Open trial of cyclosporine in patients with severe active Crohn's disease refractory to conventional therapy

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ABSTRACT: Fifteen patients with severe active Crohn's disease, refractory to conventional therapy, were given a 16 week course of cyclosporine at an initial oral daily dose of 10 mg/kg, adjusted to maintain cyclosporine serum trough levels between 100 and 200 ng/ml. Five patients withdrew early because of side effects, poor absorption or noncompliance. The remaining 10 patients all improved within four weeks as measured by three different clinical indices: Crohn's Disease Activity Index, Simple Index of Crohn's Disease Activity and Mean Score of Therapeutic Goals (MSTG). Seven patients maintained this initial improvement and prednisone was either reduced or discontinued. Four of these seven patients relapsed within four weeks of stopping cyclosporine, and three remain in remission after 75 ± 2 weeks. Side effects were minor and easily reversible. When the various clinical and laboratory indices were compared, MSTG was found to be the most useful index for the assessment of therapy. Cyclosporine appears to be a safe and effective therapy in patients with severe active Crohn's disease refractory to conventional therapy. **Can J Gastroenterol 1988; 2(1): 5-11**

Key Words: *Crohn's disease, Cyclosporine, Immunosuppressive agents*

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CROHN'S DISEASE IS A CHRONIC relapsing inflammatory condition of the bowel characterized by chronic diarrhea, abdominal pain, weight loss, fistula formation and perineal complications. In acute exacerbations of the disease, treatment with corticosteroids is effective (1,2). Treatment with 6-mercaptopurine is the only drug available for patients with chronically active, complicated disease who fail on corticosteroid therapy (3). After surgery, recurrence at the anastomosis occurs in all patients with time, with varying degrees of severity (4). Sulfasalazine has been shown to be effective, mainly when the disease involves the colon, but even then, maintenance therapy does not seem to prevent relapse (1,5).

In recent years, 5-aminosalicylic acid, the therapeutic moiety of sulfasalazine, has been used in Crohn's disease (6). Except for elimination of

side effects related to the reabsorption of the sulfapyridine portion of sulfasalazine, there is no evidence for a difference in efficacy between 5-aminosalicylic acid and sulfasalazine (7). Metronidazole appears to be effective in patients with perineal disease (8) and equally effective as sulfasalazine in treatment of colonic Crohn's disease (9). Immunosuppressive agents, such as azathioprine, and its active metabolite 6-mercaptopurine, are useful in inducing remission and in allowing corticosteroid reduction or discontinuation in otherwise induced stable remission (3), and in healing fistulae (10). Azathioprine and 6-mercaptopurine have several drawbacks which limit their use: the required treatment time for induction of remission is prolonged and severe side effects (myelosuppression, hepatotoxicity, pancreatitis) have been reported (11,12). This lack of definitive treatment has stimulated trials of new agents for treatment of Crohn's disease.

Cyclosporine, with its specific immunomodulatory action (13-15) and its efficacy and relative safety in comparison to other immunosuppressive agents, particularly in organ transplantation (15,16), and its effective prevention of autoimmunity in animal models (17,18), has prompted its experimental use in a series of autoimmune diseases in man (19), including Crohn's disease. Preliminary studies with Crohn's disease have been encouraging (20-22).

This study describes the effects of cyclosporine and its apparent safety in an open study in patients with severe active Crohn's disease who were refractory to conventional therapy.

MATERIALS AND METHODS

Patients: Since October 1985, patients with severe active Crohn's disease diagnosed according to clinical, radiologic, endoscopic and histologic criteria (2) who were refractory to conventional therapy were offered cyclosporine. The exclusion criteria included renal failure, severe hepatocellular disease, pregnancy or inadequate contraception, malignancy, impending surgery, continuous gastrointestinal bleeding, intake of nephrotoxic compounds or drugs affecting cyclosporine metabolism.

Fifteen patients (five men and 10 women) were enrolled into the open trial. The mean age was 42 years (range 20 to 67). The mean duration of illness since diagnosis was nine years (range 0.5 to 28). All patients had continuous symptoms of active Crohn's disease for a mean duration of seven months (range one to 15) at entry. Nine of the 15 patients had undergone abdominal surgery during the course of their illness. In five patients the disease was confined to the terminal ileum, and in one to the rectum, the remaining nine had disease in their ileum and colon (Table 1). The trial protocol was approved by the Victoria General Hospital Research Review Committee. Fully informed, written consent was obtained from all patients. Oral cyclosporine (Sandimmune) was supplied by Sandoz Canada Inc, Dorval, Quebec.

