patients subjected to these procedures has not been realized. Thus, the present study is particularly exciting in that it provides the first demonstration that a drug that can be administered relatively easily and with no significant side effects can prevent dumping and allow patients to gain weight, experience a sense of well-being, and return to a state of normalcy, including the ability to work full-time. Although previous studies with somatostatin have shown its ability to treat patients with the dumping syndrome, success rates have been limited (Br Med J 1985;290:886–888; Surgery 1986;99:462–467). This compromised success was caused primarily by the short half-life (1–2 minutes) of the somatostatin peptide, which required continuous IV infusion to maintain adequate blood levels of the drug. Although there was no question in these studies that dumping could be improved, the practical problem of how to administer the drug to maintain adequate blood levels without requiring continuous IV administration made its clinical application of little worth. With the development of the octopeptide analog (octreotide acetate) of the natural compound cyclic somatostatin a longer half-life (75–90 minutes) could now be achieved, enabling it to be administered by the more practical SC route. Further, because biological activity of this analog could be maintained via SC administration (Life Sci 1982;31:1133–1140), it is not surprising that it, like the parent compound, should be able to prevent dumping and ameliorate or significantly lessen the symptoms associated with the dumping syndrome.

In addition to clear-cut evidence that octreotide acetate can effectively manage the dumping syndrome, this study has also provided important insights into the possible etiology of the dumping syndrome, which has remained elusive and continues to be debated among investigators. The results of this study make it unlikely that dumping symptomatology is related to changes in either plasma vasoactive intestinal polypeptide, gastrin, or motilin, because none of these hormones were altered in the dumping patients during the placebo trial or in postgastrectomy nondumping controls. In contrast, plasma levels of pancreatic polypeptide, neurotensin, and glucagon were markedly elevated during the placebo trial, and each was correspondingly suppressed with octreotide pretreatment. Although such data implicate a role for all three of these peptides as causative agents in the development of dumping symptoms, the authors postulate that neurotensin is the most likely mediator hormone. This is based on the observation that in their asymptomatic control group, plasma levels of pancreatic polypeptide were increased in response to the breakfast meal in a fashion similar to patients developing dumping symptoms. While the role of glucagon is less certain, this agent is known to decrease gastrointestinal motility with a resultant atonic intestine (Med Clin North Am 1981;65:1111–1127), the opposite of what one clinically observes in patients with dumping. The observation that neurotensin stimulates gastrointestinal motility of both the upper and lower intestinal tracts (Gastroenterology 1982;83:569–576) and can increase motility of the colon to such an extent that diarrhea will occur (Gastroenterology 1986;90:27–31) makes this humoral agent a likely candidate hormone for the dumping syndrome. On the basis of these considerations, the authors conclude that the likely mechanism of action of octreotide acetate is a reduction in gastrointestinal motility, most probably mediated by inhibition of the release of neurotensin. Whether other humoral agents are also involved in this process will require further study. This hypothesis would not only explain the alleviation of the early symptoms of dumping but also provide a physiological explanation for the improvement in late dumping symptoms. If a delay in upper gastrointestinal motility by octreotide acetate (through inhibition of neurotensin release) prevented the increase in plasma insulin that seems to occur in response to a high carbohydrate meal in late dumping, this in turn would prevent the development of late-onset reactive hypoglycemia characteristic of late dumping.

It remains to be determined whether this long-acting somatostatin analog is in fact the long-sought-after treatment regimen to manage postgastrectomy dumping. Obviously, additional studies are needed and warranted to confirm the findings of the present study. If they can be confirmed, however, another plaguing postgastrectomy problem may now be readily solvable.

T. A. MILLER, M.D.

SULFASALAZINE VS. STEROIDS IN CROHN'S DISEASE: DAVID VS. GOLIATH?

Rijk MCM, van Hogezand RA, van Lier HJJ, et al. (University of Nijmegen, The Netherlands; and Dutch Multicenter Groups, Nijmegen, The Netherlands). Sulphasalazine and prednisone compared with sulphasalazine for treating active Crohn's disease. A double-blind, randomized, multicenter trial. Ann Intern Med 1991;114:445–450.

