Leukaemia and Sellafield: is there a heritable link?

In her review entitled “Leukaemia and Sellafield: is there a heritable link?”, 1 Dr Tawn concludes that the Seascale childhood leukaemia cluster could not have been caused by paternal pre-conception irradiation (ppi) induced germine mutation, as suggested by Gardiner et al. 2 Dr Tawn bases her conclusion in part on an assertion that there is little evidence that leukaemia is a heritable disease. Although there are cogent objections to the Gardner hypothesis based on epidemiological findings discussed elsewhere, 3,4, an examination of the evidence suggests it is premature to dismiss a role for heredity in human leukaemia. 4

Dr Tawn presents her arguments in the context of a claim for compensation by the families of two children of preconceptionally irradiated Sellafield workers. 5 These cases were effectively a legal test of the Gardner hypothesis, and therefore evidence of leukemia heritability was constrained by the adversarial nature of the litigation. Evidence of leukemia heritability considered at the trial and in the public domain cannot be taken as a rigorous scientific examination of all the issues. One factor which does not seem to have been considered is the dearth of information about familial leukemia, the only really effective measure of leukemia heritability. Direct (that is, molecular) evidence of leukemia heritability is only just being obtained, which means that the role of radiation in causing germine mutations may not be known for some time. If the events leading to the Seascale cluster were unique, such molecular investigations may never be carried out.

Part of the problem relating to the Seascale cluster lies in Gardner’s use of the term “germine mutation”, implying an alteration in DNA sequence. Perhaps “germine modification”, including non-classical genetic mechanisms such as imprinting or expanded repeat sequences/fragile sites, would have been less dogmatic. In dismissing non-mendelian effects in leukemia for lack of evidence, Dr Tawn does not tell us how many investigations of such non-classical mechanisms have actually been carried out with negative findings.

Dr Tawn also asserts that leukemia is only seen to be inherited if it is part of a “recognised syndrome”. The words “recognised syndromes” are crucial here, since the recognition of familial leukemia in the presence or absence of a syndrome depends on careful pedi-gree analysis and disease ascertainment. Whether detailed family studies were carried out in the Seascale cluster cases is not clear because such information has not been published. It is worth recalling, however, that leukemia and lymphomas were not originally the main clinical outcomes of the “recognised (preleukemic) syndromes” Fanconi anemia and ataxia telangiectasia (AT) when these were first described. Children usually either died of bone marrow failure or infection. The existence of AT as a disease entity was itself not fully recognised until 1957, its radiation hypersensitivity not until 10 years later, and the cancer and leukemia risk in heterozygous carriers of the AT gene not until 1976. Ninjeme generally syndromes, a similar but distinct approach to radiation sensitivity and preleukemic syndrome, was not described until 1981. 4

I suggest that, irrespective of the role of radiation in the Seascale cluster, the heritable component of leukemia in general has yet to be determined, and lack of evidence can in many cases be equated with lack of investigation. It is also essential to understand that it is the proportion of familial leukemia which is inherited, not leukemia itself. We also still need to know very much about the heritability of responses to radiation and other leukogenic agents to be sure that they are not an important factor in leukemia.

Whatever specific biological issues surround the Seascale leukaemia cluster, they should not deter us from investigating familial leukaemia in particular and leukemia heritability in general. Leukaemia families often feel isolated precisely because they are told that their predicament is not the result of heredity. In the UK we have no uniform system for the identification, recording, and surveillance of leukemia families. In addition to offering reassurance, investigation of leukemia families provides an opportunity to identify the genes involved in leukemia initiation, and to assess the hazards posed by radiation and other agents. There is no reason to cease the search for the heritable back-ground to human leukemia because the Seascale cluster cannot be explained in terms of classical genetics.

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This letter was shown to Dr Tawn, who replies as follows.

Dr Tawn is concerned that the adversarial nature of litigation constrains a full examination of scientific issues, and in setting my review 1 primarily in the context of the two claims for compensation against BNFL, scientific discussion is compromised. While I agree that a court of law is not the best place to settle scientific controversy, the two cases focused the minds of a considerable number of highly reputable scientists who were prepared to review evidence and give evidence for either the Plaintiffs or Defendants before a judge. This evidence came under rigorous scrutiny during cross examination, and the weakness of speculative hypotheses based on unsubstantiated theories. For some experts this continued over several days. A review of this evidence can, of necessity, only be brief and the extent to which the scientific issues were considered can be better assessed from the daily transcripts which are available. Referral to these transcripts should reassure Dr Tawn that the issues of particular concern to him, that is, familial leukaemia, imprinting, and radiation sensitivity, are being addressed in detail by experts on both sides. He should also be reassured that when scientific authorities have reviewed the evidence they have arrived at the same conclusions as the judge.

In particular, Dr Tawn criticises the dilution of information about familial leukaemia. There have, in fact, been a number of efforts to establish familial patterns. Cases associated with syndromes characterised by additional clinical abnormalities and the cancer families of the Li-Fraumeni type are well documented, but these apart, no substantive evidence has been found. Studies of twins and offspring of survivors of the disease provide little, if any, evidence of heritability. 5 It should also be noted that neither the two cases before the court nor the Seascale cases identified by Gardiner et al 6 fit the criteria of being part of a wider syndrome.

I fully accept that radiosensitivity and cancer predisposition are variable characteristics and most likely influenced by genetic factors. Nevertheless, evidence presented in my review supports the hypothesis, first put forward by the author of this review in her 1981 paper, that there is a radiation induced heritable modification of the genetic profile of the children of radiation workers that appears to be unique to Seascale, 7 the result of a combination of radiation and genes passed on to the first generation endpoint and of a magnitude hitherto unseen. Such a hypothesis cannot be sustained and any proposed mechanism to explain the excess of leukemia in the wider context of Seascale leukemia atoll. Although the Gardner hypothesis originally appeared an attractive explanation for the Seascale leukemia cluster, its far reaching implications soon drew the attention of experts from a wide range of disciplines who assessed it from their own viewpoints. Dr Taylor criticises my concentration on the genetic aspects, but this was my expressed intention. However, it is, I believe, the lack of support from a wide scientific perspective which makes the Gardner hypothesis untenable.

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