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Long-Term Complications of Laparotomy in Hodgkin's Disease

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Objective

The authors determined the incidence of complications in 133 patients who had undergone staging laparotomy with splenectomy before treatment for Hodgkin's disease (stages I–IV).

Methods and Materials

Medical records were reviewed, and the patients or their relatives were interviewed. Median follow-up after laparotomy was 15.7 years (range = 2.5–28 years).

Results

Ten episodes of overwhelming postsplenectomy infection (OPSI) were documented in nine patients (6.8%). None of 25 patients who received pneumococcal vaccine before splenectomy developed OPSI. Patients with advanced (stages III–IV) or recurrent Hodgkin's disease were at higher risk of OPSI than those with early disease, and those who received combined modality oncologic therapy were at greater risk than those receiving less intensive treatment. Surgical complications included small bowel obstruction in 13 patients (9.8%), necessitating repeat laparotomy in 9 patients (6.8%), atelectasis in 17 patients, abscess in 3 patients, and 1 wound dehiscence. No deaths occurred as a result of surgical complications. Causes of death in the 29 patients who died included Hodgkin's disease (12 patients), acute treatment-related morbidity (1 patient), leukemia (5 patients), bone marrow failure (3 patients), solid malignancy (2 patients), intercurrent disease (4 patients), unknown causes (1 patient), and OPSI (1 patient).

Conclusion

With presplenectomy pneumococcal vaccination and modern surgical techniques, the long-term risks of laparotomy with splenectomy are acceptable if knowledge of the pathologic extent of abdominal Hodgkin's disease would alter treatment regimens.

Recently, there has been interest in reducing the role of staging laparotomy in Hodgkin's disease because of concern over infectious and surgical complications associated with laparotomy. The most serious infectious complication is the development of overwhelming postsplenectomy infection (OPSI), which is heralded by nausea, vomiting, fever, confusion, and unconsciousness, and then rapidly progresses to coma and shock.[1–3] Disseminated intravascular coagulation and hypoglycemia can develop, and bilateral adrenal hemorrhage can be found at autopsy.[1,2,4] Most reported cases occurred before vaccination against pneumococcal organisms was available. The most frequent serious surgical complica-

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tion of laparotomy is the development of small bowel obstruction, usually secondary to adhesions and often necessitating repeat laparotomy. Other surgical complications include postoperative infections and wound dehiscence. Death as a result of surgical complications is rare (0.4%).[5,6]

Laparotomy findings can be predicted from clinical findings and diagnostic imaging in only small subsets of patients.[7] In addition, the pathologic or laparotomy stage differs from the clinical stage in 25% to 45% of patients undergoing laparotomy. Finally, the therapeutic cost of uncertainty regarding the presence and extent of abdominal disease may be substantial (e.g., the addition of two to six cycles of chemotherapy to the treatment regimen). Before laparotomy is eliminated from the staging of patients with Hodgkin's disease because of concern over potential infectious and surgical complications, the risks in the current era, in which many infectious complications can be avoided by appropriate prophylaxis, must be reevaluated.

This study examined the incidence of OPSI, other serious infections, and surgical complications after laparotomy in 133 patients treated for Hodgkin's disease at the University of Florida.

METHODS AND MATERIALS

All patients with Hodgkin's disease who underwent staging laparotomy with splenectomy and were treated with curative intent at the University of Florida between October 1964 and July 1989 were studied (analysis date, March 1992). One hundred forty patients were identified, but seven who were lost to follow-up after 6 to 9 years of observation with no record of complications were excluded from analysis. The remaining 133 patients were included in the study.

The current medical records of all patients were reviewed. In addition, 93 patients were interviewed personally, and close relatives of an additional 3 patients were interviewed. In eight patients who had no personal interview, medical records were available with more than 11 years of follow-up after laparotomy. In addition, the medical records of the 29 patients who died were reviewed. The median follow-up was 15.7 years (range = 2.5–28 years).

