The Place of Splenectomy in Haematological Disorders

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SUMMARY

The results of 67 consecutive splenectomies carried out in patients attending the Haematology Clinic at the Johannesburg Hospital between 1965 and 1972 are reported.

Forty patients underwent splenectomy because of the presence of cytopenia due in part at least to hypersplenism. The best results were achieved in 21 patients who were considered to have cytopenia due to a disordered immune mechanism and in whom the spleen was usually normal in size or only minimally enlarged. In addition, satisfactory results were obtained in 17 patients with a large spleen and pancytopenia. In this group the least satisfactory results were recorded in patients with advanced myelofibrosis. The results of splenectomy were also disappointing in 9 patients with lymphoma and other haematological malignancies.

Sixteen diagnostic splenectomies were performed: 11 were done as part of a 'staging' laparotomy, for lymphoma.

Although there was no operative mortality in this study, half the patients suffered complications, and in 16% of them they were severe, being usually the result of haemorrhage and/or infection.

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The frequency with which splenectomy is performed for haematological disorders has been increasing in recent years in most haematology clinics.[1] Hypersplenism, defined as the premature destruction of erythrocytes, leucocytes and/or platelets by the spleen, remains the most common indication.[2] The development of more successful therapeutic regimens for the control of malignancy of the lymphoid and blood-forming tissues has broadened the indications for splenectomy to include many patients with hypersplenism secondary to this type of neoplasia. Recently

splenectomy has also assumed an important place in the initial evaluation or 'staging' of patients with Hodgkin's lymphoma.[3-7] This article records the results of 67 consecutive splenectomies in patients referred by the Haematology Clinic of the Johannesburg General Hospital between January 1965 and April 1972.

PATIENTS AND INDICATIONS FOR SPLENECTOMY

Sixty-seven patients (42 female), their ages ranging between 16 and 74 years (mean 42 years), underwent splenectomy (Table I). Forty-three patients (64%) were suffering from some haematological malignancy. Splenectomy was performed for therapeutic as well as diagnostic indications.

TABLE I. DIAGNOSIS IN PATIENTS UNDERGOING SPLENECTOMY

Diagnosis	No. of patients
Hodgkin's disease	21
Primary immune thrombocytopenia	8
Non-Hodgkin's lymphomas	7
Myelofibrosis	7
Chronic lymphatic leukaemia	5
Primary auto-immune haemolytic anaemia	3
Primary immune thrombocytopenia + haemolytic anaemia	3
Congenital spherocytosis	2
Chronic myeloid leukaemia	2
Disseminated lupus erythematosis	2
Anaemia and splenomegaly (diagnosis uncertain)	2
Red cell aplasia	1
Felty's syndrome	1
Cirrhosis with hypersplenism	1
Multiple myelomatosis	1
Infectious mononucleosis	1

Therapeutic Indications for Splenectomy

In 51 patients the indication for splenectomy was therapeutic. The most frequent indication (40 - 78%) was a reduction in the cell count of one or more elements of the blood (cytopenia). Ten patients underwent splenectomy in an attempt to improve their marrow tolerance to chemotherapy and in 1 the operation was done only to relieve abdominal discomfort caused by the very large spleen. The diagnosis was known before splenectomy in all but 2 patients.

For the purposes of analysis patients with cytopenia were divided into three groups: those in whom cytopenia was considered to be purely on an immune basis; those in whom the spleen was considerably enlarged and splenic pooling of cellular elements was thought important; and a miscellaneous group which included patients with hereditary spherocytosis.

No satisfactory means of identifying platelet antibodies was available to us and kinetic studies were not carried out as a routine. The diagnosis of immune thrombocytopenia was therefore presumptive in any patient with a platelet count of less than 60 000/mm³ (usually <30 000/mm³), normal or increased numbers of megakaryocytes in the bone marrow, and a spleen which was either normal in size or minimally enlarged (weight <250 g) and in whom there was no history of ingestion of drugs likely to cause thrombocytopenia. One additional patient was included in this group. He had chronic lymphocytic leukaemia and a spleen that weighed 991 g. Thrombocytopenia appeared very suddenly and was not accompanied by an increase in spleen size. In addition he had auto-immune haemolytic anaemia.

Auto-immune haemolytic anaemia was diagnosed in patients with anaemia, a raised reticulocyte count and a positive Coombs test. An immune mechanism was thought to be responsible for leucopenia in only 1 patient. She had severe rheumatoid arthritis, anaemia, persistent neutropenia (approximately 200 neutrophils/mm³) and a spleen which weighed 540 g at operation.

