Insufficient sunshine as a cause of multiple sclerosis: evidence for the correlation

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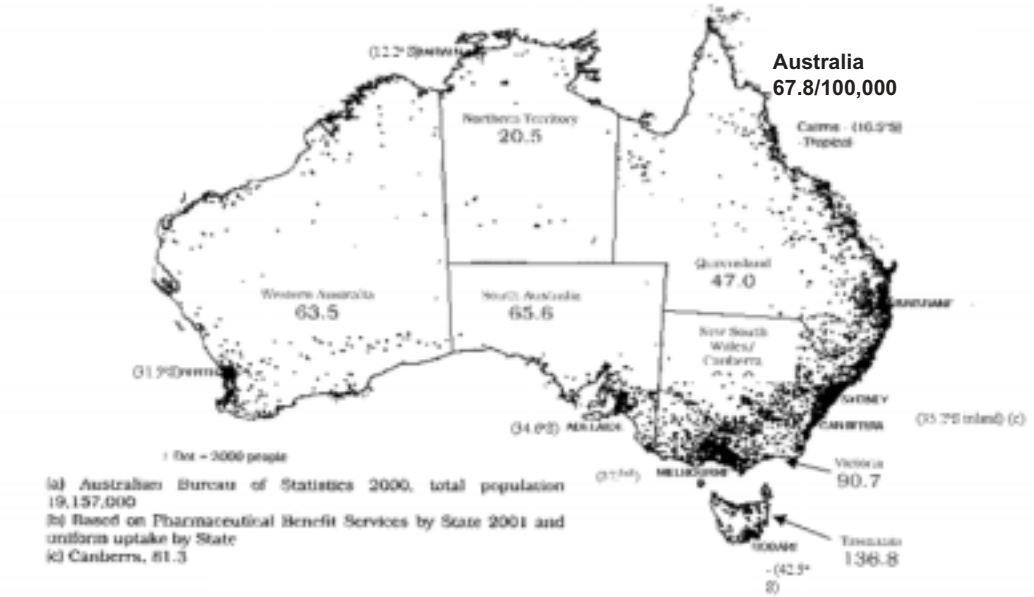
Multiple sclerosis (MS) is the commonest chronic neurological disease of young adults, and here in the UK there is a prevalence of about one in 750. In Scotland it's quite a bit higher than that, probably at least one in 500, maybe even one in 400. Sociologists say the average circle of acquaintances and friends that people have is about 2,000 and that gives you some idea of how common the disease is, because most of you are likely to know one or two people who have MS. It's a cruel disease. After 15 years about 50 per cent of MS patients are unable to walk unassisted, and after 25 years at least half will be in a wheelchair, or worse. It's familial about 20 per cent of the time.

There are enormous economic, social and medical costs. In the UK, there are about 750 new cases a year. That works out to about two a day, and the lifetime cost in each case is about £1.5 million. Very crudely, £3 million a day in terms of financial commitment accrues just for new cases and that's not counting the approximately 70,000 existing cases in the UK. So it's an enormous financial burden. I won't discuss the social costs, but they are best understood by those who've had a parent with it. This is a burden for many, many children.

Now, the information in Figure 1 has been known for a long time, although this is a relatively new slide. This is the geography of Australia, and I'm showing Australia for a particular reason. The Figure shows the distribution of MS in this sub-continent, by tracking the distribution of interferon prescriptions. It ties in extremely well with data obtained in other ways. So, in Tasmania there are 136 cases per 100,000, up in the northern territories there are about 20, and Queensland's rate is about 47. So there's a very big 5- or 6-fold difference in rate, going from the south to the subtropical north. (The MS gradient in the southern hemisphere goes from south to north, and in the northern hemisphere from north to south.)

The limitation in looking at data from Australia is that really you are not looking at a gradient per se, you are looking at the huge dominance of urban centres in a sub-continent which is largely devoid of people in the centre (the dots represent population numbers). So this is not the best way of examining potential gradients. But the differences are very, very large and they are very influential. The fact that people are diagnosed and put on the slide based upon where they happen to live isn't necessarily what you want if the risk is determined early in life. What you really want is where people are born or perhaps where they spent their childhood, and those are data which are rather difficult to get.

