Suppression of Lymphocyte Responses by Monocytes With Untreated and Treated Multiple Myeloma

By Jeremiah J. Twomey, Arline H. Laughter, Lawrence Rice, and Richard J. Ford

Studies were performed on 15 untreated and 14 treated patients with multiple myeloma. The monocyte content was normal in blood but elevated in mononuclear leukocytes (MNL) from treated but not untreated patients \((p < 0.001)\). This correlated with the severity of lymphopenia in blood \((p < 0.01)\). Three patterns of immunoglobulin (Ig) synthesis emerged. (1) Most untreated patients showed normal polyclonal responses to pokeweed mitogen. (2) Of 12 treated patients, 8 whose MNL included >30% monocytoid cells had subnormal Ig responses to pokeweed mitogen. Ig synthesis increased when adherent cells that suppressed Ig synthesis were depleted. Suppression in vitro bore no relationship to polyclonal immunoglobulin levels in serum. (3) Three patients had early blood invasion by plasmacytoid cells. Their MNL spontaneously released large amounts of the Ig class of their serum gammopathies. Proliferative responses to phytohemagglutinin by MNL from all patients were reduced, in part due to monocytoid cell suppression and in part to intrinsic T-cell hyporesponsiveness. B- and T-cell responses in vitro are sometimes suppressed with myeloma. This is related to elevated monocyte percentages in MNL preparations. This excess of monocytes is a function of lymphopenia secondary to therapy, rather than the primary malignant process itself. No evidence was found that suppression by monocytes is qualitatively altered by myeloma or its treatment.

Patients with multiple myeloma often present with bacterial infections. The risk from infections remains high throughout the course of the disease. This susceptibility to infections is due, in large part, to inadequate antibody responsiveness. Cell-mediated immunity, as expressed by delayed hypersensitivity, is relatively intact in untreated patients. The immunodeficiency is further compounded by prolonged chemotherapy. There is evidence that a number of mechanisms may contribute to humoral immunodeficiency with multiple myeloma. (A) The reduction of normal immunoglobulin (Ig) synthesis is probably related to a reduced normal plasma cell mass together with invasion of lymphoid tissues by the malignant process. (B) In some cases, Ig catabolism is accelerated. (C) It has been postulated that malignant plasma cells release a "chalone" that restricts normal B-cell differentiation. (D) Patients produce RNA which, at least in vitro, restricts the expression of membrane Ig on normal B lymphocytes to the idiotype representing the disease. (E) It has recently been shown that monocytoid cells and other third population lymphoid cells from some patients suppress normal Ig synthesis in culture.

This study takes a closer look at the latter mechanism. In particular, we examined circumstances under which suppression of responses by cultured lymphocytes were exaggerated with multiple myeloma. Data on treated and untreated patients were compared to see if elevated suppression by cultured monocytes is related to the primary disease process, or is a secondary phenomenon introduced with therapy. The question as to whether monocytoid cell suppression is elevated with this neoplasm because of quantitative or qualitative changes in these cells was addressed. The findings question the immunobiologic significance of these in vitro observations.

Materials and Methods

Studies were performed on 15 freshly diagnosed, untreated patients and 16 other treated patients with multiple myeloma. The diagnosis was based on there being >20% plasma cells on bone marrow smears and monoclonal Ig or light chain gammopathy. The monoclonal gammopathies were IgG kappa in 9 patients, IgG lambda in 6 patients, IgA kappa in 6 patients, IgA lambda in 2 patients, kappa light chains in 2 patients, and lambda light chains in 2 patients. Most patients had lytic bone lesions. None was azotemic or infected when studied. The average age of the untreated patients was 62 yr and 59 yr in the treated group; ages ranged from 30 to 83 yr. Age, sex, and race had no apparent bearing upon the results. Treatment consisted of a minimum of 8 mo of combined chemotherapy, as defined by the Southwest Oncology group. Two treated patients had also received radiation to the spine. Treated patients were studied 4–6 wk after they had last received therapy. All untreated patients were scheduled for similar chemotherapy. The serum IgG or IgA gammopathies was 4374 ± 744 mg/dl in the untreated group and 4381 ± 865 mg/dl in the treated group \((p > 0.05)\) suggesting that they were studied when they had roughly comparable tumor burdens. Thus, apart from having received therapy, the clinical status of the untreated and treated patients was about comparable. Normal blood was obtained from healthy volunteers in the third age decade; earlier experience indicated that comparable results are obtained on healthy subjects in our patients' age range.

