Splenectomy for Primary and Recurrent Immune Thrombocytopenic Purpura (ITP)

Current Criteria for Patient Selection and Results

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Of 565 patients with thrombocytopenia admitted to Duke University Hospital between 1975 and 1985, 100 had splenectomy. Ninety-eight patients had failed chronic immunosuppressive therapy and three patients had acute intracranial bleeding or total absence of platelets in the peripheral blood smear, and had urgent splenectomy. At primary splenectomy, accessory spleens were identified and resected in 18% of patients. There was no operative mortality. Fifty-eight patients had an excellent response to splenectomy and their steroids were tapered off within 3 weeks. Thirteen patients had a poor response to primary splenectomy of whom eight remitted spontaneously and five required accessory splenectomy resulting in complete remission in three patients. Twenty-nine patients were considered nonresponders, 25 of whom had radionuclide scanning for accessory spleens. Seven of these patients had accessory spleens identified but only four consented to accessory splenectomy. In three of the four patients, a complete remission was achieved. Neither platelet antibody titers nor measurements of platelet survival or turnover predicted platelet response to splenectomy. However, immune thrombocytopenic purpura (ITP) in older patients was significantly less likely to respond to splenectomy. These data support continuing use of splenectomy in selected patients with ITP and an aggressive search for accessory spleens in patients who relapse since they are easily localized at operation by hand-held isotope detector probe.

THE DEMONSTRATION IN 1913 that splenectomy benefited some patients with hemolytic anemia led Kaznelson to advocate its use for the treatment of "purpura haemorrhagica" in 1916.[1] By 1926, Whipple[2] could identify 81 patients in the literature who had had splenectomy for immune thrombocytopenic purpura (ITP). Reports of successful cases by Spence[3] in 1928, and by Eliason and Ferguson[4] in 1932, brought the collected experience to 213 patients, and established splenectomy as the only definitive therapeutic procedure for ITP. Although this new mode of therapy became rapidly accepted, the mechanism responsible for the low platelet count in ITP and the efficacy of splenectomy in some of the patients were poorly understood. The leading hypothesis included a decrease in the rate of platelet formation from megakaryocytes because of splenic inhibition of these cells. Others believed that there was an increase in the rate of platelet destruction by the spleen.

An immune mechanism was first suggested by Marino[5] in 1905. Marino produced an antiplatelet antibody by injecting rabbit platelets into guinea pigs. A few years later, Ledingham[6] caused experimental purpura in animals by the administration of antiplatelet antiserums. However, little extension of these fundamental studies into clinical states of thrombocytopenia was made until in 1938, when Evans et al.[7] presented evidence of a thrombocyte agglutinating factor in the serum of patients with ITP. Their theory that a circulating antibody was responsible for the thrombocytopenia of ITP was later proved by Harrington et al.[8] by cross-transfusion between purpuric and normal volunteers. The relationship between circulating antibodies and splenectomy was dramatically established 2 years later by Harrington,[9] who showed that the thrombocytopenic effect on normal recipients given plasma from subjects with ITP was diminished in the absence of a spleen.

It was about this time that glucocorticoids were first demonstrated to be effective in the treatment of ITP.[10] With the introduction of even more powerful immuno-

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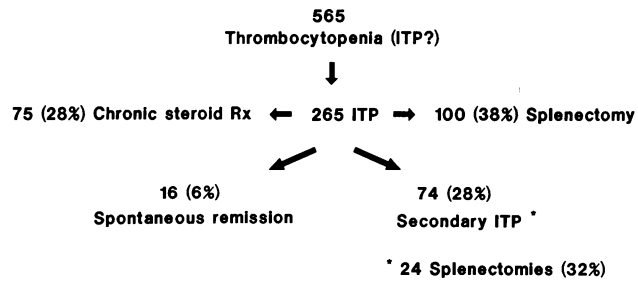

FIG. 1. One hundred patients with primary ITP had splenectomy. Twenty-four patients believed to have primary ITP had splenectomy, but in whom other diseases subsequently developed, were not included in the current study.

suppressive agents, such as azathioprine, cyclophosphamide, and the vinca akaloids, splenectomy was gradually relegated to a secondary role. Recently, hyperimmune globulin has also been demonstrated to be effective in restoring thrombocytosis, albeit transient, in selected patients with chronic ITP.

To assess the impact of this apparently changing role of splenectomy on our practice, we reviewed the experience at Duke University Medical Center. Our specific aim was to document our criteria of patient selection for splenectomy and to analyze the current results.

Materials and Methods

Patients

Between 1975 and 1985, 565 consecutive patients with thrombocytopenia of obscure cause were referred to the Hematology Section at Duke University Medical Center for evaluation and management (Fig. 1). Two hundred sixty-five of these patients satisfied the diagnostic criteria of ITP. In 16 (16%) of these 265 patients, the thrombocytopenic state remitted during a very short period of observation or treatment with low doses of steroids. These 16 patients were young, with an average age of 9 years. Seventy patients (28%) had sustained platelet responses on chronic therapy with steroids and were managed medically. Seventy-four patients (28%) who initially were believed to have primary ITP subsequently developed other diseases. Twenty-four patients in this group had had splenectomy before the onset of the secondary disease.

