Leukocyte Interferon Production, RNA Synthesis, and PHA Response in Patients With Infectious Mononucleosis

By Anne L Rassiga Pidot, L. Herbert Maurer, and O. Ross McIntyre

Sequential measurements of in vitro Newcastle disease virus-induced interferon (IF) synthesis, spontaneous RNA synthesis, and PHA-induced blastic transformation were made in leukocytes derived from ten patients with infectious mononucleosis (IM). The median leukocyte IF production on the day of diagnosis was found to be significantly depressed, 35 international units (IU) IF per 2 x 10^6 leukocytes, in comparison to a median titer of 463 IU after recovery (p < 0.002) or to a median of 406 IU found in 52 cultures from normal healthy individuals. No spontaneous production of leukocyte IF or circulating serum IF was noted. An increased rate of spontaneous leukocyte RNA synthesis during the first 2 hr of culture was noted in nine of the ten subjects (p < 0.001). Four of the ten patients showed a markedly defective response to PHA after 96-144 hr in culture. A suggestive, but not statistically significant, correlation was noted between increased spontaneous RNA synthesis, defective late PHA transformation, and defective virus-induced IF production. All defects persisted during the 1-wk study period and were resolved after recovery. We conclude that major temporary alterations occur in several parameters of leukocyte function in IM.

INFECTIOUS MONONUCLEOSIS (IM) is a disease, probably caused by the Epstein-Barr (EB) virus,1,2 that is characterized by the presence of atypical mononuclear cells in the peripheral blood that actively synthesize RNA and DNA.3,4 Interferon (IF), an antiviral protein produced in response to virus infection, is important in limiting in vivo virus proliferation.7 Since leukocytes, incubated in vitro with virus, are capable of producing IF8,9 we examined the ability of short-term peripheral leukocyte cultures, obtained at diagnosis and throughout the course of infectious mononucleosis, to produce IF either spontaneously or in response to an in vitro virus infection. In addition, spontaneous RNA synthesis and the blastogenic response to phytohemagglutinin (PHA) of these cells were examined. Serum samples were analyzed for the presence of circulating IF. Furthermore, the effects of in vivo administration of steroids on the above parameters were observed in a small group of patients.
MATERIALS AND METHODS

Patient Population and Treatment Schedule

All patients presenting to the Mary Hitchcock Memorial Hospital or the Dartmouth College infirmary with the clinical picture of IM over a period of 18 mo were entered on a prospective, double-blind study of placebo vs. 6-α-methylprednisolone therapy. The results of this clinical study will be reported elsewhere. Leukocyte cultures were obtained from ten consecutive patients (Table 1). Steroid therapy consisted of 24, 20, 16, 12, 8, and 4 mg of oral methylprednisolone given in divided doses on day 1 through day 6.

Leukocyte Cultures

Samples were obtained prior to therapy (day 0), on days 1 and 7 of disease, and 3 wk to 7 mo later when the patient was fully recovered. Leukocytes were obtained by gravity sedimentation of heparinized blood and were suspended in TC 199 medium supplemented with 20% fetal calf serum and containing 100 U penicillin/ml + 250 μg/ml streptomycin as previously described.10

IF Production

Four x 10^6 leukocytes were incubated with and without Newcastle disease virus (NDV) at a multiplicity of infection of 0.1 plaque-forming units (PFU) per leukocyte in a 2 ml volume for 24 hr.8 Residual NDV was inactivated by acidification of the supernatant to pH 2.0 for 48 hr, after which the sample was returned to a neutral pH and was stored at −70°C. The virus inhibitory substance obtained from normal leukocytes cultured under identical conditions satisfied the criteria for an interferon.11

PHA Response and 3H-Uridine Uptake

PHA, prepared according to the method of Børjensen et al.12 was added to one-half of replicate cultures of 1 x 10^6 leukocytes in 5 ml of medium. Early (0 hour) RNA synthesis in control and PHA-stimulated cultures were determined by adding 1 μCi 3H-uridine to each tube (3HUdr, New England Nuclear Laboratories; specific activity, 10.4 Ci/mM) and by incubating for 2 hr. Late RNA synthesis was determined by adding a 2-hr pulse dose of 1 μCi/tube 3HUdr after 96-144 hr of incubation. The 3HUdr incorporation, expressed as disintegrations per minute (dpm) found in the TCA precipitate obtained from saline-washed, frozen, and thawed disrupted cells, was expressed as the average of triplicate cultures.

