LEADING ARTICLE

The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications

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In recent years, investigators have readdressed the complex issues involved in the classification of inflammatory bowel diseases. In 2003, a Working Party of investigators with an interest in the issues involved in disease subclassification was formed with the aim of summarising recent developments in disease classification and establishing an integrated clinical, molecular, and serological classification of inflammatory bowel disease. The results of the Working Party were reported at the 2005 Montreal World Congress of Gastroenterology. Here we highlight the key issues that have emerged from discussions of the Montreal Working Party and the relevance to clinical practice and research activities.

In recent years, several stimuli have led investigators to readdress the complex issues involved in the classification of inflammatory bowel diseases. From the clinician's perspective, accurate classification of these diseases would have potential benefits with respect to patient counselling, assessing disease prognosis, and particularly with choosing the most appropriate therapy for each disease subtype. The perspectives of basic scientists have been subtly different, driven by an attempt to understand the pathophysiology of the different manifestations of Crohn's disease, ulcerative colitis, and indeterminate colitis. Overlap between the clinical and research based agendas has become even more apparent with identification of novel genetic determinants and serological markers which have proven useful with respect to subclassifying disease at the bedside, but may also allow new insights into disease pathogenesis.

In 2003, a Working Party of investigators with an interest in the issues involved in disease subclassification was formed, with the objective of summarising recent developments in disease classification and examining the practicability of developing an integrated clinical, molecular, and serological classification of inflammatory bowel disease. The results of the Working Party were reported at the 2005 Montreal World Congress of Gastroenterology.[1] A number of key issues were addressed at length, and controversies, consensus issues, as well as a research agenda were identified. The present review highlights the key issues that have emerged from discussions of the Montreal Working Party and the relevance to clinical practice and research activities.

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CLINICAL CLASSIFICATION OF CROHN'S DISEASE: FROM VIENNA TO MONTREAL

The issues of subclassification of Crohn's disease by phenotype have been reviewed in recent years. The International Working Party that issued its report in Rome in 1991 proposed a classification based on anatomical distribution, operative history, and clinical behaviour (inflammatory, fistulising, or stenotic disease). However, this classification was felt inappropriate for clinical application in the following years, and the World Congress of Gastroenterology in Vienna in 1998 provided an opportunity for reconsidering and reanalysis of this classification.[2] The resulting Vienna classification of Crohn's disease considered age of onset (A), disease location (L), and disease behaviour (B) as the predominant phenotypic elements. Although the Vienna classification is still not widely used in clinical practice, researchers have increasingly returned to it and have assessed its applicability and utility. The Montreal revision of the Vienna classification has not changed the three predominant parameters of age at diagnosis, location, and behaviour, but modifications within each of these categories have been made.

With respect to age of onset, the Montreal classification allows for early onset of disease to be categorised separately as a new A1 category for those with age of diagnosis at 16 years or younger, whereas A2 and A3 account for age of diagnosis at 17–40 years and >40 years, respectively (table 1). This change reflects numerous studies demonstrating that specific serotypes or genotypes are more frequently found in early onset Crohn's disease.[3–6] These findings may reflect the presence of specific biomarkers in this subset of patients but equally likely may illustrate the importance of this cohort in identification of novel genetic and serological markers. The modification was largely to allow for the investigation and categorisation of paediatric onset disease, both in clinical practice and for molecular and serological studies.

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Abbreviations: IBDU, inflammatory bowel disease, type unclassified; ASCA, anti-Saccharomyces cerevisiae antibody; ANCA, antineutrophil cytoplasmic autoantibody

Table 1 Vienna and Montreal classification for Crohn's disease

	Vienna	Montreal
Age at diagnosis	A1 below 40 y A2 above 40 y	A1 below 16 y A2 between 17 and 40 y A3 above 40 y
Location	L1 ileal L2 colonic L3 ileocolonic L4 upper	L1 ileal L2 colonic L3 ileocolonic L4 isolated upper disease*
Behaviour	B1 non-stricturing, non-penetrating B2 stricturing B3 penetrating	B1 non-stricturing, non-penetrating B2 stricturing B3 penetrating p perianal disease modifier†