Figure 1 **POPULATION DISTRIBUTION, AUSTRALIA (a) & ESTIMATED MS PREVALENCE BY STATE (b)**
(estimated MS population 13,000)



What you'd really like to have is a situation in which people don't move from where they are born and they are distributed in a way that is homogenous. Rather than them being in urban centres, you'd like to have a situation in which individuals are distributed in an even, homogenous way in the country. It's not something that springs to mind easily, but there is a place where you can actually get the ideal sort of circumstance for the geography of this disease.

It turns out, most improbably, it comes from France. In France, there are two different healthcare systems. One healthcare system is for the general population and there is a separate healthcare system for farmers and their families. What's ideal for our purposes about farmers? They don't move, they are evenly distributed throughout the country, and they are not urban dwellers. Looking at MS prevalence per 100,000 inhabitants in France, you get about a 2-fold drop as you go south, from 103 up in the north-eastern part of France down to 45 per 100,000 in Corsica. So it's very clear-cut, and based on reasonably good numbers. It shows a very clear pattern which is the inverse of Australia (see Figure 1) but climatologically coherent. There's a little bit of an anomaly along the coast. The coastal dwellers in France actually have a lower rate of MS than would be expected based on latitude. It is possible that this may have something to do with eating fish.

The work on this is being carried out by my colleague Christian Confavreux in Lyons. Interestingly, George Chaplin and I have been able to correlate some rather high-tech information to it, drawing on NASA data for France relayed by the Toms satellite, which has been orbiting the earth eight times a day for over 30 years. It calculates the ultraviolet radiation virtually anywhere in the world, through a variety of paradigms that have been validated over a number of years. Its picture of the UV MED, or minimal erythematous dose (the dose of UV causing minimal pinkness of skin) is similar to the map of MS prevalence in France which the Lyons group has put together.

A number of years ago I initiated a network of clinics in Canada which essentially spans the country. There are 16 university centre sites where MS patients are looked after, and over a period of about 20 years we were able to put together a population which is now in excess of 25,000 MS patients. This allowed us to ask some questions that can only be answered by very large numbers.

The first thing we did was studies of twins. It took us about 20 years to collect 450 pairs, which is pretty much the number of twins you would expect to be found, based on the prevalence rate in Canada. We found that if you are an identical twin, your risk of MS is 30% if your twin has it, whereas if you are a fraternal or non-identical twin, which is for genetic purposes the same as having a non-twin brother or sister, then the rate is 4% – a big difference between identical twins and fraternal twins.

Because the rate for fraternal twins wasn't much different from the rate for just brothers and sisters who are not twins, this indicated that the increased familial environment that you would have in fraternal twins – by being the same age, and sharing the same maternal environment and many other things more than would ordinarily be shared by brothers and sisters – didn't seem to have any impact on risk. That was the first indication that the prevailing notion at the time, that MS had something to do with some sort of viral infection, probably wasn't going to be right.

The next thing we did was a study in people who were adopted at birth, and it took 20,000 MS cases to do this study because adoptions are relatively uncommon. In Canada 1.2% of the population is adopted and most of those are adopted around the time of birth. We knew that the rate for a biological brother and sister was 40 times greater than the general population rate of one in 1,000. Of course that could be genes, or it could be environment. So we decided to look at the rate of MS in those individuals who grew up with a non-biological relative destined to get MS, compared to a biological relative; for example, the unrelated adoptive brothers and sisters of someone destined to get MS.

The answer was black and white. The rate for the non-biological relative in the same environment was one in 1,200, which is the same as the general population rate of one in 1,000, whereas you would have expected 25 cases to have occurred based on the biological risk among sufferers' actual brothers and sisters. It was clear-cut that the risk within a family was not determined by the common familial environment. So familial risk is genetic and we could not show any effect of shared familial environment on risk.

The next studies were done in half-sibs, the first systematic half-sib studies in any disease. We didn't expect that we would get as much out of them as we did. These studies are very well-utilised in animal husbandry and if any of you have an agricultural background you will know a lot about half-sib studies because that's what people in agriculture do. They have a sire or a dam that will have offspring with one common parent, but not two. A lot of the original studies that bear very strongly on gene/environment effects actually come from agriculture.

