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Immunologic Studies Before and After Splenectomy in a Patient with the Wiskott-Aldrich Syndrome

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Sequential studies of cellular and humoral immunity were conducted in an infant with the Wiskott-Aldrich syndrome prior to and after a splenectomy for uncontrollable hemorrhage. All measures of cellular immunity showed gradual improvement during the 8-month period after surgery. Serum isohemagglutinins, diphtheria and tetanus antibodies, and the percentage of immunoglobulin-bearing B cells did not change significantly from presplenectomy values. The serum IgE concentration declined from a high of 10,800 IU/ml at 1 month postsplenectomy to a low of 860 IU/ml at 5 months after surgery and the IgG concentration gradually decreased from a high of 1880 mg/dl presplenectomy to a low of 620 mg/dl 8 months later. The platelet count ranged from 64,000 to 206,000/mm^3 for the first 6 months after splenectomy. It decreased precipitously 6.5 months after the operation; at the same time there was a marked rise in platelet-bound IgG antibody (PB-IgG). The PB-IgG declined rapidly following vincristine therapy and, after another rise, declined more gradually following steroid therapy.

KEY WORDS: Wiskott-Aldrich syndrome; splenectomy; immunologic studies; platelet-bound antibody; IgE.

INTRODUCTION

The Wiskott-Aldrich syndrome is an X-linked primary immunodeficiency disorder characterized clinically by the triad of eczema, megokaryocytic thrombocytopenic purpura, and recurrent infections (1-3). Various immunologic abnormalities have been described, among the most prominent of which are an inability to produce antibodies to polysaccharide antigens and decreased number and function of T cells (4-8). Other features of the disorder include hypercatabolism of immunoglobulins and albumin (9) and a tendency for paraprotein development (10). The condition causes significant morbidity and mortality, due not only to recurrent severe bacterial and viral infections but also to hemorrhage from the gastrointestinal tract, lungs, and oral cavity and/or into the brain, severe vasculitis (11), and an increased incidence or reticuloendothelial malignancy (12). Thrombocytopenia in this condition has been attributed both to decreased thrombocytosis and to increased destruction of platelets due to intracorpuscular defects (13, 14). Platelet-bound IgG antibodies have also been implicated as a cause for increased destruction of platelets in some (15) but not all Wiskott-Aldrich patients (14).

Splenectomy in treatment of the thrombocytopenia has for many years been considered to be contraindicated because of the additional increased susceptibility to overwhelming sepsis of splenectomized patients (2, 15, 16). Recently Lum *et al.* (15) presented evidence in a retrospective study that splenectomy, when combined with prophylactic antibiotics administered regularly, may be acceptable in the management of hemorrhagic problems due to severe thrombocytopenia. This paper presents the results of prospective and sequential immunologic studies in a patient with the Wiskott-Aldrich syndrome who required splenectomy for management of serious hemorrhagic problems due to severe thrombocytopenia. Also presented are serial mea-

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surements of platelet-bound IgG antibody after splenectomy.

METHODS

Immunoglobulin and Antibody Studies

Immunoglobulin and antibody determinations were measured as previously described (17). Briefly, serum concentrations of IgG, IgA, and IgM were measured by single radial diffusion using goat antisera and primary reference standards prepared in this laboratory. The patient's immunoglobulin values were compared with previously published normal data for this laboratory and the 95% confidence intervals from those data (17). Serum IgE concentrations were determined by double antibody radioimmunoassay, using reagents and normative data developed in this laboratory (18). Isohemagglutinin titers were measured by a modification of a microtiter technique (19). Diphtheria and tetanus antibody titers were determined by tanned cell hemagglutination (20).

Lymphocyte Studies

Rosette formation, membrane immunofluorescence, and lymphocyte stimulation studies were carried out as previously described (21). Peripheral blood lymphocytes were obtained by Ficoll-Hypaque density gradient centrifugation, and the rosette and immunofluorescence data were corrected for monocyte contamination of the suspension. Monocytes were detected by staining with myeloperoxidase (22).

