Ischaemic bowel disease

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A supply of oxygenated blood appropriate to the tissue needs of the gut is essential to the maintenance of its vital functions. The splanchnic vascular system serves this purpose and much of our knowledge of ischaemic bowel disease has developed from studies of radiological and pathological abnormalities of this system. The purpose of this paper is to summarize current information concerning the histopathology of intestinal ischaemia in the light of our better understanding of the micro-circulation of the gut in health and disease; also to describe the difficulties we have in understanding the pathogenesis of ischaemic bowel disease because of the growing spectrum of systemic disorders with which it is associated.

Nomenclature

Until recent times ischaemic bowel disease was a clinical entity recognized usually in its irreversible fatal forms and less frequently in its reversible chronic forms. Protein clinical manifestations and resemblance to inflammatory disorders of the bowel led to a multiplicity of names for presumably separate entities with common pathological features — names such as haemorrhagic necrosis, necrotizing enterocolitis, membranous or pseudomembranous enterocolitis, infarction, gangrene, ischaemic stricture, clostridial or staphylococcal enterocolitis, uraemic enterocolitis, necrotizing enterocolitis, phlegmonous enterocolitis, etc (table I). This report describes ischaemic bowel disease in general no matter what its cause and describes gross and microscopic pathological features differentiating this entity in particular from inflammatory bowel disease.

Natural history

The natural history of ischaemic bowel disease can be described as a complex but related series of cellular and tissue reactions to anoxic injury produced by interruption of a supply of oxygenated blood sufficient for the functions of the bowel, no matter what the cause. The extent and the forms of these reactions vary with the severity and duration of the ischaemia, the adequacy of collateral avenues of blood supply and the capability of the affected cells and tissues to survive and regenerate. The alterations provoked in this cycle of reaction to injury range from minor degrees of change in the most vulnerable cells of the mucosal villi through major but reversible degrees of destruction of the mucosa and submucosa to irreversible full-thickness gangrene of the bowel wall. There are many gradations and overlaps in the stages of survival and restoration of tissues and many variations in the resultant gross and microscopic features, all reflected to varying degrees in the spectrum of clinical events and radiological findings. The section of gut affected, the extent and multiplicity of the sites involved, the patterns of involvement and secondary alterations such as stenosis, megacolon, ulceration, ‘cobbledstoning’, etc, add to the morphological diversity of the disorder and tend to obscure the identity of its cause.

Major vascular occlusion is not required to produce a serious degree of ischaemia in the bowel. The occurrence of intestinal gangrene without demonstrable vascular occlusion is recognized clinically and experimentally (Williams et al, 1967; Marston, 1972; Whitehead, 1972; Marcuson, 1974). Occlusion due to functional constriction, cardiogenic shock, low flow states or remote partial organic obstruction is usually operative in these instances. The essence of the matter is that the gut is equally susceptible to ischaemic necrosis from a summation of minor vascular deficiencies as well as from single demonstrable major occlusions.

The reaction to moderately severe ischaemia follows a predictable course of inflammation and repair divisible into three general phases: (1) acute, with haemorrhage and necrosis; (2) reparative, with...
granulation tissue formation and fibrosis and (3) later forms of residual pathology with bowel constriction and chronic complications (table II). The predominant gross and microscopic features characteristic of these phases are described in the following sections. A transient, 'self-healing' form of intestinal ischaemia is known experimentally and is thought to occur in humans also when the initial injury is slight or of short duration and collateral blood flow is adequate. Severe and prolonged ischaemia causes segmental infarction of the bowel and subsequent gangrene leading to perforation and peritonitis (Marston et al, 1966).