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Mononuclear leukocytes (MNL) were separated from heparinized blood by isopyknic floatation. The MNL added to cultures for measuring Ig synthesis were washed 4 times in fetal calf serum (FCS). Nonadherent mononuclear leukocytes (NA-MNL) were obtained by incubating 10–40 × 10^6 MNL suspended in 5 ml Hank’s balanced salt solution with 25% normal plasma for 30 min at 37°C in equilibrated syringes packed with 0.8 g glass wool. The residual 3.9% ± 1.4% monocytes among the effluent cells sufficed to promote lymphocyte responses in our culture system. Lymphocytopotoxicity was achieved by incubating 8 × 10^6 MNL-lymphocytes suspended in 2 ml RPMI medium (GIBCO, Grand Island, N.Y.) and 10% FCS (Reheis, Phoenix, Ariz.) with 0.4 ml anti-lymphocyte globulin (ALG-H3, NIH, Bethesda, Md.), and 0.4 ml guinea pig complement (Cordis, Miami, Fla.) for 60 min at 37°C. About 80% of lymphocytes treated in this fashion took up trypan blue and were unresponsive to phytohemagglutinin (PHA) in lymphoproliferative cultures. Monocytes were concentrated by binding to cold insoluble human globulins immobilized on gelatin plates as described by Bevilacqua et al. and then freed by calcium chelation with 10 mM EDTA. This yielded 80%–95% monocytes with excellent viability and suppressor activity.

Triplicate cultures were set up in flat-bottomed 0.4 ml plastic microtiter plates (Linbro-Flow Laboratories, Hamden, Conn.) when testing for T-lymphocyte proliferation. Each culture contained 10^5 lymphocytes suspended in 0.15 ml Eagle’s minimum essential medium (GIBCO) and 0.05 ml fresh normal plasma. Stimulation was with a 1:1000 dilution of phytohemagglutinin-P (Difco, Detroit, Mich.). Incubation was for 3 days in 5% CO2 and air in a humidified 37°C incubator. About 24 hr before cultures were terminated, 2 μCi 3H-thymidine (Schwarz/Mann, Orangeburg, N.Y., specific activity 3 Ci/m mole) were added to each culture. At the end of the culture period, cells were harvested and washed using a semiautomatic harvester (Hiller, Madison, Wisc.) solubilized with 0.25 ml NCS fluid (Amersham, Arlington Heights, Ill.), suspended in 4 ml scintillation fluid and counted in a liquid scintillation counter with an external standard (Tricarb, Packard, Downers Grove, Ill.). Average incorporation by each triplicate set of cultures was recorded.

When measuring Ig synthesis, duplicate cultures containing 10^6 lymphocytes suspended in 0.9 ml RPMI medium and 0.1 ml FCS with 4 mM L-glutamine and antibiotics added were incubated for 14 days in stationary round-bottomed polystyrene tubes held in the erect position. Stimulation was with 10 μl/ml pokeweed mitogen. Supernates were tested for IgG, IgA and IgM content using Immunofluor kits (Bio-Rad, Richmond, Calif.) and a fluorocolorimeter (Amino, Silver Springs, Md.) Average combined synthesis of IgG, IgA, and IgM by normal MNL was increased by 19-fold above unstimulated levels by adding pokeweed mitogen to the cultures. Suppression mediated through prostaglandin release was determined in PHA-stimulated lymphoproliferative cultures prepared (A) without adding indomethacin and (B) with 1 μg/ml indomethacin added. A similar culture system was used to measure suppression by glass-wool-adherent cells where responses by (A) MNL and (B) NA-MNL were compared. The protocol of Broder et al. was used to test for suppression of Ig synthesis by patient MNL. We measured total IgG, IgA, and IgM responses to pokeweed by (A) cultures of 0.5 × 10^6 patient plus 0.5 × 10^6 normal MNL-lymphocytes and (B) cultures containing 10^6 MNL-lymphocytes from the same patient or control donor incubated individually from which average values were recorded. In each test system, suppression was expressed as a percentage, calculated from the formula: (1 – A/B) × 100.

