THE EFFECT OF DESOXYCORTICOSTERONE ACETATE AND VITAMIN C ON CHRONIC LEUKEMIA

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THE RELATIONSHIP between adrenal cortical hormones and lymphoid tissues has been the subject of considerable recent interest since the resurgence of studies on this subject by Dougherty and White. Earlier observations date back to Thomas Addison who, in 1855, observed lymphatic hyperplasia in one of the patients who died of the condition now known by Addison's name and now recognized to be caused by deficiency of adrenal cortical hormones. Enlargement of the thymus and lymph nodes in Addison's disease was also noted by Guttman, and lymphocytosis in this condition was recorded by de la Balze, Reifenstein, and Albright. Parallel observations have been recorded in adrenalectomized animals by Zwemer and Lyons, Corey and Britton, and White and Dougherty. Administration of 11-oxygenated adrenal cortical steroids and of pituitary adrenocorticotropic produces a rapid involution of the thymus and lymph nodes, decreases the number of circulating lymphocytes, and abolishes circulation of lymphocytes in the thoracic duct. From these observations it is apparent that the number of circulating lymphocytes is, to some extent at least, under the control of adrenal cortical steroids, and that these cells are unduly sensitive—along with the eosinophiles—to the catabolic influence of these steroids. This phenomenon was first deduced clinically by Albright and later demonstrated experimentally by Gordan, Li, and Bennett. Attempts have been made to make use of this effect of adrenocorticotropic and of 11-oxygenated steroids to reduce the lymphoid overgrowth in clinical conditions. Pearson et al. at the Sloan-Kettering Institute, reported favorable results with large doses of adrenocorticotropic in lymphatic leukemia. Since the effects of adrenocorticotropic and of cortisone in rheumatoid arthritis can be reproduced to some degree by desoxycorticosterone acetate and vitamin C, it seemed worth while to investigate the possibility that the latter combination might also favorably influence the course of chronic lymphocytic or granulocytic leukemia.

It is the object of this report to present the data obtained from a series of observations made on a group of patients with leukemia who were given desoxycorticosterone acetate and vitamin C.

METHOD

Seven subjects were studied. They were undoubted cases of leukemia as ascertained by studies of the peripheral blood and sternal marrow. Four were diagnosed as chronic lymphatic (lymphocytic) leukemia.

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and three as chronic myelogenous (granulocytic) leukemia. All previous therapy was stopped two weeks before the onset of treatment as outlined. Four patients had had x-ray therapy (T. H., P. S., V. M., and E. F.), one had been on symptomatic therapy with urethane (B. M.), one had been treated supportively with frequent blood transfusions (C. E.), and one had not been treated (E. B.). V. M., a 28 year old female with chronic myelogenous leukemia, became pregnant approximately two months before the onset of the therapeutic trial. The age of the patients studied ranged from 18 to 74 years.

Treatment was given once every day for five days. The dosage consisted of 5 milligrams of desoxycorticosterone acetate given directly into the deltoid muscle, followed in two minutes by 1 gram of ascorbic acid (Roche) (sodium salt), intravenously, as described in the treatment of rheumatoid arthritis by Lewin and Wassn.17 Following a rest period of two days, another series of treatments was given over a period of five days. All patients followed this course except one (E. B.), from whom two treatments were withheld because of the sudden development of edema of the ankles at the onset of menses. This appearance of the edema was presumably due to the drug therapy. The blood pressures and total body weights of the patients were obtained in the supine position daily. Complete blood counts, which included estimation of the number of red blood cells and the hemoglobin content, the kind and number of leukocytes, as well as the number of blood platelets, were taken on each patient every day.

Case Reports

Case 1. P. S., a 50 year old white male, was first examined in the Out-Patient Department in June, 1949, at which time he had noted a generalized adenopathy. The liver and spleen were not enlarged. His white blood cell count was 161,050, of which 91 per cent were lymphocytes. Examination of the sternum marrow showed a marked increase in lymphocytes. Diagnosis of chronic lymphocytic leukemia was made. He was given total body roentgen irradiation, soon after which the white cell count decreased to 15,000 cells per cu. mm. This form of treatment was repeated at intervals of sufficient frequency to maintain the white count between 15,000 to 20,000 per cu. mm. The last treatment was received December 5, 1949, and he was given desoxycorticosterone and sodium ascorbate on January 16, 1950.

Case 2. Mrs. E. B., a 49 year old white female, reported to her physician in May, 1949, because of malaise and increasing fatigability. On examination there was no demonstrable adenopathy or enlargement of the spleen and liver. A white blood cell count, however, showed 41,000 cells per cu. mm., of which 70 per cent were of the lymphocyte variety. The red blood cell count and hemoglobin estimation were within the range of normal. The patient had been followed over a period of four months without being given any treatment, during which time the white blood cell count varied between 40,000 to 50,000 per cu. mm. She was started on desoxycorticosterone acetate and vitamin C on January 16, 1950.

