Infection in childhood and neurological diseases in adult life

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Other chapters in this issue discuss the evidence that implicates infection during infancy and childhood in the aetiology of respiratory disease. Here I argue that experience of infection in early life may also be involved in the aetiology of some diseases of the adult nervous system. The descriptive epidemiology of three neurological diseases is compatible with the hypothesis that they are delayed consequences of childhood infection. It is not difficult to imagine that the effects of an infection which results in loss of cells from an organ system, like the central nervous system, whose cell populations have lost the capacity to replace themselves by mitotic division could remain hidden until unmasked by ageing. Such a mechanism may be important in the aetiology of motor neuron disease and Parkinson's disease. Age-related differences in host response, which may be partly related to a maturing immune system, are known to influence both short- and long-term outcome for several infections. Perhaps the immune response to infection with Epstein-Barr virus, or another common micro-organism with similar epidemiology, in adolescence or early adult life is sometimes directed at antigens that are also present in the central nervous system. At present, the evidence that supports these hypotheses is largely circumstantial. But it may be possible to devise ways of testing them both epidemiologically and in the laboratory.

Time trends in infant and maternal mortality

Over the past hundred years, expectation of life for people living in the western world has improved dramatically. The improvement has occurred in all age groups but it is most striking for expectation of life at birth. A large part of the reason for this, of course, is the steady fall in infant mortality that began around 1900 (Fig. 1). In the first decades of the century, death in infancy was commonplace. At that time, infant mortality was dominated by post-neonatal mortality—that is deaths occurring between the ages of 1 month and 1 year. The main causes were respiratory and gastrointestinal infections which were associated with adverse conditions, such as poor sanitation, contaminated water supplies...
and over-crowding. In 1920 in Britain, for example, infant mortality was 80 per 1,000 live births; today the corresponding figure is 6.2.

The decline in maternal mortality has been even steeper than the fall in infant mortality. But it did not begin until several decades after infant mortality had started to fall (Fig. 1). In 1935, levels of maternal mortality (caused mainly by toxaemia of pregnancy, *inter partum* haemorrhage and *post partum* sepsis) were little different from those of 1835—about 4 per 1,000 births. Yet now in Britain, maternal deaths are so rare that their occurrence provokes a confidential enquiry. In 1993, only 27 such deaths occurred in England and Wales—a rate that is 40 times lower than in 1935.

A corollary of the decline in maternal and infant death rates is that there have been huge changes in the sort of environment in which fetuses, infants and children grow and develop. Foremost among these changes is a differing experience of infection in infancy and childhood. People born later in this century are likely to have had fewer and less severe infectious illnesses and will have had them at an older age than people born earlier. In this chapter, I suggest that some degenerative neurological diseases of adults have their origin in early life and point to epidemiological evidence that indicates how three of these diseases, Parkinson's disease, motor neuron disease and multiple sclerosis might be linked to experience of particular infections.
Parkinson’s disease

Parkinson’s disease is an extra-pyramidal movement disorder characterised pathologically by neuronal loss from the substantia nigra and reduced concentrations of dopamine in the striatum. Its causes are poorly understood. Despite several large case-control studies, no strong environmental risk factors for Parkinson’s disease have been identified. Positive associations of the disease with rural residence, drinking water from wells, and exposure to herbicides and pesticides have been reported, but the associated relative risks were small and the findings of different studies have not always been consistent. Nor has the search for powerful genetic determinants of the disease yet been very successful. The prevalence of the condition in first-degree relatives of cases is not significantly different from controls and concordance rates in mono- and dizygotic twins are similar. Although the CYP2D6 allele associated with slow metabolism of desbrisoquine is over-represented in patients with Parkinson’s disease, its prevalence is low and the proportion of cases that can be attributed to this polymorphism is small.

A possible reason for the lack of success in the search for environmental risk factors for Parkinson’s disease is that most epidemiological studies have been focused on exposures occurring in adult life. If, as has been suggested, Parkinson’s disease results from the combination of an environmental insult and the subsequent age-related loss of dopaminergic neurons, the initial event that leads to the disease may occur many years prior to the onset of symptoms. A few investigators have studied environmental factors encountered during childhood, infancy or fetal life. Associations between recall of several common viral infections of childhood and risk of Parkinson’s disease have been reported but only a negative relation with recall of measles and a positive relation with croup, diphtheria and rheumatic fever were statistically significant. None of these relations was strong. One study investigated whether birth weight or growth during the first year of life, as indicated by weight at 1 year of age, influenced risk of Parkinson’s disease but found no relation. However, an analysis of mortality data from England and Wales concerning deaths from Parkinson’s disease that occurred in the period 1950–1992 provides evidence that people born at the beginning of the century are at unusually high risk of the disease. An old idea about the aetiology of Parkinson’s disease—the cohort hypothesis—deserves re-evaluation.

