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Dr James H Renwick,
Mrs Anne M Possamai
and Mrs Madeleine R Munday
(London School of Hygiene & Tropical Medicine, London WC1E 7HT)

Potatoes and Spina Bifida

Anencephaly and spina bifida (ASB) are important human malformations: four in every 1000 births, including stillbirths, have one or other of these major birth defects in the UK as a whole (0.4%). In the Western world, spina bifida, though usually more frequent than anencephaly, behaves more or less the same as anencephaly in its epidemiology. *Where* one is common, the other is common, e.g. in Ireland. *Where* one is rare, the other is rare, e.g. in London, where it is about five times rarer than in Belfast. *When* one is common, the other is common, e.g. in winter, and a bad year for one tends to be a bad year for the other. Both afflict the poor more than the wealthy by a factor of about four. Both occur at higher rates in older mothers and among those mothers with more children. The previous birth of an anencephalic leads the mother to have a 5% risk of anencephaly or spina bifida in a later pregnancy; the previous birth of a spina bifida child also leads to a comparable risk of either malformation.

For these reasons of similarity, particularly this mutual relationship within sibships, and because both are defects of one or other end of the neural tube, probably in the fourth week of embryonic life, we can treat the two as one condition (ASB), in this country at least.

Preventability

Most of these variables – time, place, class, mother's age and parity – are in principle controllable. An extremely favoured child has a risk over a thousand times smaller than a disfavoured child has, so there is certainly preventability in principle.

Two years ago, and until 8.11.73, our hypothesis was that short-term potato avoidance would prevent 95% of ASB in this country. Apparently, ASB is not so simple and the present position is as follows.

The seasonal peak of ASB incidence rates suggests damage particularly in May, as noted by Leck & Record (1966). They later recognized (unpublished) that this is the time of year when the overwintered potatoes are at their worst quality.

Then there is the rough regional concordance within countries between the birth incidence rates of ASB and the prevalence of potato blight, a fungal disease of potato. The wet west of the British Isles has a high incidence of both blight and ASB; the dry east has less of each. In the USA, the humid east has some blight and some ASB; the dry west has little of either, and the same is true of Canada. It has been doubted whether France and Sweden fit the geographical relationship, but there is no cause for this doubting. Given the unreliability of inferences across international boundaries when there are so many uncontrolled variables (potato varieties, cooking habits, &c.), the low ASB rates are quite reconcilable with a large consumption of potatoes. It is quality that matters rather than quantity. Tuber blight in most of France or Sweden is of low frequency by British standards despite the blighting of the haulms. Culinary pride is perhaps more prevalent there than here and may lead to the more frequent discarding of partly blemished potatoes. The ASB rate is accordingly rather low.

From the seasonal and geographical relationships, we predicted that an epidemic of late blight, caused by *Phytophthora infestans*, would be followed by an ASB epidemic. The eating of an

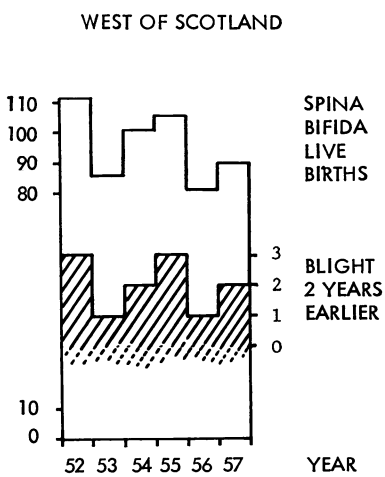

Fig 1 Histogram showing yearly blight scores for West Scotland (Cox & Large 1960), two calendar years previous to the live spina bifida births for West Scotland (Findlay 1969). The yearly number of such births is adjusted to constant birth population size (55 000 live births per annum). $P = 2!\,2!\,2!/6! = 0.011$. *(After Renwick 1972a)*

overwintered potato in, say, May 1901 that was blighted in the autumn of 1900 would perhaps damage an embryo later to be born in the following February, 1902. So, when the data are available only for calendar years, as are those in Fig 1 from West Scotland, we expect a phase lapse of two calendar years between the blight and the spina bifida births. There is a clear relationship as predicted between these variables.

