastal cities-including Guangzhou and Zhanjiang in Guangdong-were opened up as well although not to the extent of the economic zones (Tseng and Zebregs, 2003).

By macroeconomic indicators favored by establishment economists, the policy was a success. Between 1978 and 1993 China's trade-to-GNP ratio grew from 9.7% to 38.2% (Perkins, 1997). Most of this growth stemmed from manufactured goods produced by foreign-funded joint ventures and township and village enterprises (TVE) allowed greater autonomy from central control. Foreign direct investment (FDI) increased from nothing to US \$45 billion by the late 1990s, with China the second greatest recipient after the US. Sixty percent of the FDI was directed to cheap-labor Chinese manufacturing. Given

the extent of China's small-holder farming, little FDI was initially directed to agriculture (Rozelle et al., 1999).

That has since begun to change. Through the 1990s poultry production grew at a remarkable 7% per year (Hertel et al., 1999). Processed poultry exports grew from US \$6 million in 1992 to US\$774 million by 1996 (Carter and Li, 1999). The Interim Provisions on Guiding Foreign Investment Direction, revised in 1997, aim to encourage FDI across a greater expanse of China and in specific industries, agriculture included (Tseng and Zebregs, 2003). China's latest 5-year plan sets sights on modernizing agriculture nationwide (Tan and Knor, 2006). Since China joined the WTO in 2002, with greater obligations to liberalize trade and investment, agricultural FDI has doubled (Whalley and Xin, 2006). But much opportunity for AgFDI remains available to a wider array of sources of investment. By the late 1990s, Hong Kong and Taiwan's contribution to China's FDI had declined to 50% of the total, marking an influx of new European, Japanese, and American investment.

In something of a bellwether, in August, 2008, days before the Olympics, U.S. private equity investment firm Goldman Sachs bought ten poultry farms in Hunan and Fujian for US\$300 million (Yeung, 2008). Although the image of a band of New York brokers knee-deep in chicken shit may prompt a cackle, Goldman Sachs has contracted third parties to run the farms. The outright ownership appears a step beyond the joint ventures in which Goldman Sachs had until then participated. Goldman Sachs already holds a minority stake in Hong Kong-listed China Yurun Food Group, a mainland meat products manufacturer, and 60% of Shanghai-listed Shuanghui Investment and Development, another meat packer. Goldman Sachs' new purchase, further up the filiere, signals a shift in the global fiscal environment. The firm has voted with its feet, deftly moving out of high-risk US mortgages and, during a global food crisis, into Chinese farming.

Guangdong remains at the cutting edge of the economic shift. It hosted the central government's first efforts at internationalizing the rural economy (Zweig, 1991; Johnson, 1992; Xueqiang et al., 1995). Starting in 1978, agricultural production was redirected from domestic grain to Hong Kong's market. Hong Kong businesses invested in equipment in return for new output in vegetables, fruit, fish, flowers, poultry and pig. In something of a return to its historical role, Hong Kong ('the front of the store') also offered Guangdong ('the back of the store') marketing services and access to the international market (Sit, 2004; Heartfield, 2005). In a few short years Guangdong's economy again became entwined with and dependent upon Hong Kong's economic fortunes. And vice versa. As of the Hong Kong outbreak, investment in China comprised 4/5 of Hong Kong's FDI outflow (Heartfield, 2005). Much of Hong Kong-funded production is now conducted in Guangdong, with Hong Kong's industrial base increasingly hollowed out as a result.

Eighty-five percent of the agricultural FDI brought in during the 1990s was funneled into Guangdong and several of the other coastal provinces (Rozelle et al., 1999). Guangdong was allowed to invest more in its transportation

infrastructure, an invitation for further investment. Many of the province's companies were allowed to claim 100% duty drawbacks. Guangdong also developed trading arrangements with many of the 51 million Chinese overseas (Gu et al. 2001, Heartfield 2005). As a class the expatriates, nearly 200 years abroad, control large percentages of regional market capital, including in Indonesia, Thailand, Vietnam, the Philippines, Malaysia, and Singapore. At the time of the first H5N1 outbreaks overseas Chinese collectively comprised the group with the greatest investment in mainland China (Haley et al. 1998).