Platelet-Bound IgG (PB-IgG) by Antiglobulin Consumption Test

The platelet-bound IgG was determined by appropriate modification of the antiglobulin consumption test previously described (23). In brief, sheep red blood cells were coated with human IgG obtained from patients with multiple myeloma and purified by DEAE-Sephadex chromatography. This protein was attached with dilute glutaraldehyde by the method of Kaden *et al.* (24). An "optimal" dilution of rabbit antibody specific for antigenic determinants on IgG—the dilution of antibody which, in the presence of fresh guinea pig serum as a source of complement, will lyse the majority of sheep cells coated with human IgG—was determined. This amount of antibody was incubated with either platelets or purified IgG. The degree of reduction (inhibition) of lysis of the IgG-coated sheep cells by guinea pig serum was determined. The reduction engendered by a known number of platelets and the amount of IgG per platelet were then estimated.

Human Investigation

The investigational studies done in this patient were performed with the written informed consent of the parents and the approval of the Duke University Committee on Human Investigations.

CASE HISTORY

JBH, a 19-month-old white male, was first admitted to Duke University Hospital when he was 9 months of age for evaluation of thrombocytopenia and a history of recurrent drainage from the ears, repeated episodes of pneumonia, and a pruritic, eczematoid skin rash. At that time, his eczema was mild, with only scattered dry pruritic patches in the antecubital fossae, on the cheeks, in the nuchal region, and on the legs. *Pseudomonas* was cultured in drainage from the ears. He was severely anemic (Hgb of 3 g/dl) with reticulocytosis (7.2%). The stool contained occult blood. The direct antiglobulin (Coombs) test was positive with anti-IgG. The platelet count was 5000 cells/mm^3. His condition improved following treatment with antibiotics and transfusions of irradiated packed red blood cells and platelets. The HLA type of the patient and all first-degree relatives was determined and no compatible potential donors of bone marrow were found. Infused platelets appeared to have a shortened survival and the patient remained severely thrombocytopenic (platelet counts usually less than 5000 cell/mm^3). Because of life-threatening hemorrhages despite repeated platelet transfusions, splenectomy was performed 2.5 weeks after admission. The platelet count rose immediately and stabilized after 9 days postsplenectomy, ranging between 64,000 and 206,000/mm^3 over the next 6 months (Fig. 1). The direct antiglobulin (Coombs) test became negative without further therapy. Six and one-half months after splenectomy, he again developed severe thrombocytopenia. He did not have an accessory spleen by liver-spleen scan. He received

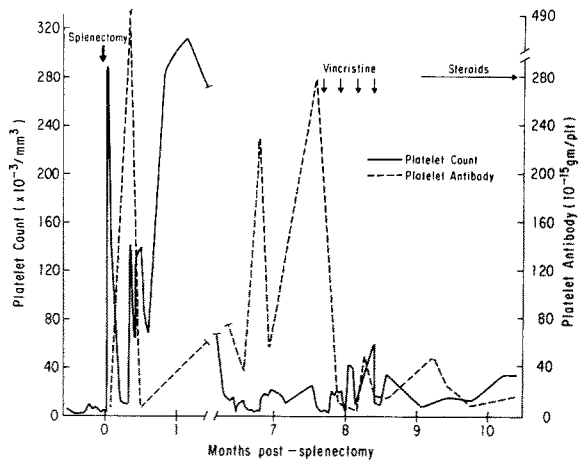

Fig. 1. Peripheral blood platelet counts and platelet-bound IgG antibody values in a patient with the Wiskott-Aldrich syndrome before and during the first 10 months after splenectomy.

intermittent platelet transfusions over the next 5 weeks for treatment of oral, gastrointestinal, and renal bleeding. Because his platelet count failed to rise, he was then given four intravenous infusions of vincristine (1 mg/M^2). Following each of those infusions his platelet count increased modestly, ranging between 10,000 and 59,000/mm^3. He remained free of serious bleeding but continued to have some oozing of blood from his lower lip at a site of self-inflicted trauma.

At 18.5 months of age (9 months postsplenectomy) the patient developed hemolytic anemia with a positive direct antiglobulin (Coombs) test. He had a recurrence of severe thrombocytopenia; the platelet count was about 1000/mm^3, and he had severe oral and gastrointestinal bleeding. Therapy with adrenocortical steroids was initiated, with eventual resolution of his anemia and a gradual rise in his platelet count. The platelet count has remained in the 30,000/mm^3 range for several weeks and steroids are being tapered. He is maintained on chronic trimethoprim and sulfa therapy and has received monthly intravenous infusions of an investigational modified immune serum globulin since 8 months postsplenectomy.

