

FALK SYMPOSIUM 46

Inflammatory Bowel Diseases – Basic Research and Clinical Implications

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Contents

List of Contributors	xiii
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SECTION 1 PATHOLOGY AND PATHOGENESIS

1 Ultrastructural pathology of Crohn's disease <i>A. M. Dvorak</i>	3
2 Dysplasia in ulcerative colitis <i>R. H. Riddell</i>	43
3 Colonic glycoproteins in ulcerative colitis: potential meaning in heterogeneity <i>D. K. Podolsky</i>	49
4 Absorption and secretion in relation to inflammatory bowel disease <i>K. Ewe</i>	57
5 The role of colonic mucosal metabolism in the pathogenesis of ulcerative colitis <i>W. E. M. Roediger</i>	69

SECTION 2 VIROLOGY—BACTERIOLOGY

6 Viral and other transmissible agents in inflammatory bowel disease <i>W. L. Beeken</i>	81
7 Mycobacteria in inflammatory bowel disease <i>W. R. Thayer, R. Chiodini, H. van Kruiningen and J. Coutu</i>	89

SECTION 3 IMMUNOLOGY

- 8 Activation and regulatory function of lamina propria T cells: implications for inflammatory bowel disease 95
S. P. James, M. Zeitz, M. E. Kanof, C. Fiocchi and W. Strober
- 9 Altered secretion patterns of IgA and IgG subclasses by IBD intestinal mononuclear cells 105
R. P. MacDermott
- 10 Immunocytotoxicity and lymphokines in inflammatory bowel disease 113
C. Fiocchi, K. Kusugami, J. Trudel, B. Y. Lieberman, Q. Ouyang and M. El-Youssef
- 11 Autoimmunity in chronic inflammatory bowel disease 121
I. O. Auer
- 12 Neutrophils and macrophages in inflammatory bowel disease 131
D. P. Jewell

SECTION 4 EICOSANOIDS

- 13 Prostaglandins in inflammatory bowel disease 137
D. Rachmilewitz
- 14 Leucotriene B4 in inflammatory bowel disease 143
W. F. Stenson
- 15 Effect of anti-inflammatory drugs on human colonic leucotriene formation 153
B. M. Peskar and Ch. Coersmeier
- 16 Effect of therapy on eicosanoid formation in inflammatory bowel disease 161
K. Lauritsen, L. S. Laursen, K. Bukhave and J. Rask-Madsen
- 17 The role of eicosanoids in animal models of inflammatory bowel disease 175
N. K. Boughton-Smith and B. J. R. Whittle

SECTION 5 EPIDEMIOLOGY AND GENETICS

- 18 Genetic aspects of inflammatory bowel disease 203
J. Purrmann
- 19 Smoking and inflammatory bowel disease 215
R. F. A. Logan

CONTENTS

20	Sugar intake and Crohn's disease <i>K. W. Heaton</i>	225
21	Genetic studies in Crohn's disease <i>S. W. Bender and Paediatric Crohn's Disease Study Group</i>	233
SECTION 6 ROUND TABLE: TRENDS IN EPIDEMIOLOGY OF IBD		
22	Trends in epidemiology of inflammatory bowel disease in Denmark/Scandinavia <i>V. Binder</i>	237
23	Epidemiology of IBD in Central Israel 1970–1980 <i>T. Gilat</i>	239
24	Prospective analysis of the frequency of chronic inflammatory bowel disease in an urban population (Ruhr) <i>H. Goebell, E. Dirks and S. Förster</i>	241
25	Inflammatory bowel disease epidemiology in the United States <i>A. I. Mendeloff</i>	243
26	Epidemiology of inflammatory bowel disease in regio Leiden, the Netherlands <i>S. Shivananda, M. L. Hordijk, A. S. Peña and E. J. Ruitenberg</i>	245
27	The incidence of inflammatory bowel disease at the tip of Africa <i>J. P. Wright</i>	249
SECTION 7 ACTIVITY AND PROGNOSIS		
28	Different activity indices in Crohn's disease and their possible role <i>H. Goebell</i>	253
29	Prognostic indices on Crohn's disease <i>G. Lanfranchi, C. Brignola, A. Tragnone and P. Farruggia</i>	259
SECTION 8 NATURAL COURSE OF IBD		
30	Natural course of Crohn's disease <i>R. G. Farmer</i>	267
31	The course of Crohn's disease after surgery: factors affecting recurrence <i>R. N. Allan</i>	275