The remaining 100 patients (38%) identified as having primary ITP were the focus of this study. After evaluating the impact of splenectomy, each patient could be categorized as a *responder* or a *nonresponder.* Response was defined strictly by the patient's ability to sustain a platelet count (measured by the Duke Special Hematology Laboratory) of greater than 150,000/μL after primary and/or accessory splenectomy, and on no medical therapy during the follow-up period. Nonresponders failed to respond to primary and/or accessory splenectomy or relapsed after an initial response. Nonresponders required chronic immunosuppressive therapy to prevent their platelet counts from plunging into dangerously low levels.

Platelet Counts and Platelet Antibody Titers

Platelet antibody titer measurements were paired with their corresponding platelet counts, before and after splenectomy.

Before 1981, the platelet antibody titers were determined by a complement lysis inhibition assay using rabbit antihuman IgG. Since 1981, the antibody titers have been measured by a specific radioimmunoassay using a platelet radioactive antiglobulin test.

For the purpose of our analysis, the platelet antibody titers were standardized by dividing each measured value by the corresponding normal value for the technique of antibody measurement by which it was determined. Among the *responders,* 95 observations were made before splenectomy and 126 were made after operation. Fifty-eight presplenectomy and 123 postoperative observations were recorded in *nonresponders.* Platelet antibody titers in patients with accessory spleens were considered only when the measurements were made before primary splenectomy (preoperative titer) and again after accessory splenectomy (postsplenectomy titer).

The data were then normalized by taking the logarithmic transformation of both the standardized platelet antibody titer and of the corresponding platelet count. The partial correlation and regression coefficients between these two variables were then calculated for each category before and after splenectomy, blocking on individuals for whom there were multiple observations. The probability associated with testing each coefficient against the null hypothesis was calculated using the z-statistic for the partial correlation coefficients and the t-statistic for the regression coefficients. A chi-square test using Fisher's transformation was used to test the equality of the partial correlation coefficients, and the z-statistic was used to test the equality of the regression coefficients.

Platelet Survival and Platelet Turnover

Platelet survival and turnover were determined using autologous platelets labelled with indium III oxyquinoline. The platelet separation and labeling were performed according to techniques originally described by Thakur et al.[11] Blood samples are obtained at 15 minutes, 1 hour, 2 hours, 4 hours, and daily after injection of the radiolabeled autologous platelets. Two milliliters of whole blood from each sample and a standard of the

injectate are counted on the last day of sample collection in an automatic scintillation well counter. Survival is calculated using a computer program that uses the gamma function (multiple hit) model.[12] The recovery of labeled platelets in the circulation is calculated from the activity per milliliter of each sample and from the estimated blood volume.

The platelet turnover was calculated by a standard formula:[13]

$$\text{platelets}/\mu\text{L/h} = \frac{\text{platelet count } (\mu\text{L}) \times 90\%}{\text{life span (hours)} \times \text{initial recovery}}$$

where the 90% figure represents the percentage of platelet recovery in normal subjects without spleens.

Eighteen patients had platelet survival studies, in 12 of whom the initial recovery was available for calculation of platelet turnover. The Pearson Product moment correlation coefficient was then calculated between both the logarithmic transformation of both platelet survival and turnover and the log transformation of the platelet count at 6 weeks after splenectomy. The probability associated with testing each coefficient against the null hypothesis of no linear relationship was then calculated.

Radionuclide Imaging of Accessory Spleens and their Intraoperative Localization Using a Hand-held Isotope Detector Probe

Eleven patients in whom ITP was refractory to primary splenectomy had conventional liver spleen scintigraphy with technitium 99 sulfur colloid to include anterior, posterior, lateral, anterior oblique, and posterior oblique images. If no splenic tissue is identified, a posterior image with increased intensity is performed to determine if a small amount of splenic tissue is present that is not detectable on the routine images. With the introduction of indium 111-labeled autologous platelets in 1981 at Duke University Medical Center, 19 of our patients with no response to splenectomy had an indium 111 radionuclide study. After injection of the radiolabeled autologous platelets, images are obtained with a wide field of view scintillation camera (Siemens LFDV, Siemens Medical Systems, Inc., Iselin, NJ) equipped with a medium energy parallel hole collimator. Symmetric 20% windows around the 173 Kev and 247 Kev photopeaks of indium 111 are used. Anterior, posterior, and left lateral views of the abdomen are obtained.

If an accessory spleen is detected, the patient is taken to the operating room within 12 hours of the radiolabeled platelet injection. A hand-held isotope detector probe is used for intraoperative localization of accessory spleens. The active detector, a cylindrical crystal of thallium-activated sodium iodide, detects gamma photon energies up to 160 Kev, is coupled to a photomultiplier by a light-pipe combination consisting of an inactive sodium iodide crystal and an acrylic coupler section. The active detector, photomultiplier, and electrical networks necessary in connecting the two are contained within a lead shield. Two 20-foot cables, one for high voltage and one for signal, connect the probe to its associated electronics. The probe is gas sterilized and used intra-abdominally during surgery to detect accumulation of indium 111-labeled platelets at the site revealed by the scan. The focus is removed and demonstrated *ex vivo* to have increased activity, whereas activity at the focus site is demonstrated to have returned to background levels. Finally, immediate pathologic confirmation of splenic tissue is obtained by submitting the resected specimens for frozen section examination.

TABLE 1. *Presentation of Immune Thrombocytopenic Purpura, Duke University 1975–1985*

Sign	Percentage of Patients (N = 100)
Easy bruising only	28
Routine platelet count	17
Petechiae, purpura, ecchymosis	14
Bleeding (gum, epistaxis, gastrointestinal, genitourinary)*	41

* Two patients with intracranial hemorrhage had urgent splenectomy.

