3. Gottlieb MS, Schroff R, Schanker HM, et al. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. N Engl J Med. 1981; 305:1425-31.
4. Masur H, Michelis MA, Greene JB, et al. An outbreak of community-acquired *Pneumocystis carinii* pneumonia: initial manifestation of cellular immune dysfunction. N Engl J Med. 1981; 305:1431-8.
5. Siegal FP, Lopez C, Hammer GS, et al. Severe acquired immunodeficiency in male homosexuals, manifested by chronic perianal ulcerative herpes simplex lesions. N Engl J Med. 1981; 305:1439-44.
6. Friedman-Kien A, Laubenstein LJ, Rubinstein P, et al. Disseminated Kaposi's sarcoma in homosexual men. Ann Intern Med. 1982; 96:693-700.
7. Mildvan D, Mathur U, Enlow RW, et al. Opportunistic infections and immune deficiency in homosexual men. Ann Intern Med. 1982; 96:700-4.
8. Brovall C, Schacter B. Radiation sensitivity of human natural killer cell activity: control by x-linked genes. J Immunol. 1981; 126:2236-9.
9. Lachenbruch PA. Discriminant analysis. New York: Macmillan, 1975.
10. Stepwise discriminant analysis (Program BMDP7M, BMDP Statistical Software). Berkeley, Calif.: University of California Press, 1981:519-37.
11. Stahl RE, Friedman-Kien A, Dubin R, Marmor M, Zolla-Pazner S. Immunologic abnormalities in homosexual men: relationship to Kaposi's sarcoma. Am J Med. 1982; 73:171-8.
12. Kornfeld H, Vande Stouwe RA, Lange M, Reddy MM, Grieo MH. T-lymphocyte subpopulations in homosexual men. N Engl J Med. 1982; 307:729-31.
13. Goeden JJ, Neuland CY, Wallen WC, et al. Amyl nitrite may alter T lymphocytes in homosexual men. Lancet. 1982; 1:412-6.

T-LYMPHOCYTE SUBPOPULATIONS IN PATIENTS WITH CLASSIC HEMOPHILIA TREATED WITH CRYOPRECIPITATE AND LYOPHILIZED CONCENTRATES

JAY E. MENITOVE, M.D., RICHARD H. ASTER, M.D., JAMES T. CASPER, M.D., STEPHEN J. LAUER, M.D., JEROME L. GOTTSCHALL, M.D., JAMES E. WILLIAMS, M.D., JOAN C. GILL, M.D., DANA V. WHEELER, R.N., VICKI PIASKOWSKI, B.S., PHYLLIS KIRCHNER, B.S., AND ROBERT R. MONTGOMERY, M.D.

PATIENTS with the acquired immunodeficiency syndrome (AIDS) include male homosexuals, intravenous drug abusers, and Haitian immigrants to the United States.[1-3] Approximately half the patients have contracted *Pneumocystis carinii* pneumonia, a third Kaposi's sarcoma, and 10 per cent concurrent Kaposi's sarcoma and *P. carinii* pneumonia. The mortality rate approaches 40 per cent. Persistent generalized lymphadenopathy and diffuse undifferentiated non-Hodgkin's lymphoma have also been reported in homosexual males and are considered part of the AIDS.[4,5] Nine patients (six with Kaposi's sarcoma and three with *P. carinii* pneumonia) were found to have had sexual contact with other AIDS patients.[6]

From the Blood Center of Southeastern Wisconsin, the Great Lakes Hemophilia Foundation, and the Departments of Medicine, Pediatrics, and Pathology of the Medical College of Wisconsin, Milwaukee. Address reprint requests to Dr. Montgomery at the Great Lakes Hemophilia Foundation, 1701 W. Wisconsin Ave., Milwaukee, WI 53233.

Supported in part by the MACC Fund, Milwaukee, and a grant (HL-13629) from the National Heart, Lung, and Blood Institute. Dr. Montgomery is an Established Investigator of the American Heart Association.

