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EDITORIAL

Childhood leukaemia and radiation exposure of fathers—the end of the road, perhaps?

When Martin Gardner and his team announced the results of the West Cumbria leukaemia and lymphoma case-control study in 1990 [1] there was uproar. Just over six years previously a television programme had identified a highly unusual cluster of childhood leukaemia cases in the Cumbrian coastal village of Seascale, next door to the Sellafield nuclear complex, and Gardner and his fellow researchers thought they had discovered the cause. They had found statistical associations between childhood leukaemia and comparatively high film badge doses received by fathers while working at Sellafield before the conception of their children—for both the cumulative preconceptional dose of external radiation and the dose received in the period immediately preceding conception. Gardner and his colleagues suggested that these associations could account for the Seascale cluster. The implication was clear: paternal preconceptional irradiation (PPI) at Sellafield materially increased the risk of childhood leukaemia through changes induced in fathers' sperm, to an extent that a pronounced excess of cases had been generated in Seascale. Media coverage was intense, anxiety among radiation workers and their families was rife, a big legal battle for compensation ensued, and the Government quickly initiated a number of studies including one by the Health and Safety Executive (HSE).

The HSE investigation principally consisted of a case-control study of cancer among children born in West Cumbria and whose fathers worked at Sellafield. The primary purpose was to assess the possible impact upon the risk of leukaemia and other childhood cancers of paternal occupational exposure to external and internal sources of radiation and to chemicals. Unlike the Gardner study, which used estimates of PPI doses based upon annual summaries of cumulative film badge readings, the HSE study used original radiation dose records that allowed more accurate external dose estimates and the consideration of doses to the testes from internally deposited radionuclides. As in a number of similar studies of this subject, the HSE examined leukaemia combined with non-Hodgkin's lymphoma (NHL), given the rather blurred distinction between certain types of these malignant diseases in childhood. Naturally, there was considerable overlap between the Gardner and HSE studies—the HSE considered only two cases of leukaemia that were not also included among the ten cases of leukaemia and NHL (LNHL) that generated Gardner's results—so the HSE findings for external radiation are not independent of those of Gardner.

The results of the HSE study were published in 1993–94 [2, 3]. The HSE team placed most weight upon whether there existed a trend of increasing incidence of childhood LNHL with increasing PPI dose. The children of radiation workers may not be the same as other children in respect of their background risk of leukaemia because, for example, of various lifestyle factors; but an association between LNHL and the level of exposure (i.e. PPI dose) is a stronger, although not definitive, pointer to a radiation-induced effect. The HSE researchers found an increase of LNHL among the children of Sellafield radiation workers and were able to confirm the association between childhood LNHL and the cumulative dose of external radiation received by a father prior to the conception of his child, although the association was heavily dependent upon a single high-dose case. However, the use of detailed external dose data by the

HSE led to the association with the dose received in the period shortly before conception, in some respects the more persuasive PPI association in the Gardner study, becoming weak and statistically non-significant—it was the cumulative PPI dose that seemed to matter. The HSE was also able to demonstrate that the cumulative external dose was not acting as a surrogate for the internal dose to the testes, since no internal PPI dose association was found.

The HSE team examined various aspects of the association between LNHL and the cumulative dose of external PPI. The most remarkable finding was the dramatic contrast in the strength and statistical significance of the PPI dose association for children born in Seascale and that for those born in the rest of West Cumbria—in Seascale the six cases of LNHL generated a striking dose-response whereas outside this village nothing exceptional was found. Indeed, there was a highly significant difference between the dose-response gradients. The possible interpretation of this pattern of results was one of the subjects addressed by the Committee on Medical Aspect of Radiation in the Environment (COMARE) in its Fourth Report [4].

One of the other studies spawned by the Gardner study was the Cumbrian birth cohort study led by researchers based at the University of Newcastle-upon-Tyne. This ambitious study aimed to produce a computer database of all births from 1950 to mothers resident in Cumbria and to link parents of these children to workers at Sellafield. The first publication from this birth cohort study [5] showed that less than 10% of the children of Sellafield fathers were born in Seascale, and yet the childhood leukaemia cases associated with comparatively high PPI doses appeared to be concentrated among Seascale births. This paper confirmed the highly disproportionate contribution of Seascale children to the results originally reported by Gardner.

Recently, the Newcastle team published a paper [6] reporting the findings of a follow-up of cancer incidence before the age of 25 years among over a quarter of a million Cumbrian births, which included 13 cases of LNHL among 9859 births to male Sellafield radiation workers. The dose-response obtained for the children born outside Seascale did not differ materially from that found in the HSE study. However, this consistency did not extend to the dose-response for children born in Seascale—in contrast to the steep and highly statistically significant gradient found in the HSE study, the analysis of the Cumbrian birth cohort data produced a shallow and marginally significant slope. The substantial difference in the dose-response findings for Seascale births, based upon exactly the same six cases of LNHL, was perplexing, to say the least. This difference is the primary subject of a paper jointly authored by the Newcastle and HSE researchers that appears in this issue of the journal [7], and the underlying reason is of some interest. The explanation would appear to be mainly due to the unusual dose distribution of cases and controls in Seascale. About two-thirds of the 791 Seascale births to male Sellafield radiation workers are associated with PPI doses less than 50 mSv, and yet the six affected children all have doses lying between 90 mSv and 200 mSv, hence the strong dose-related association found in the HSE study. However, about 4% of Seascale births have doses in the range 200-600 mSv, and the sample of controls included in the HSE case-control study does not include any of these births although, of course, they are all included in the birth cohort study. This long upper tail of doses has a pronounced downward leverage effect on the dose-response in the birth cohort study, which is absent from the case-control study, and this seems to provide the answer to the puzzle of the difference in the slopes.

