pigs fail to contract in response to leukotriene D concentrations that have substantial effects on strips of guinea-pig pulmonary parenchyma.[7] If a human contractile-tissue equivalent of such tracheal spirals responded to histamine and was the site of hyperresponsiveness in asthmatics, and if the human contractile response to leukotriene D occurred in contractile tissues equivalent to guinea-pig parenchyma — tissues that were equally responsive in both normal and asthmatic persons — an effect similar to that found in this study could result. The implication of this hypothesis is that the airway hyperresponsiveness of asthma may not be a generalized airway disorder, as previously thought, but rather a response of specifically located contractile elements to a diverse group of agonists and irritants.

Another possible hypothesis for the effects observed in this study is that the hyperresponsiveness of asthma may itself be a consequence of the action of mediators such as leukotriene D. For example, it is known that impure SRS-A increases the apparent spasmogenic potency of histamine for the guinea-pig ileum.[15] If this is the case, then the leukotrienes elaborated by the various triggering steps in asthma act both directly and by contributing to airway hyperresponsiveness to other substances.

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COINCIDENT CLASSIC HEMOPHILIA AND "IDIOPATHIC" THROMBOCYTOPENIC PURPURA IN PATIENTS UNDER TREATMENT WITH CONCENTRATES OF ANTIHEMOPHILIC FACTOR (FACTOR VIII)

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HOME treatment of classic hemophilia with lyophilized concentrates of antihemophilic factor (factor VIII) is now widely practiced. We studied a syndrome resembling chronic idiopathic thrombocytopenic purpura in five patients with severe classic hemophilia who were receiving such therapy. Laboratory studies are summarized in Tables 1 through 3. The presence of increased amounts of platelet-associated IgG, the favorable response in four patients treated with prednisone, and remission after splenectomy in one patient all suggest that the patients' disorder resembled idiopathic thrombocytopenic purpura. In addition, studies in four patients demonstrated evidence of impaired cell-mediated immunity in three.

Case Reports

Patient 1

A 21-year-old man with severe hemophilia (factor VIII titer <0.01 unit per milliliter) was admitted to University Hospitals of Cleveland on December 22, 1981, for study of a petechial rash of three or four weeks' duration. He had been in a home therapy program for five years, using the concentrate of a single manufacturer every three or four weeks. Laboratory studies demonstrated severe thrombocytopenia (30,000 to 36,000 platelets per microliter) and plentiful megakaryocytes in a marrow aspirate. The platelet count rose to 78,000 per microliter upon administration of prednisone (80 mg per day), but that level could not be sustained at lower doses. Splenectomy, with the patient protected by infusions of lyophilized concentrates of factor VIII, was performed on February 2, 1982, and was followed by remission; the platelet count on August 10, 1982, was 293,000 per microliter. The excised spleen weighed 355 g; slight follicular hyperplasia and reactive plasmacytosis of the red pulp were present.

Patient 2

A 30-year-old man with severe hemophilia (factor VIII titer <0.01 unit per milliliter) had been in a home therapy program for six years, giving himself a transfusion containing lyophilized concentrates of factor VIII about once a month. Over the years he had used concentrates prepared by three different manufacturers. He had had episodes of hepatitis after these transfusions at ages 18 and 25 years; before the first episode, he had also received transfusions of cryoprecipitates. In June 1981 the platelet count was 85,000 per microliter, and in January 1982 the count was 43,000 per microliter, but the patient had no unusual bleeding. When he was admitted to the

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hospital on April 11, 1982, numerous vascular spiders were noted on his thorax and arms. The platelet count was 37,000 per microliter, and a marrow aspirate demonstrated numerous megakaryocytes and erythrocytic hyperplasia. Slight enlargement of the spleen was noted on a liver–spleen scan. In addition, a direct Coombs' test was positive for IgG, and the reticulocyte count was slightly elevated. A partial remission followed the administration of prednisone. A recommendation for splenectomy was rejected by the patient. His platelet count on May 26, 1982, was 81,000 per microliter.