Results

Demographic

There were 58 females and 42 males with an overall average of 41.4 years (range: 5–84 years). The ratio of blacks to whites was 1 to 4.

Presentation Diagnosis

A history of viral illness could be elicited from 19 patients. Seven patients received diazide, three patients received quinidine, and one patient gave a history of exposure to industrial solvents. The remaining patients had no recent infection or drug exposure that could be implicated in their thrombocytopenic state.

Abnormal bleeding was the most common sign of ITP, occurring in 41% of patients (Table 1).

Easy bruisability occurred in 28% and was associated with purpura, ecchymosis, or petechiae in 14 patients (14%).

In 17% of patients, the diagnosis was uncovered when an incidental complete blood count showed low levels of platelets (Table 1).

In addition to their clinical presentation, the diagnosis of primary ITP was supported by the absence of spleno-

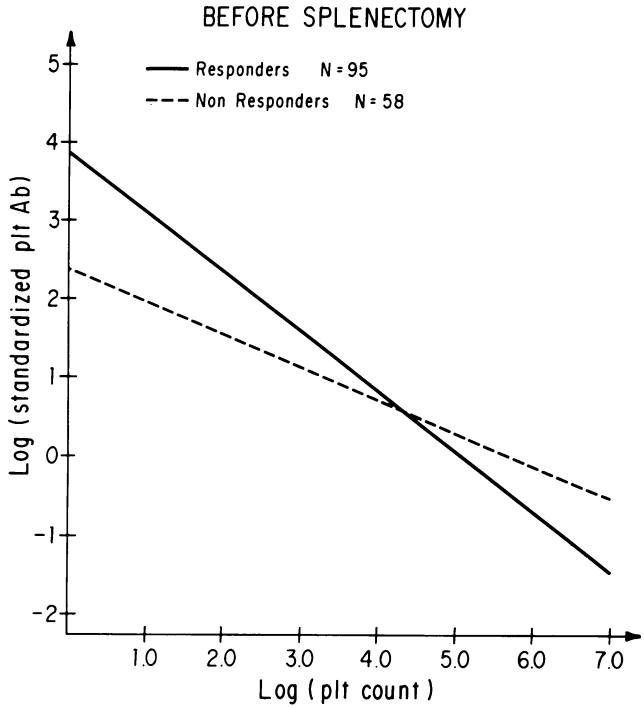

FIG. 2A. Regression lines between log (standardized platelet antibody titer) and log (platelet count) before splenectomy. Although the inverse relationship between these two variables is strongly negative ($p < 0.05$), there was no difference between responders and nonresponders ($p > 0.05$).

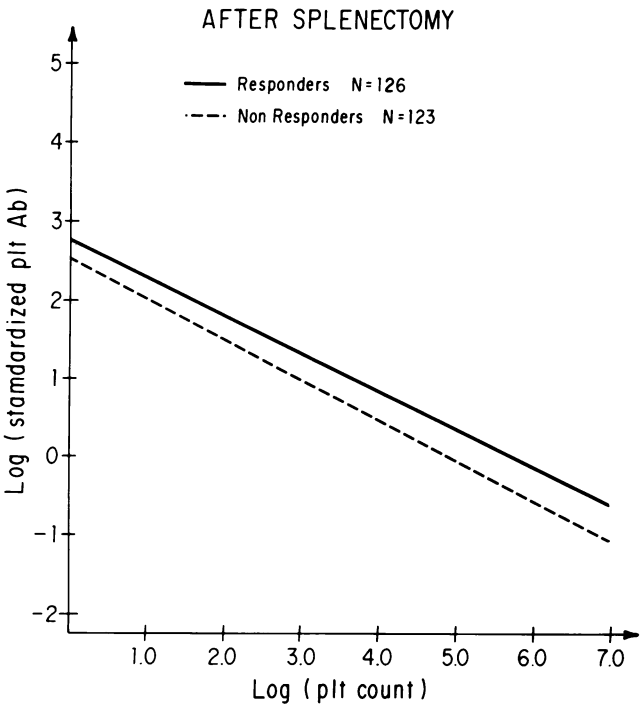

FIG. 2B. Regression lines between log (standardized platelet antibody titer) and log platelet count after splenectomy. Slopes of regression lines remain strongly negative ($p < 0.05$) and are not different from the preoperative values. After splenectomy, the slope of the regression lines are identical between responders and nonresponders.

megaly on physical examination and scintigraphic scans, low platelet counts associated with abnormally high titers of antiplatelet antibody, a bone marrow aspirate showing normal or increased number of megakaryocytes with decreased platelet budding, and normal maturation of the erythrocytic and granulocytic cell lines. Serologic tests were consistently negative for connective tissue disorders in all patients throughout the follow-up period (26–120 months).

Platelet Count and Platelet Antibody Titers

The overall average platelet count of the patients at presentation was 21,000/μL. The regression coefficients relating log platelet count and their corresponding log platelet antibody titers were negative in both responders (-0.77 ± 0.14) and nonresponders (-0.38 ± 0.18) before splenectomy (Fig. 2A). Although these coefficients were not different from each other ($p = 0.09$), they were significantly negative when individually tested against the null hypothesis ($p < 0.05$) (Figs. 2A and 2B).

Before splenectomy, the partial correlation coefficient between log platelet count and log platelet antibody titer for responders was −0.50 and was −0.31 for the nonresponders (Fig. 3). The difference between the two was significant ($p = 0.05$).