Results in groups of subjects are expressed as means ± standard errors of the means. The significance of differences on data from different groups was determined using the Wilcoxon rank sum test. To see if results on a group of subjects were more likely to be above or below a certain value, the chi-square test was employed. Correlation coefficients were an expression of total variation about the mean that can be explained by the regression, with P values derived from the Student’s t test.

**RESULTS**

**Cell Preparations**

Percentage and absolute lymphocyte counts were significantly reduced in whole blood from treated patients (p < 0.01), but were normal in patients who had not been treated (Table I). Monocyte counts on whole blood from all patients, irrespective of prior therapy, were normal. However, MNL separated from the blood of treated, but not from untreated patients, contained significantly elevated percentages of monocytes (p < 0.001). There was an inverse relationship between absolute lymphocyte counts on whole blood and monocyte percentages in MNL preparations from the same collections of blood (p < 0.01); the highest monocyte percentages were found in MNL preparations obtained from treated patients who were most severely lymphopenic.

**Ig Synthesis in Culture**

Ig secretion by MNL from 13 untreated patients, 12 treated patients, and 17 healthy subjects was measured after 14 days of culture with and without pokeweed mitogen. Two untreated and one treated patient had 3%–10% plasmacytoid cells in their MNL preparations. Unstimulated MNL from these 3 patients spontaneously released 2335 ng of IgG, 1733 ng of IgG, and 3235 ng of IgA per 10^6 cultured lymphocytes, respectively. The heavy chain specificity of these spontaneous releases were the same as the gammapathies present in their sera. Their MNL produced little polyclonal Ig even when stimulated with pokeweed mitogens. Coculture experiments showed that their MNL were not suppressive of normal Ig synthesis. Excluding these

<table>
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<tr>
<th>Table 1. Percentage and Absolute Lymphocyte and Monocyte Counts on Whole Blood and Monocyte Percentages in MNL*</th>
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<td><strong>Preparations</strong></td>
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<tr>
<td>Blood lymphocytes</td>
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<tr>
<td>Percent</td>
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<td>MNL monocytes</td>
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<td>Percent</td>
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*MNL, mononuclear leukocyte.
†Number of subjects tested.
three patients, unstimulated Ig synthesis was 445 ± 101 ng by normal MNL, 354 ± 127 ng by untreated myeloma MNL, and 169 ± 68 ng by treated myeloma MNL per 10⁶ lymphocytes. The latter was significantly reduced (p < 0.05). Responses to pokeweed mitogen were normal by MNL from the 11 untreated patients whose blood was not overtly invaded with plasmacytoid cells (Fig. 1). In contrast, stimulated IgG and IgM synthesis by MNL from the treated group of patients was significantly lower than in paired control incubations (p < 0.01), while IgA synthesis was within the normal range for this laboratory.

Suppression of Ig synthesis by patient MNL was tested as previously described¹³ in cocultures with MNL from healthy subjects. Overall, suppression by MNL from control donors in coculture with MNL from paired allogeneic control donors was 8% ± 7% (Fig. 1). Likewise, suppression by MNL from untreated myeloma patients cocultured with MNL from healthy subjects was also negligible at −6% ± 8% (p > 0.5). MNL from none of the normal donors or untreated myeloma patients suppressed in coculture by more than 28%. In contrast, suppression exceeded 50% in cocultures that contained MNL from 8/12 of the treated myeloma patients (p < 0.01). When Ig responses to pokeweed mitogen were normal, as was the case with 3 treated patients, MNL from the same patients did not suppress Ig synthesis by MNL from healthy donors in concomitant cocultures. The suppression by MNL from treated patients was not altered by preincubation with antilymphocyte globulin plus complement. However, suppression was removed after adherent cells were depleted from MNL obtained from treated patients (Table 2). Stimulated Ig synthesis by normal NA-MNL varied considerably because of variable loss of B lymphocytes during preincubation with glass wool. Cocultured normal NA-MNL did not appreciably increase Ig synthesis when compared with