Table 1. Patient Population

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Peripheral WBC x 10^9</th>
<th>Atypical Lymphocytes (%)</th>
<th>Maximum Heterophile Titer</th>
<th>Days III Before Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo Rx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. L. R.</td>
<td>18</td>
<td>F</td>
<td>17.6</td>
<td>73</td>
<td>64</td>
<td>1:1792</td>
</tr>
<tr>
<td>2. B. A.</td>
<td>20</td>
<td>M</td>
<td>10.0</td>
<td>64</td>
<td>46</td>
<td>1:224</td>
</tr>
<tr>
<td>3. E. D.</td>
<td>21</td>
<td>M</td>
<td>15.0</td>
<td>88</td>
<td>80</td>
<td>1:896</td>
</tr>
<tr>
<td>4. K. McC</td>
<td>20</td>
<td>F</td>
<td>5.7</td>
<td>57</td>
<td>18</td>
<td>1:1792</td>
</tr>
<tr>
<td>5. W. G.</td>
<td>19</td>
<td>M</td>
<td>16.0</td>
<td>63</td>
<td>52</td>
<td>1:448</td>
</tr>
<tr>
<td>6. F. C.</td>
<td>22</td>
<td>M</td>
<td>8.2</td>
<td>66</td>
<td>38</td>
<td>1:3584</td>
</tr>
<tr>
<td>7. D. R.</td>
<td>17</td>
<td>M</td>
<td>13.0</td>
<td>71</td>
<td>46</td>
<td>1:448</td>
</tr>
<tr>
<td>Steroid Rx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. B. B.</td>
<td>18</td>
<td>F</td>
<td>6.2</td>
<td>58</td>
<td>39</td>
<td>1:112</td>
</tr>
<tr>
<td>9. E. K.</td>
<td>20</td>
<td>M</td>
<td>14.4</td>
<td>60</td>
<td>49</td>
<td>1:7168</td>
</tr>
<tr>
<td>10. C. W.</td>
<td>20</td>
<td>F</td>
<td>12.1</td>
<td>48</td>
<td>39</td>
<td>1:896</td>
</tr>
</tbody>
</table>

* Per cent of total leukocyte count that were atypical lymphocytes.
LEUKOCYTE INTERFERON PRODUCTION

IF Assay

IF was assayed by the dye uptake method.\textsuperscript{11} The IF titer was expressed as the reciprocal of that dilution of 1 ml of sample that protected a monolayer of foreskin-derived fibroblasts against the challenge virus (vesicular stomatitis virus) by 50\%, when the log of the dilution was plotted against the per cent dye uptake. All values represent the amount of IF produced by 2 × 10\textsuperscript{6} leukocytes and are expressed in international units on the basis of titration of international human reference IF 69/19 in our assay system.

Monolayer protection of 25\% or greater with a decrease in protection with increasing sample dilution was required before we designated a sample as containing IF, since nonspecific monolayer protection was frequently observed in samples containing no significant amount of IF.

In addition, since normal plasma was found to be occasionally cytotoxic to the assay monolayer, all plasma samples were run with a control vial, and the IF titer was calculated from the lowest dilution at which no cytotoxicity was observed.

RESULTS

IF Production by Leukocyte Cultures

The amount of NDV-induced IF produced by the leukocyte cultures obtained on day 0 from patients with IM was significantly less (less than 4.3–291 IU; median 35 IU) than that produced after recovery (203–1379 IU; median, 462 IU) (p < 0.002), or by 52 leukocyte cultures obtained from 28 normal healthy individuals (less than 0.7–2654 IU; median, 406 IU) (p < 0.001) (Fig. 1). The percentage of mononuclear cells in the cultures on day 0 (65 ± 11.4) was greater than that observed after recovery (55.6 ± 18.8) or in the 52 normals (46.2 ± 15.3).