INFLAMMATORY BOWEL DISEASES

- 32 Ileal pouch-anal anastomosis for benign colonic diseases: critical analysis of the Cleveland Clinic Foundation experience 279
V. W. Fazio and M. H. McCafferty
- 33 Cancer in inflammatory bowel disease 289
D. B. Sacher

SECTION 9 THERAPY OF IBD (I)

- 34 Treatment of ulcerative colitis: state of the art 297
G. Watkinson
- 35 Absorption and utilization of nitrogen during enteral feeding of whole versus hydrolyzed protein in active Crohn's disease 313
H. J. Steinhardt, E. Payr, B. Henn, K. Ewe and S. Biederlack
- 36 Nutritional treatment of inflammatory bowel disease including EPA 315
C. A. Ó'Moráin

SECTION 10 THERAPY OF IBD (II)

- 37 Results of the European Cooperative Crohn's Disease Study IV 323
H. Lochs, H. J. Steinhardt, B. Klaus-Wentz and H. Malchow
- 38 Anal lesions in Crohn's disease—a surgical view 325
G. Hellers
- 39 The evolution of the new salicylates 333
S. C. Truelove
- 40 Pharmacokinetic properties of 5-aminosalicylic acid (mesalazine) 339
U. Klotz
- 41 5-ASA for the prevention of relapse in ulcerative colitis 349
M. J. Dew
- 42 Osalazine—clinical studies and relapse prevention in ulcerative colitis 353
H. Sandberg-Gertzén
- 43 Topical treatment with 5-aminosalicylic acid as rectal enemas 357
M. Campieri, P. Gionchetti, A. Belluzzi, G. M. Tabanelli, C. Brignola, M. Migaldi, M. Mignoli and L. Barbara
- 44 Cyclosporin A—still experimental or a new drug in IBD 363
J. Brynskov

