Overlap in the spectrum of non-specific inflammatory bowel disease—'colitis indeterminate'

ASHLEY B. PRICE

From Northwick Park Hospital and CRC, Harrow, Middlesex (work carried out at St. Mark's Hospital, City Road, London EC1)

SUMMARY It is stated that 10-20% of cases of non-specific inflammatory bowel disease cannot be classified. Thirty such cases, designated colitis indeterminate at the time of colectomy, were identified from the pathology files of St. Mark's Hospital. The histopathological features of the surgical specimens and any available biopsy specimens were studied. In nearly all the cases urgent surgery had been required and the features of incipient or established fulminating disease were present. The pathology of these cases of Crohn's disease and ulcerative colitis overlapped, and differentiating features were scant or unreliable. Accepted criteria of Crohn's disease—namely, fissuring ulceration, transmural inflammation, and a maintained goblet-cell population—were found in cases subsequently proved to be ulcerative colitis. Disease activity greatly affected the evaluation of morphological features. Many of the difficulties were resolved when biopsy material obtained during a quiescent phase was examined. These specimens gave a dynamic perspective of the disease process, often more valuable than the static, non-specific picture of acute disease seen in the surgical specimens. Cases of colitis indeterminate form a small but distinctive group in the spectrum of inflammatory bowel disease which is characterised by a common pattern of pathology that presents a diagnostic dilemma.

The differential diagnosis between Crohn's disease and ulcerative colitis can be made in most cases on the cumulative clinical, pathological, and radiological evidence (Lockhart-Mummery and Morson, 1960; Lennard-Jones *et al.*, 1968; Marshak and Lindner, 1975). Lockhart-Mummery and Morson (1964) and others (Farmer *et al.*, 1968; Glotzer *et al.*, 1970) have described the many distinguishing histopathological features. Recently, the diagnostic value of these features has been tested by cluster analysis and observer reliability studies in order to select those that were most dependable (Hywel-Jones *et al.*, 1973; Cook and Dixon, 1973). However, owing to the variable occurrence of even the most reliable features the diagnostic difficulty still remains (Schachter *et al.*, 1970). Thus in most series of patients with non-specific inflammatory large bowel disease a confident diagnosis cannot be made in 10-15% of cases (Hawk and Turnbull, 1966; Glotzer *et al.*, 1970; Kent *et al.*, 1970).

The difficulties in diagnosis are due to overlapping

in the pathological features of Crohn's disease and ulcerative colitis, which may even be opposite ends of a spectrum of one disease (Lewin and Swales, 1966; Margulis *et al.*, 1971). But few, apart from Lewin and Swales (1966) and Glotzer *et al.* (1970), have studied the pathology of these indeterminate cases in any detail. This paper reports a study of their histopathology which aimed firstly, to investigate the reason for the diagnostic difficulty, and, secondly, from clinical correlations, to try to place the group within the overall perspective of non-specific inflammatory bowel disease.

Material and methods

At St. Mark's Hospital between 1960 and 1973 there were 330 colectomies or proctocolectomies for ulcerative colitis and Crohn's disease. All the gross specimens had been photographed. Routine paraffin-embedded 5- μ m haematoxylin and eosin-stained sections from up to eight standard anatomical sites together with additional blocks from sites of special interest were available in all cases. The histopathological diagnoses had been made on the

criteria of Lockhart-Mummery and Morson (1960), Cook and Dixon (1973), and Schachter and Kirsner (1975). This pool of material formed the background for the study.

The cases that had caused diagnostic difficulty were identified from the hospital's pathology files under three headings: (1) colitis unclassified, 'not further categorised'; (2) colitis unclassified, 'probably/possibly Crohn's disease'; and (3) colitis unclassified, 'probably/possibly ulcerative colitis'. A case had been indexed as colitis unclassified when no confident histopathological diagnosis was made from the surgical specimen. When some diagnostic attributes were present but were insufficient for a confident diagnosis, or atypical features were present that prevented a confident diagnosis, the category colitis unclassified had been qualified by the appropriate suffix, probably/possibly Crohn's disease or probably/possibly ulcerative colitis. Thirty such cases were found: 13 colectomies and 17 proctocolectomies. The pathological diagnosis on the surgical specimen had been made without reference to any available biopsy material.