RESULTS

Immunologic Studies

Evaluation of the patient's cellular immunity prior to splenectomy revealed abnormally low percentages of E and En rosetting blood lymphocytes (15 and 25%, respectively; Table I) and depressed proliferative responses to all three mitogens and to both antigens (Table II). Following splenectomy, the percentages of E and En rosetting cells gradually increased toward normal, with the values at 8 months postsplenectomy being 41 and 55%, respectively. The percentages of surface immunoglobulin-positive cells did not vary significantly and on most occasions were within the normal range. Lymphocyte proliferative responses also increased over the first 8 months following splenectomy, with the latest relative response values being (PHA) 75, (Con A) 43, (PWM) 64, (*Candida*) 23, and (tetanus) 11% of those of the simultaneously evaluated normal control donor (Table II).

Initial studies of humoral immunity revealed elevated serum IgG, IgA, and IgE concentrations, a

Table I. Lymphocyte Membrane Receptor Studies in a Patient with the Wiskott-Aldrich Syndrome Before and After Splenectomy

	Rosettes (%)				Surface Ig-bearing cells (%)	
Time	E	En	HEA	HEAC	IgM	IgD
Presplenectomy						
−2 weeks	15	24	—	—	—	—
Postsplenectomy						
+4 days	15	25	8	14	7	5
+1 month	19	34	6	13	9	3
+2.5 months	33	43	2	3	10	8
+5 months	46.8	49.9	—	—	14.7	12
+8 months	41	55	—	—	9.4	4.7
Normal control subjects[a]	55.4 ±9.0	75.9 ±5.4	6.2 ±3.9	15.1 ±5.9	7.6 ±3.0	4.5 ±3.6

[a]The means and standard deviations of rosette and immunofluorescence data derived from studies on the following numbers of normal subjects: E, 62; En, 17; HEA, 13; HEAC, 39; and IgM and IgD, 23 (24). Abbreviations: E, sheep erythrocyte rosettes; En, neuraminidase-treated sheep erythrocyte rosettes; HEA, rabbit IgG-coated human erythrocyte rosettes; HEAC, rabbit IgM- and mouse C3b-coated human erythrocyte rosettes.

Table II. Responses to Mitogens and Antigens by Lymphocytes from a Patient with the Wiskott-Aldrich Syndrome Before and After Splenectomy

Time	cpm of ^{3}H-thymidine incorporation				
	PHA	Con A	PWM	*Candida*	Tetanus
Presplenectomy					
−2 weeks	14,900	16,900	1,200	0	0
	(16)[a]	(22)	(30)	(0)	(0)
Postsplenectomy					
+4 days	63,000	24,900	5,400	1,700	6,000
	(62)	(23)	(10)	(18)	(47)
+1 month	79,700	22,100	19,000	200	900
	(67)	(19)	(18)	(—)	(—)
+2.5 months	49,200	33,600	7,950	0	650
	(78)	(51)	(21)	(0)	(72)
+8 months	45,000	26,700	32,400	4,500	1,700
	(75)	(43)	(64)	(23)	(11)

[a]Values in parentheses indicate normalized responses, expressed as percentages, calculated according to the following formula using data from a simultaneously evaluated normal control: response = {[cpm (stimulated) − cpm (unstimulated) patient]/[cpm (stimulated) − cpm (unstimulated) normal control]} ×100.

low IgM value, and no detectable antibodies to type A or B human red blood cells (patient's blood type: Group O, Rh positive) or to diphtheria or tetanus toxoids (Table III). Since splenectomy, his IgG, IgA, and IgE values have remained elevated. Surprisingly, however, his IgE concentration decreased from a high of 10,800 IU/ml at 1 month postsplenectomy to a low of 860 IU/ml at 5 months after splenectomy, and the markedly polyclonally elevated presplenectomy serum IgG concentration fell to 620 mg/dl 8 months later. His serum IgM concentration rose to normal during the first 5 months after surgery but again became abnormally low (20 mg/dl) at 8 months after splenectomy. For a few months after surgery he had low titers of isohemagglutinins and very low titers of diphtheria and tetanus antibodies, but it is possible that these could have been passively acquired from the many transfusions he received. No paraproteins were detected in his serum.