Among homosexual patients, studies of immunologic functions have demonstrated lymphopenia, cutaneous anergy, reduced helper T-lymphocyte (T4) subpopulations, increased suppressor T-lymphocyte (T8) subpopulations, inverted helper/suppressor T-lymphocyte (T4/T8) ratios, an abnormal lymphocyte response to mitogen stimulation, decreased natural-killer-cell activity, and paradoxically, hypergammaglobulinemia.[7-12] Altered T-lymphocyte subpopulations were also found in asymptomatic homosexuals, although the abnormalities were less severe than those seen in homosexuals with Kaposi's sarcoma or *P. carinii* pneumonia.[13,14] In one study an increased frequency of the HLA-DR5 phenotype was found in homosexual men with Kaposi's sarcoma.[10]

Recently, three cases of *P. carinii* pneumonia were diagnosed in patients with hemophilia A.[15] Although these patients had hemophilia, they had not received immunosuppressive therapy and did not have other underlying diseases. They were heterosexuals with no history of intravenous drug abuse. Their immunologic evaluation revealed dysfunction of cellular immunity (inverted T4/T8 ratio, an impaired lymphocyte response to mitogen stimulation, and a reduced number of circulating T cells). All had been treated with large doses of commercially prepared lyophilized factor VIII concentrates as part of the treatment of their coagulation defect. Two of the three received transfusions for prophylaxis almost daily, and the third received them every four to five days. One patient used concentrates prepared by six different manufacturers; another, concentrates prepared by five manufacturers; and a third, concentrates prepared by three or four. None used the same lot of factor VIII concentrate. Another case of *P. carinii* pneumonia and one of cryptospirilliosis occurring in patients with hemophilia A are currently being investigated (Evatt BL: personal communication).

The clustering of AIDS in patients with common sexual contacts and the occurrence of *P. carinii* pneumonia among users of factor VIII concentrates have led to speculation that AIDS may be transmitted to patients with hemophilia through factor VIII infusion.[16] To evaluate this possibility we performed immunologic studies on healthy patients with hemophilia treated either with cryoprecipitate obtained from volunteer blood donors or with commercially prepared, lyophilized factor VIII concentrates. Eight of 22 patients had abnormal T4/T8 ratios. None of the cryoprecipitate users and 57 per cent of the users of commercially prepared lyophilized concentrates had abnormal T4/T8 ratios ($P<0.003$).

METHODS

Patients with hemophilia who were being followed in the Comprehensive Hemophilia Program of the Great Lakes Hemophilia Foundation were divided into three groups: those being treated only with cryoprecipitate prepared from plasma obtained from volunteer blood donors at the Blood Center of Southeastern Wisconsin, those using high amounts of commercially prepared factor VIII concen-

trates (>3000 units of factor VIII per kilogram of body weight per year), and those using moderate amounts of factor VIII concentrates (1000 to 3000 units per kilogram per year). Twenty-two patients were selected from these groups for immunologic study on the basis of their availability for blood testing. None were known to be homosexuals. All were specifically examined for enlargement of lymph nodes, liver, and spleen. Sixteen age-matched subjects without hemophilia were used as controls.

Complete blood counts, including differential white-cell counts on 200 cells, were performed.

Quantitative determinations of serum IgG, IgA, and IgM were performed on a Hyland Laser Nephelometer PDQ (Deerfield, Ill.). The mononuclear-cell population of heparinized venous blood was separated by centrifugation through Ficoll–Hypaque. The mononuclear cells were evaluated for cell-surface markers, and the remaining cells were frozen in 10 per cent dimethyl sulfoxide and stored in liquid nitrogen for less than two weeks for assessment of natural killer cells.

Levels of membrane immunoglobulin were determined by direct immunofluorescence of viable cells incubated at 4°C for 30 minutes with fluorescein-conjugated goat antihuman immunoglobulin (Meloy, Springfield, Va.). The proportion of cells expressing the T-cell antigens T4 (helper) or T8 (suppressor) were enumerated with use of OKT monoclonal antiserum (Ortho Diagnostic Systems, Raritan, N.J.), and cells were quantitatively assessed for OKM1 positivity (natural killer cells are usually OKM1 positive). E rosettes were assayed by incubation with sheep red cells treated with 2-amino-ethylisothiouronium bromide hydrobromide (Sigma, St. Louis, Mo.). HLA-A, B, C, and DR phenotyping was performed. Statistical comparisons included linear discriminate and regression analysis, two-tailed Student's t-tests (adjusted for multiple comparisons), and chi-square analysis, when appropriate. Because of the small sample size, negative results have poor statistical power. Consequently, caution should be exercised in interpreting all negative findings in this paper.