The result of splenectomy in patients with cytopenia was considered excellent if there was a return to normal of all haematological values and no further treatment for the cytopenia was required, good if there was a return to normal of all haematological values but further treatment was required, partial if some benefit short of a return to normal resulted, and poor if there was no apparent benefit.

Diagnostic Indication for Splenectomy

Between 1969 and 1972 11 previously untreated patients with clinical stage I, II or IIIA Hodgkin's disease were submitted to splenectomy as part of a laparotomy designed to determine the pathological stage of the disease. In these patients the operation also included careful examination of the abdominal cavity, excision biopsy of involved lymph nodes, multiple liver biopsies and removal of a wedge of iliac crest bone. A similar operation was also performed on 1 patient with non-Hodgkin's lymphoma. The spleen was removed for diagnostic purposes in a further 5 patients, but in these subjects it was not part of a 'staging' laparotomy.

RESULTS

With 1 exception patients were followed until death or until December 1972. If we exclude 1 patient lost to follow-up after her discharge from hospital on the 10th postoperative day, the period of follow-up varied from 1 month to 6 years (mean 1,7 years).

Immediate Results of Surgery and Complications of Splenectomy

Through an abdominal approach a total splenectomy was performed in all cases. The spleens varied in weight from 70 g to 6,3 kg (mean 867 g). Spleniculi, sought for in all patients, were found in 7 cases (10%), but were not all confirmed histologically. One suspected spleniculus had the microscopic features of a lymph node.

There were no operative deaths, and only 1 late hospital death (after one month) was not felt to be related to the operation. However, major complications occurred in 11 patients (16%) and minor complications in a further 22 patients (33%). The most frequently encountered complications were haemorrhage and infection, but pancreatitis, intestinal obstruction, atelectasis of the lung and urinary retention also occurred. No patient developed thrombotic complications, although routine measures other than physiotherapy were not taken against thrombosis. Only 2 patients, both with myelofibrosis, have subsequently required chemotherapy for thrombocytosis.

Two patients died of overwhelming pneumococcal septicaemia and were considered to represent late complications of splenectomy. The first patient was a 58-year-old man who underwent splenectomy because of the presence of pancytopenia and hepatosplenomegaly of unknown aetiology. No specific cause was found at operation but after splenectomy the blood count returned to normal. Eight months after spelenectomy, the patient was admitted to hospital, critically ill, with a short history of fever, having had no specific treatment since the splenectomy and a normal white count immediately before his last illness. There were clinical and laboratory findings suggesting disseminated intravascular coagulation and pneumococci were grown from a blood culture. In spite of vigorous treatment the patient died within hours of admission. The second patient was a 21-year-old woman with Hodgkin's disease. She was admitted in a comatose condition 16 months after splenectomy. She was in complete remission and had received no treatment for 6 months before admission; the white cell count was normal. There was a short history of fever. She was found to have pneumococcal meningitis and died within a few hours of admission.

Results of Therapeutic Splenectomy

'Immune' cytopenias: All patients with immune thrombocytopenic purpura and auto-immune haemolytic anaemia had a trial of corticosteroid treatment at first. Splenectomy was performed if this was unsuccessful or if an unacceptably high dose of steroids (15 mg/day or more of prednisone or its equivalent) was required to maintain a remission. Three patients with immune thrombocytopenic purpura also had an inadequate response to azathioprine before splenectomy.

Thrombocytopenic purpura: In 8 out of 12 patients with immune thrombocytopenic purpura (Table II), no underlying disease was found. The remaining patients each suffered from one of the following conditions: Hodgkin's disease, nodular lymphocytic lymphoma, infectious mononucleosis and systemic lupus erythematosis.

The response to splenectomy was graded as excellent in 9 patients (75%). At the time of analysis they had been followed for from 1 month to 6 years (mean 2,4 years), and had maintained satisfactory platelet counts without further treatment for thrombocytopenia. One patient, however, required appropriate treatment for Hodgkin's disease. One patient who showed an excellent initial response later relapsed; he subsequently responded to a 3-month course of azathioprine.

Auto-immune haemolytic anaemia: There were 4 patients in this group, 3 with idiopathic anaemia and 1 with anaemia secondary to systemic lupus erythematosis.

Two patients showed an excellent haematological response and over 2 years later both were still normal without further treatment. One man who redeveloped haemolytic anaemia after a 3-month remission responded promptly to steroids.

