An analysis of the reliability of detection and diagnostic value of various pathological features in Crohn's disease and ulcerative colitis

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SUMMARY Two pathologists have independently applied 95 separate pathological criteria to 50 cases of inflammatory large bowel disease firmly diagnosed clinically as 25 cases of Crohn's disease and 25 cases of ulcerative colitis.

The observer agreement in the recording of each feature has been calculated and correlations have been made between the pathological features and the final agreed diagnosis in order to obtain an estimate of the value of each feature in differential diagnosis.

The features which have been found to be most accurately observed and useful in the diagnosis of Crohn's disease include confluent linear ulcers, deep fissures, an aggregated inflammatory pattern, and sarcoid-like granulomata. The features which have been shown to be most accurate and valuable in the diagnosis of ulcerative colitis include a 'healed granular' mucosa, a continuous inflammatory pattern, an irregular gland pattern, and the absence of fissures.

The authors consider that the use of such accurate and valuable pathological criteria in the examination of inflammatory bowel disease would facilitate retrospective correlation with the clinical findings and help to clarify those intermediate cases which are at present a source of diagnostic difficulty.

Crohn's disease and ulcerative colitis, although fully described by many workers, including Rappaport, Burgoyne, and Smetana (1951), Van Patter, Bagen, Dockerty, Feldman, Mayo, and Waugh (1954), Morson (1968), and Mottet (1971), continue to present a problem in differential diagnosis. The two diseases share many pathological features and the distinguishing points are often subtle and ill defined, hence there have been many attempts to delineate the two (Lennard-Jones, Lockhart-Mummery, and Morson, 1968; McGovern, 1969; Kent, Ammon, and DenBesten, 1970). At present some cases which are difficult to classify pathologically may show clinical or radiological signs which enable at least a working diagnosis to be made. This seems unsatisfactory from a pathological point of view; the pathologist may merely endorse the clinical classifications by selecting those features which fit the clinical diagnosis. This can be taken as support for what may be an overrigid simplification by the essentially pragmatic clinician and may be masking a diversity of diseases which if investigated separately

would more readily be understood in pathogenetic terms.

It seems appropriate therefore that the pathological diagnosis of this group of diseases should be analysed as objectively as possible with a view eventually to classifying them into pathological rather than largely clinical entities. With this in mind the present study had two main objectives. First, we have set out to determine the degree of observer variation between two pathologists in their assessment of the macroscopic and histopathological features, the definition of these having been agreed beforehand. Our second objective was to correlate the detailed grading of these pathological features with the clinically and pathologically agreed diagnosis in order to assess their value in differential diagnosis.

Methods and Materials

The observations were made on 50 specimens of inflammatory bowel disease which had been resected between 1957 and 1971 and were selected randomly by a congruential method, using program SAS 59 implemented on a Mathatronics Mathatron 848

biostatistician computer, from two groups: Crohn's disease and ulcerative colitis, which had been firmly diagnosed clinically. The 25 cases of Crohn's disease were qualified in that they all had large bowel involvement so that they were more directly comparable with the 25 cases of ulcerative colitis.

The specimens had been stored in 10% formal saline and the original paraffin wax blocks and stained sections were also available.

The 95 criteria to be applied to these specimens were derived from the publications of Morson (1968), Mottet (1971), McGovern (1969), Williams (1964), Skinner, Whitehead, and Piris (1971), Filipe and Dawson (1970), Davis, Dockerty, and Mayo (1955), Montes, Milch, Berman, and Culver (1970), and from our own experience. They are enumerated in table I. This table also demonstrates the way in which each feature was recorded in some cases by grading into

