Chlorambucil in Sarcoidosis*

Yash P. Kataria, M.D., F.C.C.P.†

Ten patients with biopsy-proven sarcoidosis with progressive disease were treated with chlorambucil alone or in combination with corticosteroids. Eight of these ten patients showed some degree of improvement which may be attributable to chlorambucil. The responsive patients showed beneficial effects within three months of starting chlorambucil therapy. It is concluded that chlorambucil may be a trial in patients with progressive disease unresponsive to corticosteroids or where corticosteroids are contraindicated.

Sarcoidosis, a disease of unknown etiology, is associated with widespread noncaseating granulomata in the body. The course of the disease is variable, characterized by frequent remissions in the first three years, but may become chronic and progressive in a small percentage of patients. For the treatment so far, the drugs of choice are the corticosteroids. In patients in whom corticosteroid therapy is contraindicated, or when, despite this form of therapy, disease is progressive, alternative drugs such as chloroquine or oxyphenbutazone have been recommended. However, long-term use of these drugs can result in serious toxic effects. In situations where conventional therapy fails, immunosuppressive agents may be helpful. The published reports on the use of immunosuppressive agents are scarce, and there is a lack of information on long-term usefulness of these agents. In this study, we report our experience with chlorambucil in the treatment of patients with sarcoidosis. It should, however, be understood that the study presented is anecdotal rather than random controlled trial.

MATERIALS AND METHODS

Ten patients with biopsy-proven sarcoidosis with progressive disease were treated with chlorambucil. Assessment of progressive disease was made by serial evaluation of patients, prior to starting chlorambucil, by clinical, roentgenographic, lung function and arterial blood gas examinations. The pertinent data on individual patients relating to indications for chlorambucil therapy and its effects on clinical, roentgenographic, and lung function status are shown in Tables 1 and 2. The drug regimen and its effects are shown in Table 3.

The criteria for chlorambucil therapy were as follows: (1) failure of response to corticosteroids; (2) relapse after initial response to corticosteroids in patients with progressive weight gain; and (3) a contraindication to corticosteroids. The patient population included in the study presented with a variety of principal clinical manifestations, not necessarily confined to lungs, and served as its own control.

The chlorambucil was started in a single daily dosage of 4 to 6 mg. If required, it was increased weekly by 2 mg to a maximal dosage of 12 mg daily. It was given alone or in combination with corticosteroids. The dosage of chlorambucil was monitored with weekly white blood cell and platelet counts. An effort was made to maintain total white blood cell count about 3,500/cu mm and platelets about 1 × 10^9/cu mm. The laboratory tests were periodically repeated during and after discontinuation of the chlorambucil therapy. The case histories are briefly described as follows.

CASE 1

A 55-year-old white woman, known insulin-dependent, obese (90.8 kg), diabetic since 1952, developed erythema nodosum skin rash on both legs in February 1976, followed by a generalized pruritic maculopapular erythematous skin rash and palpable subcutaneous nodules at the sites of insulin injections. X-ray films of both hands revealed poorly circumscribed lytic areas in the metaphyseal ends of the phalanges bilaterally. The chest roentgenogram and the remainder of the work-up were normal. A diagnosis of sarcoidosis was made by biopsy of the skin lesion and a subcutaneous nodule. Because of diabetes mellitus and obesity, she was treated with chlorambucil alone.

Comment. In six weeks, the pruritic skin rash showed considerable improvement and in three months complete resolution. On follow-up, she relapsed twice but responded to chlorambucil with similar amounts.

CASE 2

A 45-year-old black woman was seen in August 1975, for progressive symptoms of generalized maculopapular skin rash, fatigue, and dryness of eyes and mouth since September 1970. She was anemic and had a few small cervical lymph nodes palpable on the right side. The skin lesions varied in size from a few millimeters to a few centimeters and were erythematous and/or scaly. Additional findings included bilateral rales in the chest, hepatomegaly 6 cm below the right costal margin, and palpable tip of the spleen. The chest roentgenogram revealed diffuse interstitial infiltrates.