In attempting to determine whether the combination of sulfasalazine and prednisone is more effective than sulfasalazine alone in the treatment of mild to moderately active Crohn's disease, the investigators performed a multicenter, randomized, controlled trial comparing a fixed dose of sulfasalazine (6 g/day) with a combination of sulfasalazine (6 g/day) and a fixed, tapering schedule of prednisone (30 mg/day for 2 weeks followed by tapering by 5 mg/2 wk to 10 mg/day, at which point the prednisone was maintained at 10 mg/day) until the completion of the 16-week study. The Van Hees Activity Index [composed of stool consistency, presence of extraintestinal lesions, presence of a mass, temperature, Quetelet index (weight/height), sex, previous resection, erythrocyte sedimentation rate, and albumin level] was the primary measure of disease activity, although the Crohn's Disease Activity Index (CDAI) was also determined and individual variables of both indices were compared. Patients were randomized according to disease location (ileitis, ileocolitis, and colitis) and evaluated at 2-week intervals.

Of 175 patients examined for eligibility (Van Hees Activity Index >140), 71 patients were randomized and 60 completed the study. Although the investigators state that there were no significant baseline differences between the study groups, the mean CDAI was greater in the combination group (305 vs. 255), probably because of differences in the number of liquid stools between groups (32/wk vs. 20/wk). The mean intake of sulfasalazine was >5 g in both study groups.

At the completion of the first 6 weeks of the study, the Van Hees Activity Index improved from 12% to 14% in the sulfasalazine group and from 27% to 34% in the combination group while the CDAI improved from 7% to 29% in the sulfasalazine group and from 28% to 42% in the combination group. Statistically significant differences were noted only in the Van Hees Activity Index and only in patients with ileocolitis or colitis, and the differences were more prominent in patients with more severe disease (Van Hees Activity Index >175). During the last 4 weeks of the trial, the reduction in the Van Hees Index (and CDAI) had stabilized with a 30% reduction from baseline in the sulfasalazine group and a 27%–48% reduction in the group receiving combination therapy. Statistical significance between treatment groups was observed only in patients with

initial Van Hees Activity Index >175; the components of that index that were most distinguishing between treatment groups were diarrhea, weight gain, and reduction in the erythrocyte sedimentation rate, which improved in a greater proportion of patients receiving steroids.

The authors conclude that the use of prednisone in addition to sulfasalazine results in a significantly faster initial improvement but not in significantly better results after 16 weeks of treatment when disease is measured by the Van Hees Activity Index.

Comment. The investigators have attempted to determine whether combination therapy with sulfasalazine and prednisone induces more rapid improvement in active Crohn's disease than sulfasalazine alone, whether there is persistent improvement after 16 weeks of therapy, and whether the disease location has an impact on the response to combination therapy. The study did not directly address whether or not sulfasalazine alone was effective in the study population because the authors relied on historical data rather than including a placebo-treated control group for comparison. Unfortunately, the absence of a control group will hinder the interpretation of the study results because the present study does not replicate the context of previous trials of sulfasalazine in Crohn's disease. Indeed, although sulfasalazine is a commonly recommended therapy for mild to moderate active Crohn's disease, data regarding its efficacy in controlled trials have been equivocal and unresounding. Anthonisen et al. (Scand J Gastroenterol 1974;9: 549–554) performed a double-blind, cross-over study comparing sulfasalazine, 3 g/day, for 4 months in 14 patients with recurrent Crohn's disease after a resection and 17 nonresected patients were used to assess "clinical benefit." Qualitative differences in symptoms and a variety of laboratory parameters were observed. No significant benefit was identified in the patients who had previously undergone surgery, although a modified "sign test" showed statistical superiority of sulfasalazine in those who had not undergone surgery. Disease location and activity were not controlled or compared between the patients who had undergone surgery and those who had not. Subsequently, the National Cooperative Crohn's Disease Study (NCCDS) (Gastroenterology 1979;77:847–869) compared sulfasalazine as a single agent to corticosteroids and the European Cooperative Crohn's Disease Study (ECCDS) (Gastroenterology 1984;86:249–266) compared sulfasalazine alone or in combination with corticosteroids. In the NCCDS, sulfasalazine was administered at a dose of 1 g/15 kg (to a maximum of 5 g/day) and prednisone, ¼–¾ mg/kg (to a maximum of 60 mg/day) according to the initial CDAI over 17 weeks; the ECCDS compared sulfasalazine, 3 g/day, with methylprednisolone, 48 mg/day initially with a weekly taper by 6 mg to a maintenance dose of 8 mg after 6 weeks, and with the two drugs in combination. The CDAI was the primary measure of efficacy in both studies, and the results were analyzed according to the site of disease (although the patients were not stratified at entry according to disease site or initial CDAI). The overall results of the NCCDS showed that only prednisone was superior to placebo in inducing remissions (CDAI < 150), although the retrospective subgroup analysis showed that sulfasalazine was superior to placebo in patients with ileocolitis or colitis but not ileitis, whereas prednisone was superior to placebo for ileitis and ileocolitis but not colitis [although the number of patients with colitis was small (n = 8) in both treatment groups]. In the ECCDS, steroid therapy alone or in combination with sulfasalazine was superior to placebo for all sites of disease, whereas sulfasalazine alone was effective only for colonic disease. Again, steroid therapy alone or in combination with sulfasalazine was more effective than sulfasalazine in inducing remission. Neither study showed a significant maintenance effect of sulfasalazine once remission was achieved. Van Hees (Gut 1981;22:404–409) also compared sulfasalazine, 6 g/day, with placebo in a smaller study of 26 patients followed over 26 weeks evaluated by their own (van Hees) index. Benefit was defined as a 25% reduction in the baseline score, and the investigators described a 62% response rate in the sulfasalazine group compared with an 8% response rate in the placebo group. The mean decrease in the index was 26% in the sulfasalazine group. In another Cooperative Crohn's Disease Study in Sweden (Gastroenterology 1982;83:550–562), sulfasalazine, 3 g/day, was compared with metronidazole, 800 mg/day, over 16 weeks, and both drugs appeared equally effective with a mean decrease in the CDAI of >50%. Patients with disease limited to the small intestine had inferior responses to both medications.