Patient 3

A 16-year-old boy with severe classic hemophilia (factor VIII titer <0.01 unit per milliliter) had been administering his own transfusions at home for five years, using five different lyophilized preparations of factor VIII over this period; he had recently been using factor VIII about once a week. In June 1982 he became aware of a transient punctate red rash on the top of his foot, which recurred several times. Beginning in September he had increasing fatigue. A platelet count on September 23 was 40,000 per microliter, and on October 7 the count was 15,500 per microliter. Results of marrow aspiration were similar to those of Patients 1 and 2. A direct Coombs' test was positive for IgG, and the serum haptoglobin level was severely depressed. Therapy with prednisone was followed by a partial remission, but the platelet count fell within three weeks after discontinuation of treatment and was 55,000 per microliter on December 13, 1982.

Patient 4

An 18-year-old boy with severe classic hemophilia (factor VIII titer <0.01 unit per milliliter) had been in a home therapy program for seven years, self-administering lyophilized factor VIII about once a week. Late in 1981 his physician detected a few cutaneous petechiae. The platelet count was 8000 per microliter, and increased numbers of megakaryocytes were seen in a marrow aspirate. During therapy with prednisone, the patient's platelet count varied from 25,000 to 61,000 per microliter. Therapy was discontinued, and the platelet count on June 29, 1982, was 54,000 per microliter.

Patient 5

A 71-year-old man with severe classic hemophilia (factor VIII titer <0.01 unit per milliliter) had been receiving home therapy for nine years. For the first two years, he self-administered cryoprecipitated factor VIII, and since then, lyophilized concentrates of factor VIII. For five years he had mild thrombocytopenia, with platelet counts ranging from 82,000 to 150,000 per microliter. No examination of bone marrow was performed. His mild thrombocytopenia was not treated.

Discussion

The coincidence of chronic "idiopathic" thrombocytopenic purpura and classic hemophilia is most unusual. Hruby[1] has described two such cases. One was in a 19-year-old boy with mild hemophilia (factor VIII titer, 0.10 unit per milliliter) who ultimately responded to splenectomy. In the other, thrombocytopenia was detected when the patient was 14 months of age, and it recurred intermittently during the succeeding five years, ultimately remitting after splenectomy. This patient (factor VIII titer <0.01 unit per milliliter) had been given a transfusion with commercial lyophilized concentrates of factor VIII when he was about two months old, during surgical correction of pyloric stenosis (Maurer H: personal communication). More recently, Suffredini and Qureshi[2] reported a third case, in a 22-year-old man with severe hemophilia (factor VIII titer <0.01 unit per milliliter) who had been treated for three years with factor VIII concentrates. The patient had a partial remission coincident with prednisone therapy. An instance of acute idiopathic thrombocytopenic purpura in an 18-year-old boy has also been recorded.[3]

The five patients whose cases have been summarized here were all severely affected classic hemophiliacs who had received repeated transfusions with lyophilized preparations of antihemophilic factor. In each, a syndrome developed that resembled idiopathic thrombocytopenic purpura, and four responded to a greater or lesser degree to therapy with prednisone. Splenectomy was performed in one patient and was followed by remission of thrombocytopenia. It is worth noting that the weight of the patient's spleen was greater than is usual in idiopathic thrombocytopenic purpura.[4]

Four of the patients had evidence of mild hepatic damage (Table 1). Platelet-associated IgG[5] was elevated in four patients, but not in the fifth, who was tested after splenectomy-induced remission (Table 1). The extent to which this reflected an increased concentration of serum IgG (Table 2) is uncertain. One patient had serum antibodies against platelets, as detected by an immunofluorescence test for non-complement-fixing antibodies[6] and by a test for ^{51}Cr release, which is a complement-dependent assay.[7] In addition, two patients had positive direct Coombs' tests for IgG. One of these patients had a slightly elevated reticulocyte count, and the other a decreased concentration of haptoglobin, but neither had the anemia that is typical of Evans' syndrome.