Platelet Survival and Platelet Turnover

Platelet survival, which is normally 200–220 hours, was shortened to an average of 61.5 hours in the 34 patients in whom it was measured. Average platelet turnover increased in 2179 platelets/μL/h (N = 1200–1600 platelets/μL/h) in 12 patients in whom it was calculated.

Initial Therapy

All patients represented failures of chronic nonoperative therapy, except for three patients who had urgent splenectomy (Table 2). Emergency splenectomy was advised in two patients with acute intracranial bleeding and in one patient who showed a total absence of platelets in repeated peripheral blood smears.

The average time from presentation and institution of medical therapy to primary splenectomy was 8 months (range: 0.5–96 months) (Table 2).

Fifty-one per cent of patients were unresponsive to prednisone at doses in excess of 60 mg/day. In 35 patients, prednisone was used in combination with other immunosuppressives (vincristine, cytoxan, or azathioprine), either because of the patient's inability to tolerate prednisone in high doses or because the prednisone dosage could not be tapered to lower levels without the platelet count dropping to clinically unacceptable low levels.

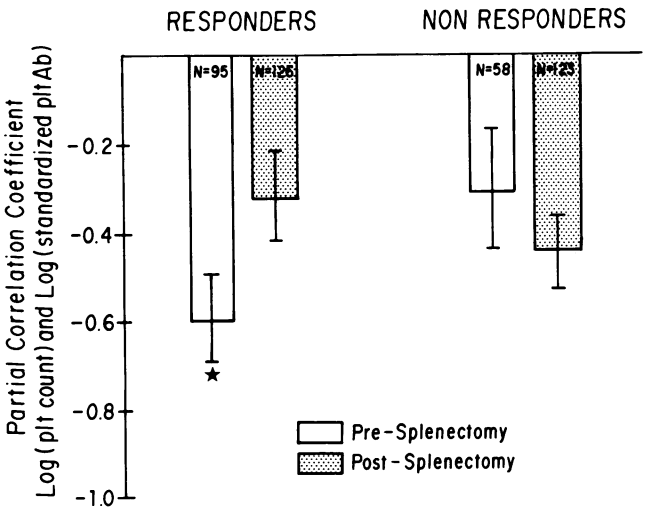

FIG. 3. The partial correlation coefficient between log (platelet count) and log (platelet antibody titer) in the responders before splenectomy was significantly higher (*$p < 0.05$) than in all other categories. The partial correlation coefficient between these two variables was not different in the nonresponders before and after splenectomy ($p > 0.05$).

Eleven per cent of patients had a good response to prednisone in the 20–60 mg/day dose range but unfortunately had severe side effects of steroid therapy or adverse effects of steroids on the patients' other coexisting medical conditions.

Although patients who ultimately responded well to splenectomy had been treated medically on average for a shorter time than had the nonresponders (7 months *vs.* 12 months), this difference is probably due to physicians' reluctance to refer older patients for surgical therapy (Table 2, Fig. 4).

Primary Splenectomy

All 100 patients received preoperative pneumococcal vaccination as well as steroid preparation. In general, the patients received 100 mg of hydrocortisone on the day before operation and approximately 300 mg of hydrocortisone on the day of surgery and the immediate postoperative period. The dosage of steroids was then gradually reduced depending on the patient's platelet response.

In an effort to investigate the possible role of preoperative infusions of intravenous gamma globulin for establishing preoperative thrombocytosis and thus obviate the need for platelet transfusions, we studied six patients. Four patients received 400 mg/kg/day of gamma globulin (IV-IG) on each of 5 days. Shortening the protocol, two patients were given 1000 mg/kg/day for 2 days. All six patients achieved platelet counts in excess of 100,000/μL and did not require perioperative platelet transfusion.

TABLE 2. *Therapy Before Primary Splenectomy, Duke University 1975–1985*

	Therapy No. of Patients				Duration (Months)
	S̄	S + I	S	N	Average (Range)
Responders	39	19	10	3†	7* (0.5–96)
Nonresponders	12	16	1	0	12 (1–74)
Total	51	35	11	3	8 (0.5–96)

* Significantly shorter than in nonresponders. ($p < 0.05$)
† Underwent urgent splenectomy.
S̄ = High-dose prednisone (50 mg) with poor response.
S + 1 = 20–40 mg of prednisone/day and one other form of immunotherapy with poor response.
S = 20–60 mg of prednisone/day with good response but intolerance.
N = No medical therapy before splenectomy.

Fifty-one patients with an average platelet count of 45,000/μL were given platelet transfusions during operation. The remaining 43 patients had an average preoperative platelet count of 83,000/μL on steroids and did not receive platelet transfusions.