**Ischaemic bowel disease**

**Phases of Injury and Repair**

<table>
<thead>
<tr>
<th>Category</th>
<th>Types of Response</th>
<th>Tissue Alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acute</td>
<td>Oedema, haemorrhage, necrosis</td>
</tr>
<tr>
<td>2</td>
<td>Repair</td>
<td>Epithelial regeneration, granulation tissue formation, chronic inflammation, mural fibrosis</td>
</tr>
<tr>
<td>3</td>
<td>Residual pathology</td>
<td>Panmural fibrosis, Stenosis</td>
</tr>
</tbody>
</table>

Table II Natural history of ischaemic bowel disease

**Location of ischaemic bowel disease**

The location and extent of ischaemic lesions of the intestine reflect the anatomy and physiology of the blood supply and the anastomosing network of secondary vessels which supply the various divisions of the alimentary tract. The ischaemic lesions themselves vary from focal forms such as the sharply localized annular ulcers of the ileum associated with the intake of enteric-coated potassium tablets to the massive forms of infarction seen with acute mesenteric arterial thrombosis or venous occlusion. In some instances the location of the ischaemic injury is determined by the anatomy of the blood supply and the precipitating cause, i.e., compression of the superior mesenteric artery by an adhesive bond or occlusion of the inferior mesenteric artery by aortic aneurysm. In other cases the injury is so extensive that it can only be the manifestation of a generalized vascular disorder such as heart failure or hypotension, as occurs in myocardial infarction or by a widespread small vessel occlusion due to spasm or intravascular coagulation.

Ischaemia may involve any portion of the colon. However, the area of maximum susceptibility is the watershed area between the superior and inferior mesenteric vessels and thus the common site of ischaemic lesions is the region of the splenic flexure. The splenic flexure is the point where the superior and inferior mesenteric arteries anastomose; it has been shown that the blood supply at this point is precarious as the anastomosis is frequently deficient (Marston, 1972). Ischaemic stricture of the right colon is rare perhaps because this part of the gut has a rich blood supply.

Whilst rectal involvement was considered initially rare or even non-existent, rectal lesions are now recognized with increasing frequency (Kilpatrick et al, 1968). The distribution and the pattern of involvement bear no relationship to the severity of the ischaemia, but specific precipitating causes of ischaemic damage appear to show a predilection for certain areas. Thus ligation of the inferior mesenteric artery usually results in ischaemic lesions of the sigmoid colon, while low-flow state affects primarily the splenic flexure. Similarly the length of bowel involved varies with the aetiology: atheromatous occlusion produces short segmental damage, while low-flow states result in much longer lesions (Marston et al, 1966).

Analysis of 358 clinical examples of ischaemic colitis in which segmental location of the lesion was described gives the following distribution (fig 1) (McGovern and Goulston, 1965; Marston et al, 1966; Möller and Stjernvall, 1971; Marcuson, 1972, 1974; Kaminski et al, 1973; Williams and Willenberg, 1975).

<table>
<thead>
<tr>
<th>Location</th>
<th>Cases</th>
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</thead>
<tbody>
<tr>
<td>Right colon</td>
<td>27</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>54</td>
</tr>
<tr>
<td>Splenic flexure</td>
<td>84</td>
</tr>
<tr>
<td>Descending and sigmoid colon</td>
<td>99</td>
</tr>
</tbody>
</table>

Fig 1 Distribution of 358 cases of ischaemic colitis.
The blood supply of the small intestine benefits from the abundant system of anastomosing arcades which are less numerous in the colon and which perhaps explain the less frequent occurrence of vascular damage in the small bowel. Segmental ischaemic lesions of the small intestine are usually confined to the jejunum and ileum and most often result from external vascular obstruction due to compression or twisting (adhesive band, volvulus, internal hernias, neoplasms, trauma). Ischaemia due to intramural vascular occlusion is caused by small vessel thrombosis or stenosis and is usually associated with systemic vascular disorders, hypotension or the use of the enteric-coated potassium or thiazide treatment for hypertension.

In 27 cases of ischaemic enterocolitis reported by McGovern and Goulston there were 12 instances of involvement of the small intestine (McGovern and Goulston, 1965). The ileum alone was involved in one case (internal hernia). The terminal ileum and right colon were involved in three cases (myocardial infarction; hypertension). The ileum and the transverse colon were involved in one case (aortic insufficiency due to atherosclerosis). The entire small bowel was involved in one case due to postoperative hypotensive shock and in six cases these authors reported infarction of the entire small bowel and colon (myocardial infarction; rheumatoid disease).

