Autism, Viral Infection and Measles-Mumps-Rubella Vaccination

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There is clear evidence from developed countries that the incidence of autism is rising. The beginning of the recent dramatic increase can be traced back to children who were born in the 1970s in the United States [1] and the 1980s in Britain [2] [Figure 1]. What has changed to cause the sudden and sequential increased risk of this disorder in different countries that use the same diagnostic criteria? It cannot simply be genetic, nor are these trends readily accounted for by supplemental hypothetical models of genetic anticipation.

There is growing concern, among both parents and professionals, that recent increases in the numbers of children with autistic regression and other developmental disorders may be associated with exposure to the combined measles-mumps-rubella vaccine. In order to assess the validity of such a concern, the characteristics of the autistic phenotype deserve scrutiny. It is evident that, for the great majority of this subgroup of autistics, one is not dealing with the classical observation that the child does not develop in the way of normal siblings and peers, where parental concerns about the child's development are often expressed in the second year of life when such differences become evident. In children with autistic regression, the emerging behavioral phenotype is of regression in a previously developmentally normal child [3]. This is consistent with an early-onset disintegrative psychosis [4]. Furthermore, loss of speech and language are accompanied by symptoms of excessive thirst, bowel disturbances, self-injury, and a self-limited diet associated with cravings for particular foods. Atopy and recurrent, refractory upper respiratory tract infections are prominent features. These symptoms do not feature in the exclusively behavioral descriptors of DSM-IV [5]. A further indication of a changing phenotype is presented in the data from the California Report [1], which recorded a much lower proportion of autistic children with mental retardation among those entering the Developmental Services system in the late eighties than those entering 10 years previously. It is possible that this difference reflects a changing pattern of exposure to an environmental trigger(s) that is delayed in latter birth cohorts, occurring only after a period of normal development of the central nervous system.

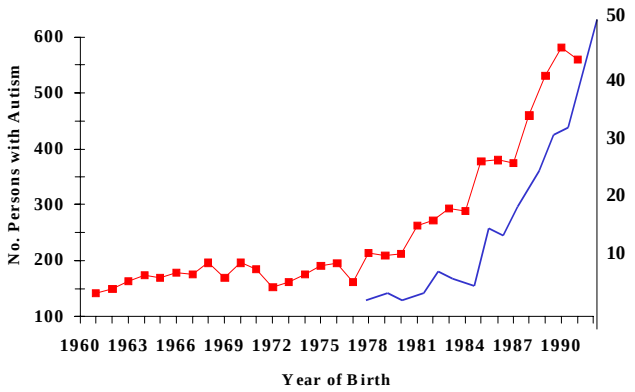

Figure 1. Temporal trends for autism in California, U.S. [1] and North West London, UK [2]. The Y axis indicates number of newly diagnosed children: California (left) and North West London (right). The baseline rate of autism (number of new cases per year) in California remained below 200 until the mid-1980s, whereafter a steep and sustained increase is observed. In 1998 the expected numbers of newly diagnosed autistic children in California should have been 105–263 cases, according to DSM.IV; the actual figure was 1,685 new cases. The temporal trend in North West London is identical, although the rise is delayed by approximately a decade. The two countries use the same diagnostic criteria. The sequential trends are consistent with the timing of introduction of MMR to both countries.

It has long been recognized that a diagnosis of autism could be the result of several differing etiological processes that can influence the disease phenotype. Important clinical and pathological correlates of the regressive autistic phenotype are emerging. These include gut pathology — ileocolonic lymphoid nodular hyperplasia and colitis — and a subtle immunodeficiency (autistic enterocolitis) [6,7]. Affected children exhibit impaired cellular immunity to common recall antigens, lymphopenia, increased HLA class II antigen expression within the colonic lamina propria but not in the epithelium, and epithelilal infiltration by γδ-Tcells [8]. This is accompanied, in some children, by persistent measles virus N-protein in follicular dendritic cells of the reactive ileal lymphoid tissue and a supranormal measles immunoglobulin G immunoreactivity [9]. The emerging picture suggests the possibility of a virally mediated mucosal immune dysregulation with T helper cell type 2 (T_H2) skewing, data that are consistent with studies of autistic children in the U.S. [10]. T_H2 im-

mune skewing is indicative of a suboptimal antiviral immune response and a tendency to atopy. Previous experience with adverse outcomes of other measles vaccines may be relevant in this context. Early administration of high titer measles vaccines to children in developing countries was associated with increased delayed morbidity, mortality — in which diarrheal deaths (for at least 2 years following vaccination) were prominent — and impaired cell-mediated immunity compared with more conventional measles vaccine regimens. When describing this phenomenon, Hilleman of Merck wrote: "the process bears resemblance to AIDS" [11].

