OBSERVATIONS ON INFLAMMATORY BOWEL DISEASE - 1985: PRESENT STATUS AND FUTURE PROSPECTS

J.B. KIRSNER

All at present known in medicine is almost nothing in comparison with what remains to be discovered. - R. Descartes (1596-1650)

INTRODUCTION

One hundred and twenty-five years have passed since Samuel Wilks of England in 1859 first described ulcerative colitis and probably also Crohn's disease of the small bowel (inflammatory bowel disease - IBD). While studied in a few medical centers during this period, IBD has attracted worldwide attention only in recent years. The Second International Symposium on IBD, held in Jerusalem, September 9-11, 1985, is the latest such meeting, the previous one having been held in September 1981. Despite the increased clinical and investigative interest, the etiology and the pathogenesis of IBD remain obscure. Medical treatment continues to be largely empirical. Surgical techniques have improved, but ablative procedures, no matter how necessary or skilled, hardly represent the ideal solution.

From the perspective of 50 years of involvement with IBD, both as an investigator and as a clinician, the presence of approximately 500 inquiring physicians and scientists from many parts of the world was the most impressive feature of the 1985 meeting. What then has been the progress in our understanding of IBD during the past four years?

Epidemiology and demography. Epidemiologic and demographic studies continue to reflect interesting but incompletely characterized world-wide patterns of distribution and trends: The stabilization of ulcerative colitis (except possibly for the Grampian area in northeastern Scotland); the generally rising prevalence of Crohn's disease, in some areas approximating or exceeding ulcerative colitis; the increasing incidence of Crohn's disease in Japan, South Africa and among the black populations of the United States, its infrequency among the Chinese of Hong Kong; the occurrence of mild to moderate ulcerative colitis and Crohn's disease in Kuwait; the increasing frequency of Crohn's disease among older age male and female patients; and perhaps most significantly, the apparent stabilization or decreasing prevalence of Crohn's disease in places such as Stockholm, Sweden; Aberdeen, Scotland; Cardiff, Wales; and Baltimore, Maryland (USA); intriguing observations that suggest "external," environmental agents in the pathogenesis of Crohn's disease and perhaps also ulcerative colitis. The implication of various foods (cereals, refined sugars, margarine) remains speculative. The possible involvement of certain drugs, e.g. oral contraceptives among young women, awaits more data.

The international multicenter study of possible risk factors for IBD among children does not support the "sheltered child" hypothesis, nor the role of bottle feeding, infantile gastroenteritis, cereal consumption, psoriasis, asthma and milk allergy. The increased frequency of respiratory infections treated with antibiotics coincides with my experience that earlier, often unwarranted and excessive use of antibacterial drugs (e.g. penicillin orally for mild respiratory illness) may precede the onset of IBD or precipitate its recurrence. The higher incidence of eczema, of

D. Rachmilewitz (ed.), *Inflammatory Bowel Diseases 1986*

appendectomy among patients with Crohn's disease, and of major cardiovascular and gastrointestinal diseases among the fathers of patients with Crohn's disease are puzzling findings.

The variable and incomplete epidemiological findings indicate the need for additional collaborative, world-wide studies by expert epidemiologists. Such projects require, in addition to conventional data on age, sex, race, ethnicity, socio-economic factors, psychologic factors, and familial aggregation, accurate IBD diagnoses; more thorough definition of the populations at risk, more information on the circumstances antedating diagnosis; and the separation of potential genetic and environmental factors. The more inclusive surveys from Rochester, New York, and from Copenhagen, Denmark, appear especially promising.

The paucity of smokers among patients with ulcerative colitis and the excess of smokers among patients with Crohn's disease, now confirmed in both Europe and the United States, is an intriguing epidemiologic clue, although a relative scarcity of active smokers also characterizes patients with the irritable bowel syndrome. In view of the deleterious effects of tobacco upon the heart and the lungs, the increased incidence of pulmonary, pancreatic and colonic cancer, the damaging effects of tobacco upon DNA, the complement system (activation of alternative pathway via modification of C3), and altered hormonal responses, it is difficult to conceive of a beneficial effect of nicotine in ulcerative colitis, or indeed, any disease. Multidisciplinary studies of the biologic effects of tobacco combined with thorough and repeated epidemiologic and demographic studies of these population groups may clarify the smoking/non-smoking issue in IBD.

SOME CLINICAL ASPECTS

Endoscopy and cat scans - Endoscopy (flexible sigmoidoscopy, colonoscopy, upper G.I. endoscopy and now small intestinal endoscopy by the Japanese), facilitating multiple intestinal and colorectal biopsies, has contributed objectively to the diagnosis of IBD and has permitted histologic, histochemical and immuno-histological characterization of ulcerative colitis and Crohn's disease. Examination of the "early" aphthoid lesions of Crohn's disease in the mouth and in the colon may facilitate the search for microbial or viral agents. Cat scans of the abdomen now provide an additional diagnostic technique for the clinical evaluation of inflammatory bowel disease, possibly in differentiating ulcerative colitis and Crohn's disease, but more in the recognition of such complications as abscess and fistula formation. The continued development of imaging technology will further expand the clinical appraisal of IBD.

Colorectal cancer - Continued study of the dysplastic changes associated with the increased risk of adenocarcinoma of the colon and rectum in ulcerative colitis and in Crohn's colitis, supplemented by tissue measurements of sialomucin content, oncofetal antigens (e.g. CEA) and other markers of "pre-neoplasia" should improve the earlier detection of colon cancer. The chromosomal alterations (aneuploidy) noted by flow cytometric DNA analysis in long-standing ulcerative colitis, while secondary, additionally reflect the cancer risk in IBD.

The lower incidence of colon cancer in ulcerative colitis reported from Czechoslovakia, Denmark, Italy, Yugoslavia, Greece, contrasting with Great Britain, the United States and the Scandinavian countries, re-emphasizes the potential role of environmental factors, probably diets (high animal fat and protein food intakes) and their modification of the intestinal microflora (increased anaerobes) in the development of intestinal cancer.

Emotional considerations - As recognized at least since 1930, emotional disturbances are common both in ulcerative colitis and in Crohn's disease. They probably do not cause ulcerative colitis or Crohn's disease, but they increase the severity of IBD, and precipitate recurrences and blunt the response to treatment. While animal studies have provided evidence of the damaging effects of "natural" or experimental stress upon the gastrointestinal tract, such approaches seem unlikely to clarify the complex issue of the psyche and inflammatory bowel disease. Human illness, after all, is an outcome of the interaction of multiple etiologic and pathogenetically contributory processes (biomedical, psychosocial and psychocultural). The IBD psychoanalytic theories of the 1930s, 40s and 50s, emphasizing characteristic personality profiles, including dependency, immaturity, compulsive traits and alexithymia, have been replaced by concepts of fauly adaptation to life situations and various behavioral psychologic hypotheses; "modern" approaches that also are vulnerable to methodologic flaws, subjectivity, bias and non-quantifiability. The increased frequency of depression among patients with Crohn's disease, contrasting with ulcerative colitis, is of interest but requires further validation, including the study of additional "control" groups of patients. A large number of neuropeptides from the pituitary gland, sensory ganglia, brain secretions and automonic nervous system, influencing endocrine, immunological and gastrointestinal functions have been identified in recent years. The interactions between the central nervous system and the gastrointestinal tract, via such neuropeptides, seems promising in clarifying the role of the psyche in IBD. Recent observations linking the central nervous system and emotional stress to depression of the immune system are intriguing. Perhaps attention also should be directed to the possible beneficial biological effects of positive emotions (hope, joy, love) and of strong family and social support upon body defences and homeostasis.