We had the opportunity of collecting these, and we had a bit of an advantage sociologically, stemming from the rising divorce rate. Because the divorce rate has risen so rapidly over the last generation or two, there are a lot of half-sibs, so it's actually a much more common situation now. In a family where you've got one parent in common

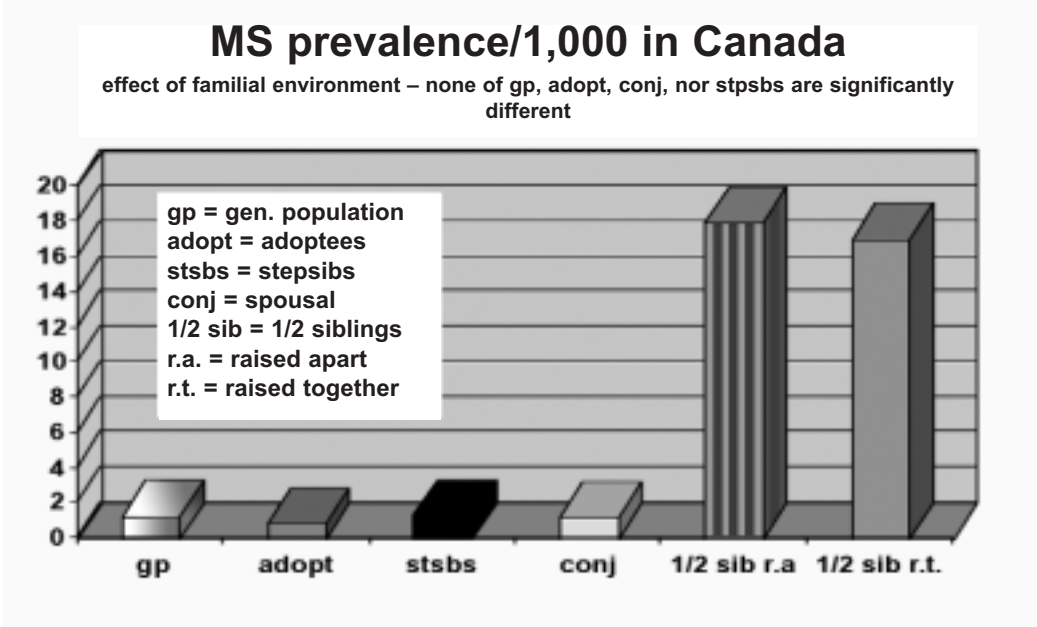
but not two, you can ask some interesting questions.

Conveniently, it turns out that among half-sibs, roughly half are raised together and about half are raised apart. That's helpful because it's kind of like the twin study approach where you get identical twins separated at birth, reared apart and then try and see what happens to them. Of course, you can't do that study in MS or any other particular disease because there just aren't enough people on the planet in that position, it's a rare event. And they would have to be separated, not only just apart but apart by risk and, of course, that almost never happens. So in fact the half-sib study is what you really want. It's much more powerful than a twin study and once you realise the potential of this then you have increasing admiration for our agricultural colleagues who twigged to the power of this methodology a long time ago.

In half-sibs it turns out their risk is about half that of full sibs, and that's important. The reason is that it tells you something about the complexity of inheritance. What it says is that if the risk only drops by half that means the complexity genetically can't be very great, and that's contrary to what everyone has been thinking. So now you can ask, what's the rate for those raised together and those raised apart, and you can also ask, if one parent is in common but not two, does it matter which parent it is? Does it matter if it's the father in common or if it's mother in common? And it turns out it matters a lot and the raised together/raised apart issue also turns out to be very important.

Figure 2 (below) is a graph showing the rate of MS per 1,000 in Canada, looking at a variety of different populations. It includes the general population of one in 1,000; the adopted relatives, one in 1,000; the rate for step-sibs of MS patients, which is one in 1,000, and the conjugal one, looking at the rate for husbands and wives of MS patients, and that's one in 1,000. So we can demonstrate no effect of shared common familial environment all the way from birth right through to marriage. What happens in the half-sibs that are raised apart compared to the half-sibs that are raised together? We found that the ones who were raised apart have a slightly higher rate than those who were raised together. So there is no effect of the common familial environment.