*L4 is a modifier that can be added to L1–L3 when concomitant upper gastrointestinal disease is present.
†"p" is added to B1–B3 when concomitant perianal disease is present.

mutually exclusive. The major difficulty had arisen with the inability of the Vienna classification to allow upper gastrointestinal disease to coexist with more distal disease. As investigations for upper gastrointestinal involvement become more accessible and feasible with the introduction of wireless capsule endoscopy, it is apparent that upper gastrointestinal disease is relatively common, and may coexist with ileal and with colonic disease. Therefore, in the revised Montreal classification these parameters are no longer mutually exclusive.

Finally, two critical issues were identified for integration into the Montreal classification regarding disease behaviour. There are now substantial data that perianal fistulising disease is not necessarily associated with intestinal fistulising disease, and it was felt that perianal disease alone required separate subclassification.[7] A further issue with regard to classification of disease behaviour is the observation that disease behaviour is dynamic over time. Recent studies have reinforced this, demonstrating that patients with predominantly inflammatory disease at diagnosis are very likely to develop either fistulising or stricturing complications within 5, 10, and 20 years.[7] The authors of the Montreal classification considered at length whether a stipulated time point should be given before disease behaviour might be classified. This approach was seen to have both benefit as well as limitations, particularly in comparing studies from different centres, and also in retrospective analyses. The consensus statement allows for a stipulated time to be set in studies of this aspect of disease. It should also be noted that these changes to disease location and behaviour are supported by an evolving body of evidence demonstrating that site of disease, behaviour, and disease progression are all variables that are likely to be identified by genetic and serological markers.[8–11]

ULCERATIVE COLITIS

In contrast with Crohn's disease, neither the Rome nor the Vienna Working Parties had addressed subclassification of ulcerative colitis. On reviewing the present literature, a subclassification system for ulcerative colitis incorporating an assessment of disease extent and severity of an individual relapse of disease were felt to be of critical relevance for recommendation by the Working Party. However, unmet needs were clearly apparent in discussion, of which the most acute appeared to be the need for a classification of longitudinal disease progression, or disease behaviour over time—that is, the frequency of disease relapse and course of disease during the natural history.

The Montreal classification of disease extent of ulcerative colitis allows extent to be defined into three subgroups (table 2).

The subclassification was felt to have clear biological relevance in terms of the response of patients to medical therapy (differential response to topical therapy), and also to be validated by the natural history of the disease, with respect to rates of medication usage, hospitalisation, or colectomy. Moreover, the risk of colorectal malignancy was also felt to provide further validation for this subclassification. In addition, numerous studies show association of specific serological and genetic markers with extensive ulcerative colitis, making this subset of particular importance in the study of its pathophysiology.[12 13]

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The major drawback of the extent based classification system was clearly identified to be instability of disease extent over time, once again underlining the dynamic nature of inflammatory bowel disease. Progression of disease extent over time, together with regression, have been well identified and accepted. The actual risk of proximal extension of proctitis over 10 years is estimated to be as great as 41–54%.[1] Progression of left sided colitis may be even higher. The contrary observation is also valid—that disease extent may regress over time, with regression rates estimated from a crude rate of 1.6% to an actual rate of 71% after 10 years.[1] In light of this, the Montreal classification proposes the maximal extent of involvement as the critical parameter.

Table 2 Montreal classification of extent of ulcerative colitis (UC)

Extent		Anatomy
E1	Ulcerative proctitis	Involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction)
E2	Left sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3	Extensive UC (pancolitis)	Involvement extends proximal to the splenic flexure

Table 3 Montreal classification of severity of ulcerative colitis (UC)

Severity		Definition
S0	Clinical remission	Asymptomatic
S1	Mild UC	Passage of four or fewer stools/day (with or without blood), absence of any systemic illness, and normal inflammatory markers (ESR)
S2	Moderate UC	Passage of more than four stools per day but with minimal signs of systemic toxicity
S3	Severe UC	Passage of at least six bloody stools daily, pulse rate of at least 90 beats per minute, temperature of at least 37.5˚C, haemoglobin of less than 10.5 g/100 ml, and ESR of at least 30 mm/h

ESR, erythrocyte sedimentation rate.

