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CROHN'S DISEASE - CURRENT VIEWS ON AETIOLOGY AND ITS IMPACT ON MANAGEMENT

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Crohn's disease was probably first described by Dalziel in 1913[1] and its cause remains obscure despite years of research. It was so called following the description of several similar cases affecting the distal ileum in young people by Crohn, Ginzburg and Oppenheimer in New York.[2] Over the last few years, useful information generated from advances made in research on genetics and immunology has accumulated. The rapid growth in knowledge in this area raises the hope that a cure for this disease may be found soon.

Crohn's disease is common and can affect any part of the gastrointestinal tract from the mouth to the anus. The terminal ileum and ileo-caecal region are the commonest sites, with the inflammatory process being restricted to the colon in about 20% of cases. It has an approximate incidence of 2-4 cases/100,000 population/year.[3,4] A steady increase in incidence was observed between the mid-1950s to mid-1970s but this trend has recently plateaued.[5,6] Crohn's disease tends to affect females more frequently than males.

The disease occurs at any age but presents mostly between the ages of 20 and 60 years. It is especially prevalent in the developed countries, occurring more commonly in the white population and also in Jews born in Europe or North America.[7] No particular occupational group is affected preferentially, but the disease tends to occur more frequently in people of a higher socio-economic grouping.[8] Overall the disease may be less common in country dwellers.[9,10]

A typical history includes abdominal pain, diarrhoea, weight loss or rectal bleeding. A family history of inflammatory bowel disease is often elicited.[11] The patient may look pale and unwell, and be malnourished; oral ulceration, a right *iliac fossa* mass or perianal disease are other presenting features. The platelet count and inflammatory parameters are frequently elevated and an iron deficiency anaemia is often present. Endoscopic examination can reveal patchy ulceration in the small and large bowel with unaffected 'skip' lesions; sometimes the mucosal changes are more subtle. Later in the disease a cobblestone appearance can be seen.[12,13]

Histology shows typically a transmural infiltrate of lymphocytes, plasma cells, macrophages and eosinophils with the formation of non-caseating granulomas in 68% of cases. A small bowel enema may show rosethorn, aphthous or linear ulceration, (Figures 1a, 1b, 2) or fistulation (Figures 3, 4, 5). Ultrasound can be useful to investigate a right *iliac fossa* mass (Figure 6). A labelled white cell scan is particularly helpful if other investigations are negative (Figure 7). This involves labelling neutrophils with 99-technetium linked to a carrier hexamethylpropyleneamine oxime (HMPAO) and re-injecting the white cells into the patient. The autologous leukocytes migrate preferentially to areas of active inflammation.[13] Further studies on imaging are being carried out at the Royal Postgraduate Medical School in London, involving the

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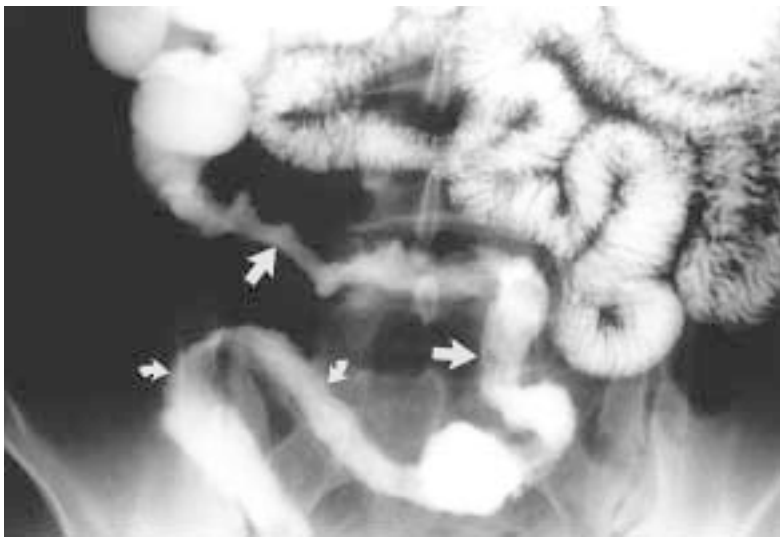

FIGURE 1a
Small bowel enema. Note the normal appearance to the jejunum and proximal ileum. There is extensive Crohn's disease of the mid ileum with a long stricture of variable calibre (arrows) with associated bowel loop separation.