Platelet Antibody Studies

Platelet-bound IgG antibody rose to a peak of 494 $\times 10^{-15}$ g/plt at 8 days postsplenectomy, then decreased to 7.0 $\times 10^{-15}$ g/plt at 14 days after splenectomy (normal, < 4.0 $\times 10^{-15}$ g/plt). It then remained moderately elevated for several months until the patient experienced a precipitous drop in his platelet count at 6.5 months postsplenectomy, at which time his platelet-bound IgG antibody rose to 74.7 $\times 10^{-15}$ g/plt. During the next 5 weeks it reached levels of 238 and 290 $\times 10^{-15}$ g/plt. Following the first dose of vincristine, platelet-bound IgG decreased dramatically to a nadir of 4.2 $\times 10^{-15}$ g/plt but then rose again to 48.1 $\times 10^{-15}$ g/plt between the third and fourth doses. It declined again following the fourth dose but rose again to 48 $\times 10^{-15}$ g/plt, concomitant with the development of severe thrombocytopenia and immune hemolytic anemia at 9 months postsplenectomy. The platelet-bound IgG antibody de-

Table III. Humoral Immune Profile of Patient with the Wiskott-Aldrich Syndrome Before and After Splenectomy

Time	Age (months)	IgG[a]	IgA[a]	IgM[a]	IgE[b]	αA	αB	αDiphtheria	αTetanus
Presplenectomy	9	1880	120	22	9,100	0	0	0	0
Postsplenectomy									
4 days[c]	9	1120	355	43	3,700	1:8	1:4	0	1:27
1 month	10	1180	330	59	10,800	1:2	1:4	1:81	1:243
3 months	12	1580	355	130	1,700	0	0	1:27	1:27
5 months	14	1350	443	105	860	0	1:2	0	1:9
8 months	17	620	443	20	—	—	—	—	—
Normal range	7-9	268-717	27-73	12-124		>1:32	>1:16	>1:2,000	>1:10,000
for age	10-18	363-971	27-169	28-113		>1:32	>1:16	>1:2,000	>1:10,000

[a]mg/dl.
[b]IU/ml.
[c]Irradiated whole blood transfusions received shortly before these determinations.

creased slowly following the initiation of steroid therapy to 9.0×10^{-15} g/plt at the latest determination, and in association with this, platelet counts gradually rose to the current level of about 30,000/mm^3.

DISCUSSION

In addition to fear of increasing susceptibility of Wiskott-Aldrich patients to overwhelming sepsis by splenectomy, clinical immunologists have had serious reservations about the potential immunologic consequences of the removal of a major lymphoid organ from patients with this partial combined immunodeficiency, particularly as the spleen is known to be a rich source of suppressor cells (26). Splenectomy might thus increase the propensity of patients with the Wiskott-Aldrich syndrome to develop autoantibodies to platelets and red cells, to have serious vasculitis, and to produce excessive amounts of IgE antibodies. The studies presented here are the first in which cellular and humoral immunologic parameters were evaluated prospectively and compared with those obtained at frequent intervals postsplenectomy in this condition. Surprisingly, rather than having an adverse effect, splenectomy was followed by improvement in several aspects of the patient's immunity. Both the number and the function of his T cells gradually increased toward normal over the 8-month period following surgery; most values were more than double those prior to splenectomy. Conceivably this could have been secondary to loss of excessive or even normal T-T suppressor cell activity that had been contributed by the spleen. This is difficult to evaluate since studies of cellular immunity have shown great variability among patients with this condition (4–8, 14); less variability is seen within the same patient, however. Similarly, the effect of intercurrent illness on *in vitro* studies of T-cell function must be considered in evaluating these data. However, the patient was having severe hemorrhagic problems and had an elevated sedimentation rate at the time of both his lowest and his highest *in vitro* cellular immune responses (blood for those studies was collected on each occasion immediately prior to transfusion with irradiated packed red cells); he was clinically well at the times of the other evaluations. Results of humoral immunologic measurements did not change significantly except for the marked decline in his serum IgE concentration and a lesser decline in the IgG concentration. As with the cellular immune changes, these changes could simply reflect natural variability within this condition, although there are other possible explanations. The improvement noted in his T-cell function (whether or not a consequence of the splenectomy) could possibly account for the drop in his serum IgE concentration, since IgE production is known to be regulated by both antigen-specific and nonspecific suppressor T cells (26). Possibly relevant to this is the observation by Parkman *et al.* (27) that the atopic dermatitis of their patient with Wiskott-Aldrich syndrome improved dramatically with T-cell engraftment following bone marrow transplantation from a matched sibling donor. The decline in his IgG concentration could possibly have been due to "feedback inhibition" by exogenous IgG antibodies administered in blood or in immune serum globulin.

