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Immunological studies in angioimmunoblastic lymphadenopathy

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SUMMARY

Immunological studies were carried out on two female patients with angioimmunoblastic lymphadenopathy (AIL). Both presented with fever, lymphadenopathy, hepatosplenomegaly, rash and apparent ampicillin hypersensitivity. During the active phase of the disease, cellular immunity was depressed and T cell blastogenesis induced by lectins was abnormal.

In the first patient, a non-dialysable plasma factor was found that inhibited normal lymphocyte blastogenesis, the removal of which enhanced the activation of AIL lymphocytes. This inhibitory plasma factor was also observed in the second patient during relapse of the disease. The latter patient responded well to steroid and levamisole therapy, showing clinical remission and a return of *in vivo* and *in vitro* parameters of cellular immunity. Defective B cell regulation due to impaired suppressor function, followed by immunoglobulin overproduction, is suggested to occur in AIL.

INTRODUCTION

Angioimmunoblastic lymphadenopathy (AIL) was described as a new disease entity by Lukes & Tindle (1973) and Frizzera, Moran & Rappaport (1974). Previous reports of clinical conditions involving generalized lymphadenopathy, hepatosplenomegaly and immunological abnormalities used the terms 'chronic pluripotential immunoblastic syndrome' (Westerhausen & Oehlert, 1972) and 'diffuse plasmacytic sarcomatoses' (Flandrin *et al.*, 1972). The disease is believed to result from a non-neoplastic proliferation of the lymphoid system, characterized by intense immunoblast and plasma cell infiltration in the lymph nodes, with proliferation and aborization of small lymphatic blood vessels.

The aetiology remains unclear, but much data point to immunological abnormalities leading to polyclonal gammopathy (Lukes & Tindle, 1975) and depressed delayed hypersensitivity (Pruzansky, Sutton & Pantolony, 1976). The tendency for the disease to develop after administration of drugs has led to the suggestion that an exogenous agent may be of importance in the aetiology (Lukes & Tindle, 1975; Lapes, Vivacque & Antoniades, 1976; Schultz & Yunis, 1975). Such drugs have included penicillin, ampicillin, griseofulvin, dilantin and the sulphonamides.

As the clinical and immunological findings are reminiscent of lymphoma, cytotoxic drugs have been employed (Frizzera *et al.*, 1974), but without clear beneficial effect. Although steroid therapy is reported to cause some relief (Frizzera *et al.*, 1974) the mortality of the disease remains high.

Levamisole has been found to restore depressed cellular immune responses *in vivo* (Symoens & Rosenthal, 1977) and was reported to lead to a reduction of immunoglobulin levels and return of delayed hypersensitivity in AIL (Ellergaard & Boeson, 1976; Bensa *et al.*, 1976). It was therefore desirable to test whether levamisole could be used to reduce the need for large doses of steroids.

In the present report, immunological studies are described for two patients with AIL, one of whom was treated with levamisole in addition to steroids.

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MATERIALS AND METHODS

Cellular immune responses were evaluated *in vivo* and *in vitro*. Tests of delayed hypersensitivity were read 24 and 48 hr after the intradermal injection of 0·1 ml of the following antigens: PPD (purified tuberculin, 20 TU/ml); candida (dermatophyton 0, 1/1000, 1/100, 1/40, Hollister-Stier Laboratories); streptokinase/streptodornase (varidase, 40 u/ml streptokinase and 10 u/ml streptodornase, Lederle Laboratories); trichophiton (dermatophyton, 1/1000, 1/100, 1/40, Hollister-Stier Laboratories).

In vitro parameters of immune function included the measurements of immunoglobulin and complement levels, the formation of E and EAC rosettes by the patients' lymphocytes, and their capacity to respond *in vitro* to PHA, Con A and pokeweed mitogen. Immunoglobulins and complement IgG, IgA, IgM, C3 and C4 were measured by radial immunodiffusion using Oxford and Boehring plates. To assess the concentration of B and T lymphocytes in the peripheral blood, rosette formation using sheep red blood cells or complement labelled red cells were tested (Bentwich *et al.*, 1973).

