Interrelations between interleukin-6, interleukin-1β, plasma C-reactive protein values, and in vitro C-reactive protein generation in patients with inflammatory bowel disease

M Z Mazlam, H J F Hodgson

Abstract
Acute phase proteins are released from the liver in response to cytokines, and measurement of serum concentrations offers a valuable means of assessing inflammatory bowel disease. C-reactive protein (CRP) is a participating prominent component of the acute phase response in active Crohn’s disease. This study aimed at determining the comparative role of the cytokines interleukin-1β (IL-1β) and interleukin-6 (IL-6), in driving CRP production in inflammatory bowel disease, and to test the hypothesis that there is a difference in the profile of cytokines generated in these two conditions. Serum CRP, the release of the cytokines IL-1β and IL-6 from monocytes, and the ability of monocyte conditioned medium to stimulate CRP synthesis by hepatocytes in an in vitro system was measured in patients with ulcerative colitis and Crohn’s disease. Monocytes from patients with Crohn’s disease produced more IL-1β than monocytes from patients with ulcerative colitis or normal controls. There was no increased tendency for monocytes from Crohn’s disease patients to produce more IL-6, so the greater circulating values of IL-6 reported by a number of authors in Crohn’s disease may reflect the participation of a larger number of cells of the monocyte-macrophage series, or production of IL-6 by other cell types. Correlation of cytokine production by monocytes with in vitro CRP release from cultured hepatocytes in response to monocyte conditioned medium showed that, in that system, IL-1β was the stronger stimulus to CRP production. Some of the differences in the inflammatory processes of ulcerative colitis and Crohn’s disease may reflect differences in the amount of IL-1β and IL-6 generated from macrophages and monocytes.

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Multiple nucleated cells including macrophages and circulating blood monocytes are capable of producing cytokine mediators such as interleukin-1β (IL-1β), tumour necrosis factor (TNF-α), and interleukin-6 (IL-6).1 Attention has now turned to these as potential mediators of inflammation in inflammatory bowel disease. Cytokines may play this part in the mucosa, and in addition be responsible for some systemic reactions in inflammatory bowel disease. Many clinical and biochemical features of ulcerative colitis and Crohn’s disease including fever, increased production of acute phase reactants, hypoalbuminaemia, and fibroblast proliferation with fibrosis may be attributable to the actions of cytokines.2

Activated macrophages and monocytes produce a panel of cytokines with different but sometimes overlapping actions. IL-1β and TNF-α are notably proinflammatory, being important early signals in the inflammatory process that can induce regulatory changes in a wide variety of cell types, as well as initiating the release of a cascade of other mediators.3 4 IL-1β and TNF-α can also stimulate each others’ production in vitro and in vivo.5 There are differences in the spectrum of actions of IL-6,6 which can be induced by IL-1 and TNF-α, does not stimulate IL-1β or TNF production, and indeed has been shown to inhibit their synthesis by macrophages in vitro, implying that at least some of its actions downregulate the amplificatory actions of cytokines.7 8 A growing body of evidence, referred to later, points to an enhanced production of many cytokines in inflammatory bowel disease.

Our interest in the role of cytokines developed from two related aspects of inflammatory bowel disease. The uncertain relation between ulcerative colitis and Crohn’s disease – whether different conditions or part of a continuous disease spectrum – prompts careful examination of those differences that can be defined. The interest in our laboratory on the assessment of the inflammatory activity of these conditions, particularly the use of acute phase reactants, highlighted one such difference, the tendency to find greater increases in circulating C-reactive protein (CRP) in patients with active Crohn’s disease compared with ulcerative colitis.9 10 CRP is generated by the liver in response to cytokines, and both IL-1β and IL-6 enhance CRP production, the first at a translational and the second at a transcriptional level.10 11 We reported that – for each monocyte – cells from Crohn’s disease patients produce more IL-1β than cells from ulcerative colitis patients or controls, compatible with the suggestion that there is an innate difference between the tendency for patients with Crohn’s disease and ulcerative colitis to produce this cytokine when stimulated.12

Patients with Crohn’s disease were also recently reported to have increased plasma IL-6 concentrations compared with ulcerative colitis.13 14 The first aim of this study was therefore to confirm whether production of IL-6 by peripheral blood monocytes, as representatives of the monocyte macrophage lineage, was increased in Crohn’s disease compared with
溃疡性结肠炎，再次探索其是否为质性而非仅仅量化的区别。在这些两种条件下，我们测量了IL-6的产生。在Crohn病和溃疡性结肠炎中，我们调查了刺激脂多糖与巨噬细胞和癌细胞的反应。我们还测量了IL-1β的产生。

