CHILDHOOD LEUKAEMIA AND LOW-LEVEL RADIATION - ARE WE UNDERESTIMATING THE RISK?

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INTRODUCTION

In November 1983 a television documentary claimed that the number of cases of childhood leukaemia which had occurred in the coastal village of Seascale, situated next to the nuclear complex at Sellafield in Cumbria, England, was around 10 times the number of cases expected in the period since the start of nuclear operations at Sellafield in 1950. This report was based upon just 6 cases of childhood leukaemia. The television programme generated public concern in the UK and the Government ordered an independent inquiry into the claim. In summary, this official inquiry confirmed that an excess of childhood leukaemia cases had occurred in Seascale, although the cause of this excess could not be identified (1). The inquiry recommended that a programme of scientific research should be undertaken to investigate the possible causes of the Seascale childhood leukaemia "cluster". This research has led to a variety of suggested explanations for the Seascale "cluster" and the history of these investigations illustrates the great care with which "cluster" reports need to be interpreted.

THE PROBLEMS OF EPIDEMIOLOGICAL INFERENCE

Epidemiology is the study of patterns of disease in groups of humans with the objective of identifying the causes of disease. It is an observational (i.e. not an experimental) science and as a consequence the findings of epidemiological studies must be interpreted with considerable caution. Although a statistical association between a disease and some factor may be indicative of an underlying cause-and-effect relationship, alternative explanations must always be considered. These explanations are that the association could have been produced through the effects of chance, or that certain biases are present within the study such that the association is an artefact, or that the association is due to confounding so that an underlying causal factor is related to both the disease and to the non-causally associated factor identified in the study.

The problems of interpretation of epidemiological associations have generated a considerable literature over the years. The eminent British epidemiologist, Sir Austin Bradford Hill, suggested nine criteria of causality against which epidemiological associations could be judged, and these are still used today in the scientific assessment of associations (2). Among the more important of the Hill criteria are the strength of the association, the consistency of the association across a variety of studies, evidence for a dose-response relationship (a "biological gradient"), and the evidence of biological plausibility.

The results of the studies carried out in the wake of the Seascale "cluster" must be viewed in the light of the nature of epidemiological research. They are a cautionary tale for those interested in the interpretation of epidemiological findings.

A PLETHORA OF "CLUSTER" REPORTS

The Seascale "cluster" generated other reports of childhood leukaemia "clusters" in the vicinity of nuclear installations in the UK, apparently indicating consistent evidence for a raised risk of childhood leukaemia around nuclear sites. These reports generated considerable publicity and independent investigations were conducted as a consequence. Closer examination of these findings, however, reveals that the evidence is not as persuasive as would appear at first sight (3,4). A number of the studies would seem to have been conducted on the basis of some prior knowledge of the pattern of childhood leukaemia in the vicinity of the particular installations investigated, and this prior knowledge

complicates the interpretation of results. As a consequence, secure statistical and epidemiological inference is lacking. Indeed, a recently published study of childhood leukaemia around nuclear installations in England and Wales which did not suffer from these sorts of inferential problems found that, apart from Sellafield, the evidence of any general spatial relationship between nuclear installations and childhood leukaemia was "extremely weak" (5). The "cluster" investigations carried out around nuclear sites do demonstrate the need for particular care in the design and execution of epidemiological studies carried out on an issue which is receiving wide publicity, with the consequent pressure on researchers to produce results.

POSSIBLE EXPLANATIONS

Direct Exposure to Ionising Radiation

Initial reactions to the report of the Seascale childhood leukaemia "cluster" were that the excess cases were due to an unpredicted effect of exposures to radionuclides discharged from Sellafield, or that the risk of radiation-induced childhood leukaemia had been underestimated. However, detailed radiological assessments have consistently demonstrated that the radiation doses received as a consequence of Sellafield discharges were too small by at least a factor of 100 to account for the observed excess of cases (6). By the end of the 1980s, it was widely acknowledged that direct exposure to radiation was most unlikely to be the cause of the Seascale "cluster" (7,8). This conclusion was reinforced by a recent comprehensive reassessment of radiation-induced leukaemia risk in Seascale (9).

Indirect Exposure to Ionising Radiation

In February 1990, the initial results of the West Cumbria leukaemia and lymphoma case-control study were published which suggested that the cause of the Seascale "cluster" might be indirect rather than direct exposure to ionising radiation (10). The study found a statistical association between childhood leukaemia and the radiation dose received by fathers while employed at Sellafield before the conception of their children. The authors suggested that the association was sufficient to account for the excess of childhood leukaemia in Seascale. This study received appreciable publicity and generated anxiety among radiation workers; but the association was based upon just 4 cases of leukaemia and the scientific support for a causal interpretation of association was, at best, weak. Nevertheless, this study led to one of the largest trials concerned with a personal injury claim to be heard in the English courts (11).

Evidence which has accrued since 1990 has demonstrated that the association is confined to those offspring of the Sellafield workforce who were born in Seascale, and does not extend to the great majority of the children of Sellafield workers who were born outside this village (12,13,14,15). Further, the association has not been found in any of the substantive studies carried out elsewhere (16). A causal interpretation of this association has now effectively been abandoned by scientific authorities (17,18). It would seem that this is an example of a statistical association which has been generated by the play of chance.

Population Mixing

One fascinating consequence of the Seascale "cluster" report is the series of studies conducted by Kinlen and his colleagues into the effect of unusual population mixing upon the risk of childhood leukaemia, which suggests an infective basis for childhood leukaemia. Sellafield is a large industrial complex sited in a remote rural area, and the employment demands of the site have generated unusual population movements in its vicinity. Kinlen has proposed that the consequent population mixing has produced an unusual pattern of infections which could elevate the risk of childhood leukaemia. He has now produced compelling evidence from a variety of detailed studies involving unusual population mixing in areas not associated with nuclear installations that such mixing does raise the risk of childhood leukaemia (19,20). This would appear to be the explanation for the Seascale "cluster"

which carries the most convincing scientific support. Kinlen's studies illustrate just how important it is to consider confounding as a possible explanation of an epidemiological association.

CONCLUSIONS

The Seascale childhood leukaemia "cluster" can be interpreted as indicating that the risk of childhood leukaemia arising from low-level exposure to ionising radiation has been underestimated. Indeed, several variants of such an interpretation have been advanced. These include exposure to particular radionuclides, an underestimation of the radiation risk coefficient for childhood leukaemia, and the existence of a previously unrecognised risk of childhood leukaemia from the preconceptional irradiation of fathers. However, the scientific assessment of epidemiological associations is a complex matter, and such associations must be interpreted with caution. It would now seem most likely that the Seascale "cluster" does not represent an unanticipated effect of the exposure to ionising radiation, but rather the effect of unusual population mixing generated by the Sellafield site which has produced an increase in the infection-based risk of childhood leukaemia. This episode in the history of epidemiological research provides a timely reminder of the need for great care in the interpretation of novel statistical associations.

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