Fig 2 gives another confirmation of the prediction of year-to-year correlation. This is much more impressive, particularly in numbers – seven million births are involved; this time in England and Wales in the 1960s. The correlation coefficient is +0.85 and statistically highly significant. This one study embodies nearly twice as many births as all previous and subsequent studies put together. The anencephaly data were given in quarter years by Knox (1972) and, by averaging, the interval between blight and birth was fixed, as it should be, at $1\frac{1}{8}$ years from the end of the blight year, reflecting in part the storage of potatoes over the winter and in part the storage of the embryo in the uterus. The latter period is shortened by about 7 weeks by anencephaly (modal estimate), by comparison with normal or spina bifida gestations.

So we have three relationships, seasonal, regional, and year-to-year, one of which was predicted from the other two and then found. The jump from these to preventability by potato avoidance involves certain untested assumptions.

One of these assumptions, not explicitly recognized at the time, is that the effect of the teratogen, whatever substance that may be, can be avoided by short-term exclusion from the current diet. But maternal blood levels of any teratogen may reflect in part a background of slow release from body stores as well as current intake. The precise proportion of ASB that may be preventable by avoiding current intake then depends on the relative magnitudes of the two contributions. The blight correlations demand merely that the contribution from current intake is not rendered negligible by the blood level from storage sites.

If we make the perhaps rash supposition that fresh intake ceases altogether at one season of the year, then the relative contribution of the fresh intake to the total teratogenic effect can be estimated (but unfortunately overestimated) by the proportional excess from seasonal fluctuations over the minimal monthly rate. From Kinlen & Hewitt (1973), the estimate for Scotland is 11.6% (273/2348) for 1959–1963 and slightly larger, 14.7%, for 1939–1958. Rather less than 11% of anencephaly in Scotland might, on this model, be preventable by short-term avoidance of fresh intake of the teratogen – a small effect too

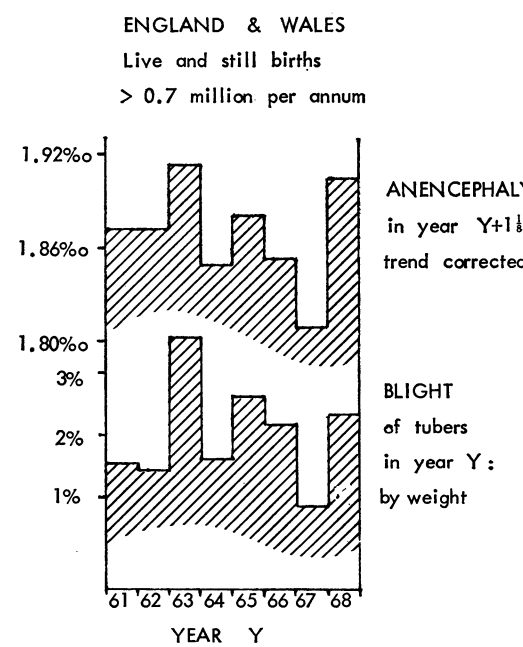

Fig 2 Anencephaly incidence rates (Knox 1972), for year $Y + 1\frac{1}{8}$, *based on live and still births in excess of 700 000 per annum and corrected for annual time trend of −0.05%. The lower histogram represents the percentage of potato tubers (by weight) blighted in year Y (Cox & Large 1960).* $r = +0.85$, $P = 0.005$ *(one-tailed test). (After Renwick (1973) incorporating various corrections)*

difficult to detect by a preventive trial. For most of the remaining 89%, body stores would have to be depleted. Further, the special population of mothers who have already borne one ASB child would tend, on this model, to have above-average body stores of the teratogen, so the degree of preventability by short-term avoidance of teratogen by these mothers would be even smaller.

For Birmingham, England, the size of the contribution from fresh intake is also falling, relatively and in absolute terms; but it is estimated to be greater than in Scotland: 41.2% for 1940–1958 and 20.7% for 1958–1963 (Leck & Record 1966). The diminishing influence of season in both Scotland and Birmingham is consistent with a decline in fresh intake which in turn would accord with the overall downward trend in anencephaly incidence, a 25% fall in the past decade in England and Wales (Knox 1972). Here, about 6.2% of the current incidence may be related to fresh intake, if this intake is entirely seasonal, and if the rest is attributable to body stores.

