

The Evolution of Schizophrenia: A Model for Selection by Infection, with a Focus on NAD

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Abstract: Schizophrenia is a common, debilitating mental illness that has persisted over the generations. For a disease with a strong genetic component, such prevalence has been difficult to understand in evolutionary terms. A model for its prevalence as a phenotype is presented in this manuscript, based on reports of specific differences in gene expression, metabolite levels and historical epidemiology. The selective force that underlies the proposed model is tuberculosis, a scourge of huge proportions that itself evolved to interact with the human host in a manner ensuring both its long term persistence in the host and its transfer to other carriers prior to the host's unfortunate death. The focal point of the interaction between humans and *M. tuberculosis* is hypothesized to be the *de novo* synthesis of NAD via activation of the kynurenine pathway. The strategy that *M. tuberculosis* employed to circumvent this aspect of the host's response to mycobacterial infection, and how that strategy interacted with a poor diet to force human evolution towards increased risk for schizophrenia, forms the basic premise of this paper. The model has implications for treatment of both diseases and generates hypotheses to be tested.

Key Words: Nicotinic acid, tuberculosis, schizophrenia, evolution.

INTRODUCTION

Schizophrenia is one of many examples of genetic liabilities harbored in the human genome which persist in the population despite exerting a negative effect on the ability to acquire a mate and support subsequent offspring [1-3]. To understand the persistence of this complex genetic disease, requires a whole-hearted embrace of Darwin's principles. Natural selection has taught us repeatedly that successful mutations which confer an advantage in one aspect of life, often involve a loss of fitness in other aspects that are less important for survival of offspring [4-9]. The loss of fitness can be diffuse or lack penetrance, the more numerous the genes involved and can also be diluted by the haplotype of the particular allele in question [10,11]. The degree of loss of fitness should be commensurate with the degree of selective pressure. If the selective pressure exerts a very high mortality rate prior to reproduction, the selected mutation can confer a high but non-lethal loss of fitness in other aspects of life and still be a successful gene. Furthermore, heterozygous advantage in carriers can offset the disadvantage presented by the unlucky homozygote, as best illustrated by the oft-cited example of sickle-cell disease which confers advantage against malarial infection in the heterozygous carriers [12]. A large study in Finland has demonstrated that normal siblings of schizophrenic individuals do not have enhanced fertility [13], ruling out a straightforward effect of enhanced fertility in the carriers, at least in that population.

Few would argue with the contention that schizophrenia represents a significant loss of fitness, and thus the search for

selective factors must include agents with the ability to cause a high mortality rate during the evolutionary time period that schizophrenia emerged as a relatively common mental disorder. There is some argument, however, as to when schizophrenia became as prevalent as it is today. Historically, the ability of the lay public or medical professionals to recognize schizophrenia may not have been as foolproof as the ability of today's psychiatrists, but a broad definition which includes all psychotic disorders would not be that dissimilar to the diagnostic criteria applied centuries ago.

It is with this perspective that E. Fuller Torrey and Judy Miller [14] undertook a study of the prevalence of schizophrenia and other psychotic illnesses through modern history. In their remarkable book, *The Invisible Plague*, Torrey and Miller document the rapid increase in the construction of insane asylums in the British Isles during the time period of the mid to late industrial revolution. What factor could account for such a rapid increase? The many changes in lifestyle included less time outdoors, moving from a rural environment to the city, and more crowded quarters, where the spread of disease occurred more readily. Torrey and Miller also focus on the changing patterns of pet ownership, which coincided with the industrial revolution. Animals which were once regarded as working stock, to clear the environment of rodents or to protect the premises, became pets, and as such, spent much more time in intimate quarters with their human owners. This, they argue, represented the perfect recipe for the spread of illness from animals to humans, and facilitated the spread of some infectious agent capable of eliciting schizophrenia in those infected.

