The "Genius Germs" Hypothesis: Were epidemics of leprosy and tuberculosis responsible in part for the great divergence?

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There is evidence to suggest that infectious agents may be involved in the chain of causation of schizophrenia - a disease characterized by abnormal lipid metabolism in the brain and increased creativity. Manipulation of host lipid pathways represents a significant mechanism for *Mycobacterium tuberculosis* and *Mycobacterium leprae* to cause and sustain infection. Leprosy and tuberculosis epidemics endemic to Europe but not to Asia are therefore speculated to positively select for schizotypal genes or alteration of the lipid metabolism phenotype in this population resulting in "evolutionary disproportionate" increases in cerebro-diversity and cognition beyond the threshold required to affect scientific or technological paradigm change - as occurred in the Renaissance and during the Industrial Revolution. This hypothesis serves as a biochemical explanation to the so-called "Needham puzzle" - why did the Industrial Revolution not occur in China?

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Introduction

MANY HYPOTHESES have been presented to explain why sustained industrial growth began in northwestern Europe, despite immediate pre-industrial similarities between advanced areas of Europe and eastern Asia – the "great divergence". These explanations exploit many hypotheses, either evidence-based or otherwise, to explain this phenomenon.

Pomeranz (1) has argued for the importance of two factors that had important effects on the economy: the distribution of energy-generating resources and the accident that Europe discovered the New World, whereas China did not. England's coal deposits, the major energy-generating resource for the Industrial Revolution, were located in close proximity to manufacturing sites, therefore transportation costs were low and were made still lower by the ready availability of efficient water transport. This development-friendly geographic distribution in Europe was completely at odds with the geographic distribution in China. Al-

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though China was blessed with large coal reserves, they were located for the most part in the thinly populated northwest, hundreds of miles from the potential manufacturing centers in the south and east. Thus, China was at a relative disadvantage compared to Europe in terms of the availability and appropriation of favorable resource stocks. The fortuitous circumstance of the European discovery of the Americas, which led to the subsequent availability of resources for the Industrial Revolution, boosted European economic development at a critical time. China enjoyed no advantage even remotely comparable.

The Protestant work ethic is based upon the notion that the Calvinist emphasis on the necessity for hard work is a person's calling, and worldly success is a sign of personal salvation. It is argued that Protestants reconceptualised worldly work as a duty which benefits both the individual and society as a whole. Max Weber (2) suggested that this Protestant work ethic contributed to the rise of European capitalism in various ways – by relaxing the restraints which hitherto had largely served to impede its growth, by fostering the economic virtues of diligence, frugality, honesty, prudence, and sobriety, and, most of all, by providing a psychological fillip to the development of the "spirit" of capitalism, "the temper of single-minded concentration upon pecuniary gain".

Landes (3) describes the Industrial Revolution as the result of superior European characteristics that permitted intellectual autonomy, the development of the scientific method of analysis, and the development of research as a routine human activity, with its own language and methods, developed and accepted across national boundaries and independent of religious considerations.

Diamond (4) argues that the Asian areas in which major civilizations arose had geographical features conducive to the formation of large, stable, isolated empires which faced no external pressure to correct policies that led to stagnation. On the other hand, Europe's many natural barriers divided it into competing na-

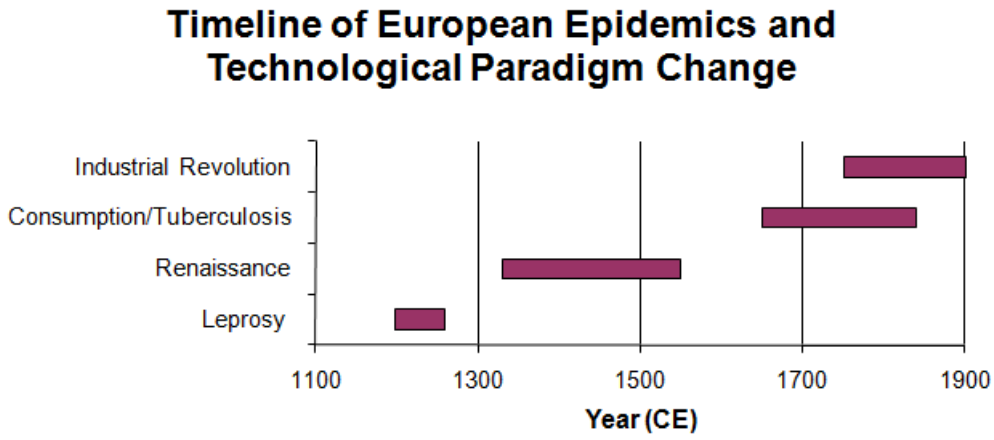

Figure 1 | Infectious disease as a factor in contributing to the "great divergence".

tion-states, and this competition forced the European nations to encourage innovation and avoid technological stagnation. This is why the dominant powers of the last 500 years have been west European rather than east Asian.