The patients' median age was 24 years. The male-to-female ratio was 2:1, with a preponderance of male patients in the younger age ranges. The majority of patients (95%) had stage I, II, or III disease, with approximately equal numbers of patients in each stage (29%, 34%, and 32%, respectively). Only seven patients (5%) had stage IV disease. Ninety-one patients (68%) were treated with radiotherapy alone and 42 patients (32%) were treated with chemotherapy and radiation therapy. As expected, patients with less advanced disease were more likely to receive radiotherapy alone, and those with advanced disease were more likely to receive combined modality treatment (Fig. 1).

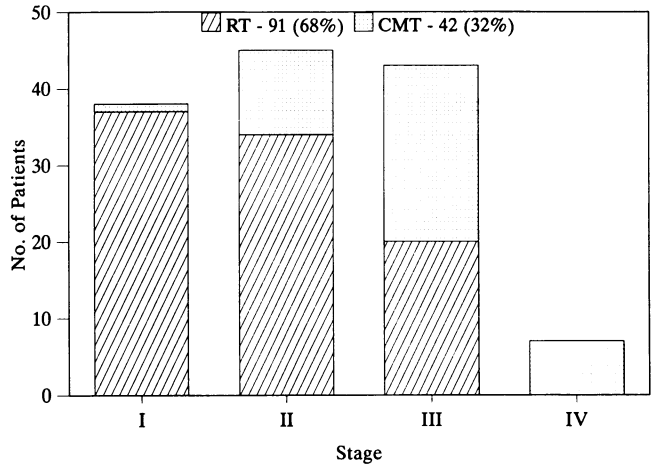

Figure 1. Stage and treatment (n = 133).

During interviews, patients were questioned concerning the occurrence of infections and surgical complications, such as small bowel obstruction, postoperative infections, and wound dehiscence. In addition, each patient's vaccination history, with regard to pneumococcal, *Haemophilus influenzae,* and *Neisseria meningitidis* vaccinations, was ascertained. Medical records from the University of Florida and outside institutions were used to confirm data obtained from the patient interviews. In addition, hospital discharge summaries, laboratory data, and progress notes were obtained to document laparotomy complications.

For the purpose of this study, OPSI was defined as a microbiologically documented meningitis or septicemia occurring acutely in previously nonfebrile and noninfected persons, in the absence of severe myelosuppression.[8] "Other serious infections" were defined as pneumonia or other infections requiring hospitalization that did not fit the criteria for OPSI.

RESULTS

OPSI

Ten episodes of OPSI in 9 patients were observed, representing an incidence of 6.8%. Six of the ten episodes involved organisms associated classically with postsplenectomy infections (Table 1), including four cases caused by *Streptococcus pneumoniae* and two cases caused by *H. influenzae.* The remaining four OPSIs involved organisms not associated typically with postsplenectomy infections. The only OPSI mortality resulted from one of these nonclassic infections.

Table 1. OPSI ORGANISMS

Infection	Patients	Comment
Classic		
S pneumoniae	4	
H influenzae	2	One occurred 4 months before diagnosis of "extensive lung cancer"
Other		
Klebsiella	1	In patient taking prednisone for idiopathic thrombocytopenia
Cryptococcus	1	Postchemotherapy for recurrent disease
DF/0-2	1	Gram-negative organism cultured from dog's mouth
Pseudomonas	1	Iatrogenic
Total	10	