An alternative view is that rather than causing schizophrenia through the infectious process, some infectious agent exerted selective pressure to cause genetic change over human generations, resulting in a higher prevalence of a resis-

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tance gene that conferred a greater predisposition to schizophrenia as an unlucky consequence. How many generations would be required to cause a change in gene frequency depends on the selective pressure. For a selective pressure that involves a fatal outcome prior to reproduction, a change in the frequency of a protective gene in the population can occur in one generation. There are many highly infectious, fatal diseases that would have increased in incidence in the crowded quarters prevalent during the industrial revolution. However, diseases that are uniformly fatal to their host do not persist, since the host is required for spread. Between the extremes of excessive mortality and mild morbidity, different models of pathogen success come into play [15]. Persistence of the selective pathogen across the generations is a necessary component for persistence of the advantageous gene, although a decline in the gene frequency more gradual than the original increase can occur once the selective force is removed. From the beginning of the industrial revolution in the mid-1700's to the peak of the increase in the prevalence of insanity in Ireland and England at the turn of the 20th century [14], the elapsed time was approximately 6 generations.

A disease that could exert a strong and consistent effect over 6 to 8 generations would have to be one that was frequently, but not uniformly, fatal, and perhaps one that persisted for some time in the survivors. In those that did not succumb quickly, the effect was likely a decrease in reproductive fitness during the course of infection. Episodic outbreaks, such as the plague, were less likely to have exerted the consistent selective pressure necessary to achieve and maintain a phenotype as complex as schizophrenia. The infections of greatest interest are those that preferentially strike the young before reproduction has ceased and those that could have remained endemic. One leading candidate for such an endemic agent is *M. tuberculosis*.

TUBERCULOSIS

Tuberculosis (Tb) blossomed during the industrial revolution in Europe and maintained a steady hand on the fate of humankind [16] until the advent of effective drugs in the mid-1900's. At its peak, Tb was responsible for 25% of all deaths in Western Europe [17]. It became an endemic infection, one that initially exerted a significant fatality rate in a population, but as the genetic background of each population shifted slightly, the fatality rate diminished [16]. As typical of infectious disease, newly exposed groups showed much less resistance. What was different about Tb was that the differential resistance of populations to *M. tuberculosis* did not appear to be in acquired immunity, i.e. resulting from antibodies to the organism, but rather from differences in the innate immune system, i.e. genetically-derived features of the immune response that can differ between population groups due to differences in selective pressure [18-24]. Differential innate resistance can be seen in one generation of selectively bred animals [25].

NIACIN, NAD AND *M. TUBERCULOSIS*

What are the components of the innate immune system that confer resistance to Tb? There are many cytokine responses that are thought to be crucial, including interferon

gamma and TNF-alpha [23]. Additional clues can be derived from the strategies of *M. tuberculosis* itself, strategies likely designed to overcome the host response. Perhaps the most remarkable feature of this bacterium is one that led to a method to identify its presence in culture. When grown in culture, *M. tuberculosis* produces copious quantities of niacin [26,27].

Niacin (nicotinic acid) is one of the vitamin B3s. It serves as an important precursor to the energy carrier NAD in animals and yeast, and when present in sufficient quantities, makes unnecessary the *de novo* synthesis of NAD from tryptophan (Fig. 1). The host's NAD levels can diminish the infectivity of some microorganisms, as NAD represses the gene expression they require to launch a successful infection [28]. Whether it acts in a similar fashion for Tb is not yet known. Shibata *et al.* [29] found that the effective anti-tubercular drug pyrazinamide acted to increase NAD contents of the cell. What has also been shown is that, under some culturing conditions, this organism lacks the enzymatic activity to convert niacin into NAD [26,30], although subsequent work has illustrated that under anaerobic culturing conditions, nicotinamide is efficiently converted into NAD by mycobacterial enzymes [31]. This ability is not necessary *in vivo*, because mutants in the recycling pathway were as successful at mounting a successful infection as the wild type organism [31], a finding consistent with the observations of Lurie [25] that the organism targets well-oxygenated tissues.

Thus, the bacterium is fully capable of acting as a drain on the host's NAD supply. Several decades ago, that was shown to be the case in tuberculous mice which exhibited liver NAD contents one half the level of controls [32,33] and this depletion has also been noted in lung-tissue adapted *M. tuberculosis* cells [31]. Notably, the decrease in the content of oxidized nicotinamide adenine dinucleotides (NAD and NADP) was reported to be more pronounced than the decrease in the reduced forms [33]. The cause was traced to increased NADase activity, originally presumed to be the nicotinamide adenine dinucleotide glycohydrolase activity of the host [34-37]. However, subsequent work demonstrated otherwise, that indeed the responsible enzyme was derived from human strains of *M. tuberculosis* itself [38]. This enzyme was not found to degrade NaMN to niacin (which can occur *via* bi-directional NaPRTase in some organisms), nor did crude extracts of *M. tuberculosis* show NaMN conversion to niacin. The route to niacin from the NADase activity was determined to be first the production of nicotinamide from NAD *via* nicotinamide adenine dinucleotide glycohydrolase and then the production of niacin from nicotinamide by nicotinamidase (Fig. 1), an enzyme found to be significantly elevated in human *M. tuberculosis* as compared to other strains [38].