In four patients (W.G., F.C., D.R., C.W.), leukocyte cultures were also studied at higher virus challenge doses (1.0 and 5.0 PFU NDV/leukocyte). As has been previously found for leukocytes from normal individuals,\textsuperscript{8} increasing the virus dose did not result in increased IF production.

The amount of leukocyte IF production was relatively constant and remained depressed during the week of observation for all patients except for F.C., who produced the highest leukocyte IF titer observed on day 7. This patient was felt to be in the early recovery phase of his illness at the time of initial clinical examination.

The amount of IF produced by the patient’s leukocytes after recovery was not different than that produced by cultures from normal individuals.

Spontaneous IF Production

The supernatants obtained from leukocyte cultures incubated without NDV were examined to see if cultures containing atypical lymphocytes were spontaneously producing IF. No measurable IF could be detected either on day 0 (less than 2.9 IU to less than 10.5 IU; median, less than 6.7 IU) or after recovery (less than 0.58 IU to less than 15.6 IU; median, less than 2.9 IU).

Plasma IF Levels

The plasma of all patients was examined for the presence of circulating IF. In 12 normal individuals, plasma IF titers varied from less than 0.04 IU to 33 IU (median, less than 9.7 IU). Plasma samples from the patients with IM were not significantly different from normal either on day 0 (less than 2.6 IU to less than
INITIAL RECOVERY

OBSERVATIONS


Fig. 1. Leukocyte IF production. NDV-induced IF titers and median value for normal individuals are shown on left; the IF titers produced by patients with IM studied on day of diagnosis and after recovery are shown on right.

32.4 IU; median, less than 5.3 IU) or after recovery (less than 1.3 IU to less than 18.2 IU; median, less than 13.7 IU).

Spontaneous Leukocyte \(^{3}H\)Udr Uptake

In nine of the ten patients with IM, the baseline incorporation of \(^{3}H\)Udr into RNA during the first 2 hr of culture was greater in the cultures obtained on day 0 than in the recovery phase cultures (Table 2). \((p < 0.002, \text{ Wilcoxon-Mann-Whitney rank sum test})\). This elevation of the early spontaneous RNA synthesis
LEUKOCYTE INTERFERON PRODUCTION

Table 2. Early (0 Hr) $^3$HUdr Incorporation by Leukocytes From Patients With IM *

<table>
<thead>
<tr>
<th>Patient</th>
<th>Placebo Rx</th>
<th></th>
<th>Steroid Rx</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control PHA</td>
<td></td>
<td>Control PHA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 1</td>
<td>Day 7</td>
<td>Recovery</td>
</tr>
<tr>
<td>1. L. R.</td>
<td>1244</td>
<td>1150</td>
<td>642</td>
<td>630</td>
</tr>
<tr>
<td>2. B. A.</td>
<td>374</td>
<td>439</td>
<td>445</td>
<td>409</td>
</tr>
<tr>
<td>3. E. D.</td>
<td>301</td>
<td>273</td>
<td>310</td>
<td>265</td>
</tr>
<tr>
<td>4. K. McC.</td>
<td>29</td>
<td>19</td>
<td>31</td>
<td>44</td>
</tr>
<tr>
<td>5. W. G.</td>
<td>134</td>
<td>157</td>
<td>122</td>
<td>136</td>
</tr>
<tr>
<td>6. F. C.</td>
<td>66</td>
<td>76</td>
<td>61</td>
<td>64</td>
</tr>
<tr>
<td>7. D. R.</td>
<td>185</td>
<td>180</td>
<td>269</td>
<td>184</td>
</tr>
<tr>
<td>8. B. B.</td>
<td>1235</td>
<td>774</td>
<td>939</td>
<td>942</td>
</tr>
<tr>
<td>9. E. K.</td>
<td>307</td>
<td>433</td>
<td>480</td>
<td>500</td>
</tr>
<tr>
<td>10. C. W.</td>
<td>213</td>
<td>206</td>
<td>144</td>
<td>139</td>
</tr>
</tbody>
</table>

*Expressed as dpm/1 x 10^6 leukocytes.

persisted through day 7, although a significant decline in isotope incorporation occurred between day 0 and day 7.