Results

Table 1 lists the results for the controls and the patients with hemophilia A. The T4/T8 ratio was found to be abnormal in 36 per cent of the patients. In addition, the patients had decreased percentages of helper T-lymphocytes ($P<0.03$), increased percentages of suppressor T-lymphocytes ($P<0.03$), and increased levels of serum IgG ($P<0.02$).

To determine whether the type of antihemophilic factor used influenced these abnormalities, the hemophilia group was divided into those who received cryoprecipitate and those who received commercial factor VIII concentrates. Discriminant analysis of the 10 variables in Table 1 (omitting product usage) was performed to compare the results for the patients who received cryoprecipitate with those for the patients who received lyophilized commercial concentrate. The T4/T8 ratio was found to be the greatest discriminating factor. The cryoprecipitate users were further divided into those using small amounts (100 to 999 units per kilogram per year) and those using moderate amounts (≥1000 units per kilogram per year), and the concentrate users were divided into those using very high amounts (more than 3000 units per kilogram per year) and those using moderate amounts (1000 to 3000 units per kilogram per year). Although use in the moderate cryoprecipitate group was similar to that in the moderate factor VIII concentrate group, none of the former had abnormal T4/T8 ratios, whereas four of the seven in the latter group had abnormal ratios ($P<0.02$). The T4/T8 ratios were abnormal in 57 per cent of each of the two concentrate groups (Fig. 1). When Student's t-test was used, the T4/T8 ratios in patients receiving cryoprecipitate did not differ from those in the controls, but the ratios in patients receiving factor VIII concentrate differed significantly from those in patients receiving cryoprecipitate ($P<0.003$). The age of the patients and the severity of hemophilia were similar in the various groups, but concentrate users received more intensive antihemophilic-factor therapy than cryoprecipitate users. However, there was no correlation between the amount of exposure to factor VIII and the ratio of T4 to T8 within the concentrate group. Since multiple lots and four different commercial sources of product were used, no association with a lot was identified.

OKM1-positive cells, those presumed to have natural-killer activity, were slightly decreased in the hemophilic group (20 per cent) as compared with the controls (27.5 per cent), but this was not statistically significant.

Serum IgG levels were higher among the patients than among the controls ($P<0.02$), but levels in cryoprecipitate users did not differ from those in concentrate users (Table 1). However, patients with abnormal T4/T8 ratios had higher IgG levels (1860 mg per

Table 1. Lymphocyte Subpopulations, Factor VIII Use, Platelet Counts, and IgG Concentrations in Controls and in Patients with Hemophilia A Treated with Cryoprecipitate or Factor VIII Concentrates.*

Subjects (No.)	Age	Factor VIII	T4 Cells	T8 Cells	T4/T8 Ratio	OKM1 Cells	B Cells	T Cells	Lymphocytes	Platelets	IgG
	yr	units/kg/yr	%			%			cells × 10^{-3}/mm^3		mg/dl
Controls (16)	24.6	—	50.4	24.6	2.06	27.5 †	11.8	73.1	2.41	253.33	972.1 ‡
	±3.5	—	±0.9	±0.6	±0.06	±2.6	±0.4	±0.6	±0.23	±12.71	±68.5
Hemophiliacs (22)	19.5	2746.0	45.9	28.6	1.73	19.9	13.4	72.1	2.22	233.36	1467.8
	±3.1	±459.6	±1.7	±1.6	±0.12	±3.0	±0.9	±0.7	±0.14	±15.82	±169.6
Treated with concentrate (14)	17.6	3689.1	44.0	32.2	1.44	19.6	12.9	72.9	2.33	225.21	1607.3
	±2.8	±559.7	±2.6	±1.9	±0.14	±3.7	±1.2	±0.8	±0.19	±21.21	±257.8
Treated with cryoprecipitate (8)	22.9	1095.6	49.3	22.3	2.23	20.4	14.4	70.9	2.03	247.63	1223.6
	±7.1	±336.0	±0.8	±0.8	±0.07	±5.5	±1.0	±1.2	±0.19	±23.61	±88.7

*Data are reported as means ±S.E.M. The percentages of T8 cells and the T4/T8 ratios were significantly different in the control and concentrate groups ($P<0.01$ or less) and in the cryoprecipitate and concentrate groups ($P<0.003$). Use of factor VIII was significantly lower in the cryoprecipitate group than in the concentrate group ($P<0.001$).