Preferential degradation of NAD would lead to a higher NADH to NAD ratio. That the mycobacterium may strive to maintain a relative high ratio during infection can be inferred from the following findings: 1) studies showing that resistance to isoniazid results from a mutation in an NADH oxidoreductase, resulting in slower conversion of NADH to NAD by the mycobacterium and an increase in the NADH/NAD ratio [39] 2) NAD increases gene silencing [28] and

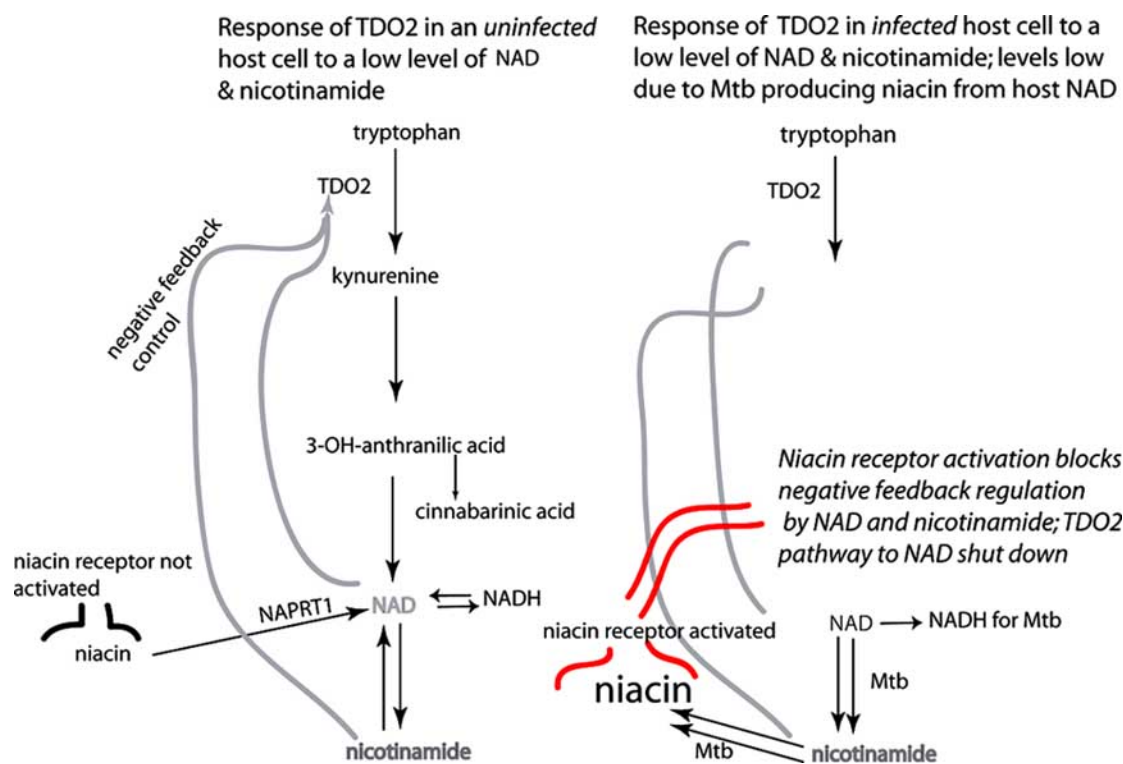


Fig. (1). Model of the interaction of *M. tuberculosis* with the host's kynurenine pathway. Left panel: The normal response of the uninfected host cell to a low level of NAD, low level of nicotinamide and a physiologic level of niacin that does not activate the niacin receptor. Right panel: The response of an infected host cell to the low levels of NAD and nicotinamide, coupled with a high level of niacin brought about by *M. tuberculosis* infection. Under conditions of pre-existing niacin and tryptophan deficiency in the diet, the host's tryptophan level will have been depleted, a condition that will make the pathway more vulnerable to negative regulation [50] by excess niacin. Not shown is INDO which, when activated by IFN γ , catalyzes the same reaction as TDO2. INDO has not been shown to be regulated by NAD.