After 96–144 hr in culture, the spontaneous rate of RNA synthesis was markedly lower in all cultures ($p < 0.002$) (Table 3) and was not different from the baseline level of $^3$HUdr incorporation seen in the unstimulated cells of recovery-phase cultures.

$^3$HUdr Uptake in PHA-stimulated Cultures

The addition of PHA did not result in stimulation, or suppression, of the early isotope uptake in leukocytes obtained at any time during the course of IM or after recovery (Table 2).

The blastogenic response to PHA of the leukocytes obtained on day 0 after 96–144 hr in culture was highly variable (Table 3). Four patients (L.R., B.A., E.D., E.K.) showed a markedly defective response to PHA persisting for the first week of illness and returning to normal after recovery. A statistically significant difference between the initial and recovery PHA responses for the group as a whole, however, was not achieved.

Correlation Between RNA Synthesis and IF Production

In Table 4, the patients are ranked according to the amount of spontaneous $^3$HUdr uptake occurring during the initial 2 hr of incubation in cultures obtained on day 0. In general, the cultures that were most actively synthesizing RNA spontaneously produced little or no IF in response to NDV infection, transformed poorly in response to PHA, and contained fewer numbers of normally appearing small lymphocytes. Statistical significance could not be achieved. No correlation was found between the number of atypical lymphocytes, as determined by morphologic examination, and the amount of early spontaneous or late PHA-induced $^3$HUdr incorporation, or NDV-induced IF production. There was also no relationship between these parameters and the duration of clinical illness prior to study (Table 1).
<table>
<thead>
<tr>
<th>Patient</th>
<th>Control</th>
<th>PHA</th>
<th>Control</th>
<th>PHA</th>
<th>Control</th>
<th>PHA</th>
<th>Control</th>
<th>PHA</th>
<th>Control</th>
<th>PHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIDOT</td>
<td>0.09</td>
<td>0.89</td>
<td>0.09</td>
<td>0.89</td>
<td>0.09</td>
<td>0.89</td>
<td>0.09</td>
<td>0.89</td>
<td>0.09</td>
<td>0.89</td>
</tr>
<tr>
<td>MAURER</td>
<td>0.09</td>
<td>0.89</td>
<td>0.09</td>
<td>0.89</td>
<td>0.09</td>
<td>0.89</td>
<td>0.09</td>
<td>0.89</td>
<td>0.09</td>
<td>0.89</td>
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<tr>
<td>MCINTYRE</td>
<td>0.09</td>
<td>0.89</td>
<td>0.09</td>
<td>0.89</td>
<td>0.09</td>
<td>0.89</td>
<td>0.09</td>
<td>0.89</td>
<td>0.09</td>
<td>0.89</td>
</tr>
</tbody>
</table>

**Table 3.** Late (96-144 hr) ³H]thymidine incorporation by leukocytes from patients with IM.®

*Expressed as dpm/1 x 10⁶ leukocytes.