第二目的是这项研究要观察这些癌细胞在Crohn病和溃疡性结肠炎中的活性。我们调查了这些癌细胞参与的炎症反应。我们还测量了IL-1β在这一第二系列患者中的产生。

这些第二目的研究显示了肿瘤因子呈质性，而不是仅仅量性。

患者的和方法

患者和控制

有炎症性肠病的患者，包括在本研究中22名患者，与Crohn病的11名男性和11名女性，年龄范围为37-9 (23-62) y和22名患者，与溃疡性结肠炎的12名男性和10名女性，年龄范围为45-0 (19-79) y。11名健康志愿者，包括6名男性和5名女性（年龄范围为39-9 (30-62) y）作为正常对照。

疾病活动

在Crohn病的11名患者中，7名是静息态（Harvey-Bradshaw指数为1）和11名有活跃疾病（Harvey-Bradshaw指数为6.2 (0-8)）。在疾病程度中，9名患者有图利，5名有小肠溃疡，和8名有上腹痛。11名患者有溃疡性结肠炎（Truelove和Witts），7名是中度和4名是轻度。在疾病分布中，一名患者有阑尾炎，17名有左侧结肠，14名有回肠炎（proctosigmoiditis），13名有回肠炎（sigmoid），和7名有结肠炎（descending colon），和4名有结肠炎（transverse colon），和4名有疾病限制到回肠。

治疗组

在Crohn病的8名患者中，4名患者正在接受硫化物的治疗；5名患者也正在接受益生菌治疗。3名患者被分为5-ASAP（5-ASA）；2名患者被分为接受益生菌治疗。4名患者正在接受益生菌治疗，一名患者正在接受益生菌治疗和莫沙必利，一名患者正在接受益生菌治疗和莫沙必利。

在溃疡性结肠炎的12名患者中，5名患者正在接受益生菌治疗；5名患者也正在接受益生菌治疗。12名患者被分为5-ASA；10名患者被分为接受益生菌治疗。12名患者正在接受益生菌治疗，一名患者正在接受益生菌治疗和莫沙必利，一名患者正在接受益生菌治疗和莫沙必利。

巨噬细胞分离

从每名患者中获取了有炎症性结肠炎和Crohn病的正常对照，20名EDTA的血液被采集和稀释1:3与Hanks的盐水溶液（HBSS），并与单核细胞分选的细胞在针对Isopaque-Ficoll密度梯度（Lymphoprep,Nycomed,UK）的分离血清中进行分选的单核细胞的分选。外周血单核细胞被从细胞分选的细胞中收集，洗去两次，一次在HBSS，一次在RPMI 1640中固定（Gibco,UK）。细胞被洗去两次，一次在HBSS，一次在RPMI 1640中固定（Gibco,UK）。细胞被洗去两次，一次在HBSS，一次在RPMI 1640中固定（Gibco,UK）。

细胞因子的产生

从参与细胞因子的产生和Crohn病的正常对照，20名EDTA的血液被采集和稀释1:3与Hanks的盐水溶液（HBSS），并与单核细胞分选的细胞在针对Isopaque-Ficoll密度梯度（Lymphoprep,Nycomed,UK）的分离血清中进行分选的单核细胞的分选。外周血单核细胞被从细胞分选的细胞中收集，洗去两次，一次在HBSS，一次在RPMI 1640中固定（Gibco,UK）。细胞被洗去两次，一次在HBSS，一次在RPMI 1640中固定（Gibco,UK）。细胞被洗去两次，一次在HBSS，一次在RPMI 1640中固定（Gibco,UK）。

在 vitro CRP的产生

来自人类肝细胞细胞系，Alexander细胞（PLC/PRF/5）。202' IL-6和IL-1β被释放到细胞培养基中，由检查CRP的产生和此细胞培养基中CRP浓度在患者中这些癌细胞被分离并已经分离出来。

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Cytokines and CRP in duplicate and a OF amount detection limit Serum C02:95% medium conditioned medium and fresh complete medium were added and incubated in a 5% CO2:95% air tissue culture incubator. After 72 hours supernatant medium was collected and stored at –20°C.

MEASUREMENT OF CRP Serum was separated from clotted venous blood and stored at –20°C. Serum CRP estimation and the amount of in vitro CRP release were analysed by a double ligand sandwich ELISA performed in duplicate as previously described. The lower detection limit of the CRP assay was 0.05 ng/ml, with a 7% coefficient of variation in assay and 15% between assay.