In this article, an attempt will be made to logically theorize (but not necessarily prove) that infectious disease may also have been a factor in contributing to the "great divergence". In particular, the European epidemics of leprosy in the early 13th century that preceded the Renaissance and that of tuberculosis in the middle of the 17th century that preceded the Industrial Revolution are hypothesized to positively select for genes associated with (cognitive ability enhancing) schizotypal behavior and/or directly contribute to its causation by alteration of host lipid metabolic pathways (see Figure 1).

This hypothesis does not suggest that pre-existing genetic differences between geographically distinct populations caused, or were correlated to, the "great divergence". Rather, it is postulated that genes that predispose to, or played a role in, the causal chain of (cognition-enhancing) traits such as schizophrenia or lipid metabolism disorders were positively selected for in European populations in response to bacterial infections of leprosy and tuberculosis, caused by *Mycobacterium leprae* and *Mycobacterium tuberculosis*, respectively.

Infectious agents may be causative or may play a role in the chain of events that cause schizophrenia

Epidemiologic studies indicate that infectious agents may contribute to some cases of schizophrenia (5), a concept first proposed in 1896 (6). Epidemiological evidence also demonstrates geographical and seasonal correlation of schizophrenia with Multiple Sclerosis (7) – for which an infectious vector has been proposed as well (8). Exposure to human influenza virus has been demonstrated to decrease *Reelin* mRNA in murine models (9). Significantly lowered levels of Reelin, a protein in the brain that modulates synaptic plasticity, have been found in schizophrenia and psychotic bipolar disorder. Numerous studies indicate that schizophrenia and manic/bipolar disorder are associated with a significantly greater chance

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of winter-spring excess of births (10). An infectious agent that varies seasonally could infect the developing fetus via transplacental transmission from the mother.

The alteration of the frequency of a specific genetic marker in a particular population may provide resistance to certain infectious diseases. For example, people with genetic hematological disorders, thalassemia and sickle cell anemia, are resistant to malaria. As a corollary, it has been suggested that infectious diseases such as plague epidemics may have altered the frequency of certain genetic markers. For example, it has been suggested that the C282Y mutation in the *HFE* gene was selected for during the European plagues caused by the *Yersinia* species. This cysteine to-tyrosine substitution is associated with hemochromatosis, a hereditary disease characterized by excessive absorption of dietary iron, which could confer

protection against certain iron-dependent pathogens (11). Analogously, genes associated with schizophrenia or schizotypal behavior may have been selected for by the *Mycobacteria* species. Schizophrenia has been shown to have a strong inverse correlation with Rheumatoid Arthritis, such that it may confer protection against the latter (12).

Mycobacteria disruption of host lipid transport pathways or lipid metabolism may be implicated in the causal chain of Schizophrenia

Mycobacteria are a large group of Gram positive microorganisms that inhabit a diverse range of natural environments. For instance, *Mycobacterium leprae* and *Mycobacterium tuberculosis,* the causative agents of leprosy and tuberculosis, respectively, are capable of infecting humans and animals.

Numerous studies have found correlations between lipid membrane abnormalities and schizophrenia (13). Genes that code for apolipoprotein D (involved in lipid metabolism), the rat homolog of the Stearyl-CoA-desaturase 2 (*SCD2*) gene (involved in the synthesis and regulation of long chain unsaturated fatty acids) and for the myelin oligodendrocyte glycoprotein (*MOG*) are co-expressed by oligodendrocytes in the CNS (14). Reeler mutant mice, in turn, show decreased levels of Reelin brain lipid-binding protein (15).

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Bacteria belonging to the genus *Mycobacterium* that have been harvested from infected tissues preferentially metabolize host fatty acid substrates over carbohydrates. Genes involved in fatty acid catabolism have undergone extensive duplication in this genus (16). Furthermore, deletion of genes required for growth that utilize lipids as a sole carbon source render these bacteria incapable of growth *in vivo*. Utilization and manipulation of host lipids and lipid pathways therefore represents a significant mechanism for these bacteria to cause and sustain infection.