Lymphocyte transformation was measured after their separation according to the method of Boyum (1968) with slight modifications. The heparinized whole blood was centrifuged at 1500 r.p.m. for 15 min and the plasma separated into sterile tubes. The collected buffy coat was diluted 1:5 in RPMI medium (Biolab) and the lymphocytes were separated on a Ficoll–Hypaque gradient. After washing, the cells were resuspended in the medium, buffered with 10 mM HEPES and enriched with 15–20% autologous plasma, unless otherwise stated. The lymphocytes were cultured for 72 hr at 37°C in air tight plastic sealed, round bottom culture plates (NUNC) at a concentration of 10^5 cells/0·1 ml per well. PHA (Burroughs-Wellcome), pokeweed mitogen (GIBCO) and Con A (Miles) were used to test blastogenesis. Each was employed at three concentrations, optimal, sub-optimal and super-optimal. On the third day, 4 hr after adding ^{3}H-thymidine at a concentration of 2 μCi-well, the cells were washed and collected on filters, using an automatic cell harvester (Tissue Tek). The dried filters were read in a β scintilation counter.

CASE REPORTS

Patient 1

A 77-year-old woman, originating from Iran, was admitted for the investigation of fever and progressive dyspnea of 3-weeks duration. During the weeks preceding admission she had developed cough and shortness of breath which had led to the diagnosis of pneumonia. However, treatment with ampicillin proved ineffective. On physical examination her temperature was 38·2°C (pulse 110/min and blood pressure 120/70). Enlarged lymph glands were palpated in the posterior triangle of the neck, the axillae and inguinal areas. The liver was enlarged 8 cm below the costal margin and sensitive to palpation; the spleen was felt 4 cm below the costal margin.

On admission, the following observations were made: sedimentation rate 70 mm (first hr); haemoglobin 11·9 g/100 ml; haematocrit 34%; white cell count 5300/mm^3, with 57% neutrophils, 3% band forms, 9% eosinophils, 18% monocytes and 14% lymphocytes. The thrombocyte count was 95,000/mm^3. Urine analysis and serum glucose, creatinine, electrolytes, calcium and phosphate were all normal. The total protein was 5·1 g%, albumin 2·9 g% and globulin 2·2 g%. Transaminase levels: SGOT 150 u/ml. The chest X-ray showed an infiltrative process in the right lower lobe with pleural effusion.

Shortly after admission and while on ampicillin medication, the patient developed a pruritic maculopapular rash. The fever continued and the pleural effusion increased. Four hundred millilitres of exudate were removed from the pleural cavity. Microscopic examination of this fluid showed a high percentage of plasma cells. The bone marrow aspirate revealed hyperplastic mononuclear cells with large nuclei and nucleoli resembling immunoblasts; biopsy of an inguinal lymph gland confirmed the diagnosis of AIL.

Discontinuation of ampicillin therapy was followed by the disappearance of the rash. Within the first week of hospitalization, however, a marked change in serum protein levels took place. Albumin decreased to 1·7 g% and globulin increased to 7 g%. Electrophoresis revealed no abnormal serum protein. The Coombs test, anti-nuclear factor, rheumatoid factor and LE cell test were all negative. However, a high titre of antibody to Epstein–Barr virus (1/2048) was found.

The patient's condition deteriorated progressively, although blood, urine and sputum cultures remained negative for bacterial infection. Broad spectrum antibiotic therapy was begun, but this had no effect on the fever which fluctuated between 38–40°C. Therapy with prednisone (Meticorten) (40 mg/day) did not change her clinical condition. Two days prior to death, hypotension, diffuse intravascular coagulation and oliguria developed. The patient expired 28 days after admission.

