"Even When the Wound Is Healed, the Scar Remains"

The above maxim was coined by the Roman author Publilius Syrus when referring to wounds of most tissues or body parts.[1] Because hepatic regeneration was recognized (as evidenced by the story of Prometheus's liver being eaten daily by an eagle only to regenerate the next day) in Syrus's time, his dictum was too far too simplistic when applied to the liver. One must delve more deeply into the mechanism of liver injury to ascertain just when hepatic scaring persists or when it disappears.

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Clearly, the infant liver sustains a significant "wound" from prolonged exposure to parenteral nutrition (PN). It is known that intestinal failure-associated cholestasis is closely associated with endotoxemia and exposure to phytosterols from soy-based lipid emulsions.[2] Although this pernicious, acute hepatic insult may be ameliorated by either reduction in lipid load or transition from a soy-based lipid to a fish oil-based lipid, hepatic fibrosis may persist or progress even after replacing the soy emulsion with a fish oil emulsion. However, it appears that some of the reported patients may have been alimented with soy for a long enough period for epithelial to mesenchymal transition to become permanent. It is quite clear that the cohort reported by Matsumoto et al[3] had progressed to advanced hepatic fibrosis because the histology examined came from hepatic explants at the time of transplant. The biopsies of patients taken by Soden et al[4] and by Mercer et al[5] had not progressed to liver failure when first transitioned to fish oil-based emulsions, but at the very least, they displayed stage 2 fibrosis. Thus, it appears that in these populations, fibrosis had reached a point of no return.

Noncholestatic liver injury in older children and adults can also be observed from administration of a high glucose load or a high energy load, and this injury may sometimes result in persistent hepatic fibrosis even months after children are weaned off PN. Mutanen et al[6] demonstrated a perfect example of that phenomenon insofar as their patients were provided essentially lipid-free PN yet 88% displayed fibrosis after 77 months of PN and 64% displayed fibrosis after 34 months off PN.

The report by Gura et al[7] in this volume of *The Journal* provides data to support the observation by Pastor-Clerigues et al[8] that serum profibrotic markers and monocyte-produced transforming growth factor $\beta 1$ are downregulated in patients transitioned from soy-based lipid to fish oil-based lipid. In the multicenter, cross-sectional study by Gura et al,[7] a surrogate marker for hepatic fibrosis, the aspartate amino transferase to platelet ratio index (APRI), was measured longitudinally in a cohort of patients treated with fish oil-based lipid. This was compared with that calculated retrospectively and longitudinally from historic control groups from Boston Children's Hospital and Mattel Children's Hospital who had received 2-3 g per kg per day of soy-based lipid. For those whose cholestasis resolved when treated exclusively with soy-based lipid, the APRI rose from a baseline of 0.540 to 2.564 upon resolution of cholestasis and to 2.098 upon termination of the study. Those who received fish oil-based lipid had a baseline APRI of 1.235 and it fell to 0.810 upon resolution of cholestasis and subsequently to 0.758 when the study was terminated. Notably cholestasis resolved in 65% of patients on fish oil emulsion and only 16% of those receiving soy emulsions. Death rates were similar at either the initial direct bilirubin of 2 mg/dL or the terminal bilirubin level of 12.87, but liver or liver/bowel transplantation rates were much lower in the fish emulsion group than in the soy emulsion group. These data suggest that hepatic fibrosis can be reversed if fish oil is provided instead of soy oil at an early age before advanced fibrosis and epithelial to mesenchymal transition has fully occurred.

Certain caveats exist. First, the APRI is an excellent tool for identifying patients whose hepatic fibrosis has progressed to stage 4 fibrosis; it does not discriminate well between those with no fibrosis and stage 2 or 3 fibrosis. Thus, some of these patients may have exhibited progressive, albeit mild to moderate fibrosis, while maintaining a relatively low APRI. Second, it is common for portal hypertension to be due to perisinusoidal fibrosis among children experiencing intestinal failure associated liver disease. Perisinusoidal fibrosis may result in all of the clinical manifestations of cirrhosis without demonstrating an elevated APRI. Third, because the control population received 2-3 times the parenteral lipid as those who received fish oil emulsion, the progression to severe fibrosis may have been relatively accelerated in the soy emulsion group. Fourth, the progression of fibrosis in some of the patients may have been the result of energy or glucose overload as suggested by Mutanen et al.[6] Finally, the blood stream infection rate in the soy emulsion group was twice that of the fish oil emulsion group. The increased rate of infections among the soy emulsion group may have exposed them to more endotoxin and greater liver damage over time.

Those caveats notwithstanding, Gura et al provides hope that not only cholestasis and also fibrosis may improve on fish oil-based emulsions. It also suggests that infants on PN should receive fish oil emulsions earlier in their course rather than later. Furthermore, acoustic radiation force impulse imaging and/or shear wave elastography[9] are available in most

APRI	aspartate amino transferase to platelet ratio index
PN	parenteral nutrition

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medical centers; one of these techniques should be applied periodically to follow the progression of fibrosis among young recipients of PN. In addition, now that soy, medium chain triglyceride, olive, and fish (SMOF) lipid[10] is being utilized in most medical centers, infants and children receiving this emulsion should be carefully studied to understand whether hepatic fibrosis occurs among them.

Gura et al expands our knowledge of how the liver is wounded by PN, it is now incumbent upon us to minimize the scarring. ■

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Gastrointestinal Bleeding: Expanding the Shortened Telomere Disorder Phenotype

Telomere biology disorders are a group of disorders characterized by an elevated malignancy risk, mucocutaneous abnormalities, pulmonary and hepatic fibrosis, and bone marrow failure secondary to severely reduced cellular telomere length.[1,2] The presence of vascular alterations in patients with telomere biology disorders, including pulmonary arteriovenous malformations and retinal vessel disease, have been increasingly recognized.[3] In this volume of *The Journal*, Himes et al sought to further elucidate the frequency and etiology of gastrointestinal hemorrhage in patients with an underlying telomere biology disorder. The cause of gastrointestinal bleeding in patients with telomere biology disorder, including those without a diagnosis of Coats plus syndrome with its known elevated intestinal hemorrhage risk resulting from vascular anomalies,[4] is undoubtedly multifactorial. Hepatic fibrosis may be significant, leading to portal hypertension and resultant esophageal varices or gastropathy.[3] Bowel inflammation, including severe colitis and enteropathy, can be present.[5] With an elevated malignancy risk, gastrointestinal bleeding episodes may be the initial presentation of an esophageal or colonic cancer.[1]

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Bleeding risk may further be increased secondary to bone marrow failure/hematologic malignancy associated thrombocytopenia or hepatic dysfunction associated coagulopathy.[2]

Through retrospective analysis, 16 patients with telomere biology disorders with a history of significant gastrointestinal hemorrhage were analyzed, with a median age at time of first bleeding occurrence of 12.5 years. Hematochezia or melena was the most common initial gastrointestinal hemorrhage manifestations, and recurrence was frequent with 15 of 16 patients suffering from subsequent bleeding episodes. Despite a high prevalence of thrombocytopenia among the study subjects, the authors did not believe that their presentation clinically was concerning for a bleeding diathesis. The majority of patients had normal hepatic laboratory studies during their initial hemorrhagic episode, and esophageal varices were only observed in 1 out of 3 of those assessed. Of particular interest, evidence of angiodysplasia was seen in 67% of those undergoing endoscopies. Less than one-third of the patients

HSCT Hematopoietic stem cell transplantation

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