Design: The initial cyclosporine dosage was 10 mg/kg given twice daily, adjusted, thereafter, to maintain

TABLE 1
Summary of data on 15 patients with Crohn's disease at entry to cyclosporine trial with their course and final outcome

Patient	Sex, age (years)	Duration of illness (years)	Duration of activity (months)	Prior surgery	CDAI	Site of disease	Other treatment (daily dose)	Course and final outcome
1	F,67	14	6	None	360	Ileocolitis, enteroenteral fistula	Pred (25 mg) *Aza 100 mg) Sulfa (4 g)	Pred discontinued; relapse 4 weeks after stopping CyA
2	F,56	21	2	Total colectomy, ileostomy	345	Ileitis, enterocutaneous fistula	Pred (25 mg) TPN	Started on iv CyA because of short bowel syndrome; dose was doubled after undetectable CyA serum trough levels; acute threefold rise in creatine resulted in stopping CyA in week 2
3	F,55	7	2	Right hemicolectomy, multiple small bowel and sigmoid resections	397	Ileocolitis enteroenteral fistula	None†	CyA serum trough level remained undetectable after fourfold increase in CyA dose by week 4; iv CyA was initiated, but patient's condition had worsened warranting surgery.
4	F,20	3	4	None	413	Ileocolitis	Pred (60 mg) TPN	After initial improvement and reduction of pred to 10 mg, relapsed in week 10 of CyA trial

Continued

TABLE 1 *continued*

5	F,37	13	10	Right hemicolectomy, small bowel resection	328	Ileitis	Pred (40 mg)	Pred reduced to 10 mg; in remission 78 weeks after stopping CyA
6	F,41	5	4	Right hemicolectomy, terminal ileal resection	429	Ileocolitis	Pred (35 mg) *Aza (25 mg) Sulfa (2 g)	Pred discontinued; in remission 78 weeks after stopping CyA
7	F,25	0.5	6	Partial cecotomy, terminal ileal resection	295	Ileitis	None	Although improving; withdrew for noncompliance in week 4 of CyA trial
8	F,25	9	10	Subtotal colectomy, ileostomy	216	Perineal fistula	None	After initial improvement, relapsed in week 12 of CyA trial; later had rectal stump resected
9	M,34	8	2	None	307	Ileocolitis	Pred (20 mg) *Aza (100 mg)	Pred discontinued; relapsed 2 weeks after stopping CyA
10	F,63	3	10	Right hemicolectomy, terminal ileal resection	371	Ileitis	5-ASA (1.2 g)	In remission 70 weeks after stopping CyA
11	M,53	28	13	Terminal ileal resection	282	Ileitis	Pred (20 mg)	Withdrew in week 2 of CyA trial because of gastrointestinal intolerance
12	M,45	8	1	None	224	Ileitis	Pred (20 mg)	Withdrew in week 4 of CyA trial because of gastrointestinal intolerance
13	M,26	3	15	None	160	Ileocolitis	Pred (40 mg) Sulfa (2 g) Metr (750 mg)	Pred reduced to 10 mg; relapsed 4 weeks after stopping CyA
14	M,52	4	10	None	338	Ileocolitis	Pred (10 mg)	Pred discontinued; relapsed 2 weeks after stopping CyA
15	F,34	14	12	Right hemicolectomy, small bowel and later ileocolic anastomosis resections	160	Ileocolitis	Sulfa (3 g) Bet (5 mg)	After initial improvement, relapsed in week 12 of CyA trial; was started on TPN and Pred (40 mg)

** Treatment was discontinued at entry to cyclosporine trial; † Severe prior side effects to prednisone; CDAI Crohn's Disease Activity Index; Aza Azathioprine; Bet Betamethasone enema; CyA Cyclosporine; Metr Metronidazole; Pred Prednisone; Sulfa Sulfasalazine; TPN Total parenteral nutrition; 5-ASA 5-acetylsalicylic acid; iv Intravenous*

serum trough levels of cyclosporine between 100 and 200 ng/ml, measured 11 h after the previous dose. Patient 2, who was on home total parenteral nutrition program because of short bowel syndrome after multiple intestinal resections, was started on intravenous cyclosporine at a daily dose of 2.5 mg/kg. Blood samples for serum cyclosporine level were taken twice a week, where necessary. All levels were determined by radioimmunoassay using the Cyclosporine RIA-Kit (Sandoz, Basle, Switzerland). In 10 patients cyclosporine was initiated on an outpatient basis.

