A Synthetic Pentasaccharide for the Prevention of Deep-Vein Thrombosis

To the Editor: Turpie et al. (March 1 issue)\(^1\) report the findings of a rigorously performed double-blind, randomized trial comparing a synthetic pentasaccharide (Org31540/SR90107A) and a low-molecular-weight heparin (enoxaparin) in patients undergoing total hip replacement. The patients were randomly assigned to receive one of five daily doses of the pentasaccharide beginning 6 hours postoperatively (range, 4 to 8) or enoxaparin beginning 12 to 24 hours postoperatively. Two studies\(^2,3\) evaluated the effect of prophylaxis with low-molecular-weight heparin administered in close proximity to surgery, either within two hours before surgery or six hours after surgery, in patients undergoing elective hip surgery and found that low-molecular-weight heparin was more effective than oral anticoagulants. In contrast, the effectiveness of therapy with low-molecular-weight heparin begun 12 hours preoperatively\(^4\) or 12 to 24 hours postoperatively\(^5\) was similar rather than superior to that of oral anticoagulants. The timing of prophylaxis is crucial; antithrombotic prophylaxis administered in close proximity to surgery is more effective than delayed prophylaxis.

The conclusion of Turpie et al. that, as compared with low-molecular-weight heparin, the synthetic pentasaccharide has the potential to improve the risk–benefit ratio for the prevention of venous thromboembolism is sound. However, in the light of the evidence that initiating antithrombotic prophylaxis in close proximity to surgery is more effective than delaying prophylaxis, it is apparent that the superiority of the pentasaccharide also reflects its initiation in the early postoperative period. Further trials are required to compare the two antithrombotic treatments, such as the pentasaccharide, with low-molecular-weight heparin initiated in close proximity to elective hip surgery (six hours postoperatively).

To the Editor: In their dose–response trial comparing the synthetic pentasaccharide Org31540/SR90107A with enoxaparin for the prevention of deep-vein thrombosis after total hip replacement, Turpie et al. mention epidural and spinal anesthesia in passing in the Methods section, but they fail to provide any safety data regarding the sites of major bleeding. According to Table 4 of their article, 9 of 260 patients in the control group (3.5 percent) had major bleeding complications, as compared with 30 of 673 patients in the pentasaccharide group (4.5 percent). Since in the setting of continuous epidural or spinal anesthesia, the administration of low-molecular-weight heparin has been associated with major bleeding complications, we recommend that the committee that will be charged with the task of developing guidelines for the prevention of venous thromboembolism in orthopaedic surgery should include recommendations regarding the use of antithrombotic prophylaxis in patients undergoing total hip replacement who receive epidural or spinal anesthesia.

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Editor’s note: Drs. Hull and Pinoe have received grants-in-aid from Dupont, Emisphere Technologies, Leo Pharmaceutical Products, and Pharmacia.


INSTRUCTIONS FOR LETTERS TO THE EDITOR

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neuraxial hematomas and even permanent paraplegia.\textsuperscript{1,3} Turpie et al. should outline their protocol’s recommendations for removing the catheter (if one was inserted) and report whether any such events were observed in the intent-to-treat population.

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The authors reply:

To the Editor: We agree with Hull and Pineo that much remains to be learned about the optimal scheduling of anticoagulants when they are used before or soon after major surgery. Our trial cannot contribute to the answer, since it was essentially a dose–response study of the pentasaccharide. Our comparison with the currently recommended regimen of enoxaparin prophylaxis was exploratory and preliminary to formal phase 3 comparisons.

The optimal time to begin thromboprophylaxis with low-molecular-weight heparin — preoperatively or postoperatively — is still controversial.\textsuperscript{2} The attractive concept that administering low-molecular-weight heparin in close proximity to surgery may increase its efficacy is based on indirect comparisons between approved regimens and nonapproved regimens, with warfarin as the reference treatment.\textsuperscript{2} This concept has not, however, been unequivocally proved, since a dose of 30 mg of enoxaparin twice daily that was initiated within 24 hours after hip replacement proved more effective than warfarin.\textsuperscript{3}