<table>
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<tr>
<th>Cell Preparation</th>
<th>IgG (ng/Ig/10⁶ Lymphocytes)</th>
<th>IgA</th>
<th>IgM</th>
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<tbody>
<tr>
<td>Normal MNL</td>
<td>4,300</td>
<td>1,620</td>
<td>7,640</td>
</tr>
<tr>
<td>Patient MNL</td>
<td>600</td>
<td>120</td>
<td>1,500</td>
</tr>
<tr>
<td>Normal MNL + patient MNL</td>
<td>840</td>
<td>320</td>
<td>1,400</td>
</tr>
<tr>
<td>Normal MNL + ALG† treated patient MNL</td>
<td>500</td>
<td>270</td>
<td>850</td>
</tr>
<tr>
<td>Normal MNL + patient NA-MNL ‡</td>
<td>12,740</td>
<td>4,200</td>
<td>21,400</td>
</tr>
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* MNL, mononuclear leukocyte.
† ALG, antilymphocyte globulin.
‡ NA-MNL, nonadherent mononuclear leukocyte.

synthesis in cocultures of MNL preparations from which the nonadherent cells were derived.

T-Cell Proliferation

³H-Thymidine incorporation by PHA-stimulated MNL from both treated and untreated patients was significantly subnormal (p < 0.01) (Table 3). This deficit was not increased after administration of therapy (p > 0.05). Responses by normal MNL were increased by only 12% ± 1% when indomethacin was added to cultures. The added presence of indomethacin increased responses by MNL from untreated myeloma patients by 21% ± 3% and treated patients by 29% ± 6% (p < 0.05). Overall, this effect of indomethacin was not significantly greater on treated than untreated patients (p > 0.2). Depletion of adherent cells by preincubation with glass wool reduced responses to PHA by normal cells by 13% ± 2% and did not materially alter responses by untreated patients. However, responses by lymphocytes from the treated patients were increased by 18% ± 10% (p < 0.05). Neither addition of indomethacin to cultures nor depletion of cells that adhere to glass wool elevated responses by T lymphocytes from untreated or treated patient to normal levels.
Table 3. The Effect of Adding 1 μg/ml Indomethacin to Cultures or Depleting Glass-Wool-Adherent Cells 3H-Thymidine Incorporation Stimulated With PHA

<table>
<thead>
<tr>
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<th>Normal Donors (24†)</th>
<th>Untreated Patients (13)</th>
<th>Treated Patients (12)</th>
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</thead>
<tbody>
<tr>
<td>MNL†</td>
<td>146,129 ± 7,817</td>
<td>97,064 ± 11,937</td>
<td>62,117 ± 23,405</td>
</tr>
<tr>
<td>MNL + indomethacin</td>
<td>164,804 ± 9,328</td>
<td>123,108 ± 15,621</td>
<td>85,950 ± 18,941</td>
</tr>
<tr>
<td>NA-MNL§</td>
<td>129,104 ± 6,522</td>
<td>99,569 ± 12,404</td>
<td>75,150 ± 12,246</td>
</tr>
</tbody>
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*PHA, phytohemagglutinin.
†Number of subjects tested.
‡MNL, mononuclear leukocyte.
§NA-MNL, nonadherent mononuclear leukocyte.
∥Mean ± SEM cpm.

Correlates of Elevated Monocyte Percentages in MNL Preparations

In our laboratory, normal MNL usually include 18% ± 1% monocytes. Monocyte percentages exceeded 30% in MNL from 7 treated patients, but from none of the untreated patients. Data on these and the other 18 myeloma patients whose MNL preparations included <30% monocytes (irrespective of prior therapy) were compared. The patients whose MNL included >30% monocytes were significantly more lymphopenic (Table 4), had significantly higher suppression of T-cell proliferation by indomethacin-sensitive or glass-wool-adherent cells, produced significantly less Ig when MNL were cultured with pokeweed mitogen, and caused significantly higher suppression of Ig synthesis when cocultured with normal MNL than was the case with the other 18 patients whose MNL preparations included <30% monocytes. Normal values for all of the above parameters were recorded on the 18 patients whose MNL contained <30% monocytes.