NADH inhibits gene silencing [40,41], actions which have opposite effects on the infectious success of some microorganisms [28]; 3) alcohol consumption, which notably increases the concentration of NADH [42], increases susceptibility to *M. tuberculosis* [43]; 4) the most effective anti-tubercular drug, isoniazid, forms adducts with NAD [44], and finally, 5) the NADH to NAD ratio is increased in lung-adapted cultures of *M. tuberculosis* as compared to those adapted to *in vitro* conditions [31].

Why the build-up of niacin by *M. tuberculosis* fails to lead to increases in NAD *via* the host NaPRT1 (Fig. 1) is not clear. In order to so deplete the levels of NAD in the animal host in the presence of excess niacin production, one might predict that *M. tuberculosis* has devised an inhibitor of the host's NaPRT1, the enzyme which converts niacin to NAD. The mammalian host is reported to have no means to generate niacin [45], but when niacin is available, it is the preferred substrate for NAD production *via* NaPRT1 [46,47].

The main compensatory response to depletion of NAD is up-regulation of the kynurenine pathway, the route for *de novo* synthesis of NAD from tryptophan, as happens in pellagra [48]. At least one mechanism for kynurenine pathway up-regulation is loss of feedback inhibition by NAD [49]. NAD and its congener, NADP, act as a feedback inhibitors of one of the initiating enzymes of the pathway, tryptophan 2,3-dioxygenase (TDO2). TDO2 is also subject to substrate-induced activation by tryptophan, which serves to stabilize the holo-enzyme [50]. In contrast, INDO has not been shown

to be regulated by NAD, rather it is up-regulated at the gene expression level by IFN γ , and would be expected to remain activated if IFN γ signaling is adequate during infection. It is the cell types that express less INDO that may be more vulnerable to depletion of NAD by Tb.

Of potential relevance for kynurenine pathway activation during *M. tuberculosis* infection is the mammalian receptor for niacin. The endogenous role of the receptor for niacin is not fully understood, but it is thought that the K_d for niacin (100 nM) may be quite a bit higher than the levels in mammalian tissue [51]. Certainly, dietary intake should lead to transitory fluctuations in concentrations, during which the K_d of the receptor could likely be reached. One purpose of the niacin receptor may therefore be sensory, analogous to olfactory receptors, to serve as a detection system for daily dietary niacin supply, transitory though the response may be. When dietary intake of niacin is high, the receptor may signal that ample niacin reserves have been made available to synthesize NAD, so that *de novo* synthesis of NAD from tryptophan is unnecessary and long-term changes in gene expression do not take place. Thus, by creating excess niacin, *M. tuberculosis* may create the illusion of adequate niacin stores for conversion to NAD, when the reality for NAD levels is quite the opposite.

Host mutations that would overcome this devious strategy by *M. tuberculosis* would include those that constitutively up-regulate the *de novo* synthesis of NAD from tryptophan *via* the kynurenine pathway.

EVOLUTION OF A RESPONSE TO INFECTION: KYNURENINE PATHWAY DYSFUNCTION IN SCHIZOPHRENIA

As eloquently proposed by Rongvaux *et al.* [52], the evolution of redundant biosynthetic routes to NAD has allowed those pathways to acquire effects unrelated to NAD biosynthesis. Such is undoubtedly the case for the kynurenine pathway. Several independent research groups have reported evidence for kynurenine pathway up-regulation in schizophrenia (Fig. 1) as well as other disorders associated with psychosis [53-57]. The kynurenine pathway is regarded as one of the first line defenses against many invading microorganisms [58-60], functioning to deplete tryptophan, the rarest of the amino acids, and one required for rapid growth. The central role of this pathway in balancing the intersection of immunity and autoimmunity has been reviewed by Penberthy [61]. In addition, the kynurenine pathway generates NAD, which as discussed above, can silence the gene expression required for infection. Finally, kynurenine pathway activation generates at least one endogenous antibiotic, cinnabarinic acid [62,63], a pigmented molecule that is derived from 3-hydroxyanthranilic acid.