	Grade					
	1	2	3	4	5	6
<i>Macroscopy</i>						
Length of ileum (cm)	0	1-5	6-10	11-20	21-40	> 40
Length of colon (cm)	0	1-30	31-60	61-80	81-100	> 100
Anal canal	Absent	Normal	Ulcerated	Sinus or fistula	Mucosal tag	Skin tag
Appendix	Absent	Present				
Site of main disease	Rectum	Rectum and proximal extension	Total large bowel	Patchy large bowel	Ileum and large bowel	Colon, sparing rectum
Length of main disease	1-10	11-30	31-60	61-80	81-100	> 100
Length of normal margin						
Proximal	0	1-5	6-10	11-20	21-30	> 30
Distal	0	To anal canal	1-10	11-20	21-30	> 30
Number of skip lesions	0	1	2	3	4	5 or more
Site of skip lesions	0	Ileum	Caecum	Colon	Rectum	Ileum and colon
Length (cm) of skip lesions (average)	0	1-3	4-6	7-10	11-20	> 20
Thickness of wall in diseased area	Normal	Thick	Thin			
Width of lumen in diseased area	Normal	Narrow	Dilated			
Internal fistulae	Present	Absent				
Number of polyps	0	0-20	21-100	> 100		
Average polyp size (mm)	0	1-4	5-8	> 8	> 8 with bridging	Deep fissure
Character of mucosa in area of disease	Healed or granular	Superficial, discrete	Superficial, irregular, confluent	Superficial, linear confluent		Cobblestoning
Adhesions	Present	Absent				
<i>Microscopy</i>						
Site of inflammation	Superficial	Superficial and submucosal	Transmural			
Inflammatory pattern	Continuous	Aggregated				
Submucosal thickening	Absent	Slight	Moderate	Marked		
Lymphoid aggregates (5 sections)	0	1-5	6-10	11-20	21-30	> 30
Lymph follicles (with germinal centres) (5 sections)	0	1-5	6-10	11-20	> 20	
Fissures (5 sections)	0	1-5	6-10	11-15	16-20	> 20
Polyps	Absent	Granulation	Epithelial	Adenomata		
Glandular dysplasia	0	Slight	Moderate	Severe		
Intestinal metaplasia	0	Slight	Marked			
Glandular hyperplasia	0	Slight	Marked			
Depth of ulceration	Absent	Superficial epithelium	Full gland	Muscle necrosis		
Spacing of glands	Normal	Slight to moderate increase	Marked			
Pattern of glands	Regular	Slight to moderate, irregular	Marked			
Height of glands	Normal	Slight to moderate, shortening	Marked			
Crypt abscesses (5 sections)	0	1-10	11-25	26-40	41-60	> 60
Crypt dilatations (5 sections)	0	1-10	11-25	26-40	41-60	> 60
Crypt abscesses with mucosal lymph aggregates (5 sections)	0	1-5	6-10	11-20	> 20	

Table I *Pathological features of the colitides and the method of grading*

one of six possible alternatives.

Most of the features are self explanatory, but a few points perhaps need to be clarified. In the category 'the character of the mucosa in the diseased area', by the term 'healed granular' we mean a non-ulcerated mucosa which does show a loss of mucosal folds and a 'morocco-leather-like' appearance. 'Superficial discrete ulcers', often circular and less than 3 cm in

diameter, are separated by intact mucosa, whereas 'irregular confluent ulcers' often extend in a serpiginous fashion throughout the length of the disease. 'Linear confluent ulcers' show a distinct parallel directionalism along the axis of the bowel, although they are by no means smoothly outlined. They may be seen in exaggerated form as 'deep fissures' or with fine crevices running transversely between