ELISA FOR IL-1β Quantitative estimation of IL-1β was performed in duplicate. High binding ELISA plates (Greiner, UK: 655061) were coated with 100 µl/well, rabbit-recombinant human IL-1β (Universal Biologicals, UK) at a concentration of 5 µl in coating buffer (0.05 M carbonate; pH 9-6) for at least three days (88 hours) at 4°C. After washing three times with phosphate buffered saline containing 0.05% TWEEN-20 (PBS/0.05% Tween-20; wash buffer) plates were blocked with blocking buffer (PBS with 1% BSA; 100 ml/well) for four hours at room temperature. After three washes 100 ml of supernatant medium samples containing IL-1β or recombinant human IL-1β standards (British Bio-technology, UK) in doubling dilutions (20 pg/ml-100 ng/ml; standards diluted in complete medium), were added and the plates incubated overnight (16 hours) at 37°C in a moist box. After four washes 100 µl/goat anti-human IL-1β (British Bio-technology, UK) at a concentration of 1 mg/ml (diluted in conjugate buffer; PBS/0.05% BSA) were added and the plates incubated for two hours at 37°C. After four washes, 100 µl/ml peroxidase conjugated affinity pure donkey anti-goat IgG (Jackson Immunoresearch Laboratories, USA) diluted 1:2000 in conjugate buffer (PBS/0.05% BSA) was added and the plates incubated at room temperature for a further two hours. After five washes substrate solution (H2O2-OPD; 100 ml/well) was added and the plates were incubated in the dark at room temperature. The reaction was terminated by adding 100 µl3M sulphuric acid and absorbance read at 492 nm in an ELISA plate reader. The lower detection limit was 20 pg/ml, with a 7.1% within and 5.4% between assay coefficient of variation.

ELISA FOR IL-6
IL-6 estimation was performed in duplicate. High binding ELISA microtitre plates (Greiner, UK; 655061) were coated with 100 µl/well rabbit anti-recombinant human IL-6 (genzyme) at a concentration of 5 mg/ml in coating buffer (0.05 M carbonate; pH 9-6) for at least two days (64 hours) at 4°C. After washing three times with phosphate buffered saline containing 0.05% TWEEN-20 (PBS/0.05% Tween-20; wash buffer) plates were blocked with blocking buffer (PBS with 1% BSA; 100 ml/well) for two hours at room temperature. Plates were then washed again three times before adding 100 ml of supernatant medium samples containing IL-6 or IL-6 standards in doubling dilutions (50 pg/ml-50 ng/ml; standards diluted in complete medium). The plates were then incubated for two hours at 37°C in a moist box. After four washes 100 µl goat anti-human IL-1β (British Bio-technology) at a concentration of 1 mg/ml (diluted in conjugate buffer; PBS/0.05% BSA) was added and the plates incubated for a further two hours at 37°C. After four washes, 100 µl/well peroxidase conjugated affinity pure donkey anti-goat IgG (Jackson Immunoresearch Laboratories, USA) diluted 1:2000 in conjugate buffer (PBS/0.05% BSA) was added and the plates then incubated for a further two hours at room temperature. After five washes 100 µl/well substrate solution (H2O2-OPD) was added and the plates incubated in the dark at room temperature to the desired extinction. The reaction was stopped by adding 100 µl 3M sulphuric acid and absorbance read 492 nm in an ELISA plate reader.

In this assay system recombinant human interleukin-1β used for the standard curve was obtained from British Bio-technology. Recombinant human interleukin-6 (code 88/514) and interleukin-1α standards (code 86/632) used in these assays were also kindly provided by National Institute for Biological Standards and Controls (NIBSC), Blanche Lane, South Mimms, Potters Bar, Hertfordshire, England. The antibodies used include rabbit anti-recombinant human IL-1β (Universal Biologicals, UK) and goat anti-human IL-1β British Bio-technology, which has no cross reactivity with IL-1α, IL-2, IL-6, and TNF (α or β). Rabbit anti-recombinant human IL-6 (genzyme; LP-716) and goat anti-human IL-6 (British Bio-technology) do not cross react with IL-1 (α or β), TNF (α or β), and GM-CSF. The lower detection limit of the IL-6 assay 50 was pg/ml, with a 0% between and within assay coefficient of variation. There was no cross reaction between these assays; and in addition IL-1α did not interfere with the assay.