None of these trials provide definitive evidence of a benefit from sulfasalazine in active (or quiescent) Crohn's disease, yet there remains a belief that sulfasalazine does have a role in the treatment of a subgroup of patients (Am J Gastroenterol 1987;82:848–853) and the drug is frequently prescribed as a first-line therapy for mild to moderate disease. There are several explanations for the equivocal findings of these trials. First and foremost is the absence of a gold standard of measurement for Crohn's disease activity and, as the Rijk study emphasizes, the different indices measure different parameters. Although Rijk et al. were able to discern statistical significance between treatments according to the Van Hees Activity Index, the CDAI did not discriminate between sulfasalazine and combination therapy. This study also suffered from small patient numbers that may have resulted in inequalities in baseline features of disease activity (e.g., diarrhea) that had different impacts on the alternative indices and probably affected the degree of improvement with different therapies (i.e., a greater impact on diarrhea by corticosteroids?). The need to stratify patients according to disease location further hampers the statistical power and interpretation of results in all of these trials that have randomized small numbers of patients into each strata where other potential confounders may impact on outcome. The dose of sulfasalazine has been different in most of these trials, ranging from 3 to 6 g/day, and unlike the situation in ulcerative colitis, there has been no attempt at defining a dose-response. In many cases, the 6-g/day dose is not attainable because of intolerance.

There does appear to be a consistent trend in benefit from sulfasalazine for colonic Crohn's disease, in which, ironically, the NCCDS did not show a benefit from corticosteroids (again possibly due to small sample size), but in general the effects of sulfasalazine when used in combination with corticosteroids are subjugated by acute corticosteroids effects. Whether the effects of corticosteroids would persistently overwhelm sulfasalazine has not been addressed by these studies, which have used a fixed tapering schedule irrespective of the individual patient's response. Here, the studies clearly eschew clinical practice, in which the patient's response dictates dosing. Hence, none of the trials are decisive regarding the expected results of sulfasalazine in Crohn's disease where clinical trials remain hampered by the lack of definitions of disease, disease activity, and guidelines for controlled trials to provide consistency needed to compare results within and between therapeutic trials.

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RECURRENT HEPATITIS B IN LIVER TRANSPLANT RECIPIENTS—NO EASY ANSWERS

Demetris AJ, Todo S, Van Thiel DH, et al. (Department of Pathology, Division of Transplantation, and Department of Surgery, Presbyterian University Hospital, University of Pittsburgh, Pittsburgh, Pennsylvania). Evolution of hepatitis B virus liver disease after hepatic replacement: practical