Recurrences - The recurrences of ulcerative colitis and of Crohn's disease, characteristic of IBD, remain as mystifying as the etiology. Among patients operated on for Crohn's disease of the small bowel and experiencing recurrences, early and late, age, sex, location and duration of the disease, length of bowel resected and histology of the resected margins, proved non-predictive. The elevated levels of IgG in the resected intestinal margins, reported elsewhere, reflect existant rather than future disease. The usual clinical emphasis upon emotional disturbances (meaningful life events), dietary indiscretions, intercurrent enteric infections and respiratory illnesses as precipitants of recurrence are factors we can recognize today; there also must be circumstances we cannot yet identify. Such laboratory measurements as C-reactive protein, serum orosomucoid, alpha-2 globulin and fecal alpha-1 antitrypsin may have predictive usefulness for recurrences, but this possibility awaits more study. Goethe has encapsulated the situation: "Was man weiss, man sieht." The recurrence problem in IBD is linked with the fundamental nature of the disease and with the mechanisms facilitating perpetuation of the tissue reaction. Until more is learned of the "fundamental" nature of ulcerative colitis and of Crohn's disease, clinical studies of recurrence will remain limited.

Tissue observations - We do not yet know why ulcerative colitis is limited to the colon and starts as a mucosal process and why Crohn's disease so often affects the small intestine and is a transmural reaction. Could there be selective cell sites for the attachment and penetration of the bowel epithelium by the etiologic agents for the two diseases? Intriguing morphologic features of Crohn's disease, in addition to the granulomas, include its predilection for the terminal ileum or the neo-terminal ileum

(after intestinal resection) in proximity to sphincters, the skip lesions, initiation of the process in lymphoid follicles of Peyer's patches, and the prominence of the lymphoid follicles (and, infrequently, lymphocytic lymphangitis).

The distribution of the focal lesions of Crohn's disease in relation to the gut-associated lymphoid tissue suggests some type of microbial infection gaining access via Peyer's patch M cells and its selective receptor sites. The M cell, originating in undifferentiated crypt cells, is specially adapted for antigen transport and is an important pathway for the direct access of intestinal antigens to the lymphoid tissue of the bowel. The role of the dendritic veiled cells in the bowel mucosa of active IBD, of the intestinal mast cell, more numerous and degranulated in the tissue reaction of active IBD, deserve additional study.

The selective decrease in mucin species IV, a relative decrease in mucin fraction III and the increase in fraction V, in ulcerative colitis (not Crohn's colitis) noted also in quiescent disease and apparently in uninvolved mucosa suggest a defective intestinal barrier to the entry of antigens and other potentially harmful agents. A similar mucin deficiency has been described in the cottontop marmoset colitis. Could these changes be secondary to an already established process? It is of interest to recall the earlier, but as yet unconfirmed, observation of decreased secretory IgA in the epithelium of involved rectal mucosa in idiopathic proctitis and in 40% of instances of normal-appearing proximal mucosa. Rather than gross structural abnormalities, a more subtle, perhaps metabolic or immunologic abnormality of the IBD bowel wall seems more likely.

The hyperplasia and abnormal appearance of VIP-containing nerve fibers in Crohn's disease, observed not only in the presence of histological evidence of disease, but also in its absence, contrasting with normal VIP content in ulcerative colitis, is unexplained, but probably represents a consequence rather than an antecedent of the disease. The functions of such neuro-humoral substances as P-containing neural elements in the small intestine of Crohn's disease, presumably involved in the motor activity of the gut, also remain to be clarified. The hyperplasia of Meissner's plexus of the colon in Crohn's disease, not in ulcerative colitis, probably is another secondary "neurogenic" observation.

Therapeutic approaches in relation to inflammatory mediators (Arachidonic acid cascade) - Analysis of therapeutic responses in IBD does not reveal significant pathogenetic clues. Medications such as sulfasalazine, 5-aminosalicylic acid, antibiotics, steroids, 6-mercaptopurine and azathioprine, while often helpful in controlling the inflammatory process, do not cure ulcerative colitis or Crohn's disease. Their therapeutic benefits appear to derive, in part at least, from inhibitory effects upon various links of the arachidonic acid cascade.

Sulfasalazine's beneficial effects, especially in ulcerative colitis, may be related to the inhibition of prostaglandin E2 and other inflammatory mediators (superoxide radicals, neutrophil lipoxygenase and platelet thromboxane synthetase). 5 amino salicylic acid, the therapeutically active component of sulfasalazine, blocks cyclo-oxygenase and leukotrine synthetases. Related compounds, azodisalicylate, disodium azodisalicylate, asacol, balsalazide and 4 amino salicylic acid probably act similarly. Whether or not this mechanism explains their therapeutic benefit in ulcerative colitis is not yet clear. Drugs inhibiting prostaglandin E production also act as stimulants of cellular immune functions (T cell proliferation, lymphokine production). Drugs suppressing superoxide radicals (superoxide dismutase) and of leukotriene synthetase (experimental) and diets

including fish oils with eicosapentaenoic acid, (EPA) capable of suppressing LTB4 production are under investigation; but their clinical effects probably are not specific to IBD. EPA competitively inhibits the utilization of arachidonate by cyclo-oxygenase and also inhibits the metabolism of arachidonic acid to LTB4. Arachidonic acid metabolites formed by both the cyclo-oxygenase and lipoxygenase pathways may contribute to the diarrhea of IBD, via increased intestinal chloride secretion, decreased active absorption of sodium and chloride and by alterations in intestinal motility, but they are not primarily responsible for IBD. The concentration of LTB4 in the colonic mucosa of patients with IBD is 50 times greater than that in normal mucosa, and LTB4 is the major mediator of neutrophil chemotaxis in IBD. The increased amounts of 5 HETE and the leukotriene LTB4, originating in increased numbers of mucosal neutrophils, macrophages and mast cells in ulcerative colitis, also are found in the experimental acetic acid colitis of the rat. The increased quantities of the eicosanoids (prostaglandins) in ulcerative colitis bowel similarly appear to be measurable epiphenomena of the colorectal inflammation, probably originating in lamina propria cells. Present evidence does not support a primary role for eiconsanoids in the pathogenesis of either ulcerative colitis or Crohn's disease. The exact role of the soluble mediators of inflammation (kinins, C3, C5a of the complement pathway, and leukotrienes) in IBD, is yet to be determined. They probably contribute to the tissue reaction and their inhibition, partially or completely, thus helps to control the tissue reaction.

Other therapeutic considerations - Metronidazole, after ten years of use, remains a helpful antibacterial drug in some patients with Crohn's disease of the colon, occasional patients with enteric fistulas and in perianal Crohn's disease. However, the clinical effects are variable, the side effects may be considerable and the mechanisms of action, apart from a presumed anti-anaerobic effect, remains unknown.