STATISTICS
Non-parametric procedures were used for statistical significance testing. Comparisons between groups were assessed by Mann-Whitney U test, and correlation coefficients were calculated using Kendall rank correlation test.

Results

IN VITRO PRODUCTION OF IL-1β
The potential of monocytes from Crohn’s disease to generate IL-1β was found to be significantly higher than ulcerative colitis. Spontaneous IL-1β release by monocytes in Crohn’s disease (mean (SEM) 562 (282) pg/ml) was significantly raised compared with ulcerative colitis (75 (29) pg/ml; p<0.05) and normal controls (29 (7) pg/ml; p<0.05). Lipo polysaccharide stimulated IL-1β generation in Crohn’s
In patients with inactive Crohn's disease both spontaneous and lipopolysaccharide-stimulated IL-1β (mean (SEM) 5.3 (0.4)×10^8/ml) was not significantly different compared with ulcerative colitis (4.6 (0.35)×10^8/ml; p>0.05) although the difference was only significant when compared with normal controls. Among the patients with inflammatory bowel disease, those who had active inflammation (mean (SEM) 5.4 (0.4)×10^8/ml; p<0.05) had significantly greater monocyte counts than those without (4.6 (0.35)×10^8/ml) similar to the findings described above.

**IN VITRO PRODUCTION OF IL-1β RELATED TO TOTAL MONOCYTE COUNT**

Calculated spontaneous and lipopolysaccharide stimulated production of IL-1β, related to total count of monocytes per 10 ml blood, were both strikingly and statistically significantly raised in Crohn's disease compared with ulcerative colitis and normal controls (Table). Both spontaneous and lipopolysaccharide stimulated IL-1β release related to total monocyte count per 10 ml blood from patients with inactive Crohn's disease were significantly raised compared with inactive ulcerative colitis. In active Crohn's disease lipopolysaccharide stimulated IL-1β production related to total count of monocytes per 10 ml of patients blood was raised compared with active ulcerative colitis. There was no statistical difference between the concentrations of IL-1β generated spontaneously in active Crohn's disease and active ulcerative colitis.

**In vitro interleukin-1β (IL-1β), and interleukin-6 (IL-6) production related to total monocyte count per 10 ml blood obtained from patients with ulcerative colitis, Crohn's disease, and controls**

<table>
<thead>
<tr>
<th></th>
<th>Spontaneous IL-1β pg/ml (mean (SEM))</th>
<th>LPS stimulated IL-1β pg/ml (mean (SEM))</th>
<th>Spontaneous IL-6 pg/ml (mean (SEM))</th>
<th>LPS stimulated IL-6 pg/ml (mean (SEM))</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD (n=22)</td>
<td>1949 (929)</td>
<td>49 151 (19 716)</td>
<td>3992 (603)</td>
<td>8540 (1276)</td>
</tr>
<tr>
<td>UC (n=22)</td>
<td>134 (43)</td>
<td>8 613 (2362)</td>
<td>2572 (365)</td>
<td>5479 (546)</td>
</tr>
<tr>
<td>Controls (n=11)</td>
<td>50 (135)</td>
<td>6 730 (2006)</td>
<td>25 49 (579)</td>
<td>4220 (552)</td>
</tr>
<tr>
<td>Inactive CD (n=11)</td>
<td>3412 (1770)</td>
<td>35 329 (20 253)</td>
<td>3828 (991)</td>
<td>8354 (2107)</td>
</tr>
<tr>
<td>Inactive UC (n=11)</td>
<td>77 (33)</td>
<td>6 620 (2340)</td>
<td>2198 (592)</td>
<td>5033 (773)</td>
</tr>
<tr>
<td>Active CD (n=11)</td>
<td>486 (237)</td>
<td>62 973 (34 413)</td>
<td>4155 (727)</td>
<td>8727 (1547)</td>
</tr>
<tr>
<td>Active UC (n=11)</td>
<td>192 (77)</td>
<td>10 607 (4139)</td>
<td>2546 (445)</td>
<td>5924 (783)</td>
</tr>
</tbody>
</table>

*p<0.05 compared with Crohn's disease, p<0.01 compared with Crohn's disease, p<0.005 compared with Crohn's disease, and p>0.05 compared with active Crohn's disease, Crohn's disease used as controls.

