An Infective Basis in Childhood Leukaemia: the Evidence of Epidemiology

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If the long-standing suspicion of an infective origin in childhood leukaemia is correct, it must (like all known infection-linked cancers) belong to that large group of illnesses that are rare responses to the relevant infection. For otherwise studies of space-time clustering, the main focus of earlier investigations, would have produced more striking evidence; but the disease is clearly not contagious. This underlying infection, therefore, would, like polio virus infection, be mainly immunizing and subclinical. The population mixing hypothesis originated in the raised levels of childhood leukaemia in Seascale and around Thurso, near the nuclear sites at Sellafield and Dounreay respectively, which could not be explained in terms of radiation exposure; for these remote and isolated rural areas had experienced highly unusual population movements. From the well established premises that epidemics depend upon the presence of sufficient numbers of susceptible individuals and that these are more prevalent in rural areas because of the reduced opportunities for contacts with a wider infective pool, it was argued that a localized epidemic of an underlying infection would be promoted by large scale rural-urban population mixing (i.e. by the increased level of contacts between susceptible and infected individuals)\(^1,2\). Large doses of an infective agent are more likely to be received in an epidemic than in sporadic infection and, by analogy to leukaemia in cats, these may further heighten the risk of leukaemia.

From this idea began a series of studies which eventually covered all known examples of extreme rural-urban mixing in Britain in the past 60 years, each of which revealed a significant temporary excess of childhood leukaemia\(^3\). In the first example studied, the mixing was in the bringing together of many people from dispersed rural communities in the Scottish rural new town of Glenrothes\(^1\), and excesses of childhood leukaemia were subsequently found in the equivalent rural new towns of England and Wales\(^4\). Further examples include excesses of childhood leukaemia: in rural areas that received large numbers of wartime evacuees from towns and cities\(^5\); in rural areas that experienced the greatest increases of servicemen in the days of national military service\(^6\); in areas around large rural (non-nuclear) construction projects\(^7\); in rural Scottish communities (including the Dounreay area) where a large proportion of men had worked away from home in the North Sea oil industry\(^8\) and in the children present in Orkney and Shetland during the wartime occupation of those islands by large numbers of servicemen\(^9\). Observations outside Britain have also confirmed the importance of unusual patterns of contact in relation to childhood leukaemia\(^10-16\), particular examples being the concentrations of construction workers near the La Hague nuclear installation in France\(^15\) and in isolated rural counties in the USA that experienced large population movements\(^16\). These excesses of childhood leukaemia have been relatively short-lived, an exception being the protracted Seascale cluster. Here it is notable that the turnover of young families was exceptionally high, so that a continued supply of new (susceptible) children was maintained, and the protracted requirement for large-scale construction work at Sellafield ensured the long-term presence of large numbers of itinerant workers\(^2\). In view of its relevance as the source of the population mixing hypothesis, it is of some interest that a model of population mixing and childhood leukaemia in Cumbrian wards other than Seascale, when applied to Seascale, was able to explain the excess there\(^17,18\).
A different hypothesis of delayed antigenic stimulation has been proposed for the common type of acute lymphoblastic leukaemia (ALL) in the childhood peak ages of 2-6. This holds that infections, to which modern life tends to delay exposure until after infancy, induce non-specifically proliferation and hence mutations in non-fully differentiated, vulnerable lymphocytes. However, evidence that the relevant infections do act non-specifically is lacking and it would seem prudent to continue the search for specific (probably viral) agents in all types of childhood ALL.

The population mixing hypothesis has recently received unexpected confirmation in the USA. In rural (largely desert) Churchill County, Nevada no less than 10 cases of childhood leukaemia were diagnosed in only two years (8 in 2000, 2 in 2001), compared to less than one expected, and mainly in the small town of Fallon (population 7,536). In fact, no more striking childhood leukaemia cluster in the world has been traced and its extreme nature, even at the county level \((p=4.3 \times 10^{-9})\), has recently been demonstrated. What is particularly striking, however, is that at the nearby Fallon Naval Air Station, the numbers of servicemen temporarily assigned there reached the extraordinary level of 55,000 in 2000 from an earlier annual level of 20,000 in the early 1990s. The indirect exposure of Fallon in only a few years to over 100,000 people from outside the area represents a more extreme example of rural-urban population mixing than any of those studied in Britain. That the world’s most sharply defined cluster of childhood leukaemia should occur in association with the most extreme example of rural-urban population mixing so far recorded could not be more arresting.

References