When two different drugs are compared, factors other than the timing of their initial administration may contribute to differences in efficacy. Moreover, the optimal duration of prophylaxis is still debated.\textsuperscript{1} Several studies suggest that the risk of venous thromboembolism after hip replacement may begin during surgery but may persist for up to two months. Thus, the overall efficacy of a regimen is unlikely to reflect only the effect of the timing of the first dose, and the superior efficacy of pentasaccharide over enoxaparin is likely to be due to its selective inhibition of activated factor X, its rapid onset of action, and its long half-life, which results in a complete, 24-hour antithrombotic effect.\textsuperscript{4,5}

The reports of neuraxial hematomas referred to by Dr. Landow led to strengthened precautions for the use of anticoagulation in conjunction with epidural or spinal anesthesia. Our patients underwent randomization postoperatively and only after the removal of any epidural catheter. Injections were prohibited within two hours after the removal of the catheter. In this dose-ranging study, one of the first randomized patients who received 6 mg of pentasaccharide, which is more than twice the dose selected for further trials, had a neuraxial hematoma after five attempts to place an epidural catheter preoperatively were unsuccessful.

Subsequent patients could enter the trial after receiving regional anesthesia only if the puncture was clean, was made on the first attempt, and was uncomplicated by bleeding. No further neuraxial hematomas occurred.

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Editor’s note: Drs. Turpie and Gallus have received grants from and served as consultants to Sanofi–Synthelabo Research, which, along with Organon, is the manufacturer of the anticoagulant pentasaccharide.


Low-Molecular-Weight Heparin in Patients with Deep-Vein Thrombosis

To the Editor: The clinical importance of rapidly achieving a therapeutic activated partial-thromboplastin time with respect to the treatment of venous thromboembolism with unfractionated heparin has been underscored in various studies\textsuperscript{1} and reviews.\textsuperscript{2} Bredin et al. (March 1 issue)\textsuperscript{3} compared intravenous unfractionated heparin with subcutaneous weight-adjusted reviparin, given once or twice a day, as a therapy for deep-vein thrombosis. Reviparin (a low-molecular-weight heparin) was more effective than unfractionated heparin in reducing the size of the thrombus, and twice-daily administration of reviparin prevented recurrent thromboembolism better than did treatment with unfractionated heparin. The patients received fixed initial doses of unfractionated heparin, with the doses adjusted according to daily measurements of the activated partial-thromboplastin time. This approach led to an unacceptably high number of patients with a subtherapeutic activated partial-thromboplastin time after 48 hours (33 percent). A regimen involving doses of heparin adjusted for the patient’s weight, as proposed by Raschke et al.,\textsuperscript{4} would probably have led more rapidly to therapeutic heparin levels and thus to fewer recurrent thromboembolic events. The statement that reviparin regimens are more effective than a regimen of unfraction-
ated heparin can be considered true only in the context of a suboptimal heparin regimen.

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To the Editor: We would like to ask Breddin et al. to specify a detail of the treatment protocol. Reviparin was given either once or twice daily, at doses adjusted for body weight. Does this mean that the twice-daily group actually got twice the total daily dose received by the once-daily group, or was the total dose given in a 24-hour period the same — that is, the twice-daily group received half the dose per injection?

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The authors reply:

To the Editor: Regarding the comments of Pechlaner and Gritsch: we stated that patients in both the reviparin groups received the same daily dose of reviparin, given either in two divided subcutaneous injections every 12 hours or as a single subcutaneous injection every 24 hours.

Regarding the comments of Stricker and Mombelli: we would like to point out that conventional practice is to administer unfractionated heparin by intravenous infusion, with the dose adjusted according to daily measurements of the activated partial-thromboplastin time to achieve a value 1.5 to 2.5 times the base-line level. To our knowledge, a randomized, controlled trial has never been performed comparing the efficacy of a heparin infusion adjusted for the activated partial-thromboplastin time with a weight-adjusted dose with the use of an objective method of assessing thrombus regression and recurrent thromboembolic events. Therefore, it remains speculative whether a weight-adjusted regimen of unfractionated heparin would be more effective in increasing thrombus regression and thus reducing the frequency of recurrent thromboembolism.