The susceptibility of the colon to ischaemia can be demonstrated at necropsy when careful microscopic examination often reveals early mucosal lesions, many of which could be agonal in nature.

**Pathology: Acute phase**

Classic descriptions of the pathology of acute ischaemic bowel disease start with the phase of impending infarction. The bowel segment is bloated, purple-red, moist and soggy with a dull granular serosa, thickened wall and oedematous, focally haemorrhagic mesentery. Arteries are usually contracted and veins dilated and sometimes plugged with clotted blood. The lumen may be distended or contracted and contains serosanguinous fluid, mucus and cellular debris. The mucosal surface appears flattened due to elevation and widening of its rugal folds and the submucosa thickened by oedema and haemorrhage (fig 2). The whole wall is soggy or tense depending on the state of dilatation or contraction and the serosa is commonly hyperaemic and marked by petechial haemorrhage, oedema and early inflammation. The muscularis mucosae is visible as a thin band separating the wide zone of oedematous submucosa from the more compact hyperaemic mucosa. Careful inspection of the surface of the mucosa with the aid of a magnifier may be necessary in order to detect small slits and erosions or ulcerations where the epithelium has become haemorrhagic and necrotic. Unless there is full-thickness gangrene of the mucosa or megacolon, the muscularis propria is preserved, but the subserosa usually reflects to an appreciable degree the oedema and haemorrhage so conspicuous in the submucosa and mucosa. The serosa may be marked by fibrin deposits and blood. Generally the gut is soft, flexible and resistant to tearing but it may also be so diffusely congested and oedematous that it is friable and easily torn.

The microscopic alterations of the acute phase of ischaemic bowel disease are dominated by vascular congestion, oedema, haemorrhage and necrosis (fig 3). The latter may be only microscopic and it is possible to have multiple fields with oedema, congestion (fig 4) and petechial haemorrhage of the submucosa without necrosis or ulceration of the mucosae. However, in surgical specimens, it is common to find focal necrosis of the surface epithelial cells of the mucosa and petechial haemorrhage in the lamina propria. The muscularis mucosae is thin and intact until ulceration of the mucosa disrupts it by oedema and inflammation and the muscle fibres separate and

**Fig 2** Acute ischaemic necrosis of the ileum. Massive haemorrhage and oedema of the submucosa impart a pseudopolypoid character to the mucosal surface. This macroscopic appearance corresponds to the radiological sign of 'thumb-printing'.
Ischaemic bowel disease

Fragment. Unless ischaemic damage has been severe, the muscularis propria is minimally affected. Oedema along the vascular pathways, slight separation of muscle fibres (fig 5), swelling and cytoplasmic vacuolization of ganglia, venous engorgement and loose scatterings of lymphocytes and occasional neutrophil leucocytes are often the only signs of the damage which has occurred at the mucosal and submucosal levels. More definite changes such as oedema, congestion, petechial haemorrhage, fibrin deposition and early inflammation may be observed in the subserosal and serosal zones.

In specimens with more severe acute ischaemia, the markings of mucosal ulceration and/or pseudomembranous enterolitis may predominate. The latter is sometimes better appreciated after one or two hours of fixation in formalin. This exposure imparts enough hardening and pallor to the mucosal exudate to produce a discrete mottling and coarse granularity which is resistant to scraping although mixed with mucus. Ulcerations and pseudomembranes may both be present. These macroscopic features are the result of a combination of oedema of the submucosa and patchy necrosis of the mucosa associated with partial or complete destruction of glands, outpouring of mucus from gland lumens and mingling of epithelial cells, mucus, fibrin, erythrocytes and acute purulent exudate on the internal surface of the gut with the formation of a tenaceous 'pseudomembrane'. The uniqueness of this histological pattern is accentuated by the presence of zones of intact mucosa between these islands of necrosis and partially destroyed, hypersecreting mucus glands along with zones where the mucosa has been totally destroyed.