What is the chance that this sort of retention of the unknown teratogen occurs? No answer can yet be given but there are many toxins that are known to be retained for periods of months or years, among them DDT, some steroids, iophenoxic acid – which has a plasma halflife of 2½ years in dogs (Wade *et al.* 1971) – methyl mercury and chloramphenicol. Some are stored in the fat or in various organs; others are excreted in the bile then reabsorbed in a perpetual recycling process, the enterohepatic recirculation. Since we do not know what the potato-related or blight-related teratogen is, we cannot test its storage behaviour; but solanine, a known potentially lethal toxin in potatoes, particularly green ones, is one of the possible candidates. It is itself a steroid derivative and it is stored for a time in rats (Nishie *et al.* 1971). Solanine is antifungal, so there is likely to be more in those potatoes that survive a winter after a bad blight year.

The work of Goldman (1972) hints at another type of storage mechanism. One interpretation of his work on rats is that teratogenic quantities of one specific enzyme inhibitor are bound by the ovum. The relevant ASB teratogen, if stored at all, may be stored in the body in any of these ways – in storage depots, in the enterohepatic circulation or in the ovum itself. If it is stored, removal of risk would require a period of potato avoidance preceding conception and the corresponding abative hypothesis would be extremely difficult to test.

This possibility of storage in the body becomes of potential importance now that a Belfast study has shown that short-term avoidance of potato does not prevent ASB. On 8.11.73, Dr Norman Nevin in Belfast told me of 2 ASB and 16 normal infants born to mothers who chose to exclude potatoes from the house during and shortly before conception; these mothers had at least one ASB child, the mean number of such previous ASB children being 1.22. The standard recurrence risk in each of these pregnancies would be about 6%. It was clearly not reduced to the 95% degree demanded by the potato hypothesis that 95% of ASB could be prevented in the UK by short-term potato avoidance. The hypothesis must therefore be abandoned and a new one sought that accommodates the new facts. So far, we have not framed a new, testable hypothesis. The Belfast exceptions, and four similar but anecdotal failures of potato avoidance elsewhere, have caused us to reconsider the assumptions, particularly the non-storage assumption. As mentioned above, storage of a natural toxin in the body, with slow release into the blood over several months or even years, might not be a rare phenomenon and could conceivably account for the failures of short-term potato avoidance.

Experimental Teratology

Can any guidance be obtained from experiments on animals? Such experiments are being undertaken in several centres following the demonstration of teratogenesis for marmosets of a potato preparation (Poswillo *et al.* 1972, 1973). The 4 out of 11 young that were affected with an osseous cranial defect were the dizygotic twin offspring of the two marmoset mothers that had been on the potato-containing diet for the longest time before conception. This is consistent with a cumulative effect and with a storage effect. Of the various classes of chemical agents that might conceivably be responsible for the marmoset defect, two are noteworthy – the cytochalasins and the solanines.

Cytochalasin B produces spina bifida in chick embryos (Linville & Shepard 1972), and another member of the cytochalasin family was found in the teratogenic potato preparation of Poswillo *et al.* Solanine increases the spina bifida rate in chick embryos from 20% in controls to 80% (Hughes 1973), and produces a different spinal and and rib anomaly in rats (Swinyard & Chaube 1973). Cytochalasins and solanines have not yet been adequately studied from the storage angle, and nor have their teratogenic potentialities been explored in the marmoset or other primate. Inference from animals to man may be dangerous and, even from primates, it must be treated cautiously.

Non-potato Interpretations

Some alternative interpretations of the blight correlations involve neither consumption nor body storage of a potato-related teratogen. The spores liberated from the fungus growing on the

potato tops, and from other fungi that flourish in bad blight years, alight on other food crops and might initiate synthesis of antifungal substances (phytoalexins). It is known that most if not all higher plants respond to fungi by such syntheses and that pathogenicity of the fungus is, in general, not required for this. Other vegetables must therefore be considered and the requirement of a time lag before the effect on births is visible suggests that root vegetables and some of the Brassicæ might repay study.

Discussion

A solution to this important problem of ASB prevention seems to be coming closer, though we are not yet ready to put forward a testable new hypothesis. In the meantime, we do have the blight correlations as pointers and, to consolidate these, criticisms that have been raised concerning them are discussed.

The year-to-year correlation discovered on the massive data from England and Wales was attacked by Carter (1973). First, he objected to the lack of a zero on the histogram. Its insertion would, of course, not alter the correlation coefficient of +0.85 ($P=0.005$ by a one-tailed test). Secondly, he found no significant deviation from a linear time trend. But the point under test was not the linearity of the trend but rather the resemblance or otherwise between the patterns of ASB incidence and of blight severity over the years. He neglected to state that even the incomplete data he chose to analyse, livebirths excluded, gave a correlation coefficient of +0.34. He would have obtained a higher and more nearly correct coefficient if he had allowed for the fact that an embryo damaged by a dietary teratogen in, for instance, May may be born as late as mid-February of the following year. (This allowance could not be made on births for 1970 so he, like us, would have had to ignore that year.)