The cohort hypothesis of Parkinson’s disease

In 1963, Poskanzer and Schwab reviewed nearly 1000 cases of a Parkinsonian syndrome seen at the Massachusetts General Hospital.
The mean age of cases diagnosed between 1955–1959 was 27 years older than that of cases diagnosed between 1920–1924. They suggested that the increase in age of patients at the time of the onset of symptoms could be explained if Parkinsonism was a condition which affected the cohort of people aged between 5–59 years in 1920 and proposed the pandemic of *encephalitis lethargica* that occurred between 1919–1926 as a likely aetiology. A Parkinsonian syndrome is a recognised complication of encephalitis but only 11% of their cases could be linked to an overt encephalitic illness. To account for the majority of cases of Parkinsonism without a history of an encephalitic illness, they conjectured that, while a severe, clinically apparent episode of encephalitis was often followed by a rapidly developing Parkinsonian syndrome, milder, subclinical and undiagnosed attacks of the same infection might lead to Parkinsonian symptoms only after an interval of many years.

This hypothesis, as the authors frankly admitted in the published report, was devised *post hoc*. At the time, it was largely dismissed by neurologists, partly because a delayed sequel to a subclinical viral infection was considered an implausible pathogenetic mechanism and partly because postencephalitic Parkinsonism and idiopathic Parkinson’s disease were believed to be separate entities that could be distinguished clinically by their different signs and symptoms and histologically by their different pathological features\(^8\,9\). Later reports of the time trends of Parkinson’s disease in several countries\(^10\,11\) have been consistent with an increase in the disease following the pandemic of *encephalitis lethargica*, but the hypothesis has remained largely unnoticed.

Age specific mortality rates from Parkinson’s disease for England and Wales for the period 1950–1992 are shown in Figure 2. Mortality has declined in younger age groups while increasing 5-fold in those 80 years and older. Age–period–cohort analysis proved helpful in the interpretation of these diverging trends. This is a statistical technique that attempts to dissect the trends in mortality data into three components—the separate effects of age at death, time period of death and cohort of birth. The method is described in detail elsewhere\(^14\). Its purpose is to provide a more profound insight into the influences that determine changes over time than could be gained by a simple inspection of age-specific death rates. Diseases in which long intervals elapse between exposure to the cause of the disease and death from that disease tend to show changes between successive generations. Such changes are known as birth cohort effects. Diseases whose causes operate with a shorter latency are likely to affect all age-groups more synchronously, even if different age-groups are affected to a different extent, and reveal themselves as period of death effects.
The independent effects of age at death, time period of death and cohort of birth in these data for Parkinson's disease are summarised in Figures 3–5. Mortality rises exponentially with age in both men and women until the oldest age groups (Fig. 3). At all ages, mortality for women is about a third less than mortality for men.
The effect of time period of death is shown in Figure 4. The decline in magnitude from 1950 to 1980 parallels that seen in other chronic diseases. It is likely to be due to gradual improvements in general medical care and perhaps also to the introduction of levodopa for the treatment of Parkinson's disease in the late 1960s. The rise that began around 1980 coincided with the introduction of the 9th revision of the International Classification of Diseases and may be partly artefactual.

Independently of the effects of age and period of death, risk of death from Parkinson's disease increases steeply in successive birth cohorts from 1869–1878 to a peak in the cohorts born 1889–1908 and then falls equally sharply (Fig. 5). People born around the turn of century experienced an unusually high risk of death from Parkinson's disease. They were 2–3 times more likely to die from Parkinson's disease than people born before 1888 or after 1924. The birth cohort effect is sufficiently large to provide an explanation for the diverging trends in mortality from Parkinson's disease in younger and older age groups.