From here onwards in this paper I substitute the term 'colitis indeterminate' in preference to that of 'colitis unclassified' used in the hospital pathology files, and, for simplicity, the subdivisions are considered as one in Table 1.

The surgical specimens from 30 confidently indexed cases of colonic Crohn's disease and from 30 confidently indexed cases of ulcerative colitis from the same period were selected for comparison. It was soon evident that the indeterminate group were almost all examples of acute severe disease, and two additional control groups were therefore

selected. They comprised confidently indexed cases that had undergone urgent surgery, this being defined as surgery performed within 24 hours of the decision to operate (Ritchie, 1974). Thirty examples of ulcerative colitis were chosen, but only two such examples of Crohn's colitis could be identified from the records. The mean number of sections examined per case was 11.

Without knowledge of the diagnostic category each case was assessed for a limited number of attributes with positive discriminating value for Crohn's disease or ulcerative colitis. The attributes were derived from the work of Lockhart-Mummery and Morson (1960, 1964), Lennard-Jones (1971), and Cook and Dixon (1973). They are shown in Table 1.

After this the available preoperative and post-operative material was examined and classified as either 'diagnostic' or 'not diagnostic'. Ulcerative colitis was diagnosed when the accepted collective appearances of mucin depletion, diffuse mucosal inflammation, and glandular irregularity or atrophy were seen. Crohn's disease was diagnosed when a granuloma was noted or when the following combination of features was seen: focal mucosal inflammation, regular glands with preserved epithelial mucin, aggregates of lymphocytes adjacent to crypts, submucosal inflammation (Price and Morson, 1975). Crohn's disease was also diagnosed if a normal rectal mucosa was found at follow-up examination in a case with a longstanding and typical clinical history.

There were preoperative biopsies in 23 cases, which had been carried out at a time varying from one day to as long as six years before surgery.

Table. 1 Incidence of selected discriminating attributes in each diagnostic category

	Colitis indeterminate	Ulcerative colitis		Crohn's disease	
		Urgent surgery	Elective surgery	Urgent surgery	Elective surgery
Number of cases	30	30	30	2	30
Attributes suggestive of Crohn's disease:					
Discontinuous disease or continuous disease but uneven distribution	2	—	—	1	27
Granulomas	14	2	—	1	—
Typical 'Crohn's' fissures	—	—	—	2	23
Transmural inflammation	4	—	—	2	12
Normal goblet cells with a regular glandular pattern and focal mucosal inflammation	28	20	—	2	30
	20	5	2	2	27
Attributes suggestive of ulcerative colitis:					
Continuous disease involving rectum	14	28	30	—	3
Goblet-cell depletion with glandular irregularity ± diffuse mucosal inflammation	10	25	28	—	3
Attributes suggestive of acute disease ± dilatation:					
Myocytolysis and capillary engorgement	21 (13 toxic megacolon)	22 (10 toxic megacolon)	—	—	—
Acute V-shaped clefts	18	6	—	—	—

From 10 of these 23 cases follow-up material was available. The follow-up period ranged from four months to nine years.

The clinical details were studied along with the radiological findings, and a final clinicopathological correlation was made.

Results

CLINICAL ACTIVITY AND OCCURRENCE OF ACUTE DILATATION

It was obvious early in the study that the activity of the disease process at the time of major surgery affected the subsequent pathology. Of the 30 cases, 27 (90%) indexed as colitis indeterminate had undergone urgent surgery. The figure contrasts with the overall hospital incidence of 30% among the confidently indexed cases of Crohn's disease and ulcerative colitis seen during the same period. Thirteen cases in the indeterminate group had radiologically proved toxic megacolon as had 10 cases among the confidently indexed cases of ulcerative colitis (Table 1). The urgent surgery in the two indexed cases of Crohn's disease was for localised perforation not for incipient dilatation.

PATHOLOGY

Two additional criteria were recorded (Table 1) that reflected the incidence of established or incipient colonic dilatation. These were myocytolysis with transmural capillary engorgement and multiple V-shaped clefts or fissures (Roth *et al.*, 1959). These

and the other features presented in the Table are now described in more detail.

