

LETTERS TO THE EDITOR

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 preconception irradiation (ppi) induced germline mutation, as suggested by Gardner *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 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.³ These cases were effectively a legal test of the Gardner hypothesis, and therefore evidence of leukaemia heritability was constrained by the adversarial nature of the litigation. Evidence of leukaemia 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 leukaemia, the only really effective measure of leukaemia heritability. Direct (that is, molecular) evidence of leukaemia heritability is only just being obtained, which means that the role of radiation in causing germline 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 "germline mutation", implying an alteration in DNA sequence. Perhaps "germline 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 leukaemia 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 leukaemia is only seen to be inherited if it is part of a "recognised syndrome". The words "recognised syndrome" are crucial here, since the recognition of familial leukaemia in the presence or absence of a syndrome depends on careful pedigree 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 leukaemia and lymphoma were not originally the main clinical outcomes of the "recognised (preleukaemic) syndromes" Fanconi anaemia 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 leukaemia risk in heterozygous carriers of the AT gene not until 1976. Nijmegen breakage syndrome, a similar but distinct radiation sensitivity and preleukaemic syndrome, was not described until 1981.⁴

I suggest that, irrespective of the role of radiation in the Seascale cluster, the heritable component of leukaemia 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 propensity to develop leukaemia which is inherited, not leukaemia itself. We also still know very little about the heritability of responses to radiation and other leukaemogenic agents to be sure that they are not an important factor in leukaemia.

Whatever specific biological issues surround the Seascale leukaemia cluster, they should not deter us from investigating familial leukaemia in particular and leukaemia 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, testing, and surveillance of leukaemia families. In addition to offering reassurance, investigation of leukaemia families provides an opportunity to identify the genes involved in leukaemia initiation, and to assess the hazards posed by radiation and other agents. There is no reason to cease the search for the heritable background to human leukaemia because the Seascale cluster cannot be explained in terms of classical genetics.

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- 1 Tawn EJ. Leukaemia and Sellafield: is there a heritable link? *J Med Genet* 1995;32:251-6.
- 2 Gardner MJ, Snee MP, Hall AJ, Powell CA, Downes S, Terrell JD. Results of a case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. *BMJ* 1990;300:423-9.
- 3 Wakeford R, Tawn EJ. Childhood leukaemia and Sellafield: the legal cases. *J Radiol Prot* 1994; 14:293-316.
- 4 Taylor GM, Birch JM. The hereditary basis of human leukaemia. In: Henderson ES, Lister TA, Greaves MF, eds. *Leukemia*. 6th ed. Cambridge, Mass: W B Saunders (in press).

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

Dr Taylor is concerned that the adversarial nature of litigation constrains a full examination of scientific issues, and in setting my review¹ 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 the scientific issues and give evidence for either the Plaintiffs or Defendants before a judge. This evidence came under rigorous scrutiny during cross examination, thus exposing the weaknesses of speculative hypotheses based on unsubstantiated theories. For some expert witnesses this continued over several days. A review of this evidence² 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 Taylor that the issues of particular concern to him, that is, familial leukaemia, imprinting, fragile sites, were addressed in appreciable detail by experts for both sides. He should also be reassured that when scientific authorities have reviewed the evidence^{3,4} they have arrived at the same conclusion as the judge.

In particular, Dr Taylor criticises the dearth 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.^{3,5} It should also be noted that neither the two cases before the court nor the Seascale cases identified by Gardner *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, the Gardner hypothesis⁶ implies a radiation induced heritable modification of the genetic profile of the children of radiation workers that appears to be unique to Seascale,^{7,8} the result of which is confined to one first generation endpoint and of a magnitude hitherto unseen. Such a hypothesis cannot be sustained^{3,4} and any proposed mechanism to explain the excess of leukaemia in the village of Seascale will have to be applicable in the wider context of leukaemia aetiology.

Although the Gardner hypothesis originally appeared an attractive explanation of the Seascale leukaemia 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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- 1 Tawn EJ. Leukaemia and Sellafield: is there a heritable link? *J Med Genet* 1995;32:251-6.
- 2 Wakeford RJ, Tawn EJ. Childhood leukaemia and Sellafield: the legal cases. *J Radiol Prot* 1994; 14:293-316.
- 3 Doll R, Evans HJ, Darby SC. Paternal exposure not to blame. *Nature* 1994;367:678-80.
- 4 United Nations Scientific Committee on the Effects of Atomic Radiation. *Sources and effects of ionizing radiation* (UNSCEAR 1994 Reports.) New York: United Nations, 1994.
- 5 Hawkins MM, Draper GJ, Winter DL. Cancer in the offspring of survivors of childhood leukaemia and non-Hodgkin lymphomas. *Br J Cancer* 1995;71:1335-9.
- 6 Gardner MJ, Snee MP, Hall AJ, Powell CA, Downes S, Terrell JD. Results of a case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. *BMJ* 1990;300:423-9.
- 7 Health & Safety Executive. *HSE investigation of leukaemia and other cancers in the children of male workers at Sellafield*. Sudbury: HSE Books, 1993.
- 8 Health & Safety Executive. *HSE investigation of leukaemia and other causes in the children of male workers at Sellafield: review of results published in October 1993*. Sudbury: HSE Books, 1994.