The tail of the pancreas was protected during operation and every effort made to remove the spleen intact to avoid the liberation of fragments resulting in splenosis. Careful examination of the gastrocolic omentum, the retroperitoneum along the splenic vessels especially near the hilum, the bowel mesenteries, and the pelvis in the female patients, was performed in all cases. Eighteen patients (18%) had one or multiple accessory spleens at the time of primary splenectomy. Thirteen (72%) of

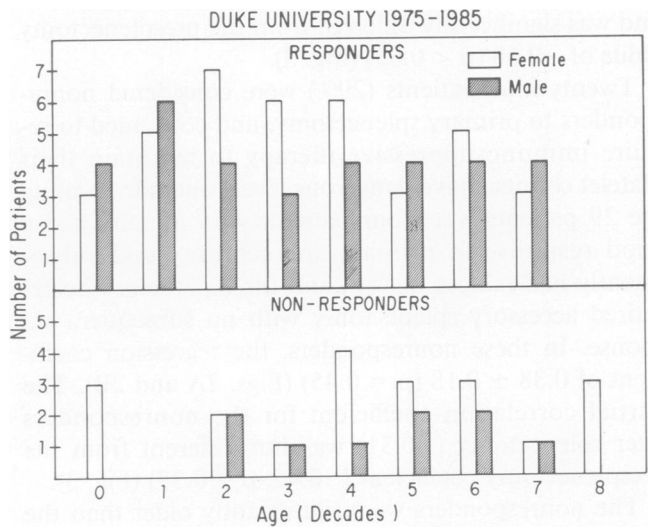

FIG. 4. Age and sex distribution in 100 patients who had splenectomy for ITP. The nonresponders (mean age: 49.3 ± 4.3) were significantly older than the responders (mean age: 38.2 ± 2.5; $p < 0.05$). The nonresponders were predominantly female but the gender differences did not achieve statistical significance ($p > 0.05$).

these accessory spleens were found in patients under 40 years of age.

The average weight of the spleen was 147 g (range: 39–340 g) and no distinctive alterations of their gross architecture were found. Histologic examination revealed an increased number of secondary follicles with large and active center in about 50% of patients. Sinusoidal dilatation in the red pulp was present in most patients.

Outcome after Primary Splenectomy

Seventy-one patients had a good response to splenectomy achieving a platelet count above 150,000/μL while receiving no medication. There were 38 females and 33 males with a mean ± SEM age of 38.2 ± 2.5 years (Fig. 4). Of these patients, 58 had an excellent response to primary splenectomy over a mean follow-up period of 10 months (range: 1–61 months); their steroid regimen was tapered within the first week after operation and they were completely off steroids an average of 2.3 weeks after operation. Another 13 patients had an initial poor response to primary splenectomy; eight remitted spontaneously during medical therapy for an average of 34 months (range: 1–84 months) after primary splenectomy and five had accessory splenectomy with good result in three of these patients who have required no further treatment.

After splenectomy the regression coefficient between the log platelet count and their corresponding log platelet antibody titers for these responders was -0.48 ± 0.15 and was not different from the presplenectomy coefficient of -0.77 ± 0.14 ($p = 0.17$) (Figs. 2A and 2B). However, the partial correlation coefficient was -0.32 and was significantly different from the presplenectomy value of -0.60 ($p < 0.05$) (Fig. 3).

Twenty-nine patients (29%) were considered nonresponders to primary splenectomy, and continued to require immunosuppressive therapy to maintain their platelet counts above dangerous levels. Included among the 29 patients were four patients who initially had a good response to primary splenectomy and subsequently had relapse of ITP, and three patients who required accessory splenectomy with no subsequent response. In these nonresponders, the regression coefficient of 0.38 ± 0.18 ($p = 0.45$) (Figs. 2A and 2B). The partial correlation coefficient for the nonresponders after splenectomy (-0.31) was not different from the presplenectomy coefficient (-0.45, $p = 0.37$) (Fig. 3).

The nonresponders were significantly older than the responders and although they were predominantly female, the gender differences did not achieve statistical significance (Fig. 4).

The Pearson correlation coefficient between the log preoperative platelet survival or turnover and the log postoperative platelet count were 0.017 and 0.33, respectively, which are not statistically significant ($p > 0.05$). Thus, neither platelet survival nor turnover predicted postoperative response of platelet count in these patients.

There was no operative mortality. Two patients who had recovered completely from operation died 3 months after operation, one of generalized sepsis and the second of multiple pulmonary emboli. The operative morbidity rate was 8%, consisting of three patients with subphrenic abscesses (one requiring drainage), one case of upper gastrointestinal bleeding that stopped after the saline lavage, two cases of multiple pulmonary emboli, and one case each of generalized sepsis and perirectal herpes simplex. Both patients with intracranial bleeding recovered completely.

Accessory Splenectomy for Persistent or Recurrent ITP

Of the 29 patients classified as nonresponders, 25 patients had a total of 30 radionuclide imaging studies. Six patients had only a technitium 99m sulfur colloid scan, which identified accessory spleens in three patients. Fourteen patients had only an indium 111-labeled platelet scan, revealing accessory spleens in eight patients. Both types of imaging were used in five patients. The presence of an accessory spleen was questioned on the Tc 99m scan in one patient but was very clearly imaged by the indium 111 scan. A second patient who had an accessory spleen identified by technitium 99m sulfur colloid scan was operated on but had persistent thrombocytopenia after excision of the accessory spleen. An indium 111 scan was performed that identified a second accessory spleen. The patient's ITP remitted completely after the second accessory splenectomy.

Accessory splenectomy for recurrent (5 patients) or persistent (4 patients) ITP was done in nine patients (Table 3). The average interval between primary and accessory splenectomy was 168 months (range: 1–504 months). The accessory splenic tissue was localized during operation using the isotope detector probe in six patients. The accessory spleens ranged in size from 0.5–7 cm in largest dimension. Six of the nine patients (66%) who had accessory splenectomy had complete remission of ITP and are no longer receiving steroids. No mortality was associated with accessory splenectomy but significant morbidity occurred in one patient in whom a left subdiaphragmatic hematoma developed that required surgical drainage.