From the start of the study, prednisone dose reduction at a rate of 2.5 to 5.0 mg/week was attempted. Azathioprine was discontinued prior to starting cyclosporine. Sulfasalazine, 5-aminosalicylic acid and metronidazole were maintained throughout the trial period. Cyclosporine was administered for 16 weeks at the end of which it was discontinued without tapering. The 16 week period was chosen following the design and results of previous Crohn's disease studies (1,23) and because of the known reversibility of renal side effects after short term use of cyclosporine (24,25). Patients were seen regularly during and after cyclosporine therapy and their Crohn's disease course to relapse documented.

Assessment: Patients were seen at entry, then at two, four, eight, 12 and 16 weeks for overall clinical assessment and the measurement of disease activity by three clinical indices: Crohn's Disease Activity Index (CDAI) (26,27); Simple Index of Crohn's Disease Activity (SICDA) (28); and Mean Score of Therapeutic Goals (MSTG). Since its publication in 1976, CDAI has become a standard for the quantitative assessment of efficacy in clinical trials of therapy for Crohn's disease. An inconvenient problem inherent in the CDAI is the need to collect data for seven days before patient enrollment (28,29). This lead to the development of a simplified version, the SICDA. However, both are considered to be relatively unsatisfactory because they depend on many subjective criteria

(30). The authors' main criticism of these indices is their heavy reliance on the number of bowel movements without consideration for the presence or extent of previous intestinal resections. Neither the CDAI nor the SICDA takes into account a factor for a therapeutic drug effect in Crohn's disease. Consequently, a patient may be considered in remission when the CDAI is less than 150 even when the patient requires a high maintenance dose of corticosteroids. A further limitation is the weighting CDAI places on hemoglobin level — a problem in cyclosporine studies because of the known propensity of this drug to induce a reversible drop in hemoglobin between 2 and 4 g/dL (24).

Therefore, the authors modified and adapted a grading system, dependent on the setting of individual therapeutic goals similar to the one used in the study of 6-mercaptopurine for Crohn's disease (3). These therapeutic goals were categorized into four items: well-being (weight, appetite, sense of well-being); symptoms and signs (diarrhea, fever, mass, pain, tenderness); corticosteroids (dose-raising, dose-lowering or introducing); and other complications (activity of fistulae, extraintestinal manifestations).

At entry, depending on the clinical presentation of each patient, two to four therapeutic goal items were chosen and an initial score of zero given for each item in all patients. The degree of improvement or worsening for each item was graded using a scale from +3 for complete disappearance of symptoms or signs (or total withdrawal from corticosteroids); +2 for substantial symptom or sign alleviation short of 100%; +1 for any slight but already discernible symptomatic improvement; 0 for no change; −1 for slight symptomatic worsening; −2 for moderate symptomatic worsening; −3 for severe complications (or resumption of prednisone at a dose of 40 mg/day or higher). The MSTG was the arithmetic mean of the scores of all the therapeutic goal items graded for each interval. At the end of the 16 week period patients with positive MSTG were considered improved.

Blood samples were taken biweekly for monitoring of Crohn's disease activity and side effects of therapy. Blood samples were evaluated for complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein, orosomucoid, creatinine, liver functions and other routine serum biochemical tests. At least twice during the 16 week period reticulocyte count, vitamin B12, ferritin, serum and erythrocyte folate levels were also determined.

The side effects were either reported by the patient, or sought by the examiner, and recorded according to severity as slight, moderate or severe (requiring discontinuation of therapy). The cyclosporine dose was reduced by 25 to 50% when serum creatinine rose more than 50 to 75% above pretreatment value or above 150 μmol/L.

Statistical analysis was performed using the Wilcoxon matched-pairs signed-ranks test with a significance level of 0.05 or less (two-tailed). All results are given as mean ± SEM.