CONTENTS

POSTER ABSTRACTS

- 1 Electron microscopic studies in acute and chronic ulcerative colitis I. Alterations of the mucosa
M. Balázs, T. Kertész and A. Kovács, János Hospital, Budapest 369
- 2 Erythrocyte-associated laminin in normal mucosa and in Crohn's disease
A. Stallmach, U. Hahn, E. G. Hahn and E. O. Riecken, Free University of West Berlin 370
- 3 Induction of experimental ulcerative colitis in mice, with special reference to the change of intestinal microflora
I. Okayasu, G.-F. Kao, S. Hatakeyama, M. Yamada, T. Okhusa, Y. Inagaki, C. Ekataksin, T. Chida and R. Nakaya, Tokyo Medical School and Dental University, Tokyo 371
- 4 Collagenous colitis. Retrospective study
P. Egerszegi and G. Vadász, János Hospital, Budapest 372
- 5 Interaction of human monocytes and mycobacteria: preliminary studies comparing Crohn's patients with controls
D. Y. Graham and D. C. Markesich, VA Medical Center and Baylor College of Medicine, Houston 373
- 6 Mucosal T lymphocytes and HLA-DR expression in grossly involved and uninvolved ileum of patients with Crohn's disease
F. Tavela Veloso and J. V. Saleiro, University Hospital S. Joao, Porto, Portugal 374
- 7 Peripheral blood lymphocyte subpopulations in inflammatory bowel diseases
K. Pecze and X. Balogh, University Medical School, Debrecen, Hungary 375
- 8 Neutrophil activation in inflammatory bowel disease
T. McCall and C. A. Ó'Moráin, Trinity College Medical School, Dublin 376
- 9 T cell and OKM1-positive monocyte populations in the intestinal lamina propria mucosae and in the peripheral venous blood in Crohn's disease: a quantitative immunochemical analysis
G. Schürmann, R. Decker, M. Betzler, P. Möller, A. V. Herbay and K. Koretz, University of Heidelberg 378
- 10 Immunoreactive cells in tissues of Crohn's disease by the monoclonal antibody in measles virus
H. Miyamoto, T. Tanaka and S. Nishioka, Wakayama Medical School, Japan 379
- 11 Evidence of contrasuppression mediated by *Vicia villosa* agglutinin (VVA) binding T cells in patients with Crohn's disease
A. Raedler, H. J. Lenz, A. de Weerth, K. Sandgren, K. H. Schultz, H. G. Thiele and H. Greten, University of Hamburg 380
- 12 The metabolism and function of peripheral blood neutrophils (PBN) in patients with ulcerative colitis (UC)
A. Stadnicki, A. Hyrcek and H. Stasiura, Silesian School of Medicine, Katowice, Poland 381
- 13 Significance of autoimmune reactions to pancreatic juice in Crohn's disease
W. Stöcker, M. Otte and P. C. Scriba, Medical University of Lübeck 382
- 14 Characterization and immunologic manipulation of the progression of chronic inflammatory bowel disease of the colon in a rat model
P. L. Beck, G. P. Morris and J. L. Wallace, Queen's University, Kingston, Ontario 384
- 15 Tumor-necrosis-factor (TNF) production by peripheral monocytes in inflammatory bowel disease (IBD) patients
T. Morita, K. Nara, H. Odagiri, M. Yokoyama, D. Seitoh, M. Sasaki, M. Konn and K. Ono, Hirosaki University School of Medicine, Japan 385
- 16 Studies on interleukin-2 in patients with ulcerative colitis
K. Kuroe, A. Nikai, Y. Murata, M. Akiyama and Y. Yoshida, Hirosaki University School of Medicine, Japan 386
- 17 Deficient spontaneous and interferon-induced natural killer cell activity and antibody-dependent cellular cytotoxicity in Crohn's disease
P. Knoflach, Ch. Mueller and C. C. Zielinski, University of Vienna 387