Corticosteroids influence immune reactions via inhibition of macrophage function, suppression of damaging lymphocytes in the tissue reactions and depletion of circulating monocytes, among many other properties. However, their beneficial effects in IBD relate as much to their non-specific anti-inflammatory actions as to their immunosuppressive properties. Corticosteroids, by inhibiting phospholipase A, block the release of arachidonic acid from membrane phospholipids, decreasing the elaboration of damaging superoxide radicals, leukotrienes, prostaglandins and thromboxanes. Comparison of effective steroids in IBD (prednisone, prednisolone, methylprednisolone, hydrocortisone acetate and beclomethasone) with ineffective steroids (cortisone, triamcinolone, beta methasone, dexamethasone) does not reveal a therapeutic mechanism unique to IBD. The development of locally effective non-absorbable steroids for ulcerative proctitis (e.g. tixocortal pivalate) represents a modest therapeutic advance; in the effort to minimize or avoid steroid side effects. Perhaps the most important development in the past four years is increased awareness of the limitations and the hazards of longterm steroid therapy; and their more judicious use in the management of IBD.

"Immunosuppressants" - immune modulators - 6MP and azathioprine are beneficial in some patients with Crohn's disease, particularly in sustaining an already established therapeutic response and in facilitating decreases or the elimination of steroids. Their clinical effects are limited to the period of administration; and recurrences follow discontinuance of the drug. As long as 6 months may be required for the helpful effects to develop. In the dosages currently prescribed (2.5-3.0 mg per kg body weight)

6MP and azathioprine probably have little or no true immunosuppressive action. Their immunological effects apparently include the normalization of lymphoblastoid antibody production to tetanus toxoid booster immunization, the decrease or elimination of NK and T-cell suppressor populations, inhibition of the expression of SRBC receptors on mitogen-stimulated and non-stimulated lymphocytes and normalizing deficient humoral immune responses. Thus, 6MP and azathioprine in the doses employed in inflammatory bowel disease appear to function more as immune modulators than as immunosuppressants. Why these drugs are more effective in Crohn's disease than in ulcerative colitis is another intriguing, unanswerable question.

Cyclosporine A has been administered to a few patients with Crohn's disease, with results too few to evaluate. Cyclosporin blocks the production of interleukin 2 by activated lymphocytes. Two new derivatives of cyclosporine: (NVA^2)-cyclosporine and (Val^2)-dihydrocyclosporine lack the nephrotoxic effects of cyclosporine. The compound ciamexone, an alpha 2 cyanaziridine derivative, holds the promise of more selective modulation of the immune system. The precise role of these so-called immunosuppressants in IBD is yet to be defined. At present, their role is likely to be adjunctive in selected IBD patients.

Nutrition - One of the more obvious therapeutic advances of the past four years has been recognition of the importance of nutrition in the management of IBD: maintaining good general health, normal healing capacity, and adequate pharmacologic responses to medication. Oral and parenteral hyperalimentation are particularly indicated in undernourished and malnourished patients with IBD, as a preparation for IBD surgery, and in attempting to control severe recurrent Crohn's disease in patients who already have undergone multiple operations with recurrence. Hyperalimentation per se does not cure IBD; does not permanently eliminate enteric fistulas; and may or may not control perianal Crohn's disease. However, apart from the issue of "cure," hyperalimentation is of great value in restoring the nutritionally depleted IBD patient to a reasonable state of good health and in preparation of the patient for necessary surgery. Retardation or cessation of growth in children with IBD is the result of insufficient energy (caloric) intake as well as excessive outgo of nutrients in severe active disease. Nutritional restoration with sufficient calorie intake, together with control of the inflammatory process, is the proper therapeutic approach.

Surgery - The surgical management of ulcerative colitis has improved substantially in the past four years. Increased communication between gastroenterologists and surgeons has clarified the indications and the timing of operation. Greater awareness of the nutritional requirements of the IBD patient, more skillful operative techniques, expert anesthesia and informed postoperative care have reduced surgical morbidity and mortality.

Proctocolectomy and ileostomy remain the most consistently successful operations for patients with ulcerative colitis requiring surgery. The Kock continent ileostomy by the experienced surgeon is an acceptable option for patients, young women especially, seeking to avoid a stoma and the need for an ileostomy bag. Devices to "cap" the stoma and gradually dilate the distal ileum are under investigation; but at present, do not appear promising. The various ileoanal anastomoses, with and without an ileal pouch, are still in the process of development, but are being utilized with increasing frequency. The results, in the hands of the expert surgeon, generally are favorable; though much yet remains to be learned about the physiology of the new anatomical arrangement. Present information indicates that after proctocolectomy and the establishment of an ileoanal reservoir

(for ulcerative colitis) most of the electrical and motor properties of the terminal ileum are retained; due to its large capacity, the reservoir acts as a storage organ and overall motility of the ileal pouch is reduced.

The current approach in surgery for Crohn's disease is conservative. Fewer surgeons are advocating the extensive resections of earlier years, in the effort to avoid incapacitating nutritional deficits attributable to the "short bowel syndrome." The stricturoplasty of Alexander-Williams, widening narrowed segments of Crohn's diseased small bowel appears to be a useful surgical advance. Balloon dilatation of accessible areas of intestinal narrowing is being attempted. As more is learned about the nature of fibrosis of the bowel, a medical approach to the IBD stricture may be possible in the future. Strictures of the colon in ulcerative colitis, on the other hand, may be a serious development; since studies at the University of Chicago have demonstrated a high incidence of colonic neoplasia in IBD patients with stricture and mucosal dysplasia.

Outcome - Estimates of the outcome of ulcerative colitis and Crohn's disease have varied considerably and often have lacked sufficient encouragement and hope for the patient and the physician. The "population studies" of Binder and her colleagues in Copenhagen County, Denmark, indicate a more favorable prognosis for both ulcerative colitis and Crohn's disease than the earlier literature had indicated.

The variable observations as to therapeutic response and prognosis reemphasize the need for universally acceptable clinical indices of disease severity and response to treatment applicable to medical centers throughout the world and permitting comparison of different patient populations. Much of the variability of clinical IBD data and the differing therapeutic opinions appear attributable, in part at least, to the study of insufficiently characterized heterogeneous patient groups, by variable clinical and laboratory criteria. The forthcoming meeting of British and American IBD investigators on clinical indices of severity in IBD under the auspices of the National Foundation for Ileitis and Colitis should be helpful.

ETIOLOGY AND PATHOGENESIS

Naturally occurring IBD - The many naturally occurring enteric and colonic inflammatory diseases in animals (dogs, cats, rodents, swine, lambs), including a transmissible ileitis in pigs, an ulcerative enteritis in birds, an enterocolitis in quail (cl. colinum), granulomatous ileitis in horses, Johne's disease in cattle (mycobacterium paratuberculosis), regional enterocolitis in cocker spaniel dogs, a fatal ulcerative colitis in Siamang gibbons, and a histiocytic ulcerative colitis in boxer dogs and in cats do not duplicate IBD (Table 1). The histopathologic features of a chronic ulcerative colitis of unknown etiology in domestically-bred cottontop marmosets (S. oedipus oedipus) resemble ulcerative colitis (crypt abcesses, mononuclear cell and neutrophil infiltration) apparently responds to sulfasaline and after several years is complicated by a high incidence of colon cancer. Corona viruses have been found in some animals and their possible role is being explored. The possible role of environmental, stress-inducing circumstances manifest among these animals in captivity, resulting in behavioral maladjustments, also requires consideration, especially in view of earlier observations documenting the association of such circumstances with ulcerative colitis (D.A. Drossman, personal communication, 1985). The relationship of marmoset colitis to IBD seems questionable.