Pathology: Reparative phase

The phase of acute inflammatory reaction is followed in a sequential manner and to varying degrees by subacute and chronic inflammation of a proliferative or 'productive' type because granulation tissue formation (fig 6) and fibroplasia are its major attributes. Where islands of mucosa have survived, the intervening ulceration is the area where necrotic mucosa has been sloughed and digested and replaced...
Fig 5  Histology of an acute ischaemia. In severe ischaemic injury the necrosis extends to the more resistant muscularis propria. In this picture the circular layer shows signs of an early necrosis with lysis and separation of the muscle fibres (H & E x 90).

Fig 6  Histology of reparative phase. Proliferative inflammation with granulation tissue formation extends into the muscularis propria breaking up and partly replacing the muscle bundles (H & E x 90).
Ischaemic bowel disease

by a matrix of granulation tissue and a mixed population of acute and chronic inflammatory cells. Pockets of suppuration may be present or dense infiltrates of plasma cells and lymphocytes predominate in the field. Capillary proliferation, macrophage activity and fibroblast production complete the chief activities until the mucosal epithelium begins to regenerate. Microscopic fissures may lead down to or into the muscularis propria at points of deeper anoxic damage. Entrapped particles of foreign material may provoke a giant-cell reaction. The granulation tissue reaction is generally exuberant and, in conjunction with the residual islands of inflamed and sometimes hyperplastic mucosal glands, presents a pattern mimicking Crohn's disease or chronic active ulcerative colitis. Eosinophil leucocytes and iron pigment-laden histiocytes are a variable element. The presence of iron-positive granules in histiocytes is associated with prior haemorrhages in the submucosa and mucosa and is important in differentiating ischaemic from inflammatory bowel disease. Epithelial cell regeneration is visible at the margins of the mucosal ulcers in the form of young cells growing in a thin sheet over the bed of inflamed granulation tissue or mingling with the fibrin and leucocyte exudate and the population of lymphocytes and histiocytes on the gut luminal surface. Bacteria can sometimes be demonstrated at the mucosal surface but rarely penetrate deeper tissues unless gangrene is present.

Pathology: Late sequelae

The portion of gut thus altered undergoes continuing change in the form of tissue repair and functional restoration or further deterioration due to additional vascular deficiency. Survival is manifested by progressive fibrosis and mucosal reorganization. The end result is ischaemic constriction (fig 7). Usually mucosal ulcers persist and the lamina propria when present continues to be inflamed. Frequently, the mucosal epithelium regenerates sufficiently to cover most of the luminal surface and rests on a bed of granulation tissue. Atrophic glands in disarray and infiltrates of plasma cells, lymphocytes and histiocytes mark this attenuated regenerated mucosa. The reepithelialized luminal surface is often flat and smooth and productive of copious mucus. In some cases islands of surviving mucosa acquire a pseudo-polypoid character and further obstruct the narrowed gut lumen.

The submucosa gradually is converted into a diffuse zone of dense, hyalinized connective tissue poor in blood vessels and lymphatics but vested with foci of persistent inflammation in which histiocytes, plasma cells and lymphocytes predominate. This collar of diffuse, unyielding fibrosis filling the submucosal zone of the bowel wall extends minimally or extensively into the muscularis propria (fig 8) involving in severe cases the serosa and mesenteric tissues. Tubular stenosis or discontinuous sauculations of the bowel are radiological and gross expressions of this reparative scarring of the gut wall. Vascular and lymphatic and neural structures are trapped in the fibroplasia and examples of vascular intimal fibrosis or luminal recanalization can usually be found. A distinctive form of atrophy and linear separation of fibres of the inner zone of the muscularis propria resulting from ischaemia and fibrosis is a mark of diagnostic significance (Morson, 1971). Serosal fibrosis and adhesion formation may also be conspicuous. Mesenteric lymph nodes are not enlarged and are free of granulomas. Although the rectum is usually spared, recent reports by Kilpatrick et al (1968) and Shearburn et al (1955) describe necrotic, ulcerating and fibrosing alterations characteristic of ischaemia here as elsewhere in the bowel.

