LETTERS

Toxic Effects of Interferon

Recent articles in *Science* (News and Comment, 19 Nov., p. 772) and the lay press have called attention to the potential toxicities of interferon. Much of this attention has centered on the cardiac toxicities seen in the French leukocyte interferon trials. We are in the process of formally reviewing all the interferon trials at the National Cancer Institute to determine the toxicities associated with the different forms of interferons we have tested in our program. In addition, we are making inquiries of the major pharmaceutical firms and the American Cancer Society with regard to their interferon trials.

Because the quotes attributed to me in the *Science* Briefing are potentially misleading, some clarification is required. We have tested a recombinant interferon (Hoffmann–La Roche), as well as extracted "natural" interferons (lymphoblastoid interferon, Wellcome Foundation; "Cantell" interferons). The recombinant interferon and the "Cantell" preparation were domestically produced, and the lymphoblastoid interferon was from England (Wellferon, Wellcome Foundation). As far as we can determine, in approximately 300 patients in Phase I and early Phase II trials with recombinant alpha interferon, there are some indications of cardiac effects. We are aware of fewer than ten patients who have had arrhythmias associated with recombinant interferon. Several patients have had atrial arrhythmias (paroxysmal atrial tachycardia and atrial fibrillation), and a few have had ventricular arrhythmias (premature ventricular contractions and complexes thereof) after receiving interferon. In general, most of these patients were older, with evidence of preexisting heart disease. Some had received Adriamycin and other potentially cardiotoxic drugs, and many had experienced similar arrhythmias before receiving interferon. Their arrhythmias recurred with fever and increased heart rate after the interferon treatment. In our series, more than 150 patients are being treated with recombinant interferon; one patient with preexisting heart disease (previous myocardial infarction and on medication for angina) had a fatal myocardial infarction during treatment. I am aware of only one other similar event in other recombinant interferon trials. These observations have primarily occurred after patients have received doses of 30 million units or greater per square meter (body surface area) and have been accompanied by fever, fatigue, and other toxic effects of interferon. The low frequency of these events is in contrast to the frequency reported from France.

Our preliminary recommendation would be that patients with heart disease, preexisting arrhythmias, and any preexisting exposure to cardiotoxic drugs should be carefully evaluated before entering an interferon trial. We currently exclude patients from our trials with New York Heart Association Class 3 and 4 heart disease. Perhaps patients with recent myocardial infarctions or recent problems with serious arrhythmias, as well as those on medications for their heart disease, should be further excluded from interferon trials. As always, clinical judgment is important in such exclusions, as patient alternatives, the effects of the disease, and the potential toxicities must all be considered. In trials using nonrecombinant interferons, more than 300 patients have been treated in Phase I and early Phase II trials with these preparations. Thus far we know of no documented arrhythmias or myocardial infarctions in the context of these trials. In these and other trials monitored by the Wellcome Foundation, more than 50 patients have been treated with doses greater than 30 million units per square meter for more than 1 week.

Phase II trials of both recombinant and nonrecombinant interferons are under way throughout the United States. It is important for investigators to recognize that interferons can have toxic effects (*1*) and that certain exclusions for preexisting problems are appropriate. These exclusions may be similar to those described above for heart disease and should also be made for severe hepatic and renal dysfunction. We have documented proteinuria induced by high doses of interferon in at least two patients, and because of preliminary evidence that interferon is metabolized by the kidney, patients with preexisting renal damage should be carefully evaluated before entering an interferon trial. It is clear that the interferon preparations can have hepatic toxicity when given at high doses. Thus, patients with abnormal liver function should be evaluated carefully before interferon therapy, and any change in hepatic enzymes should be carefully monitored. At least one patient has experienced hepatic failure, and two have had coagulation abnormalities during an interferon trial (*2*). Finally, symptoms of toxicity in the central nervous system (confusion, electroencephalogram changes, and seizures) have been reported after patients received higher doses of interferon (*3*).

Many of the toxicities of interferon are dose-dependent (*1*). Therefore, the patient evaluations required and the exclusions needed for an interferon trial should relate to the amount of interferon to be given. Interferon trials with low doses may require less extensive monitoring than those in patients receiving high doses.

We expect more data on the toxic effects of interferons to result from the review we are conducting. While there is no clear evidence from our trials that these preparations have direct cardiotoxic effects, further studies along these lines are appropriate.

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References

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2. Burroughs Wellcome Company, personal communication.
3. A. Rohatiner, P. Prior, F. Balkwill, T. Lister, "Central nervous system toxicity of interferon," paper presented at the Third Annual International Congress for Interferon Research, Miami, Fla., 1 to 3 November 1982.

Nuclear Plant Safety

Eliot Marshall, in the briefing "Brittle reactors: NRC has a plan" (News and Comment, 24 Dec., p. 1290), discusses a hypothetical situation in nuclear plants known as pressurized thermal shock (PTS) and states that "When the NRC [Nuclear Regulatory Commission] voted on 9 December, it decided to do three things."

One of the things the NRC decided, as reported by Marshall, was that

> "Some sort of regulatory inducement will be devised to get the Babcock & Wilcox Company to provide the NRC with data on the vessels it has sold. Thus far B & W has been uncooperative, perhaps because it is enmeshed in litigation over the reactor at Three Mile Island. As a result, the NRC is uncertain about the exact condition of the B & W vessels.

What was actually decided at the NRC meeting can be clarified by quoting a paragraph from a 23 December staff memorandum from S. J. Chilk to W. J. Dircks. The relevant paragraph states:

> The Commission, by a vote of 5–0, requested that the staff consider what special measures, if any, should be required of B & W reactors to ensure that they are adequately protected against pressurized thermal shock