A causal relation between infusions of lyophilized factor VIII and the occurrence of thrombocytopenia has not yet been established. We have not observed concomitant thrombocytopenia in the many patients we have studied who were not treated with lyophilized preparations of factor VIII, but this association could easily have been overlooked. The three cases studied at University Hospitals of Cleveland occurred among 97 patients in home therapy programs in northeastern Ohio, and we know of 60 additional patients in this area who have been treated with lyophilized concentrates but are not receiving home therapy. Similarly, the two cases studied at the Blood Center of Southeastern Wisconsin were among 98 receiving home therapy and an additional 23 who had been treated with lyophilized concentrates under the guidance of the Great Lakes Hemophilia Foundation. The syndrome did not appear to be linked to concentrates prepared by a single manufacturer. The possibility exists that some concentrates may contain an agent or agents that induce what is apparently an immune thrombocytopenia. Whether such an agent is derived from some element of blood or is of infectious origin remains to be determined.

Two recent reports from the Centers for Disease Control[8,9] describe seven patients in whom classic hemophilia was complicated by *Pneumocystis carinii* pneumonia. All had been treated with concentrates of factor VIII. In each of six patients tested, the number

Table 1. Hematologic Values in Patients with Coincident Classic Hemophilia and Chronic "Idiopathic" Thrombocytopenic Purpura.

	Patient Number					Normal Values
	1	2	3	4	5	
Lowest platelet count (/μl)	30,000	37,000	15,500	8000	82,000	150,000–400,000
Platelet IgG (fg/platelet)	5.3 *	27.9	32.6	9.8–19.1	15.2	4.3±0.8 †
Platelet IgM (fg/platelet)	—	—	13.6	19.5	<0.6	<0.6–1.8
Serum anti-platelet antibodies						
Immunofluorescence	Neg	Neg	Neg	Neg	4+ ‡	Neg
Chromium release	Neg	Neg	Neg	Neg	4+ §	Neg
Hematocrit (%)	47	42	42	41	47	42–52
Reticulocyte count (%)	—	2.4	1.8	—	—	0.5–1.5
Haptoglobin (mg/dl)	—	43.4	2.3	—	—	30–205
Direct Coombs' test	Neg	Pos (IgG)	Pos (IgG)	—	—	Neg
White cells (/μl)	8100	7100	3900	2800	5600	4800–10,800

*Tested after splenectomy-induced remission (platelet count, 293,000 per microliter). †Mean ±S.D.
‡In 1977; 2+ in 1982. §In 1977; negative in 1982.

and proportion of helper T cells were decreased. Furthermore, in two of these patients lymphocytes did not respond normally to mitogenic stimulation. These changes are similar to those observed in homosexual men with an acquired immunodeficiency syndrome. Among 24 patients with severe hemophilia who were under treatment with lyophilized factor VIII and whom we studied in our laboratories, 14 had impaired cellular immunity.[10,11] Similar changes have been observed in other patients with hemophilia treated with lyophilized factor VIII.[12] Impaired cellular immunity was found in three of the four patients with thrombocytopenia who are described in this report (Table 3). In these persons, the relative number of OKT4 (helper) cells was decreased, and the relative number of OKT8 (suppressor) cells was increased, reversing the normal ratio of OKT4 to OKT8 cells. In addition, natural-killer activity and lymphocyte proliferative responses to mitogens were decreased in Patients 1 and 3.