One problem in interpreting these time trends concerns the validity of mortality data. Parkinson's disease is under-reported on death certificates at present and the degree of under-reporting may have been more severe in the past. But as Marmot has pointed out, it is unlikely that the observed birth cohort effect could be a result of inadequacies in death certification. To produce such an effect, medical practitioners...
certifying deaths in the 1950s and 1960s would have to have been biased towards a diagnosis of Parkinson’s disease in a 60 year old person but against it in a 80 year old. By the 1980s, this bias would need to have been reversed. Previous analyses of mortality data for England and Wales, carried out over a decade ago, produced evidence of a birth cohort effect in Parkinson’s disease\textsuperscript{11,12}. Analysis of an additional 10 years of data confirms the strength of the effect and identifies the cohort at greatest risk more precisely.

Since 1950, more than 76,000 deaths from Parkinson’s disease have been recorded in England and Wales. Modelling these data as functions of age at death, time period of death and cohort of birth reveals that patterns of mortality in these countries are dominated by the influence of cohort of birth. People born around 1900 experienced a risk of death from Parkinson’s disease twice as high as people born around 1920 and 5 times higher than people born around 1930. This finding supports a hypothesis, first formulated by Poskanzer and Schwab over 30 years ago, that the majority of cases of Parkinson’s disease are the result of a cause that acted intensely in the early part of the twentieth century but whose effect rapidly declined. \textit{Encephalitis lethargica} is one candidate for this aetiological factor.

The cause of \textit{encephalitis lethargica} has never been determined, although circumstantial evidence links it to the preceding epidemic of influenza that swept the world in 1918 and 1919\textsuperscript{16,17}. Contemporary
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accounts indicate that *encephalitis lethargica* affected men more often than women. The incidence was greatest in adolescents and young adults. The birth cohort effect present in mortality data for Parkinson’s disease from the last 4 decades and the relative rates in men and women are both compatible with the idea that exposure to the causal agent of *encephalitis lethargica* is part of the aetiology of Parkinson’s disease. If the hypothesis is correct, it follows that Parkinson’s disease will become rarer as members of the exposed birth cohorts die. Projections from the age period cohort model predict that numbers of deaths from Parkinson’s disease in England and Wales are about to reach their peak and that before the year 2000 they will begin to decline rapidly.

**Poliomyelitis and motor neuron disease**

Motor neuron disease is a condition, usually occurring in late adult life, in which there is progressive loss of first and second order motor neurons. It is almost invariably fatal within a very few years of the onset of symptoms. A small proportion of cases are familial and, in some of these families, the disease has been linked to a mutation of the *SOD1* gene. But, for the large majority of cases which are sporadic, the aetiology is unknown. The possibility that there might be a connection between infection with poliovirus and motor neuron disease has been discussed by neurologists for more than a century. The idea is attractive because of the similarities in some of the clinical and pathological features of the two diseases; however, the fact that the majority of patients with motor neuron disease cannot recall ever having suffered from paralytic poliomyelitis in the past is usually considered an insurmountable objection.

But this objection fails to take account of the nature of poliovirus infection. Only a very small proportion of non-immune individuals exposed to the virus develop neurological symptoms and, even in those that do, the severity of the illness is very variable. It ranges from a mild aseptic meningitis through transient weakness of a limb to generalised paralysis and death. In primates, neuronal and inflammatory lesions can be found in the nervous systems of animals that have never shown signs of infection. It is quite possible that similar subclinical forms of poliomyelitis exist in humans. Such individuals would, in all probability, never have been diagnosed as having poliomyelitis but, nevertheless, they might have lost substantial numbers of motor neurons. If so, motor neuron disease might be a delayed sequel either because of further neuronal loss through ageing or as a result of a second insult.
One way to examine this idea further is to compare the geographical patterns and time trends of the two conditions. If there is an aetiological link, current patterns of motor neuron disease should mirror the epidemiology of poliomyelitis half a century earlier. Studies in both the UK and in the US have shown that mortality from motor neuron disease approximates closely to its incidence. Mortality can, therefore, be used to examine current patterns of motor neuron disease. Poliomyelitis became a notifiable disease in 1911 in the UK and information about notification rates in individual counties and county boroughs was included in the Registrar General's annual reports from 1921 onwards. These data can be used to explore past patterns of poliomyelitis.

Table 1 shows the correlation coefficients between mortality from motor neuron disease in the period 1968–1978 and notification rates for poliomyelitis in the period 1931–1939 for the 142 counties, county boroughs and London boroughs for which notification rates of infectious diseases are available separately in England and Wales. A positive relation between the two diseases is present. The relation is specific: correlation coefficients between motor neuron disease and other notifiable infectious diseases are either very small or negative. Table 2 shows that this specificity is maintained when other current causes of death are correlated with rates of poliomyelitis in the 1930s.