The Working Party has suggested the classification of severity of relapse into four disease activity/severity categories (table 3).

The term fulminant colitis is in variable use, and the Working Party felt that the research agenda in ulcerative colitis must address whether this term has prognostic, value or clinical utility, contrasted with severe relapse of ulcerative colitis, or should be abandoned. Further issues for the research agenda in classification of ulcerative colitis have been identified, and these will need to be addressed. The issue of classification of disease behaviour over time has considerable importance with respect to clinical management, and may also have a direct implication with respect to genetic studies. One of the few studies to have addressed this to date are the detailed studies from Copenhagen where patients with ulcerative colitis were classified into those with prolonged remission, those with intermittent symptoms, and those with continuous disease activity.[14] Validation of this classification system and introduction into a further classification scheme may well be directly helpful but will require examination of cohorts of patients, identified either retrospectively or prospectively.

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At the present time, evidence to introduce age of onset as a separate subgroup in ulcerative colitis was felt to be unproven, either with respect to clinical utility or in a basic research agenda. Other issues that clearly require consideration in a research agenda would be the need for separate classification of colonic disease associated with sclerosing cholangitis. Disease behaviour, extent, and malignancy risk in cohorts of patients with concomitant primary sclerosing cholangitis is increasingly well characterised and, although uncommon, the need for these patients to have a separate classification may well become apparent in further studies.

INDETERMINATE COLITIS

There is considerable confusion about the appropriate use of the term indeterminate colitis. The Working Party reviewed the initial definition introduced by Ashley Price in 1978.[15] Price suggested that the diagnosis be made only following colectomy in patients in whom the features were not sufficient to allow a diagnosis of either Crohn's disease or ulcerative colitis but were sufficient to allow a diagnosis of inflammatory bowel disease affecting the colon. In subsequent years, the use of the term has been widened by clinicians to allow for patients in whom inflammatory bowel disease affecting the colon is apparent on clinical and endoscopic features but in whom histology and all other clinical parameters do not allow a clear diagnosis of either Crohn's disease or ulcerative colitis.

The Montreal Working Party has recommended that the term ''indeterminate colitis'' should be reserved only for those cases where colectomy has been performed and pathologists are unable to make a definitive diagnosis of either Crohn's disease or ulcerative colitis after full examination. In contrast, the term ''inflammatory bowel disease, type unclassified'' (IBDU) is suggested for patients in whom there is evidence on clinical and endoscopic grounds for chronic inflammatory bowel disease affecting the colon, without small bowel involvement, and no definitive histological or other evidence to favour either Crohn's disease or ulcerative colitis. In these patients, clearly infection would have been ruled out before the term IBDU might be applied.

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The Working Party discussed the prospects for the use of serological and genetic markers in refining the classification of indeterminate colitis and IBDU further. Both established serological markers (anti-Saccharomyces cerevisiae antibody (ASCA), antineutrophil cytoplasmic autoantibody (ANCA)) and novel markers currently emerging (OmpC, cBir flagellin, I2) were felt to carry the potential for helping further the understanding of the classification of these entities.[13] The research agenda in this area focused heavily on the need for further integration of serological and genetic markers in these patients, and the need for prospective analyses as to whether a combination of currently available markers might help in predicting the further course of patients with colonic IBDU. In addition, it was felt strongly that the increasing use of capsule endoscopy, and novel diagnostic methods in the relatively near future, lead to a further need to revisit this classification scheme.

INTEGRATED MOLECULAR DIAGNOSIS OF IBD

Although the initial catalyst for the inception of the Working Party had been the goal of developing an integrated classification scheme, involving clinical, serological, and genetic markers, there was widespread agreement within the Working Party that such an integrated classification is not at present justified. However, the progress and interest in this area is evident, and subgroups of the Working Party examined in detail the current stage of knowledge with respect to serological markers, specific genetic markers, and the importance of geographical and ethnic variation: all of these reports were felt essential in defining a further research agenda for an integrated classification.