Case 3. T. H., a 74 year old white male, was first examined in the Out-Patient Department in June, 1946 during a routine physical examination. Eighty-six per cent of these cells were classified as lymphocytes. Bone marrow removed from the sternum and biopsy of a lymph node were consistent with the diagnosis of chronic lymphatic leukemia. The patient had been given total body roentgen irradiation at frequent enough intervals to reduce his white count to 10,000 cells per cu. mm. He had received no roentgen irradiation for six weeks prior to the time he was given desoxycorticosterone acetate and vitamin C.

Case 4. C. E., a 68 year old white male, had been under observation since July, 1947, because of lymphatic leukemia. When first examined he presented generalized adenopathy, and the liver and spleen were slightly enlarged. The red blood cell count was 1,940,000 cells per cu. mm., the white blood cells were 97,000 per cu. mm., and the hemoglobin measured 5.2 grams. A differential count showed 92 per cent lymphocytes. The spleen, lymph nodes and the white cell count were considerably reduced with roentgen irradiation. At the time of treatment with desoxycorticosterone acetate and vitamin C the white blood cell count was 41,000 per cu. mm.

Case 5. Mrs. B. M., a 35 year old white female, was first seen in the Out-Patient Department of the University of California Hospital in February, 1949, because of frequent epistaxis. On physical examination she was found to have a slight enlargement of the spleen. The red blood cells were 3,140,000 per
cu. mm., the white blood cells were 467,000 per cu. mm., and the hemoglobin was 8.9 grams. The differential count showed 59 per cent polymorphonuclear neutrophiles, 2.2 per cent metamyelocytes, 10 per cent promyelocytes, 6 per cent myeloblasts, and 3 per cent lymphocytes. She was given urethane orally, which was followed by a reduction in the white cell count to 10,000 per cu. mm. The patient had not received treatment of any kind for several months prior to the administration of desoxycorticosterone acetate and vitamin C.

Case 6. E. F., an 18 year old white male, had reported to the Out-Patient Department on December 16, 1949, because of increasing fatigability and the development of dyspnea. There was marked enlargement of the spleen to such an extent it almost filled the entire left half of the abdomen. The white blood cell count was 492,000 per cu. mm., of which 1 per cent were reported to be myeloblasts, 1 per cent promyelocytes, 28 per cent myelocytes, 21 per cent metamyelocytes, 47 per cent polymorphonuclear neutrophiles and 1 per cent lymphocytes. A diagnosis of chronic granulocytic leukemia was made, which was substantiated by the cytologic changes of the bone marrow removed at puncture of the sternum. At the time of treatment with desoxycorticosterone acetate and vitamin C on January 16, 1950, the white blood cell count was 378,000 per cu. mm.
Case 7. Mrs. V. M., a 28 year old white female, was examined on July 19, 1949. The edge of the spleen was palpable 10 cm. below the left costal margin and the liver edge 1 cm. below the right costal margin. The white blood cell count was recorded as 162,500 per cu. mm. A diagnosis of chronic granulocytic leukemia was made, and the patient was treated with total body irradiation. On January 16, 1950, the total white cell count was 50,000 per cu. mm., of which 5/10 per cent were myeloblasts, 2.5 per cent promyelocytes, 9 per cent metamyelocytes, 39 per cent nonfilamented, and 19 per cent filamented neutrophiles.

DISCUSSION

The exact role of ascorbic acid in the adrenal cortex is not known. It is, however, a major component of this division of the adrenal gland, and seems to be removed with cholesterol in time of stress or after administration of ACTH. The role of ACTH and cortisone in altering the course of rheumatoid arthritis and leukemia is now known. It is equally well substantiated that desoxycorticosterone alone has no lympholytic actions. However, since, in combination with vitamin C, it resulted in striking improvement in many cases of rheumatoid arthritis, an attempt was made to assay the effects of this combination in patients with leukemia. In view of the absence of any significant changes in either the blood modalities or physical status of the patients thus subjected to the combined therapy, it seems evident that no analagous role to the arthritic changes induced by these drugs can be made. It also serves to impress further the probability that the addition of ascorbic acid to desoxycorticosterone in this dose does not result in the formation of an 11-oxygenated steroid.

SUMMARY

1. Four patients with chronic lymphatic (lymphocytic) leukemia, and 3 patients with chronic myelocytic leukemia were given ten daily treatments of desoxycorticosterone acetate (5 milligrams) and vitamin C (1 gram) parenterally.
2. No significant immediate or post-treatment effects resulting from this treatment were observed in either group.
3. Desoxycorticosterone acetate and vitamin C in combination have no lympholytic action in patients with chronic lymphatic leukemia.

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