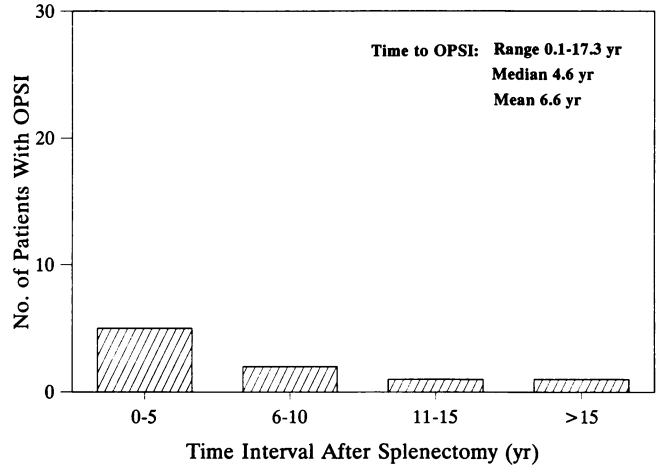

Figure 2. Time interval between splenectomy and OPSI. Ninety-five per cent of patients had a minimum 5-year follow-up, 78% of patients had follow-up for a minimum of 10 years, and 56% of patients had follow-up for a minimum of 15 years.

None of 25 patients who received pneumococcal vaccine before splenectomy developed OPSI. However, 5 of 44 (11%) patients who were vaccinated after splenectomy developed OPSI. Four of 64 (6%) patients who did not receive pneumococcal vaccine developed OPSI. In addition, there were six documented cases of pneumococcal pneumonia in patients other than those who developed OPSI. Five of six patients who developed pneumococcal pneumonia were not vaccinated before splenectomy.

Patients with more advanced or recurrent disease and those who received more aggressive therapy appeared more likely to develop OPSI. Specifically, only 3 of 83 (3.6%) patients with stage I and II disease developed OPSI, whereas 4 of 43 (9.4%) patients with stage III and 2 of 7 (28.6%) patients with stage IV disease developed OPSI. Twelve per cent of patients in this series who ultimately developed recurrent disease developed OPSI compared with 5% of the patients who never developed a recurrence. Similarly, 12% of patients who received combined modality therapy developed OPSI, compared with 4% of patients treated with radiotherapy alone.

In each of the nonclassic OPSIs and in one of the *H. influenzae* OPSIs there was a significant confounding variable that may have predisposed the patient to infection. Of the four nonclassic OPSIs, one patient developed *Klebsiella* sepsis while on prednisone therapy for idiopathic thrombocytopenia purpura. Another patient developed cryptococcal meningitis immediately after completing chemotherapy for recurrent Hodgkin's disease. A third patient, whose Hickman catheter was flushed inadvertently with a nonsterile saline solution, subsequently developed a near-fatal *Pseudomonas* sepsis. A fourth patient suffered a gram-negative sepsis caused by an organism (DF/0–2) cultured subsequently from his dog's mouth. Finally, an OPSI caused by *H. influenzae* occurred in a patient who was diagnosed with extensive lung cancer 4 months after the infection.

The time interval between splenectomy and the first episode of OPSI ranged from 0.1 to 17.3 years, with a median of 4.6 years. Five of nine patients who developed OPSI did so within the first 5-year interval immediately after splenectomy (Fig. 2). In addition, the number of patients developing OPSI decreased in the second, third, and fourth 5-year intervals after splenectomy, suggesting that the first 5 years after splenectomy may be the period of highest risk for developing OPSI.

Other Serious Infections

Other serious infections observed in this study include 26 episodes of clinical pneumonia in 23 patients (Table 2). The organisms responsible for pneumonia are not

Table 2. OTHER SERIOUS INFECTIONS

Infection	Patients	Episodes
Pneumonia*	23	28
Associated Condition		
Postsurgical (nonlaparotomy)	4	
Immunosuppression	8	
Otherwise healthy	14	
Septicemia	2	2
Tinea pedis	1	
Postoperative	1	
Other†	5	7

* Organism encapsulated, 7; nonencapsulated, 7; unknown, 14.
† Pharyngitis, 1; cellulitis associated with anal cancer, 1; fungal infection associated with chemotherapy, 1; herpes zoster, 4.