Patient 2

This 17½-year-old girl, born in Israel to parents originating from India, was previously healthy except for hospitalization for meningoencephalitis as a child. Fever, joint pains and swelling in the knees had developed 2 weeks prior to admission. On admission, she had a fever of 39°C, signs of joint inflammation and a periarticular rash on both hands. No other pathological findings were noted at the time and there was no recent history of sore throat. The fever did not respond to salicylate therapy. In the electrocardiogram, flattening and inversion of T waves were observed. A therapeutic trial with a broad spectrum antibiotic, and later on with a tetracyclin–streptomycin combination did not lead to reduction of fever. Leucocytosis up to 40,000/mm^3 developed without evidence of neoplastic disease. Bone marrow puncture was non-diagnostic. The patient's state continued to deteriorate and signs of hepatitis developed as expressed by increased transaminase (100 u/ml) and alkaline phosphatase (up to 8 u/ml) levels.

A small lymph node appeared in the neck and was biopsied after removal, but the histology was non-diagnostic. Since a collagen disorder was thought to be a likely diagnosis, prednisone treatment was started and dramatic clinical improvement was observed. The fever decreased, liver function returned to normal, leucocytosis was reduced and the EKG became normal. However, marked lateral cervical lymphadenopathy and splenomegaly subsequently developed. Five months after the first admission, several lymph node biopsies were carried out. These showed features suggestive of AIL.

Laboratory findings were as follows: the sedimentation rate was 120 mm/hr with hypergammaglobulinaemia and leucocytosis (10,400 on first admission rising to 46,000/mm^3 after 4 weeks). She had a relative anaemia of 10 g% Hgb and a haematocrit of 31%. The urine contained a trace of protein. Blood levels of glucose, urea, creatinine, electrolytes, phosphate and calcium were all normal. Anti-streptolysin titre was in the normal range. C-reactive protein, Coomb's test, anti-nuclear factor, anti-DNA antibodies, LE and Weil Felix tests were all negative, as were blood and urine cultures and thick film examination for malaria. Fibrinogen was elevated to 630 mg%.

When the steroid doses were increased, the lymph nodes and spleen decreased in size. Because the patient had developed severe Cushingoid features 9 months after the disease, levamisole therapy in combination with low doses of fluocortolone was considered. Levamisole (150 mg/day p.o.) was administered for 3 consecutive days every 2–4 weeks (see Fig. 4). After six courses, levamisole had to be discontinued as the patient did not return for further treatment. Two months after the last levamisole course, her skin tests for delayed hypersensitivity had become positive. The patient has maintained a clinical remission while on low steroid therapy of 10 mg/day fluocortolone which was reduced subsequently to 5 mg/day, and is asymptomatic 2 years after her first admission.

RESULTS OF IMMUNOLOGICAL TESTS

Patient 1

Complement and immunoglobulin levels were measured shortly after discontinuation of ampicillin therapy and again 2 weeks later, 2 days before the death of the patient.

On both occasions, C3 and C4 were found to be low, 42 mg% and 14 mg% respectively. The immunoglobulin levels changed markedly after prednisone treatment (Table 1).

B and T cell counts were performed on one occasion during prednisone treatment; 14% B cells and only 25% T cells were found. The lymphocyte response to PHA was tested on the two occasions (A and B). On the first, when the patient was in a reasonably good clinical condition, her lymphocytes were completely non-responsive to PHA alone, but they transformed at about 15% of the normal control value when ampicillin (0·1 mg/0·1 ml culture containing 10^5 cells) was present in the culture medium in addition to PHA (Fig. 1).

Fig. 2 shows that after prednisone treatment, the lymphocytes still responded to PHA at less than the normal control rate. The patient's plasma was inhibitory to her own and to lymphocytes from a healthy donor. When the patient's lymphocytes were cultured in medium containing control plasma they responded more efficiently to PHA. However, the patient's plasma almost completely inhibited the PHA-induced stimulation of ^{3}H-thymidine uptake by the control lymphocytes.