†n = 6. ‡n = 7.

deciliter) than patients with normal ratios (1243 mg per deciliter). Four of the eight patients with T4/T8 ratios lower than 1.5 had serum IgG levels greater than 1500 mg per deciliter. No difference in serum IgA or IgM concentrations was found in the group.

Only two patients had absolute lymphocyte counts below 1500 per cubic millimeter. One, a concentrate user, also had an abnormal T4/T8 ratio (0.57) and hypergammaglobulinemia (2040 mg per deciliter).

HLA-A, B, C, and DR phenotyping was performed on six patients with abnormal T4/T8 ratios. The DR phenotypes (DR5,8; DR1,2; DR4,−; DR1,7; DR7,−; DR4,7) were not different from those that would be expected by chance.

One of the 22 patients had marked generalized lymphadenopathy and splenomegaly (7 cm below the left costal margin) on physical examination. His T4/T8 ratio was abnormal, with 32 per cent OKT4 cells, 32 per cent OKT8 cells, and 2 per cent OKM1 cells. The lymphocyte count was 1600 per cubic millimeter, and the serum IgG concentration was 4694 mg per deciliter.

Only one of the 22 patients had a positive test for hepatitis B surface antigen. He used only cryoprecipitate and had been an asymptomatic carrier for more than four years. His T4/T8 ratio was normal.

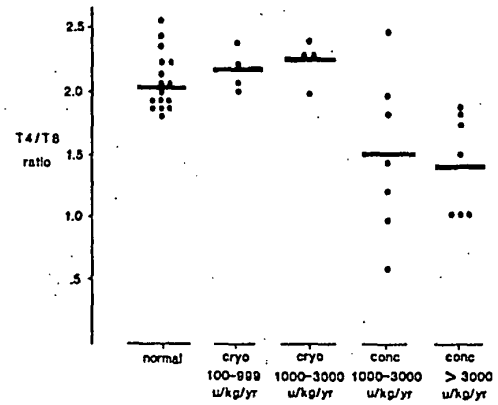

Figure 1. Comparison of T4/T8 Ratios in Patients with Hemophilia, According to Type of Product Used and Total Dose Administered over the Past Year.

Cryo denotes cryoprecipitate prepared from plasma of volunteer blood donors, and conc denotes lyophilized antihemophilic-factor concentrates obtained from commercial sources. Mean values are indicated by solid bars. T4/T8 ratios in patients treated with cryoprecipitate are similar to those in controls, but the ratios in patients receiving concentrate are significantly lower ($P<0.001$). Four of the seven patients using 1000 to 3000 units of concentrate per kilogram per year had abnormal T4/T8 ratios as compared with none of those using a similar amount of cryoprecipitate ($P<0.02$).

Discussion

Except in isolated reports on patients with hemophilia who died with *P. carinii* pneumonia, abnormalities of T-lymphocyte subpopulations have not been described in patients with hemophilia. Our studies demonstrated abnormal T4/T8 ratios in 36 per cent of the entire group with hemophilia and in 57 per cent of the users of factor VIII concentrate. Since our studies were performed only once or twice in each patient, it is not yet known whether these abnormalities are persistent. The abnormal T4/T8 ratios, decreased OKM1 positive cells, and increased serum IgG were similar to earlier findings in homosexuals.[1-14]

Only one of our patients in this study appeared to be clinically affected by persistent (>18 months), marked generalized lymphadenopathy and splenomegaly. These findings are similar to those in some of the reported cases of AIDS. After this study was completed, a second patient with generalized lymphadenopathy and hemophilia A, but without splenomegaly, was seen in our clinic and found to have an abnormal T4/T8 ratio of 1.21.

Caution must be exercised in interpreting the meaning of these laboratory findings. We do not know whether the abnormalities in laboratory tests will prove to be persistent or transient. Although users of cryoprecipitate had normal T4/T8 ratios, studies of patients receiving larger amounts of cryoprecipitate will be needed to determine whether the AIDS-like picture is associated with commercial factor VIII only. In addition, we cannot say that the amount of factor VIII used or the type of commercial product is causally related. None of the patients we studied reported intercurrent viral or bacterial infections during the period of the study.

Interestingly, autoimmune thrombocytopenic purpura has recently been reported in homosexual patients[17] and has likewise been observed in five patients with hemophilia A (unpublished data). This association may be coincidental, although T4/T8 ratios were abnormal in three of the four patients studied in the latter group.