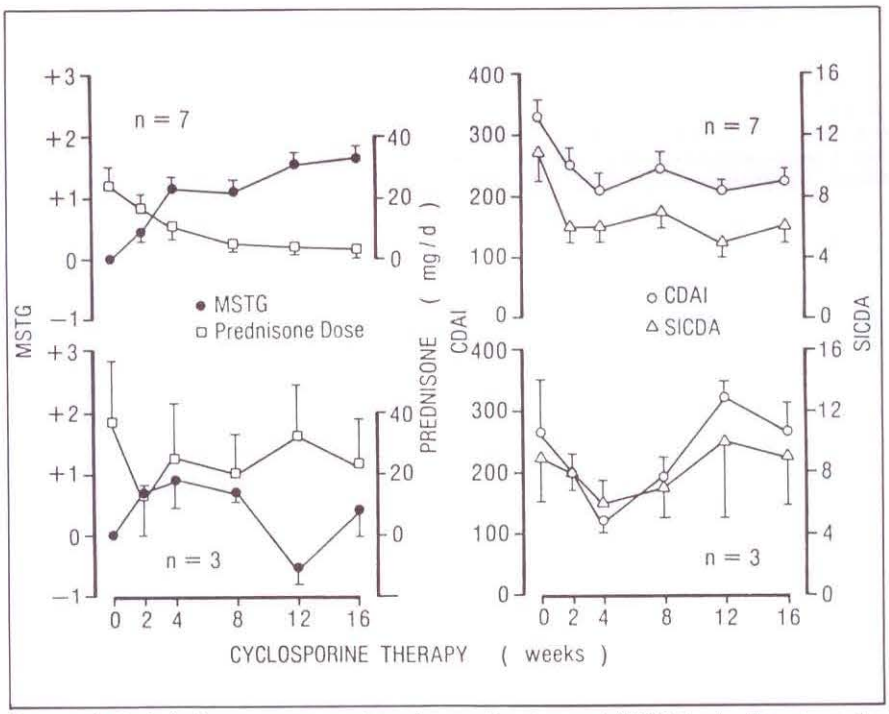

Figure 1) *Crohn's disease activity and prednisone dose (mean ± SEM) in the 10 patients that completed the 16 week course of cyclosporine therapy. By week 4, all 10 patients improved by the three clinical indices measured in this trial: Mean Score of Therapeutic Goals (MSTG), Crohn's Disease Activity Index (CDAI), and Simple Index of Crohn's Disease Activity (SICDA); however, only seven maintained this initial improvement (upper panel) while tapering off prednisone, and three relapsed (lower panel) on cyclosporine*

RESULTS

Table 1 summarizes the data for patients at entry to the trial with their course and outcome. All nonoperated patients who tolerated cyclosporine came into remission and all relapsed within eight weeks after discontinuing the 16 week course of medication. In contrast, of those with recurrent disease after surgery, three patients were in remission after one year of follow-up. They had four to 10 months of continuous active disease at entry to this study.

Five patients withdrew early in the course of the trial, three because of side effects related to cyclosporine therapy, one because of poor absorption of the drug and one noncompliance.

All 10 patients who completed 16 weeks of cyclosporine therapy improved significantly within the first four weeks by all criteria. MSTG increased from a score of zero at entry to +1.1 ± 0.2 after four weeks of cyclosporine therapy ($P<0.01$); CDAI

TABLE 2
Outcome of all 15 patients who entered cyclosporine trial 59 ± 3 weeks after stopping cyclosporine

	Completed 16 week course		Drop-outs
	Improved	Relapsed	
Number of patients	7	3	5
In remission, no corticosteroids	3	—	—
Required abdominal surgery	1	2	2
On home total parenteral nutrition	—	1	—
Corticosteroid-dependent	3	—	3

dropped from 308 ± 31 at entry to 109 ± 26 ($P<0.01$); and SICDA dropped from 10 ± 1 to 6 ± 1 ($P<0.01$). In addition, prednisone dose was reduced from 28 ± 7 mg/day at entry to 16 ± 6 mg/day by the end of week 4 ($P<0.01$).

Seven of the 10 patients maintained their improvement throughout the 16 week trial period (Figure 1). Prednisone was discontinued in four of these seven patients and reduced to 10 mg in two patients within 9 ± 1 weeks of starting cyclosporine therapy. The remaining three patients became worse around week 12. In two of the three patients this was related to reduction in prednisone dose. All three completed the trial period with disease activity returning to pretreatment levels.