TABLE 1. Immunoglobulin and complement levels after steroid treatment (patient 1)

	Prior to steroid administration (mg %)	After prednisone treatment (mg %)
IgG	6240	3200
IgA	612	546
IgM	1100	556
C3	42	46
C4	14	12

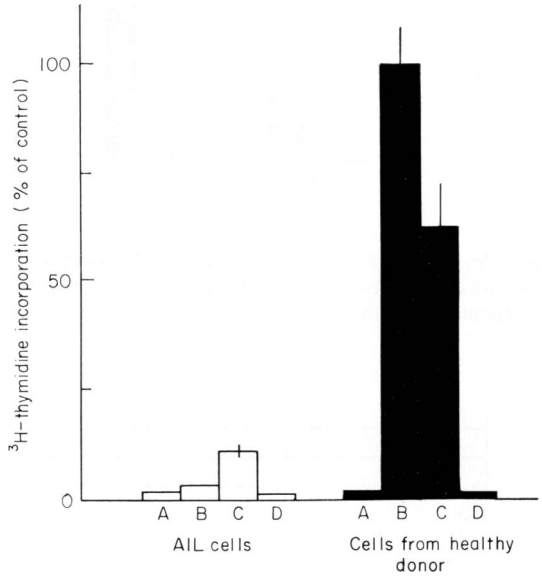

FIG. 1. Effect of PHA and/or ampicillin on ^{3}H-thymidine incorporation by control and AIL lymphocytes (patient 1, prior to steroid therapy). Medium contained 15% autologous plasma. (A) No PHA; (B) PHA; (C) PHA and ampicillin (1 mg/ml); (D) ampicillin (1 mg/ml).

The degree of inhibition of DNA synthesis depended on the concentration of the patient's plasma. Fig. 3 shows the results of an experiment in which the patient's plasma was mixed in varying proportions with control plasma (final plasma concentration 15% v/v). In order to determine whether the inhibitory factor was a small molecule (such as prednisone) dialysis for 18 hr at 4°C against the tissue culture medium was carried out. This procedure had only a slight effect upon the inhibitory action of the patient's plasma.

Patient 2

This patient has been followed by us for a period of more than 18 months (Fig. 4). At the time of admission, the patient was hypergammaglobulinaemic, IgG values rising to 3250 mg% and to 4720 mg% 5 months later. IgA levels remained consistently high; IgM values, though generally above normal limits, were not markedly increased. On steroid therapy, IgG levels fell to 2200 mg%, but the reduction in IgA was much less. The immunoglobulin levels did not change markedly during the succeeding 7 months. C3 values were generally high (slightly above 200 mg%), and C4 remained within normal limits throughout, fluctuating between 20–53 mg%. Measurements of B and T lymphocytes by sheep red blood cell rosetting were carried out at periodic intervals (Fig. 4). T cell numbers were initially low (40–57%) increasing to normal values after the start of levamisole therapy.

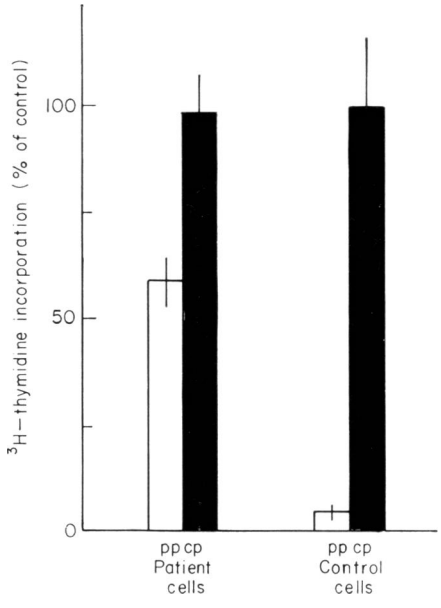

FIG. 2. Effect of AIL plasma (from patient 1, after steroid therapy), on PHA-induced transformation of lymphocytes from patient and a control subject. Results expressed as a percentage of transformation of control lymphocytes, measured by incorporation of ^{3}H-thymidine. pp = patient plasma, cp = control plasma.