INFLAMMATORY BOWEL DISEASES

- | | |
|---|-----|
| 18 Experimental immune complex-mediated intestinal disease leading to protein-losing enteropathy
<i>P. Knoflach, B. Albini and M. M. Weiser, University of Vienna</i> | 388 |
| 19 Effect of 16,16-dimethyl prostaglandin E ₂ (dmPGE ₂) and sulfasalazine (SASP) on arachidonic acid (AA) metabolism by colonic tissue from guinea pigs with an immune colitis
<i>L. Da Costa and P. Dinda, Queen's University, Kingston, Ontario</i> | 389 |
| 20 Development of the epidemiology of chronic inflammatory bowel disease (IBD) in the county of Tübingen from 1970 to 1984
<i>W. Daiss, M. Scheurlen and H. Malchow, University Medical Clinic, Tübingen</i> | 390 |
| 21 Regional differences in the distribution of inflammatory bowel disease (IBD) in the county of Tübingen
<i>M. Scheurlen, W. Daiss and H. Malchow, University Medical Clinic, Tübingen</i> | 392 |
| 22 Bowel permeability to ⁵¹ Cr-EDTA in patients with Crohn's disease
<i>R. T. Jenkins, J. K. Ramage, R. L. Goodacre, R. H. Hunt and J. Bienenstock, McMaster University, Hamilton, Ontario</i> | 394 |
| 23 ^{99m} Tc-HMPAO and ¹¹¹ In-oxine labeled granulocyte scans in chronic inflammatory bowel diseases; clinical experience in 120 patients
<i>W. Becker, W. Fischbach, M. Jenett and W. Börner, University Medical Clinic, Würzburg</i> | 395 |
| 24 ^{99m} Tc-HMPAO labeling of leukocytes in the assessment of patients with Crohn's disease (CD)
<i>J. Schölmerich, C. Schümichen, E. Schmidt and W. Gerok, University of Freiburg</i> | 396 |
| 25 ⁷⁵ SeHCAT-test for characterization of ileal involvement in Crohn's disease
<i>K. Balzer, E. Dirks, N. Breuer and H. Goebell, University of Essen</i> | 398 |
| 26 Fecal blood loss in inflammatory bowel disease
<i>O. P. van der Ven, L. K. Ko, J. W. O. van der Berg and E. A. R. Knot, Erasmus University, Rotterdam</i> | 400 |
| 27 Determination of the small bowel transit time using barley groats
<i>R. J. Vonk, C. H. P. Collin, J. J. de Vries and C. M. A. Bijlveid, University Hospital, Groningen</i> | 401 |
| 28 Study on colonic transit in man using colonoscintigraphy
<i>K. Murakami, H. Nakano, N. Inatsugi, H. Fujii, T. Hashimoto and T. Shiratori, Nara Medical University, Japan</i> | 402 |
| 29 Neopterin serum levels in Crohn's disease
<i>E. F. Strange, W. E. Fleig and H. Ditschuneit, University Clinic, Ulm</i> | 403 |
| 30 Ultrasound in Crohn's disease
<i>P. P. Michielsen, T. J. Hartoko, P. A. Pelckmans, J. H. Pen and Y. M. van Maercke, University Hospital of Antwerp</i> | 404 |
| 31 Prospective endoscopic follow-up of the evolution of Crohn's recurrence at the ileocolonic anastomosis after surgery
<i>P. Rutgeerts, K. Geboes, G. Vantrappen, J. Beyls, G. Coremans and R. Kerremans, University Hospital Gasthuisberg, Leuven</i> | 405 |
| 32 Prospective endoscopic and histologic study in patients with ulcerative proctitis
<i>G. Geboes, P. Rutgeerts, N. Ectors and G. Vantrappen, University Hospital Gasthuisberg, Leuven</i> | 407 |
| 33 Early recurrence of Crohn's disease (CD) after curative resection. First results of a prospective study using colonoscopy
<i>C C Singe, S. Biederlack and K. Ewe, Medical University, Mainz</i> | 408 |
| 34 Recurrence of Crohn's disease in patients with curative resection as compared to conservatively treated patients
<i>E. Dirks, K. Schaarschmidt, H. Goebell and F. W. Eigler, University of Essen</i> | 410 |
| 35 A classification of small bowel strictures in Crohn's disease
<i>P. McDonald, R. Petras, V. Fazio and S. Galandiuk, Cleveland Clinic Foundation, Cleveland, Ohio</i> | 411 |
| 36 Antithrombin III levels and thromboembolic complications in inflammatory bowel disease
<i>D. Hüppe, U. Kamp, R. Tönissen and H. D. Kuntz, University Clinic, Bochum</i> | 412 |