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Biventricular Pacing in Patients with Heart Failure

To the Editor: Cardiac output is determined by heart rate and stroke volume. Since the latter is reduced in patients with ventricular systolic dysfunction, the cardiovascular reserve during exercise in patients with heart failure depends heavily on the increment of the pulse rate. Unfortunately, chronotropic insufficiency is often found in these patients. Moreover, substantial prognostic value has been attributed to this abnormality.1 We were therefore surprised that Cazeau et al. (March 2 issue),2 in their report of the Multisite Stimulation in Cardiomyopathies trial, did not provide information on the maximal heart rates achieved during exercise before and after three months of multisite biventricular pacing. Although this information was not mentioned in the article, we assume that the minute-ventilation sensor of the implanted device was set to provide rate-responsive pacing. If this was indeed the case, part of the improved exercise capacity could have resulted from a more physiologic exercise-adapted increase in the heart rate.

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The authors reply:

To the Editor: During the active-pacing period of the six-month crossover phase, the pulse generator was programmed in an atrial-synchronous or VDD biventricular pacing mode with a basic pacing rate of 40 beats per minute (bpm), which meant that the atrium was used only for sensing and was never paced. In all patients, the rate-responsive function was set to “off.”

We did not observe any significant difference in the maximal heart rates at peak exercise at base line (117±25 bpm), at randomization (125±24 bpm), at the end of the period of active pacing (124±24 bpm), or at the end of the period of inactive pacing (122±21 bpm).

It clearly appeared that the improvement in exercise tolerance with atrioventricular pacing, as reflected by the increased distance walked in six minutes (P<0.001) and improved peak oxygen uptake (P=0.02), did not reflect the correction of chronotropic insufficiency but was probably due to the cardiac-resynchronization effect alone.

In that respect, it is worth recalling the results of our study of the acute hemodynamic effects of temporary pacing3 in which we showed that atrioventricular dual-chamber (DDD) pacing with an optimized atrioventricular delay resulted in cardiac output that was, on average, 35 percent greater than that achieved with atrial pacing alone with preserved intrinsic conduction. In that study, we used a fixed pacing rate (10 percent faster than the intrinsic atrial rate) in patients who, like those included in the more recent study,

The authors reply:
had severe heart failure and major intraventricular conduction delay.

**Underuse of Coronary Revascularization Procedures**

*To the Editor:* Hemingway et al. (March 1 issue)1 conclude that, according to a criteria set by an expert panel, coronary revascularization procedures are underused; patients who should have undergone a surgical intervention were incorrectly treated medically. But what is the basis for the criteria of the expert panel?

Current recommendations regarding surgery are derived largely from data from the 1970s and early 1980s,2 which preceded the development of aggressive medical therapies both for the management of ischemia (e.g., nitrates and beta-blockers) and for the reduction of risk factors (especially cholesterol levels). Even the most recent study comparing surgical treatment with medical management, conducted in the mid-1990s, did not include the goal of aggressive lipid lowering.3 Less than 25 percent of the patients in the medical-treatment group in the study by Hemingway et al. were receiving hypcholesterolemic agents. Yet it is clear from other data that aggressive lipid management leads to clear benefits within six months of initiating therapy.

Other data that aggressive lipid management leads to clear benefits. Yet it is clear from the mid-1990s, did not include the goal of aggressive lipid lowering. Less than 25 percent of the patients in the medical-treatment group in the study by Hemingway et al. were receiving hypcholesterolemic agents. Yet it is clear from other data that aggressive lipid management leads to clear benefits within six months of initiating therapy. As compared with coronary angioplasty, aggressive lipid lowering with 80 mg of atorvastatin (bringing the ratio of total cholesterol to high-density lipoprotein cholesterol down to 2.8) decreased the rate of ischemic events by 36 percent over a period of 18 months.4 Since no trial has compared state-of-the-art medical management (especially aggressive lipid lowering) with surgery, it is difficult to conclude that coronary revascularization is underutilized, especially for patients with chronic cardiac symptoms.

**To the Editor:** Hemingway et al. conclude that patients who would be considered by an independent panel to be appropriate candidates for coronary-artery bypass grafting (CABG) have a greater risk of adverse outcomes if they are treated medically than if they receive CABG. This conclusion may be valid if the base-line characteristics of the medically and surgically treated patients are uniform. However, important differences existed in this study.