The key to unlocking the mystery: changing patterns of childhood infection

An answer to this etiological puzzle lies in the changing pattern of exposure to infectious disease in childhood. Patterns of exposure to common childhood viral infections play a large part in determining both the severity of the acute disease and the risk and nature of delayed consequences of the infection. Acting possibly through bystander mechanisms, childhood exposure to microbial antigens also plays a crucial role in early immune programming and, thus, the subsequent handling of environmental antigens unrelated to the original infection [12]. Once again, the pattern of exposure may be fundamental to the integrity of this immune programming.

Patterns of exposure to common childhood infections have changed over time — dramatically so over the course of the twentieth century. Important determinants of these changing patterns of exposure include cultural and material conditions, family structure, including size and birth order [13], and latterly, vaccination. An example of how age-of-infection can influence the virus–host interaction, and thus the ensuing disease phenotype, is paralytic poliomyelitis. As material conditions improved at the beginning of the twentieth century, paralytic poliomyelitis became more common. Prior to this time the virus was encountered in early infancy, and exposure resulted in mild fever and life-long immunity. As material conditions improved, the virus was encountered in later childhood and even in adult life when the risk of paralytic disease is greater [14]. Accordingly, the disease first appeared in people of higher social classes, whose exposure to poliovirus was more likely to be delayed.

For measles virus, birth order and material circumstances in childhood, as proxy measures for dose and age of infection, have emerged as risk factors for persistent infection and delayed disease, such as in subacute sclerosing panencephalitis [15]. Similar data are emerging for IBD[1] [16–18]. Measles has also played an important role in early immune conditioning, and changing patterns of exposure to measles have been strongly linked to the emergence of immunopathologies in the latter half of the twentieth century. Whereas wild measles infection appears to be protective against atopic disease, in a recent study from Sweden that compared schoolchildren of families with an anthroposophic lifestyle to those in mainstream schools, MMR vaccine — but not other vaccines — emerged as a strong risk factor for atopy [19].

In order to understand how an apparently novel immunopathology — autistic enterocolitis — might have emerged in the face of a changing pattern of childhood infectious exposure, one can gain clues from data emerging on the etiology of classical forms of IBD, Crohn's disease and ulcerative colitis. As with some forms of autism and other immune-mediated diseases, a rising incidence of Crohn's disease has been observed over the twentieth century. While this chronic disease typically has its onset and diagnosis in young adult life, there is compelling evidence that infectious exposures in early life, rather than events in adult life, influence the risk of developing disease [16–18,20]. The European Community study of inflammatory bowel disease (EC-IBD) found significant differences in the incidence of adult-onset Crohn's disease in different countries during the same time period [21]. Use of the same standardized protocols ensured that these differences were not due to variations in diagnostic procedure. The uniformity of the pattern of clinical presentation throughout the study confirmed that differences in the use of health services or diagnostic delay were not responsible for the variation in incidence rates [22]. Neither could adult-life factors known to influence the risk of Crohn's disease explain why different countries had such different incidence rates [21]. Based upon the a priori hypothesis that infectious exposures in *early life* are important, the data were reanalyzed, focusing on markers of infection during infancy [17]. Since infant mortality rate is a powerful indicator of risk and outcome of acute infection, its relation with subsequent adult-onset Crohn's disease was examined. A powerful inverse relationship was found between infant mortality rate during infancy and subsequent adult-onset Crohn's disease. Countries with the lowest infant mortality rates had the highest incidence rates of Crohn's disease some 20–40 years later, confirming the importance of environmental factors in early life in the etiology of Crohn's disease. These data are corroborated by similar studies of the relationship of infant mortality with the incidence of Crohn's disease over time [18].

There are three possible explanations for the relationship between Crohn's disease and infant mortality rate, none of which are mutually exclusive. The first is that exposure to a primary etiological factor for Crohn's disease may be fatal during periods of high infant mortality. The second, and more likely, explanation is that an environmental risk factor for Crohn's disease may become more common as material conditions improve. Another possibility is that people who are innately vulnerable to developing Crohn's disease may be more likely to survive

[1] IBD = inflammatory bowel disease

in improved conditions. However, this third possibility can be discounted since a relatively low proportion of monozygotic twins, where at least one twin has IBD, is concordant for disease [23], confirming that *exposure* rather than susceptibility is important. It is of interest that for both Crohn's disease and autism, a birth-cohort effect has been identified that is linked temporally to measles epidemics [24,25].

Evidence from immigrant populations also emphasizes the importance of environmental risk factors in *early life*. Several studies have reported an apparent excess of young southern Asians with IBD in Britain [26], including a nationally representative birth cohort [20]. None of the parents of cohort members who were born in southern Asia, where Crohn's disease is extremely rare, had IBD. However, their children, who were born in Britain in considerably improved material circumstances, were at an increased risk of IBD when compared with the indigenous British population. This is consistent with the fact that improved material circumstances in early life increase the risk of developing subsequent IBD. Perhaps a higher prevalence of the genotypes predisposing to IBD among southern Asians is due, at least in part, to fewer cumulative selective pressures experienced by previous generations.