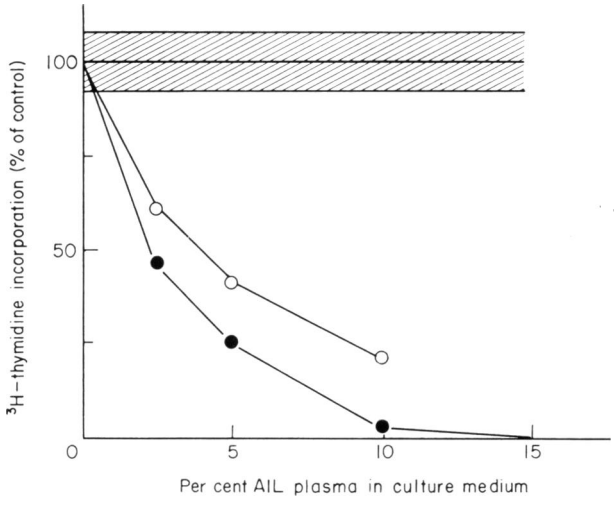

FIG. 3. Inhibitory effect of AIL plasma, before and after 18 hr dialysis, on PHA-induced DNA synthesis by control lymphocytes. AIL plasma (from patient 1) was mixed with control plasma at varying ratios to give a final 15% v:v total plasma concentration in the culture medium. (●—●) Before dialysis, (○—○) after dialysis. Hatched area indicates control.

Lymphocyte responses to PHA, Con A and PWM were tested on various occasions before and after levamisole treatment (Fig. 4) and (Table 2). At the time when the diagnosis of AIL by lymph node biopsy was carried out, the patient's lymphocytes in autologous plasma were found to be almost completely non-responsive to PHA. Meticorten treatment led to a marked improvement in the patient's condition, accompanied by a return of lymphocyte reactivity, although tests for delayed hypersensitivity remained negative and the T cell count remained low.

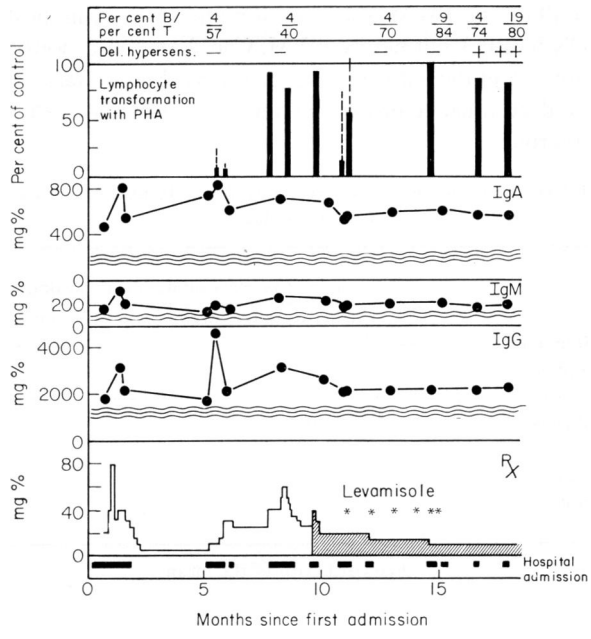

FIG. 4. Immunological parameters in AIL patient 2. Dotted lines on part of graph pertaining to lymphocytic PHA response show the increase in ^{3}H-thymidine incorporation after replacing AIL plasma with plasma from a healthy donor. (□) Meticorten, (▨) fluocortolone.

TABLE 2. Response of AIL lymphocytes to PHA, Con A and PWM during levamisole therapy (patient 2)

Time since admission (months)	Clinical state	Levamisole therapy	^{3}H-thymidine incorporation Ratio AIL/control*		
			PHA	Con A	PWM
8	Fair	—	0·90†	0·54	0·59
8·5	Relapse	—	0·11	1·63	1·91
9	Improved	‡	0·57	1·93	1·75
14·5	Remission	‡	0·98	0·89	0·32
16·5	Remission	—	0·82	1·43	3·23
18	Remission	—	0·80	0·50	1·68

* Control lymphocytes were obtained from healthy persons at the same time as the test on the patient's cells. Though different control subjects had to be used each time, their responses lay within normal expected values.

