Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

Edited by James F. Crow and William F. Dove

J. B. S. Haldane (1949) on Infectious Disease and Evolution

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CHARLES Darwin was gratefully aware of the advances in microbiology and infectious disease (ID) associated with his contemporaries, Louis Pasteur and Robert Koch. Nevertheless, in none of his works does he make substantial mention of the role of ID as a driving force in natural selection. In contemporary observation, this seems self-evident, with frequent decimation of species by ID: viruses, bacteria, protozoa, or fungi. With rare exceptions, the paleontologists have remained as oblivious as Darwin, but the evolutionary responses to ID leave few qualitative marks on the fossil record. We can only speculate how many faunal extinctions may have stemmed from ID panzootics. We must, of course, marvel at the intricacies of the immune defensive systems that have evolved to keep pace with microbial invasion. As far as current knowledge informs us, these are remarkably uniform among vertebrates, and their main outlines were laid down 200 million years ago. However, we still have a long way to go in tracing the adaptations that may distinguish species that enable rodents and carrion eaters to pursue a lifestyle that deters humans and felines.

Fifty years ago, J. B. S. Haldane (1949) published a speculative review that is now often cited as inspiring new thinking about disease and evolution. Its original venue was a supplement to La Ricerca Scientifica, recording the papers from a "Symposium on Ecological and Genetic Factors in Speciation Among Animals." This was organized by Adriano Buzzati-Traverso and held at the Istituto Sieroterapico Milanese. Among the few recent citations to any other papers presented there were a handful referring to Helen Spurway and Th. Dobzhansky. But Dobzhansky (1951) did not refer to the Haldane paper in his *Genetics and the Origin of Species* (Ed. 3). Others present at the Symposium included R. A. Fisher and Luca Cavalli-Sforza, but there is scant record of their interventions.

In his paper, Haldane recites common knowledge of ID and its potential potency as an agent of natural selection. His most pungent remark was, "It is much easier for a mouse to get a set of genes which enable it to resist *Bacillus typhimurium* than a set which enable it to resist cats." That may well be; he overlooks the unmatched evolutionary potential of the bacilli, which guarantees this will be an unending contest.

A special feature of ID is its density dependence, and Haldane looks to it as the ultimate restraint on population size. Noting Stalker's parlous efforts to cultivate Scaptomyza in the laboratory, as an alternative to Drosophila, he predicts that the Drosophila industry will succumb when it gets too large. This prevision was half right if we give it credit as an anticipation of the global spread of *P* elements in laboratory cultures. As with many other "parasites," the nuisance they bring is at least partly compensated for by new insights they provoke.

In a more subtle argument, Haldane points to ID as an accelerator of speciation. Briefly summarized, this occurs when each parasite foments a specialized ecological niche, namely resistance to it.

With few exceptions, Haldane brought no experimental data of his own to the discussion, and this was the case here. He was, however, well acquainted with the established polymorphisms of blood group factors and other antigens, and he assumed these were driven as adaptations to still unidentified ID. He also cited examples from phytopathology, the Puccinia (rusts) infecting wheat, and the participation of specific genes. He was probably also likely aware of the work initiated at the Rockefeller Institute on rat strains resistant to Salmonella infection (Irwin and Hughes 1933) and of Gowen's (1952) studies on mice. While these and many other works had affirmed widely held intuitions that genetic constitution plays an important role in response

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to ID, the science was too ill formed to admit clear-cut mechanistic pathways of genetic determination.

Haldane's most often remembered attribution, to malaria, oddly enough does not appear at all in the formal article but in the discussion footnotes. Therein, Montalenti acknowledges a verbal communication from Haldane suggesting that thalassemia heterozygotes may be more resistant to malaria. In his rejoinder, Haldane goes on to suggest that "microcythemic heterozygotes may be at an advantage on diets deficient in iron or other substances, thus leading to anemia" (Haldane 1949, p. 76). This has been widely viewed as an anticipation of much later research on heterozygote advantage of blood dyscrasias in relation to malaria.[1]

In this regard, the work of A. C. Allison (1954) is well known. However, he remarks (private e-mail communication, April 26, 1999):

> At the time of publication of my finding that sickle-cell heterozygotes have some protection against malaria (1954), I was unaware that J. B. S. Haldane had made a similar suggestion for thalassemia. After my publication I was invited to make a presentation at University College, London, and we had a friendly discussion. Haldane said that he had recognized that heterozygotes for the thalassemia gene are likely to have some advantage to counterbalance selection against homozygotes and suggested several possible candidates, among them malaria and better absorption of iron. He added that to speculate about the problem was one thing and to provide experimental evidence for a solution was altogether another. This was the first evidence that natural selection operates in humans.

In a published retrospective, Allison (1968) adds that "others were pleased soon afterwards to draw attention to my lack of originality, concluding also that I must be wrong: the whole thing was far too simple to be true" (p. 181). I am reminded of an aphorism that has appeared in many forms, but most reliably attributed to William James, about " . . . the classic stages of a theory's career. First, you know, a new theory is attacked as absurd; then it is admitted to be true, but obvious and insignificant; finally it is seen to be so important that its adversaries claim that they themselves discovered it."