1 dpm PHA-stimulated cultures/dpm control cultures.
Table 4. Correlation Between Spontaneous RNA Synthesis and Leukocyte Responsiveness in Patients With IM at Diagnosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Early (0 Hr)</th>
<th>Late (96-144 Hr)</th>
<th>PHA-stimulated Uptake</th>
<th>Late (96-144 Hr)</th>
<th>PHA Stimulation Ratio</th>
<th>Atypical Lymphocytes (%)</th>
<th>Small Lymphocytes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spontaneous 3HUr Uptake</td>
<td>PHA Titer</td>
<td>3HUr Uptake</td>
<td>PHA Titer</td>
<td>Ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. R.</td>
<td>1244</td>
<td>42</td>
<td>0.89</td>
<td>64</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. B.</td>
<td>1235</td>
<td>1339</td>
<td>18.1</td>
<td>39</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. A.</td>
<td>374</td>
<td>&lt;9.7</td>
<td>42</td>
<td>1.3</td>
<td>46</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>E. K.</td>
<td>307</td>
<td>&lt;19.2</td>
<td>170</td>
<td>5.2</td>
<td>49</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>E. D.</td>
<td>301</td>
<td>&lt;4.5</td>
<td>97</td>
<td>3.5</td>
<td>80</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>C. W.</td>
<td>213</td>
<td>&lt;4.3</td>
<td>412</td>
<td>11.1</td>
<td>39</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>D. R.</td>
<td>185</td>
<td>51</td>
<td>2894</td>
<td>51.7</td>
<td>46</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>W. G.</td>
<td>134</td>
<td>291</td>
<td>1770</td>
<td>40.2</td>
<td>52</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>F. C.</td>
<td>66</td>
<td>62</td>
<td>1053</td>
<td>20.7</td>
<td>38</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>K. McC.</td>
<td>29</td>
<td>163</td>
<td>944</td>
<td>32.6</td>
<td>18</td>
<td>39</td>
<td></td>
</tr>
</tbody>
</table>

*Expressed as dpm/1 x 10^6 leukocytes.
†Expressed as IU/2 x 10^6 leukocytes.
§dpm PHA-stimulated cultures/dpm control cultures.
\(^{1}\)Per cent of total leukocyte count that were atypical lymphocytes.
\(^{2}\)Per cent of total leukocyte count that were small lymphocytes.

Effect of Steroid Therapy

Three patients received methylprednisolone. The early spontaneous uridine uptake for this group was not significantly different from the seven placebo-treated subjects before treatment or on day 1 or 7, nor was the change in spontaneous uridine incorporation between day 0 and day 1 or day 0 and day 7 different from the placebo group (Table 2). Likewise, no significant effect of steroid therapy on the ability of the leukocytes to transform in response to PHA (Table 3) or to produce IF was observed.

DISCUSSION

Addition of NDV to the leukocyte cultures obtained from patients with IM resulted in no detectable IF production in four patients, and in low normal IF titers in another four. These results are statistically highly significant. This defect persists for at least a week. After recovery, normal virus-induced leukocyte IF titers were observed. Our findings differ from those of Hayashi et al.,\(^{13}\) who reported normal leukocyte IF titers in five patients with IM and decreased IF production in one patient, and from Gergely et al.\(^{14}\) who found approximately equal IF titers in acute- and convalescent-phase leukocyte cultures from ten children with IM.

Whole leukocyte cultures were employed in our studies, since it has been shown that the presence of macrophages augments the blastogenic response of lymphocytes to PHA,\(^{15}\) and the IF production in response to PHA or antigens.\(^{17}\) It is not possible to explain defective PHA response or IF production on the basis of variations in the absolute number of mononuclear cells in our experiments, since the cultures obtained on the initial day of study contained a significantly greater proportion of mononuclear cells than those obtained after recovery or in normals.

Defective, in vitro virus-induced leukocyte IF production has previously been reported in leukemias, lymphomas, and other diseases.\(^{18,23}\) When the above
studies are critically examined, defective leukocyte IF production, probably due to intrinsic leukocyte defects, has previously been well defined only in uremia, in some patients with untreated Hodgkin’s disease, and as a transient phenomenon in normal individuals. In certain of these cases, improvement in leukocyte IF production was correlated with recovery, providing further evidence that transient defects in leukocyte IF production may occur.

It is tempting to speculate that this defect of leukocyte IF production is due to the EB virus that is known to be present in the peripheral leukocytes of individuals with IM. Support for this hypothesis comes from the observation that an initial in vitro exposure of human leukocytes to virus that resulted in measurable IF production rendered them unresponsive, as measured by lack of IF production, to a subsequent virus infection. In vivo, animal studies have shown that such a hyporesponsive period is not detrimental to the host, as a high degree of antiviral resistance is present despite the inability to detect or to induce IF. It would be interesting to test whether these cells in IM that fail to be induced by virus to produce IF are, in fact, more resistant to the in vitro replication of a test virus.