	Grade					
	1	2	3	4	5	6
<i>Microscopy</i>						
Ulcerated lymph aggregates (5 sections)	0	1-5	6-10	11-20	>20	
Mucosal cellularity	Normal	Slight increase	Moderate	Marked		
Mucosal cell type	Normal	Lymphocytes and plasma cells	Lymphoid cells and polymorphs	Lymphoid cells and histiocytes		
Eosinophils	Normal	Increased				
Submucosal cellularity	Normal	Slight increase	Moderate	Marked		
Submucosal cell type	Normal	Lymphoid cells and polymorphs	Lymphoid	Lymphoid and histiocytic	Predominant histiocyte and fibroblast	
Numbers of histiocytes	Normal	Slight increase	Many	Many transmural		
Epithelioid cell follicles (5 sections)	0	1-5	6-10	11-20	21-30	>30
Sarcoid-like granulomata (5 sections)	0	1-3	4-6	7-10	11-20	>20
Vascularity	Normal	Moderate increase	Marked increase			
Lymphangiectasia	Absent	Slight	Marked			
Submucosal oedema	Absent	Present				
Muscularis mucosae	Thin	Normal	Thick			
Submucosal oedema	Absent	Present				
Neuronal changes	Normal	Numerous bundles and/or ganglia	Neurofibromatoid change			
Arteritis	Absent	Present				
Paneth cells in colon	Absent	A few present	Numerous			
Fibrin	Absent	Present				
ZN	Negative	Positive				
Submucosal fibrosis	Normal	Slight	Moderate	Marked		
Mast cells	Reduced	Normal	Increased			
Mucosal argentaffin cells (2 sections)	0-10	11-20	21-40	41-70	71-100	>100
Reticulin (base of tubules)	Intact	Disturbed				
Glandular mucin H and E	Increased	Normal	Slight decrease	Partial decrease	Subtotal decrease	Total decrease
Gland mucin aldehyde fuchsin	Reduced	Normal	Increased			
Gland mucin alcian blue	Reduced	Normal	Increased			
Gland mucin PAS	Reduced	Normal	Increased			
PAS muciphages in lamina propria	Normal	Increased	Decreased			
PAS staining in granulomata	No granulomata	Negative	Positive			
Appendix	Absent	Normal	Acute	Histiocytic inflammation	Granulomata	
Anal canal	Absent	Normal	Acute inflammatory	Chronic inflammatory	Histiocytosis	Granulomatous
Lymph nodes (total no.)	1-10	11-20	21-30	31-40		
Lymph node sinus catarrh (%)	0	1-20	21-40	41-60	61-80	81-100
Lymph node follicular hyperplasia (%)	0	1-20	21-40	41-60	61-80	81-100
Lymph node sinus histiocytosis (%)	0	1-20	21-40	41-60	61-80	81-100
Epithelioid cell follicles (%)	0	1-20	21-40	41-60	61-80	81-100
LN sarcoid-like granulomata (%)	0	1-20	21-40	41-60	61-80	81-100
Lymph nodes follicular reticulin	Abundant	Sparse or absent				
Diagnosis	Ulcerative colitis	Crohn's	Atypical ulcerative colitis	Atypical Crohn's		
Previous clinical diagnosis	Ulcerative colitis	Crohn's				

Table I Pathological features of the colitides and the method of grading—continued

nodular elevations of mucosa thus forming a 'cobblestone' effect.

We included in the category of 'epithelioid cell follicles' collections of histiocytes or epithelioid cells even when rather small and ill defined, whereas the category of 'sarcoid-like granulomata' was reserved for well defined follicles of epithelioid cells complete with multinucleate giant cells of Langhan's type. 'Crypt dilatations', a reflection of glandular irregularity, are flask-shaped empty glands often with depleted mucin.

Before the study began the two observers worked together for a time to familiarize themselves with the conventions. During the actual study each observer was unaware both of the previous diagnosis of each specimen and of the other pathologist's verdict. The data were recorded by filling in a blank version of table I for each case and each pathologist.

Five sections for detailed microscopic study were selected during macroscopic examination of the specimen from diseased areas in the large bowel and special stains—aldehyde fuchsin, alcian blue, periodic acid Schiff, Martius scarlet blue, diazo reaction for argentaffin granules, Ziehl Neelsen, reticulin (Gordon and Sweet)—were performed on these five sections in order to demonstrate certain histological features.

Representative haematoxylin-and-eosin-stained sections from all other parts of the specimen were also examined.

The observations were stored and correlated on

a Jason suite of data preparation programs implemented on an English Electric KDF9 computer.

Results

The data contained on the two completed forms per patient were used to compare the observations of the two pathologists. A 100% agreement not only indicated agreement on the presence or absence of a feature but also showed that the same grading of severity or type was recorded. The percentage agreement of the observations of a feature was calculated as a proportion of the total positive incidence of that feature rather than of the number of cases in the series, ie, 50. Observer agreement of 90% and over was regarded as very accurate and between 70 and 90% as moderately so. Many observations were found to be accurate only when the grading was made less fine and in the analysis of the data many of the original groups were retrospectively amalgamated.

Table II shows those features for which the observers' agreement was moderate or good. The remainder, including such commonly used features as cobblestoning and lymphangiectasis, had less than 70% agreement. Table II also shows how some grades were fused together to attain better agreement.