Two enzymes initiate the kynurenine pathway, tryptophan 2,3-dioxygenase (TDO2) and indoleamine dioxygenase (INDO). The former is activated under conditions of niacin deficiency (pellagra; [48, 64]) and the latter primarily by the immune-system activator interferon- γ [58]. Of the two enzymes, it is TDO2 that is increased in schizophrenia [55,56]. One model to explain this increase is that it results from either low levels of niacin and NAD, or defective signaling of the sensor for niacin, i.e. the niacin receptors (HM74 and HM74A). It is of note that the mouse orthologue of the niacin receptor genes (GPR109) resides in a chromosomal region that shows some evidence for linkage to a gene conferring resistance to the wasting effects of murine tuberculosis (D5Mit95; [65]).

INDIRECT EVIDENCE FOR A DEFICIENT NIACIN RECEPTOR IN MANY INDIVIDUALS WITH SCHIZOPHRENIA

The first evidence for a defect in the receptors for niacin in schizophrenic individuals stemmed from studies carried out by the psychiatrist Abram Hoffer in the 1950s and 1960s [66,67]. This was a time period that followed on the heels of the Great Depression and the war years, when dietary deficiencies were common, and pellagra-induced psychosis reached epidemic proportions, particularly in areas where corn (relatively deficient in tryptophan and niacin, particularly when compared to meat) became the staple food. The fact that niacin cured pellagra-induced psychosis lead some to speculate that it might be beneficial for other types of psychosis as well. However, Abram Hoffer looked at this question from a different perspective, hypothesizing that niacin, as a methyl receptor, might act as a sink for methyl groups that would otherwise go towards the production of catecholamines [67]. Niacin is a substrate for catechol-O-methyltransferase (COMT; [68]), resulting in the production of methylnicotinate. Hoffer cites numerous examples of successful treatment of schizophrenia with niacin, in an era

that preceded the advent of traditional neuroleptics. Subsequent studies by others were met with mixed success (reviewed by Kleijnen and Knipschild [69]). But it is what Hoffer observed about their cutaneous response to niacin that is most pertinent to the question at hand. Schizophrenic individuals, as a group, show a diminished flush response when niacin is ingested. This led other researchers to test the cutaneous response directly by applying niacin (or its even more potent derivative, methylnicotinate) to the skin. The predominant response in schizophrenic individuals is a blunted flush compared to controls [70-75, though not 76]. The effect of medication was partially addressed in two studies that included unmedicated schizophrenics [77,78], the former concluding that the effect of medication does not explain the blunted niacin flush and the latter showing if the effect of antipsychotic medication is to blunt the niacin flush response, it does not appear to do so in those treated chronically. Nevertheless, the potential for interaction should continue to be addressed, in particular with regard to the therapeutic mechanism of neuroleptics.

The most straightforward cause of a blunted flush response would be a defect in the receptor that initiates the flush response to niacin. In 2001 a niacin responsive human receptor was identified [79,80] and later confirmed as that which responds to niacin to elicit the flush response [81]. The signaling cascade involves the production of prostaglandin D2 and E2, both of which cause vasodilation and flush. The primary cutaneous mediator is thought to be prostaglandin D2 [82].

Other evidence for a defect in the niacin receptor in schizophrenia includes the remarkably low incidence of rheumatoid arthritis in that population [83]. As rheumatoid arthritis is thought to be mediated in part by the production of excess prostaglandin E2 [84], a deficient niacin receptor would also explain these epidemiological findings.

DIRECT EVIDENCE FOR A DEFICIENT NIACIN RECEPTOR IN MANY INDIVIDUALS WITH SCHIZOPHRENIA

A study of postmortem brain tissue was undertaken in this laboratory to quantify the protein for the high affinity niacin receptor. Although peripheral tissue bears more relationship to the blunted cutaneous flush response, it is obviously brain function that is most relevant to the schizophrenic condition. A comparison of postmortem brain samples derived from controls and schizophrenia patients revealed that the protein for the high affinity niacin receptor was significantly decreased in the schizophrenia group [85]. This raised the possibility of a genetic defect that would impair the amount of protein synthesized and thereby result in a compensatory up-regulation of the mRNA transcript for the niacin receptor.

Subsequent genetic association studies in a substantial cohort have confirmed that a polymorphism in the niacin receptor HM74 gene is associated with schizophrenia and bipolar disorder [86]. Furthermore, the identified polymorphism affects gene expression in a manner consistent with the gene-expression difference seen between cases and controls.