Discussion

In this study, 58% of patients achieved platelet counts in excess of 150,000/μL within 1 week of operation and were weaned off steroids by the end of the third postop-

TABLE 3. *Accessory Splenectomy: Summary of Cases, Duke University 1975–1985*

Patient #	Primary Splenectomy Age/Sex	Primary Splenectomy Duration of Response (Months)	Accessory Spleen Time from Initial Splenectomy (Months)	Accessory Spleen Spleen Size (cm)	Response*
1	48/F	3	9	1.8	Excellent
2	9/F	72	506	0.6	No response
3	60/F	0	40	2.5	Good
4	34/F	24	72	2.0 (×2)	Relapsed
		0	96	2.0	Excellent
5	27/F	0	1	1.5 (×2)	Excellent
6	20/F	2	156	3.0	Fair
7	25/M	72	108	1.4 (×2)	Excellent
8	47/F	0	180	1.5 (×2)	Fair
9	7/F	360	444	7.0	Good

* Excellent = platelet count >100,000/μL; no steroids. Good = platelet count >100,000/μL; steroids for limited period. Fair = platelet count >100,000/μL; receiving steroids.

erative week. This immediate response rate increased to 71% as some patients who had an initial poor response to splenectomy remitted during follow-up on steroid therapy or responded to accessory splenectomy. This pattern of response is similar to the average complete response rate of 72% reported by others (Table 4). However, patient selection among these series was not uniform. Although none of the patients received steroid therapy before 1951,[3,14–16] most patients who had splenectomy after that date had failed immunosuppressive therapy. In the current series all patients failed intensive immunosuppressive therapy except for the three patients who had urgent splenectomy.

Does presplenectomy response to steroid therapy predict platelet response to splenectomy? Mintz et al.[22] observed a postsplenectomy remission rate of 92% in patients who had responded to steroids before operation and only a 68% response rate in those who had not shown response to preoperative steroids. However, the complete remission rate reported by others among patients who showed preoperative response to steroids ranged from 67–82%[23–25] and was not different from the overall response rate of 56–85% (Table 4). In the current study none of the 75 patients who had a sustained response to immunosuppression and who could tolerate steroids needed splenectomy (Fig. 1).

Although some previous reports suggest that a long duration of medical therapy before splenectomy is associated with poor response,[22,26–28] the current data suggest that the longer duration of medical therapy among the nonresponders reflects a selection bias on the part of primary physicians who were reluctant to refer older patients for surgical therapy. Age was an important predictor of response in the current study as the nonresponders were significantly older than the responders (Fig. 4). These observations concerning the predictive value of age are similar to those previously reported by Coon[21] and DiFino et al.[24] However, age did not appear to be a significant predictor of response in the series reported by Charlesworth and Torrance[29] and by Burger et al.[30]

The selection of patients with immune thrombocytopenic purpura for splenectomy on the basis of the form of disease was recognized very early. Splenectomy was

TABLE 4. *Splenectomy for ITP, Results in 872 Collected Cases*

Series	Year	No. of Patients	Remission (%) Complete	Remission (%) Partial	Failure (%)	Operative Mortality (%)
Spence[3]	1927	101	69 (68)	6 (6)	5 (5)	21 (21)
Wintrobe et al.[14]	1937	73	44 (60)	21 (29)		8 (11)
Evans and Perry[15]	1943	24	14 (58)	7 (29)		3 (13)
Elliott and Turner[16]	1951	68	38 (56)	11 (16)	14 (21)	5 (7)
Meyers[17]	1961	54	46 (85)	2 (4)	4 (7)	2 (4)
Jiji et al.[18]	1973	51	36 (70)	10 (20)	5 (10)	0 (0)
Schwartz et al.[19]	1980	120	106 (88)	3 (3)	6 (5)	5 (4)
Musser et al.[20]	1983	65	50 (77)	9 (14)	5 (8)	1 (2)
Coon[21]	1987	216	156 (72)	56 (26)		4 (2)
Current report	1987	100	71 (71)		29 (29)	0 (0)
Total		872	630 (72)	193 (22)		49 (6)

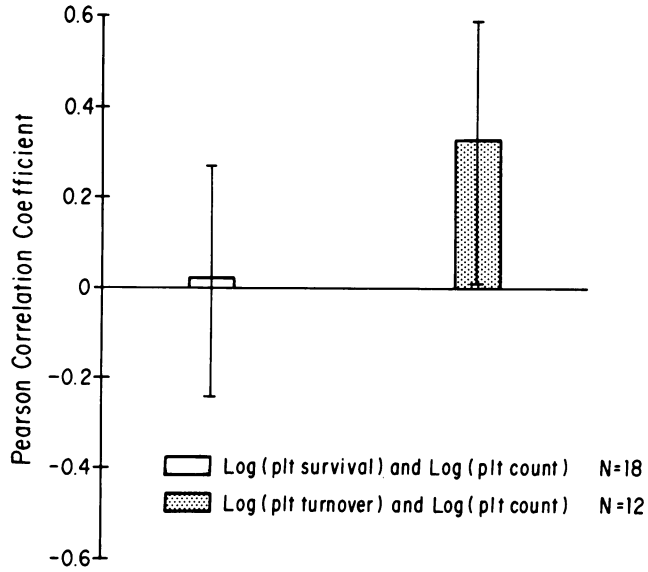

FIG. 5. Pearson correlation coefficients and relationship of preoperative indium 111 platelet survival and turnover to postoperative platelet count. No significant correlation exists between either presplenectomy log (platelet survival) and postsplenectomy log (platelet count) ($p = 0.9$) or presplenectomy (platelet turnover) and postsplenectomy log (platelet count) ($p = 0.3$).