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Table 1—Effect of Chlorambucil Therapy on Clinical and Roentgenographic Status in Patients With Sarcoidosis*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Indications for Chlorambucil Therapy</th>
<th>Clinical Improvement</th>
<th>Roentgenographic Stage†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before Therapy</td>
<td>During Therapy</td>
</tr>
<tr>
<td>1</td>
<td>Diabetes mellitus</td>
<td>Pruritic skin rash, subcutaneous nodules, fatigue</td>
<td>+++</td>
</tr>
<tr>
<td>2</td>
<td>Unresponsive to prednisone</td>
<td>Skin rash, fatigue</td>
<td>+++</td>
</tr>
<tr>
<td>3</td>
<td>Unresponsive to prednisone</td>
<td>Skin rash</td>
<td>+ to -</td>
</tr>
<tr>
<td>4</td>
<td>Diabetes mellitus</td>
<td>Exertional dyspnea, fatigue, cough</td>
<td>++</td>
</tr>
<tr>
<td>5</td>
<td>Steroid psychosis</td>
<td>Cough, fatigue, exertional dyspnea at rest</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>Unresponsive to corticosteroids</td>
<td>Fatigue, dyspnea</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>Unresponsive to prednisone</td>
<td>Cough, fatigue, exertional dyspnea</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>Unresponsive to prednisone</td>
<td>Galactorrhea, eye and head pains</td>
<td>+++</td>
</tr>
<tr>
<td>9</td>
<td>Unresponsive to prednisone</td>
<td>Exertional dyspnea</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>Unresponsive to prednisone</td>
<td>Chronic cough, exertional dyspnea</td>
<td>-</td>
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</tbody>
</table>

*+++ indicates complete remission; +++, significant improvement; +, some improvement; and -, questionable or no improvement.
†Stage I indicates bilateral hilar adenopathy; stage II, bilateral hilar adenopathy and lung infiltrates; stage III, diffuse lung infiltrates; and stage 0, normal.

Prednisone therapy was begun, 60 mg daily, and was eventually reduced to a maintenance level of 10 mg daily. She showed marked improvement with return of energy, complete healing of skin lesions, and marked regression of hepatosplenomegaly but had gained a considerable amount of weight. In June 1976, she had reactivation of skin lesions. Because of marked weight gain, she refused to take increased dosage of prednisone. A regimen of chlorambucil, 6 mg daily, was added.

Comment. When seen in September 1976, the skin lesions had completely resolved. Chlorambucil therapy was discontinued in November 1977. When last seen in November 1978, she was taking prednisone, 5 mg daily, her skin lesions remained healed, and the chest roentgenogram showed further improvement. For this patient, chlorambucil appeared to have a corticosteroid-sparing effect.

CASE 3

A 28-year-old black woman was seen on March 31, 1976, for skin rash and intermittent polyarthralgias of one year's duration. The skin rash started as two papules on the right side of her face and subsequently it spread to involve skin of the ears, eyebrows, periorbital areas, elbows, nose, and scalp. The rash was maculopapular with scattered reddish brown lesions, varying in size from a few millimeters to 3 cm. Some of these lesions were indurated and scaly. The lesions also extended to involve the mucosa of nostrils, eyelids, and mouth. Biopsy specimen from one of the lesions showed the presence of noncaseating granulomas. She also had peripheral lymphadenopathy. The chest roentgenogram showed mediastinal and bilateral hilar adenopathy.

Because of the progressive disfiguring skin lesions, a regimen of prednisone, 60 mg daily, was started. After five weeks, because of no significant improvement, the prednisone regimen was reduced to 40 mg daily and combined with chlorambucil in a daily dosage of 6 mg. In three months, the prednisone therapy was reduced to 25 mg per day, and there was some resolution of the skin lesions. However, she ran out of chlorambucil, which resulted in relapse of skin rash, despite continued use of prednisone. Several weeks after beginning chlorambucil therapy again, only slight improvement was observed, despite increased prednisone dosage to 60 mg daily. Chlorambucil therapy was discontinued. In April 1977, she was again started on a regimen of chlorambucil and methylprednisolone (Medrol). That resulted in significant regression of skin lesions, but in September 1977, she developed menorrhagia in the presence of normal coagulation studies as she had done once in the past. The chlorambucil therapy was discontinued and that resulted in flaring of skin lesions. Subsequently, she became unresponsive to chlorambucil and/or methylprednisone. Finally, therapy with
Table 2—Effect of Chlorambucil on Lung Function Showing a Change From Base Line in Patients With Sarcoidosis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Before Therapy</th>
<th>During Therapy</th>
<th>After Therapy</th>
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<td>84</td>
<td>76</td>
<td>12.8</td>
<td>ND</td>
<td>15.3</td>
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</table>