In the untreated patient with immune thrombocytopenia, there is a close relationship between the increase in PB-IgG and the diminution of the platelet count (23). Thus, in the present patient, exacerbations of thrombocytopenia were accompanied by marked increases in PB-IgG, strongly suggesting that platelet-bound IgG antibody played a major role in the pathogenesis of the thrombocytopenia developing several months postsplenectomy. While antiplatelet antibodies have been suspected of contributing to the severe thrombocytopenia in patients with the Wiskott-Aldrich syndrome, particularly those refractory to platelet transfusions (15), there has been no previous attempt to correlate the quantities of such antibodies to the degree of thrombocytopenia.

Because vincristine has been found very effective in treating non-Wiskott-Aldrich patients with chronic immune thrombocytopenic purpura (28) and because it is administered only over a 3- to 4-week period, we selected this form of immunosuppression in place of adrenocortical steroids in the treatment of the initial episode of immune thrombocytopenia. It appeared to reduce the level of PB-IgG with no apparent adverse effects. Adrenocorticosteroids were used for treatment of the second exacerbation because the patient had an associated severe Coombs-positive hemolytic anemia. Although this treatment was beneficial, the effect occurred more slowly and was much less dramatic than that seen with vincristine. As noted by others, relapses in immune thrombocytopenia tend to occur frequently when the dose of steroids is gradually reduced (29). In patients with immune thrombocyto-

penia who are treated with prednisone, the relationship between platelet count and PB-IgG is not so close as is seen with untreated patients (Rosse WF, unpublished data). In some patients, the measured PB-IgG is nearly normal whereas the platelet count may remain low, as occurred in this patient. The reason(s) for this is obscure. We speculate that the persisting thrombocytopenia in our patient, despite low antiplatelet antibody, may be due to hyperplasia of other elements of his reticuloendothelial system.

The course of our patient following splenectomy was very similar to that of a patient reported by Lum *et al.* (15) who was only 14 months of age at the time of splenectomy. Like our patient, the infant went on to develop severe immune thrombocytopenia at 10 months postsplenectomy. As pointed out by those authors, a young age may be a contributing factor to the propensity for this complication after splenectomy, since most of the cases found in their review of the literature were under 3 years of age and several of those failed to increase their platelet counts to normal after splenectomy.

CONCLUSIONS

Removal of the spleen of an infant with Wiskott-Aldrich syndrome was followed by improvement in all measures of cellular immune function and a decline in serum IgE concentration. The platelet count returned to normal for 6.5 months postsplenectomy, following which an IgG antibody-mediated immune thrombocytopenia developed. Vincristine and, to a lesser extent, adrenocorticosteroid therapy were useful in controlling the latter. For Wiskott-Aldrich patients with immune thrombocytopenic purpura who do not have an associated Coombs-positive hemolytic anemia, vincristine would appear to be an effective and relatively safe form of therapy.