As a result of the area-specific liberalization, Guangdong accounted for 42% of China's total 1997 exports and generated China's largest provincial GDP (Lin, 2000; Gu et al., 2001). Of the coastal provinces, Guangdong hosted the greatest concentration of joint-venture export-oriented firms, with the lowest domestic costs for each net dollar of export income (Perkins 1997). Guangdong's three free economic zones (Shenzhen, Shantou and Zhuhai) boasted an export-to-GDP ratio of 67%, compared to a national average of 17%.

By 1997, and the first H5N1 outbreak in Hong Kong, Guangdong, home to 700 million chickens, served as one of China's top three provinces in poultry production (Organisation for Economic Co-operation and Development, 1998). Fourteen percent of China's farms with 10,000 or more broilers were located in Guangdong (Simpson et al., 1999). Guangdong's poultry operations were by this point technically modernized for breeding, raising, slaughtering, and processing birds, and vertically integrated with feed mills and processing plants. AgFDI helped import grandparent genetic stock, support domestic breeding, and introduce superior nutrition feed milling/mixing (Rozelle et al., 1999). Production has been somewhat constrained by access to interprovincial grain and the domestic market's preference for native poultry breeds less efficient at converting feed. Of obvious relevance, production also suffered from inadequate animal health practices.

The rate and magnitude of poultry intensification poultry appears to have combined with the pressures placed on Guangdong wetlands by industry and a burgeoning human population to squeeze a diversifying array of influenza serotypes circulating year-round through something of a virulence filter. The resulting viral crop-for 1997, H5N1 by molecular happenstance-is exported out by easy access to international trade facilitated in part by expatriate companies.

Guangdong's ascension wasn't without its detractors. Domestic producers in Hong Kong competed with Hong Kong-Guangdong joint ventures for export licenses (Zweig, 1991). Landlocked provinces meanwhile chafed at the liberalization the central government proffered coastal provinces alone. With so much domestic currency on hand, the coastal provinces could outcompete inland provinces for livestock and grain produced by the inland's own TVEs. The coastal provinces were able to cycle their competitive advantage by turning cheap grain into more profitable poultry or flat-out re-exporting the inland goods, accumulating still greater financial reserves. At one point rivalries became so intense that Hunan and Guangxi imposed trade barriers

upon interprovincial trade. The central government's efforts to negotiate interprovincial rivalries included spreading liberalization inland (Tan and Khor, 2006). Provinces other than Guangdong and Fujian began to become entrained into market agriculture, albeit at a magnitude still outpaced by their coastal counterparts. Industrial poultry's expanding extent increases the geographic scope for H5N1's emergence and may explain the roles Yunnan and Hunan appear to have played in serving up H5N1 abroad.

An additional source of conflict, often forgotten in the cacophony of macroeconomic indicators, requires comment—the Chinese people themselves. China's state capitalism has induced such a polarization of wealth that, along with threatening its own economic growth, impoverishes hundreds of millions of Chinese. In engaging in internally imposed structural adjustment China has largely turned away from its real and ideological investment in the health and wellbeing of its population (Hart-Landsberg and Burkett, 2005a). Tens of millions of state industrial workers have been laid off. Labor income as a share of Chinese GDP fell from about 50% in the 1980s to under 40% by 2000 (Li, 2008). FDI and private companies—under no obligation to offer housing, healthcare, or retirement benefits—are used to discipline Chinese workers who were long used to a living wage, basic benefits, and job protections (Hart-Landsberg and Burkett, 2005b). Discipline, however, does not always take. Protests running now into the tens of thousands, some turning into riots requiring army deployment, have battered provincial governments accused of corruption, land confiscation, expropriating state assets, wage theft, and pollution. In something of an ironic twist, in defending foreign capital against its own people China's communist leadership has taken on the role of the comprador class it defeated in 1949 (Heartfield, 2005).