Gross pathology

Fifty-eight of the confidently indexed cases of ulcerative colitis and 29 of the 32 confidently indexed cases of Crohn's disease had characteristic macroscopic appearances. In the indeterminate group 28 cases had a continuous pattern of disease, and in 23 of them this amounted to a total colitis. In 14 the distribution was uneven, regardless of its extent, and conformed to one of two patterns both of which would normally bias towards a diagnosis of Crohn's disease.

The first pattern was that of relative rectal sparing, sufficient to suggest segmental disease (Fig 1). Of the seven cases with this pattern, three were considered to be 'probably ulcerative colitis' on cumulative histological evidence. In only two cases was a diagnosis of Crohn's disease thought to be more likely. On histological examination the rectal mucosa was mildly abnormal in all seven. In the three judged to be 'probably ulcerative colitis' glandular irregularity was noted, but in the remainder the inflammation was mild and the features were equivocal.

The second pattern, that of intermittent ulceration (Fig. 2), was also seen in seven cases. This superficial resemblance to skip-like lesions was due to the variable intensity of the disease in different parts of the colon. The histology of the mucosa between the ulcers was of mild mucosal inflammation in

Fig. 1 A total proctocolectomy in a case indexed colitis indeterminate—probably/possibly ulcerative colitis. Relative rectal sparing is seen which, with the normal ascending colon, gives the impression of a segmental disease pattern. There is severe ulceration and dilatation of the transverse colon.

Fig. 2 *A total colectomy in a case indexed colitis indeterminate—probably/possibly ulcerative colitis. The variable intensity of disease in a severe total colitis with its patchy pattern of ulceration leaves areas that may, on superficial inspection, be mistaken for skip-like lesions.*

Fig. 3 *A typical fissure in Crohn's disease. The tract is lined by inflammatory cells with healthy muscle on each side. Accompanying mucosal ulceration is a minor feature. (Haematoxylin and eosin $\times 10$)*

Fig. 4 Multiple acute clefts with myocytolysis and capillary engorgement. These 'fissures' are characteristic of fulminant colitis, in this instance from a case indexed colitis indeterminate, probably ulcerative colitis. The diagnosis was confirmed by the histology of the subsequent proctectomy. (H and E $\times 15$)

Fig. 5 Severe myocytolysis and capillary engorgement, histological markers of incipient or established dilatation (H and E $\times 55$)

all instances. Three of these seven cases showed areas of glandular irregularity that were more like ulcerative colitis. The cumulative evidence favoured Crohn's disease as the probable diagnosis in two others of this group, and in two of the seven no tentative diagnosis could be offered.

Histopathology

Granulomas Granulomas are considered to be an absolute distinction between Crohn's disease and ulcerative colitis. They were present in 25 of the 32 confidently indexed cases of Crohn's disease and were absent in all the other categories of cases.

Fissuring ulceration Two qualitatively different forms of fissuring ulceration could be distinguished. Characteristic fissuring of Crohn's disease was seen in 14 of the 32 confidently indexed cases. The fissures were mostly single and narrow, had a prominent lining of inflammatory cells, and extended down into muscle (Fig. 3). They were not usually found in areas of extensive mucosal denudation. The muscle nearby, apart from the presence of an aggregated pattern of lymphocytes, was intact. They were also seen in four cases in which the other histological criteria were so atypical (Table 1)

that a diagnosis of Crohn's disease was not justified.

A second form of fissuring ulceration was present in 18 of the 30 cases indexed as colitis indeterminate. These were squat, V-shaped clefts, sparsely lined by inflammatory cells, often multiple, and usually in areas of extensive ulceration. Accompanying myocytolysis and capillary engorgement were invariably present in the adjacent bowel wall (Figs. 4, 5). They were seen in six patients who had undergone urgent surgery but in whom the cumulative attributes allowed a confident diagnosis of ulcerative colitis to be made.

It was not always possible to separate the two forms of fissure from each other or from deep undermining ulceration. The latter was a prominent feature in all cases of ulcerative colitis that had required urgent surgery (Fig. 6). Only unequivocal examples of each form were recorded.