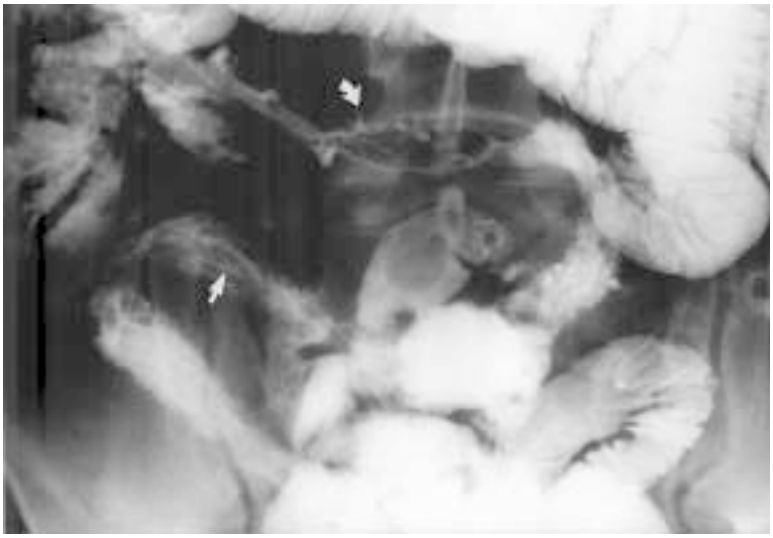

FIGURE 1b
Further view from same patient showing double contrast view of the diseased segment. This identifies rosethorn ulceration (curved arrow) and linear ulceration (straight arrow) within the diseased segment. This later film shows more distal small bowel loops within the pelvis which are filled and are not diseased.

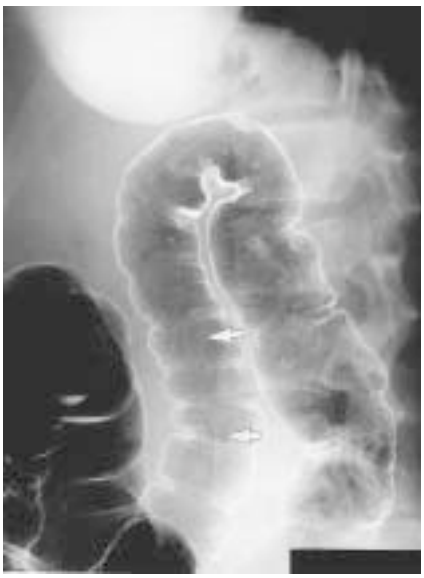

FIGURE 2
Double contrast barium enema - spot view of splenic flexure. Throughout the visualised colon there are multiple small niches of barium, many of which have a surrounding radiolucent halo (arrows) typical of extensive apthous ulceration in Crohn's colitis.

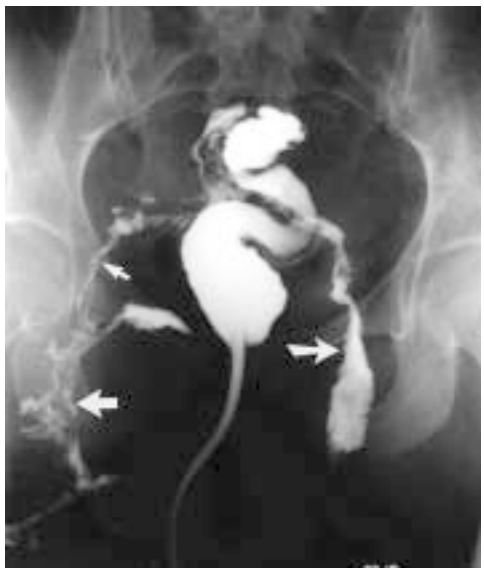

FIGURE 3
Single contrast barium enema/proctogram in patient with Crohn's disease with a watering can perineum/severe perianal fistulation. Contrast has been introduced into the rectum with a Foley catheter. Multiple fistulating tracts are seen extending from the rectum into the pelvis and ischio-rectal fossae bilaterally (arrows).