*ND indicates not done.

hydroxychloroquine sulfate (Plaquenil), 200 mg daily, was begun in April 1978.

Comment. After some earlier improvement, her skin lesions eventually became nonresponsive to combined therapy. When last seen in October 1978, the skin lesions had regressed considerably in response to hydroxychloroquine.

Case 4

A 51-year-old black woman, known insulin-dependent, obese (weight, 99.9 kg) diabetic for seven years, was seen in February 1975, with symptoms of progressive exertional dyspnea, fatigue, and nonproductive cough since November, 1974. The chest roentgenogram showed bilateral hilar adenopathy and diffuse ill-defined parenchymal infiltrates. A diagnosis of sarcoidosis was made by mediastinal lymph node biopsy specimen. She also had a history of angina pectoris, relieved with nitroglycerin. Because of marked obesity and diabetes mellitus, a regimen of chlorambucil, 6 mg daily, was begun and continued for six months.

Comment. She showed significant improvement as assessed by lung function studies and clinically by increased exercise tolerance and absence of cough.

Case 5

A 33-year-old white woman was evaluated in August 1975, for nonproductive cough and progressive exertional dyspnea of one year's duration. A review of a 1971 chest roentgenogram showed diffuse interstitial lung infiltrates. In the past, her symptoms were diagnosed as bronchial asthma at the age of ten years, with recurrence of asthmatic symptoms invoked by upper respiratory tract infections. The physical findings included occasional ronchi in the chest and palpable tip of the spleen. Chest roentgenogram revealed infiltrates, both alveolar and interstitial, involving both upper lobes. A diagnosis of sarcoidosis was made by open-lung biopsy. She responded to prednisone therapy with some symptomatic improvement but it was discontinued because of the appearance of serious psychoneurotic side effects. She was given a course of chlorambucil, 6 mg daily, for a period of three months.

Comment. This patient showed significant clinical improvement. The P (A-a) O₂ also showed a significant drop of 20 mm Hg.

Case 6

A 39-year-old, markedly obese, white woman was seen in January 1976, with a history of progressive shortness of breath and fatigue since 1966. A diagnosis of sarcoidosis had been made by biopsy of the right scalene node. Her condition had steadily deteriorated despite repeated courses of corticosteroids in therapeutic doses. At the time of consultation, she was being treated with a regimen of methylprednisolone, 32 mg daily, but without any response. The physical signs included respiratory rate of 28 per minute; diminished chest expansion, and accentuation of the pulmonary component of the second heart sound. The chest roentgenogram showed an enlarged heart, bilateral hilar and mediastinal lymphadenopathy, and diffuse poorly defined nodular infiltrates throughout both lung fields. She was markedly hypoxemic, and the lung function studies suggested severe restrictive lung disease. The remainder of the work-up results were normal. Because of progressive weight gain, the dosage of methylprednisolone was gradually tapered to 16 mg on alternate days, and therapy with chlorambucil, 8 mg daily, was begun for three months.

Comment. She showed improvement as assessed clinically, roentgenographically, and by lung function studies. The P(A-a)O₂ showed a drop of 7 mm Hg. However, seven months after stopping chlorambucil therapy, she relapsed, despite continued corticosteroid therapy. At present, the patient is being maintained on therapy with methylprednisolone.

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and beclomethasone dipropionate inhaler, to which she is responding satisfactorily.