Lymphoid aggregates and transmural inflammation

Two cases among those indexed as colitis indeterminate showed a transmural pattern of aggregated groups of lymphocytes. Even in these two it was poorly developed. It is a feature accepted as highly significant in the diagnosis of Crohn's disease (McGover and Goulston, 1968) and was present

Fig. 6 Florid undermining ulceration from a case confidently indexed ulcerative colitis. The muscle layer has not been breached, myocytolysis and the vascular element are absent (H and E $\times 10$)

Fig. 7 An acute fissure with an adjacent surviving mucosal island. Note the surprising lack of inflammation in the mucosa with such a severe disease process present. This case was indexed colitis indeterminate probably Crohn's disease. (H and E $\times 22$)

in 26 of the 32 control cases of Crohn's colitis. It was absent from all indexed cases of ulcerative colitis. In addition, non-aggregated, full-thickness, transmural inflammation with a mixed cellular pattern was seen in all the confidently indexed cases of Crohn's disease. It was also present in 28 of the 30 cases indexed as colitis indeterminate, and in 20 of the control cases of ulcerative colitis that had required urgent surgery (Table 1). In all the cases indexed ulcerative colitis (urgent surgery) and colitis indeterminate the transmural inflammation was related to regions of severe ulceration.

Mucosal glandular pattern and goblet-cell population

A regular glandular pattern with a preserved goblet-cell population and a focal distribution of mucosal inflammation was the dominant feature in 29 of the 32 confidently indexed cases of Crohn's

disease. Mucin depletion, an irregular or atrophic mucosa, and diffuse mucosal inflammation predominated in 53 of the 60 confidently indexed cases of ulcerative colitis. In the colitis indeterminate group these features were obscured or modified by extensive ulceration and stripping of the mucosa. However, in islands of surviving mucosa the inflammation was surprisingly mild, the epithelium regular, and the goblet-cell population well maintained (Fig. 7)—features that favour a diagnosis of Crohn's disease but seen here in cases that on cumulative evidence had been judged as 'indeterminate', which included four of the six cases subsequently proved to be ulcerative colitis.

Biopsy data

A confident diagnosis was made in seven cases from the indeterminate group of 23 with preopera-

tive biopsy reports available. In three cases the findings in a series of biopsies were diagnostic of ulcerative colitis. At the time of surgery the acute disease obscured any diagnostic pathology. Four cases could be classified as Crohn's disease before surgery. In two the findings in repeated rectal biopsies were normal, and in the other two, granulomas were present. Again, at surgery acute changes predominated. Furthermore, no granulomas were found.

Follow-up material permitted a confident diagnosis in an additional eight cases. Three were classified as ulcerative colitis and all showed a characteristic follicular proctitis in the rectal stump. The other five cases were indexed Crohn's disease. In two, the findings in multiple follow-up rectal biopsies remained normal, and in a third case they showed the characteristic inflammatory pattern of Crohn's disease. In the remaining two, granulomas were found in follow-up biopsies, one of which was four years after colectomy.

A final confident diagnosis was therefore made in 15 of the 23 cases with biopsy material available. When this final diagnosis was compared with the tentative diagnosis at the time of major surgery—for example, colitis unclassified, probably/possibly ulcerative colitis or Crohn's disease—a change was necessary in only two cases.

CLINICAL CORRELATIONS

The preoperative clinical diagnosis on the 30 indeterminate cases are shown in Table 2. In two, no diagnoses were made, and in 12, an element of doubt was expressed by the clinician. Initially, these were also correlated with the tentative diagnoses in the pathology index. There was clinicopathological disagreement in six of the 30 cases. At the end of the study there were 11 cases that carried a firm clinical opinion and a final confident pathological diagnosis. Clinicopathological conflict was present in two.

Table 2 *Clinical diagnoses in cases indexed colitis indeterminate*

2	Equivocal—no diagnosis
12	Crohn's disease (7 clinical doubt)
16	Ulcerative colitis (5 clinical doubt)

Discussion

I have applied the term 'colitis indeterminate' to a small group of cases in which there had been difficulty in distinguishing Crohn's disease from ulcerative colitis in the excised specimen. They form from 10 to 15% of the cases in many series of non-specific inflammatory disease (Hawk and Turnbull, 1966; Glotzer *et al.*, 1970; Kent *et al.*, 1970).

