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

events and submit their recommendations when the Notice of Proposed Rulemaking is sent to the Commission."

There is no mention of devising "some sort of regulatory inducement . . . to get the Babcock & Wilcox Company to provide the NRC with data on the vessels it has sold." Furthermore, it is neither necessary nor logical within the regulatory process for such actions to be considered.

Marshall's statement regarding the litigation over the reactor at Three Mile Island has no basis. In fact, B & W has worked very closely with the owner of the Three Mile Island reactor, GPU Nuclear, on the PTS issue and has performed a thermal shock evaluation of the Three Mile Island Unit I (TMI-1) vessel. It was concluded in this evaluation that no safety concern exists for the full lifetime of the vessel. GPU Nuclear submitted these results to the NRC in July 1982.

With regard to Marshall's statements about the NRC's not knowing the "exact condition of the B & W vessels," B & W and the utilities with nuclear steam supply systems designed by B & W initiated a Reactor Vessel Materials Program in 1977. Extensive data from this program were submitted to the NRC in March 1981. Other formal submittals were also made to the NRC. In fact, to quote S. H. Hanauer of the NRC from the 1 December NRC meeting on PTS: "B & W has completed a very extensive, perhaps the most extensive review of vessel material properties. . . ."

Finally, three points put the B & W activities related to PTS in proper perspective:

1) B & W, in conjunction with the utilities owning nuclear steam supply systems designed by B & W, led the early PTS investigations and made the first extensive submittals within the industry to the NRC in 1980 and 1981.

2) B & W believes that generic screening criteria are appropriate for determining which plants should ultimately perform plant-specific evaluations to address the PTS issue. Such evaluations have already been submitted to the NRC on the Oconee-1 and TMI-1 plants. Other plant-specific evaluations will be completed as appropriate.

3) On the basis of the data provided by B & W and others, the NRC has calculated values for ranking the operating nuclear plants that are most susceptible to PTS. The list was contained in Enclosure A of "SECY 82-465, NRC staff evaluation of pressurized thermal shock, November 1982" (available at the 9 December NRC meeting). As can be seen from this list, the plants with nuclear steam supply systems designed by B & W have substantial margins and, clearly, are not at the top of the list.

We plan to continue to cooperate with both the NRC and our utility customers to ensure that the PTS issue is responsibly addressed.

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Roy's assertion that the NRC did not discuss means of getting information out of Babcock and Wilcox is incorrect, as may be verified by reading the 9 December transcript of the NRC proceedings (pp. 29, 63, and 67).

It is a matter of record that B & W has been enmeshed in litigation, not on pressurized thermal shock, but on related safety issues arising from the Three Mile Island accident. Many of the company's highest officials, including Roy, gave evidence in a trial that began in November and ended on 20 January.

—ELIOT MARSHALL

Academic Economics Continued

Of the 60 comments on my letter "Academic economics" (9 July, p. 104), all except the two that have been printed in *Science* (8 Oct., p. 108; 10 Dec., p. 1070) express strong, often enthusiastic, support for my criticism of academic economics. None came from the theoretical economists and econometricians whom I challenged.

Jacob Cohen's response (Letters, 10 Dec., p. 1070) itself illustrates what is wrong with the present state of academic economics. He has "no doubt that theory is more glamorous than fact-grubbing" and cites the rational expectations theory as the "hottest [!] theory extant in economics."

According to that theory, government can be shown to be powerless to affect the state of the economy by means of any rationally designed measures of economic policies—the reason for this being the ability of private business to anticipate accurately all rational government moves and assess correctly their potential effects and then to neutralize these effects by means of equally rational (profit-maximizing) counteraction.

A survey similar to that presented in my first letter shows that 57 percent of the 44 papers on the subject of rational expectations published over the last 2 years in seven of the most important U.S. professional journals (*1*) are purely mathematical exercises. Thirty-six percent also contain attempts at empirical implementation of these intricate theoretical constructs. Such attempts involve routine application of elaborate methods of indirect statistical inference applied to a small number of aggregative indices (such as total employment, general price-level, and total gross national product). Only two of the 44 researchers saw fit to engage in the grubby task of ascertaining by means of direct observation how business actually arrives at assessment of future government actions and their potential effects, and whether that assessment was actually rational and correct (as is assumed by proponents of rational expectations theory.)

It is not surprising that, after 20 years of this type of research, "scientific opinion" is still split. Many opponents of government intervention in the operations of the economic system agree with Cohen's characterization of the theory of rational expectations as a "most powerful" and "widely applicable methodological generalization," while their more skeptical colleagues—Robert A. Gordon, for instance—cite (*2*) that theory as an example of a development "in which theory proceeds with impeccable logic from unrealistic assumptions to conclusions that contradict historical record."

Psychologist Robert Glassman's broad philosophical comments (Letters, 8 Oct., p. 108) seem to reflect conditions prevailing in his own discipline. While far from having attained a state of internal cohesion as in the physical sciences, economics certainly can advance beyond the early stage characterized by swings between compulsive empiricism and footloose theoretical speculation. Whatever disagreement exists between proponents of different approaches, the necessity of maintaining a close complementary relationship between construction of theoretical models and their empirical implementation does not seem to be questioned, at least in principle. My strictures are directed against pure theorists and statistical curve-fitters who prefer to leave the grubby fact-finding task to others. Too sharp a division of labor between theoretical and experimental work can lead to mutual misunderstanding, even in so-called exact sciences; in softer disciplines, it is bound to bring about a total impasse.

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