The time trends of the two diseases also run in parallel. Figure 6 shows that mortality from motor neuron disease at all ages has increased in successive birth cohorts from 1900 onwards. Rates of poliomyelitis also increased over the first half of the century. The epidemiology of poliomyelitis is unique amongst infectious diseases in that it becomes commoner rather than rarer as hygiene and social conditions improve. The explanation is found in the changes in the age of first exposure to poliovirus that accompany rising standards of living. In conditions where hygiene is poor, infection invariably occurs during the first few
Table 2  Correlations of leading causes of death (1968–1978, ages 55–74 years, both sexes) with notifications of poliomyelitis (1931–1939, <25 age years, both sexes) in 142 areas of England and Wales

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>-0.57</td>
</tr>
<tr>
<td>Bronchitis and emphysema</td>
<td>-0.50</td>
</tr>
<tr>
<td>Stroke</td>
<td>-0.50</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>-0.49</td>
</tr>
<tr>
<td>Cancer of Stomach</td>
<td>-0.48</td>
</tr>
<tr>
<td>Ovary</td>
<td>0.28</td>
</tr>
<tr>
<td>Breast</td>
<td>0.34</td>
</tr>
<tr>
<td>Motor neuron disease</td>
<td>0.42</td>
</tr>
</tbody>
</table>

months of life at a time when the infant is still partially protected by maternal antibody. The virus remains confined to the lymphoid tissue of the gastrointestinal tract because the viraemic phase necessary for it to reach the central nervous system is inhibited by circulating antibody. As conditions improve, age of first exposure to the virus increases. The child is no longer protected by maternal antibody and the incidence of paralytic disease increases. In the population, the pattern of disease changes from one of low rates of endemic infantile paralysis to recurrent epidemics of acute paralytic poliomyelitis affecting children and young adults. Over the first 50 years of this century, the UK and other countries of the developed world experienced a striking increase in the incidence of
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paralytic poliomyelitis. Studies in the UK, the US and Norway have recently shown that motor neuron disease is now behaving in a similar way.\textsuperscript{18-21}

The hypothesis that past infection with poliovirus is causally linked to risk of motor neuron disease is compatible with the current geographical and social patterns of motor neuron disease. It is able to account for the gradual increase in mortality from motor neuron disease over the past two decades. Time will tell if the hypothesis is right. If it is, rates of motor neuron disease will continue to increase for the next 10–15 years until the first cohort of people to have been immunised against poliovirus in childhood reach the age at which motor neuron disease usually presents. If there is a causal link with poliovirus infection, a fall in incidence of motor neuron disease can be expected around the year 2010 and it will occur in the youngest age-groups first.

Multiple sclerosis

Multiple sclerosis has been the subject of a large number of epidemiological investigations in many parts of the world and, although gaps in our knowledge remain, we have a fairly clear account of the patterns of occurrence of the disease. The disease is rare in the tropics and common in temperate regions. In the continents of North America and Europe, rates of the disease tend to be higher in the north than in the south, while in the southern hemisphere, this gradient is reversed. The most important exception to the general pattern of increasing rates of multiple sclerosis with increasing distance from the equator is Japan, where surveys have shown multiple sclerosis to be uncommon. The disease is probably rare in other countries of the Far East too, but information for these countries is less reliable.

How migration affects risk of multiple sclerosis has also been extensively studied. Two consistent patterns can be discerned in the results of migrant studies. The first of these patterns can be seen clearly in Figure 7, which shows changes in prevalence of the disease after migration. Migrants who have moved from a country of origin where multiple sclerosis is common to a host country where the disease is rarer, show a decrease in rate of disease. Only one study, of migrants to Hobart, Tasmania, from the UK, is an exception to this rule. The second pattern concerns migrants whose journey has been in the opposite direction. Here the evidence is less secure because fewer studies have been carried out but, as can be seen in Figure 8, this pattern contrasts with the first. People who have moved from a place where multiple sclerosis is rare to a place where the disease is commoner experience...
Migration from High to Low

S Europe to S Australia (crude)
UK to S Australia (crude)
Europe to Queensland, Aust. (crude)
UK/Ireland to Queensland, Aust. (crude)
Europe to Hobart, Tasmania
Europe to Newcastle, Australia
Europe to Perth, Australia
England to Hobart, Tasmania
Europe to Queensland, Australia
England to Perth, Australia
England to Queensland, Australia
S Europe to Israel (crude)
N & C Europe to Israel (crude)
UK to South Africa

Fig. 7 Change in prevalence of multiple sclerosis with migration from country of high risk to country of lower risk

little change in risk of the disease. Instead, it seems that they retain the low risk of their country of origin.