The results presented here suggest that most of them conform to a recognisable pathological and clinical pattern. In twenty-seven out of the 30 cases the patient had undergone urgent surgery and the pathological features were those associated with acute severe colitis, with or without accompanying toxic megacolon. The pathology of Crohn's colitis in the acute phase and that of ulcerative colitis have much in common (Roth *et al.*, 1959; Morson and Dawson, 1972). This was borne out here and was the cause of the diagnostic dilemma. Certain gross attributes of discriminating value in the chronic state are common to both conditions in the incipient or established fulminant phase. Relative rectal sparing, for example, is an accepted feature of the cumulative evidence for a diagnosis of Crohn's disease (Schachter and Kirsner, 1975). In this study it was seen in some indeterminate cases subsequently proved to be ulcerative colitis (Fig. 1). These unusual macroscopic appearances were probably accentuated by the healing effect of the topical and systemic corticosteroids given in all the cases.

A second misleading macroscopic appearance was of intermittent ulceration caused by the variable intensity of the disease in the acute episode (Fig. 2). Such a pattern suggests a diagnosis of Crohn's disease but was a feature of some cases proved by follow-up biopsies to be ulcerative colitis. Careful histological examination of these atypical macroscopic sites will avoid major errors in classification. Although no diagnostic pathology was seen minor changes suggesting previous inflammation were present in those cases eventually proven to be ulcerative colitis.

Certain accepted microscopical discriminating attributes also require careful interpretation in fulminant disease. A regular glandular pattern with a well-maintained goblet-cell population in diseased areas (Fig. 7) is normally a criterion for the diagnosis of Crohn's disease. Yet this was a marked feature in up to 60% of the indeterminate cases in which there was no other evidence for a diagnosis of Crohn's disease. Furthermore, some were subsequently proved to be ulcerative colitis. The sudden extensive but irregular stripping of the mucosa that occurs in the fulminant episode seems to leave intact less damaged mucosal islands. This would account for the intermittent pattern of ulceration seen macroscopically (Fig. 2) and the minimal inflammation of the mucosa covering many 'inflammatory pseudo-polyps' (Price, 1978). These are recognised as the hallmarks of an episode of previous severe disease.

Fissuring ulceration is another accepted diagnostic criterion of Crohn's disease (Lennard-Jones, 1971)

but in some of the cases presented here it was a feature of developing fulminant ulcerative colitis. However, the fissuring ulceration in the acute episodes of both Crohn's disease and ulcerative colitis had certain qualitative differences from that of the typical chronic case of Crohn's disease. In the latter they were usually single serpiginous tracts lined by inflammatory cells and penetrating through intact muscle (Fig. 3). The acute fissures that characterised the indeterminate cases seen in this study occurred mostly in areas of severe mucosal ulceration. They were multiple, short, V-shaped clefts sparsely lined by inflammatory cells. The adjacent muscle was always diseased, showing myocytolysis and intense capillary congestion (Figs. 4, 5), these two features being forerunners to the onset of dilatation. It is important to distinguish the two forms of fissuring. Only one is an attribute of Crohn's disease. Unfortunately, in the four cases that had the characteristic fissures of Crohn's disease but in which all the other features were atypical no biopsy material was available on which to make a final diagnosis. Although it seems safe to use the characteristic fissure as an unequivocal

distinguishing feature of Crohn's disease from ulcerative colitis, in this series the proof was still incomplete.

The acute fissure seems to be the end result of deep undermining ulceration, for a complete range was seen from one to the other (Figs. 3, 4, 6, 8). It is particularly difficult to differentiate acute fissuring from deep undermining ulceration and the fissure of chronic Crohn's disease when the acute variety occurs singly rather than in multiple groups (Fig. 8).

The absence of granulomas and well-formed lymphoid aggregates can be explained by case selection. Granulomas certainly occur in the acute forms of Crohn's disease (Glass and Baker, 1976; Fisher *et al.*, 1976; Anslem *et al.*, 1973), but from the literature the incidence appears to be less than that in chronic disease—25% as opposed to 60%.