**Case 7**

A 19-year-old black woman was seen in February 1976, with complaints of persistent cough, fatigue, and progressive exertional dyspnea for ten years, despite repeated courses of prednisone in therapeutic doses. A diagnosis of sarcoidosis had been made by biopsy specimens from skin and liver. The chest roentgenogram showed diffuse patchy infiltrates and scattered fibrotic changes in the upper lobes. The physical signs included poor chest expansion, decreased breath sounds with occasional rales over both lower lobes, and accentuation of the pulmonic component of the second heart sound. Both the liver and the spleen were palpable. She was treated with combined daily therapy of chlorambucil, 6 mg, and prednisone, 40 mg, for 11 months, after which she was maintained on a regimen of prednisone, 15 mg per day.

**Comment.** She showed significant clinical response with the relief of cough, fatigue, and to a lesser extent of the shortness of breath. The chest x-ray film and lung function studies also showed some improvement.

**Case 8**

A 34-year-old black woman was referred to us in July 1976, with a two-week history of inappropriate behavior and spiking fevers. In the past, since January 1974, she had been treated with corticosteroids for numerous episodes of decreased vision bilaterally but with diminishing response and eventually resulting in blindness in June 1975. Results of extensive evaluation were negative. In January 1976, she presented with headache, and she was found to have markedly increased intracranial pressures. Her optic discs were pale with sheathed white fibrotic-appearing retinal arteries. In addition, she had galactorrhea. The laboratory work-up suggested pan-hypopituitarism. On physical examination, she was a markedly obese, blind, combative, and disoriented woman with signs of miningismus. The cerebrospinal fluid (CSF) was sterile but revealed elevated protein level of 124 mg/100 ml (N:20-40); WBC, 100/cu mm (85 percent lymphocytes). Findings from chest roentgenogram, tuberculin skin test, liver biopsy specimen, CAT scan, and convalescent CSF serology for viral titers were all normal. Patient improved spontaneously over ten days. At this time, a possibility of sarcoidosis was considered. She had relapses of low grade fever, intermittent confusion and increasing galactorrhea. The Kveim test was found to be positive in September 1976. At that time, prednisone therapy, 100 mg on alternate days, was begun. The symptoms of recurrent eye and head pain, fever, confusion, and galactorrhea at first abated but subsequently returned with attempted reduction of steroid dose. Serum prolactin level had increased. In November 1976, chlorambucil therapy was added and prednisone therapy continued in a reduced dosage of 60 mg on alternate days. With combined therapy, the patient enjoyed partial relief of her symptoms for several months.

In May 1977, she developed herpes zoster in the left hip area that subsequently became generalized. Total WBC was 3,600/cu mm (76 percent neutrophils). Chlorambucil therapy was discontinued while prednisone was continued. The skin lesions had healed significantly over the next ten days. Two weeks later, while in the bathroom, she fell but was responsive. Soon after, she had a convulsive seizure following which she suddenly died. Diagnosis of sarcoidosis involving the areas of optic nerves, optic chiasma, and the rest of the optic pathways was confirmed at autopsy. The pituitary (1.35 g) as well as sella turcica were enlarged. No granulomata were found in any other organs of the body.

**Comment.** This was a rather unusual case of sarcoidosis involving primarily the optic pathways. It was too late to expect any improvement in vision because of the irreversible pathologic changes. However, some symptomatic improvement, especial-
ly in galactorrhea, was observed with combined therapy.

**CASE 9**

A 38-year-old white woman was first seen in July 1973, with four years' history of nonspecific intermittent chest pains. A diagnosis of sarcoidosis was made by open lung biopsy. Subsequently, she became progressively dyspneic on exertion, despite repeated courses of corticosteroids in therapeutic doses. The physical examination revealed bibasilar rales and scattered rhonchi. The chest roentgenogram showed diffuse interstitial fibronodular infiltrates bilaterally with blunting of the right costophrenic angle. On skin testing, she was anergic to a battery of common antigens.

**Comment.** She was nonresponsive to combination therapy with methylprednisone and chlorambucil given for six months.

**CASE 10**

A 43-year-old black woman, a mild smoker, was seen in consultation in August 1975, because of increasing exertional dyspnea and productive cough of eight months' duration, and progressive paresthesias of both feet, weakness of legs, and stumbling gait for two weeks. The physical signs included evidence of peripheral neuropathy involving both legs, bilateral anterior uveitis, and bibasilar rales on auscultation of chest. The chest roentgenogram showed bilateral hilar adenopathy as well as diffuse lung infiltrates. A diagnosis of sarcoidosis was made by biopsy of the right scalene node.