First, there were significantly more patients with heart failure and fewer treated with beta-blockers in the medically treated group. Beta-blockers reduce mortality among patients with heart failure,3 so the differences in mortality that were observed in the study could be associated with their underuse. Second, the medically treated group included a higher percentage of patients with diabetes and patients with previous myocardial infarction. The mortality rate among patients with diabetes with multivessel coronary disease is reduced with the use of CABG.2 Previous CABG also has a cardioprotective effect in patients with diabetes who have a myocardial infarction.4 Thus, the overall results may be skewed by a significant effect on a small group of high-risk patients in whom revascularization has proven benefit.

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**Underuse of Coronary Revascularization Procedures**

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**To the Editor:** I am concerned that the article by Hemingway et al. may overstate the benefits of cardiac revascularization because of a possible bias in the data resulting from the failure to consider the social class of patients. The group that received medical treatment may have included a disproportionate number of patients from lower socioeconomic classes. I base this conclusion on the fact that nonwhite patients were overrepresented in the medical-treatment groups as compared with the groups assigned to percutaneous transluminal coronary angioplasty (PTCA) (17 percent vs. 12 percent) and CABG (20 percent vs. 14 percent) and the fact that in the United States nonwhite race
is associated with lower social class, which I believe is also the case in the United Kingdom.

There is a well-established association between socioeconomic class and death rates from heart disease. Including a disproportionate number of lower-class patients in a study group can be expected to result in increased death rates, independently of the treatment the patients receive. Until the authors can control for differences in social class between their treatment groups, their conclusions about improved outcomes with revascularization may need to be muted somewhat.

In addition, it appears that in the United Kingdom, as in the United States, nonwhite patients with heart disease are referred for revascularization less often than white patients with a similar level of disease. This finding is as important as the difference in treatment outcomes. The adverse health effects of racial bias in the availability of revascularization procedures far outweigh the effects of underuse of these procedures among predominantly white, upper-class patients.

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To the Editor: Hemingway et al. report data suggesting that the use of explicit measures of appropriateness may result in a more judicious use of revascularization procedures. We wonder whether patients in this study were assigned to the CABG group on an intention-to-treat basis or on the basis of the treatment they received. Specifically, if a patient who was going to receive CABG died before he was able to undergo surgery, in which group was he counted? We note in Figure 1 of the article that large numbers of deaths or nonfatal myocardial infarctions occurred soon after the initial angiography was performed, particularly in the medically treated group. Thus, the failure to categorize the patients according to the intention-to-treat principle would bias the results of this study against medical treatment.

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The authors reply:

To the Editor: The correspondents raise important issues in interpreting the finding in the Appropriateness of Coronary Revascularization study of the underuse of CABG after angiography. However, these further considerations (the subjects of detailed reports published elsewhere) do not alter the main conclusion of the study. We report here hazard ratios for death among patients in whom CABG was deemed appropriate, comparing patients who received no revascularization with those who underwent CABG. Hazard ratios greater than 1.0 denote an underuse of CABG.

In order to address the suggestion made by both Modest and Ray et al. that optimizing medical management might alter our findings, we carried out subgroup analyses among patients who were taking a statin or a beta-blocker and calculated hazard ratios of 4.47 (P=0.002) and 3.79 (P<0.001), respectively. The similarity between these hazard ratios and the ratio of 4.96 we reported suggests that optimizing medical management may make little difference in the effect of the underuse of CABG on mortality.

Ray and colleagues note an excess of diabetes, myocardial infarction, and heart failure among the medically treated group. Adjustment for these factors (in Tables 3, 4, and 5 of our article) had little effect on our results; analyses that excluded patients with any of these coexisting conditions actually found a stronger effect of the underuse of CABG on mortality (hazard ratio, 5.97; P<0.001).

As Barr suggested, we have now controlled for social class and race; neither of these factors attenuated the effect of the underuse of CABG on mortality, with hazard ratios of 4.49 (P<0.001) and 3.89 (P<0.001), respectively. We found no evidence that South Asian patients were less likely than whites either to be deemed appropriate candidates for revascularization or to be referred for a revascularization procedure.