Increased cerebro-diversity and cognitive dysfunction have been linked to schizophrenia and schizotypal behaviour and to lipid metabolism dysfunction

Evidence from recently sampled populations suggests that schizophrenia does not exhibit anthropo-parity (17). However, because its incidence is accepted to have fluctuated over time, this does not rule out the possibility that it may have exhibited anthropo-parity in the past. This is not implausible considering that a significant correlation has been demonstrated between processes that have changed during human evolution and biological processes affected in schizophrenia (18). It is therefore not unreasonable to assume that the genetic basis for the disease was incorporated into the human genome prior to the separation of the races – approximately 50,000 to 100,000 years ago. Schizophrenia has been demonstrated to be associated with creativity, artistic achievement and interest in religion (19, 20). Because these characteristics are representative of those that divide emergent human from pre-human societies, it has been proposed that schizophrenia and the origins of humans may be causally related (21).

Progression of schizophrenia over several millennia from initially exhibiting anthropoparity, to demonstrating variation across cultures and continents today, may implicate divergent evolutionary pathways globally, that may, in turn, partly be driven by infectious diseases such as leprosy or tuberculosis.

Schizophrenia is characterized in part by alterations in total membrane phospholipid content, fatty acid content and cholesteryl esters in the membranes from the frontal cortex (22). Numerous studies have demonstrated that disruption or alteration of host lipid transport pathways, lipid metabolizing enzymes (23), lipid binding proteins and/or levels of essential unsaturated fatty acids significantly correlates to schizotypal behavior and/or schizophrenia in humans.

It has been suggested that sphingolipid storage mutations that occur with increased frequency among Ashkenazi Jews, were positively selected for in this population because of their association with axonal growth and branching, dendritogenesis and – consequently – increased IQ (24). This type of mutation has been implicated in Gaucher's disease, Tay-Sachs disease, Niemann-Pick syndrome, and Mucolipidosis IV.

It has been argued that there is not only a continuum of illness between schizophrenia and manic-depression, but a continuum may also exist between schizophrenia, schizotypal personality and normality (21). Therefore, an increase in cognitive ability does not necessarily need to correlate with extreme schizophrenic behavior, although such individuals may exhibit differing degrees of schizotypal personality, but will nevertheless conform to established and acceptable societal norms.

Geographical non-uniformity in the positive selection of schizotypal genes and the alteration of host lipid metabolism by infectious agents

Infectious agents that select for schizophrenia-associated genes may not do so uniformly across geographically separated populations. For example, the *DISC1*/*TRAX* locus on chromosome 1q42, which shows susceptibility linkage with schizophrenia (25), and the schizophrenia susceptibility dysbindin (*DTNBP1*) gene (26), do not seem to be significantly linked to schizophrenia in the Japanese and Korean populations, respectively, as contrasted with the European population. If such a differential selection mediated by infectious agents for schizophrenia-associated genes across geographically distinct populations were to exist, it would not discount the possibility that epidemics related to the same causative organism that occurred with similar severity and at similar times across geographically distinct regions would not necessarily select for, or alter the frequency of similar genes in these varied populations. Even if they did, these positively selected genes would not necessarily render geographically distinct populations equally susceptible to lipid-associated disease. Put differently, the "insanity" pandemic that immediately followed – and may have been selected for by – leprosy at a time during the transition from the Middle Ages to the Renaissance may have been endemic only to Europe and not to East Asia (27). This may have been the temporal link between increased cerebrodiversity or schizotypal behavior and tuberculosis that occurred at the turn of the 17th century, the eve of the Industrial Revolution in Europe (28). The literature is replete with references that demonstrate ethnic differences in lipid metabolic pathways. These include differential

mutations in genes encoding lipid metabolizing enzymes, differences in plasma lipoproteins and triglycerides and lipid transport and binding proteins. When differential dietary patterns of Asians and Europeans, such as differences in essential fatty acids uptake, are superimposed on such genetic traits, it is not unreasonable to assume that infection by the same species of bacteria may not necessarily alter lipid metabolism, transport, and/or signaling to the same extent in different geographic populations.