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REFERENCES

1. Aldrich RA, Steinberg A, Campbell DC: Pedigree demonstrating a sex-linked recessive condition characterized by draining ears, eczematoid dermatitis and bloody diarrhea. Pediatrics 13:133-138, 1954
2. Huntley CC, Dees SC: Eczema associated with thrombocytopenic purpura and purulent otitis media. Pediatrics 19:351-360, 1957
3. Wolff JA: Wiskott-Aldrich Syndrome: Clinical, immunological and pathologic observations. J Pediatr 70:221-232, 1967
4. Cooper MD, Chase HP, Lawman JT, Krivit W, Good RA: Wiskott-Aldrich Syndrome: An immunologic deficiency disease involving the afferent limb of immunity. Am J Med 44:499-511, 1968
5. Blaese RM, Strober W, Brown RS, Waldmann TA: The Wiskott-Aldrich Syndrome: A disorder with a possible defect in antigen processing or recognition. Lancet 1:1056-1061, 1968
6. Blaese RM, Strober W, Waldmann TA: Immunodeficiency in the Wiskott-Aldrich Syndrome. Birth Defects 11:250-254, 1975
7. Oppenheim JJ, Blaese RM, Waldmann TA: Defective lymphocyte transformation and delayed hypersensitivity in Wiskott-Aldrich Syndrome. J Immunol 104:835-844, 1970
8. Spitler LE, Levin AS, Stites DP, Fudenberg HH, Huber H: The Wiskott-Aldrich Syndrome: Immunologic studies in nine patients and selected family members. Cell Immunol 19:201-218, 1975
9. Blaese RM, Strober W, Levy AL, Waldmann TA: Hypercatabolism of IgG, IgA, IgM and albumin in the Wiskott-Aldrich Syndrome. J Clin Invest 50:2331-2338, 1971
10. Radl J, Dooren LJ, Morell A, Skvaril F, Vossen MJJ, Vittenbogaart CH: Immunoglobulins and transient paraproteins in sera of patients with the Wiskott-Aldrich Syndrome: A follow-up study. Clin Exp Immunol 25:256-263, 1976
11. Filipovich AH, Krivit W, Kersey JH, Burke BA: Fatal arthritis as a complication of Wiskott-Aldrich Syndrome. J Pediatr 95:742-744, 1979
12. Kersey JH, Spector BD, Good RA: Primary immunodeficiency diseases and cancer: The immunodeficency-cancer registry. Int J Cancer 12:333-347, 1973
13. Baldini MG: Nature of the platelet defect in the Wiskott-Aldrich Syndrome. Ann NY Acad Sci 201:437-444, 1972
14. Ochs HD, Slichter SJ, Harker LA, von Behrens WE, Clark RA, Wedgwood RJ: The Wiskott-Aldrich Syndrome: Studies of lymphocytes, granulocytes and platelets. Blood 55:243-252, 1980
15. Lum LG, Tubergen DG, Carcish L, Blaese RM: Splenectomy in the management of the thrombocytopenia of the Wiskott-Aldrich Syndrome. N Engl J Med 302:892-896, 1980
16. Weiden PL, Blaese RM: Hereditary thrombocytopenia: Relation to Wiskott-Aldrich Syndrome with special reference

to splenectomy. J Pediatr 80:226-234, 1972
17. Buckley RH, Dees SC, O'Fallon WM: Serum immunoglobulins. I. Levels in normal children and in uncomplicated childhood allergy. Pediatrics 41:600-601, 1968
18. Buckley RH, Fiscus SA: Serum IgD and IgE concentrations in immunodeficiency diseases. J Clin Invest 55:157-165, 1975
19. Wegman TG, Smithies O: A simple hemagglutination system requiring small amounts of red cells and antibodies. Transfusion 6:67-73, 1966
20. Buckley RH, Dees SC: Serum immunoglobulins. III. Abnormalities associated with chronic urticaria in children. J Allergy 40:294-303, 1967
21. Schiff RI, Buckley RH, Gilbertsen RB, Metzgar RS: Membrane receptors and in vitro responsiveness of lymphocytes in human immunodeficiency. J Immunol 112:376-386, 1974
22. Kaplow LS: Simplified myeloperoxidase stain using benzidine dihydrochloride. Blood 26:215-219, 1965
23. Dixon R, Rosse W, Ebbert L: Quantitative determination of antibody in idiopathic thrombocytopenic purpura: Correlation of serum and platelet-bound antibody with clinical response. N Engl J Med 292:230-236, 1975
24. Kaden BR, Rosse WF, Hauch TW: Immune thrombocytopenia in lymphoproliferative diseases. Blood 53:545-551, 1979
25. McGeady SJ, Buckley RH: Depression of cell-mediated immunity in atopic eczema. J Allergy Clin Immunol 56:393-406, 1975
26. Tada T, Okumura K: The role of antigen-specific T cell factors in the immune response. Adv Immunol 28:1-87, 1979
27. Parkman R, Rappaport J, Geha R, Bello J, Cassady R, Levey R, Nathan DG, Rosen FS: Complete correction of the Wiskott-Aldrich Syndrome by allogeneic bone marrow transplantation. N Engl J Med 298:921-927, 1978
28. Ahn YS, Harrington WJ, Seelman RC, Eytel CS: Vincristine therapy of idiopathic and secondary thrombocytopenias. N Engl J Med 291:376-380, 1974
29. Ahn YS, Harrington WJ: Treatment of idiopathic thrombocytopenic purpura (ITP). Ann Rev Med 28:299-309, 1977