**IN VITRO CRP**

Release of CRP from Alexander cells by unstimulated and lipopolysaccharide stimulated monocyte conditioned medium from patients with inactive Crohn's disease (mean (SEM) 0.79 (0.20) ng/ml and 1.50 (0.32) ng/ml respectively) was not significantly different compared with inactive ulcerative colitis (0.68 (0.14) ng/ml and 2.0 (0.19) ng/ml respectively) and normal con-
Cytokines and CRP production in IBD

Figure 1: Release of C-reactive protein (CRP) from Alexander cells by unstimulated and lipopolysaccharide (LPS) stimulated monocyte conditioned medium from patients with ulcerative colitis (UC) and Crohn's disease (CD). CRP release in response to active Crohn's disease conditioned medium is significantly increased (see text) in both cases, compared with active ulcerative colitis and controls.

CORRELATION OF IL-1β AND IL-6 IN CONDITIONED MEDIUM WITH STIMULATION OF IN VITRO CRP SYNTHESIS

Among individual patient groups, Crohn's disease and ulcerative colitis, active and inactive, significant correlations between in vitro CRP values and the value of either IL-1β or IL-6 in conditioned medium did not emerge.

Analysis performed on all inflammatory bowel disease patients combined showed statistically significant correlations between in vitro CRP synthesis in response to monocyte conditioned medium, and the IL-1β and IL-6 values in the medium, when the conditioned medium was obtained in the absence of lipopolysaccharide (r=0.74; p<0.001 and r=0.18; p<0.05 respectively) but not in the presence of lipopolysaccharide (r=0.14; p>0.05 and r=0.14; p>0.005 respectively).

SERUM CRP CONCENTRATIONS

Serum CRP concentration in inactive Crohn's disease (mean (SEM) 5.7 (2.6) mg/l) was not significantly different from inactive ulcerative colitis (3.0 (1.5) mg/l) although it was significantly more than normal controls (1.6 (0.6) mg/l; p<0.05).

Serum CRP concentration in patients with active Crohn's disease (5.3 (6.2) mg/l) was however considerably raised compared with active ulcerative colitis (10.7 (2.3) mg/l; p<0.02) and normal controls (p<0.002), as well as active Crohn's disease (p<0.005) (Fig 2).

CORRELATION OF SERUM CRP WITH IN VITRO CRP RELEASE

In inflammatory bowel disease patients we found a significant correlation between serum CRP, and in vitro CRP release in response to monocyte conditioned medium in the absence of lipopolysaccharide (r=0.28; p<0.005) but not in the presence of lipopolysaccharide (r=0.17; p>0.05).

Discussion

In this study we investigated differences in the following parameters between ulcerative colitis and Crohn's disease: (a) serum CRP concentrations, (b) release of the cytokines IL-6 and IL-1β from monocytes, and (c) the effects of these monocyte conditioned media on an in vitro model of CRP release.

Figure 2: Serum C-reactive protein (CRP) concentration is considerably raised in patients with active Crohn's disease (CD) (n=11) compared with active ulcerative colitis (UC) (n=6) and normal controls (p<0.02) and normal controls (p<0.002). In inactive CD (p>0.05) serum CRP is not significantly different compared with inactive ulcerative colitis (UC). Results expressed as mean (SEM).
This study confirms previous reports that serum CRP concentration is significantly higher in patients with active Crohn’s disease compared with active ulcerative colitis.19-22 Further findings were then made using a human hepatoma cell line, Alexander cells, as a means of assessing the comparative contribution of different cytokines to the CRP response,19 albeit by the use of a cell line whose responses to cytokines may not fully represent physiological events. In this system we showed that cytokine rich medium conditioned by monocytes from patients with active Crohn’s disease resulted in significantly greater CRP release than monocyte conditioned medium from active ulcerative colitis and normal controls. The results support the hypothesis that differences in serum CRP concentrations in ulcerative colitis and Crohn’s disease may reflect differences in cytokine production in the two diseases.

There is emerging evidence from a number of studies of differences in the tendency of patients with Crohn’s disease and ulcerative colitis to produce cytokines IL-1β and IL-6. Raised serum concentrations of IL-1β have been reported in patients with acute exacerbations of Crohn’s disease, but not those with quiescent disease.14,24-26 In patients with ulcerative colitis IL-1β activity was rarely found in the plasma even during active disease.26 Several groups report that circulating IL-6 concentrations are higher in Crohn’s disease compared with ulcerative colitis.19-26 We have investigated one source of these cytokines, the monocytes from peripheral blood as a representative of the monocyte-macrophage series, and have attempted to discover if there are differences in IL-1β and IL-6 production between the two diseases.