A corollary to the hypothesis presented by Fincher *et al.* (29), although not explicitly stated as such, is that the number of epidemics (as contrasted with the "background" number of sporadic, intermittent infections) in the so-called (tropical) collectivist societies such as China, where pathogens are prevalent, are likely to be lesser than the number of epidemics in the (temperate) individualist societies such as Europe, where pathogens are not as prevalent (29). Therefore, even though there exists a record of "epidemics" almost every year in China from the late 15th century (30), none of these are as widely spread in geographical area or have such a high mortality rate as the leprosy or tuberculosis plagues in Europe, which by many accounts decimated between a fourth to a third of the population.

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If certain germs increase cognition, why did sustained technological and scientific change not come about much earlier?

The presence of *Mycobacterium tuberculosis* complex DNA in ancient skeletal and mummified material dates back to ~2000 BCE, while that for *Mycobacterium leprae* dates back to ~600 BCE. If it is assumed that epidemics involving these species occurred before recorded history, then why would the increase in cognitive ability not have occurred earlier as well?

First, the evolutionary pressures on humans (climate, population, diet, frequency of contacts between civilizations) that existed in the second millennium BCE may not have been similar to those that existed in the first millennium CE (a span of three millennia), so that the magnitude of *Mycobacteria* enabled positive selection of genes involved in host lipid metabolism/pathways, may not have been similar at these two time periods in history. Second, the evolutionary pressures on *Mycobacteria* that enabled extensive duplication of genes involved in lipid catabolism may not have originated or accelerated until ~1200 CE. Third, because *Mycobacteria* have been postulated to be involved in the chain of events leading to the positive selection for schizotypal genes, or alteration of the lipid metabolism phenotype in specific geographic populations, infection by these agents may have been a necessary but not a sufficient factor to propel the "cognitive increase" beyond the threshold required for scientific or technological paradigm change – as occurred during

the Renaissance and the Industrial Revolution.

Conclusion

Infectious *Mycobacteria* vectors that are capable of modulating host lipid metabolism, lipid transport or lipid synthesis pathways may predispose to or cause cognitive dysfunction or increased cerebro-diversity by positively selecting for genes that may manifest as mild, moderate or severe schizotypal personality. Such genes may not be uniformly selected for across geographically separated populations. Such a disease-driven emergence of a schizotypal phenotype in Europe, but not in Asia, may have been sufficient to propel the "cognitive increase" beyond the threshold required to affect scientific or technological paradigm change – such as that which occurred during the Renaissance and the Industrial Revolution.

The concept that infectious disease may play a role in the causal chain of events that lead to "evolutionary disproportionate" increases in cerebro-diversity and cognition in certain populations may be a chilling thought; but it does serve as a useful tool to explain in biochemical terms the solution to the so-called "Needham puzzle" – why the Industrial Revolution did not originate in China.

It is also a disconcerting thought as to what "evolutionary advantages", cognition-enhancing or otherwise, are being suppressed by modern medicine due to its relentless crusade against infectious diseases.

References

(1) Pomeranz K. The great divergence. China, Europe, and the making of the modern world economy. Princeton: Princeton University Press; 2000.

(2) Webber M. The Protestant ethic and the spirit of capitalism. Penguin Classics; 2002.

(3) Landes DS. The wealth and poverty of nations: why some are so rich and some so poor. W.W. Norton; 1999.

(4) Diamond J. Guns, germs, and steel: the fates of human societies. W.W. Norton; 1997.

(5) Torrey EF, Yolken RH. *Toxoplasma gondii* and schizophrenia. *Emerg Infect Dis*, 2003; 9(11): p. 375-1380.

(6) Is insanity due to a microbe? [editorial] *Sci Am*, 1896; 75: p. 303.

(7) Fritzsche M. Geographical and seasonal correlation of multiple sclerosis to sporadic schizophrenia. *Int J Health Geogr*, 2002; 1(1): p. 5.

(8) Kurtzhe JF. Epidemiologic evidence for multiple sclerosis as an infection. *Clin Microbiol Rev*, 1993; 6(4): p. 382-427.

(9) Fatemi SH, Emamian ES, Kist D, Sidwell RW, Nakajima K, Akhter P, *et al*. Defective corticogenesis and reduction in Reelin immunoreactivity in cortex and hippocampus or prenatally infected neonatal mice. *Mol Psychiatry*, 1999; 4(2): p. 145-154.