It is well documented that transmural inflammation, an attribute usually associated with Crohn's disease, may be seen in severe ulcerative colitis (Lumb *et al.*, 1955; Roth *et al.*, 1959). This was confirmed in this investigation. As a diagnostic sign it must be evaluated with reference to the

Fig. 8 An early stage in the formation of the acute fissure. A penetrating ulcer is seen encroaching on the muscle in which there is some myocytolysis and numerous dilated vascular channels. The adjacent mucosa once again shows little evidence of the overall severity of disease. From a case indexed colitis indeterminate, probably/possibly ulcerative colitis. (H and E $\times 15$)

Fig. 9 Diagrammatic representation of the spectrum of pathology in non-specific inflammatory bowel disease. In the small percentage of cases pursuing the course represented by the thin lines, separation of Crohn's disease from ulcerative colitis begins to become difficult at point B (incipient dilatation) and may be impossible at point A (toxic megacolon). Biopsies at times represented by either end of the chart often solve the diagnostic dilemma.

disease activity. The data in Table 1 suggest that it is a good discriminating attribute in non-urgent cases but a non-specific feature in acute disease.

Focal or widespread myocytolysis plus intense mural and mucosal capillary engorgement were confined to the acute cases and were good indicators of incipient fulminant disease. The dissolution and disintegration of the muscle plays a constant role in the development of dilatation (Lumb *et al.*, 1955; Roth *et al.*, 1959) and is common to toxic megacolon of any cause. Its precise aetiology, however, is unknown. Drug therapy and damage to the neural plexus have been cited as precipitant causes (Norland and Kirsner, 1959).

From the review of the biopsy material in 23 of the cases a final confident diagnosis was made in 15. This emphasises the importance of establishing a sequential record of pathological changes in every case of non-specific inflammatory bowel disease. The surgical specimen represents only one instant in time in these two chronic diseases—a time in the case of a severe exacerbation when a confident diagnosis may not be available.

In those cases where a final histopathological diagnosis was possible agreement with the tentative pathological diagnosis was noted in 85% and with a confident clinical diagnosis in 80%. Justification for the use of the temporary terminology 'colitis indeterminate', probably/possibly ulcerative colitis or Crohn's disease, is that it avoids permanent errors in classification and is intellectually honest. Furthermore, it stimulates the clinician to seek for other confirmatory evidence yet acts as a therapeutic guideline.

Finally, the position of the cases labelled colitis

indeterminate in the spectrum of inflammatory bowel disease is illustrated (Fig. 9). They formed a small but distinctive group in which the diagnostic difficulty was due to a common pattern. They were clinically acute, severe cases that had undergone urgent surgery. Macroscopically there was usually a total colitis, sometimes with rectal sparing or an intermittent ulcerated pattern. Histologically the dominant pattern was of severe ulceration with non-specific transmural inflammation. In all cases there were foci of myocytolysis. Acute fissuring was prominent. The islands of surviving mucosa showed only minimal inflammation, were intensely congested, and had maintained a regular glandular pattern with preservation of mucin. Colonic dilatation was a variable finding. Most of these features would suggest a diagnosis of Crohn's disease in the chronic phase. Outside the acute phase of the disease reliable diagnostic attributes may again be found.

I thank Dr B. C. Morson, Mr H. E. Lockhart-Mummery, Dr J. Ritchie, Mr Norman Mackie, the Medical Illustration Department at Northwick Park Hospital, and Mrs S. McHale for their help in preparing this manuscript.

References

- Anslem, K., Rosenblum, S. A., and de Marco, V. (1973). Toxic megacolon in granulomatous colitis. *Henry Ford Hospital Journal*, **21**, 69-74.
- Cook, M. G., and Dixon, M. F. (1973). An analysis of the reliability of detection and diagnostic value of various pathological features in Crohn's disease and ulcerative colitis. *Gut*, **14**, 255-262.
- Farmer, R. G., Hawk, W. A., and Turnbull, R. B. Jr. (1968). Regional enteritis of colon: a clinical and pathologic comparison with ulcerative colitis. *American Journal of Digestive Diseases*, **13**, 501-514.
- Fisher, J., Mantz, F., and Calkins, W. G. (1976). Colonic perforation in Crohn's disease. *Gastroenterology*, **71**, 835-838.
- Glass, R. E., and Baker, W. N. W. (1976). Role of the granuloma in recurrent Crohn's disease. *Gut*, **17**, 75-77.
- Glutzer, D. J., Gardner, R. C., Goldman, H., Hinrichs, H. R., Rosen, H., and Zetzel, L. (1970). Comparative features and course of ulcerative colitis and granulomatous colitis. *New England Journal of Medicine*, **282**, 582-587.
- Hawk, W. A., and Turnbull, R. B., Jr (1966). Primary ulcerative disease of the colon. *Gastroenterology*, **51**, 802-805.
- Hywell-Jones, J., Lennard-Jones, J. E., Morson, B. C., Chapman, M., Sackin, M. J., Sneath, P. H. A., Spicer, C. C., and Card, W. I. (1973). Numerical taxonomy and discriminant analysis applied to non-specific colitis. *Quarterly Journal of Medicine*, **42**, 715-732.
- Kent, T. H., Ammon, R. K., and Denbesten, L. (1970).