The current status of epidemiological verification and mechanistic interpretation of the Hb S effect, and other dyscrasias, has been reviewed by Hill and Motulsky (1999) and by Vogel and Motulsky (1997). The geographic correlations with malaria are unmistakable, but many details are still under study. Whether mechanistic correlations in contemporary evaluations can match the historic context of natural selection must always be in question.

Outside the domain of malaria and the erythrocyte, the pickings for established polymorphisms in relation to human disease are rather thin. Why have they predominated for malaria? Its geographic, climatic, and altitudinal restrictions—related to the habitats of vector mosquitoes—lend themselves to epidemiological revelation. In addition, few diseases, barring mainly tuberculosis, have a prevalence and fitness-impairing morbidity so high that subject genes will have significant penetrance. Most other morbid infections will attack a small sector of the population, thus introducing high "environmental" variance into the heritability calculations. This is also compounded by maternally inherited immunity and, needless to say, elements of culture (including salutogenic technology). Most of our successes have entailed the ascertainment of candidate genes, *e.g.*, the blood group and MHC polymorphisms, and searches for disease correlations to them. These are abundant and can be partially explained by specializations in epitope presentation to the immune system or antigenic mimicry between parasites' surface antigens and self-antigens of the host.

A. V. S. Hill (1998) has provided current reviews in a rapidly moving field. A compelling finding has been the impact of chemokine receptor gene-5 (CCR-5) deletion on blunting the infectivity and disease progression of HIV. This has, in turn, promoted speculations (I have seen these so far only in press reports) as to the historic origins of selection for the deletion—perhaps Yersinia plague. A candidate gene, NRAMP1, affecting macrophage activation in mice, has been found to have a human homolog, some alleles of which are correlated with tuberculosis in West Africa. With the elaboration of our knowledge of the human genome and the rapid accumulation of single nucleotide polymorphism (SNP) markers densely covering the map, further studies will be greatly facilitated. For example, a deadly strain of H5N1 influenza broke out in chickens and other birds in Hong Kong during 1997. It displayed a very high case-fatality rate (6/18), but, blessing to the world, did not spread from human to human. It is a reasonable possibility that these 6, or 18, out of Hong Kong's millions may have had a genetic susceptibility to H5N1. Without careful oversight, such idiosyncrats might also be bridges to infecting the rest of the species, so the stakes to perfect our understanding of these relationships are high. Likewise, humans with a Prp-200 mutation are more prone to Creutzfeldt-Jakob disease and, in addition to their own vulnerability, may bridge the readier transmission of prion diseases from animal sources to human (Prusiner 1997).

[1]Dr. Krishna Dronamraju has unearthed some old correspondence between Haldane and Montalenti about a paper that Montalenti and his colleagues had written and that eventually appeared in Nature (Silvestroni *et al.* 1950). The exchange extended over 2 years, mainly because of Haldane's delay in answering letters. The paper suggested that matings between thalassemia heterozygotes produced more children than did other matings. Haldane added some extensive (and almost illegible) algebra, showing that the fertility of this mating would have to be at least twice that of the others to yield a stable equilibrium, contrary to the data. But, ironically, malaria is not mentioned in any of this. Haldane suggested this only by word of mouth, presumably on a visit to Milan in 1949.

The precedents of work on Puccinia rusts affecting wheat have already been mentioned. I had become aware of that fine work through Johnson's (1946) presentation at the Cold Spring Harbor symposium and, indeed, the earlier symposium publication (Moulton 1940), on *The Genetics of Pathogenic Microorganisms*, with papers by Craigie, Christensen, and Stakman. While these were even further ahead of their times in pursuing the genetics of the microbe, they also alluded to host resistance genes, which had provided enormous economic value to wheat farmers. We are all aware of devastating epiphytotics that have had strong influence on human history, like the Phytophthora potato blight that depopulated Ireland starting in 1845. In the course of the present writing, I knew these studies had long preceded Haldane (1949), but had no idea by how much.

My own pursuit of that historical background led me to a happy encounter with the name of Rowland Harry Biffen (Engledow 1950). [I owe this revelation to Professor Albert H. Ellingboe (1981) of the University of Wisconsin.] A pioneer member of the School of Agriculture at Cambridge, Biffen (1905) published the first paper in the new *Journal of Agricultural Science*. Promptly after the rediscovery of Mendel's laws in 1900, he had set out to validate their application to wheat. He found, "For a detailed study of Mendel's laws the wheats appear to be peculiarly suitable. They offer all the advantages for which Mendel originally selected peas. Thus there are a large number of varieties in cultivation . . . autogamous" (p. 8). He soon found a plethora of morphological markers and exploited them to full advantage. Left to the future would be complications of ploidy and other chromosomal deviations.

On page 40, Biffen goes on to report "immunity and susceptibility to the attacks of yellow rust." Hybridizing two varieties, he found the F_1 to be susceptible, and in a rust-prevalent season he found an F_2 segregation of 64:195 immune:susceptible. We must agree this is a good approximation to 1:3 and "fair proof that susceptibility and immunity are definite Mendelian characters, the former being the dominant one" (p. 41). Nearly a century later, animal pathogenetics has barely caught up with this level of clarity. In the plant world, these studies have founded a sophisticated tradition of enquiry about confrontation of individual genes of parasites and their hosts (Johnson 1992; Staskawicz *et al.* 1995).

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