Farmers have been particularly hard hit by the government's capitalist turn. While decollectivization of agricultural land to household control propped up by governmental price supports led to a doubling in rural incomes by 1984, rural infrastructure and attendant social support deteriorated (Hart-Landsberg and Burkett, 2005a). In the late 80s, agricultural incomes stagnated, eaten away by inflation and a decline in price supports. Families began to abandon farming for informal industrial work in the cities. There, many rural migrants are treated as a reviled caste, discrimination codified by levels of officially designated migrant status and with attendant effects on income (Fan 2001). China's macroeconomic growth has been unable to absorb many of the 100 million migrants.

Urbanization meanwhile has diffused out to the rural regions, eating up peasant land. One million Chinese hectares have been converted from agriculture to urban use (Davis, 2006). Remote sensing shows from 1990 to 1996 13% of agricultural land in a ten-county region in Guangdong's Pearl River delta was converted into non-agricultural use, in all likelihood China's most rapid conversion (Seto et al., 2000). Rural towns have been transformed into growing industrial cities, some supporting populations tipping a million people (Lin, 1997).

The termination of the commune system has left hundreds of millions of peasants without access to medical care and health insurance (Shi 1993). Universal health coverage has degraded to 21% of the rural population insured (French, 2006). The number of affordable doctors has precipitously declined. Infant mortality has risen across many provinces. Rural public health has largely collapsed. Hepatitis and TB are now widespread. HIV incidence has increased in several southeastern provinces, Guangdong included (Tucker et al., 2005). STI incidence by province is correlated with immigration associated with surplus men from rural regions separated from their families. Multitudes of malnourished and immunologically stressed peasants cycle-migrating back and forth from what may be the geographic origins of an influenza pandemic would appear to compromise World Health Organization plans for intervening at any new infection's source.

6.4.6 Asian financial flu

It is hard to talk of 1997 without mentioning two events of geopolitical significance. On July 1 Hong Kong, long a British colony, was officially transferred to China as a Special Administrative Region, the first in a series of steps to full integration to be undertaken up through 2047. The next day the Bank of Thailand floated the baht off the US dollar. The baht had been hammered by currency speculation and a crippling foreign debt. International finance fled the baht and soon, with the economic strength of Thailand's neighbors also under suspicion, from other regional currencies. The FDI-dependent economies of the Philippines, Malaysia, Indonesia, Taiwan, and South Korea suffered in the ensuing wave of devaluation. The rest of the world too felt the effects of the infectious 'Asian flu,' as the crisis came to be called, with stock markets worldwide free-falling in response. Although the transfer of Hong Kong to China and the Asian financial crisis followed the first outbreaks of avian influenza in March, the events marked long-brewing shifts in regional political economy with apparent impact on viral evolution and spread.

Hong Kong's role in China's internally imposed structural adjustment, as we explored above, is amply documented. The intensification of Guangdong poultry went hand in hand with the ongoing transformation of the province's border with Hong Kong (Breitung 2002). The resulting poultry traffic, however, is in no way unidirectional. Hong Kong exports to mainland China large amounts of poultry, fruits, vegetables, nuts, oilseeds, and cotton (Carter and Li 1999). There is too a large illegal trade. At the time of the outbreak, Hong Kong chicken parts smuggled into China alone may have amounted to over US\$300 million per year (USTR, 1998; Carter and Li, 1999). Hong Kong is clearly less a victim of Guangdong's avian influenza ecology, as often portrayed, than a willing participant.