There is little doubt that the Cumbrian birth cohort study provides the definitive data for the dose-response analysis since it does not depend upon the sampling strategy aimed at obtaining a representative set of controls. However, as noted by COMARE in its Seventh Report [8], this does not necessarily imply that the dose-response obtained by the Newcastle team is an ideal description of the variation of LNHL incidence among the Seascale births by PPI dose. The dose distribution of the cases is undoubtedly unusual in relation to that of the unaffected

children and this difference may not be described adequately by the exponential dose-response model assumed in the Newcastle analysis. Nonetheless, there is only so much that can be done in an analysis of half a dozen cases, and the salutary lesson that should be learned from the saga of PPI and Seascale is that firm conclusions cannot be drawn from such limited data by themselves.

So where does that leave us? In the absence of the Seascale births to male Sellafield radiation workers there is little if any epidemiological evidence to indicate that irradiation of fathers materially increases the risk of leukaemia in offspring. I summarised the dose-response findings of those studies which used data independent of the Cumbrian data that generated the original Gardner association in a recent issue of the journal [9]—the trends of LNHL with cumulative PPI dose obtained in the five independent studies were all (non-significantly) negative. One possibility that has been entertained in some discussions of this subject is that PPI increases the susceptibility of children to some leukaemogenic agent acting after conception: an interaction between PPI and some other factor [8]. So, for example, there is growing evidence that childhood leukaemia may be a rare response to a common infection and that unusual mixing of infected and susceptible individuals can give rise to localised epidemics of the infection and a consequent increase in the incidence of childhood leukaemia [10]. One impressive study carried out using the Cumbrian birth cohort database constructed a model of childhood leukaemia and population mixing using the births outside Seascale, and this model was found to predict with reasonable precision the number of childhood leukaemia cases in Seascale where population mixing is extreme [11]. Perhaps, then, the unusual dose distribution in Seascale is indicative of some PPI-induced predisposition to the leukaemogenic action of a childhood infection. However, if this interpretation is to hold water one must ask what evidence exists for such an interaction operating among births outside Seascale? Presumably, the relevant infectious agent is active in the rest of Cumbria and is responsible for many of the cases of childhood LNHL that have occurred there—the assumption made by the Newcastle researchers when they produced their model of population mixing [11]. There is no shortage of children associated with high PPI doses born in Cumbria outside Seascale (in excess of ten times the number of high dose births in Seascale) so one might expect to find a clear signal of an excess risk of LNHL if these children really are at an enhanced susceptibility. But there are only two cases of LNHL born in Cumbria outside Seascale associated with PPI doses greater than 50 mSv, and this contrast with the Seascale births is more pronounced when it is appreciated that these two cases do not conform to the pattern of childhood LNHL that typifies the Seascale experience—five of the six Seascale cases were in the age range 1-6 years considered by the Newcastle researchers to be the age group most affected by population mixing [6, 11]. The two cases are an infant (<1 year of age at diagnosis) leukaemia, which as noted by COMARE [8] is thought to be distinct from leukaemia in childhood, and a NHL in a young woman in her early twenties. The absence of cases of LNHL among young children associated with high doses born in Cumbria outside Seascale is stark. Not only that, but why do none of the other studies reveal this putative PPI-induced susceptibility to childhood leukaemia? Seascale may be extreme in the level of population mixing experienced there, but surely there should be some indication elsewhere of this marked predisposition generated by PPI if it is real?

What happens now? There are a few further pieces of information that might help. A recent paper [12] has shown that the raised risk of LNHL in the children of male radiation workers in Britain is limited to the offspring of those workers who were employed at the date of conception or during the year of diagnosis; there is no excess risk among children of radiation workers who left employment prior to conception. The authors interpret these findings as further evidence that the raised (but not dose-related) incidence of LNHL among

the children of British male radiation workers is due to factors other than PPI, most likely their unusual pattern of exposure to infectious agents. In addition, the offspring of cancer survivors who received radiation therapy and the children of nuclear workers in the former USSR may be groups worthy of study. However, it is pertinent to ask whether the essentially isolated oddity of the PPI dose distribution of the six Seascale-born LNHL cases should continue to seriously trouble those concerned with radiological protection given the evidence that is now available. It may be recalled that PPI cannot account for all of the Seascale cluster [13], or for the excesses of childhood leukaemia that have been reported from the vicinities of certain other nuclear installations [14]. Perhaps we can now consider ourselves to be effectively at the end of the road we set out upon almost 14 years ago with the publication of Martin Gardner's study?

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