The proposed explanations for AIDS include infections (cytomegalovirus), drug use (inhaled nitrites), and exposure to foreign antigens (spermatozoa). Our data are consistent with the possibility that commercially prepared lyophilized factor VIII concentrates can induce an AIDS-like picture, but a large number of patients must be studied before a definite conclusion can be drawn. In addition, we cannot hypothesize about the emergence of this apparently new syndrome at this time. Whether the abnormalities found in our patients will evolve into clinical disorders remains to be determined, but we urge those involved in the care of patients who use factor VIII concentrate to follow them carefully for stigmata of AIDS and changes in immunologic status.

We are indebted to Jay Hunter and the Tissue Typing Laboratory of the Blood Center of Southeastern Wisconsin for their technical assistance, to the Laboratory and Clinical Medicine Department of Mount Sinai Medical Center in Milwaukee for performing the serum immunoglobulin determinations and complete blood counts, to Alfred J. Anderson of the Department of Biostatistics at the Medical College of Wisconsin for statistical analysis, and to Wendy Stinebaugh for the preparation of the manuscript.

References

1. Update on Kaposi's sarcoma and opportunistic infections in previously healthy persons — United States. Morbid Mortal Weekly Rep. 1982; 31:294-301.
2. Opportunistic infections and Kaposi's sarcoma among Haitians in the United States. Morbid Mortal Weekly Rep. 1982; 31:353-61.
3. Centers for Disease Control Task Force on Kaposi's Sarcoma. Epidemiologic aspects of the current outbreak of Kaposi's sarcoma and opportunistic infections. N Engl J Med. 1982; 306:248-52.
4. Persistent, generalized lymphadenopathy among homosexual males. Morbid Mortal Weekly Rep. 1982; 31:249-51.
5. Diffuse, undifferentiated non-Hodgkins lymphoma among homosexual males — United States. Morbid Mortal Weekly Rep. 1982; 31:277-9.
6. A cluster of Kaposi's sarcoma and *Pneumocystis carinii* pneumonia among homosexual male residents of Los Angeles and Orange Counties, California. Morbid Mortal Weekly Rep. 1982; 31:305-7.
7. Gottlieb MS, Schroff R, Schanker HM, et al. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. N Engl J Med. 1981; 305:1425-31.
8. Masur H, Michelis MA, Greene JB, et al. An outbreak of community-acquired *Pneumocystis carinii* pneumonia: initial manifestation of cellular immune dysfunction. N Engl J Med. 1981; 305:1431-8.
9. Siegal FP, Lopez C, Hammer GS, et al. Severe acquired immunodeficiency in male homosexuals, manifested by chronic perianal ulcerative herpes simplex lesions. N Engl J Med. 1981; 305:1439-44.
10. Friedman-Kien AE, Laubenstein LJ, Rubinstein P, et al. Disseminated Kaposi's sarcoma in homosexual men. Ann Intern Med. 1982; 96:693-700.
11. Mildvan D, Mathur U, Enlow RW, et al. Opportunistic infections and immune deficiency in homosexual men. Ann Intern Med. 1982; 96:700-4.
12. Follansbee SE, Busch DF, Wofsy CB, et al. An outbreak of *Pneumocystis carinii* pneumonia in homosexual men. Ann Intern Med. 1982; 96:705-13.
13. Stahl RE, Friedman-Kien A, Dubin R, Marmor M, Zolla-Pazner S. Immunologic abnormalities in homosexual men: relationship to Kaposi's sarcoma. Am J Med. 1982; 73:171-8.
14. Kornfeld H, Vande Stouwe RA, Lange M, Reddy MM, Grieco MH. T-lymphocyte subpopulations in homosexual men. N Engl J Med. 1982; 307:729-31.
15. *Pneumocystis carinii* pneumonia among persons with hemophilia A. Morbid Mortal Weekly Rep. 1982; 31:365-7.
16. Marx JL. New disease baffles medical community. Science. 1982; 217:618-21.
17. Morris L, Distenfeld A, Amorosi E, Karpatkin S. Autoimmune thrombocytopenic purpura in homosexual men. Ann Intern Med. 1982; 96:714-7.

AN INFLAMMATORY PSEUDOTUMOR OF THE LUNG IN Q FEVER PNEUMONIA

DAVID THOMAS JANIGAN, M.D., AND THOMAS JAMES MARRIE, M.D.