Idiopathic thrombocytopenic purpura and auto-immune haemolytic anaemia (Evans' syndrome): Four patients were found to have the combination of these two conditions. One suffered from chronic lymphocytic leukaemia, but in the remaining 3 no underlying disease was found. The response to splenectomy was excellent in 3 subjects and they remained in good health 13, 14 and 18 months respectively after operation; appropriate therapy for the disease was, however, required in the patient with chronic lymphocytic leukaemia. Thrombocytopenia without hae-

TABLE II. RESULTS OF SPLENECTOMY IN PATIENTS WITH CYTOPENIA

	Indications for splenectomy		No. of patients	Excellent	Good	Partial	Failure
Immune cytopenias	Thrombocytopenia	Primary	8	7	—	—	1
		Secondary	4	2	1	—	1
	Anaemia	Primary	3	1	1	—	1
		Secondary	1	1	—	—	—
	Thrombocytopenia and anaemia	Primary	3	2	—	1	—
		Secondary	1	1	—	—	—
	Neutropenia		1	1	—	—	—
Pancytopenia and large spleen	Lymphoma	Chronic lymphocytic leukaemia	4	4	—	—	—
		Hodgkin's disease	2	2	—	—	—
		Non-Hodgkin's lymphoma	2	1	1	—	—
	Myelofibrosis		6	—	—	3	3
	Cirrhosis		1	1	—	—	—
	Diagnosis uncertain		2	1	—	1	—
Congenital spherocytosis			2	2	—	—	—

molytic anaemia recurred 3 months after splenectomy in the fourth patient, causing death.

Neutropenia: A patient with severe rheumatoid arthritis, a 540-g splenomegaly, anaemia and persistent neutropenia (200 neutrophils/mm³) was diagnosed as having Felty's syndrome. She presented with recurrent fever despite quiescent arthritis; the fever was attributed to septicaemia. A splenectomy was performed. Over a subsequent follow-up period of 2 years a gradual rise in the neutrophil count was observed. One year after operation it reached 3 000/mm³ and remained at about this level. During the first 7 months after surgery the haemoglobin rose to 16 g/100 ml, at which level it stabilised. No further pyrexial episodes occurred.

Pancytopenia with a large spleen: Eight patients with lymphoma, pancytopenia and a considerably enlarged spleen were splenectomised. Four had chronic lymphatic leukaemia, 2 Hodgkin's disease and 2 non-Hodgkin's lymphoma. The spleens weighed between 998 and 5 017 g (mean 1 938 g). The duration of illness before splenectomy varied from 5 months to 14 years (mean 5 years).

All patients had normal haematological values after splenectomy. Three were alive and well 9, 18 and 24 months after operation: 1 required no further treatment, 1 was later treated with total body irradiation and 1 subsequently received chemotherapy. Five patients died between 5 and 44 months after splenectomy. All had normal blood counts to within a few weeks of death. One patient died of an auto-immune haemolytic crisis 5 months after operation, 1 of a cerebrovascular accident and the remaining 3 succumbed to the lymphoma. In this group of patients relief of mechanical symptoms caused by the splenectomy was often a major benefit of surgery.

Myelofibrosis: There were 6 patients in this group; 1 was known to have progressed from polycythaemia vera. They were all cytopenic before operation and required repeated blood transfusions.

Three of the 6 patients were judged to have had little benefit from the operation. One patient had entered a blastic crisis before operation; he was pancytopenic and chemotherapy was very poorly tolerated, and he died 2 months later of gastro-intestinal haemorrhage. Two other patients showed little improvement, continued to require regular transfusions and died 6 and 10 months after operation. Two patients showed an improvement in haematological values and greatly decreased transfusion requirements, 1 died of bronchopneumonia and septicaemia 4 months after operation, and the others succumbed to a blastic crisis after 5 months. The patient who was in the best general and haematological condition at the time of operation benefited most from splenectomy; at follow-up 15 months later he was alive and well and no longer required transfusion. He received chemotherapy for thrombocytosis after operation, but control was achieved easily.

This group of patients had the highest incidence of postoperative complications. All of them suffered some complication and 5 had major complications. Two developed septicaemia and 2 severe haemorrhage postoperatively, while another suffered from acute pancreatitis. The average postoperative hospital stay was 32 days.

Cirrhosis and hypersplenism: A young man with cryptogenic cirrhosis and a 1 018-g splenomegaly had a haemoglobin of 13,3 g/100 ml, a white cell count of 1 900/mm³ and a platelet count of 25 000/mm³, with a troublesome bleeding tendency. After splenectomy the blood count returned to normal and remained so for the 18 months to follow-up.