† Standard error of the mean was approximately ±20% for each value.

‡ Levamisole was administered on six occasions between the eleventh and fifteenth month after the first admission (see Fig. 4).

It is of interest that on one of the two occasions when lymphocyte reactivity to PHA was poor, during periods of clinical relapse, culture of the patient's cells in serum from a healthy control subject led to full return of reactivity (Fig. 4).

Table 2 shows that PHA, Con A and PWM responses did not vary in unison. When PHA responses were depressed during a period of relapse, effects of the latter two mitogens were enhanced.

Before administering levamisole to the patient, the drug was tested under *in vitro* conditions (Table 3).

Levamisole enhanced the PHA and PWM responses of lymphocytes from healthy donors and the activation of the patient's cells by PHA but not by PWM. Con A responses were inconsistent.

Administration of levamisole to the patient on six occasions (Fig. 4) was associated with an improvement of clinical status, and eventual return of delayed hypersensitivity; she could be maintained on minimal doses of corticosteroids.

TABLE 3. Effect of levamisole on mitogen-induced transformation *in vitro* of AIL and control lymphocytes

Source of lymphocytes	% thymidine incorporation with levalmisole in culture / thymidine incorporation without levamisole	
	PHA	PWM
Control subjects (no.)	147 ± 20* (11)	134 ± 24 (7)
AIL patient 2 (no. of tests)	140 ± 17 (4)	105 ± 14 (4)

* Standard error of the mean.

DISCUSSION

Angioimmunoblastic lymphadenopathy is reported to occur mainly in the elderly, although cases in young people have occurred, as in this report. Initial clinical symptoms include an acute onset with fever, chills, sweating, malaise and weight loss. Maculopapular rashes and pruritis may occur (Moore, Harrisson & Weiland, 1976). Marked hyperimmunoglobulinaemia is characteristic of about 80% of cases. Anaemia, red cell lysis, thrombocytopenia, eosinophilia and positive Coomb's test may be found. Concurrent thyroiditis and vasculitis have been reported (Averback, Salama & Moinuddin, 1977). Histologically, lymph node architecture shows diffuse alteration and obliteration due to small vessel proliferation, deposition of amorphous acidophilic interstitial material in the lymph nodes and pleomorphic cellular infiltration of many small lymphocytes, plasma cells and immunoblasts (Lukes & Tindle, 1975; Moore *et al.*, 1976). Pangalis, Moran & Rappaport (1978) reported distinctive bone marrow changes by a large increase in number of immunocytes. Clinically, the disease may easily be confused with malignant lymphoma, generalized infections or collagen diseases. The mean survival period is reported to be 19 months, systemic infection being a major factor in mortality (Moore *et al.*, 1976).

In both of the cases reported here, the histological changes in the lymph nodes fitted the criteria for AIL as specified by Lukes & Tindle (1975). We also confirm the *in vivo* and *in vitro* evidence for dimunition of T cell function (absence of delayed hypersensitivity, reduced T cell numbers measured by rosetting and diminished lymphocyte transformation by PHA). The surviving patient showed marked clinical improvement using combined steroid and levamisole therapy.

A biological mechanism put forward to explain these findings must remain highly speculative at the present time. Decreased cellular immune function in AIL was described by Ellergaard & Boeson (1976) and by Matz *et al.* (1977). They suggested, like Miller (1975), Frizzera *et al.* (1974) and Pruzansky *et al.* (1976) that the hyperplasia and hyper-reactivity of the B cell system could be due to a diminished activity of the T suppressor system as Kuroyanagi, Kura & Arao (1978) have reported. This possibility is also supported by the findings of Kreisler *et al.* (1977), who reported increased levels of autoimmune antibodies against smooth and skeletal muscle, mitochondria and thyroid in a patient with AIL. The number or circulating B cells was increased and their blastogenic response to lipopolysaccharide was greater than normal. However, a theory involving decreased suppressor cell activity would not explain the diminished cellular immune response, unless the entire T cell system, including the T suppressor cells, were assumed to be depressed in AIL.