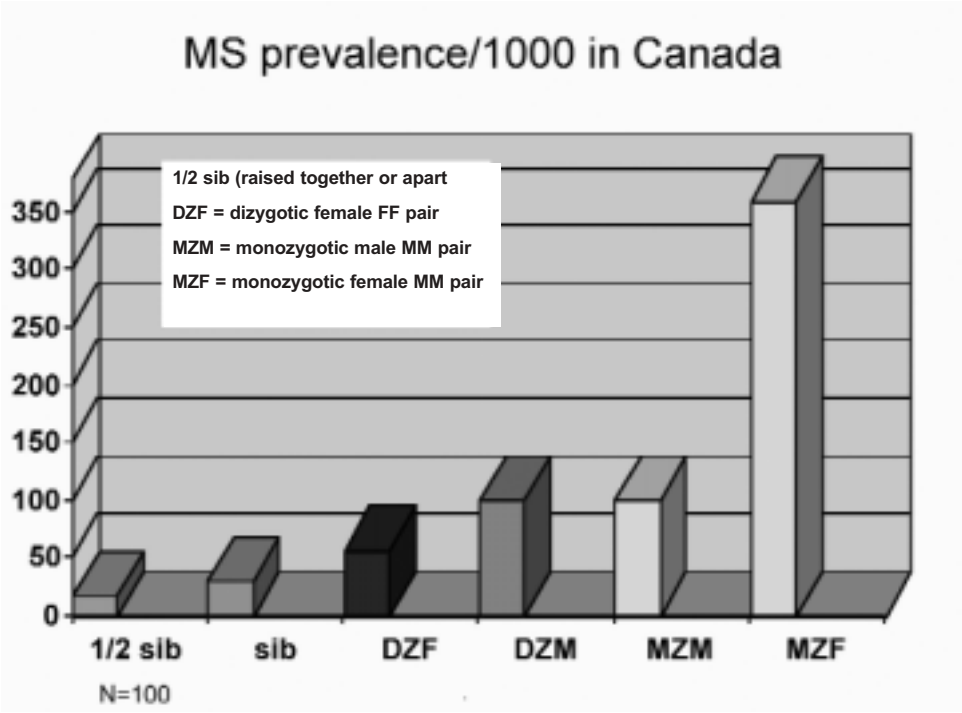
Figure 2



Half-sibs raised together and apart, as shown in Figure 2, are a kind of anchor point for Figure 3, because now we are seeing an almost 400-fold difference in risk. The half-sibs raised together (1/2 sib r.t.) bar at the right end of Figure 2 is now to the left in Figure 3. The incidence in monozygotic female twins concordant for MS is 380 per 1,000 twins (right hand side of Figure 3) which is almost 400 times the general population incidence of one in 1,000. The incidence in concordant monozygotic female twins is about seven times that in concordant dizygotic female twins, but the incidence of MS in sibs is only twice that in half-sibs. From the point of view of genetics these two ratios might be expected to be the same. This provides an important clue about the nature of susceptibility to MS. Unlikely as it may seem, susceptibility to MS appears to have gender specificity.

The familial microenvironment can't be demonstrated to contribute anything to risk, yet there is a huge

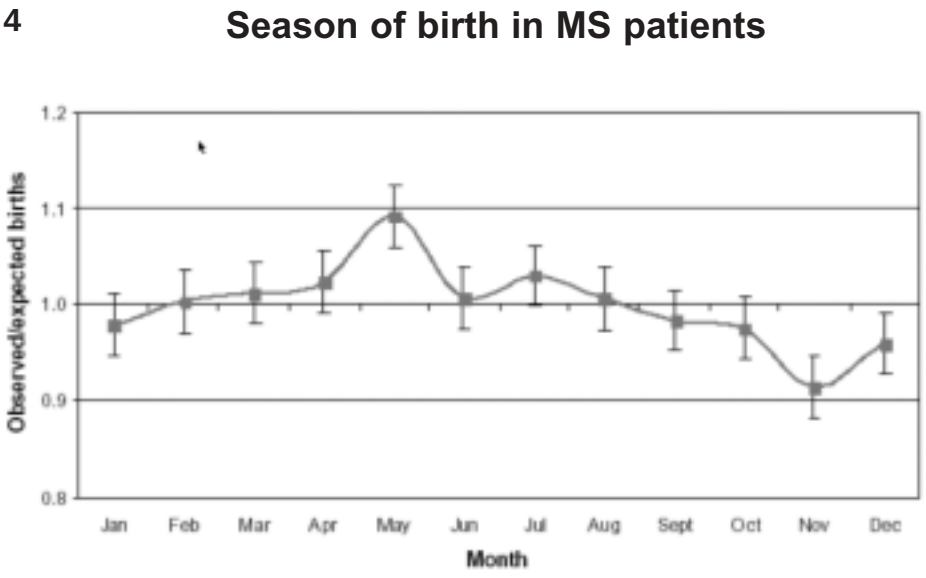
Figure 3



environmental effect reflected in an unambiguous latitude gradient in every country that's been studied. Basically, this leaves climate or diet or even the consequences of that to explain the influence of environment in MS. And actually, diet is not very attractive because in fact it's largely familial unless there are differences in regional diets, which does happen in some countries. People in a family tend to eat the same things, so you would have expected to see some impact of that common familial diet. But we can't see anything.