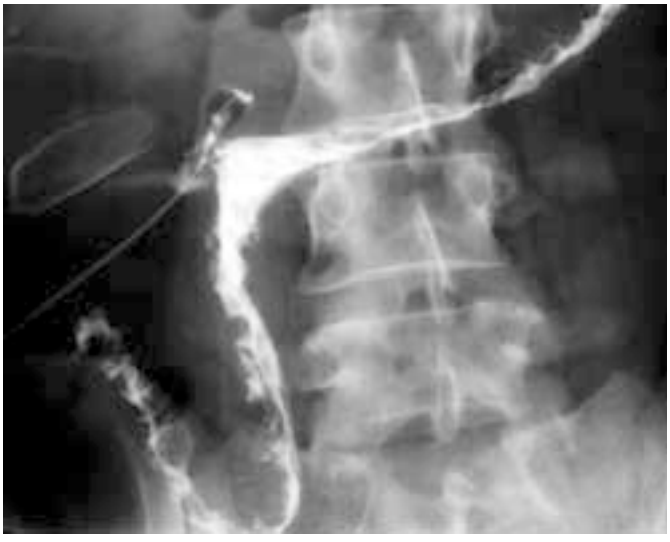

FIGURE 4
Fistulogram demonstrating enterocutaneous fistula communicating directly with a very diseased loop of small bowel. A Foley catheter has been introduced into the cutaneous opening and water soluble contrast injected. There has been direct filling of a long loop of small bowel which shows extensive ulceration.

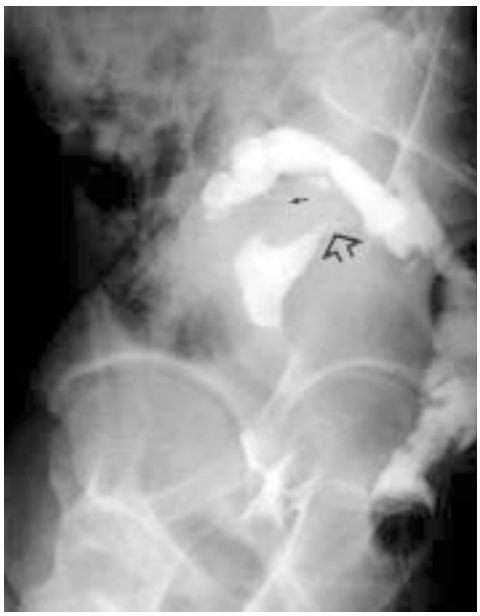

FIGURE 5
Water-soluble proctogram via balloon Foley catheter in rectum. There has been filling of the rectum and sigmoid colon. In addition, contrast is seen filling the uterine cavity via a small tract (open arrow). Filling of a fallopian tube can be identified (black arrow).

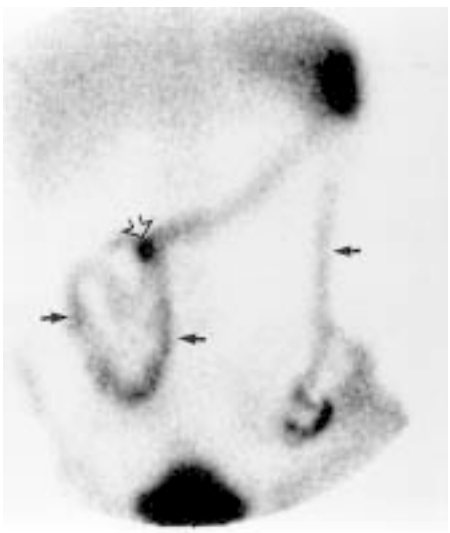

FIGURE 7
White blood cell labelled radioisotope scan in patient with known Crohn's disease (same patient as Figure 4). This one-hour film shows normal high uptake in the spleen and urinary bladder from renal excretion. Moderate uptake is also seen within the liver and bony skeleton. In addition, uptake is seen within the diseased segment of bowel. High uptake is seen in the region of the enterocutaneous fistula (open arrow) with further high uptake within the bowel indicating active inflammation (black arrows).