Alternatively, as suggested by Lawrence *et al.* (1978), the defect might involve an abnormal T to B cell interaction by which B cells escape regulation by T suppressors. As a result of the high immunoglobulin production, T cell suppressors would then be produced in abundance, thus leading indirectly to a decrease of T cell activity.

Our recent observations (this paper and Skibin *et al.*, 1977) of a plasma factor inhibiting T cell transformation would support the former possibility if it were assumed that a general overall decrease in T cell function occurred (including that of T cell suppressors) as a result of the action of the proposed inhibitory factor. Soluble serum factors influencing lymphocyte responses have been described in mice (Bullock & Moller, 1972) and in a wide variety of patients including children with chronic infection (Tomasi, 1977; Waksman & Namba, 1976; Newberry *et al.*, 1973; Fitzgerald & Hosking, 1976). Little is known about their mode of action.

Lymphocytotoxic immunoglobulins that suppress T lymphocytes have been suggested to occur in AIL (Neiman *et al.*, 1978). Lukes & Tindle (1975) described one patient in which an anti-lymphocyte-like factor was demonstrated in serum, gradually disappearing as the patient's clinical condition improved without therapy. The patient's lymphocytes failed to survive in autologous serum, but survived and responded to PHA in calf serum. In our second patient, the putative inhibitory factor was found only during occasions of clinical relapse. In these cases the response of cultures of the patient's lymphocytes in healthy serum to PHA improved when compared to the cultures in autologous serum.

Equally unclear is the mechanism of action of steroids in AIL. In our second case, as reported by Matz *et al.* (1977) and by others, the clinical condition responded well to steroid therapy, with decrease of immunoglobulin levels and a return of *in vitro* parameters of cellular immunity.

Experiments on acute effects of corticosteroids by Fauci & Dale (1974) showed that these drugs induce a profound lymphopenia hours to days after administration, characterized by a loss and presumed redistribution of circulating T cells. The parodoxical return of the PHA response of lymphocytes from AIL patients treated with steroids therefore requires consideration. Saxon *et al.* (1978) demonstrated that steroids caused a specific reduction of suppressor T lymphocyte function, with no loss of helper activity. In addition, direct steroid-induced inhibition of immunoglobulin synthesis by B cells was demonstrated. Although these studies involved rapid and temporary effects of steroids, rather than of long term administration, redistribution and decrease of circulating T suppressor cells caused by steroids might be important in the return of T cell reactivity. The steroid-induced fall in immunoglobulins might therefore be explained by taking into account the direct effect on the antibody-producing function of the B cell line.

Redistribution of lymphocyte subpopulations may also provide an explanation for the non-parallel responses to lectins observed in the lymphocytes of the second patient (Table 2). Whereas pokeweed mitogen can stimulate B cells, PHA and Con A are considered to be T cell activators, and the latter mitogen has also been characterized as a potent effector of human suppressor cells (Schwartz *et al.*, 1977).

Levamisole was administered to the patient in the hope that her increasing requirement of steroids could be reduced. Our findings in the second patient showed a reduced requirement for steroid therapy and a return of *in vitro* and *in vivo* parameters of cellular immunity after levamisole was used. The patient's condition appears to have stabilized in apparent good health 10 months after the first administration of the drug.

The young age of the second patient is of particular interest, since most cases of AIL are advanced in age. A 7-year-old boy with AIL was also described by Howarth & Bird (1976). The condition can therefore occur at any age.

Both patients were admitted with fever of unknown origin and systemic manifestations which in both cases followed ampicillin therapy prior to the histological diagnosis of AIL. Therefore, the condition should be considered among the possible causes of fever of unknown origin.

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