She responded to prednisone therapy with rapid resolution of neuropathy when seen in September 1975. However, cough and exertional dyspnea persisted. A diagnosis of bronchiectasis, possibly secondary to endobronchial involvement with sarcoidosis, was entertained and subsequently confirmed by endobronchial biopsy specimen and bronchography.

**Comment.** The respiratory symptoms were nonresponsive to chlorambucil given for five months.

**METHODS FOR ASSESSMENT OF RESULTS**

Improvement was assessed clinically, and roentgenographically, by change in P(A-a)O₂ and by lung function studies. The chest roentgenograms were evaluated independently by a radiologist unaware of the protocol as well as by the author. Both of them were in agreement of the results. The results of clinical and roentgenographic improvement were graded as complete remission, +++; significant improvement, +++; some improvement, +; and questionable or no improvement, -. A significant change in lung function study results or arterial blood gas determinations was defined as deviation by 20 percent from the original values of forced vital capacity, maximal voluntary ventilation and single breath carbon monoxide pulmonary diffusion capacity (DLco).

**RESULTS**

**Clinical Improvement**

As shown in Table 1, eight of the ten patients studied showed some degree of improvement. Two had complete remission, two significant improvement, and the remaining four, some improvement. Three of these patients received chlorambucil therapy alone and the rest, combined therapy (Table 3).

On follow-up, after the end of therapy, of the eight responsive patients, three maintained their improvement, three relapsed, one died, and one was lost to follow-up. One patient relapsed twice and was treated successfully on each occasion. The period of follow-up varied from 7 to 47 months, with a mean of 21 months (Table 3).

**Roentgenographic Improvement**

Results of roentgenographic improvement are shown in Table 1. Two patients had normal chest roentgenograms all along. Of the remaining eight patients, during therapy, chest roentgenograms improved in three and remained unchanged in five.

On follow-up of the chest roentgenograms in three patients with initial improvement, two remained stable and one had a deteriorated condition; of the remaining five patients, the chest roentgenograms showed some improvement in one, remained unchanged in three, and one patient was lost to follow-up.

**Lung Function Studies**

Results of lung function studies are summarized in Table 2. Five of the eight clinically responsive patients showed some degree of improvement in their lung function studies during or after the termination of chlorambucil therapy. One of these patients subsequently relapsed. Of the remaining three clinically responsive patients, two had normal study results all along, and in one, studies were not performed. Two of these patients had normal chest roentgenograms all along. In the two clinically nonresponsive patients, the lung function study results remained essentially unchanged.

**DISCUSSION**

Eight of the ten sarcoidosis patients showed some clinical improvement when treated with chlorambucil. Roentgenographic and physiologic improvement was also noted in some patients. Three patients were treated for cutaneous sarcoidosis; two underwent complete remission; and the third, although improved initially, became eventually unresponsive. Dyspnea, particularly on exertion, was the feature in four patients. All the four patients showed some improvement which was associated with either chest roentgenographic clearing or improvement of lung function studies, or both. One
patient with the involvement of optic pathway showed a significant improvement in galactorrhea. One patient with bronchiectasis and another one with diffuse interstitial fibrosis remained unresponsive.

Reports of chlorambucil in the treatment of sarcoidosis are sparse. Israel et al. administered chlorambucil to eight patients who appeared to have severe, progressive disease not responding to prednisone. Three of their patients recovered fully and one was markedly improved. Two patients were unchanged and two progressed. However, no mention is made of the course of disease following discontinuation of chlorambucil therapy. In our study, the patients were followed-up for a period varying from 7 to 47 months, with a mean of 21 months (Table 3). Of the eight out of the ten patients who had shown improvement with chlorambucil, four remained sta-