Serological markers

The two most widely studied serological markers in inflammatory bowel disease in recent years have been p-ANCA and ASCA. The clinical utility of p-ANCA or ASCA testing in the diagnosis of inflammatory bowel disease, in patients with non-specific gastrointestinal symptoms, is limited because of the varying seroprevalence of these antibodies in patients with inflammatory bowel disease and the inadequate sensitivity of the assays. The Working Party

felt unable to recommend the use of these serological markers in routine clinical practice as diagnostic tools at present; the potential advantages of non-invasive testing, even in triaging patients for definitive investigation, particularly in children, were noted and discussed.

The prospects for widening the panel of serological markers, to increase diagnostic specificity and sensitivity and also to help subclassify inflammatory bowel disease, was reviewed in some detail, in view of the number of recent papers suggesting that serological responses to microbial antigens may help advance this area. Most progress has been made with respect to substratification of Crohn's disease, with the identification of novel markers (anti-OMPC and anti-I2, and most recently the anti-CBir1 flagellin antibodies).[16] Consistent data now suggest that the combination of ASCA, ANCA, anti-OmpC, and anti-I2 may help in the subclassification of Crohn's disease, in particular that these serological markers are associated with a complicated and severe disease behaviour, including need for surgery.[10 11]

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The research agenda for this field included the need for independent validation and the need for a minimal dataset for research studies. In concluding the assessment of the role of serological markers at the present time, the Working Party determined that the use of these markers for diagnosis is not currently justified, given the limited sensitivity of available markers. Similarly, therapeutic decisions in patients with indeterminate colitis may not at the present time rely on serological markers alone. However, the prospects for development in this area were emphasised by the Working Party—identification of novel markers and novel serotype-phenotype relationships—and may not only help understand disease pathophysiology but also be of clinical use. The need for independently executed studies with consistent phenotypic description of the patients involved was felt to be a critical item for progress.

Role of genetic markers in disease classification: progress and prospects

Although identification of the NOD2/CARD15 gene was again a strong catalyst for the research carried out by the Working Party, members of the Working Party were unanimous in feeling that integration of NOD2/CARD15 genotype, or other genetic markers, could not be justified on current evidence. The current literature supports the finding that CARD15 variants are consistently more common in Caucasian patients with Crohn's disease than in healthy controls, and that a gene dosage effect exists. The overall risk for developing Crohn's disease in simple heterozygotes (in whom there is one variant and one wild-type chromosome) is suggested by recent analysis and by meta-analysis to be in the region of 2.4 (95% confidence intervals 2.0–2.9) and the risk for persons with two mutant chromosomes (simple homozygotes or compound heterozygotes) was estimated at meta-analysis to be 17.1 (confidence intervals 10.7–27.2).[17] In Asians, Arabs, Africans, and African Americans the contribution of these variants and genotype risks are either reduced or entirely absent.[18] However, even within Europe there is clearly variation in the importance of the NOD2/CARD15 allelic variants in contributing towards disease susceptibility—the importance of these variants in Northern Europe (Scandinavia, Scotland, Ireland) is less than in the index studies reported from Central Europe, and the intriguing possibility that different founder effects are important in Northern European populations with Crohn's disease has emerged.[19 20] The complexities of heterogeneity between populations is further compounded by the heterogeneity within populations and genotype-phenotype relationships.

> ''The conclusions with respect to the NOD2/CARD15 experience in inflammatory bowel disease have led to recommendations with respect to clinical classification of disease''

In the majority of phenotypic analyses, NOD2/CARD15 mutations are associated with ileal rather than colonic Crohn's disease. Meta-analysis demonstrated that the odds ratio for ileal disease, compared with colonic disease, was 2.5 (confidence intervals 2.0–3.2).[14] Association between NOD2/CARD15 status and complicated Crohn's disease, fistulising or stenosing, has emerged. Data from individual studies are not entirely consistent, reflecting not only the complexity of disease but also the inconsistency of clinical classifications used in studies reported thus far. A series of other genotype-phenotype relationships with respect to the NOD2/CARD15 gene have been examined. Areas that have been subjected to study, with positive associations, have concluded increased risk for surgery, lower weight at diagnosis, younger age at diagnosis, presence of granulomas, and disease response to drug therapy. Once again, as for serological markers, the conclusions with respect to the NOD2/CARD15 experience in inflammatory bowel disease have led to recommendations with respect to clinical classification of disease.