Follow-Up Studies After Chemotherapy

Two of the untreated patients were available for follow-up studies >18 mo after initiating chemotherapy. One patient was not rendered lymphopenic by therapy. When retested, his MNL included 19% monocytes, indomethacin and adherent cell depletion raised PHA-stimulated 1H-thymidine incorporation by <20%, and Ig synthesis was not suppressed in coculture. Thus, his MNL behaved normally in our test systems.

The second patient, with 690 lymphocytes/cu mm of blood, had become severely lymphopenic during therapy. Her MNL included 33% monocytes, indomethacin reversible suppression was 77%, and adherent cell suppression was 85% in PHA-stimulated lymphoproliferative cultures. Pokeweed mitogen stimulated the release of only 100 ng of Ig per 10⁶ lymphocytes by her cultured MNL.

Quantitative Studies on Monocytoid Cell Suppression

Cocultures were set up containing 0.5 × 10⁶ MNL-lymphocytes in 0.5 ml medium from a healthy donor, plus increasing volumes of irradiated (2500 R) MNL also suspended at 10⁶ MNL-lymphocytes per ml from an allogeneic donor; volumes were adjusted to 1 ml with medium. The effect of adding increasing numbers of irradiated MNL from a healthy subject that included 12% monocytes and increasing numbers of irradiated MNL from 2 treated lymphopenic patients with multiple myeloma that included 37% and 39% monocytes, respectively, is shown in Fig. 2. Clearly, higher numbers of irradiated MNL from both patients were more suppressive of Ig synthesis by cocultured normal MNL than were irradiated MNL from the healthy donor. The arrows identify the number of
Fig. 2. A comparison of suppression of stimulated Ig synthesis by increasing numbers of the MNL from two lymphopenic treated patients (solid lines) and a normal donor (dotted line). Percentages in parenthesis represent the monocyte content of the MNL preparations.

patient MNL that added a comparable number of monocytes to the number of monocytes in 0.5 ml of irradiated normal cells. There was no evidence that patient monocytes were qualitatively more suppressive than a comparable number of normal monocytes.

Monocytes were also concentrated to >80% purity on immobilized cold-insoluble globulins and added at 20%-67% concentrations to 1 ml cultures containing 10⁶ adherent-cell-depleted lymphocytes from a healthy allogeneic donor. Monocyte preparations from 2 untreated and 2 treated patients and 4 normal donors were tested for suppression of Ig synthesis by the cocultured lymphocytes when stimulated with pokeweed mitogen. Suppression was observed with all preparations, increased with higher monocyte percentages and was comparable with all three groups studied (data not shown).

Correlations With Ig Synthesis In Vivo

As is usual with multiple myeloma, none of our patients had an IgM gammopathy. Thus, serum IgM levels reflected their capacity for normal polyclonal IgM synthesis in vivo. Serum IgM levels were 60% ± 12% mg/dl in the untreated patients and 53 ± 11 mg/dl in the treated patients (p > 0.05) (normal range 50–225 mg/dl). Serum IgM levels were <50 mg/dl on 5/11 untreated patients and 8/12 treated patients. Serum IgM levels were not significantly different in patient groups with greater than or less than 30% monocytes in their MNL preparations. Patients whose MNL suppressed Ig synthesis in culture did not have lower serum IgM values than the other patients.

DISCUSSION

This study demonstrated three patterns of Ig synthesis by cultured MNL from patients with multiple myeloma. (1) Unstimulated and mitogen-stimulated Ig synthesis are usually quantitatively normal with untreated patients. (2) Both unstimulated and stimulated Ig synthesis are usually reduced after prolonged therapy. (3) The presence of low numbers of, presumably malignant, circulating plasmacytoid cells is associated with the spontaneous release of large amounts of Ig with the same heavy chain specificity as the patient's gammopathy. Differences observed between treated and untreated patients cannot be ascribed to differences in patient population or tumor burden.