CORRESPONDENCE BETWEEN VULNERABILITY TO Tb AND SCHIZOPHRENIA, AT THE INDIVIDUAL AND POPULATION LEVEL

There are no data to indicate that untreated tuberculosis is associated with psychosis [87] or well-controlled studies to indicate that differential resistance to Tb exists in individuals with schizophrenia versus the general population [88]. Anecdotal observations led some to consider whether Tb might be more prevalent than expected in the schizophrenic population (reviewed by Lindelius and Kay [89]), but the expected prevalence was not adjusted for the greater exposure that most definitely occurred during institutionalization or for dietary factors that differed between schizophrenia patients, other hospitalized patients and controls. The topic was addressed by Alstrom [90] who observed that the vulnerability related to weight loss, particularly in the catatonic patients. Adequate nutrition is very important for the host to combat *M. tuberculosis* [25,91-95]. Studies comparing the rates of Tb between major diagnostic categories of mental patients have found higher rates in the mentally retarded than in the schizophrenia group [96]. Furthermore, the incidence of Tb was typically not adjusted for demographic factors such as ethnic background.

As the spread of Tb coursed through Europe, those left unexposed until the rapid advent of the industrial revolution were uniquely susceptible. Living on an island was certainly one geographical means of protection from the scourges that swept the continent. Other factors may have increased the isolation, such as economic depression that discouraged travel. Certainly, travel between economically depressed Ireland and the continent was much less common than between London and the continent during the preamble to the industrial revolution. When the industrial revolution finally came to Ireland and factories were set up, the change in exposure to infection was sudden and the Irish were more vulnerable than their British counterparts [16].

Although an early study by Kallman [97] reported that the relatives of schizophrenia probands in the U.S. were more likely to be affected with Tb than the general population, the population from which many of the mental patients came in this country in the 19th and early 20th centuries included a large proportion of Irish descendants [98,99]. The important question to have asked was whether the risk of Tb infection was greater or lower in the schizophrenia patients when compared to their ethnically matched counterparts in the same or similar environment, a difficult undertaking even now.

The observations that the representation of the Irish in the dementia praecox wards exceeded their representation in the general population [14,98,99] should not be ignored. The percentage of dementia praecox admissions that were Irish was 1.85-fold their representation in the community at large, whereas the percentage of dementia praecox that were first generation English, German and Italians was lower than their representation in the community at large [98]. The stress of immigration is a known risk factor for schizophrenia [100], but the increased incidence of schizophrenia in the Irish extended to their home country, particularly noticeable in the late 1800's and early 1900's [14,101]. Selection for this genetic liability may have been the price paid over the genera-

tions as the Irish began to overcome their greater vulnerability to Tb. The selective force exerted on the Irish may have been accentuated by their relatively poor diet, shifting to substantial consumption of "Indian meal" or "stirabout" (cornmeal) for much of the latter part of the 1800's following the potato famine [102,103]. Cornmeal is relatively depleted in tryptophan [104] and the niacin content is largely in the unavailable, bound form [105] unless treated with lime [106]. The lack of availability of niacin in corn has profound implications for growth [105], and for the development of pellagra [107], or other niacin-deficiency effects.

Nowhere was the vulnerability to Tb more dramatic than in the Saskatchewan Cree Indian population of the 1800's, when they were relocated to reservations in the Q'Appelle Valley. Even more than the Irish, they had been protected from Tb exposure until, in the vortex of poor diet on the reservations, crowding and exposure to the infectious organism, they exhibited the worst outbreak of Tb ever recorded [108]. The diet relied heavily on white flour [109], which is not only deficient in niacin but in tryptophan as well [110]. Tb was rarely seen in tribes of North America until the first major outbreaks following settlements in reservations or prison camps in the 1880's [17], peaking at the turn of the century. Lacking the requisite innate immune response, the death rate was staggering, up to 9000 per 100,000 of population (as a point of reference, the Tb mortality rate in continental Europe reached peaks of 200-500 per 100,000 [92,111]). A couple of generations hence (1961-1966), the Saskatchewan Cree were reported to suffer from a remarkably high rate of schizophrenia [112], second only to the incidence found for a remote Swedish isolate, as reported in a review of the prevalence of schizophrenia compiled by Warner [113]. This high prevalence of schizophrenia is unlikely to have been an artifact of Western psychiatry misinterpreting Native American behavior. As a point of reference, the Cherokee Indian population was reported to exhibit a remarkably low prevalence of schizophrenia [114]. This particular tribe had also been spared a massive epidemic of Tb, with a prevalence rate reported by Kober [115] to be less than 1/10 that reported for the Saskatchewan Cree of the Q'Appelle Valley.