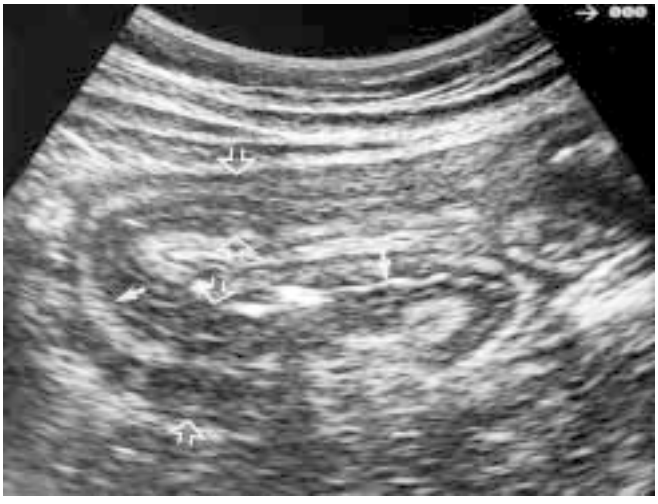

FIGURE 6
Trans-abdominal ultrasound scan of patient with Crohn's disease and a palpable right *iliac fossa* mass. A long segment of bowel wall thickening is seen. The lumen of the bowel appears as an echogenic line (white arrows). The bowel wall is identified as a hypoechoic band on either side of this (open arrows). Note the bowel wall is thickened up to 1.5 cm - normally the bowel wall measures less than 5 mm.

technique of E-selectin which is overexpressed in endothelial cells at sites of inflammation.

Less common sites of involvement are the stomach or duodenum where ulcers may be found. The complications of Crohn's disease include: small bowel bacterial overgrowth, gallstones, fistulae between affected loops of bowel, bladder or vagina, abscess formation and small bowel obstruction. Ileo-caecal disease may also result in right ureteric stenosis and pyelonephritis. Extra-abdominal manifestations include: erythema nodosum, pyoderma gangrenosum, arthritis involving large joints or a sacro-iliitis; eye problems including uveitis or conjunctivitis; amyloidosis, and occasionally carcinoma in the affected bowel.[12,13] Acute bowel dilatation, perforation and haemorrhage are less common than in ulcerative colitis.

AETIOLOGY

Numerous suggestions have been put forward as to the causes of Crohn's disease. A very similar condition in cattle called Johnes disease is due to *Mycobacterium paratuberculosis*.[1] This possibility has been examined in humans but support for the proposition is thin, and many researchers have failed to show convincing evidence of mycobacteria in Crohn's specimens.[15-18] Conflicting, but generally disappointing, results have been noted in treatment with antimycobacterial agents: some of the trials have been promising,[19-25] others negative.[26-29]

Debates still persist as to whether Crohn's disease and ulcerative colitis are separate entities or related. The epidemiological data, including smoking and sugar intake, in tandem with genetic studies suggest that the two are distinct.[12] Strong evidence for a genetic predisposition for inflammatory bowel disease has emerged from one study in which the concordance rate for monozygotic twins with Crohn's disease was 8 out of 18 and, for dizygotic twins, 1 out of 16;[30] in contrast, for ulcerative colitis 1 one out of 16 monozygotic twins was concordant. This gives a coefficient of inheritability of 1.0 in Crohn's disease and 0.53 in ulcerative colitis. Crohn's disease therefore has a similar rate of concordance to insulin-dependant diabetes, and a higher rate than schizophrenia, 0.68. First-degree relatives of patients with inflammatory bowel disease have approximately a ten times increased risk of developing the disease, and this is even higher if relatives have Crohn's disease.[30,31]

At Oxford there is currently a study of those genes that might confer susceptibility to inflammatory bowel disease. Satsangi *et al*[32] have shown linkage between chromosomes 12, 7 and 3, and inflammatory bowel disease. In particular, markers on chromosomes 2 and 6 were linked with susceptibility to ulcerative colitis, whilst chromosome 6 was linked with susceptibility to Crohn's disease. The data suggests that Crohn's disease and ulcerative colitis are related polygenically-determined disorders.

The presence of some genes in the HLA system seems to confer susceptibility to ulcerative colitis. In Japanese[33] and Jewish patients,[34] HLA DRB1 1502 CDR2 is important in increasing susceptibility to ulcerative colitis. In non-Jewish patients HLA genes only predict the extent of disease severity and the presence of extra-intestinal manifestations.[35]

Certain candidate genes which have been mapped in these locations have been looked at: MUC3 encodes for intestinal mucins[36] (deficiencies of which have been reported in patients with inflammatory bowel disease).[37] Others include hepatocyte growth factor and epidermal growth factor receptor which are located close to the linked region on chromosome 7.