Meanwhile, the financial crisis slowed China's economy. But because of the central government's intervention China avoided the worst of the flu (Lin, 2000). By staking billions in public works and loans, China kept the economic

engine primed in the face of slowing exports. Prophetically, four years previous, the central government introduced fiscal austerity measures to cool off inflation and the possibility of an overheated economy. An associated regulation package was initiated to control the kind of short-term speculation that would soon strain China's regional neighbors. The central state maintains tight control over the macroeconomy, capital flows, and corporate structure even as it cedes much of the day-to-day operations to provincial authorities. Concomitantly, China's economy is more than export-driven. Even as austerity leaves millions of Chinese destitute in its wake (Hart-Landsberg and Burkett, 2005), the domestic economy continues to grow, albeit increasingly dependent on luxury goods and real estate speculation. Finally, exports out of China were until the crisis largely destined for East and Southeast Asia. During the crisis' aftermath China redirected more of its trade to Europe, North America, Africa, Latin America, and Oceania. China, then, was able to maintain a trade surplus, retain foreign investment, and prop the yuan against the fiscal buffet from abroad.

At the same time, China was something more than a bystander to the crisis. Its economy's growing size and hemispheric reach may have exposed its neighbors to the worst excesses of the neoliberal model (Hart-Landsberg and Burkett, 2005a; Tan and Khor, 2006). In attracting FDI at rates above and beyond those of its neighbors, China has become the prime exporter in the region: textiles, apparel, household goods, televisions, desktop computers, an increasing array of high-end electronics-you name it. The smaller economies are forced to restructure production in such a way as to complement China's increasingly diverse commodity output, in a type of regional division-of-labor. China's transnational impact on supply lines forces each country to depend on producing a smaller array of parts to be put together in China for final export.

The resulting economies are more dependent on what few foreign multinationals they are able to attract. The company town becomes the company country. Such economies are more 'brittle'-less robust in reacting to and re-orienting around downturns in any single industry, a particularly pernicious problem as the US begins to falter in its role of importer of last resort. The capital flight exposes countries to the temptations of currency speculation. To attract additional investment, establishment economists declare these countries, once burned by such speculation, must now remove remaining barriers to the movement of money, goods, and capital, leaving domestic production unprotected, the very conditions that brought about the 1997 crisis in the first place.

It would appear bird flu and the financial flu are intimately connected, their relationship extending beyond serendipitous analogy. Although agriculture has until recently been less export-dependent than manufacturing, in part from its perishability and now endangered trade protections (Hertel et al., 2000), there are already a number of epidemiological ramifications. These include a geographically expanding and intensifying poultry production, greater

exposure to transnational poultry, wider illegal poultry trade, and a truncation in animal health infrastructure by austerity measures domestically imposed in return for international loans (Rweyemamu et al., 2000). More acutely, the aftermath of the financial flu may have also provided China a window for expanding regional poultry exports. A hypothesis worth testing is that some of these shipments seeded avian influenza outbreaks abroad.

How do we operationalize this model? How do we determine whether transnational companies breed and spread avian influenza? Identifying poultry crates carrying H5N1 country-to-country remains a difficult, but important, task (Kilpatrick et al., 2006). Tracing pathogens through commodity chains is increasingly an important topic of study and mode of intervention (Duffy et al., 2008). One difficulty centers about the willingness of government regulators to inspect poultry plants, including conditions under which pathogen virulence may evolve. At the same time, there is a danger such efforts, once successful, may detract from the larger political ecology that shapes avian influenza evolution. With billions annually at stake, a few unlucky contract farmers or truck drivers may be sacrificed to protect a system stretching across a hemisphere's interlocking markets. We've explored here the possibility a deadly avian influenza is an unintended but not unexpected accessory to multinational efforts to export a growing portfolio of Chinese agricultural commodities. The problem of avian influenza is more than a police matter. It is systemic, buried deep in political tissue.