Fig 7 Ischaemic stricture of the sigmoid colon. There is an abrupt stenotic deformity of the bowel wall associated with mutual thickening, cicatrising serositis and patchy mucosal ulceration.
Acute pseudomembranous enterocolitis does not occur in Crohn’s disease and ulcerative colitis. Slit-like fissuring ulcers pathognomonic of Crohn’s disease are never seen in ulcerative colitis and ischaemic bowel disease. Primary gangrene of the full thickness of the gut wall does not occur in Crohn’s disease and ulcerative colitis and is pathognomonic of severe ischaemia. Sacculation of the bowel wall between zones of stricturing ulceration and fibrosis rarely occurs other than with ischaemia. The extensive circumferential denudation of mucosa with replacement by richly vascularized granulation tissue is a pattern rarely occurring except in ulcerative colitis. Mucosal pseudopolypsis is common in the inflammatory colitides and uncommon in ischaemic disease. Acute dilatation of the colon is a well-known complication of ulcerative colitis but also occurs in ischaemic colitis without prior gangrene. Spontaneous fistulae and perianal granulomatous inflammation are significant manifestations of Crohn’s disease but rarely if ever are seen in ischaemic proctitis or ulcerative colitis. Microscopic transmural inflammation, focal lymphoid tissue aggregates in the submucosa, sarcoïd-type granulomas and slit-like fissures of the mucosa are pathognomonic of Crohn’s disease. Cryptabscess formation, goblet cell depletion, atypical glandular proliferation in the mucosa and sparing of the muscularis propria despite widespread destruction of the mucosa and submucosa are hallmarks of ulcerative colitis. Patchy mucosal necrosis associated with marked submucosal oedema and pseudomembranous exudate rich in mucus, fibrin and bacteria is characteristic of ischaemic colitis. Serositis is minimal in ulcerative colitis and always present in established Crohn’s disease and ischaemic bowel disease. Diffuse stricturing fibrosis involving the submucosa and extending into the muscularis propria is characteristic of ischaemic enterocolitis. Indeed, it is often the destruction of the muscle layers by granulation tissue and fibrosis which is the most useful feature in separating ischaemic bowel disease from inflammatory bowel disorders.

Aetiology and pathogenesis

In the strict sense the aetiology of ischaemic bowel disease is irreversible anoxic injury to cells of the intestines and its pathogenesis concerns mechanisms initiating this type of injury and alterations of inflammation and repair which follow. Allowing for uncontrollable variations, it is possible to analyse many of the anatomical and functional changes occurring in cells and tissues of the gut affected by ischaemia in terms of alterations or causes which are intrinsic to the bowel and those which are extrinsic.
Ischaemic bowel disease

I Arterial occlusion by atherosclerosis
II Pathology of mural vascularature
  Vasculitis: collagen diseases: compression: intravascular
  coagulation: Buerger's disease: amyloidosis
III Venous occlusion
Oral contraceptives: blood dyscrasias: volvulus
IV Non-occlusive ischaemia
Cardiac failure: hypovolaemia—shock: splanchnic
  vasconstriction—drugs; trauma

Table III Pathogenesis of ischaemic bowel disease

(table III).
Chief among the extrinsic causes of ischaemia of the gut are obstructive disorders of the major branches of the splanchnic arterial circulation. This system and its pathology are well described by Marston (1972) and Thompson (1972). Congenital anomalies, atherosclerosis, thrombosis, embolism, dissecting aneurysms, surgical interference, traumatic occlusion or rupture, volvulus, intussusception, strangulated hernia, haemorrhage (as in haemophilia and in patients on anticoagulant therapy), complications of abdominal angiography, complications of neoplasia (compression, invasion or secondary metabolic effects), intravascular coagulation and arteritis are principal among the many conditions which may seriously interrupt or modify the supply of blood to the gut through major extrinsic arterial channels. Phlebitis and venous thrombosis may be equally serious because the perfusion of oxygen in the target tissues of the intestinal mucosa and submucosa is turned off by retrograde venous blood flow as well as by collapse of the blood supply and pressure gradients on the arterial side of the circulation. Countering all of these obstructive conditions is the important role of anastomoses between the superior and inferior mesenteric arteries and the capacity of these and other natural channels of collateral circulation to expand sufficiently to maintain an adequate supply of blood to the tissues at risk from anoxia.