There are a number of animal models including mutants, and transgenic animals

which have been used to study Crohn's disease. These include the severe combined immunodeficiency (SCID) mouse; the HLA-β27-β_2 - microglobulin transgenic rat; mice mutant for IL-2, IL-10 or T cell receptors; and also those derived from peptidoglycan polysaccharide, cyclosporin, and *lymphogranuloma venereum* infection. Bacteroides is ubiquitous in the expression of the disease of these models but is thought to be responsible for prolonging the disease rather than initiating it.[38]

Dietary studies suggest that patients with Crohn's disease have a high intake of refined sugar.[39-42] However, no other dietary factor appears relevant, although the beneficial effect of an elemental diet in treatment suggests that further research in this area could be of interest.

The oral contraceptive pill has been implicated in the aetiology of Crohn's disease, several studies having demonstrated a moderately increased risk of the disease in 'pill' users.[43-44] This observation could be coincidental to the fact that many users of the oral contraception tablets are also smokers. A comprehensive volume of data supports a correlation between smoking and Crohn's disease, giving an approximate two to four times increased risk.[45-49]

Measles virus antigens have been detected in Crohn's disease tissue using an immunogold antibody technique;[50] other studies have failed to replicate this.[51,52] There are epidemiological data linking perinatal measles with the eventual development of Crohn's disease; children born during an outbreak of measles are 1.5 times more likely to develop Crohn's disease.[53] Interestingly a decrease in measles infections due to infantile immunisation has not been associated with a reduction in Crohn's disease but has been associated with an increase in prevalence[54] The putative explanation is that it is the measles vaccination itself which could somehow trigger the disease. A study from Guinea-Bissau[55] which examined the incidence of atopy in adults compared with whether they had been vaccinated for measles found atopy to be virtually twice as common in those that had received the measles vaccination and avoided measles.

There has been speculation that Crohn's disease may be of primary vascular origin[56] involving focal microscopic infarction of the intestine. The granulomas found in Crohn's disease do seem to be closely associated with vascular structures; in one study of 485 granulomas from 15 patients, 85% were associated closely with vascular injury.[57]

An increase in intestinal permeability has also been suggested as a cause of Crohn's disease. Increased mucosal permeation of polyethylene glycol has been demonstrated in unaffected first-degree relatives of Crohn's patients[58] but other studies using sugar or ethylenediaminetetracetic acid have not confirmed these observations.[59] However, 10% of relatives have an increased small intestinal permeability.[60]

THE INFLAMMATORY PROCESS AND CROHN'S DISEASE

Partly because of the failure to identify a specific causative organism or process, research interest has focused on the inflammatory process itself, and possible ways of controlling or modulating it. By identifying key components of inflammation which are deranged in this disease, direct therapy to accentuate or diminish such responses could be sought. Significant interest has focused on cytokines, adhesion molecules and, to a lesser extent, prostaglandins and reactive oxygen species or free radicals.

Cytokines are mediators of signals between inflammatory cells, and their individual biological effects frequently overlap. They can be broadly divided into pro- or anti-inflammatory in nature. IL-1β, IL-6 and TNFα are pro-inflammatory and macrophage-derived, and these are elevated in Crohn's disease[61,62] as are IL-2 and γIFN which are T- cell derived.

IL-4, IL-10 and IL-13 are anti-inflammatory. IL-10 can suppress *in vitro* all pro-inflammatory cytokines; IL-13 and IL-4 can suppress IL-1β (Table 1).[63]

TABLE 1
Brief classification of cytokines.