In view of the morphologic similarities between ulcerative colitis and Crohn's disease in man and infectious colitis in animals (pigs, rats), (erosions in association with lymphoid follicles, mucus depletion, crypt abs-

cess and inflammatory cellular infiltration), there continues to be insufficient attention to "spontaneous" enteritis and colitis in animals, a potentially useful source of clues to human IBD.

TABLE 1

NATURALLY OCCURRING INFLAMMATORY BOWEL DISEASE IN ANIMALS

Animal	Description	Cause
Dog	Terminal ileitis, perianal fistulas	Unknown
Dog	Chronic, histiocytic canine colitis	Unknown
Horse	Toxic colitis	?Endotoxin
Horse	Granulomatous ileitis	Unknown, but Mycobacterium avium isolated in one case
Cattle	Ileitis, colitis	Mycobacterium johnei
Pig	Terminal ileitis, occasionally colon	Unknown
Hamster	Ileitis	Transmissible agent from diseased tissue. Slow lactose-fermenting E. coli cultured
Rat	Cecitis	Unknown
Mouse	Colitis with rectal prolapse	Citrobacter freundii
Gibbon	Acute colitis	Associated with stress
Gorilla	Acute colitis	Associated with stress
Cotton Top Marmoset	Acute colitis	Complicated by colon carcinoma

Experimental IBD - The small intestine and the large intestine of the experimental animal are readily damaged by a wide variety of injurious agents; but animal models of chronic, self-perpetuating ulcerative colitis or Crohn's disease have not been reproduced (Table 2). The colitis induced by the mucosal or serosal application of a 10% solution of acetic acid and by enema in the rat generates a sequence of inflammatory mediators from the arachidonic acid cascade, resembling the pattern of human ulcerative colitis and inhibited by the anti-prostaglandin E2, indomethacin. The findings are non-specific and probably can be observed in many forms of bowel injury. The experimental circumstances of the colitis induced by carrageenan in the guinea pig, involving Bacteroides Vulgatis, responding to metronidazole, are too extreme to compare with human IBD. A granulomatous enterocolitis has been induced in rabbits by the mesenteric intra lymphatic injection of dilute formalin solution, characterized by ulcerations, granulomas, fistulas and hyperplastic lymphoid tissue, but the approach is unusual and the process, while it directs attention to the gut lymphoid apparatus, does not duplicate Crohn's disease. Colonic inflammation has been induced experimentally by bacteria and bacterial products, including an acute colitis in rhesus monkeys (Shigella flexneri), a granulomatous ulcerative proctocolitis in cynomolgous monkeys (human isolates of serotypes of LgV-2 trachomatis, and a tissue reaction resembling regio-

nal enteritis in goats fed a mycobacterial variant (mycob. Linda). A granulomatous enterocolitis has been induced in Sprague-Dawley rats by the intestinal subserosal and intramural injections of an aqueous suspension of group A and group D streptococcal cell wall peptidoglycan-polysaccharide fraction. The process may continue for three to six months, but does not replicate human IBD. The peptido-glycan polysaccharide complex, together with lipopolysaccharides, may be involved in the development of some of the extraintestinal complications of IBD (E. Bruce Sartor, personal communication, 1985).

TABLE 2

EXPERIMENTAL INJURY TO BOWEL

Vitamin deficiency	A, Folic acid, Pantothenic acid
Bacteria, viruses	Shigella, Salmonella, Spirochetes E. Coli, Citrobacter, TGE virus Peptidoglycan Polysaccharides intramurally
Bacterial anaerobes	Carrageenan (B. Vulgatis)
Bact. Endotoxins	Shiga, Staph
Enzymes	Collagenase, Lysozyme, Trypsin
Chemicals	Acetic acid (10%), Ricin Phenylbutazone
Pharmacologic	Adrenaline, Histamine, Cholinergics
Vascular ischemia	Circulating insufficiency, Microspheres I.V.
Lymphatic obstruction	Silica oral, Formalin intralymph.
Neurogenic	CNS stimulation (monkey) "Stress" (gibbon)
Immunologic	Arthus, Immune complex (Auer-Kirsner) Shartzman, DNCB, Runt D.
Animals	Rabbit, Dog, Guinea pig, Pig, Monkey Mouse, Rat, Chinchilla, Hamster

Since ulcerative colitis in the colon and Crohn's disease in the small and large intestine, originate in areas populated by large amounts of aerobic and anaerobic bacteria in the lumen and attached to the epithelium, a microbial contribution to their development seems likely. Additional transmission studies introducing ileostomy dejecta into jejunal fistulas of the chimpanzee have been suggested. Similar experiments utilizing surgically constructed ileocolonic pouches in dogs in our laboratory many years ago failed. The ideal experimental circumstances, i.e. appropriate test animal (perhaps primate) with the necessary host (genetic?) vulnerability and the altered immune responsiveness, probably have not yet been identified. Apart from the production of an enteritis or colitis, the experimental challenge also must include a mechanism for self-perpetuation of the inflammatory process, a characteristic of human IBD. This objective may be impossible, given the multifactorial (including psychosocial) nature of human illness.

Microbial possibilities - As emphasized frequently in the past, the clinical and pathological features of ulcerative colitis and Crohn's disease are compatible with an infection, but extensive microbiological search has

been unproductive. Both diseases are mimicked by known infectious agents, i.e. shigella, campylobacter and salmonella dysentery for ulcerative colitis and yersinia and chlamydia for Crohn's disease. Studies since the 1930s have implicated a wide variety of organisms, beginning with the diplostreptococcus and subsequently including cell-wall deficient bacterial L forms, chlamydia trachomatis, mycoplasma, Esch. coli, bacterium morgagni, histoplasmum capsulatum, K1 pneumoniae, Ps. aeruginosa, Sph. necrophorus, Cl. perfringens, shigella, lymphopathia venereum virus, and cytomegalovirus. In each instance, an etiologic relationship could not be established.

The recognition of new microbial causes of entero-colitis, unrelated to IBD, in recent years - Yersinia pseudotuberculosis, campylobacter SSP jejuni, E. coli 0157.H7, plesiomonas shigelloides, Edwardsiella tarda, aeromonas hydrophilia and cryptosporidia - has rekindled interest in the possible role of micro-organisms, their components and their metabolic products (endotoxins, hemolysins, neurotoxins) in the pathogenesis of IBD.

Mycobacterium Linda is the latest microbe to attract attention. This organism does not conform to any of the presently recognized species of mycobacteria, though closely resembling mycobacterium paratuberculosis. Stringent, selective techniques have been necessary to recover this organism. Patients with Crohn's disease have a statistically significant increase in antibody titers to M. paratuberculosis, compared to healthy controls, but the significance of this finding awaits more study. The mycobacterium has been isolated from four patients with Crohn's disease and the spheroplasts from 12 additional patients. The organism is pathogenic on mice, not rats, guinea pigs, rabbits or chickens. The oral administration of this mycobacterium to young goats, after periods up to 12 months, has produced a non-caseating tuberculoid granulomatous inflammation in the distal small bowel. Mycobacterium "Linda" apparently as recovered from all of the inoculated goats and from none of the controls. Mycobacteria Linda also can infect primates, suggesting a more appropriate animal model than the young goat.