(10) Torrey EF, Miller J, Rawlings R, Yolken RH. Seasonality of births in schizophrenia and bipolar disorder: a review of the literature. *Schizophr Res*, 1997; 28(1): p. 1-38.

(11) Moalen S, Percy ME, Kruck TPA, Gelbart RR. Epidemic pathogenic selection: an explanation for hereditary hemochromatosis? *Med Hypotheses*, 2002; 59(3): p. 325-329.

(12) Torrey EF, Yolken RH. The schizophrenia – rheumatoid arthritis connection: infectious, immune or both? *Brain Behav Immun*, 2001; 15(4): p. 401-410.

(13) Fenton WS, Hibbeln J, Knable M. Essential fatty acids, lipid membrane abnormalities, and the diagnosis and treatment of schizophrenia. *Biol Psychiatry*, 2000; 47(1): p. 8-21.

(14) Schaeren-Weimers N, Schaefer C, Valenzuela D, Yancopoulas GD, Schwab MB. Identification of new oligodendrocyte and myelin-specific genes by a differential screening approach. *J Neurochem*, 1995; 65(1): p. 10-22.

(15) Hartfuss E, Forster E, Bock HH, Hack MA, Leprince P, Luque JM, *et al*. Reelin signaling directly affects radial glia morphology and biochemical maturation. *Development*. 2003; 130(19): p. 4597-4609.

(16) Cole ST, Brosch R, Parkhill J, Garnier T, Churcher C, Harris D, *et al*. Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence. *Nature*, 1998; 393(6685): p. 537-544.

(17) McGrath JJ. Variations in the incidence of schizophrenia: data versus dogma. *Schizophr Bull*, 2005; 32(1): p. 195-197.

(18) Khaitovich P, Lockstone HE, Wayland MT, Tsang TM, Jayatilaka SD, Guo AJ, *et al*. Metabolic changes in schizophrenia and human brain evolution. *Genome Biol*, 2008; 9(8): R124.

(19) O'Reilly T, Dunbar R, Bentall R. Schizotypy and creativity: an evolutionary connection? *Pers Individ Dif*, 2001; 31(7): p. 1067-1078.

(20) Folley BS, Park S. Verbal creativity and schizotypal personality in relation to prefrontal hemispheric laterality: a behavioral and near-infrared optical imaging study. *Schizophr Res*, 2005; 80(2-3): p. 271-282.

(21) Horrobin DF. Schizophrenia: the illness that made us human. *Med Hypotheses*, 1998; 50(4): p. 269-288.

(22) Horrobin DF, Bennet CN. New gene targets related to schizophrenia and other psychiatric disorders: enzymes, binding proteins and transport proteins involved in phospholipid and fatty acid metabolism. *Prostaglandins Leukot Essent Fatty Acids*, 1999; 60(3): p. 141-167.

(23) Gattaz WF, Brunner J. Phospholipase A2 and the hypofrontality hypothesis of schizophrenia. *Prostaglandins Leukot Essent Fatty Acids*, 1996; 55(1-2): p. 109-113.

(24) Cochran G, Hardy J, Harpending H. Natural history of Ashkenazi intelligence. *J Biosoc Sci*, 2006; 38(5): p. 659-693.

(25) Zhang X, Tochigi M, Ohashi J, Maeda K, Kato T, Okazaki Y, *et al*. Association study of the *DISC1/TRAX* locus with schizophrenia in a Japanese population. *Schizophr Res*, 2005; 79(2-3): p. 175-180.

(26) Joo EJ, Lee KY, Jeong SH, Ahn YM, Koo YJ, Kim YS. The dysbindin gene (*DTNBP1*) and schizophrenia: no support for an association in the Korean population. *Neurosci Lett*, 2006; 407(2): p. 101-106.

(27) Foucault M. Madness and civilization: a history of insanity in the age of reason. Random House; 1965.

(28) Gericke GS. Is there an emerging endosymbiotic relationship between *Mycobacteria* and the human host based on horizontal transfer of genetic sequences? *Med Hypotheses*, 2006; 67(6): p. 1419-1428.

(29) Fincher CL, Thornhill R, Murray DR, Schaller M. Pathogen prevalence predicts human cross-cultural variability in individualism/collectivism. *Proc Biol Sci*, 2008; 275(1640): p. 1279-1285.

(30) McNeill W H. Plagues and peoples. New York: Bantam Doubleday Dell; 1977.