Cytokine	UC	CD	Effects
γ-IFN	N/d	i	Pro-inflammatory; activation of Th1 cells and macrophages increases release of IL-1
IL-1	i	i	Pro-inflammatory; activation of macrophages, T cells, polymorphs, mesenchymal cells and endothelial cells; increases release of IL-2
IL-2	N/d	i	Proliferation and activation of Th1 and cytotoxic lymphocytes; increases release of γ-IFN and IL-9
IL-3	d	d	Pro-inflammatory; stimulation of stem and mast cells
IL-4	d	d	Regulatory; activation of Th2 cells, suppression of Th1 cells
IL-5	?	?	Eosinophil and mast cell product; eosinophil differentiation
IL-6	i	i	Pro-inflammatory; stimulation of the acute-phase response
IL-7	?	?	Intestinal epithelial and goblet cell product; growth factor for intra-epithelial lymphocytes
IL-8	i	i	Chemokine; polymorph chemotaxis
IL-9	?	?	T-cell product; anti-apoptotic; responsive to IL-2
IL-10	i	N	Regulatory; down-regulation of Th1 cells and macrophages
IL-11	?	?	Marrow-derived growth factor for megakaryocytes and murine intestinal stem cells
IL-12	N	i	Pro-inflammatory and regulatory; stimulates Th1 and NK cells
IL-13	?	?	Monocyte down-regulation (especially of TNF-α)
IL-IRA	i	i	Regulatory; inhibits IL-1
TNF-α	N/i	N/i	Pro-inflammatory; activation of macrophages, polymorphs, mesenchymal and endothelial cells
TGFβ	N	N/i	Chemokine/healing/repair; monocyte chemotaxis, suppression of lymphocyte proliferation, increased collagen synthesis
IGF-1	??	i	Healing/repair; epithelial cell and fibroblast proliferation increased collagen synthesis
GM-CSF	ii	i	Product of many cell types; proliferation of granulocyte and monocyte precursers
EGF	?i	?i	Healing/repair; intestinal stem cell product in response to ulceration
MCP-1	i	i	Chemokine; macrophage chemotaxis

UC: ulcerative colitis; CD: Crohn's disease; I: increased; d: decreased; N: normal; IFN: interferon; IL: interleukin; TNF: tumour necrosis factor; TGF: transforming growth factor; IGF: insulin-like growth factor; GM-CSF: granulocyte/macrophage colony stimulating factor; EGF: epidermal growth factor; MCP: monocyte chemoattractant protein; NK: natural killer.[13]

There is an increasing amount of information on cell adhesion molecules, which play a fundamental role in mediating how cells behave with each other. They can be classified into integrins, selectins, the immunoglobulin supergene family and carbohydrate-containing molecules. The vascular cell adhesion molecule (VCAM-1) plays several important roles in leucocyte adherence to the endothelial lumen in inflammation. One study has found elevated levels in inflammatory bowel disease,[64] another has not.[65] Endothelial leucocyte adhesion molecule (ELAM-1) is increased in inflammatory bowel disease,[64] as is the intercellular adhesion molecule (ICAM-1) which promotes Tcell/macrophage interaction.[65-67] At present it is difficult to ascertain whether the associations between these cell adhesion molecules and inflammatory bowel disease are causative or merely an end-product and the non-specific sequelae of inflammation.

Other facets of the inflammatory process are abnormal in Crohn's disease. Platelet activating factor (PAF) is increased in some but not all patients.[68-70] The lipid soluble eicosanoids are raised in Crohn's patients with both prostaglandin E2[71] and leucotriene B4[72,73] being elevated in active disease.

Free radicals have also been implicated in colonic damage[74] with patients having a decreased oxygen-scavenging capacity.[75] A decreased superoxide anion production from neutrophils was shown *in vitro* in patients with Crohn's disease leading to the suggestion that a reduction in membrane 6 type cytochrome occurs in patients with Crohn's disease.[76]

This brief resumé indicates that there are many potentially productive avenues of research.

MANAGEMENT

The thrust of medical management is to induce remission and avoid surgery at all costs. Treatment of terminal ileal disease has been aided by the introduction of a locally-acting steroid budesonide which to a large extent does not exhibit the side-effect profile of the more conventional steroids. Several studies have shown significant advantages of this drug over prednisolone.[77-81] The beneficial effects of budesonide are found mainly in disease of the terminal ileum and Crohn's disease elsewhere does not respond to budesonide and is optimally treated with prednisolone.