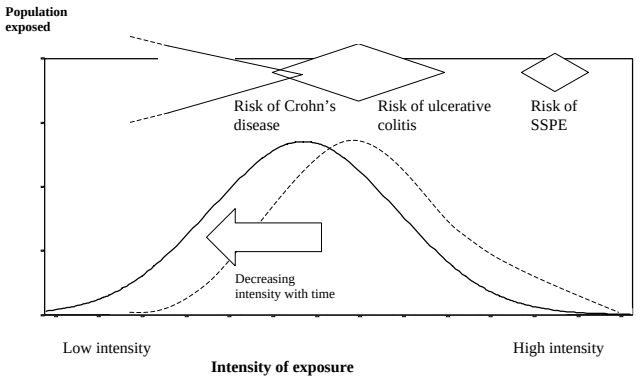

Figure 2. A hypothetical model for patterns of infection, viral persistence and the changing phenotype of delayed disease over time. Viruses such as measles may establish a persistent infection that is associated with delayed disease under conditions of intensive (high zone) exposure [15] or subclinical (low zone) exposure [40]. At the population level, such patterns of exposure to measles virus may be considered atypical, with the majority of individuals being infected at doses that induce effective antiviral immunity. Other factors may compound the risk of persistent infection such as concurrent viral exposure. The changing position of this curve with time, from higher towards lower dose, is consequent upon the changing patterns of transmission of measles virus over time. This may explain the changing phenotype of associated chronic diseases over the course of the twentieth century. The majority of SSPE cases are consistent with a high zone model that has virtually disappeared due to improvements in material circumstances and measles vaccination that have reduced the frequency of high zone exposure. Inflammatory bowel disease emerged during the twentieth century and, consistently, ulcerative colitis emerged prior to Crohn's disease [37] in different countries. Crohn's disease eventually becomes the dominant IBD phenotype [37] and the emergence of Crohn's disease in children is a relatively recent phenomenon. Has the intensity of the exposure, among other factors, determined the phenotype shift? The epidemiology of IBD is consistent with a higher dose infection as a risk for ulcerative colitis and a lower dose increasing the risk for Crohn's disease [35,36] . Both may be compounded by other factors such as concurrent exposure. We hypothesize that autistic enterocolitis is an emergent IBD phenotype that follows a low-dose compound viral exposure.

Why should improvements in material circumstances in early life increase the risk of subsequent immune-mediated diseases, including IBD? The most compelling evidence points to the infectious exposures that we experience in infancy and childhood. Throughout evolutionary history children have been exposed to infectious agents that have played an important part in programming the developing immune system, both in terms of antigen-specific responses and in overall pattern of immune functioning. At the level of the immune response, a newborn tends towards a T helper cell type 2 (T_H2) response to pathogens and gradually shifts towards a T helper cell type 1 (T_H1) response with age [27]. If this transition does not take place appropriately, the infant is likely to be at greater risk of mounting aberrant immune responses in later life, as seen in patients with allergies. Given that under normal circumstances the age of this transition will be different for different children, it seems inevitable that a ubiquitous viral exposure of all 15-month-old children could induce an immune response that is consistent with the individual dynamics of this $T_H2 - T_H1$ transition.

Compound Effects

Parental reports have implicated the polyvalent MMR vaccine, but rarely monovalent measles vaccine, in autistic regression. Is such a causal association consistent with what is known of the risks for acquired forms of this disease? Certainly, atypical patterns of exposure to common childhood infections — measles, mumps, rubella and chickenpox — have been associated with autism [28] and autistic regression [29]. *In utero* and infant exposures have been identified as periods of apparent susceptibility, when both the brain and the immune system are undergoing rapid development. It is notable that a close temporal relationship in the exposure to two of these infections during the periods of susceptibility may compound both the risk and severity of autism [28]. Although in historical cohorts these rare patterns of exposure may have accounted for only a proportion of autism, the widespread use of a combination of the candidate agents in a single vaccine may have changed this. Recently, measles-containing vaccines were linked to developmental regression [30]. In order to understand why autistic enterocolitis might be a compound effect — where the interaction of multiple viral exposures is important — it is helpful, once again, to examine the patterns of childhood infection that have been identified as risk factors for persistent infection and delayed disease.