Hypersplenism of undiagnosed cause: A young woman presented with severe anaemia and high transfusion requirements. A bone marrow study suggested erythraemic myelosis. The mean red cell life, calculated from radio-chromium data, was 10 days. White cell counts and platelet counts were mildly depressed. A 750-g spleen was removed. It showed myeloid metaplasia but a bone marrow trephine biopsy was entirely normal. The blood count returned to normal after the operation and remained so for the 16 months during which she was followed up.

A middle-aged man presented with severe pancytopenia and hepatosplenomegaly. He was treated unsuccessfully with blood transfusions, phytohaemagglutinin and androgens. However, the blood count returned to near normal on steroid therapy. He later developed avascular necrosis of the head of the femur; a splenectomy was performed and the steroids stopped. The blood count remained normal apart from a platelet count of 100 000/mm³. The patient remained well for 8 months and then succumbed to pneucococcal septicaemia.

Congenital spherocytosis: Two patients with congenital spherocytosis, which was diagnosed when they presented with intercurrent minor illnesses, were splenectomised. The results, as expected, were excellent.

Impaired Tolerance to Chemotherapy

Lymphoma: Six patients with lymphoma were splenectomised in an effort to improve their tolerance to chemotherapy. Five patients had Hodgkin's disease and 1 a diffuse lymphocytic lymphoma. The duration of illness before operation was between 2½ and 7 years (mean 4 years 7 months). They had received extensive treatment with chemotherapy, and all but 1 had had radiotherapy. The most recent chemotherapy was a combination of Mustine hydrochloride, a vinca alkaloid, procarbazine and prednisolone (MOPP). Each had received between 2 and 10 courses of MOPP treatment (mean 5 courses). Severe cytopenia was a feature in each patient. As a result, effective doses of chemotherapy could not be given. All patients had active disease and needed treatment for the control of symptoms. It was felt that the poor tolerance to chemotherapy in these patients was due to varying combinations of hypersplenism, bone marrow depression and bone marrow infiltration. Apart from 1 patient with leucopenia and thrombocytopenia, all subjects had blood counts in the low normal range at the time of operation.

At operation the spleens were found to vary in weight from 167 to 796 g. Three patients had an improved tolerance to chemotherapy after splenectomy, in so far as it was possible to give more adequate doses of chemotherapy. However, there was no patient in whom better than partial control was achieved by subsequent therapy.

Chronic myeloid leukaemia: Two patients with chronic myeloid leukaemia were submitted to splenectomy. They had had the disease for 6 and 8 years respectively. Both had very large spleens (1 000 g and 1 508 g). An incipient blast crisis was diagnosed in each and the reason for splenectomy was an inability to tolerate chemotherapy. After operation both patients were given daunorubicin and cytosine arabinoside. One achieved remission but subsequently relapsed and died 17 months after operation. The other patient had a short-lived remission after a supralethal dosage of total body irradiation, chemotherapy and bone marrow transplantation from an identical twin sister.

Myeloma: A patient with a 6-year history of myeloma and a 825-g spleen developed pancytopenia and was unable to tolerate chemotherapy. A splenectomy was performed, but there was no real change and the patient died one month later without leaving hospital.

Miscellaneous

Red cell aplasia: An elderly woman with pure red cell aplasia and no apparent underlying cause required blood transfusions every 4 - 6 weeks. She was treated with anabolic steroids and cyclophosphamide, but both forms of therapy proved ineffective. Review of the cases of red cell aplasia that had been reported to respond to chemotherapy at that time showed that coincidentally all had been splenectomised. With this in mind it was decided to splenectomise the patient and again administer chemotherapy. This was done but was without effect and the need for repeated blood transfusions continued.

Myelofibrosis: Finally 1 patient with myelofibrosis which followed polycythaemia vera was submitted to splenectomy solely because of fairly severe mechanical symptoms. His symptoms were relieved and he was well 12 months after operation. He required chemotherapy for thrombocytosis after operation but control was achieved easily.

Results of Diagnostic Splenectomy

There were 16 patients in this group; 13 had Hodgkin's disease, 2 had histiocytic lymphoma and 1 was diagnosed as a lymphocytic lymphoma. Eleven had a 'staging' laparotomy. In 9 the clinical stage (4 stage IA, 4 stage IIA and 1 stage IIIA) was confirmed. One patient who did not have clinical splenomegaly was found to have histological involvement of the spleen, and on this basis the stage of the patient's Hodgkin's disease was changed from stage IIB to IIIB and the proposed treatment changed from radiotherapy to quadruple chemotherapy. The remaining patient, who was considered to have stage IIIA Hodgkin's disease on the basis of a palpable spleen and who had no histological evidence of splenic or abdominal lymph node involvement, was accordingly reclassified stage IA and treated by total nodal irradiation.

