sures too low or too recent for bone sarcomas to be seen[8,9].

I was once asked to discuss why leukaemia was not found after α-particle irradiation. A re-examination of the data provided strong circumstantial evidence that unrecognized leukaemia had occurred in dial painters but only in those few subjects with the highest body burdens[10], not in the several hundred dial painters in the United States and United Kingdom with body burdens 100–1,000 times less than the highest. Conversely leukaemia, but not bone sarcoma, has often been seen after injection of Thorotrast[3] (a preparation of colloidal ^{232}Th), but dose in individual cells within 100 μm of a Thorotrast deposit is rarely from a single α-particle, that is, rarely as low as 1 Gy. Each deposit emits a series of α-particles as ^{232}Th and its daughters undergo a sequence of nuclear transformations.

When experimental α-particle irradiation gives a linear dose–response without threshold and low LET, for example, X-ray irradiation gives a curvilinear dose–response without threshold, the ratio of dose for equal effect, the RBE, must increase asymptotically to an infinite value as dose tends to zero (compare the figure in ref. 2). Such contrasting dose–responses are often found, but the legitimacy of extrapolation below the lowest dose used in an experiment must depend on the presumed mechanism underlying the particular radiation effect under consideration (about which there may be little agreement). Recent work on cell survival at very high levels (after fractionated X-ray doses < 0.5 Gy in tissues *in vivo*[11] and after lower single doses in V79 cells in culture (B. Marples and M. C. Joiner, personal communication)) shows that below a critical dose level responses to low LET radiation can change abruptly with a corresponding progressive decrease in RBE for neutrons, so denying both legitimacy of extrapolation from a dose–response when its lowest dose is not sufficiently low and the inference that RBE must increase monotonically as damage (dose) decreases (see ref. 2).

More generally, when considering leukaemogenesis and carcinogenesis, it seems more acceptable to base inferences on the actual occurrence *in vivo* of leukaemia (or cancer as the case may be) on evidence on native cells in tissues, rather than on extrapolation from evidence on transformed or untransformed cells maintained in culture. Nevertheless the new and unexpected findings on genetic instability after *in vitro* exposure to α-particles[1] do have a special interest as a possible explanation of an unexpectedly low incidence of leukaemia after low-level exposure of humans to α-particles.

The proportion of clones without aberrations after 0.25, 0.5 and 1 Gy was 0.6, 0.5 and 0.6, respectively[1] (no dose response). It is not known whether the observed chromosomal instability in a clonogenic cell was caused by the action of a single α-particle or more than one α-particle.

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* Sadly, Dr Mole died a few days after submitting this letter.

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SIR — The results of Kadhim *et al.*[1] on the incidence of nonclonal chromosomal aberrations in stem cells of the bone marrow subject to two or less α-particle passages on the average, but not in cells exposed to γ-rays, and the interpretation of radiation-induced chromosomal instability are of great potential importance in a wider context than leukaemogenesis. A similar interpretation can be advanced to explain some earlier results obtained by Lüning and colleagues[2,3] in studies on the induction of dominant lethality in mice by ^{239}Pu α-particles.

In these, male mice were injected with ^{239}Pu citrate solution, sequentially mated to unirradiated females every week and dominant lethality (expressed as early and late intrauterine death) was measured at 18 days post-mating. Late as well as early deaths were observed in conceptions deriving from irradiated post-meiotic and peri-meiotic germ cells.

There were two surprising findings: (1) in successive mating intervals, there was a shift in favour of late deaths, in contrast to the situation recorded for X-irradiation (a shift in favour of early deaths[4]); and (2) when females were allowed to litter and the F_1 males from matings in the 9th, 14th and 16th weeks (those descended from irradiated stem cell spermatogonia) were used in dominant lethal tests, there were significant increases in both late and early deaths, suggesting 'transmission' of dominant lethality. None of the 410 F_1 males (and 122 controls) showed evidence of semi-sterility, thus excluding radiation-induced reciprocal translocations as a causal factor. In common with the findings of Kadhim *et al.*[1], such 'transmission of dominant lethality' was not observed with X-rays in the same strain of mice.

Nonclonal aberrations cannot be explained in terms of stable sequence changes in the genomic DNA. However, a mechanism can be envisaged on the basis of the concept of the existence of a dynamic steady state between DNA degradation and repair as it applies to radiobiology[5]. Whether, in estimating genetic risks of α-particle exposures, one should take into account the possibility of genomic instability in addition to RBE considerations, and if so, how, can only be answered by further studies.

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WRIGHT REPLIES — It is quite likely that many of the chromosome aberrations we reported[1] may represent lethal events for the murine cells, and Robin Mole's proposition that this is a possible explanation of an unexpectedly low incidence of leukaemia after low-level exposure of humans to α-particles is one of several interesting speculative implications of our data.

Other investigations in the MRC Radiobiology Unit using the strain of mice from which we obtained the marrow cells have demonstrated that injection of bone-seeking α-emitters resulted in the development of acute myeloid leukaemia in some of the animals[2]. It is possible that the phenomenon of chromosomal instability contributes to the development of leukaemia in such animals, but it should be noted that our experiments do not address the question of leukaemia incidence.

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