LETTERS TO THE EDITOR

Leukaemia and Sellafield: is there a heritable link?

In her review entitled "Leukaemia and Sellafield: is there a heritable link?", Dr Tawn concludes that the Seascle sieve childhood leukaemia cluster could not have been caused by paternal post-conception irradiation (ppi) induced germline mutation, as suggested by Gardner et al. 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, an examination of the evidence suggests it is premature to dismiss a role for heredity in human leukaemia.

Dr Tawn presents her arguments in the context of a claim for compensation by the families of two children of preconceptionally irradiated Sellafield workers. 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 germ line mutations may not be known for some time. If the events leading to the Seascle cluster were unique, such molecular investigations may never be carried out.

Part of the problem relating to the Seascle 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, would have been more accurate. 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 pedi gree analysis and disease ascertainment. Whether detailed family studies were carried out in the Seascle 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 (preleukemic) syndromes" Fanconi anaemia and ataxia telangiectasia (AT) when these were first described. Children usually either died of bone marrow failure in isolation. The existence of AT as a disease entity was 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. Nijmen gen breakage syndrome, a similar but distinct radiation sensitivity and preleukemic syndrome, was not described until 1981.

I suggest that, irrespective of the role of radiation in the Seascle 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 propagation of the disease 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 Seascle 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, recording, 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 Sea scle cluster cannot be explained in terms of classical genetics.

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 review 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 scientific issues and give evidence for either the Plaintiffs or Defendants before a judge. This evidence came under rigorous scrutiny during cross examination, and the emergence of weaknesses in speculative hypotheses based on unsubstantiated theories. For some expert witness 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 Taylor that the issues of particular concern to him, that is, familial leukaemia, imprinting, leukaemogenic effects, and the genetics of radiation sensitivity by experts on both sides. He should also be reassured that while scientific authorities have reviewed the evidence they have arrived at the same conclusion as the judges and decision makers.

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 the survivors of the disease provide little, if any, evidence of heritability. It should also be noted that neither the two cases before the court nor the Seascle cases identified by Gardner et al. 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, Gardner's observation implies a radiation induced hereditary modification of the genetic profile of the children of radiation workers that appears to be unique to Seascle, the result of which could lead to one first generation endpoint and of a magnitude hitherto unseen. Such a hypothesis cannot be sustained and any proposed mechanism to explain the excess of leukaemia in the vicinity of Seascle would appear to be applicable in the wider context of leukaemia aetiology.

Although the Gardner hypothesis originally appealed an interesting explanation for the Seascle 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 misinterprets 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.

JANET TAWN
Genetics Unit, Westlakes Research Institute, Geoffrey Schofield Laboratory, Westlakes Science and Technology Park, New Road, Cumbria CA24 9JE, UK.