Three patients with established disease had incidental splenectomies at laparotomy; for intestinal obstruction in 1 case; for an abdominal lesion of uncertain aetiology in the second case, and for possible abdominal relapse in the third case. Two more patients with pyrexia of unknown origin and a high suspicion of abdominal lymphoma proved to have Hodgkin's disease at operation.

There were few immediate complications of operation in this group. One late death from pneumococcal meningitis occurred.

DISCUSSION

Splenectomy for haematological diseases has been the subject of several recent reports of large series of cases,[8,9] and several review articles.[2,10] In general, our own findings and opinions are very similar to those reported.

The importance of looking for accessory spleens in patients undergoing splenectomy is underlined by the fact that they were found in 10% of our patients. A high incidence of macroscopic accessory spleens at splenectomy for haematological diseases has previously been reported by Olsen and Beaudoin,[21] who suggested that minute nests of splenic tissue are normally present in the splenic pedicle and mesentery, and that these increase in size in patients with blood diseases.

Splenectomy for haematological disease is usually attended by a low mortality rate, but in certain groups of patients the morbidity rate may be high.[1,8,9,12,13] The most important complications, both in terms of incidence and severity, are haemorrhage and infection. The factors leading to a high morbidity are a very large spleen, severe or extensive underlying disease, severe thrombocytopenia which does not respond satisfactorily to the operation, and the age of the patient. Splenectomy appears specifically to increase the risk of certain infections. Malaria is a more serious disease in splenectomised animals and probably in splenectomised man.[14] Care should therefore be taken that adequate prophylaxis is prescribed for splenectomised persons who may be exposed to malaria. A syndrome of overwhelming pneumococcal infection after splenectomy is now well recognised and documented.[15-17] It occurs more commonly in children than adults, usually in the first year after operation, and is often overwhelming. It is frequently accompanied by evidence of disseminated intravascular coagulation. While it appears to be more common in patients with serious underlying diseases such as lymphoma, cases have also been reported in adults without underlying disease.[16] A similar risk may also be present with other encapsulated organisms, especially *H. influenzae*. A recent report has suggested that herpes zoster infection is more common in patients with Hodgkin's disease who have been splenectomised.[17]

It has been the general experience that the immune cytopenias, in particular thrombocytopenic purpura, respond well to splenectomy even when steroids have failed. Most reported series contain a high proportion of children, and note that they do better than adults.[19] The present series, which contains no children, demonstrates that very satisfactory results may also be obtained in adults. Complications of splenectomy were not found to be a serious problem, which is in keeping with other series.[12,20]

There is still some uncertainty about the exact pathological mechanism responsible for the neutropenia in

Felty's syndrome, and the place of splenectomy in its treatment is still debated. Moore et al.[21] found that neutropenia was relieved in 10 of their 15 patients, and that the incidence of infection decreased significantly in those patients whose blood counts responded, as was our experience in 1 patient. An interesting feature in this patient was the marked and unexplained delay before the full effect of the operation on the haemoglobin and white cell counts was seen.

Another group in whom worthwhile results were obtained, was that of patients with lymphomas with associated splenomegaly and hypersplenism. Christensen et al.[8] comment on the fairly high incidence of complications due mainly to infection and haemorrhage, and attribute this to comparatively old age, granulocytopenia, thrombocytopenia and impaired immunological responsiveness. They make a plea for earlier operation in the patient with lymphoma and massive splenomegaly whose haematological values are beginning to decline.

The place and timing of splenectomy in myelofibrosis has also been the subject of recent reports.[22-25] The idea was previously held that splenectomy might cause deterioration by removing a site of haemopoiesis. At the same time there is some evidence that better results are obtained in those patients in whom medullary erythropoiesis is still demonstrable.[25] Operation, although hazardous late in the course of the disease, as noted in the present series, is not contra-indicated if proper precautions are taken.[13] Crosby et al.[24] recommended that, since almost all patients with myelofibrosis will eventually need splenectomy, their spleens should be removed at presentation when the risk of all complications except thrombocytosis is least. Thrombocytosis can be controlled by chemotherapy, started if necessary before surgery. Gomes et al.[23] suggest the compromise of splenectomy as soon as a decline in blood count values is noted or symptoms of splenomegaly are significant. Certainly the 2 patients in our series in whom this policy was followed derived the most benefit from their operations. Several of the other patients had suffered months or years of discomfort from massive splenomegaly and repeated blood transfusions before 'last resort' splenectomy, with its attendant morbidity, was undertaken.