- Differentiation of ulcerative colitis and regional enteritis of colon. *Archives of Pathology*, **89**, 20-29.
- Lennard-Jones, J. E. (1971). Definition and diagnosis. (Skandia International Symposia, 5) edited by A. Engel and T. Larsson., pp.105-112. *In Regional Enteritis (Crohn's Disease)*, Nordiska Bokhandels Förlag, Stockholm.
- Lennard-Jones, J. E., Lockhart-Mummery, H. E., and Morson, B. C. (1968). Clinical and pathological differentiation of Crohn's disease and proctocolitis. *Gastroenterology*, **54**, 1162-1170.
- Lewin, K., and Swales, J. D. (1966) Granulomatous colitis and atypical ulcerative colitis. *Gastroenterology*, **50**, 211-223.
- Lockhart-Mummery, H. E., and Morson, B. C. (1960). Crohn's disease (regional enteritis) of the large intestine and its distinction from ulcerative colitis. *Gut*, **1**, 87-105.
- Lockhart-Mummery, H. E., and Morson, B. C. (1964). Crohn's disease of the large intestine. *Gut*, **5**, 493-509.
- Lumb, G., Protheroe, R. H. B., and Ramsay, G. S. (1955). Ulcerative colitis with dilatation of the colon. *British Journal of Surgery*, **43**, 182-188.
- McGovern, V. J., and Goulston, S. J. M. (1968). Crohn's disease of the colon. *Gut*, **9**, 164-176.
- Margulis, A. R., Goldberg, H. I., Lawson, T. L., Montgomery, C. K., Rambo, N., Noonan, C. D., and Amberg, J. R. (1971). The overlapping spectrum of ulcerative and granulomatous colitis: A roentgenographic—pathologic study. *American Journal of Roentgenology Radium Therapy and Nuclear Medicine*, **113**, 325-334.
- Marshak, R. H., and Lindner, A. E. (1975). Radiologic diagnosis of chronic ulcerative colitis and Crohn's disease of the colon. In *Inflammatory Bowel Disease*, Edited by J. B. Kirsner, and R. G. Shorter, pp. 241-276. Lea and Febiger, Philadelphia.
- Morson, B. C., and Dawson, I. M. P., Eds. (1972). *Gastro-Intestinal Pathology*, p. 467. Blackwell, Oxford.
- Norland, C. C., and Kirsner, J. B. (1969). Toxic dilatation of colon (toxic megacolon): etiology, treatment and prognosis in 42 patients. *Medicine*, **48**, 229-250.
- Price, A. B. (1978). Inflammatory and lymphoid polyps of the large intestine. In *Pathogenesis of Colorectal Cancer*. (Major Problems in Pathology), edited by B. C. Morson., W. B. Saunders Company, Philadelphia (In press).
- Price, A. B., and Morson, B. C. (1975). Inflammatory bowel disease. The surgical pathology of Crohn's disease and ulcerative colitis. *Human Pathology*, **6**, 7-29.
- Ritchie, J. K. (1974). Results of surgery for inflammatory bowel disease: a further survey of one hospital region. *British Medical Journal*, **1**, 264-268.
- Roth, J. L. A., Valdes-Dapena, A., Stein, G. N., and Bockus, H. L. (1959). Toxic megacolon in ulcerative colitis. *Gastroenterology*, **37**, 239-255.
- Schachter, H., Goldstein, M. J., Rappaport, H., Fennessy M. B., and Kirsner, J. B. (1970). Ulcerative and 'granulomatous' colitis—validity of differential diagnostic criteria. *Annals of Internal Medicine*, **72**, 841-851.
- Schachter, H., and Kirsner, J. B. (1975). Definitions of inflammatory bowel disease of unknown etiology. *Gastroenterology*, **68**, 591-600.

Requests for reprints to: Dr A B. Price, Histopathology Department, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ.