nic reviewed 130 patients over a 16-year period and showed a 48% five-year survival rate for those treated with ACTH or corticosteroid therapy compared with only 13% for untreated patients. These results agree with those reported by the British Medical Research Council[12] but differ somewhat from the opinion expressed by Rupe.[13]

It is also interesting to note that in 4 of the 18 cases of necrotizing vasculitis reviewed by Owano and Sueper[3] there was involvement of veins as well as of small arteries and arterioles.

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Hodgkin's Disease Complicated by Infection with *Mycobacterium kansasii*

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PATIENTS with Hodgkin's disease have an increased incidence of tuberculosis. This was recognized by Ewing[1] in 1940: ". . . in New York, where the disease is very common, tuberculosis follows Hodgkin's disease like a shadow". In 1947 Jackson and Parker[2] cited a 20% incidence of active tuberculosis in patients with Hodgkin's disease. In 1959, Razis, Diamond and Craver[3] reported 20 cases of tuberculosis in a series of 1024 patients with Hodgkin's disease seen at The Memorial Hospital in New York, an incidence of 1.8%. Evidence of tuberculosis was found in 12 (5.1%) of 234 autopsies in that series.

The report below describes the first case of Hodgkin's disease complicated by pulmonary infection with *Mycobacterium kansasii.*

In November 1959, C.W., a 51-year-old white man, complained to his family physician of fatigue, weight loss and fever. Physical examination revealed enlarged axillary and anterior and posterior cervical lymph nodes. A chest radiograph showed hilar lymphadenopathy. In December 1959, Hodgkin's granuloma was diagnosed from a cervical node biopsy. The patient was treated with nitrogen mustard and a complete clinical remission of the disease followed. In July 1960, palpable nodes were found in the left cervical, left axillary and both inguinal regions. After radiotherapy there was another complete remission. In November 1960 and again in March 1962, enlargement of the lymph nodes recurred in the same areas but disappeared after additional treatment with nitrogen mustard. In February 1963, local radiotherapy was successful in the treatment of enlarged nodes in the right cervical and in both axillary areas.

In August 1963, the patient was referred to our hospital with symptoms of fever, night sweats, nausea and vomiting. Physical examination showed enlarged left posterior cervical nodes and left axillary nodes. The oral temperature was 103° F. The hemoglobin was 13.6 g. per 100 ml.; the leukocyte count was 2800 and the platelet count was 106,000 per c.mm. A lymphangiogram was normal. The patient was given cyclophosphamide 100 mg. daily. All symptoms and clinical evidence of disease disappeared. In June 1964 a spontaneous left pneumothorax developed; this was successfully managed by closed suction of the pleural cavity. His disease remained in complete remission while he was receiving cyclophosphamide (75 to 150 mg. daily, depending on the leukocyte count) until August 1964.

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Then the patient developed fever, nausea and vomiting, and lost 10 lbs. Enlarged nodes were found in the right axilla and in both inguinal areas. Liver function tests were reported as abnormal. A chest radiograph showed right middle-lobe pneumonia. The patient was admitted to hospital and his pneumonia successfully treated with penicillin. A liver biopsy revealed Hodgkin's granuloma. Cyclophosphamide was discontinued and the patient was given vinblastine sulfate (Vincaleucoblastine) 10 mg. weekly; once more, all clinical and laboratory evidence of Hodgkin's disease disappeared. This drug was then given only once a month and the patient continued in remission.

In December 1964 he developed herpes zoster involving the right fifth cranial nerve; this resolved without sequelae. In November 1965 a recurrence of the right middle lobe pneumonia was again successfully treated with penicillin, as was yet another recurrence in March 1966. A routine chest radiograph in January 1968, at a time when the patient was asymptomatic and with no clinical evidence of disease, showed bilateral apical cavitating and infiltrative lesions. Treatment with para-aminosalicylic acid and isoniazid was begun at once. No acid-fast bacilli were seen in repeated smears of sputum specimens. However, after four weeks, cultures of sputum specimens grew atypical acid-fast organisms, identified as *Mycobacterium kansasii*. *In vitro* sensitivity tests showed resistance to isoniazid, para-aminosalicylic acid, streptomycin and viomycin, but sensitivity to ethionamide and cycloserine. The medications were changed to ethionamide 250 mg. three times daily and cycloserine 250 mg. twice a day. There has been progressive resolution of the pulmonary lesions. Complete remission of the Hodgkin's disease continues; the patient is still receiving vinblastine sulfate, 10 mg. per month.

Immunologic studies were first performed at a time when the Hodgkin's disease was in full clinical remission and when there was progressive resolution of the patient's pulmonary acid-fast disease, i.e. one week after he had received the first monthly maintenance dose of vinblastine sulfate.

Serum immunoglobulin levels determined by radial immunodiffusion gave values of IgG, IgA and IgM of 1350 mg. (normal: 650 to 1750), 140 mg. (normal: 75 to 330) and 41 mg. per 100 ml. (normal: 30 to 225), respectively. Electrophoresis of the serum proteins performed by the microcellulose acetate technique showed normal values for all fractions.

The patient was immunized with 5 mg. of Keyhole limpet hemocyanin (KLH) given subcutaneously one week after treatment with vinblastine sulfate. In man this antigen elicits delayed hypersensitivity and humoral antibody formation.[6] It also stimulates *in vitro* lymphocyte blastogenesis in the cultured lymphocytes of immunized individuals.[7] Antibody was measured by the tanned-cell hemagglutination method and the difference between 19S and 7S antibody distinguished by sensitivity to 2-mercaptoethanol.[6] The patient developed 19S antibody at seven days and switched over to 7S antibody formation at 28 days after immunization (Table I). This qualitative sequence followed a normal pattern.[6, 8] However, the quantity of antibody produced was less than that in a control population.

TABLE I.—HUMORAL ANTIBODY FORMATION* IN RESPONSE TO KEYHOLE LIMPET HEMOCYANIN (KLH)

	Days after immunization				
	0	*7*	*14*	*21*	*28*
19S antibody	0 (0)	1 (4-4.5-5)	2 (5-6-7)	2 (-)†	1 (0-2-7)
7S antibody	0 (0)	0 (0-0-1)	0 (0-0-1)	0 (-)†	2 (0-3-6)

*Range for control population given in parentheses.[8] Middle figure represents median. Titres are reported as $\log_2$ highest serial dilution showing macroscopic hemagglutination.

†Values not obtained.

TABLE II.—SKIN TESTS FOR DELAYED HYPERSENSITIVITY TO PURIFIED PROTEIN DERIVATIVES OF MYCOBACTERIAL ANTIGENS

	Reaction at 48 hrs. (mm.)
PPD-B* (non-chromogen "Battey" type)	0 x 0
PPD-S* (mammalian tubercle bacilli)	7 x 8
PPD-Y† (photochromogen)	15 x 19
PPD-G† (scotochromogen)	8 x 9

*Obtained from U.S. Public Health Service National Communicable Disease Center, Atlanta, Georgia.

†Obtained from U.S. Public Health Service Tuberculosis Research Department, Bethesda, Maryland.

The result of testing with mycobacterial tuberculins is given in Table II. Each skin-test injection of 0.1 ml. contained 0.0001 mg. of tuberculin (purified protein derivative). The pattern of skin reactions is compatible with infection by photochromogens.

Intradermal injections of 0.1 ml. of streptokinase-streptodornase (Varidase, Lederle, 100 units), Candida dilution 1:10 (Monilia Mix, Hollister-Stier Laboratories) and Dermatophytin "0" dilution 1:10 (Hollister-Stier Laboratories) at 48 hours showed redness and induration of 20 x 25 mm., 5 x 6 mm. and 5 x 5 mm., respectively. In response to intradermal challenge with 100 μg. KLH seven days after immunization the patient gave a normal reaction of 8 x 6 mm.[8]

The *in vitro* lymphocyte blastogenesis response was measured by the method of Hersh and Harris.[9] There was little response to phytohemagglutinin at 7 or 14 days after treatment with vinblastine sulfate (Table III). The response was also below the normal range when assessed at 21, 28 and 35 days after therapy. The patient's lymphocytes first responded *in vitro* to KLH seven days after immunization. There was a progressive rise in the response during the 28-day period of evaluation which followed immunization. The responses were below the lower value of the ranges in normal controls.

TABLE III.—*In vitro* LYMPHOCYTE BLASTOGENESIS* IN RESPONSE TO PHYTOHEMAGGLUTININ† AND KEYHOLE LIMPET HEMOCYANIN‡

	Days after immunization				
	0	*7*	*14*	*21*	*28*
Phytohemagglutinin....	161.4	85.0	9994.6	29,277.4	14,226.0
Keyhole Limpet Hemocyanin	78.9 (260-660-1400)	1097.2 (1400-1700-8200)	643.4 (2000-5450-15,000)	8608.5	2869.2 (4400-9000-19,000)

*Results of thymidine incorporation are expressed as counts per minute (cpm) per 10^6 lymphocytes. Values are those obtained after subtraction of thymidine incorporation in unstimulated control cultures.

†Median response of 10^6 lymphocytes to 0.05 ml. PHA is 3.5×10^5 cpm. Lower limit of response is 3×10^4 cpm.[25]

‡Maximal response to antigen dose varying from 1 to 200 micrograms. Normal range of response given in parentheses.[8] Middle figure represents median.

The absolute peripheral lymphocyte count averaged 1388 per c.mm. over the period January 1967 to October 1968. It was never less than 700 c.mm.

DISCUSSION

The declining incidence of tuberculosis in the general population and more effective management of early Hodgkin's disease have combined to make tuberculosis-complicated Hodgkin's disease relatively rare. Casazza, Duvall and Carbone[4] found only one case of tuberculosis in 51 patients with Hodgkin's disease who came to autopsy. In the period 1944-1967, 768 patients with Hodgkin's disease were seen at our institution. Four of these patients developed tuberculosis during the course of their illness—an incidence of 0.5%; only one of these had proved reactivation of old tuberculosis. Ten additional patients had an unquestionable history of previous tuberculous infection. Patients with Hodgkin's disease and a positive tuberculin skin test should receive prophylactic isoniazid.[5] Clinicians will continue to suspect tuberculosis in patients with Hodgkin's disease where chest radiographs are suggestive, but the possibility always exists of a pulmonary infection due to atypical acid-fast mycobacteria; these have been recognized in human disease since 1951.[10] When it occurs, such pulmonary infection is indistinguishable clinically, radiologically and pathologically from that caused by *M. tuberculosis*.[11] The atypical mycobacteria are thought to be the cause in from 1 to 10% of patients considered to have tuberculosis.[14] Extrapulmonary manifestations may occur with involvement of the lymph nodes,[11] bones or joints.[12] Disseminated disease may be associated with pancytopenia.[13] The immunologic defect in Hodgkin's disease renders patients prone to infectious granulomatous disease.[15] Complicating infections occur late in the course of the disease because prolonged therapy and disseminated disease have contributed to impairment of host defence. The identification of acid-fast bacilli in the sputum or gastric washings of a patient with Hodgkin's disease, while clearly an indication for antituberculous chemotherapy, calls for vigorous attempts to identify the acid-fast organism by culture and to determine *in vitro* drug sensitivities. Skin testing[16] with tuberculins prepared from atypical mycobacteria may be of value. The atypical acid-fast bacilli are frequently resistant to the common antituberculous drugs, so that specific chemotherapy is important in a patient whose ability to resist infection is already seriously compromised.

This patient's disease has remained in complete remission for more than four years in response to maintenance therapy with vinblastine sulfate. This is longer than the seven-month median duration of objective response recently reported for this agent in Hodgkin's disease by Sohier, Wong and Aisenberg.[17] But vinblastine sulfate is an immunosuppressive drug.[18] The numerous infectious complications experienced by this patient may have been related to his chemotherapy. Evidence of impaired immune function in the intervals between therapy is provided by the patient's poor response to immunization with KLH. The patient developed normal *in vivo* delayed hypersensitivity in response to this antigen. Established delayed hypersensitivity, as indicated by normal intracutaneous responses to tuberculin, streptokinase-streptodornase and fungal antigens, seemed also to be intact. Humoral antibody formation was less than in normal controls, and *in vitro* lymphocyte blastogenesis in response to antigen was abnormally low. Study of immune response to KLH in man has suggested that there is a correlation between humoral antibody formation and *in vitro* lymphocyte blastogenesis in this system.[8] This relationship does not hold between either of these two parameters of immune response and *in vivo* delayed hypersensitivity. Another indication of impaired immunity was the poor response of the patient's lymphocytes to phytohemagglutinin (PHA). The exact signifi-

cance of PHA-induced *in vitro* lymphocyte blastogenesis is not clear, but the test has come to be accepted as a useful index of normal lymphocyte function.[19] Immediately after chemotherapy there was little detectable response to PHA, and while improved responses were obtained over the ensuing weeks of study, these remained below the normal range.

We think that the impaired immune function in this patient is the result of chemotherapy. Additional contributing factors may have been involved. Immune function has been shown to decline with age,[20] and when tested the patient was 60. The immune deficiency state characteristically seen in Hodgkin's disease is one of impaired delayed hypersensitivity.[21] Some reports suggest that humoral antibody formation is also abnormal, but usually at a more advanced stage of the disease.[22] Although patients with Hodgkin's disease in complete remission have been shown to have normal immune function,[23, 24] occasionally patients are seen in remission with both impaired delayed hypersensitivity and abnormal humoral antibody responses.[24] This may be the result of extensive chemotherapy and radiotherapy. Such a consideration might apply in the case of the patient presented. Also, recurrent activation of Hodgkin's disease in this patient may have led to depletion of lymphocytes and exhaustion of immune capability.

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