Inflammatory bowel disease is not epidemic, contagious or related to recognizable acute viral enteritis. Time-space clustering of IBD patients implicating an external source of infection (e.g. contaminated water or food supply) has not been recorded. The later development of either ulcerative colitis or more often Crohn's disease in the initially healthy mate of an IBD patient suggests the transmission of some kind of infectious agent. However, neither ulcerative colitis nor Crohn's disease occur with increased frequency among physicians (gastroenterologists) and nurses in closer contact with IBD patients than the general population. The systemic distribution of granulomatous lesions (face, larynx, muscle, bone, lungs, blood vessels) noted occasionally in Crohn's disease suggests a "lowgrade" systemic "viral" infection. However, extensive multicenter attempts to demonstrate a viral agent by transmission experiments have been unsuccessful. Electron microscopy and molecular hybridization techniques have failed to demonstrate adenovirus DNA in resected Crohn's disease tissue. Extra-chromosomal viral DNA (representing parvoviruses, herpes viruses and retroviruses) was not demonstrable in mesenteric lymph nodes from patients with Crohn's disease. Also, no evidence was obtained for nucleic acid containing antigens of viral or microbial origin in Crohn's disease mesenteric lymph nodes. Further, there is no serologic evidence for excessive exposure of IBD patients to specific viruses, including reovirus, rotavirus, Norwalk agent, cocksackie, adeno, echo, measles, mumps and Epstein Barr virus. The increased titers to cytomegalovirus in severe ulcerative colitis and Crohn's disease, reflect the diminished immunocompetence and

increased host vulnerability of malnourished, seriously ill patients.

Despite the negative or indecisive microbiological studies, continued studies in this area seem desirable. More complete characterization of the gut aerobic and anaerobic microflora, clarification of the mechanisms of bacterial-viral entry, continued search for pathogenic strains of E. Coli specific to ulcerative colitis or Crohn's disease, adherence and penetration of the intestinal epithelium, search for viruses or perhaps viroids (low molecular weight RNA) and prions (infectious glycoprotein particles, molecular weight 27,000-30,000), possible structural or ultramicroscopic defects in the intestinal mucosa, are among the problems to be investigated. The possible involvement of bacterial toxins acting via cyclic nueclotides, and of components of the bacterial cell wall entering the bowel wall via a defect in the epithelial barrier requires further examination. The granulomatous inflammation of the intestine induced by the peptide-glycan-polysaccharide complex of group A and D streptococcus has been noted. The earlier demonstration from our laboratory of diamino pimelic acid, a constituent of the cell wall of many gram-negative bacteria, in the rectal wall of patients with ulcerative colitis, and the increased titers of antibodies to lipid A, a common component of the endotoxin complex of all gram negative bacteria, in active Crohn's disease (not ulcerative colitis) would suggest that penetration of the bowel wall by bacterial elements and the intramural incorporation of "foreign protein" may not be unusual in IBD. It also may be of interest to compare the Das 40kd protein colon antigen with such intramurally located bacterial components.

Immunologic aspects - experimental immune reactions - Immunologic interest in ulcerative colitis and Crohn's disease derives from the rich immunologic resources and the immunologic responsiveness of the gastrointestinal tract to varied antigens, the not uncommon personal and family histories of allergic disorder, the many associated immunologically-mediated conditions, the immune-related concomitants, and the favorable therapeutic response to adrenocorticotropin and adrenal corticosteroids and to other modulators of the immune system (6 mercatopurine, azathioprine and possibly cyclosporine). Experimentally, all known tissue immunological reactions can be reproduced in the small intestine and the colon, including an acute allergic enteropathy with release of intestinal mast cell histamine. However, many immunologic attempts to reproduce ulcerative colitis or Crohn's disease have been unsuccessful. The colitis induced in animals skin sensitized to DNCB when given DNCB rectally documents the response of the colon to cell-mediated immune injury. Synthesis of PGE_2 and 5-HETE is increased in the DNCB colitis induced in rabbits, as in human ulcerative colitis. The Auer-Kirsner colitis induced in rabbits by the localization of antigen-antibody complexes within the colon (crystalline egg albumin), after mild irritation of the rectum with a very dilute formalin solution, confirms the tissue damaging effects of immune complexes. A more chronic colitis of this type has been provoked in rabbits, first immunized with the common enterobacterial antigen of Kunin, by the injection of soluble immune complexes (human serum albumin - antihuman serum albumin) after mild irritation of the rectum.

"Autoimmunity" - A major defect of the experimental attempts to reproduce an "autoimmune" human IBD is lack of knowledge as to the nature of the human bowel antigen(s) presumably responsible for inducing an "autoimmune" colitis. The detection and partial characterization of a colonic glycoprotein antigen (colonic 40kd protein) specifically recognized by ulcerative colitis tissue bound IgG antibody; and an antigen specific to Crohn's disease produced three to four months after injection of a Crohn's disease tissue filtrate into nu/nu mice, present in normal and in hyperplastic

lymph nodes and localized in macrophages and B cell lineage cells (K.M. Das) are therefore intriguing observations requiring confirmation in other laboratories and further study.

The observations that IBD sera and intestinal mucosa-derived mononuclear cells are reactive with intestinal epithelial cell-associated components of murine origin now have been extended to surgically-resected macroscopically normal colonic mucosa, and suggest that antigen-specific cell-mediated mechanisms may play a role in ulcerative colitis (and perhaps Crohn's disease). In view of the intricate compartmental organization of the cell and its countless functions, including the processing of thousands of proteins, the foregoing observation may be regarded as an introductory approach to the extremely complex problem of cellular antigens.

Humoral immunity - The many studies of humoral immunity in ulcerative colitis and Crohn's disease, including measurements of serum immunoglobulins, agglutinins against various bacteria, and antibodies to a wide variety of antigens, including intestinal basement membrane, have yielded variable results, not correlating with the age or sex of the patient, a family history of IBD or with the site, extent, duration or activity of IBD. The anti-epithelial cell antibodies demonstrable in occasional IBD patients lack disease specificity, do not produce cell damage and have been ascribed to the excessive exposure of the mucosal immune system to bacterial antigens which induce synthesis of antibodies cross-reacting with antigen specificities on intestinal mucus glycoproteins. A subset of patients with ulcerative colitis secondarily develop hyposplenism, decreased reticulo-endothelial function and increased vulnerability to infection. The pathogenesis of this "secondary" phenomenon remains to be clarified. An antecedent abnormality in humoral immunity has not been demonstrated in IBD and apparently has not been investigated among as yet unaffected members of IBD families.

Similarly, there are no prior demonstrable deficiencies in the major components of complement in IBD. Numerous alterations in various constituents of complement are noted during active disease; they return to normal upon subsidence of the disease and thus behave as acute phase reactants. The increased frequency of the F and FS phenotypes of C3 (C3F, C3FS) in patients with Crohn's disease of the small intestine (not in Crohn's disease of the colon) is an interesting unexplained observation from Denmark. Subnormal generation of chemotactic activity by the alternative pathway has been reported among families with Crohn's disease, but its relationship to the pathogenesis of the bowel disorder is not known.