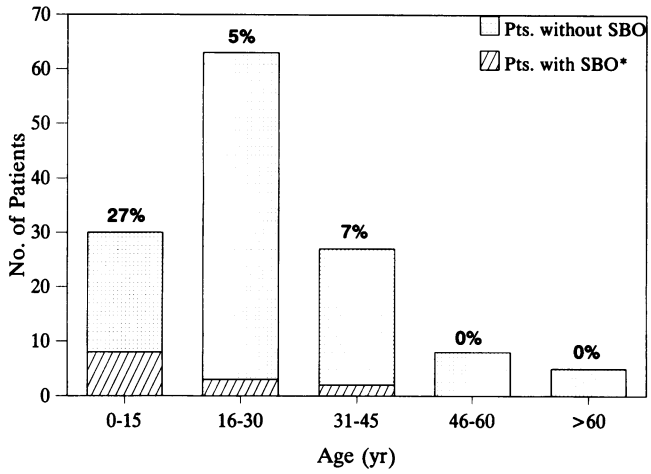

Figure 3. Incidence of small bowel obstruction.

known because most patients were treated empirically with antibiotics appropriate for the most common causes of pneumonia. Fourteen of the pneumonias occurred in otherwise healthy patients. Eight patients were immunosuppressed when they developed pneumonia. Four episodes occurred postoperatively after another operation after laparotomy for Hodgkin's disease. Also, two episodes of non-OPSI septicemia were documented, and seven other miscellaneous infections were observed.

One episode of gram-positive sepsis, thought to have occurred as a result of a complicated tinea pedis infection, responded readily to antibiotic therapy. However, the second non-OPSI sepsis was more complicated and ultimately caused the patient's death. The patient had been treated with chemotherapy for several months for recurrent Hodgkin's disease when he went to the hospital with symptoms clinically consistent with *Pneumocystis carinii* pneumonia. The patient underwent left-sided thoracotomy with lung biopsies, but *P. carinii* was not demonstrated. Postoperatively, the patient's respiratory condition deteriorated and intubation was necessary. After a complicated hospital course lasting 3 weeks, blood cultures demonstrated *Pseudomonas aeruginosa.* Postmortem blood cultures revealed *Klebsiella* also.

Surgical Complications

No deaths occurred as a result of surgical complications. Small bowel obstruction, the most serious surgical complication, occurred in 13 patients (9.8%). Four patients were treated nonoperatively, whereas 9 patients (6.8%) required repeat laparotomy. Atelectasis occurred in 17 patients (12.8%), non-OPSI sepsis occurred in 2 patients (1.5%), and abscess occurred in 3 patients (2.2%) (two with suture abscesses, 9 and 17 months postlaparotomy, and one with a subdiaphragmatic abscess 3 weeks postoperatively; in each case, culture of material from the abscess cavity revealed *Staphylococcus saprophyticus*).

The frequency of small bowel obstruction varied inversely with age at the time of laparotomy. Twenty-seven per cent of patients who were 15 years of age or younger at laparotomy developed small bowel obstructions, compared with only 5% of patients between 16 and 30 years of age and 7% of patients between 31 and 45 years of age. No patient older than 45 years at laparotomy developed a small bowel obstruction (Fig. 3).

Mortality

Twenty-two per cent of the patients in this study have died. The causes of death are shown in Table 3. No deaths resulted from surgical complications. The single death from OPSI occurred in a patient who underwent laparotomy at age 62 for stage IIA Hodgkin's disease and was treated with radiotherapy to the mantle, paraaortic nodes, left preauricular nodes, splenic pedicle, and pelvic nodes. She was not vaccinated against common OPSI organisms before splenectomy and was on prednisone therapy for idiopathic thrombocytopenia purpura at the time of the OPSI, 10.25 years after laparotomy. The fatal OPSI was a *Klebsiella* sepsis and concurrent *Pseudomonas* pneumonia, neither of which is considered a classic postsplenectomy infection.