In this second study, in a new series of patients, we confirmed our previous report that interleukin-1β production by peripheral blood monocytes is greater in Crohn’s disease than ulcerative colitis.17 We showed this with a fixed number of monocytes from each patient, so the difference in IL-1β production between the two conditions was not due to the trivial explanation that a greater number of monocytes were studied in the cell population sampled in Crohn’s disease. The results suggest a genuine difference in the capacity of Crohn’s disease monocytes to produce IL-1β. In addition, however, the greater number of circulating monocytes implies that in Crohn’s disease IL-1β expression may be even greater, and at the tissue level macrophages are particularly prominent in Crohn’s disease. Thus, a higher IL-1β circulating concentration in Crohn’s disease compared with ulcerative colitis probably reflects both a greater potential for cells of the monocyte-macrophage series to generate this cytokine and also a greater number of cells affected.

In contrast with the above findings we found that IL-6 production by a given number of monocytes, both spontaneously and after stimulation with lipopolysaccharide, did not differ between Crohn’s disease, ulcerative colitis, and normal controls. The greater number of circulating monocytes, however, in the group of patients studied implies the potential for more IL-6 release from this source, and may contribute to the raised circulating IL-6 concentration in Crohn’s disease. Interleukin-6 expression can also be induced in many other cell types. In normal subjects the IL-6 gene is transcribed at high values in the spleen, liver, and kidney, and endothelial cells, fibroblasts, T cells, B cells, and other cell types can produce IL-6 in response to a wide range of stimuli.27-30 With this diversity of cells and signals stimulating IL-6 production, it is clearly difficult to establish the contribution of individual cell types to circulating IL-6 concentrations.

The concentration of IL-1β and to a lesser extent IL-6 in monocyte conditioned medium correlated significantly with the ability of those media to induce in vitro CRP release from the human hepatocyte derived cell line. The correlation was with unstimulated cytokine production, as would be expected if in vitro cytokine production from monocytes reflects contemporaneous in vivo cytokine production; the stimulated production with maximal lipopolysaccharide doses is likely to reflect the maximum potential capacity to respond. While both cytokines may therefore sometimes be elevated in inflamed tissue, the correlation between IL-1β and CRP release was stronger than that between IL-6 and CRP release, suggesting that the in vitro system that we studied for IL-1β is probably the more powerful stimulant of CRP release. On these grounds, the higher circulating CRP concentrations in Crohn’s disease may largely be attributed to the greater level of IL-1β drive.

One may speculate that there are other clinical differences between ulcerative colitis and Crohn’s disease that reflect differences in the profiles of cytokines between Crohn’s disease and ulcerative colitis. The tendency to transmural granulomatous inflammation and fibrosis and resultant gut stenosis are among the most striking differences between Crohn’s disease and ulcerative colitis. IL-1 is possibly important in the initiation of granuloma. This has been reported in animal models. Shikama et al18 induced granulomas in vitro by culturing murine spleen cells with artificial microparticles and showed that culture supernatants contained high values of IL-1 activity, correlating with granuloma size. Additionally, granulomas were produced by culturing spleen cells in the presence of agarose beads coupled to recombinant IL-1. Increased fibrosis reflects enhanced collagen synthesis by fibroblasts that can be regulated by a number of inflammatory mediators. Several macrophage derived cytokines are potentially fibrinogenic, including IL-1β and TNF-α. IL-1β and TNF, individually, stimulate the proliferation and collagen production although findings differ among various studies.35-38 They can directly increase the transcription of type I, III, and type IV collagen,36-39 and increase fibroblast proliferation.40 Another intriguing aspect with regard to cytokine release is the potential involvement of smoking habits. Smokers, as a population, have higher CRP concentrations than non-smokers,41 and alveolar macrophages from smokers produce more IL-1 on stimulation42; could the striking association with Crohn’s disease reflect the effect of this environ-
mental agent on IL-1β release? It may be that patients who have Crohn's disease manifest this form of inflammatory disease in the bowel reflecting a combination of a genetically determined tendency and environmental influences towards the generation of a cytokine network that leads to transmural inflammation and considerable fibrosis, while patients with ulcerative colitis have a tendency to generate a cytokine network that causes diffuse mucosal inflammation.

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22 Taylor AW, Ku N-O, Mortensen RF. Both IL-1 and IL-6 induce synthesis of C-reactive protein (CRP) by PLC/PRF/5 hepatoma cell line. Ann NY Acad Sci 1989; 557: 532-3.
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