advocated in the chronic form of ITP[2,31] and contraindicated in the acute form.[32] The acute form of the disease is seen most commonly in children and occurs 2–3 weeks after a virus infection. It often remits within 3 or 4 weeks and almost always within 6 months. Sixteen of our patients (6%) with a mean age of 9 years (range: 0.5–65 years) represented this group. The chronic form occurs most frequently in adults. The onset is insidious and is preceded by no infection or prodromes. Although some of our patients who had splenectomy were younger than 15 years of age and had had viral infections, their courses became more of the chronic type, with failure to remit after an average follow-up period of 15 months (range: 5–22 months). On the other hand, some of our adult patients had typical signs of viral illness.

The three patients who had urgent splenectomy deserve comment. Although we were reluctant to subject these difficult patients to urgent operation, their subsequently benign courses are a tribute to modern anesthetic and postoperative management. These early results encourage a continuing cautiously aggressive approach to patients in these desperate circumstances.

Platelet antibody titers failed to predict response to splenectomy as evidenced by almost similar regression lines before and after splenectomy for both responders and nonresponders (Figs. 2A and 2B). These observations confirm the earlier report of Kayser et al.[33] The strong inverse relationship between platelet count and platelet antibody titer in both responders and nonresponders, before and after splenectomy, confirmed the utility of the antibody titer as an adjunct in the diagnosis of ITP.

A correlation between the level of platelet associated IgG and the platelet count in ITP could not be confirmed by Kernoff and Malan[34] and by Kelton et al.[35]

We observed that among the responders the partial correlation coefficient between log platelet count and log antibody titer was significantly lowered by splenectomy. The coefficient among the nonresponders was unchanged by operation and was similar to that of the responders after operation (Fig. 3). An attractive hypothesis is that there is a difference in the rate of extent of clearance of platelets, initiated by the adherence of IgG-coated platelets to the surface Fc (IgG) receptors on tissue macrophages.[36] These receptors may be higher in number or may be better expressed in the spleens of responders. The number of receptors may not be as great and/or as well expressed in the spleen of nonresponders. Splenectomy would thus have little impact in this group of patients.

In newly diagnosed patients with ITP, Kernoff and Malan[34] described a significant correlation between the amount of platelet-bound antibody and the rate of platelet destruction. However, Mueller-Eckhardt et al.[37] could not correlate platelet-bound antibody with platelet survival. Although this relationship could not be examined in our patients, it is well established from our studies and others[38,39] that patients with ITP have low platelet survival. However, our study failed to confirm the value of presplenectomy platelet survival in predicting platelet response to splenectomy (Fig. 5). Moreover, platelet turnover, which reflects thrombopoiesis, ranged from subnormal to high in our patients and also failed to predict response to splenectomy (Fig. 5). Previous work by MacMillan et al.[40] has shown that cultured splenic cells in patients with ITP will synthesize IgG, which binds specifically to megakaryocytes. Other authors have also suggested that impaired thrombopoiesis plays a role in the pathogenesis of ITP.[41,42] This view might be supported by the subnormal range of turnover in some of our patients but is not true in the other patients with high turnovers. Our investigation also confirms that the pattern of presplenectomy platelet sequestration did not predict the outcome of splenectomy. This observation is in agreement with previously published chromium 51 and indium 111 studies, which show no association between the pattern of platelet destruction and platelet counts obtained after splenectomy.[39,43,44]

Although the labeling of platelets with indium 111 oxine has many advantages over the chromium 51 label for the study of platelet kinetics,[45,46] the superior gamma emitting properties of indium 111 allows more accurate

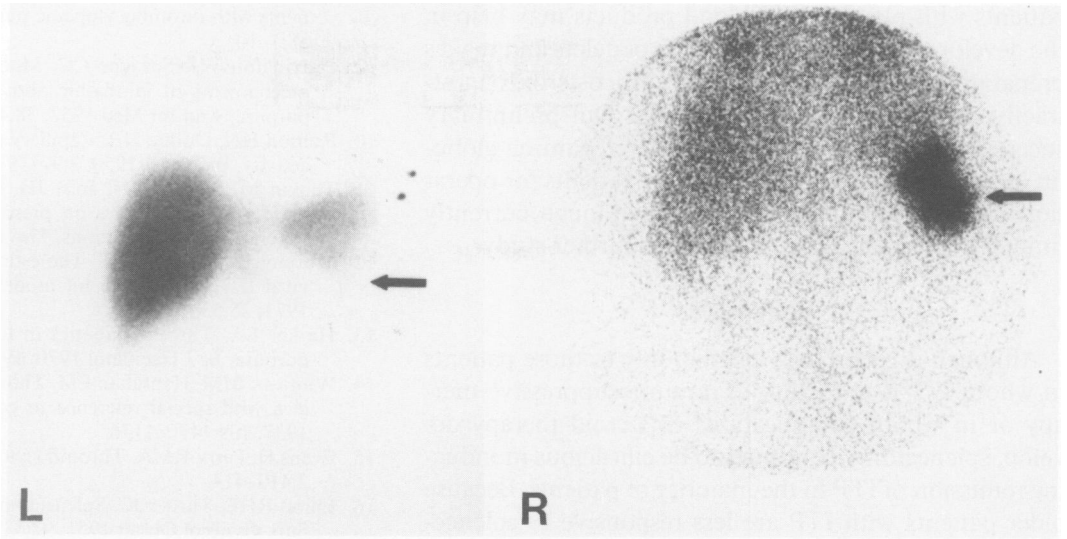

FIG. 6. Technitium 99m sulfur colloid scan (*left*) barely shows uptake in left upper quadrant accessory spleen in this previously splenectomized patient. The indium 111-labeled platelet scan (*right*) of the same patient clearly images the large accessory spleen confirmed at operation.