6.4.7 Layers of complication

Ending poultry production as we know it could make a great difference in Guangdong as elsewhere. But there are additional layers of complication. There is no easy one-to-one relationship between poultry density and H5N1 outbreak at a variety of spatial scales. Across Asia, some areas where outbreaks have occurred support comparatively few poultry, while other areas with millions of chickens have been so far left untouched. There is something of a stochastic component to disease spread. Epidemics start somewhere, in this case in southern China, and take time to wend their way elsewhere, starting with regions nearby and, in part by due cause and in part by chance, farther abroad. There are, however, demonstrable causes other than those inside the poultry industry.

Thailand offers one such example. As mapped by ecologist Marius Gilbert and colleagues (Gilbert et al., 2006; Gilbert et al., 2008), the distribution of Thai broilers and backyard poultry appear little associated with H5N1 outbreaks. Local outbreaks appear better fitted to the densities of ducks that are allowed to graze freely outside. After harvests these ducks are brought in to feed on the rice that is left over on the ground. Satellite pictures show rice harvests matching duck densities. The more annual rice crops, the more ducks (and the greater the association with H5N1 outbreaks). It seems these ducks, free to graze outdoors, exposed to migratory birds, and tolerant of

a wider range of influenzas, serve as epidemiological conduits for infecting nearby poultry. While a rather ingenious agricultural practice, raising a cohort of ducks on fallen waste rice may carry serious epidemiological overhead. Double- and even triple-cropping is practiced in other avian influenza zones, including southeastern China, the final stretches of the Xun Xi River, the Ganges floodplain, and on the island of Java (Leff et al., 2004).

We have, then, an integrated viral ecology with highly complex dependencies. The variety of farming practices, for one, splits a-twain a number of facile dichotomies. There is a panoply of farm types, beyond the rough polarities of 'small' and 'large.' In Thailand alone there are closed-off farms, open structures with netting to block passerine birds, the aforementioned free-grazing ducks, and backyard poultry (Songserm et al., 2006).

Even then, such a taxonomy implies a compartmentalization often absent in the field. On a recent trip to Lake Poyang in Jiangxi Province, China, a team of international experts discovered an astonishing farming ecology in which domesticated free-range ducks fed in fields, bathed in local estuaries, swam in the lake, and intermingled and presumably interbred with wild waterfowl. Some flocks daily commuted across dikes from their sheds to the open water and back. The epidemiological implications are obvious. Indeed, the facility by which pathogens spread and evolve in the area is of an order that, according to local farmers, chickens cannot be raised around the lake. For some poultry species the region is epidemiologically radioactive.

Absent too from the taxonomy are profound structural changes imposed by economic pressures upon world farming (Weis, 2007). For the past three decades, the International Monetary Fund and the World Bank have made loans to poorer countries conditioned on removing supports for domestic food markets. Small farmers cannot compete with cheaper corporate imports subsidized by the Global North. Many farmers either give up for a life on periurban margins or are forced to contract out their services—their land, their labor—to livestock multinationals now free to move in (Manning and Baines, 2004; Lewontin, 2007). The World Trade Organization's Trade-Related Investment Measures permit foreign companies, aiming to reduce production costs, to purchase and consolidate small producers in poorer countries (McMichael, 2006). Under contract, small farmers must purchase transnational-approved supplies and are given no guarantee their birds will be bought back by their transnational partner. The new arrangements belie the superficial distinction that has been made between factory farms exercising 'biosecurity' on the one hand and small farmers whose flocks are exposed to the epidemiological elements. Factory farms ship day-old chicks to be raised piecemeal by small farmers. Once grown (and exposed to migratory birds), the grown birds are shipped back to the factory for processing. The violation of 'biosecurity' appears built directly into the industrial model.

A third complication is the historical shift in the relationship between nature and farming. Maps in Phongpaichit and Baker (1995) show since 1840 Thailand has been transformed from primary wilderness into an agricultural

state, a veritable bread-basket. Agriculture's new girth comes at the expense of wetlands worldwide, either out-and-out destroyed, polluted, or irrigated dry. The latter abuse serves as another basis for conflicts between agribusiness and small farmers. Socially stratified power struggles over the Chao Phraya basin have wracked Thailand for hundreds of years (Molle, 2007).