Within four weeks of stopping cyclosporine, four of the seven patients relapsed, with indices returning to pretreatment levels. As of January 1988 three patients remain in remission, 59 ± 3 weeks after stopping cyclosporine. The outcome, by the end of January 1988, for all 15 patients who entered the trial is summarized in Table 2.

Table 3 shows the partial correlation coefficients between the clinical and laboratory indices used in this trial. The MSTG correlated well with CDAI and SICDA. When MSTG was compared to the laboratory indices, only orosomucoid correlated slightly with MSTG. The equations for the linear relation between the different clinical indices were derived: CDAI = 326 − 73 × (MSTG); SICDA = 8.4 − 2.5 × (MSTG); and CDAI = 124 + 21 × (SICDA).

Side effects: Table 4 lists side effects noted by the 15 patients entering the trial. In general, these side effects were not severe enough to warrant discontinuation of cyclosporine except for epigastric pain or nausea which contributed to withdrawal by two patients. Three of the 15 patients had a 'flu-like syndrome that cleared spontaneously. There was a rise in creatinine and urea nitrogen in almost all patients; in one patient therapy was withdrawn, and in three patients the dose of cyclosporine was reduced by more than 25%. Renal function returned to pretreatment ranges after reduction or discontinuation of the drug. Mild hyperuricemia in eight patients and borderline hyperkalemia in three patients were noted. There was a transient mild increase in the blood pressure of three patients who were borderline hypertensives before the initiation of cyclosporine. Hepatic toxicity was noted in only one patient whose serum transaminases rose sixfold, returning to normal after the dose of cyclosporine was reduced by 25%.

TABLE 3
Partial correlation coefficient of various clinical and laboratory indices

	MSTG	CDAI
CDAI	−0.67*** (n = 72)	
SICDA	−0.57*** (n = 72)	+0.81*** (n = 95)
Orosomucoid	−0.35* (n = 42)	+0.31* (n = 58)
C-reactive protein	−0.26 (n = 68)	+0.33** (n = 90)
Erythrocyte sedimentation rate	+0.05 (n = 67)	+0.18 (n = 89)

*MSTG Mean Score of Therapeutic Goals; CDAI Crohn's Disease Activity Index; SICDA Simple Index of Crohn's Disease Activity; n Number of occasions where the indices were measured in the 15 patients who entered the cyclosporine trial. ***P <0.001; **P <0.01; *P<0.05*

TABLE 4
Symptomatic side effects of cyclosporine in 15 patients who entered the trial

Side effect	Number of patients
Paresthesia/hyperesthesia	9
Epigastric burning/nausea	8*
Tremor	8
Hypertrichosis	7
Anorexia	3
Fatigue	2
Gingival hypertrophy	2
Breast tenderness	1
Mild depression	1

**Caused two patients to drop out of the study*

A mean drop of 1.4 ± 0.4 g/dL in hemoglobin ($P<0.01$) with no change in percentage reticulocyte count (2.0 ± 0.3%) occurred in all patients who completed the 16 week therapy. This drop in hemoglobin was characterized by normochromic, normocytic changes. There was a trend towards an increase in ESR, C-reactive protein and platelet count in cyclosporine-treated patients, which did not reach statistical significance. In the seven patients who improved clinically ESR increased from 30 ± 11 to 46 ± 12 mm/h, C-reactive protein rose from 0.9 ± 0.5 to 1.5 ± 0.6 mg/dL, and platelet count increased from 375,000 ± 53,000 to 411,000 ± 65,000/μL (all nonsignificant changes).

DISCUSSION

The failure to isolate an infectious agent, and the favourable response of Crohn's disease to corticosteroids and 6-mercaptopurine suggests that immunological mechanisms play a role in the initiation and/or perpetuation of tis-

sue damage in the disorder. Considerable evidence points to the sensitization of circulating T lymphocytes to certain intestinal- and/or bacterial-related antigens (31), with reduction of suppressor T lymphocyte function in severe active Crohn's disease (32). Cyclosporine may reverse this process by selectively inhibiting helper T lymphocyte production of interleukin-2 essential for B lymphocyte and cytotoxic T lymphocyte differentiation and proliferation, while allowing the expansion of suppressor T lymphocyte populations (16).