The Cree epidemic preceded the development of effective anti-tubercular drugs by only a few decades or so (approximately two generations). Although the risk for contracting Tb is still reported as higher for all non-Caucasian health care workers than for Caucasians [116], the available treatment has significantly decreased mortality. As of the 1990's, the fatality rate of those with clinical symptoms in Western Europe, Canada and the U.S. was reduced from over 35-40% to less than 10% [16]. Currently, the most significant reservoirs for future epidemics are those with latent infections [117].

THE INTERESTING PARADOX CONCERNING DRUGS FOR Tb AND PSYCHOSIS

Many of the drugs effective for treatment of Tb either cause psychosis or are anti-psychotic. The drugs that are pro-psychotic have not been reported to exert that effect in those undergoing treatment for latent Tb; rather, the psychosis is reported for those undergoing treatment for active Tb [118-122]. As the *M. tuberculosis* is eliminated, its production of

niacin and hence, feedback inhibition of the kynurenine pathway would also be eliminated. As is commonly seen in biochemical systems, there may then be a brief re-bound period during which the kynurenine pathway is upregulated.

The antipsychotic, antitubercular drugs are the phenothiazines, all of which are effective oxidants of NADH *in vitro* to NAD [123] and *in vivo* [124]. The mechanism of their antitubercular effects has not been well-studied, though the mechanism of their antipsychotic effects are purported to relate to dopamine receptor antagonism [125]. In the kynurenine pathway model, the NAD generated by oxidation of NADH would be expected to feedback-inhibit the kynurenine pathway [49], and exert an antipsychotic effect in that manner.

THE VALUE OF AN EVOLUTIONARY MODEL

Of what advantage is a model for the mechanism by which a particular genetic disease increased in prevalence through natural selection? Some might argue that there is no intrinsic benefit to such thinking, as we are stuck with the consequences no matter what. However, a model based on scientific principles holds the potential to illuminate otherwise obscure and seemingly unrelated sets of data. Predictions can then be made and hypotheses tested. Darwin's principles revolutionized our thinking about the origins of life itself, and the current importance of those principles goes far beyond identifying fossilized bones in the sediments.

THE MODEL

Populations which were geographically protected from exposure to *M. tuberculosis*, and which subsequently sustained a sudden, extreme exposure under the unfavorable environmental conditions of crowding and very poor diet, were uniquely vulnerable to the natural selection that *M. tuberculosis* can exert on its human host. The poor diet that the Irish and the Saskatchewan Indians shared in the late 1800's was one deficient in niacin and of even more importance, deficient in tryptophan. This was a recipe for disaster, increasing the lethality of Tb and increasing its power as an agent of natural selection. The low dietary tryptophan would have made *de novo* synthesis of NAD much more difficult for the human host and its synthesis more vulnerable to feedback inhibition (Fig. 1). In this scenario, the net production of niacin by *M. tuberculosis* would have activated the receptors for niacin, even as the organism was depleting the host's NAD. *M. tuberculosis* appears to be unique in this strategy, as no other lethal organism has yet been shown to directly manipulate the levels of kynurenine pathway intermediates or products. The model proposes that stimulation of the niacin receptors represses the *de novo* synthesis of NAD from tryptophan, and that a mutation in one or the other of the niacin receptors conferred insensitivity to niacin, thereby circumventing repression of the kynurenine pathway and enhancing survival of the host. The tradeoff was a greater vulnerability to schizophrenia resulting from up-regulation of the kynurenine pathway.