Wetlands have traditionally served as *Anatidae* migration pit stops (Lemly et al., 2000). A growing literature shows many migratory birds are no sitting ducks and have responded to the destruction of their natural habitat. Geese, for example, display an alarming behavioral plasticity, adopting entirely new migratory patterns and nesting in new types of wintering grounds, moving from deteriorating wetlands to food-filled farms. The shift has for some populations substantially increased their numbers (Jeffries et al. 2004, Van Eerden et al., 2005). The population explosions have initiated a destructive feedback in which the swarms of farm-fed migratory birds overgraze their Arctic breeding grounds to the point the tundra is transformed into a mud pit. In the course of colonizing our planet's natural habitats-some 40% of the world's usable land now supports agriculture-we may have unintentionally expanded the interface between migratory birds and domestic poultry.

Clearly agribusiness, structural adjustment, environmental destruction, climate change, and the emergence of avian influenza are more tightly integrated than previously thought.

6.4.8 The political will for an epidemiological way?

Guangdong may only represent the front of a socioecological transformation spreading across much of southern China, as well as across much of the populated world. The origins of highly pathogenic H5N1 are multifactorial, with many countries and industries and sources of environmental damage at fault. Can we then place blame on the country, say, Indonesia or Vietnam or Nigeria, from which a human-to-human pandemic might first emerge? Should we blame China for repeatedly seeding outbreaks regionally and internationally? Should we blame Hong Kong for offshore farming? Or should we blame the United States, where the industrial model of vertically integrated poultry first originated, with thousands of birds packed in as so much food for flu? The answers are yes, yes, yes, and yes. Blame, much as the problem itself, must be distributed about its multiple levels of social and ecological organization.

To break avian influenza's back, or at the very least promote some sort of sustainable epidemiological mitigation, a number of radically invasive changes are required, changes that challenge core premises of present political economy, neoliberal and state capitalist alike. Whether there exists the political will to change is an open question. Denial, jockeying, and obfuscation are presently rampant. Chinese officials have expended much effort in flat-out denying responsibility for avian influenza (Wallace, 2007) or, in the epidemiological equivalent of the American practice of paying off the families of collateral damage without admitting guilt, offering small sums to affected countries.

In 2007, China donated US \$500,000 to Nigeria's effort to fight avian influenza. Never mind that Nigeria would never have needed the aid if China hadn't infected it with avian influenza in the first place. The Qinghai-like strain Nigeria now hosts first originated in southern China. Meanwhile, the US and EU, laying undue blame on a stubborn Indonesia unwilling to share H5N1 samples, have blocked efforts to reform a system of worldwide vaccine production that rewards pharmaceutical companies and the richest populations at the expense of the poorest (Hammond, 2007, 2008).

What must be done to stop avian influenza, if the political will is found by, or forced upon, governments worldwide? In the short term, small farmers must be fairly compensated for poultry culled in an effort to control outbreaks. Poultry trade must be better regulated at international borders (Kilpatrick et al., 2006; Wallace and Fitch, 2008). The world's poor must be provided epidemiological assistance, as well as vaccine and antiviral at no cost (Cristalli and Capua, 2007; Ferguson 2007). Structural adjustment programs degrading animal health infrastructure in the poorest countries must be terminated.

For the long term, we must end the poultry industry as we know it. Avian influenza now emerges by way of a globalized network of corporate poultry production and trade, wherever specific strains first evolve. With poultry batches whisked from region to region-transforming spatial distance into just-in-time expediency (Harvey, 1982/2006)-multiple strains of avian influenza are continually introduced into localities filled with populations of susceptible birds. Such domino exposure serves as the fuel for the evolution of viral virulence. In overlapping each other along the links of agribusiness's transnational supply chains, strains of avian influenza also increase the likelihood they can exchange genomic segments to produce a recombinant of pandemic potential. In addition to the petroleum wasted and the loss of local food sovereignty there are epidemiological costs to the geometric increase in food miles.