Immune complexes induce tissue injury by the activation of complement, release of lysosomal enzymes and activation of the arachidonic acid cascade. Immune complexes are heterogeneous, and different assay techniques have yielded variable and negative results in IBD. At present, an etiologic role for immune complexes in IBD cannot be postulated. If immune complexes could be demonstrated consistently, they might be isolated for analysis of their composition, especially the nature of the antigen. The abnormal clearance of immune complexes from the circulation of patients with primary sclerosing cholangitis is of interest because of the not in-

frequent association of PSC with ulcerative colitis.

Circulating lymphocytes - The numbers and proportions of circulating T and B lymphocytes probably are within the normal range. The minor fluctuations reported bear no relationship to the site, activity or duration of the disease as to therapy and probably reflect varying methodology and patients studied. The response of circulating lymphocytes to various mitogens also is highly variable. Lymphocytic reactivity is diminished nonspecifically in a wide variety of circumstances (e.g. malnutrition, zinc and folate deficiencies, emotional depression, smoking, surgical procedures and pregnancy). Antibody production by circulating B lymphocytes secreting tetanus-specific IgG after the administration of tetanus toxoid is apparently decreased both in patients with ulcerative colitis or with Crohn's disease. These patients similarly failed to produce an IgG antidiphtheria antibody response after immunization. This humoral defect apparently was corrected by the administration of 6MP.

Peripheral T lymphocytes from patients with ulcerative colitis and with Crohn's disease may demonstrate decreased production of interleukin-2 and a diminished response to IL-2, unrelated to disease location or activity. Interestingly, normal human colonic lymphocytes also may manifest a reduced response to interleukin-2.

A suppressor T cell in the peripheral blood, capable of completely suppressing immune globulin synthesis in cultures of normal B and T cells, sufficiently potent to induce hypogammaglobulinemia, has been demonstrated in two patients with Crohn's disease. After thorough purification of the patient's B cells, their capacity to synthesize immunoglobulins was regained.

Lymphocyte cytotoxicity - The in vitro cytotoxicity of circulating Fc-receptor lymphocytes for autologous colonic epithelial cells from patients with ulcerative colitis or Crohn's disease is specific for IBD and for colonic epithelial cells. However, the lymphocyte cytotoxicity bears no relationship to the extent or severity of IBD and it disappears after medical or surgical control of the disease. The nature of this phenomenon has not been further investigated and its significance in IBD remains obscure.

Gut-immune events - Since studies of immune components and immunological events in the peripheral circulation do not necessarily reflect immunological activities in the target organs of IBD, the small intestine and the colon, attention has been directed increasingly to studies of isolated lamina propria T and B lymphocytes and macrophages. Gut lymphocytes represent a population of cells different from lymphocytes in the peripheral circulation. In vivo distribution and relative proportions of in vivo and isolated gut lymphocyte subsets do not differ between IBD and controls. No consistent differences of immunoregulatory function have been detected between gut lymphocytes of IBD and controls. The many current observations are too variable for definitive interpretation (Table 3). The increased immunoglobulins, T and B lymphocytes and immune complex deposition in IBD bowel probably represent an appropriate tissue reaction to the inciting agent or mechanism, but diagnostically destructive patterns have yet to be documented. Antigen-processing in the gut wall probably is greatly increased in chronic inflammatory bowel disease and the question as to whether the gut immune apparatus is overly burdened awaits study. The role of the intra-epithelial lymphocytes, situated directly in line with macromolecules in transit across the epithelium and increasing in various diseases, remains to be explored.

The local production and the epithelial transport of IgA apparently are unimpaired in IBD. Spontaneous secretion of IgG is markedly increased by

ulcerative colitis intestinal mononuclear cells and moderately elevated by Crohn's disease intestinal mononuclear cells. Interleukin-2, a soluble product of activated T lymphocytes, important in the development of an appropriate T cell immune response, as measured in cultures of intestinal mucosal mononuclear cells derived from patients with ulcerative colitis or Crohn's disease, is decreased significantly. This finding is unrelated to the duration of the disease or to steroid therapy; if confirmed, it would indicate a defective gut immune response in IBD.

The expression of HLA-DR+ antigens by colonic epithelium in both active ulcerative colitis (9 of 13 patients) and active Crohn's disease (11 of 12 patients) (together with the expression of T9 activation antigen on peripheral lymphocytes in Crohn's disease) suggest cell-mediated immune mechanism in IBD.

TABLE 3

GUT-ASSOCIATED IMMUNE EVENTS
IN INFLAMMATORY BOWEL DISEASE

Intraepithelial lymphocytes -	T cells (OKT8+ suppressor-cytotoxic phenotype) Null cells B cells (?)
Lamina propria lymphocytes -	(40% OKT8+) T cells (OKT8- :OKT4+helper phenotype) B cells (IgA) Null cells Macrophages (HLA-DR)

IgA, IgM, IgG immunocytes increased (nonspecific)

Local production, epithelial transport of IgA, IgM Unimpaired

T.B null cells -	Normal Increased Decreased

Normal immune competency gut mucosal lymphocytes

Colonic mucosal mononuclear cells (macrophage depleted)
Cytotoxic for autologous colon epithelial cells (Ulc. colitis)

Lamina propria lymphocytes - "Specific immune reactivity"
to rat intestinal epithelial antigens

C_1, C_3, IgG (immune complexes) in Ulc. colitis

Degranulated eosinophils, basophils, mast cells

Immunoregulatory activity - Genetically-mediated or acquired imbalances in immunoregulatory cellular activity, T lymphocytes for cell-mediated immunity, B cells for humoral immunity, and macrophages, crucial in antigen presentation and lymphocyte activation, enhance the expression of damaging auto-immune reactions and are characteristic of classic experimental and clinical autoimmune diseases (e.g. systemic lupus erythematosus). The genetic control of immune responsiveness includes cell interaction (C1) genes, controlling macrophage-lymphocyte, and T-T and T-B lymphocyte interactions and also coding for molecules active in enhancing and suppressing immune

responses, and immune response (Ir) and immune suppression (Is) genes. Immune response genes (Ir) determine the ability of an individual to respond to a given antigenic determinant. Immuno-suppressive (Is) genes control stimulation of specific suppressor T lymphocytes.

Disorders of immune regulation involving alterations in any of these mechanisms are characterized by excessive antibody response, unregulated formation and deposition of immune complexes, Fc membrane receptor defects and defective clearance of immune complexes. Such studies in IBD have been undertaken only recently and the data are insufficient for definitive evaluation. Though decreased T suppressor cell activity in the gut and in the peripheral circulation would be a plausible mechanism for an immune-mediated IBD tissue reaction, a possible defect in immunoregulation in the pathogenesis of IBD is yet to be demonstrated conclusively. The sensitization to colonic epithelial cell antigens displayed by IBD intestinal mucosa-derived mononuclear cells provides some evidence for antigen-specific cell-mediated mechanisms in the pathogenesis of IBD. Helper to suppressor T cell ratios are comparable to those in individuals with other illnesses. The presence, proportions and the possible role of the so-called "switch T cells" are yet to be fully determined. In one study, patients with mild Crohn's disease manifested an increased suppressor cell activity in vitro, correlating with a subset of lymphocytes possessing an HNK-1+ Leu 2a+ phenotype. In other studies, no primary immunoregulatory defect was identified in the peripheral blood of patients with Crohn's disease in remission. Selective, modest defects in the suppression of the proliferative activity of various lymphocyte populations were restricted to active disease (non-specific Ts cell assays); re-emphasizing their secondary nature.