"INFLAMMATORY pseudotumor" is a generic term for a lung mass, usually solitary, composed of mixtures of histiocytes or macrophages (sometimes lipid-filled — i.e., "foam cells"), plasma cells, lymphocytes, fibroblasts, and collagen.[1] Because these components are present in highly variable ratios and spatial interrelations,[2-5] these lesions have been designated variously as "plasma-cell granuloma," "fibrohistiocytoma," "xanthoma," "xanthofibroma," "xanthogranuloma," "xanthomatous pseudotumor," and "post-inflammatory pseudotumor." Their clinical features, including evidence of a preceding or concurrent respiratory infection, are also quite varied.[2-4,6,7] However, the most consistent and clinically important feature is their radiologic mimicry of malignant neoplasms, so that nearly all reported examples have been found in lobectomy or pneumonectomy specimens. To date, morphologic[5,8-12] and microbiologic[3,4,6,9-11] studies have failed either to uncover an etiologic agent (or agents) or to establish the pathogenetic mechanisms. We report the development of a lung pseudotumor during the course of *Coxiella burnetii* pneumonia. The demonstration of this organism within the pseudotumor establishes it as at least one cause of these lesions.

From the Departments of Pathology, Medicine, and Microbiology, Dalhousie University and Victoria General Hospital, Halifax, N.S., Canada. Address reprint requests to Dr. Janigan at the Department of Pathology, Dalhousie University, Halifax, NS B3H 4H7, Canada.

Case Report

A 67-year-old woman was well until July 1981, when fatigue, malaise, sweats, and chills developed over two days and were followed by fever and right hypochondrial pain. On her admission to a local hospital four days later, the temperature was 40°C and mild abdominal tenderness was present in the right lower quadrant. Over the next two days the patient remained febrile and became confused. She was then transferred to our hospital; examination showed that the temperature was 40.5°C, the respiration 20, the blood pressure 90/60 mm Hg, and the pulse rate 82. Rales, decreased breath sounds, and decreased tactile and vocal fremitus were noted over the left upper lobe. The spleen was felt 6 cm below the left costal margin in the midclavicular line. Chest films (Fig. 1) and tomograms revealed a mass suggestive of lymphoma or carcinoma of the lung. Blood and urine cultures were negative. The spinal fluid was clear, with two white cells per cubic millimeter and normal levels of protein and glucose. No bacteria or viruses were isolated. The hemoglobin level was 11 g per 100 ml (falling to 9.7 g by the seventh hospital day), and the white-cell count was 5100 per cubic millimeter, with 88 per cent polymorphonuclear leukocytes, 6 per cent monocytes, and 6 per cent lymphocytes. The erythrocyte sedimentation rate was 119 mm per hour, and the platelet count 108,000. The serum alanine aminotransferase level was 43 IU per liter (716 nmol · sec^{-1} per liter), the aspartate aminotransferase 78 IU per liter (1300 nmol · sec^{-1} per liter), the alkaline phosphatase 210 IU per liter (3500 nmol · sec^{-1} per liter), and the total bilirubin 17 μmol per liter (0.98 mg per deciliter). A percutaneous liver biopsy revealed nonspecific hepatitis.

The patient remained febrile despite therapy with penicillin, cloxacillin, and gentamicin. After a left upper lobectomy on the 11th

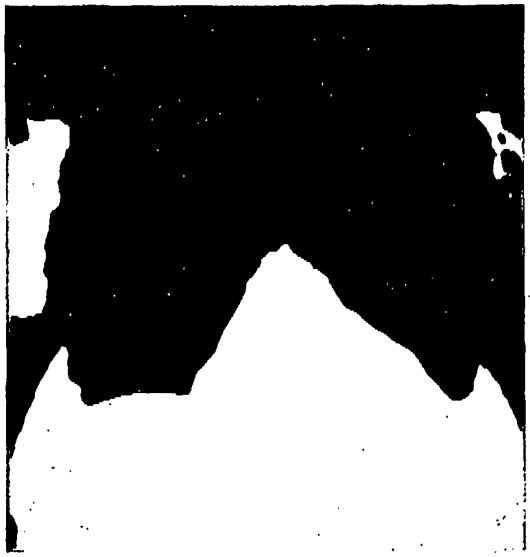

Figure 1. Mass in the Left Para-aortic Area (Chest Radiograph).