These patterns though, do not persist into the second generation. Risk of multiple sclerosis in the offspring of immigrants is very similar to that in the population of the host country. Although migrants from high-risk European countries to Israel were found to have a much higher prevalence of multiple sclerosis than migrants from low-risk Afro-Asian countries, there seemed to be little difference in prevalence between native Israelis whose fathers were born in Europe and those whose fathers were born in Afro-Asian countries\textsuperscript{22,23}. A recent update of this survey reported that age-adjusted incidence and prevalence of the disease was between 1.2–1.6 times higher in Israelis whose fathers were born in Europe or America than in those whose fathers were born in Afro-Asian countries\textsuperscript{24}. This difference is much smaller than the difference in rates between first-generation immigrants from these countries\textsuperscript{25}. The narrowing of the difference appears to be due to an increase in risk among second-generation Afro-Asians rather than a decrease in risk for second-generation Europeans and Americans. In the UK, immigrants from the West Indies, the Indian subcontinent and Africa retain their low risk of multiple sclerosis after migration\textsuperscript{26,27}. But studies of the UK-born children of such immigrants have shown that their risk of developing the disease is at least as high as that of the white UK-born population\textsuperscript{28,29}.
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Migration from Low to High

Fig. 8 Change in prevalence of multiple sclerosis with migration from country of low risk to country of higher risk.

What sort of aetiological agent could account for these patterns in the occurrence of multiple sclerosis? The explanation cannot be the straightforward one that the cause operates at a high level in places where multiple sclerosis is common and at a low level in places where the disease is rare. While this would account for the lowering of risk in migrants moving from an area where multiple sclerosis is frequent to an area where it is uncommon, it cannot explain why migrants moving in the other direction retain their low risk. The patterns can however, be explained by postulating a protective factor which operates in early life in places where the disease is rare and confers life-long protection.

One theory which combines both protective and causal effects concerns age at infection. If multiple sclerosis were a rare sequel to delayed exposure to a common infectious agent, the consistent patterns of migrant studies can be explained. The host response to many infections varies with the age at which the infection occurs. One example of this is hepatitis B; infection with this virus during early childhood commonly results in a chronic antigen carrier state, but rarely causes an overt hepatic illness; in contrast, when infection is delayed until adult life, the chronic carrier state is rare but hepatitis common. Several studies suggest that age of infection with some of the common communicable diseases of childhood tends to be older in cases of
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multiple sclerosis than in controls\textsuperscript{30,31}. Most of these reports concern measles, but there is some evidence that age of infection may also be higher with mumps and rubella. There have also been suggestions that delayed infection with Epstein–Barr virus is involved in the aetiology of multiple sclerosis\textsuperscript{32-34}. Infection with Epstein–Barr virus in early childhood is not associated with the typical symptoms of infectious mononucleosis, whereas if infection is delayed until late adolescence or young adult life, about 50\% of people develop symptoms. In many countries of the developing world there is a high rate of seroconversion to Epstein–Barr virus before adolescence and consequently a low incidence of classical infectious mononucleosis. The results of several studies that show an association between multiple sclerosis and infectious mononucleosis provide further evidence that common infections are acquired late in cases of the disease. Further, the high relative risk of multiple sclerosis associated with symptomatic Epstein–Barr virus infection raises the possibility that this virus is specifically involved in the causation of the disease and not simply a marker for delayed infection generally. This suggestion has received further support from a cohort study in Denmark that exploited the nationwide Danish multiple sclerosis registry and centralised records of serological testing for Epstein–Barr virus\textsuperscript{35}. In this study, people with serologically confirmed late Epstein–Barr virus infection had a nearly 3-fold increase in risk of developing multiple sclerosis.

As Warner and Carp pointed out more than 15 years ago, a link between delayed infection with Epstein–Barr virus and the development of multiple sclerosis is compatible with the broad epidemiological features of the disease\textsuperscript{32}. In developing countries where multiple sclerosis is rare, early infection with Epstein–Barr virus is almost universal. By contrast, in those areas of the world in which infectious mononucleosis is common and where, by implication, first exposure to Epstein–Barr virus is often delayed beyond the early years of childhood, the prevalence of multiple sclerosis is high.

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