The most common cause of death was active Hodgkin's disease (12 patients). A disseminated cytomegalovirus infection, occurring during chemotherapy, caused the only acute treatment-related death. Eleven patients died of possible long-term treatment-related causes. Five patients died of leukemia, all of whom had received at

Table 3. CAUSE OF DEATH IN PATIENTS WHO HAD LAPAROTOMY WITH SPLENECTOMY

Cause	Patients	Total Deaths (%)	All Patients (%)
OPSI	1	3	<1
Hodgkin's disease/treatment	13	45	10
AML/leukemia*	5	17	4
Bone marrow failure	3	10	2
Solid malignancy	2	7	2
Intercurrent disease	4	14	3
Unknown	1	3	<1
Total	29		22

* Associated with MOPP chemotherapy.

Two patients received 3 courses, 1 patient received 6 courses, and 2 patients received >10 courses.

Table 4. RISK OF OPSI AFTER SPLENECTOMY FOR HODGKIN'S DISEASE

	Patients	Patients with Serious Infection	Patients Dead of Serious Infection
Collected series, 1972*[28]	934	16 (<2%)	6 (<1%)
NCI, 1975[29]	92	6 (<7%)†	3 (3%)
CCSG, 1976[10]	200	18 (9%)	8 (4%)
Stanford, 1982[22]	146	16 (11%)	<4 (<3%)
IHDCS, 1984[25]	234	4 (1.7%)	0 (0%)
University of Chicago, 1985[30]	239	2 (<1%)	1 (<1%)
Bologna, 1986[8]	342	5 (1.8%)‡	3 (1%)
JCRT, 1988[31]	315	8 (2%)	2 (<1%)
UF, 1992	133	9 (6.8%)§	1 (<1%)

* Collected series from 12 institutions.
† Four of 6 episodes after relapse.
‡ Granulocytopenic with recurrent disease.
§ No OPSI in patients given presplenectomy pneumococcal vaccine; 5 cases in patients with other risk factors.

least three cycles of MOPP (mechlorethamine, vincristine, procarbazine, prednisone) chemotherapy at some point in treatment. These patients developed leukemia 1.5 to 7.5 years (mean 4.5 years) after completing chemotherapy. Three patients died of bone marrow failure and two died from solid malignancies.

In one patient, the cause of death could not be determined precisely; however, he had advanced Hodgkin's disease (stage IIB) and had undergone chemotherapy and radiation therapy for multiple recurrences.

DISCUSSION

Overwhelming postsplenectomy infection was first described in children. Although it has been reported more frequently in children than in adults, it can occur at any age.[1,9] In a review of 4846 pediatric and adult patients who had splenectomy for trauma, malignancy, and other causes, the crude frequency of OPSI was estimated to be as high as 3.9%.[6] However, in children who had splenectomy for Hodgkin's disease, the crude frequency of OPSI has been estimated as high as 10%.[10-12] The 6.8% incidence of OPSI observed in this patient population is consistent with other reports of patients undergoing laparotomy before the routine use of prophylactic, presplenectomy vaccination (Table 4). The infecting organism in OPSI is usually *S. pneumoniae,* but *N. meningitis, H. influenzae,* B-hemolytic streptococci, *Escherichia coli,* and other organisms also have been found.[1,4,13] The pathophysiology of OPSI is not understood completely; however, removal of the spleen impairs humoral responsiveness and can modify production of specific antibodies to microbial antigens. In addition, in Hodgkin's disease, both cell-mediated and humoral immune mechanisms are impaired.[14] Also, patients who have received chemotherapy often show decreased serum Immunoglobulin M levels,[14,17] and may, therefore, be at increased risk for developing OPSI. Six of the episodes in this series involved organisms associated classically with OPSI. In five of the patients who developed OPSI, including all four cases not associated with classic organisms, there were factors in addition to asplenia that may have predisposed the patients to infection.

