

tigation of Korula et al. (3) in which EST was compared with conventional therapy in patients who had survived an episode of variceal bleeding. Cumulative survival showed no significant difference between the two therapies. Reassessment of the data after all patients in both treatment groups who had had portal-systemic anastomoses were retrospectively censored, i.e., were considered to have been lost to follow-up at the time of shunt surgery and, therefore, excluded from the survival calculations, showed EST to be superior to conventional therapy in prolonging life ($p < 0.05$). This reversal in outcome resulted from the fact that portal-systemic shunts, which effectively prevented recurrence of hemorrhage, were performed in 16 of 57 patients in the conventional therapy group who bled from varices frequently, compared to only 4 of 63 in the EST group who bled infrequently. In essence, the use of the shunt in a large fraction of the control group tended to show a trend toward improved survival compared to the EST group.

The second study by Warren and his co-workers compared EST with distal splenorenal shunts (DSRS). They found during 2 years of follow-up that recurrence of bleeding occurred in 40% of the EST group compared to 14% of the DSRS group ($p < 0.01$). Eleven of the 36 (31%) of the patients who rebled after EST were considered failures of therapy and then had DSRS. Ten of the 11 had prolonged survival which resulted in better cumulative survival in the EST-DSRS-treated patients than in those treated with either EST or DSRS alone. Here, the performance of DSRS clearly rescued the patients who had failed EST.

The third investigation by Cello and associates compared acute, recurrent EST during active variceal hemorrhage with emergency portacaval anastomosis. They found survival in the two groups to be similar, but pointed out that 7 of the 16 patients (40%) who survived the initial admission after EST were considered failures of EST therapy and required elective shunt surgery after which they enjoyed long-term survival. The authors suggest that elective shunt surgery be considered for those who fail EST.

All three studies arrived in different ways at a similar conclusion: EST is usually effective in preventing variceal hemorrhage, but when it isn't, shunt therapy may be lifesaving. Implicit in this reasoning is the knowledge that elective shunt surgery has not improved cumulative survival over conventional, nonsurgical therapy in any of eight published RCTs. Perhaps studies should be designed to assess such therapeutic sequences in which patients who have recurrent variceal hemorrhage are randomized to have shunt surgery, devascularization therapy, pharmacologic reduction of portal venous pressure and/or other therapy.

Perhaps, no therapy, like no man, is entire unto itself, and each type of treatment should be considered to be a single cog in the wheel of therapy. Alternatively, these reports of shunt rescue may be regarded as artifacts of analysis that result from "cross-over" therapy.

Cross-over therapy is defined as the use of the "other" treatment when the investigational treatment selected randomly has failed. Such deviations from protocol rep-

resent investigational flaws. They are acceptable in human studies because one does not expect a physician-investigator to persist in administering a therapy that has failed, until the ultimate endpoint as is standard procedure in animal or laboratory experiments. Consequently, one may infer unanticipated clues to new therapeutic sequences, e.g., EST-portacaval anastomosis, from such unrandomized investigational misadventures that may require further investigations to elucidate.

Whether shunt rescue is an artifact of analysis or a valid phenomenon is not known, but it should at least be considered a therapeutic opportunity. After all, it has knocked three times.

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Elsewhere CORRESPONDENCE

To the Editor:

I found the comments by Dr. I. Herbert Scheinberg on zinc therapy of Wilson's disease in "HEPATOLOGY Elsewhere" (1) quite interesting and am moved to make two observations. The first is that Dr. Scheinberg has worked and published extensively on Wilson's disease, and is currently regarded as one of the leading American experts on this disease. Thus, his negative comments on the use of zinc in Wilson's disease are quite likely to be taken very seriously by many physicians treating patients with Wilson's disease.

This likelihood leads me to my second observation, namely that Dr. Scheinberg articulates no specific reasons for his sweeping conclusion that "zinc has no place in the treatment of Wilson's disease, except for those who have had a significant, irreversible reaction to both penicillamine and Trien." Dr. Scheinberg makes several assertions in support of his position: (i) penicillamine is not very toxic, and when it is, Trien can be used effectively; (ii) a controlled double-blind study of zinc efficacy

cannot be done ethically; and (iii) that years of zinc administration may reveal it to be toxic.

The first assertion is arguable, the second, irrelevant and the third hypothetical. Even if all the assertions were true, they don't justify Dr. Scheinberg's sweeping indictment of zinc therapy. If such statements were accepted, therapeutic progress would come to a screeching halt.

Regarding the first assertion, Dr. Scheinberg's own monograph (2) indicates a 20% initial hypersensitivity to penicillamine often requiring corticosteroids, a 10% initial neurological worsening and a long list of chronic toxicities from penicillamine. In his own words, "We make strenuous efforts to overcome any reactions to it before considering the use of Trien." He reports intolerance in only 2% of patients. Others mention 10% (3), which is more in keeping with our own experience. Also, a high proportion of our patients have some degree of chronic intolerance, such as proteinuria, facial wrinkling, loss of taste, thrombocytopenia or poor wound healing.

The second assertion is irrelevant because a double-blind study is not necessary to evaluate maintenance anticopper therapy in Wilson's disease. (No such trial was done with Trien, and there is much to be learned about its potential toxicity and limits of efficacy.) If the trial is properly designed to study previously decoppered patients, the intervening variables of urinary copper, nonceruloplasmin plasma copper, copper balance and oral ⁶⁴copper uptake will show lack of efficacy long before the patient is at risk of renewed symptoms from copper toxicity. Thus, no ethical issue exists.

The third assertion, that prolonged zinc therapy will produce as yet unknown toxicities is sheer speculation. Zinc has a theoretic advantage over penicillamine, in

that it is a natural body constituent and unlikely to provoke an immune reaction even after years of therapy. Late immune reactions that produce a variety of syndromes occur with penicillamine but have not yet been seen in 20 patients treated with zinc from 3 to 5 years.

Finally, if we accept the thesis that once we have an efficacious treatment for a disorder, it is unethical to try any other treatment, one of the most important components of medical progress will cease. We have very few magic bullets in medicine. We must strive to improve treatment in progressive steps that may involve combined or sequential therapy. The "proof of the pudding" in this case will be the extent to which penicillamine is used as maintenance therapy of Wilson's disease by the next generation of physicians. I'm betting that it won't be used very much because of its relatively high toxicity, which is not to say that it has not been an important and life-saving drug. Its time may well have been yesterday, and perhaps today, but certainly not tomorrow.

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