quantitation of absolute levels of activity within organs by quantitative scanning with the gamma camera.[47,48] This makes indium 111 an invaluable tool in the detection of accessory spleens (Fig. 6). Since the implication of an accessory spleen in the recurrence of ITP was suggested by Finkelstein[49] and the first evidence of its involvement in recurrent ITP by Morrison et al. in 1928,[50] various techniques have been used in its detection, including exploratory laparotomy,[51] thorium dioxide scans,[52] technitium sulfur colloid scans,[53] abdominal ultrasonography,[54] CT scan of the abdomen,[55] labeled RBC,[56] and indium 111-labeled platelet scan.[57] Although each modality enabled the detection of accessory spleens, there are not enough cases to compare one method with another except in one series where Tc 99m sulfur colloid was found to be inferior to CT scan and radiolabeled RBC opsonized with anti-D IgG.[58] We believe that the indium 111-labeled platelet scan offers the advantage of increased sensitivity and the possibility of studying platelet kinetics.

Re-exploration of the abdomen, especially of the left upper abdominal quadrant after initial splenectomy, may be difficult since the accessory spleen may be concealed by fat, adjacent organs, or scar tissue. Even though the location of the accessory spleen is suggested by a preoperative scan, this gives information only about the general location of the tissue. The use of a hand-held isotope detector probe during operation for this purpose was recently introduced by Wallace et al.[59] who used Tc 99-labeled RBC. We could detect accessory spleens as small as 0.5 cm using indium 111-labeled platelet scan and the intraoperative probe, and found another accessory spleen during a second operation in a patient using this method that was previously missed by a technitium 99 sulfur colloid scan.

The high incidence of accessory spleens found in the current study (18%) at the time of primary splenectomy, especially in the younger patients, should encourage a thorough search for accessory spleens and an aggressive approach looking for them in patients who do not respond to primary splenectomy. We are more enthusiastic about this approach because of the successful results in six (67%) of our nine patients and by the good results published by others in a total of 56 patients[51-66] and in whom the response was excellent in 41 patients (73%)[51,53,55,61,63-66] and moderate in the others (27%).[51,52,54,58,62,64-66]

However, an accessory spleen is not the cause of a relapse or poor response in the majority of patients. Although our nonresponders continued to be free of other diseases during their follow-up period, the association of ITP and other diseases should be kept in mind. Nonresponders should be continuously screened. Seventy-four of our patients (28%) (Fig. 1) had secondary ITP. Twenty-four had splenectomy before the primary disease was manifested. Connective tissue disorders and hematologic malignancies accounted for more than half of these cases of secondary ITP. Dameshek found that eight of 51 patients followed after primary splenectomy had definite SLE and two more had probable examples of that disorder.[67] Other reports have indicated the association of ITP with hematologic malignancies,[68-71] pregnancy,[72] hemolytic anemias,[7] and homosexuality,[73] as well as during infections.[74] The induction of thrombocytopenia by drugs such as quinidine has been said to be self-limited after discontinuation of the drug.[75] However, 10 of our patients who received diazide or quinidine progressed to chronic ITP requiring splenectomy.

Although the platelet antibody measured in the different states of secondary ITP may not be the same,[76] these observations tend to suggest that ITP is part of a more complex immune disorder. Transfusion of these

patients with platelets and blood products may help in the development of isoantibodies to platelets and makes preparation for splenectomy with corticosteroids an attractive option in responsive patients. Our preliminary success with intravenously administered gamma globulin in the preparation of some of our patients for operation offers yet another option that, although currently limited by its great expense, deserves further study.

Conclusions

Although it is currently offered only to those patients in whom ITP is refractory to immunosuppressive therapy or in whom complications of steroid therapy develop, splenectomy continues to be efficacious in inducing remission of ITP in the majority of patients. Because older patients with ITP are less responsive to splenectomy, the notion that nonresponders are treated medically for longer periods before splenectomy probably reflects the selection bias of primary physicians who are reluctant to refer older patients for surgical therapy.

Although platelet antibody titer and platelet survival and turnover studies using autologous indium 111-labeled platelets were important adjuncts in the diagnosis of ITP, these tests did not predict platelet response to splenectomy in the current study. However, patients who relapse or have persistent ITP after primary splenectomy should be scanned for accessory spleens using indium 111-labeled platelets. These accessory spleens are easily localized during operation by a hand-help isotope detector probe.

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Discussion

Dr. A. Aufses (New York, New York): Dr. Akwari and his colleagues are to be congratulated for presenting a beautifully documented series of 100 patients operated on for idiopathic thrombocytopenic purpura (ITP) over a 10-year period.

The manuscript that I was privileged to review is replete with extensive, prospectively derived hematologic observations and the discussion section is most complete and superbly written. I recommend its reading to all of you.

I would like to limit my remarks and questions to only one aspect of this very complete review. That is, the role of the accessory spleen in the failure of response to primary splenectomy.

Autopsy studies have shown about a 10% incidence of accessory