Continuous lymphoblastoid cell lines derived from peripheral leukocytes from patients with IM or a variety of other illnesses have been demonstrated to produce IF spontaneously. Our observed lack of spontaneous leukocyte IF production may be due to one of several mechanisms: the EB virus may be a poor IF inducer; the quantity of IF produced in vitro may be too small to be detected; or alternatively, the cells may have already produced IF and be in the hyporesponsive phase. Since viremia has been shown to occur before clinical illness, the last proposed mechanism may be at least part of the explanation and would be compatible with the low IF titers observed when the leukocyte cultures of patients are stimulated by another virus in vitro.

Many cell types are capable of producing IF in response to virus. Local IF production without detectable circulating IF has been demonstrated in infections where local viral replication predominates. In humans, elevated plasma IF titers have been observed, but generally early in the course of a viral disease, and in some instances the period of IF production can be correlated with the occurrence of fever or viremia. Failure, or low rates, of detection of circulating IF has been reported in several large series of human viral illnesses. Our failure to detect plasma IF in IM may be due to the time the sample was obtained.

The marked increase in spontaneous incorporation of $^3$H Udr by cells obtained on day 0, as compared to recovery, is in agreement with the experiments reported by Rubin and Epstein and Brecher. In contrast, incorporation of $^3$HUdr into IM mononuclear cells was no greater than normal at 20 hr of incubation in studies by Burns and Stjernholm, although a suggestive increase in incorporation after 4 hr was observed in the few patients studied in this manner. Although an increase in $^3$HUdr uptake may merely reflect a more rapid equilibrium of the added label with the intracellular uridine triphosphate pool, since $^3$H Tdr incorporation is also increased in unstimulated cells from patients with IM, we have interpreted the observed increase in $^3$HUdr uptake as reflecting increased spontaneous RNA synthesis.

The increase in spontaneous $^3$HUdr synthesis is of limited duration. After
96–144 hr, the rate of isotope incorporation into unstimulated cells obtained during the first week of illness was no higher than after recovery. This is consistent with MacKinney's data that show that only a portion of the spontaneously DNA-synthesizing cells found in IM are capable of undergoing cell division in vitro and that proliferation of these cells is completed within 36 hr. This limited period of spontaneous RNA and DNA synthesis may explain Burns and Stjernholm’s data.

In 2-hr cultures, we were not able to demonstrate an effect of PHA on RNA synthesis. In contrast, Rubin has observed that PHA present for 1.5 hr inhibited RNA synthesis in the mononuclear cells from patients with IM, whereas the RNA synthesis of normal cells was stimulated.

After prolonged exposure to PHA, 96–144 hr, the leukocytes obtained from several of the patients during the acute phase of the illness showed a markedly defective blastogenic response that returned to normal after recovery. A similar, transient suppression of PHA responsiveness has been reported in leukocytes obtained from patients with serum or infectious hepatitis and acute gastroenteritis, diseases also of presumed viral etiology. Furthermore, in vitro, several studies have demonstrated suppression of the PHA response by the addition of certain viruses to the leukocyte culture.

Our clinical data suggest that steroid therapy is of limited therapeutic benefit. Similarly, in the small number of patients observed, no significant in vitro effect of short-term in vivo steroid therapy could be detected on any of the parameters studied.

The reported studies define a new clinical situation in which a transient defect occurs in the ability to induce circulating leukocytes to produce IF in vitro. This finding is especially interesting, since this defect occurs during the course of a disease of presumed viral etiology. An additional important observation is the finding that of the cultures containing atypical lymphocytes, the ones that are the most active in spontaneously synthesizing RNA are the most defective in responding to PHA by transforming or to NDV by producing IF. In these experiments, depression of PHA-induced transformation and virus-induced IF production occurred in the same cultures. However, we would not conclude that the same mononuclear cell population is responsible for the expression of both these functions, since we have previously reported dissociations between IF production and PHA response. Such dissociations are not surprising in light of our current knowledge concerning the separate functional roles of thymic and bone marrow-derived lymphocyte populations. It is clear that the characterization of lymphocyte function in disease states requires the evaluation of several parameters simultaneously.

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