CONTENTS

37 Crohn's disease and pregnancy <i>H. Jenss, H. Eiser and P. Weber, University of Tübingen</i>	414
38 Serum retinol levels in inflammatory bowel disease <i>I. Janczewska, W. Bartnik, J. Ostrowski and E. Butruk, Medical Center of Post-graduate Education, Warsaw</i>	415
39 Vitamin D and calcium regulation in patients with Crohn's disease (CD) <i>H. Vogelsang, P. Ferenci, R. Schilling, W. Wolszczuk, F. Haschke, H. Lochs and A. Gang, University of Vienna</i>	416
40 Changes of the calcium metabolism in inflammatory bowel disease <i>J. Kocián and J. Kociánová, Faculty Hospital Bulovka, Prague</i>	417
41 Impaired cholesterol metabolism in Crohn's disease <i>M. Malavolti, G. Borghi, E. Roda, B. Grigolo, A.M. Morselli Labate, P. Simoni and L. Barbara, University of Bologna</i>	418
42 Parenteral nutrition (PN) in inflammatory bowel disease (IBD) <i>M. Cravo, M.L. Tavares, M.T. Tavares, M.E. Camilo and J. Pinto Correia, University of Santa Maria, Lisbon</i>	419
43 Therapeutic efficacy of sliding scale based cyclic home enteral alimentation in Crohn's disease <i>K. Matsueda, R. Shoda, M. Takasoe, A. Muraoka, S. Yamato, N. Kawamura, K. Morishita, E. Shimojo, N. Umeda and T. Oda, National Medical Center Hospital, Tokyo</i>	420
44 The adjuvant therapy of colitis ulcerosa with loperamide <i>I. Altaparmakov, R. Trapp and P. Czygan, Lucas Academic Hospital, Neuss</i>	422
45 A controlled randomized trial of budesonide versus prednisolone retention enema in active distal ulcerative colitis <i>A. Danielsson, G. Hellers, E. Lyrenäs, R. Löfberg, A. Nilsson, O. Olsson, S.-A. Ohlsson, T. Persson, L. Salde, R. Sjö Dahl, M. Stenstam and R. Willén, Departments of Medicine in Umeå, Karlskrona, Stockholm, Lund, Helsingborg, Eskilstuna; Department of Surgery in Jönköping, Lund, Linköping; Departments of Pathology in Lund</i>	423
46 Protective effect of metronidazole in ulcerative colitis experimentally induced by dextran sulfate sodium <i>T. Ohkusa, M. Yamada, N. Yamamoto, M. Sasabe, I. Takashimuzu, H. Fujimoto, Y. Kuyama, N. Aoki, T. Chida, M. Higaki, N. Okamura, R. Nakaya, I. Okayasu and S. Hatakeyama, Soka City Hospital, Saitama and Tokyo Medical and Dental University</i>	424
47 Results and significance of thymectomy in patients with ulcerative colitis <i>H. Yoshimatsu and K. Ando, University of Occupational Health, Japan, Kitakyushu and Shizuoka Red Cross Hospital, Shizuoka, Japan</i>	425
48 Strictureplasty in Crohn's disease <i>S. Galandiuk, V. W. Fazio and P. McDonald, Cleveland Clinic Foundation, Cleveland, Ohio</i>	426
49 Placebo controlled trial of 4-amino salicylic acid enemas in left sided ulcerative colitis <i>A. L. Ginsberg, L. S. Beck, T. M. McIntosh and L. E. Nochomovitz, George Washington University School of Medicine, Washington D.C.</i>	427
50 Prospective, randomized, double-blind comparison of salazobenzoic acid (SAB) and sulfasalazine (SASP) in the treatment of active ulcerative colitis <i>W. E. Fleig, G. Laudage, E. F. Stange and J. Riemann, University Medical Clinics of Ulm and Erlangen</i>	428
51 <i>In vitro</i> screening of alternative salicylate derivatives for therapeutic use in ulcerative colitis <i>W. E. W. Roediger, E. J. Deakin, M. J. Lawson and S. H. Nance, University of Adelaide at the Queen Elizabeth Hospital, Adelaide</i>	430
52 Crohn's disease and ulcerative colitis: treatment with 7S-immunoglobulin <i>G. Rohr, K. Kusterer, M. Schille, U. Schwedes, R. Gladisch, J. Teuber and K. H. Usadel, Mannheim Clinic, University of Heidelberg</i>	432

INFLAMMATORY BOWEL DISEASES

53	Flow cytometric DNA analysis in longstanding ulcerative colitis—a possible complement in cancer surveillance <i>R. Löfberg, O. Broström, H. Reichard, B. Tribukait and A. Öst</i>	433
54	Increased frequency of HLA-B27/44 in patients with Crohn's disease and ankylosing spondylitis <i>J. Purrmann and J. Bertrams, University of Düsseldorf and Elisabeth-Krankenhaus, Essen</i>	434
55	Dietary management in idiopathic inflammatory bowel disease (IBD) <i>H. Steinhardt</i>	436
	Index	439