A correlation was also made between the pathological observations of the senior author (M.G.C) and the diagnoses of the 42 cases in which both observers and the previous clinical diagnoses were

90%: Good Agreement	70-90%: Moderate Agreement	90%: Good Agreement	70-90%: Moderate Agreement
Macroscopy	Macroscopy	Microscopy	Microscopy
Length of ileum	Proximal margin of normality	Inflammatory pattern	Site of inflammation
Length of colon	Skip lesions (1) (2, 3, 4, 5, 6)	Fissures (1) (2, 3) (4, 5, 6)	Submucosal thickness (1, 2) (3, 4)
Anal canal	Site of skips	Depth of ulceration (1) (2, 3, 4)	Lymphoid aggregates (1, 2) (3, 4) (5, 6)
Appendix	Length of skips (1) (2, 3) (4, 5, 6)	Dysplasia (1) (2, 3, 4)	Lymphoid follicles (1) (2, 3) (4, 5, 6)
Site of main disease	Thickness of wall	Gland spacing (1) (2, 3)	Polyps
Length of main disease (1, 2) ¹	Width of lumen	Gland pattern (1) (2, 3)	Gland height (1) (2, 3)
(3, 4) (5, 6)	Polyps (1) 2, (3) (4)	Crypt abscesses (1) (2, 3) (4, 5, 6)	Crypt dilatations (1) (2, 3) (4, 5, 6)
Distal margin of normality	Average polyp size	Sarcoid-like granulomata (1)	Submucosal cellularity (1, 2) (3, 4)
Healed granular mucosa	Superficial discrete ulcers	(2, 3, 4) (5, 6)	Histiocytes (1, 2) (3, 4)
Superficial linear confluent ulceration	Superficial irregular confluent ulceration	Appendix	Epithelioid cell follicles (1) (2, 3) (4, 5, 6)
Deep fissures		LN sarcoid-like granulomata (1) (2, 3) (4, 5, 6)	Vascularity (1) (2, 3)
			Submucosal oedema
			Neuronal changes
			Submucosal fibrosis (1, 2) (3, 4)
			Argentaffin cells (1, 2) (3, 4) (5, 6)
			Glandular mucin H & E (1, 2) (3, 4) (5, 6)
			Glandular mucin alcian blue
			Glandular mucin PAS
			PAS muciphages in lamina propria (1, 2) (3)
			Anal canal normality
			Anal canal acute inflammation
			LN epithelioid cell follicles (1) (2, 3, 4, 5, 6)

Table II Observer variation in grading of pathological features of the colitides

¹Figures within brackets refer to column numbers in table I and indicate how the grades have been amalgamated to produce better agreement.

all in agreement, thereby ensuring that those cases were all entirely typical. This gave an assessment of the value of these features in the differential diagnosis. Fisher's exact probability test was used with Tocher's modification to compare the incidence of each observation in the two diseases. This enabled tables III and IV to be made, in which the observations which had a significantly different incidence in ulcerative colitis and Crohn's disease are listed with their corresponding significance. Eight cases were not included in the correlation of observations and diagnoses. Of these one case was excluded because the firm clinical diagnosis was Crohn's disease, but both pathologists diagnosed ulcerative colitis. The other seven cases were excluded because the pathologists were not able to classify them confidently although they were able to indicate which form they most resembled. Of four cases diagnosed pathologically as atypical ulcerative colitis, two were clinically ulcerative colitis and two were previously called Crohn's disease. Similarly the three cases labelled pathologically as atypical Crohn's

disease had all been regarded clinically as Crohn's disease.

Some pathological changes were not seen in the series—these were acid-fast bacilli and adhesions—and, therefore, they have not been included in any of the tables subsequent to table I. PAS positivity of granulomata was also excluded because it was invariably present and merely reflected the incidence of granulomata which could in any case be accurately recorded.

Discussion

There is a range of appearances in inflammatory diseases of the colon which form a continuous spectrum, the ends of which are easily labelled as either ulcerative colitis or Crohn's disease. Between these extremes any given feature may vary in frequency or severity and independently of the other pathological changes. This results in an infinite number of pathological appearances and great difficulty in separating the diseases into pathological

