with Rebif 22 μg. We agree that the concentration of neutralising antibodies is an important issue, and this was the reason for using different assay sensitivities and different neutralisation capacity cut-off points. However, the statement that the biological effect of neutralising antibodies is uncertain is obsolete with the knowledge of today; there is now overwhelming evidence of a detrimental effect on disease activity represented by relapses and MRI activity.

Guido Antonelli is correct that the presence of neutralising activity in serum is not a measure of impaired interferon-induced protein induction in blood cells. However, the findings that high-level neutralising antibodies (low-sensitivity and medium-sensitivity assay) were more detrimental on relapse rates than lower levels (high-sensitivity assay) certainly suggest that neutralising antibodies have clinical importance. We agree that comparisons of the immunogenicities of different interferon beta preparations are difficult and require the use of the same reliable and clinically relevant neutralising antibody assay.

In the light of our and other studies, it is hard to maintain a view that neutralising antibodies have no clinical effect, but we agree that further studies are needed for a better quantification of the effect and its dependence on the amount of antibodies.

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Health of thalidomide victims and their progeny

Sir—More than 40 years have passed since thalidomide was found to be a teratogen in humans and laboratory animals.[1] However, it is now known to be of great value in the treatment of leprosy, multiple myeloma, and AIDS. I believe that there is a need for the effects of thalidomide to be investigated further.

About 40% of the babies born in the 1950s and 1960s with thalidomide-induced malformations died in the neonatal period. The commonest causes of death were atresia of the small bowel or cardiac or renal malformations.[2]

Although thalidomide can produce malformations in any of the body systems, all the malformations seen in the thalidomide-affected individuals had been described before thalidomide was developed. Because thalidomide has been shown to interact with the DNA of laboratory animals,[3] interference with DNA synthesis might be the explanation for its teratogenic effect (and its value in the treatment of cancer).

If thalidomide is taken in pregnancy, a portion or the whole of the glutarimide molecule can bind to the DNA of some of the somatic cells, and indeed some of the germ cells if thalidomide is taken at the time of formation of the primitive gonads. If this genetic aberration is not accurately repaired, it could result in mutations or even deletion of the affected nucleotides. The incidence of mutations would be expected to be low,[4] as would the incidence of malformations and cancer.

There have been occasional reports of children born with congenital malformations who have one or both parents with thalidomide-induced malformations, leading to my hypothesis that thalidomide is a mutagen.[5] However, this suggestion aroused controversy.

Since most of the thalidomide-affected individuals from the 1950s and 1960s live in Europe, the Council for Europe should set up an official study into the health of thalidomide-affected individuals, particularly as to their incidence of cancer and the incidence of congenital malformations in their progeny.

Thalidomide has not been found to be a mutagen by current laboratory methods, but to ensure the safety of new drugs, we must be aware of the possibility of drugs and chemicals to alter the genetic code and thus be responsible for congenital malformations and cancer.

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Marketing ALLHAT

Sir—Michael McCarthy (Oct 11, p 1204)[1] reports that, to promote the results of ALLHAT,[2] Paul Whelton and colleagues are using marketing techniques. Like any marketing, the message tends to be simplified. Although Whelton and colleagues announced that the results for the primary endpoint—ie, coronary heart disease—were identical for the diuretic, the calcium-channel blocker, and the angiotensin-converting-enzyme (ACE) inhibitor, they did not mention that the incidence of new diabetes was substantially higher in the diuretic group.

Compared with the diuretic group, the relative risk of new diabetes was 0·70 (p<0·001) in the ACE inhibitor group and 0·84 (p=0·04) in the group on the calcium-channel blocker. Because the progression from insulin abnormalities to overt coronary heart disease can take many more years than the 4·9-year mean follow-up in ALLHAT,[3] the ALLHAT investigators should have paid more attention to this issue. Furthermore, the incidence of new cases of the metabolic syndrome was not reported in ALLHAT. However, it is likely to have exceeded that of new diabetes.

Such potentially serious side-effects, apart from hypokalaemia and increased blood uric acid (not reported in ALLHAT), should be given as warnings to physicians as part of the marketing campaign. No pharmaceutical company would be allowed to advertise any trials of its products without warning of such potentially serious side-effects. There is no reason why the ALLHAT investigators should adopt standards that might seem ethically flawed.

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