The group of patients that completed this open trial of cyclosporine had severe active Crohn's desease as evidenced by CDAI of 308 ± 85 (± SE), worse than patients entering previous major Crohn's disease studies: the US National Cooperative (CDAI of 245.7 ± 70.1) (1), and the European Cooperative (CDAI of 176.5 ± 98.4) (2). In addition, the present patients were symptomatic despite conventional therapy.

There was an initial improvement in 10 of the 15 patients (67%) who entered the trial, within four weeks of starting cyclosporine treatment. Some of the patients, though improved, did not achieve CDAI of less than or equal to 150, which was chosen as the limiting value to consider patients in 'remission' in previous studies (1,2). However, in the original group of patients on whom the development of CDAI was based (23), 10% of patients considered clinically 'very well' and 69% considered clinically 'fair to good', had CDAI greater than 150. In this trial, after a 16 week course of cyclosporine, seven patients achieved a significant 105 unit improvement on the CDAI scale ($P<0.05$) (Figure 1); this increases to 134 units if the 'hematocrit' item is not considered in the measurement of CDAI. A mild reversible drop in hemoglobin is a constant feature in all patients treated with cyclosporine, irrespective of clinical response.

Unlike 6-mercaptopurine, where the mean onset of response was 3.1 months (3), the effect of cyclosporine was evident within four weeks. In 10 patients that completed the trial, 70% maintained the initial improvement throughout the 16 week course.

In the present study it was possible to discontinue or reduce prednisone in a relatively short period, when previous attempts before entering the trial had failed. However, within four weeks of stopping cyclosporine, there was relapse in four of seven patients (57%) that had maintained the improvement through the 16 week period. In retrospect, the authors probably should not have been so aggressive in tapering or discontinuing prednisone dose in these patients, based on their clinical response. Perhaps there would have been less relapses at week 12 and later during the post treatment follow-up period if the prednisone dose was stable for at least four weeks.

Undesirable side effects of cyclosporine were relatively minor and reversible upon reduction or discontinuation of the drug. These were similar to those described previously (24,33). Renal toxicity was minimized by regular monitoring of serum creatinine and cyclosporine trough levels with dose adjustment where necessary. No long term side effects were noted.

The daily dose of cyclosporine was carefully titrated, based on the trough levels, making no attempt to find the minimum effective dose. Based on the present study, a six to eight week course of cyclosporine may be as effective as the planned 16 week course.

The clinical assessment of activity for Crohn's disease is controversial. The present study compared the various clinical and laboratory indices in the same group of patients. MSTG was the most useful in the assessment of Crohn's disease activity before and after treatment. This index correlated well with the currently established indices and to a lesser extent with the laboratory indices. Obviously, the effects of cyclosporine on ESR (24) and C-reactive protein make these tests unsatisfactory for assessing disease activity. Orosomucoid was, apparently, not affected by cyclosporine therapy. Of the laboratory indices, orosomucoid correlated best with the clinical assessment of Crohn's disease activity. These observations need to be confirmed, and considered before incorporating any of the laboratory indices to a practical clinical index of Crohn's disease activity as has been suggested (30).

Cyclosporine appeared to have a therapeutic value in patients with severe active Crohn's disease refractory to conventional therapy. Side effects were minor and easily reversible. This apparent benefit and safety of cyclosporine in selected patients with Crohn's disease ideally needs to be confirmed by placebo-controlled, double-blind clinical trials. However, a controlled trial of 6-mercaptopurine versus cyclosporine may be ethically more acceptable with the disadvantage of very large numbers of patient enrollment to control for the ß error.

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Clinical Quiz

Please note, there may be more answers than asked for in the question.

STOMACH

1. What are the four different phases of gastric acid secretion?
   What probable mechanisms of control may be operational for each of these phases?

2. In patients with high, low and variable acid secretion, name eight causes of hypergastrinemia.
(Answers page 34)

PANCREAS

1. Certain clinical or laboratory features obtained at admission or during the initial 48 h of hospitalization correlate with severe or complicated course and increased mortality risk in acute ethanol-associated pancreatitis. Give eight of these features.

2. List eight complications of cystic fibrosis on the gut, liver and pancreas.
(Answers page 34)