The primary, prestated intention of our study was to compare the clinical outcomes among patients who received a given treatment for coronary disease with the outcomes among those who did not, according to prespecified levels of appropriateness. Because the timeliness with which patients undergo a revascularization procedure is a crucial consideration for any investigation of the magnitude of underuse, any patient who died before receiving revascularization was included in the analyses as a member of the medical group. To do otherwise would be to create a conservative bias. However, our results are robust enough to support an intention-to-treat analysis of the type suggested by Khakoo and Rastegar. Among those classified as appropriate candidates for CABG, the patients for whom medical treatment was intended had higher mortality rates than those for whom CABG was intended, regardless of the actual therapy they received (hazard ratio, 2.05; P=0.004).

The challenge now is to determine the extent to which clinical outcomes are improved when suitably updated appropriateness criteria for angiography and revascularization are used to support clinical decisions in routine practice; the application of these criteria should not be delayed.

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The challenge now is to determine the extent to which clinical outcomes are improved when suitably updated appropriateness criteria for angiography and revascularization are used to support clinical decisions in routine practice; the application of these criteria should not be delayed.

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1. Hemingway H, Crook AM, Banerjee S, et al. Hypothetical ratings of coronary angiography appropriateness: are they associated with actual an-
Cutaneous Squamous-Cell Carcinoma

To the Editor: In their excellent review article on cutaneous squamous-cell cancers (March 29 issue), Alam and Ratner mention sunscreen use but not the prevention of these cancers in certain populations of patients at high risk. Among recipients of solid-organ transplants, the incidence of cutaneous squamous-cell carcinoma may be more than 100 times the incidence in the general population. Moreover, as many as 6 percent of renal-allograft recipients with skin cancer may die of metastases.

Prophylactic measures, including the daily use of topical tretinoin, enhance the number and function of dendritic cells within the skin, a change seen in association with a decrease in the formation of new skin cancers. In selected patients, the addition of oral retinoids may provide further benefit. However, we have observed acute allograft rejection during the use of high doses of oral retinoids, a problem that may be due to the ability of these agents to induce interferon-γ production, which may play a part in abrogating allograft tolerance. We advocate the use of 13-cis-retinoic acid at a dose of 10 mg every day or every other day as an adjunct to the use of topical tretinoin; adverse effects have not been observed at this dose. In the future, novel topical agents with potent local immune-enhancing effects, such as resiquimod, may prove to be of even greater benefit.

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To the Editor: With regard to the article by Alam and Ratner on cutaneous squamous-cell carcinoma, I would like to draw attention to the depiction of skin carcinogenesis in Figure 1. Actinic keratoses do not begin in the upper layers of the epidermis, but within the basal layer — that is, within the only layer where cells replicate. Suprabasal keratinocytes cannot replicate. Keratinocytes acquire ultraviolet-induced p53 mutations while they are within the basal layer. In conventional immunohistochemical sections, they can be seen in the upper layers as a consequence of upward migration — a feature common to all keratinocytes.

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To the Editor: As a radiation oncologist, I generally see patients with skin cancer of the head and neck, where surgery can be disfiguring. The majority of patients are elderly, and thus do not face the theoretical risk (probably no greater than 1 to 2 percent over a period of 30 years) of a secondary cancer. However, the review article does little to reassure practitioners that radiotherapy is a reasonable and very effective alternative to surgery. A previous review article stated that “radiation therapy maximizes tissue preservation,” that it “is especially advantageous in elderly, debilitated, or other patients at higher risk of surgical complications,” and that it “is most appropriate for lesions at sites where tissue preservation is essential.” Another review article on curative radiotherapy for skin cancers reported a 95 percent rate of local control for eyelid tumors and a 93 percent rate of local control for tumors of the nose. Other studies have reported excellent local control, in excess of 90 percent, with radiotherapy for squamous-cell tumors of the pinna and medial fleshly canthus.

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The authors reply:

To the Editor: We agree with Rook and Shapiro that the prevention of squamous-cell carcinoma in patients who have received a solid-organ transplant is an essential part of management. Topical and systemic retinoids are certain to have an increasing role in tumor prophylaxis in these patients, and we look forward to the development of new topical immunomodulatory agents to treat patients with human papillomavirus-associated and non–human papillomavirus-associated squamous-cell carcinoma.