The investigators examined at some length the contribution of other genetic determinants of inflammatory bowel disease. The contribution of the HLA region has been widely studied, even before genome wide scanning approaches had implicated the region. Although clear and consistent allelic associations have now emerged both in Crohn's disease and in ulcerative colitis, in addition to associations with extra intestinal manifestations, the low sensitivity and specificity of the disease associated allelic variants was again felt to limit the use in diagnosis and classification. Consistent recommendations emerge from the HLA studies with respect to the need for rigorous phenotypic classification schemes to be uniformly adopted; the need for detailed studies of sufficient magnitude to detect the effects of genetic determinants on disease susceptibility and on behaviour.[1]

Other genes and loci discussed included the IBD5 region, a strongly replicated association, but a region for which the causal genes are as yet unproven, and the roles of the multidrug resistance 1 (MDR1), drosophila discs large homologue (DLG5), and toll-like receptor 4 (TLR4) genes. Current studies implicating these novel genetic determinants suggest that geographical together with ethnic variations exist, and moreover genotype-phenotype relationships of potential value are also present. However, evidence to implicate any individual marker at the moment was felt insufficient to recommend applicability in a classification scheme.[1]

The changes suggested to the Vienna classification for Crohn's disease for age of diagnosis, disease location, and behaviour may benefit investigating relationships between genotype and phenotype, notably the distinction between perianal fistulising and abdominal fistulising disease. Incorporation of an ulcerative colitis classification system into the Montreal classification is also of key importance; specifically, many of the genetic and serological findings apply uniquely to the group with E3 ulcerative colitis. The issue of disease progression for both Crohn's disease and ulcerative colitis is critical in studies relating genotype to phenotype, as disease behaviour and severity will undoubtedly change over time and it will be critical to define the time point at which a given behaviour might be characterised. The minimal datasets in genotype-phenotype relationships was thought to be a critical matter—ethnicity and geographical distribution are both clearly

important. Once again there was uniformity of thought in recommending the need for parallel prospective studies, using a commonly accepted minimal dataset for research studies, which it was thought is likely to be considerably expanded compared with a purely clinical useful classification scheme.

SUMMARY

The Montreal Working Party has addressed aspects of clinical definition and classification within inflammatory bowel disease and the current status of genetic and serological studies. With respect to Crohn's disease, ulcerative colitis and indeterminate colitis, a number of suggestions were made for refining clinical subclassification, and the use of terminology. The recommendations with respect to Crohn's disease and ulcerative colitis were made so that these might be used in clinical practice and also for the purposes of future genetic and serological studies in inflammatory bowel disease. The course of ulcerative colitis over time is an important aspect of disease felt to be lacking in robust validated data, such that recommendations could not be adequately made.

> ''The recommendations with respect to Crohn's disease and ulcerative colitis were made so that these might be used in clinical practice and also for the purposes of future genetic and serological studies in inflammatory bowel disease''

The unsatisfactory use of the term indeterminate colitis was discussed at length and recommendations for the novel term IBDU were made. A number of aspects of the Montreal classification require validation now, and authors have acknowledged this throughout the document. The need for independent validation of the classification and assessment of interobserver variation is likely to be critical, and indeed plans are underway to compare the relative effect of interobserver variation in the Montreal classification compared with the Vienna classification. The goal of integrating molecular and serological markers is very exciting but is premature at the present time. Adoption of a uniform minimal data set for research studies will allow the sensitivity and specificity of markers available and emerging to be ratified; it is anticipated that within the next 5–10 years an integrated classification will become a feasible and sensible reality.

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