the last six monhts of the study). The confirmation or rejection of this interpretation will never be possible since the trial has, understandably, been prematurely stopped. Nevertheless, the fact is that we should not forget that exceptional events, however unlikely, do occur in exceptional circumstances.

Only future observations from other continuing studies will tell us whether the findings in Leeds are unique or not.

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REPLY—I am glad you have given Dr Amery a chance to state the position with regard to non-cancer deaths in other trials and me a chance to reply.

As Dr Amery says, there was no significant excess of non-cancer deaths in his trial or in that of Dr Wright in Seattle. I understand, in addition, that neither of them is convinced that any of the deaths that did occur showed similarity to ours.

Three things about this are important. Firstly, that the original analysis in each case omitted non-cancer deaths, considering only cancer deaths (Amery, 1976) or cancer recurrences (Wright *et al*, 1977). This is not uncommon in trial analysis although the points against have been well made (Peto *et al*, 1976, 1977) and are underlined by our experience. Secondly, they have been good enough to go over their cases since they heard our story and have each found marginally more non-cancer deaths on levamisole than on placebo. Thirdly, so far as I know, the case notes of these patients have not been submitted blind to an uninterested party. What I have seen of their data has not convinced me that it would be safe to conclude that their experience is *qualitatively* at variance with ours, although there can be no doubt that the size of the problem is quite different.

I am doubtful if the excess deaths in our trial were different in mechanism from occasional deaths after lung resection without the drug. It may be that levamisole regularly potentiates an event that is normally rare and that some other agent interacted with levamisole in our study to push this up to levels where it caused a significant difference in survival. For this reason, detection of antiheart antibody in the serum (had we had it) of any of the few placebo-treated patients dying in respiratory distress would not have disproved our hypothesised explanation and might have contributed to our understanding of the hazards of lung resection.

I was hampered in suggesting that another agent had interacted with levamisole in causing the effect by the fact that I could find no evidence for it apart from the differences between our trial and the others. Dr Amery points to an apparent *decrease* in excess deaths over the period of the trial and asks for a breakdown by centre. This does not support his contention. The deaths were randomly distributed throughout the period in one centre. In the other centre the same was true apart from a two-month period early in the trial with 4/7 deaths in levamisole and 2/7 in placebo-treated resected patients. The overall excess was comparable for the two centres so that one would be unwise to attribute the pattern to anything other than chance.

In Dr Amery's reading of the literature, levamisole does not increase and may decrease autoantibody production. However, we are not the first to attribute side effects of levamisole to autoantibody, and in view of the complexity of immunological mechanisms it would be simplistic to conclude that levamisole never increases autoantibody production when it has been shown to increase macrophage phagocytosis and pinocytosis and may therefore affect antigen presentation to B and T cells. We do not know what controls autoimmune disease, but we do know that genetic predisposition is involved since most of these diseases are commoner in individuals of group O and/or certain HLA types (Mourant *et al*, 1978).

Contrary to the implication of Dr Amery's letter, our trial entry already exceeded the planned accrual when the trial was stopped six weeks early on finding the excess deaths. Except for the patients who had just started the drug (from whom it was withdrawn) patients are continuing as planned even though any beneficial effect of levamisole will be very difficult to establish after such a disastrous start.

Like Dr Amery, we should not like this drug to be discarded on inadequate grounds, but we would beg other workers to ensure that all postoperative deaths are included in trials analyses and that repeated serum samples are obtained from all patients treated with levamisole preoperatively so that changes in titre of both viral and autoantibodies can be looked for in all cases dying in hospital.

HONOR M ANTHONY

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