Whether the impaired cellular immunity observed in our patients was causally related to their thrombo-

Table 2. Laboratory Values for Hepatic and Immunologic Functions in Patients with Coincident Classic Hemophilia and Chronic "Idiopathic" Thrombocytopenic Purpura.*

	Patient Number					Normal Values
	1	2	3	4	5	
SGOT (U/liter)	33–163	110–186	44	39	32–87	<41
SGPT (U/liter)	—	—	—	36	15–102	5–35
Lactic dehydrogenase (U/liter)	319–422	217–278	365	252	179–280	100–225
Alkaline phosphatase (U/liter)	69–95	159	328	—	125	25–115
Alkaline phosphatase (U/liter)	—	—	—	129	—	75–250
Bilirubin (mg/dl) ‡	0.8–1.0	1.2	0.5	0.6	0.8	0.1–1.2
Antinuclear antibody	<1:10	Neg	<1:10	—	—	<1:10
Anti-DNA (U/ml)	15.3	0	0	—	—	<15
LE test	Neg	—	—	—	—	Neg
Rheumatoid factor	<1:10	<1:20	<1:20	—	—	<1:20
Immune complexes (μg/ml) †	25.3	32.5	44.0	—	—	<30
CH_{50} (U/ml)	—	320	180	—	—	123–355
C3 (mg/dl)	189	108	11	—	—	83–177
C4 (mg/dl)	34.2	18.5	12.5	—	—	15–45
Serum albumin (g/dl) §	4.5	3.7	4.4	—	—	3.4–5.0
α_1 globulin (g/dl)	0.4	0.6	0.4	—	—	0.2–0.6
α_2 globulin (g/dl)	0.4	0.3	0.3	—	—	0.4–1.1
β globulin (g/dl)	0.9	0.7	1.0	—	—	0.5–1.2
γ globulin (g/dl)	1.7	2.3	3.0	—	—	0.5–1.4
IgG (mg/dl)	1680	2020	3200	—	—	600–1500
IgA (mg/dl)	151	329	374	—	—	85–380
IgM (mg/dl)	239	148	127	—	—	53–375
Fibrinogen-related antigen	—	+1:5	—	—	—	<1:20

*SGOT denotes serum aspartate aminotransferase, SGPT serum alanine aminotransferase, and LE lupus erythematosus.
†Determined by binding to solid-phase C1q.
‡To convert values for bilirubin to micromoles per liter, multiply by 17.10.
§To convert values for serum albumin to micromoles per liter, multiply by 144.9.

Table 3. Lymphocyte Subpopulations and Results of Functional Assays in Patients with Coincident Classic Hemophilia and Thrombocytopenia.*

	Patient Number				Normal Values †
	1	3	4	5	
Lymphocytes (/μl)	2,400	1,287	1,120	1,104	1519±379
OKT4 cells (%)	25.3	21.7	—	—	45±9
OKT4 cells (%)	—	—	38	43	50±4
OKT8 cells (%)	40.1	56.8	—	—	27±9
OKT8 cells (%)	—	—	38	25	25±2
OKT4/OKT8	0.63	0.38	—	—	1.84±0.70
OKT4/OKT8	—	—	1.0	1.72	2.04±0.24
Natural-killer activity (% killing)	9.8	5.8	—	—	37.8±12.2
Phytohemagglutinin response (cpm)	16,190	33,726	—	—	87,342±15,765
Concanavalin A response (cpm)	16,941	2336	—	—	58,545±13,007

*Lymphocytes bearing OKT4 (helper) and OKT8 (repressor) antigens were counted by flow cytometry. Natural killer activity was detected by ^{51}Cr release from radiolabeled K562 tumor target cells incubated with the subjects' peripheral-blood mononuclear cells (PBMC).[10,11] Lymphocyte proliferative responses were measured by ^{3}H-thymidine incorporation into PBMC that had been cultured for three days with phytohemagglutinin (1 μg per milliliter) or concanavalin A (1 μg per milliliter).[10] The data for Patient 1 have been published elsewhere in a different context.[10]

†Normal values are expressed as means ±S.D.

cytopenia is unclear. It is perhaps pertinent, however, that Morris et al.[13] have described 11 cases of severe "autoimmune" thrombocytopenic purpura in homosexual men. These studies and our observations suggest a need for careful surveillance of hemophiliacs receiving concentrates of factor VIII for disturbances of immunoregulation.

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