**Table 1—Immunologic Findings in Sarcoidosis**

<table>
<thead>
<tr>
<th>Immunologic Enhancement</th>
<th>Immunologic Impairment</th>
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</thead>
<tbody>
<tr>
<td><strong>In Vitro</strong></td>
<td><strong>In Vivo</strong></td>
</tr>
<tr>
<td>Spontaneous morphologic lymphoblastic transformation</td>
<td>Diminished lymphoblastic transformation in response to phytohemagglutinin stimulation</td>
</tr>
<tr>
<td>Spontaneous macrophage inhibitory factor release</td>
<td>Serum factor(s) inhibiting lymphoblastic transformation</td>
</tr>
<tr>
<td>T-cell proliferative factor</td>
<td></td>
</tr>
<tr>
<td>Enhanced helper cell activity</td>
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<tr>
<td>Normal phytohemagglutinin skin test</td>
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<tr>
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<td>Cutaneous anergy</td>
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<td>Activated circulating T-cells</td>
<td>Decreased numbers of circulating T-lymphocytes</td>
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<td>Diffuse granulomas</td>
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<td>Increased number of circulating B lymphocytes</td>
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<td>Circulating antigen-antibody complexes</td>
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</tbody>
</table>

**Figure 1.** Schematic representation of the proposed mechanism of granuloma formation associated with cell mediated immunity. It also shows the principal mechanisms whereby corticosteroids and chlorambucil would seem to suppress the granulomatous inflammation.

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ble, two relapsed, one died, and one was lost to follow-up. Thus, chlorambucil appears to have suppressive rather than curative effect, contrary to what was suggested in the above study. Westcott and Noehren, in their patient, reported improvement of pulmonary sarcoidosis following corticosteroid and chlorambucil therapy, but associated bronchial narrowing showed no change over a seven-year period.

The total dosage of chlorambucil and duration of therapy varied from patient to patient (Table 3). In all responsive patients, the improvement was noticeable within two to three months.

Three of the ten patients had side effects from chlorambucil (Table 3). One patient developed a few areas of maculopapular skin rash, slightly scaly and pruritic, over the forehead and trunk. The rash disappeared after discontinuation of chlorambucil therapy. Two patients had developed herpes zoster. In one, it was localized and disappeared rapidly. In the other patient, it was more extensive. She was taking prednisone, 60 mg on alternative days, along with chlorambucil. She, however, died suddenly. The cause of death could not be determined, even on autopsy.

Regarding the mode of action of chlorambucil in the treatment of sarcoidosis, we were unable to find any information in the literature. It has been suggested that the granuloma formation (Fig 1) in sarcoidosis and in diseases associated with cell mediated immunity (mycobacterial, fungal, etc) may have similar mechanisms.7 Although the source and the nature of antigenic stimulation remains elusive, nonetheless, extrapolating the results of a number of experimental observations in sarcoidosis to in vivo state may help explain the mechanism of perpetual formation of granulomas in sarcoidosis (Table 4). The principal mechanisms whereby corticosteroids may prevent the granuloma formation are their suppression of synthesis of lymphokines by the "sensitized" lymphocytes, as well as blocking the action of lymphokines on monocytes.8-10 Chlorambucil, on the other hand, seems to reduce the number of available mononuclear cells by suppressing bone marrow activity (Fig 1). The effect of chlorambucil on lymphokine kinetics has, apparently, not been studied. Our preliminary in vitro observations on the kinetics of monocyte chemotactic factor (Kataria, unpublished data) suggest that the continuous presence of chlorambucil in the phytohemagglutinin-stimulated normal human lymphocyte cultures interferes with their production of monocyte chemotactic factor. It may be inferred that the final common pathway through which these drugs exert their beneficial effects is decreased recruitment of macrophages necessary for subsequent formation of granuloma.

Further, on the basis of available evidence, we have previously14 argued that the presence of immunoglobulins in the lung granulomas of patients with sarcoidosis detected by immunofluorescence could represent the type 2 or cytotoxic immune response. This type of immune reaction may not be fully responsive to corticosteroids, but might respond better to chlorambucil alone or in combination with corticosteroids.

It is concluded that chlorambucil may be worth a trial in patients with progressive disease unresponsive to corticosteroids or where corticosteroids are contraindicated. However, it should be emphasized that corticosteroids still remain the cornerstone of treatment for sarcoidosis.

REFERENCES