POSTER 13

Significance of autoimmune reactions to pancreatic juice in Crohn's disease

W. STÖCKER, M. OTTE AND P. C. SCRIBA

Autoantibodies to exocrine pancreas (Pab) have been detected by indirect immunofluorescence in sera of patients with Crohn's disease (CD). High titres were frequent in CD, but could neither be recorded in ulcerative colitis nor in healthy subjects¹. Pab in CD were as conspicuous as autoantibodies to intestinal goblet cells (Gab) in ulcerative colitis (UC) and other autoantibodies in proven autoimmune diseases. The possible implication of pancreatic immunity in the pathogenesis of CD was discussed². Results of additional studies enhance the significance of these observations.

The association of Pab with CD could be verified by examination of new, larger collectives consisting of 150 patients with CD, 164 patients with UC and 100 healthy control persons (Co)³. Pab were predominant in CD (CD 35%, UC 2%, Co 0%). High Pab-titres were only detectable in CD (1:100 or higher in 30% of 150 patients). On the contrary, Gab were confirmed to be an exclusive marker for UC (CD 0%, UC 26%, Co 0%).

The prevalence of Pab and Gab was determined in the sera of the patients' family members⁴ who are assumed to carry an elevated risk for developing chronic inflammatory bowel disease. Since none of 185 healthy appearing first degree family members exhibited Pab or Gab, these antibodies seem to be disease-specific and do not yet indicate a disposition for CD or UC.

It was possible to isolate the CD-related autoantigen from pancreatic juice. The antigen was shown to be a macromolecule different from functionally active trypsin, chymotrypsin, amylase and lipase, and it could neutralize Pab of each positive CD-serum⁵.

The autoimmune reactions in CD differed fundamentally from those observed in disorders of the pancreas: Pab were rare in chronic (2 of 51) and acute (3 of 26) pancreatitis, their titres were low and did not exceed 1:32, they consisted only of IgA (CD: IgG or IgG + IgA) and could not be neutralized by the CD-related autoantigen⁶.

A number of sera contained Pab or Gab with only one type of light chains, kappa or lambda. This uneven distribution speaks in favour of an oligoclonal

antibody response and possibly indicates that the corresponding autoimmune reactions are phenomena of primary significance—a secondary immunization against pancreatic or goblet cell antigens in the course of CD or UC seems to be excluded⁷.

In Crohn's disease, the bowel may have developed a state of hypersensitivity against a physiologically occurring component of pancreatic juice. Pancreatitis is not predominant in CD since the bulk of autoantigens comes into contact with the immune system only outside the pancreas. As with other autoimmune diseases, the cause of sensitization cannot yet be explained, and further investigations are required to completely reveal the etiology of CD.

Determination of Pab is of great diagnostic value. In combination with Gab, they permit the diagnosis of CD or UC in one third of patients with chronic inflammatory bowel disease.

References

1. Stöcker, W., Otte, M., Ulrich, S., Normann, D., Stöcker, K. and Jantschek, G. (1984). *Dtsch Med. Wschr.*, **109**, 1963–9
2. Stöcker, W., Otte, M. and Scriba, P. C. (1984). *Dtsch. Med. Wschr.*, **109**, 1984–6
3. Burmester, E., Stöcker, W., Jantschek, G., Feiereis, H. and Otte, M. (1987). (Lübeck: Hansisches Verlagskontor) (In press)
4. Kosegarten, Th., Döscher, M., Jantschek, G., Burmester, U., Schmidt, S., Otte, M. and Stöcker, W. (1986). *Immunobiology*, **172**, 337–8
5. Finkbeiner, H., Bock, S., Burmester, U., Grage, D., Reddig, U., Struve, D., Otte, M. and Stöcker, W. (1985). *Immunobiology*, **170**, 20
6. Hellwig, D., Otte, M., Reddig, U., Struve, D. and Stöcker, W. (1986). *Immunobiology*, **173**, 337–8
7. Stöcker, W., Otte, M. and Scriba, P. C. (1984). *Immunobiology*, **168**, 123–4