Probability of the Different Incidences Occurring by Chance	Pathological Features	Incidence of Observations		Observer Agreement
		23 Cases of Ulcerative Colitis	19 Cases of Crohn's Disease	
Very low (1% or less)	<i>Macroscopy</i>			
	Bowel wall thickened	4	14	Moderate (70%)
	Superficial discrete ulcers	3	10	Moderate (84%)
	Confluent linear ulcers	0	7	Good (91%)
	Deep fissures	0	7	Good (100%)
	<i>Microscopy</i>			
	Transmural inflammation	4	18	Moderate (78%)
	Aggregated inflammatory pattern	0	16	Good (98%)
	Submucosal thickening	1	15	Moderate (82%)
	Fissures present	8	18	Good (94%)
	Submucosal cellularity increased	7	19	Moderate (80%)
	Submucosal cells:			
	lymphocyte and histiocyte	0	16	Poor (62%)
	Histiocytes numerous	2	16	Moderate (86%)
	Epithelioid cell follicles	0	19	Moderate (86%)
	Sarcoid-like granulomata	0	19	Good (90%)
	Neuronal changes	2	10	Moderate (88%)
	Submucosal fibrosis	1	12	Moderate (74%)
	Glandular mucin depletion slight	8	16	Moderate (86%)
	Anal canal granulomas	0	7	Poor (67%)
	Lymph node epithelioid cell follicles	0	18	Moderate (84%)
	Lymph node sarcoid-like granulomata	0	17	Good (90%)
	Lymph node reticulin increase	0	6	Poor (35%)
Low (1-5%)	<i>Macroscopy</i>			
	Appendix absent	2	7	Good (100%)
	Length of disease 30-80 cm	10	15	Good (92%)
	Skip lesions	0	4	Moderate (89%)
	Bowel lumen narrow	8	13	Moderate (72%)
	Cobblestoning	0	4	Poor (66%)
	<i>Microscopy</i>			
	Full mucosal thickness ulceration	10	15	Good (91%)
	Mucosal histiocytes prominent	0	4	Poor (64%)
	Mast cells increased	6	11	Poor (54%)
	PAS muciphages lamina propria normal or increased	11	15	Moderate (82%)
	Lymph node sinus histiocytosis	2	8	Poor (33%)

Table III Observations useful in the diagnosis of Crohn's disease

Probability of the Different Incidences Occurring by Chance	Pathological Features	Incidence of Observations		Observer Agreement	
		23 Cases of Ulcerative Colitis	19 Cases of Crohn's Disease		
Very low (1% or less)	<i>Macroscopy</i>				
	Length of disease >80 cm	13	2	Good	(92%)
	Bowel wall of normal thickness	17	4	Moderate	(70%)
	Healed granular mucosa	12	0	Good	(92%)
	<i>Microscopy</i>				
	Superficial inflammation	7	0	Moderate	(78%)
	Superficial and submucosal inflammation	12	1	Moderate	(78%)
	Continuous inflammatory pattern	23	3	Good	(98%)
	Submucosal thickening absent or slight	22	4	Moderate	(82%)
	Fissures absent	15	1	Good	(94%)
	Gland pattern irregular	23	13	Good	(92%)
	Gland height reduced	18	7	Moderate	(82%)
	Submucosal cellularity normal or slight increase	16	0	Moderate	(80%)
	Submucosal inflammatory cells mainly lymphoid	15	1	Poor	(62%)
	Histiocytes normal or only slightly increased	21	3	Moderate	(86%)
	Submucosal fibrosis normal or slight	22	7	Moderate	(74%)
	Anal canal normal	16	2	Moderate	(84%)
Low (1-5%)	<i>Macroscopy</i>				
	Anal canal normal	12	3	Good	(96%)
	Total large bowel disease	13	4	Good	(98%)
	<i>Microscopy</i>				
	Dysplasia	15	5	Good	(92%)
	Gland spacing increased	23	15	Good	(92%)
	Submucosal inflammatory cells: lymphoid and polymorphs	7	1	Poor	(62%)
	Muscularis mucosae thinned	7	1	Poor	(56%)
	Mast cells reduced	9	1	Poor	(54%)
	Gland mucin severely depleted	8	1	Moderate	(86%)
	PAS muciphages in lamina propria reduced	12	4	Moderate	(82%)

Table IV Observations useful in the diagnosis of ulcerative colitis

entities (Schachter, Goldstein, Rappaport, Fennessy, and Kirsner, 1970; Glotzer, Gardner, Goldman, Hinrichs, Rosen, and Zetzel, 1970).

By concentrating on those points which correlate most often with clinical impression it has been possible to define the classical clinico-pathological types and to adopt a rather casuistical approach towards the atypical cases, classifying them either according to the clinical impressions or by allowing a few pathological features to assume more importance when need arises.

The resulting confusion and imprecision mean that many patients allocated to a single diagnostic category do not share a homogeneous pathological picture and this probably explains why experimental work in these diseases is so inconsistent (Kraft, 1971). The great need is for pathologists to describe cases in detail without clinical opinion prejudicing their reporting and to concentrate less on forcing the case before them into a largely clinically defined category.