Several forms of OPSI prophylaxis are available. Oral penicillin has been used for many years, particularly in children, who are believed to be at an increased risk of developing OPSI. In addition, vaccinations against several commonly involved organisms have recently become available. Pneumovax 23 (Merck, Sharp & Dohme, West Point, PA), which was first marketed in 1977, offers protection against 90% of frequently observed pneumococcal serotypes. In 1988, the Pedvax-HIB (Merck, Sharp & Dohme, West Point, PA) became available, which affords protection against *H. influenzae* type B and *N. meningitidis.* The HibTITER (Praxis Biologics, Rochester NY), a vaccine against *H. influenzae* type B and *Corynebacterium diphtheriae,* became available in 1990.[18] Most cases of OPSI occurred in patients who were treated before the development of Pneumovax 23 (Table 4). Vaccinations against *S. pneumoniae, N. meningitidis,* and *H. influenzae* should be done as early (before splenectomy) as possible to allow time for antigen presentation and adequate antibody production within the spleen.[19-21]

Overwhelming postsplenectomy infection did not occur among the 25 patients in this series who received Pneumovax 23 before splenectomy; however, 10.4% of patients who did not receive Pneumovax 23 developed OPSI. In addition, 5% of patients who were given Pneumovax 23 after splenectomy developed OPSI, suggesting little, if any, efficacy for initial postsplenectomy vaccination (Table 5). None of the patients in this series received *H. influenzae* or *N. meningitidis* vaccinations before

Table 5. COMPLICATIONS OF STAGING LAPAROTOMY

Pneumovax Administration	Patients Developing OPSI/ Number Having Splenectomy
Before splenectomy*	0/25 (0%)
Postsplenectomy	2/41 (5%)
None	7/67 (10.4%)

* Stages I and II, 15; stages III and IV, 10.

splenectomy. Although prophylactic antibiotics also may protect against OPSI, their use may lead to the development of resistant organisms. In addition, their efficacy depends on compliance by patients. Only 28 patients in this series used prophylactic antibiotics for the 2 years after splenectomy. Among this group, there were four episodes of OPSI and six other serious infections. Some of these patients, however, may have been treated with antibiotics after developing infections. Donaldson and Kaplan[22] agree with the results of this study that patients with advanced or recurrent disease and those treated with combined modality therapy may be at higher risk for developing OPSI. These high-risk patients might benefit from aggressive use of prophylactic antibiotics, in addition to routine vaccinations, both before and after splenectomy, although the role of postsplenectomy revaccination is undetermined.[18]

It is not clear why the first 5 years after splenectomy is a high-risk period for the development of OPSI. Although OPSI sometimes occurs more than 5 years after splenectomy in patients with no other apparent risk factors, occurrence is more likely shortly after the first treatment or during treatment relapse.[23,24]

Other serious infections were relatively common, but resulted in no mortality. Because of the immunocompromised state of this patient population, it is difficult to derive any meaningful conclusions about the relationship between other serious infections and splenectomy.

Surgical complication did not cause any deaths. Repeat laparotomy for small bowel obstruction was required in 6.8% of patients. This rate is consistent with previous reports of a 1% to 10% incidence of small bowel obstruction.[25-27] Patients younger than 15 years of age at the time of laparotomy appeared to have a higher risk of developing small bowel obstruction, possibly as a result of more aggressive staging laparotomy protocols.[6] Postoperative infections were uncomplicated and responded readily to antibiotics.

Only one of nine patients developing OPSI in this series died, a fatality rate considerably lower than the 50% rate reported in 1975.[29] This may reflect a heightened awareness of the risk of OPSI among physicians over the past 20 years or better management of OPSI.

With the routine use of presplenectomy vaccination, OPSI has not occurred. If knowledge of the presence or pathologic extent of abdominal Hodgkin's disease would effect treatment recommendations, concerns about infection or surgical complications should not preclude traditional staging laparotomy with splenectomy.