Splenectomy has been reported to improve the marrow tolerance to chemotherapy[26] and radiotherapy[27] of some patients suffering from lymphoma. However, our experience in this group of patients, which included lymphoma as well as other haematological malignancies, was disappointing. Only 4 of the 9 patients in the group derived benefit from the operation, in so far as it was possible to give them more adequate doses of chemotherapy.

The place of splenectomy in the management of Hodgkin's disease has probably been the aspect of splenectomy most discussed in the literature in recent years. The value of the operation is better assessed by reference to the extensive published experience of several American groups than from our small series. However, our experience thus far is in agreement with the conclusion that the operation may be of considerable value in defining the extent of the disease, so that the appropriate form of therapy can be given.[3-7] Its value is underlined by the finding that approximately one-third of palpable spleens do not show evidence of disease, while one-third of impalpable spleens are positive histologically.[7]

REFERENCES

1. Böttiger, L. E., Edhag, O. and Forsgren, L. (1972): Acta med. scand., 192, 213.
2. Crosby, W. H. (1972): New Engl. J. Med., 286, 1252.
3. Glatstein, E., Guernsey, J. M., Rosenberg, S. A. and Kaplan, H. S. (1969): Cancer, 24, 709.
4. Meeker, W. R., Richardson, J. D., West, W. O. and Parker, J. C. (1972): Arch. Surg., 105, 222.
5. Nuland, S. B. and Prosnitz, L. R. (1973): Amer. J. Surg., 125, 399.
6. Prosnitz, L. R., Nuland, S. B. and Kligerman, M. M. (1972): Cancer, 29, 44.
7. Desser, R. K., Moran, E. M. and Ultmann, J. E. (1973): Med. Clin. N. Amer., 57, 479.
8. Christensen, B. E., Hansen, L. K., Kristensen, J. K. and Videbaek, A. (1970): Scand. J. Haemat., 7, 247.
9. Schwartz, S. I., Bernard, R. P., Adams, J. T. and Bauman, A. W. (1970): Arch. Surg., 101, 338.
10. Gomes, M. M. R., Silverstein, M. N. and ReMine, W. H. (1969): Surg. Gynec. Obstet., 129, 129.
11. Olsen, W. R. and Beaudoin, D. E. (1969): Arch. Surg., 98, 762.
12. Hodam, R. P. (1970): Amer. J. Surg., 119, 709.
13. Morgenstern, L. (1971): Ibid., 122, 288.
14. Garnham, P. C. (1970): Acta trop., 27, 1.
15. Desser, R. K. and Ultmann, J. E. (1972): Ann. Intern. Med., 77, 143.
16. Bisno, A. L. and Freeman, J. C. (1970): Ibid., 72, 9.
17. Donaldson, S. S., Moore, M. R., Rosenberg, S. A. and Vosti, K. L. (1972): New Engl. J. Med., 287, 69.
18. Goffinet, D. R., Glatstein, E. J. and Merigan, T. C. (1972): Ann. Intern. Med., 76, 235.
19. Brooks, B. L., O'Shea, M. J. and Pryor, J. P. (1969): Brit. J. Surg., 56, 861.
20. Bostrom, P. D. and Page, H. G. (1969): Arch. Surg., 98, 167.
21. Moore, R. A., Brunner, C. M., Sandusky, W. R. and Leavell, B. S. (1971): Ann. Intern. Med., 75, 381.
22. Marks, C. and Ahmadi, M. (1969): Postgrad. Med. J., 45, 261.
23. Gomes, M. M. R., Silverstein, M. N. and ReMine, W. H. (1967): Surg. Gynec. Obstet., 125, 106.
24. Crosby, W. H., Whelan, T. J. and Heaton, L. D. (1966):: Med. Clin. N. Amer., 50, 1533.
25. Milner, G. R., Geary, C. G., Wadsworth, L. D. and Doss, A. (1973): Brit. J. Haemat., 25, 467.
26. Lowenbraun, S., Ramsey, H. E. and Serpick, A. A. (1971): Amer. J. Med., 50, 49.
27. Salzman, J. R. and Kaplan, H. S. (1971): Cancer, 27, 471.