The above causes are associated with abnormal morphological states of the splanchnic vasculature but cessation of adequate blood flow to support the vital activities of intestinal tissues may also result from ‘resistance’ in the peripheral vascular bed or from ‘low flow states’ produced by heart failure with diminished cardiac output (ie, arrhythmias, coronary artery insufficient), digitalis intoxication, myocarditis, hypertension and valvular disease) or from shock secondary to trauma, burns sepsis, blood loss, poisoning and metabolic acidosis. These disturbances of blood supply and tissue perfusion act primarily within the wall of the intestine itself and are intrinsic causes of ischaemic bowel disease. In addition to general states of circulatory failure such as shock, toxaemia and pump failure, there are many other pathological conditions of the intramural blood vessels of the bowel capable of initiating ischaemia progressing to gangrene or constrictive fibrosis. These include periarteritis nodosa, systemic sclerosis, rheumatoid arthritis, disseminated lupus erythematosus, thromboangiitis obliterans, allergic vasculitis, diabetic sclerosis, potassium-induced vasculitis, uraemic vasculitis, radiation injury, intravascular coagulation syndrome, prolonged use of systemic birth control medications and immunosuppressive therapy following organ transplantation (Whitehead, 1972; Hardie, 1974; Marcuson, 1974). It is appropriate to mention in this context that tissues have needs other than oxygen—such as proteins, carbohydrates, lipids, water, electrolytes, vitamins, etc. The capacity of cells to obtain these nutrients and to extract oxygen from the blood is intimately associated with their membrane structure and internal metabolism. Ischaemia and inflammation profoundly affect these structures and their functions; as do also bacteria, intestinal metabolites, hormones and circulating drugs, antibiotics, anaesthetics and the array of chemotherapeutic agents the sick and elderly are exposed to almost daily. These may act alone or in combination to disturb the homeostatic state of the tissues and cells of the bowel.

In essence, the pathogenesis of ischaemic bowel disease can be defined at the level of molecular biology and pathology as the balance between the demand of increased tissue needs (caused by diminished blood flow, oedema, inflammation, anoxic injury and infection) and the capacity of the body to deliver the substances necessary to compensate for all serious deficiencies in cell structure and function. Conditions which create the imbalance in the vital economy of tissues and cells of the intestines may be primarily within the wall of the bowel itself or in the major and intermediate vessels of the splanchnic circulation or in disorders of the general cardiovascular and related systems. These conditions may act alone or together and they may be simultaneous or discontinuous. They can in general be classified as degenerative, inflammatory, traumatic, metabolic and of unknown aetiology. But for the general purposes of clinical diagnosis, pathological description and rational therapy these disorders are categorized as reversible or irreversible and as severe with gangrene, chronic with constrictive fibrosis, or transient and self-healing. In this discussion of pathogenesis we have considered them also in relation to causes which are extrinsic to the intestines themselves and those which are intrinsic within their walls (fig 9).

The interpretation of the pathology of ischaemic bowel disease in individual specimens and differentiation from other types of bowel disease requires systematic observation of gross and microscopic details and a knowledge of the salient features of
differential significance in each of the major enterocolitides. Moreover, experience with the subcellular morphology and experimental pathology of alimentary tract disorders is increasingly important from the standpoint of intestinal biopsy interpretation and rationale of therapy.

Ultimately the pathogenesis of ischaemic bowel disease begins with the need to restore the physical structure of intestinal cells injured by ischaemia and to re-establish the chemical equilibrium of their internal milieu and normal mechanisms of energy exchange and regeneration. This restoration is achieved by renewal of blood flow, nutrient supplies and metabolic pathways. This is the cure sought by medical treatment and the goal of surgical removal of necrotic tissues or segments of bowel threatening the normal motility and function of the gut. There is unity in the various causes and stages of development of ischaemic bowel disease. This unity flows from a recognition of its pathogenesis in terms of ischaemic cellular damage and a sequence of predictable inflammatory and reparative alterations in the tissues of the wall and mesentery.

References

Ischaemic bowel disease

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