So it leaves us with climate, the direct or indirect consequences of climate, and that's a broad area.

Figure 4



Ratios of Canadian MS births compared to controls

(inverse is seen for unaffected sibs and for S.Hemisphere patients)

Nevertheless, the notion that something within the familial environment triggers the risk can't be supported. We looked at it another way and asked about the genetics. If parents who are first cousins have a child with MS, the risk to subsequent children is increased by 100-fold, showing the impact of the shared genetics on risk.

One of the difficulties with trying to establish what actually determines MS risk has been the heavy reliance on data from migrants. For various reasons, migrants are often selected for studying the timing of differential geographic risk, but there tend to be relatively few of them. It's been possible in Canada to do a study which we would describe as an intra-familial migration study. This came up because one of my patients was an oil engineer from Edmonton who spent three years in Bahrain, and he had two children there, and four more in Edmonton. Knowing that one of them got MS, which was the one? We're in the process of finalising these data, but in the interests of passing on some knowledge, I can tell you that the results support the view that risk is determined within a family by where the individual was born. There's a clear difference between offspring born in areas of high risk or low risk.

One of my students was interested in examining season of birth in MS, and came up with the results in Figure 4, which shows the season of birth in MS patients in Canada. The last time something like this was seen, it turned out to be a very strong hint as to the cause of neural tube defects. A long time ago, in the 1950s, it was recognised that the timing of birth influenced the risk of neural tube defects, and it took another 35 years before anybody figured out what it meant. Hopefully, on this occasion, it won't take that long. But there is a season of birth effect in MS which is pretty clear. In Canada and the northern European countries, risk is increased by about 10 per cent by being born in May, and it's decreased by 10 per cent by being born in November, and if you go to the southern hemisphere, in Argentina or Australia, you see the reverse. In the unaffected sibs of these southern hemisphere individuals, you see the reverse; that is, there are more May births and fewer November births. I told my students I was not about to get up in front of an audience and say that being a Taurus would increase your risk of disease, and made them replicate this data in four other countries.

The environmental factor in MS acts at a population level and determines the risk differential between Tasmania and northern Queensland, which is 5- or 6-fold (see Figure 1). If we could convert the rate in Tasmania to the rate in Queensland, we could prevent 80% of the cases of MS there. The evidence is all circumstantial at this point. It doesn't have to be vitamin D, it could be something else related to sunlight. There are a variety of potential considerations. Vitamin D has to be entertained as a possibility.

The first trials to test whether the primary prevention of MS is related to the sun and/or vitamin D are now at the planning stage. This is probably going to happen in a couple of places. One is in Canada, where a prevention study is being geared up, the other is in Australia.

When we examined the sex ratio for incidence of MS in Canada by year of birth, going back to 1920, we found that the rate of MS in Canada appears to have been steadily increasing for the last 50 years, and I think the same is true of the UK, although there isn't much data. Everybody has been doubtful of this, including myself, because there have been changes in diagnostic methodology, and a variety of other factors confound the evidence.

Most of the increase in incidence of MS during the 20th century is due to an increase in the number of women who have contracted the disease. Contemporary reports from 1920 suggest that equal numbers of men and women developed MS at that time, although our retrospective determination of the sex ratio in 1920 puts this slightly higher. In fact we believe that the sex ratio has moved from around equity in 1920 to about 3.5 to 1 in 1975-79. More than three women develop the disease today for every man who does so. The reason for this is not yet clear but there must be a powerful environmental factor driving this difference forward. Again this suggests that understanding why women are so vulnerable to the disease will yield important information about the cause.

Just to summarise what I've said. MS is a very important disease. It's hugely important economically and socially. It looks like it may be increasing in rate. The risk is partly determined by genes and environment. The environmental part is certainly something that acts at a broad population level. Vitamin D is a good candidate, but not the only candidate. I think some additional work needs to be done. But it's very hard to get direct evidence to implicate vitamin D especially if this is operative decades before onset of the disease. If anyone can think of a way of getting direct evidence – we're going to require information on something that might have happened 25 or 30 years ago, which is notoriously difficult and believe me, we've tried – then let me know.

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