Sulphasalazine contains a sulphapyridine moiety attached to 5-aminosalicylic acid (ASA) by an azo bond. The former is thought to be responsible for the majority of side-effects of sulphasalazine, and this has led to the development of effective new formulations containing only the 5-ASA molecule which can be used in much higher dosages.[82-84]

There are a number of different 5-ASA drug preparations available. Claversal® and Salofalk® are coated with Eudragit-L which releases 5-ASA at pH 6.0 in the ileum. Asacol® is coated with an acrylic based resin and dissolves above pH 7.0 in the caecum and ascending colon. Pentasa® has a semi-permeable ethyl cellulose membrane which degrades gradually from the stomach onwards with optimal release above pH 6.0. Olsolazine is a dimer of 5-ASA linked by an azo bond and needs the azo-reductase found in colonic bacteria to break it down; it unfortunately produces significant diarrhoea in 10% of patients.[12] Balsalazide is a newer 5-ASA linked by an azobond to an inert carrier, and has its effects particularly on the left side of the colon[85] having fewer side-effects, and a quicker therapeutic effect.

Elemental diets have been used to good effect in producing remission especially in children[86] and may be most beneficial in those with long-standing severe disease of colonic origin.[87] Their use is controversial and patients can relapse when a normal diet

is resumed.[88] Generally patients should be managed on a high-fibre balanced diet, although a low residue diet is best if strictures are present. Supplements of iron, vitamin D, folate or vitamin B12 may often be required.[11]

Perianal Crohn's disease remains a challenge and is best treated with courses of metronidazole which have been shown to have a significant benefit over a placebo.[89] This antibiotic is also effective in non-perianal disease and reduces post-operative recurrence.[90] The interaction of metronidazole with alcohol, and the peripheral neutropathy which it may induce limit its usefulness.[91]

Other immunosuppressive agents have been used with variable success. Azathioprine has steroid-sparing effects with bone marrow depression and pancreatitis as the principal side-effects although both of these are rare; more common adverse reactions are gastrointestinal intolerance and myalgia.[11] Cyclosporin has yet to be generally accepted; it is thought to be useful intravenously in steroid-refractory disease;[92] others have found it ineffective when used orally for its steroid-sparing effects.[93-95] Methotrexate is of value as a short-term alternative in refractory disease.[96,97]

The interest in inflammatory mediators in Crohn's disease has generated a wide variety of therapeutic possibilities and there is intense interest in developing antibodies to pro-inflammatory or anti-inflammatory cytokines. TNFα antibody is useful in Crohn's disease when compared with conventional treatment,[98,99] and there has been some success in controlling inflammation with IL-1 antibody in animal models; both IL-2 and γ interferon antibody are of benefit in patients with Crohn's disease.[100] Oxypentiflyline, a very weak inhibitor of TNFα is of help as an inhibitor of TNFα and IL-1β,[101] although others have found its effects to be inconclusive.[102] IL-10 has been used with success in steroid-unresponsive patients,[103] and IL-13 is effective *in vitro*.[63] Results with anti-CD4 antibody are conflicting so far.[104,105]

Certain fish oils such as linoleic acid or perilla oil decrease colonic disease in rats with Crohn's disease presumably by suppressing the leukotriene B4 (LTB4) which is generated by the action of 5-lipoxygenase on archidonic acid and was shown to play a central role in the inflammatory pathway in inflammatory bowel disease.[106] Hawkey has found that eicosapentaenoic acid reduces LTB4 in patients with inflammatory bowel disease and increases the number of days in remission.[107] In ulcerative colitis, a reduction in LTB4 and increase in LTB5 was observed in response to eicosapentaenoic acid but there was no effect on disease activity.[108] In Crohn's disease, fish oils containing N–3 fatty acids have been found to reduce the rate of relapse.[109]

There is as yet no unifying hypothesis to explain Crohn's disease and despite medical treatment about three-quarters of patients with Crohn's disease will require surgery during the course of their disease. The most common indicator for surgery is the failure of the patient to respond to medical therapy; other reasons include strictures, fistulae or perianal disease. About a half of those who have had ileal or ileocaecal surgery will relapse over the subsequent ten years and require further surgery.

Crohn's disease has a significant impact on quality of life although life expectancy is not reduced It remains a challenge for the millennium. However, as our understanding of the inflammatory process expands and research into the underlying genetics of the disease unravel new associations there is a promise for more effective treatments in the future.

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