Proliferative responses by MNL, when optimally stimulated with PHA, were reduced with both untreated and treated multiple myeloma. Others have reported similar findings with cultured MNL and whole leukocyte preparations, where responses may be further modified by granulocyte inhibition. Proliferative responses to soluble antigens are more frequently impaired. Although normal T-cell responses to suboptimal or optimal concentrations of PHA have been reported with myeloma, a deficit of T-cell proliferation in culture probably exists with many patients. This has immunobiologic significance since most, but not all, T-cell responses also require T-cell proliferation. The capacity to induce delayed hypersensitivity to dinitrochlorobenzene is often also impaired, suggesting that these patients do have a T-lymphocyte deficit.

It has been shown that a circulating monocytoid cell from patients with multiple myeloma suppresses Ig synthesis in culture by normal lymphocytes. We observed this suppression only in treated patients. Monocytoid cell suppression lowered both T- and B-cell responses. Yet, T cells from patients with untreated or treated myeloma also had an intrinsic impairment of proliferation.

Monocytoid cell suppression was accompanied by elevated monocyte percentages in MNL preparations, but not in whole blood from which these MNL were derived. Instead, this excess of monocytes in MNL preparations coincided with lymphopenia in whole blood and was only found in treated patients. This excess of monocytes among MNL, which was accompanied by suppression, developed in patients after prolonged therapy, but only when therapy rendered them lymphopenic. When monocytes were added in increasing numbers, either in MNL preparations or in
Monocytoid cell suppression with myeloma

Monocytoid cell suppression of Ig synthesis was demonstrated in three of six patients of undetermined treatment status. paglieroni and McKenzie showed that monocytoid cell suppression is qualitatively more suppressive than monocytes from healthy subjects. It is known that normal monocytes, when added to cultures in sufficiently high concentrations, are potent suppressors of both T- and B-cell responses. We found no evidence that monocytes from patients with multiple myeloma, whether treated or untreated, are qualitatively more suppressive than monocytes from healthy subjects. Idiopathic membranous glomerulonephropathy may be an example of a condition where monocytoid cell suppression is qualitatively elevated.

The present study appears to be at variance with published experience. Broder et al. observed impaired Ig responses by MNL from many untreated patients. Monocytoid cell suppression of Ig synthesis was demonstrated in three of six patients of undetermined treatment status. The non-adherent suppressor cell had Fe receptors, some DR receptors, or B-lymphocyte membrane antigen. The added presence of monocytes amplified this suppression. The non-adherent cells were nonphagocytic, did not perform macrophage-promoting functions, did not form rosettes with sheep erythrocytes, did not proliferate in response to T-cell mitogens, and lacked EBV or complement receptors, or B-lymphocyte membrane antigen. The added presence of monocytes amplified this suppression. The non-adherent cells were not registered in the present study. However, the earlier work clearly points out that suppression, albeit affected by cells other than monocytes, may be an important component of the immunodeficiency of multiple myeloma.

Peritoneal macrophages from untreated plasmacytoma-bearing animals suppress both murine and human B-lymphocyte responses but do not suppress T cells. Since macrophages from the peritoneal cavity of normal mice do not suppress, murine plasmacytomas or their causation may activate suppressor macrophages or attract them to certain tissues. This suppression may be anatomically compartmentalized, since macrophages from solid lymphoreticular tissues of similar mice do not suppress in the same test systems. Modulation of immune responses by monocytes or macrophages with human multiple myeloma may differ from that with murine models of plasmacytomas.

The present study suggests that suppression by monocytes is a consequence of altered lymphocyte-monocyte ratios because of lymphopenia caused by therapy. The net result is an excess of monocytes relative to lymphocytes in MNL preparations. No evidence was found that suppression by monocytes is qualitatively increased by multiple myeloma itself or altered by therapy. It seems that elevated numbers of monocytes are added with MNL from lymphopenic blood in order to keep the number of lymphocytes added to cultures constant. Thus, on the basis of the present study, monocytoid cell suppression would no longer be considered a primary component of the immune deficiency of multiple myeloma. Failure to observe a relationship between monocytoid cell suppression in vitro and reduced serum levels of polyclonal IgM in this study supports the contention that this type of suppression in culture has little bearing on the immune deficiency of this lymphoma in vivo.

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REFERENCES

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