CAVEATS TO THE MODEL

The basis for schizophrenia cannot be attributed solely to inherited genes [126], and the potential for an environmental

“epigenetic” effect of *M. tuberculosis* in the affected populations must also be considered. The two mechanisms for tuberculosis are not mutually exclusive. Thus, as described in the review by Finch and Crimmins [127], inflammatory events that occur during development can lead to effects that do not become manifest until later in life. In fact, the “neurodevelopmental model” of schizophrenia proposes just such a scenario [128], that some toxic insult interacts with genetic susceptibility during development to change the eventual phenotype. That this may be true for early infections with *M. tuberculosis* is suggested by one report that Tb in childhood may increase the risk of schizophrenia, epilepsy and adult neurologic soft signs [129], though the numbers of childhood Tb subjects were too few in that study (two) to reach meaningful conclusions. The association of early Tb with psychosis would in theory be consistent with down-regulation of the niacin receptor induced by the excess niacin generated by Tb, with the psychosis analogous to that occurring transiently in some adults during the recovery from Tb with antitubercular drugs. Once the source of excess niacin is removed by the anti-tubercular treatment, the conversion of the niacin receptor from a down-regulated state to a more physiological state is likely not immediate, and in the case of epigenetic changes during development, the receptor may never completely revert to the normal physiologic state. Such an epigenetic change, however, would not explain longterm changes in gene frequency in a population as seen for HM74 in schizophrenia, and is inconsistent with the persistence of schizophrenia in Western populations despite being free of endemic Tb for two to three generations.

In addition, the necessary studies showing that one or more polymorphisms in HM74 confer resistance to Tb have yet to be done, whereas the evidence for other genes has already been acquired. Several genes have been demonstrated to be associated with resistance to Tb in humans and in animal models [23], as reviewed by Fortin et al.[130] and of these, TNF- α , INF- γ , IFNGR1, and IFNGR2 are known to interact directly with the kynurenine pathway through their regulation of INDO [58], also consistent with *M. tuberculosis* having selected for kynurenine pathway dysregulation. The environment, the genetic background of humans subjected to selection by Tb, and the severity of the epidemic, may have biased the outcome towards one genotype over another. What is lacking for these genes are association studies pertaining to schizophrenia.

PREDICTIONS OF THE MODEL

A genotype that confers risk for schizophrenia should occur with greater frequency in individuals resistant to Tb than in an ethnically matched cohort that is less resistant to Tb. Specifically, individuals with schizophrenia who are descendants of the Q'Appelle Valley Saskatchewan First Nation tribe should exhibit a high frequency of a genotype associated with down regulation of the high affinity niacin receptor gene (HM74A). Other once-remote populations with a similar history should also be studied.

- 1) In order to consistently exert selective pressure on the kynurenine pathway of its human host, *M. tuberculosis* should have devised a strategy to inhibit the host's NaPRT1 enzyme. Extracts of *M. tuberculosis* cultures

can be tested for specific inhibitory effects on the activity of the host NaPRT1.

- 2) Any pro-psychotic component of the kynurenine pathway should be closely allied to one that exerts an antibiotic effect. The closer the pro-psychotic component is to the component imparting antibiotic efficacy, the more likely it is that Tb (or another infectious agent) acted as a significant evolutionary selection factor converging on this pathway. NAD is clearly not psychotomimetic, but the endogenous antibiotic cinnabarinic acid, a byproduct of the NAD precursor 3-hydroxyanthranilate, should be tested for psychotomimetic effects in an animal model.
- 3) Pharmacological doses of niacin and/or nicotinamide or other agents that are capable of increasing NAD in the host without activating the kynurenine pathway, should be both anti-tubercular (as per Murray [131] and antipsychotic (as per Hoffer [66]), whereas those that elevate NAD *via* kynurenine pathway activation should be anti-tubercular but pro-psychotic.

CONCLUSIONS

A commonly accepted fallacy in modern biomedicine has been the premise that human evolution occurs very slowly, over the millennia. This view of human biology has blinded scientists to important epidemiological clues for the genetics of schizophrenia or other diseases that show changes in prevalence over relatively short time periods, and has encouraged some to downplay the genetic basis altogether. The modern field of Tb research stands alone as a discipline that has acknowledged from its inception the rapid change in gene frequency made possible by a lethal disease that afflicts the young.

NAD is central to the model presented here for the intersection of two diseases, poised in the balance between disease susceptibility and disease resistance. The sheer magnitude of the importance of NAD to bioenergetic homeostasis provided the driving force for the compromise of related pathways. Thus, the architects of new pharmaceuticals for schizophrenia and for Tb, would do well to incorporate an in-depth understanding of the many nuances of the pathways to NAD.

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ABBREVIATIONS

- IFN- γ = Interferon gamma
 INDO = Indoleamine dioxygenase
 NNAPRT1 = Nicotinate phosphoribosyltransferase
 TDO2 = Tryptophan 2,3-dioxygenase

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