What was described inaccurately as 'a similar set of data' by Smith *et al.* (1973) comprised malformations among births in a single hospital in Edinburgh – a matter of 4300 births annually compared with 700 000 annually in the data from England and Wales. No effect was seen.

Kinlen & Hewitt (1973) did not find a year-to-year relationship with tuber blight rates at harvest even in the whole of Scotland. This failure is unexpected but may indicate that, in Scotland, where burning of the potato tops (haulms) is still not extensively practised, at least on the ware crop, blight infection of the tubers by contact with infected haulms at lifting still occurs. The rate of visible blighting among tubers at lifting would then be a poor guide to what is consumed months later. Under such conditions, the haulm score may be a better guide to final tuber rate, and it was indeed the haulm score for West Scotland that was shown to be positively correlated with spina bifida incidence in West Scotland ($P=0.011$, Renwick 1972*a*) and with initiation rates for anencephaly in the whole of Scotland ($P=0.0012$, Renwick 1972*b*). The correlation coefficient with initiation rates should be even higher in the West itself, but the attempt by Kinlen & Hewitt to demonstrate this by subdividing the 1950s data by region was spoilt by their having to accept the wrong blight-birth interval. A large part of the seasonal excess of anencephalic stillbirths, and therefore a large part of the annual variation, falls after 1 January, and this part is assigned to the wrong blight year in Kinlen & Hewitt's analysis.

MacMahon *et al.* (1973) tested the year-to-year prediction using hospital births in Boston, Massachussetts, which are about four times as numerous as in Edinburgh. The sixteen years of slight or no blight are followed by an ASB rate that is 20% lower than the rate following the 14 years of severe blight. The moderate blight years show an intermediate rate. The effect in this small sample is not significant but the prediction is upheld. The stagewise analysis of the authors obscures this and would indeed be expected to do so.

In Canada, the Provinces of Nova Scotia and New Brunswick have small populations. Each yields only about twenty anencephalic births annually, even when the latter Province is augmented by Prince Edward Island. The lack of correlation observed by Elwood (1973) is therefore not necessarily of great moment. The lack extends to Quebec and Ontario. These are more populous, each producing about 150 anencephalics annually but, as the author says, the potatoes imported from Prince Edward Island and New Brunswick 'might mask a local effect'. It would be interesting to look for a correlation with blight (or other disease) in these imported tubers.

In North America there is less storage of potatoes than in the UK and when practised is indoors in partially controlled conditions of temperature and humidity. Hence the effects of blight on secondary invasion by other organisms and on the protective synthesis of antifungal agents (phytoalexins) are likely to be smaller than in the UK. Correlations between blight and ASB incidence would be loose, so a failure to demonstrate them in North America, even in the long term, need not influence the interpretation of those found in the UK. The lack of cyclic fluctuation of ASB rates with season in most USA data is also perhaps related to the shorter and better storage of potatoes.

Elwood & McKenzie (1973) note that in Ireland the year-to-year correlation coefficient is small between the number of blight outbreaks on haulms by the end of June and the ASB rate in Dublin hospital births during the following year. There is, however, a weakness in the analysis. As already mentioned, when data are available only by year, there ought to be two calendar years between the blight and the spina bifida birth. The analysis given allowed only one. For anencephaly, with a modal gestation of 33 weeks, the situation is less simple, since the cyclical peak falls near the end of the year. The effect of blight is therefore spread over two calendar years and the analysis should have taken account of this. Further, the authors themselves mention serious limitations of the data: the June count of blight outbreaks is an inadequate measure of tuber blight at harvest in the autumn, because the weather varies so much in the intervening months, and it is an even worse measure of tuber quality at consumption after storage.

Summary

The year-to-year blight/ASB correlation is open to definitive testing. So far, no other workers have been able to confirm it, but we have found it to be upheld on three large sets of published data totalling over 8 000 000 births. The simplest possible interpretation of it seems, from the recent data of Nevin (1973, personal communication), not to be the correct one. We are not decided at present which of the alternative interpretations has the most to commend it, but it is reasonable to hope than an effective preventative measure will be discovered within the next ten years.

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