One important pattern of infection that may increase the risk of delayed disease is where different viruses appear to interact, either directly, or indirectly through the host immune system. A close temporal relationship of measles and another infection, including chickenpox and encephalitogenic enterovirus infections, is a recognized

risk for SSPE[2] [31,32]. Similarly, temporally close measles and mumps infections have been identified as a risk for IBD, Crohn's disease, as well as ulcerative colitis. In a study of the population born in Great Britain during one week in 1970, details of acute childhood infections were collected prospectively and at least 6 years prior to the onset of any symptoms of IBD [33]. A close temporal relationship of measles and mumps infections was a significant risk for both later Crohn's disease and ulcerative colitis, independent of potential confounding factors such as presence of siblings, social class, household crowding, gender, and a family history of inflammatory bowel disease. All concurrent measles and mumps infections associated with subsequent inflammatory bowel disease were experienced prior to age 7 years — during a period when the immune system is developing rapidly. Interestingly, disease phenotype was influenced by another characteristic of the pattern of infection. Concurrent measles and mumps infections at an earlier age were a risk for ulcerative colitis, while later concurrent infection was a risk for Crohn's disease. Age of exposure is also likely to reflect severity of infection, with later infections tending to be less intensive than earlier infections. These results have been confirmed using another data set, showing that the presence of older siblings increases the risk of ulcerative colitis while reducing the risk of Crohn's disease [34,35]. Having older siblings increases the risk of earlier, more intense exposure to measles and other infections. It appears that very subtle differences in pattern of infection may result in significantly different disease outcomes.

Temporal changes in the epidemiology of IBD can be explained in terms of changing patterns of exposure over time. A study of Icelandic data reveals that the pattern of measles and mumps epidemics has changed, just as it would have in the majority of developed countries [36]. As transport and ease of travel have improved, the old epidemic mode of these infections has moved towards an endemic pattern, where concurrent measles and mumps infection has become far more common. In the Icelandic study, children who experienced concurrent measles and mumps epidemics between birth and age 6 years (the age of highest vulnerability identified by an earlier study in Britain [33]) were at a significantly increased risk of developing inflammatory bowel disease. Although chickenpox epidemics have also become more common, this risk was not seen for concurrent chickenpox and measles epidemics. Also, in all developed countries where conditions have improved and the intensity of infectious exposure has become milder, we have seen a shift from ulcerative colitis to Crohn's disease as the dominant phenotype [37]. This is consistent with the assertion that subtle shifts in pattern of exposure may have profound effects upon disease phenotype.

In the syndrome of autistic enterocolitis, although the gut lymphoid tissue is an important focus of disease activity, the major symptomatic impact is evident in behavior and development. Does this syndrome represent a novel phenotype of IBD where the associated developmental disorder reflects the impact of a dysfunctional gut mucosa during a period of rapid cerebral development? Current and by no means mutually exclusive hypotheses for the *liason dangereuse* between gut and brain include autoimmunity directed against neuroectodermal epitopes [38], and a direct toxic effect on the developing brain, mediated by compounds that include the dietary-derived exorphins, cesomorphine and gliadomorphine. In direct contradiction to widely held beliefs in the field of autism, there is a reversible element to the behavioral pathology. Dietary exclusion of opioid substrate is one therapeutic approach [39].

Does any of this evidence implicate MMR vaccination as a potential risk for either inflammatory bowel disease, autism, or other immune-mediated diseases? We believe that it is both biologically plausible and consistent with temporal trends. The virological and immunological evidence is supportive. It is therefore legitimate to hypothesize that the combination of three viruses that have been associated both independently and in combination with autism, may represent — through mechanisms that are not yet fully understood — a compound risk for the disorder. Clearly, although the case is not proven, MMR vaccination is a candidate worthy of investigation.

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[2] SSPE = subacute sclerosing panencephalitis

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Capsule

The siesta in the elderly — risk factor for mortality?

During the siesta, blood pressure declines like it does during night sleep. Since cardiovascular events cluster during the morning hours, when hemodynamic changes from nocturnal baseline are maximal, a group led by M. Bursztyn hyothesized that an additional sleep period during the day (the siesta) may increase cerebrovascular events, and thus mortality. They performed a prospective population-based cohort study on 455 70-year-old residents of Jerusalem, Israel, using self-reported siesta at baseline and 6.5 years of total mortality data.

The results showed that the prevalence of the practice of the siesta was 60.7%. It was more prevalent among men than women (68% vs. 51%, $P<0.001$) and in survivors of previous myocardial infarction than in those without previous myocardial infarction (78% vs. 58%, $P<0.009$). After 6½ years of follow-up (1990–1996), 75 subjects died. For those who practiced the siesta, total mortality was 20% vs. 11% for those who did not. In a multiple logistic regression model that included several lifestyle descriptors, risk factors and diseases, the siesta remained predictive of mortality ($P=0.03$; risk odds ratio, 2.1; 95% confidence interval, 1.1–3.9).

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