Cerroni is correct in stating that actinic keratoses begin in the basal layer of the epidermis as a result of p53 mutations induced by ultraviolet radiation. We tried to simplify this concept in our diagram, but unfortunately, the cells with dysfunctional p53 genes are shown too high in the epidermis. The abnormal cell population should instead be shown initially in the basal layer. After ultraviolet radiation, these cells undergo clonal expansion into the upper portions of the epidermis, instead of exhibiting downward growth.

We disagree with Pollock’s assertion that our article...
“does little to reassure practitioners that radiotherapy is a reasonable and very effective alternative to surgery.” In fact, we state that radiation as a primary treatment “may provide favorable functional and cosmetic results” for properly selected patients with squamous-cell carcinoma and that radiation may be used in combination with other types of therapy to treat aggressive or recurrent lesions. It is important to note that nonmelanoma skin cancer, which is discussed in a previous review article, consists principally of basal-cell carcinomas. Although radiation therapy may be useful to treat primary basal-cell carcinomas in elderly or debilitated patients or in other patients at increased risk for surgical complications, basal-cell carcinomas and squamous-cell carcinomas have far different rates of metastasis. Although both populations of tumors may become more aggressive if they recur after radiation therapy, recurrent squamous-cell carcinomas carry a much greater risk of metastasis than recurrent basal-cell carcinomas and are also associated with a higher mortality rate.²

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Sterile Cerebrospinal Fluid Ascites and Chronic Peritonitis

To the Editor: Sterile ascites after ventriculoperitoneal shunting is rare and usually of unknown cause.¹ We describe a patient in whom an inflammatory reaction to silicone tubing used in the creation of a shunt was a possible cause of sterile ascites.

A 28-year-old woman presented with abdominal distension of three months’ duration. She had undergone ventriculoperitoneal shunting at six months of age for hydrocephalus and subsequently required multiple revisions and replacements of silicone–elastomer shunts. She had no history of shunt infection or of abdominal or pelvic infection or surgery. She took valproic acid and carbamazepine for seizures. The results of routine blood and urine tests were normal. Computed tomography of the abdomen and pelvis showed extensive ascites. Paracentesis revealed clear fluid with 150 leukocytes per cubic millimeter (95 percent mononuclear cells) and a protein level of 2.8 g per deciliter; cytologic examination showed no malignant cells. The serum–ascites albumin gradient was 2.5 g per deciliter. No organisms grew in cultures of ascitic fluid. The results of abdominal ultrasonography, echocardiography, and a liver biopsy were normal.

Despite diuretic therapy, the patient required multiple therapeutic paracenteses, with a total of 18 liters drained over a period of six months. Laparoscopy revealed extensive abdominopelvic adhesions, numerous tiny nodules on the visceral and parietal peritoneum and inferior surface of the liver, and a fragment of a shunt tube. The laparoscopist extracted the fragment and removed 5 liters of ascitic fluid. Biopsy specimens of the peritoneum revealed lymphohistiocytic nodules and fibrosis (Fig. 1), but no polarizing material was found and no microorganisms were identified by auramine and Gomori’s methenamine silver staining. Despite therapy with prednisone (60 mg daily for four weeks), the patient’s ascites recurred. After she stopped taking the drug, the peritoneal catheter was removed and a ventriculoatrial shunt was placed. Within two weeks, her abdominal distention disappeared. No ascites was evident on ultrasonography one and a half years later.

Impaired absorption of cerebrospinal fluid across an inflamed peritoneum has been proposed as the cause of cerebrospinal fluid ascites. Diversion of cerebrospinal fluid from the abdomen is an effective treatment.¹ A patient from Spain with pathological features similar to those in our patient has been reported.² Silicone and its constituents do not cause specific immune responses,³ but silicone shunts can degrade over time and elicit nonspecific tissue inflammation.⁴

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Figure 1. Biopsy Specimen of the Parietal Peritoneum, Showing a Lymphohistiocytic Nodule (N) and Fibrosis (F) (Hematoxylin and Eosin, ×100).

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