Systemic host defences - Defects in host defences contributing to the vulnerability of the IBD patient have been suspected for many years but remain to be fully investigated. The earlier emphasis upon an increased frequency of rheumatic fever among IBD families and the recent indication of an unusual incidence of eczema among children with IBD might suggest some kind of pre-determined susceptibility; but this possible relationship is speculative. Studies of neutrophil chemotaxis and phagocytic activity have been reported variously as normal or decreased. Impaired adherence and chemotaxis of polymorphonuclear cells during the quiescent stage of IBD has been implicated in the development and potentiation of the inflammatory process through decreased phagocytosis and ineffective removal of potentially injurious substances by the scavenger cells. Defective neutrophil function has been described more often in Crohn's disease, as manifested by increased intracellular survival of staphylococcus aureus, impaired glucose-1-14_C-metabolism of granulocytes and diminished staphylococcus-induced granulocyte chemiluminescence response. The increased metabolic activity of IBD polymorphonuclear cells in some studies has been interpreted as consistent with increased phagocytic activity, probably in response to established active disease. Other studies indicate a defect in neutrophil oxidative metabolism (diminished superoxide anion, hydrogen peroxide and superoxide dismutase) but the significance of this finding is not known. The defective chemostactic responses noted occasionally in IBD also may be attributable to circulating inhibitors of cellular response. No significant defect in granulocyte migration to diseased tissue has been demonstrated.

Monocytes participate in host defences through processes of phagocytosis, intracellular killing and the action of lysosomal enzymes. The studies of monocyte activity in IBD, while suggesting increased activity, are too few

for evaluation.

Macrophages participate in host defences through direct inactivation of ingested microorganisms, microbial and cytostatic activities and participate in the effector limb of the immune response as an accessory and regulatory cell for T cells, B cells and natural killer cells. Macrophage secretory products include lysosomal enzymes, mediators, enzyme inhibitors, many complement components, interferon, and products of arachidonic acid metabolism (e.g. prostaglandins and interleukins activating T lymphocyte responses). Macrophage secretion of neutral protease plasminogen activator is increased in IBD, especially in untreated patients, but studies of circulating and intestinal macrophages as yet are too few for evaluation.

Immunological overview - There is no evidence at present for an antecedent abnormality in immunologic homeostasis preceding the onset of either ulcerative colitis or Crohn's disease, nor has this important question been investigated. No decisive evidence has been advanced for any of the customary theories of autoimmunity (altered T suppressor/helper cell proportions, macrophage defects, polyclonal B cell activation, release of sequestered antigens or abnormal immune response genes). Specific autoimmune reactions have not been demonstrated in ulcerative colitis or Crohn's disease, although the "specific" tissue bound proteins described by Das are of interest. There is no evidence of a consistent antecedent deficiency as reflected in studies of humoral and cell-mediated immunity in IBD. Most if not all of the immunologic phenomena, appearing with active IBD (often independently of the type, severity, extent and duration of the disease), subsiding with its remission, and not demonstrable as antecedents either of the initial onset or the subsequent exacerbations appear to be epiphenomena. The immunologic abnormalities often can be related to associated nutritional deficiencies (e.g. decreased lymphocyte reactivity in protein-caloric malnutrition, impaired natural killer cell activity and increased monocyte cytotoxicity associated with zinc deficiency). A recent Japanese study of moderate Crohn's disease did not reveal evidence of humoral and/or cellular immune dysfunction. Differences in methods of study, technological limitations, insufficient knowledge, and the study of small groups of incompletely characterized patients account for many of the variable immunologic observations in IBD. Nevertheless, immune reactions are fully capable of inducing tissue damage in the digestive tract and, in conjunction with other mechanisms (e.g. mast cell degranulation, Paneth cell secretion, release of inflammatory mediators) they undoubtedly contribute to the IBD tissue reaction.

Many immunologic aspects of IBD require further investigation: the possible role of the intraepithelial lymphocytes, the M cell and the non-lymphocytic dendritic or veiled cell in antigen transit and processing through the intestinal epithelium, possible defects (structural, immunologic) in the integrity of the intestinal and colonic epithelium, increased paracellular permeability secondary to reactive oxidant injury, excessive antigen (bacteria, food, other) entry into the bowel mucosa with excessive demands upon the gut immune system, possible defects in the gut immune apparatus per se, genetic control of immune responses at mucosal surfaces (Class II MHC molecules, immunoglobulin heavy chain gene complex), regulation of intestinal antibody synthesis, lamina propria T cell regulation of IgA response, the role of "switch" T cells, the functional activities of the regulatory T4 and T8 subsets from the IBD lamina propria, lymphokine regulation of cellular immunity in the intestine (interleukins 1,2,3, gamma interferon) and the immune responsiveness of IBD patients to

orally introduced antigen.

Genetic considerations - Genetic factors play a role in many autoimmune disorders and, therefore, have been implicated in IBD. Ulcerative colitis and Crohn's disease are not classic genetic disorders and faulty structural genes or DNA polymorphisms have not been described. There is no association with specific ABO, MN, Rh or other blood groups, glucose-6-phosphate dehydrogenase activity, and the secretor-non-secretor frequencies do not differ from population controls. Abnormal immunogenetic mechanisms, as described in the neonatal lupus syndrome, are not present in IBD. There is no strong association between ulcerative colitis or Crohn's disease and any particular A or B antigen comparable to that of HLA-B8 with celiac disease. However, multiple familial occurrences are noted throughout the world in approximately 20 percent of patients with ulcerative colitis and up to 40 percent in Crohn's disease, including a high degree of concordance of Crohn's disease amongst monozygotic twins. Parent-child and sib-sib combinations are noted more commonly than those involving more distant relatives. As many as 8 people in a single family have been affected. Ulcerative colitis is more common in families with probands with ulcerative colitis and Crohn's disease is more common in families of probands with Crohn's disease; but the two illnesses are intermingled in approximately 25 percent of IBD families. In a study of 10 families in which 32 cases of IBD, 3 of 4 affected sib pairs with identical HLA haplotypes had similar disease patterns. The remaining HLA identical pair had one sib with Crohn's disease of small bowel and other with ulcerative colitis. In 6 of the 10 families, those affected all had Crohn's disease or all had ulcerative colitis. In the other 4 families, the two diseases were intermingled. The specific risk to first, second and third degree family members appears to be quite low. The occurrence of IBD in family members born in different geographic areas or living apart for long periods tends to exclude a common environmental factor. A common environmental factor may be associated with Crohn's disease in that serum antibodies from both Crohn's disease patients and their household members react with murine lymphoma induced by Crohn's disease tissue filtrates. The increased frequency of ankylosing spondylitis - an established autosomal genetic disorder - in IBD patients with the HLA-B27 haplotype and the association of IBD with such genetic disorders as the Hermansky-Pudlak syndrome, with psoriasis (Crohn's disease), with the Turner syndrome characterized by an abnormal X chromosome and the familial occurrences of both ulcerative colitis and primary sclerosing cholangitis further implicate genetically mediated mechanisms. The psoriasis in Crohn's disease often precedes gastrointestinal symptoms; and has been associated with an increased incidence of the HLA-A1, B17 and DR7 haplotype and with diminished levels of properdin in the alternate complement pathway. "Familial" Crohn's disease is probably more common among Jews and tends to be more severe than the "non-familial" disease.