The situation is made more complex because there is inevitably some variation in the accuracy of observation of different pathological features. A feature may be thought to be useful but may be so difficult to define or observe that one pathologist's assessment of that point may differ from that of other pathologists. For this reason we have set out

initially to establish, at least in typical cases, which features can be accurately recorded and similarly interpreted by other pathologists before assessing the value of those same features in reaching independently an identical diagnosis to that of the clinician. Having established those features which can be accurately observed, it would be helpful in prospective work to record all such features in unselected cases, including atypical ones, and establish any correlations there might be between the pathological features and clinical and radiological findings. This may reveal those features or pattern of features which are distinctive of one or other of the two diseases. We do not now suggest that only those features listed in tables II, III, and IV as both useful and accurate should be used, since this whole study is based on cases selected for their typicality. The results, however, indicate those features which can be given greatest reliance. It is also possible that an individual pathologist can reproducibly record some features which are not similarly interpreted by other pathologists. Nevertheless, diagnosis of typical cases should be based on features of significant value, as in tables III and IV, bearing in mind the likely inaccuracy in observation of each feature and the varying pattern of incidence that occurs while still remaining highly significantly different. For example,

while the incidence of fissures and granulomata is significantly different in the two diseases, the numbers concerned for fissures are eight and 18 and for granulomata 0 and 19 in ulcerative colitis and Crohn's disease respectively.

An individual pathologist may subsequently find that he is accurate in his own observation of a particular point not listed as having good observer agreement and thus place more weight on this if it is diagnostically valuable.

Although overlapping of the appearances of ulcerative colitis and Crohn's disease is accepted (Lumb and Prothero, 1958; Glotzer *et al*, 1970; Schachter *et al*, 1970), this does not necessarily imply a unitary disease entity but merely indicates that some pathological changes are common to both diseases and that the essential features or combination of features which distinguish one disease from the other have not been defined or accepted.

Ultrastructural evidence has been provided to support the concept of Crohn's disease being a single disease entity distinct from ulcerative colitis by Turnbull and Cook (1973), who pointed to the neuronal hyperplasia, predominant lymphocyte infiltration, and relatively undisturbed epithelium as consistent features of Crohn's disease but not of ulcerative colitis. These same points were seen not only in the granulomatous Crohn's cases but in those cases free of granulomata which constitute about 40% of the total (Williams, 1964; Morson, 1971; Cook, 1972).

In the present study neuronal changes, previously reported by Davis *et al* (1955), and relatively unchanged epithelia were also found more frequently in Crohn's disease than in ulcerative colitis, the difference being highly significant. Both features were recognized with great reliability by the two pathologists.

It can be seen from tables III and IV that other features show a highly significant difference in incidence in the two diseases and are also highly accurately recorded. These include confluent linear ulceration, macroscopic deep fissures, an aggregated pattern of inflammation, and sarcoid-like granulomata as indications of Crohn's disease, and a 'healed granular' mucosa, the absence of fissures, irregular glands, and a continuous pattern of inflammation as pointing to ulcerative colitis. Some features such as cobblestoning of the mucosa and numbers of mast cells, although of significantly different incidence in the two diseases, were not consistently observed by both pathologists. Still other features previously reported as helpful in differential diagnosis, such as crypt abscesses, lymphangiectasia, submucosal oedema, and changes in the glandular reticulin pattern (Mottet, 1971), did not have a significantly

different incidence in the two diseases. Likewise we contradict the implication by Watkinson, Thompson, and Goligher (1960), Saltzstein and Rosenberg (1963), and Schachter *et al* (1970) that granulomata can be found in ulcerative colitis. This feature was invariably accurately observed and a constant indicator of Crohn's disease.

This preliminary study seems to indicate that by accurate observation of a wide range of pathological parameters it may become possible to clarify the middle ground of the colitides and we have shown that some features can be relied on more than others. Correlation of these accurately observed features with clinical data may eventually confirm Crohn's disease as a syndrome comprising a number of diseases as suggested by Hywel-Jones, Card, Chapman, Lennard-Jones, Morson, Sackin, and Sneath (1970) or indicate that it is a single entity as suggested by clinical impression and supported to some extent by ultrastructural observations. It may well be that the whole spectrum of ulcerative colitis and Crohn's disease represents the effects of two aggressive processes, one humoral and the other granulomatous, the importance of each varying from case to case.

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