We must instead devolve much of the production to regulated networks of locally owned farms. While the argument has been made that corporate chicken supplies the cheap protein many of the poorest need, the millions of small farmers who feed themselves (and many millions more) would never have needed such a supply if they hadn't been pushed off their lands in the first place. A reversal need not be solely an anachronistic turn to the small family farm, but can include domestically protected farming at multiple scales (Levins, 1993, 2007; Brown and Getz, 2008). Farm ownership, infrastructure, working conditions, and animal health are inextricably linked. Once workers have a stake in both input and output-the latter by outright ownership, profit sharing, or the food itself-production can be structured in such a way that respects human welfare, and, as a consequence, animal health. With local farming, genetic monocultures of domesticated bird which promote the evolution of virulence can be diversified back into heirloom varieties that serve as immunological firebreaks. The economic losses bird flu imposes upon global poultry can be tempered: fewer interruptions, eradication campaigns, price jolts, emergency vaccinations, and wholesale flock repopulations (Van Assel-

donk et al., 2006). Rather than jury-rigged with each outbreak, restrictions on bird movement are built naturally into the independent farm model.

The devil of such a domain shift is in its details. Richard Levins (2007), with decades experience collaborating with local researchers and practitioners on ecological approaches to Cuban agriculture and public health, summarizes some of the many adjustments a new agriculture may require,

“Instead of having to decide between large-scale industrial type production and a ”small is beautiful” approach a priori, we saw the scale of agriculture as dependent on natural and social conditions, with the units of planning embracing many units of production. Different scales of farming would be adjusted to the watershed, climatic zones and topography, population density, distribution of available resources, and the mobility of pests and their enemies.

The random patchwork of peasant agriculture, constrained by land tenure, and the harsh destructive landscapes of industrial farming would both be replaced by a planned mosaic of land uses in which each patch contributes its own products but also assists the production of other patches: forests give lumber, fuel, fruit, nuts, and honey but also regulate the flow of water, modulate the climate to a distance about ten times the height of the trees, create a special microclimate downwind from the edge, offer shade for livestock and the workers, and provide a home to the natural enemies of pests and the pollinators of crops. There would no longer be specialized farms producing only one thing. Mixed enterprises would allow for recycling, a more diverse diet for the farmers, and a hedge against climatic surprises. It would have a more uniform demand for labor throughout the year.”

The scale and practice of agriculture must be flexibly integrated into the region’s physical, social and epidemiological landscapes. At the same time, it need be acknowledged that under such an arrangement not all parcels will be routinely profitable. Whatever reductions in income farms accrue in protecting the rest of the region must be offset by regular redistributive mechanisms (Richard Levins, personal communication).

Transforming the business of farming so broadly is likely only one of many steps necessary to stop bird flu and other pathogens. For one, migratory birds, which serve as a fount of influenza strains, must concomitantly be weaned off agricultural land where they cross-infect poultry. To do so, wetlands worldwide, waterfowl’s natural habitat, must be restored. Global public health capacity must also be rebuilt (Garrett, 2001). That capacity is only the most immediate bandage for the poverty, malnutrition, and other manifestations of structural violence that promote the emergence and mortality of infectious diseases, including influenza (Kim et al., 2000; Farmer, 2004). Pandemic and inter-pandemic flu have the greatest impact on the poorest (Davis, 2005). As for many pathogens, particularly for such a contagious virus, a threat to one is a threat to all.

Only once these objectives are fulfilled will we be able to better cover ourselves against H5N1 and the other influenza serotypes now lining up like hurricanes brewing in the Atlantic.