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Discussion

DR. RICHARD G. MARTIN (Houston, Texas): I was interested in staging laparotomies because when we first started doing them, we did them for two reasons. One was that we wanted to stage the disease, and, secondly, if possible, to give as little x-ray therapy to the abdomen as possible. I have always been an advocate of one who likes to stay away from x-ray therapy to the abdomen if possible. And we have found that staging laparotomy did help in staging the disease. We found that around 34.5% changed from a stage I and II to a stage III. Also, we were able, thus, to keep from doing as much x-ray therapy as possible to the abdomen. There were complications, however, and Dr. Copeland has stressed those. I agree with all of them except that we did not seem to have as many obstructions as they did, and I cannot remember reoperating on any patient for obstruction except one that had had radiation and later required several operations for obstruction and finally ended up being a home hyperalimentation patient. In 1982, Dr. Stanley Wilson, when he was a fellow at Anderson, he reviewed all the splenectomies on our cancer patients. And the greatest number, of course, was in the Hodgkin's group. We found that approximately 91% did well at the time of surgery; however, we did develop some chronic infections, we did have subphrenic abscesses which required draining, and so forth. We did not have any deaths except one which was about 5 to 6 years post-surgery, and that was in a stage IV-B patient. And that was an acute episode of a patient dying within approximately 48 hours. So all in all, I think that the staging laparotomies have been very useful, and I think they have been worthwhile and that the complication rate is not that bad. I do agree that with the vaccines we have and the ways of caring for respiratory problems should be emphasized. And I also emphasize that the vaccine has to be given at least 2 weeks preoperative or it does very little good. I went down to the x-ray therapy department at Anderson, and also the hematology department to see how things were going, since I have not done laparotomies lately. And I found out that starting in 1988, they no longer were doing laparotomies. They are staging the patients with lymphangiography and CT scan of the upper abdomen. As you know, the lymphangiograms will not show you any disease above L-2, and that's where the laparotomies were so important. They are now treating all patients with radiotherapy and chemotherapy to the mediastinum at the upper abdomen unless on lymphangiogram they find nodes below L-2, and then they will radiate them. I think it will be very interesting when they get a good series to compare with the laparotomies and see what the outcome is and what the complication rate is. Of course, in this way they do not do splenectomies, and maybe that will make a difference. That will have to be decided at a later date. I think this has been a very excellent paper and a very enjoyable paper, and I think it is a very timely paper, and it's one that we need to adhere to, because staging laparotomies is not a benign procedure.

DR. ROBERT M. BEAZLEY (Boston, Massachusetts): I want to congratulate the Gainesville group on an important and well-presented study. I rise to make some comments about the acute effects of splenectomy. One of my associates, Dr. David McAneny, recently reviewed 101 splenectomies that had been done at Boston University, primarily for hematologic diseases but also a few for cysts and things of that sort, but none for trauma. And out of this group he found that 14 patients had other procedures done at the same time that the splenectomy was carried out affecting the GI tract, mostly appendectomies or cholecystectomies. And of those 14 patients, 4 had major complications of intra-abdominal abscess and 2 of them went on to die. If you look at the other 87 patients who did not have any sort of inadvertent or poorly planned concomitant surgery, only 1 of those patients had an abscess. So we have adopted a policy of not doing other surgery at the same time that we are doing a splenectomy, particularly for hematologic disease. I wonder if any of your patients had complications, when other types of surgery—i.e., cholecystectomy or appendectomy—were performed concomitantly?

DR. J. ALEX HALLER, JR. (Baltimore, Maryland): The authors, I think, have convinced me and, I suspect, you, that if prophylactic vaccination is used before the splenectomy, this greatly decreases the chances of post-operative infection. In their manuscript, they go into more detail, and I want to emphasize a few of those points which they could not cover in the short presentation. First of all, I want to re-emphasize that of the ten patients who developed overwhelming post-splenectomy infection, only one patient died. That has not been, of course, true of many of the patients who develop *overwhelming* post-splenectomy infection, and I think this is a tribute to the very fine care these patients have received in Gainesville. But not all patients undergoing splenectomy will have that advantage in a major medical center where there is such fine surveillance of their patients. And so there is the continuing concern and risk to those patients. I'd like also to emphasize that none of the 25 patients who received pneumococcal vaccine and