Clinical studies indicate that fecal Klebsiella possessing antigens which resemble HLA-B27 can be isolated more readily from patients with ankylosing spondylitis during active phases of the disease. The cross-tolerance hypothesis proposes that ankylosing spondylitis is a reactive arthritis following infection by gram negative bacteria (e.g. Klebsiella) and tissue damage is produced by antibacterial antibody binding to cross-reacting self-antigens.

The nature of the genetic influence in IBD, possibly an immuno-regulatory defect associated with a particular histocompatibility haplotype (e.g. C2 deficiency associated with the HLA-A_{10} and HLA-B_{18} haplotypes), is not known. One concept categorizes ulcerative colitis and Crohn's disease as

prototypes of a single disease process (one genotype) encompassing several intermediate tissue reactions; with two polygenic systems determining liability and possessing genes in common. The presence of only a few of these genes pedisposes to ulcerative colitis; whereas a more complete genotype predisposes to Crohn's disease.

Genetically determined differences in the regulation or specificity of host immune responses may influence susceptibility to IBD, with a mixture of environmental causes responsible for initiating the disease. The exact role of HLA gene products in the development of IBD, whether they are associated directly or indirectly with autoantibody production or with other interactions of cells of the immune system, is yet to be determined. Immune response and immune suppression genes are linked to HLA. HLA antigens are similar structurally and antigenically to etiologic agents and altered HLA patterns may be responsible for deficiencies in complement components, altered immunity to viral infections and for defects in cytotoxic mechanisms and immune reactivity. Genes linked to the immunoglobulin heavy chain allotype locus on chromosome 14 could govern host immune responses to as yet undefined antigens; and alterations in Gm increased frequency of the phenotype Gm (a,x,f:b,g and the haplotype $Gm^{a,x;g}$) have been reported in Crohn's disease, not ulcerative colitis, associated with a 3-fold increased risk of developing Crohn's disease (Kagnoff et al.).

HLA surveys from different geographic areas have yielded highly variable results; and no evidence for a universal and distinctive histocompatibility pattern for IBD has yet emerged. Studies to date fail to demonstrate a significant association between IBD and a single HLA-A,B or C specificity (Class I) or between a single HLA-D gene product (Class II). Despite the inconsistent data obtained thus far, further study of the possible association between the MHC and IBD particularly in the regulation of MHC Class II gene expression in desirable. Knowledge of the immune response genes and the technology for identifying gene abnormalities (e.g. gene complementation, negative (protective) gene associations, retroviral genomes in genes, genes controlling the body's immune defence system, new markers for analysis of the MHC, and identification of gene products of DR and other regions of the MHC) is expanding rapidly.

Proposed pathogenesis of IBD - Ulcerative colitis and Crohn's disease probably are distinct but "distantly related" prototypes of a disease process with limited morphologic expressions of the small and large intestine to the etiologic agent(s); and consequently characterized by overlapping morphological and biological features. The principal events in this pathogenetic process are a genetically mediated deregulation of immune response genes initiating an abnormal response to various antigens (perhaps defective clearance of damaging antigen-antibody complexes); or a genetically mediated alteration in MHC determinants on colonic epithelium, (e. g. aberrant expression of DR antigens on intestinal/colonic epithelial cells), facilitating the production of clones of damaging T and/or B cells, "priming of the gut," i.e. early sensitization of the gut-associated lymphoid tissues to microbial (enterobacterial?) viral, dietary or other antigens, gaining entry perhaps via the M cell at the time of early weaning, to initiate a secretory immune response; damaged intestinal-colonic defences (e.g. defective mucus layer, deficient IgA, increased permability of the M cell, macrophage defects); increased vulnerability to subsequent inciting events (e.g. antigen overload, acute bacterial or viral infections, antibiotics, oral contraceptives, vascular ischemia, stress); rechallenge of the gut-associated lymphoid tissue (via the interaction of antigens with sensitized mononuclear cells producing natural killer cy-

toxic cells; with loss of normal gut immunoregulatory capacity, this sequence of "preparatory" and "inciting" events probably involving multiple antigens, initiating and establishing the tissue reactions of inflammatory bowel disease, to which mast cells, Paneth cells, inflammatory mediators (e.g. prostaglandins, leukotrienes), lymphokines, among other substances, contribute. This overview thus suggests that ulcerative colitis and Crohn's disease are not necessarily uniform diseases but develop from the complex interaction of multiple antecedent circumstances and multiple pathogenetic mechanisms; with the tissue expression of each disease dependent upon the limited morphologic responses of the small and the large bowel (Table 4).

TABLE 4

PROPOSED PATHOGENESIS OF "IDIOPATHIC" INFLAMMATORY BOWEL DISEASE

Genetically-vulnerable individual (systemic, G.I.)

Abnormal immune response genes

Early immunologic priming of gut-associated lymphoid tissue (microbial, dietary, other antigens)

Impaired intestinal, colonic defences - antigen access (mucus, IgA, defective T cell regulation, M cell)

Environmental precipitants (bacteria, mycobacteria, viruses, stress, drugs)

Reactivation of sensitized G.I. mononuclear cells

Immune-initiated IBD, (antibodies(?), Ag/Ab complexes, NK cells, macrophages)

Secondary contributions (mast, Paneth cells, leukocytes)

Finally, although the cause(s) and the pathogenesis of ulcerative colitis and Crohn's disease remain elusive and although the concepts elaborated herein undoubtedly will be modified by new knowledge from molecular biology, immunology, hybridoma technology, molecular genetics and the neurosciences, the non-specific inflammatory bowel diseases today rank as one of the major clinical problems of medicine, challenging not only gastroenterologic investigators, internists and surgeons, but also scientists in all disciplines (Table 5). Their ultimate clarification will increase the understanding of not only gastrointestinal function in health and disease, but also important medical problems beyond the gastrointestinal tract.

TABLE 5

FUTURE RESEARCH IN INFLAMMATORY BOWEL DISEASE

Clinical:	Epidemiology, demography Diagnostic, Severity Criteria "Biological Markers"
Experimental:	Animal models Marmoset Colitis
Microbial:	New Bacteria, Mycobact. Viral Pathogens, "Viroids," "Prions"
Inflammation:	Inflammatory Mediators Intestinal Macrophage, Mast, Paneth, Eosinophil Cell Contributions
Psycho-neurogenic:	Brain-gut-immune Interactions (Peptides)
Immunological:	* Specific Antigens-intestinal "Autoimmunity" Immune Regulatory Activity
Host, G.I. Defences:	Intestinal Biologic, Structural Defects Intestinal "M", "Veiled" Cells Neutrophil, Monocyte Functions
Genetic:	Role in Immune Response, Immune Regulation Gene-viral Interactions
Therapeutic possibilities:	Anti-inflammatory Mediators Monoclonal Antibodies vs. Cytotoxic Lymphocytes

* Epithelial Cells, Intestinal Basement Membrane, Colon Protein (?)