

# A Simple Classification of Crohn's Disease: Report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998

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**Summary:** Crohn's disease is a heterogeneous entity. Previous attempts of classification have been based primarily on anatomic location and behavior of disease. However, no uniform definition of patient subgroups has yet achieved broad acceptance. The aim of this international Working Party was to develop a simple classification of Crohn's disease based on objective variables. Eight outcome-related variables relevant to Crohn's disease were identified and stepwise evaluated in 413 consecutive cases, a database survey, and by clinical considerations. Allocation of variables was conducted with well-defined Crohn's disease populations from Europe and North America. Cross-table analyses were performed by chi-square testing. Three variables were finally elected: Age at Diagnosis [below 40 years (A1), equal to or above 40 years (A2)], Location

[terminal ileum (L1), colon (L2), ileocolon (L3), upper gastrointestinal (L4)], and Behavior [nonstricturing nonpenetrating (B1), stricturing (B2), penetrating (B3)]. The allocation of patients to these 24 subgroups proved feasible and resulted in specific disease clusters. Cross-table analyses revealed associations between Age at Diagnosis and Location, and between Behavior and Location (all  $p < 0.001$ ). The Vienna classification of Crohn's disease provides distinct definitions to categorize Crohn's patients into 24 subgroups. Operational guidelines should be used for the characterization of patients in clinical trials as well as for correlation of particular phenotypes with putative biologic markers or environmental factors. **Key Words:** Crohn's disease—Classification—Age—Location—Behavior—Stratification—Clinical research.

## INTRODUCTION

Clinical research over the last decade has suggested that Crohn's disease (CD) is a heterogeneous entity itself that requires individual approaches for management, as indicated by the wide variations of intestine affected and the different endoscopic expressions of involvement (1).

First attempts to classify patients with CD were based on the anatomic location of disease, proposed by Farmer and colleagues in 1975 (2). These anatomic distinctions have proven implications with respect to medical therapy (3), indications for surgery (4), the risk of postoperative recurrence in childhood (5), and they have withstood the test of time. Moreover, specific disease locations have been linked to serological or genetic markers such as antineutrophil antibodies (6,7).

More recently, Greenstein et al. proposed that perforating and nonperforating indications for initial surgery may separate patients with CD into two different clinical forms (8). Indeed, recurrent postoperative disease was

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often of the same clinical pattern as the primary disease, and patients resected for perforating indications (fistula, abscess, or free perforation) also appeared to require reoperation faster than patients with nonperforating indications (obstruction, medical intractability, hemorrhage, or toxic dilatation). These two types have been linked to differences in intestinal IL-1 $\beta$  and IL-1 receptor antagonist mRNA expression (9). The ability of preoperative disease behavior to predict patterns of postoperative recurrence has been confirmed in other studies (10,11).

These phenotypic characteristics were further refined in the development of the "Rome classification" (12). Beside location (stomach/duodenum, jejunum, ileum, colon, rectum, anal—perianal) and behavior (primarily inflammatory or primarily fistulizing or primarily fibrostenotic) the Rome classification included extent of disease (localized or diffuse) and operative history (primary or recurrent). This classification could theoretically result in as many as 756 subgroups of CD. Although components, in particular location and behavior, have been used in a wide array of modifications, insufficient definitions of disease behavior types yielded only a fair interobserver agreement (13). Hence, it has not been widely adopted in its original form. The aim of this international Working Party, therefore, was to develop a simple classification of CD based on objective and reproducible clinical variables.

## MATERIALS AND METHODS

### The Working Party

Five international meetings were held between October 1996 and May 1998. At the first meeting the Working Party suggested that disease characteristics may be described as either constant (with potential impact on long-term outcome) or fluctuating (varying during the course of disease), since fluctuating parameters (e.g., symptoms) were more relevant for measuring disease activity, while constant parameters (e.g., location) were better suited for disease phenotype. The Working Party decided to focus on constant variables (Location, Extent, and Behavior), although Response to Steroids was also considered in the first test sheet (Washington draft). During the summer of 1997 the members of the Working Party tested this draft prospectively on 413 consecutive ambulatory patients at 10 centers to assess the feasibility of the classification.

By December 1997, when the Working Party met in Paris, the results from the evaluation of the Washington draft were discussed, and the panel reevaluated its previous selection of variables. It was proposed to subdivide

small and large bowel each into three parts and thereby obviate the need for a separate variable for Extent. Location was recorded at three predefined points in the course of disease (at diagnosis, during follow-up [before the first resection], and after first surgery). The term "perforating" was replaced by "penetrating" and a hierarchy for disease Behavior was established in order to avoid combinations. The variable Response to Steroids proved to be fluctuating, hard to define, not relevant to 17% of patients who had never received corticosteroids, and was therefore also omitted. It was further agreed that items sensitive to interventions should generally be avoided. By the end of the meeting, the following variables were being actively considered: Age at Onset, Family History of IBD, Location, Behavior, and Extraintestinal Manifestations (Paris draft).

Coincidentally, the Task Force on Disease Quantitation (chaired by D.B.S.) of the International Organisation for the Study of Inflammatory Bowel Disease (IOIBD) was considering the potential for developing a standardized IBD database and classification to assist in genetic studies and clinical trials. In January 1998, the IOIBD in conjunction with the Crohn's and Colitis Foundation of America sponsored a meeting in New York City. C.G. was invited to ensure coordination of efforts with the Working Party. At the meeting the variable Age at Diagnosis was added and Location was expanded to 10 subgroups. Minor changes were also made within Extraintestinal Manifestations. The New York draft then served as the basis for the database survey.

### Evaluation of the New York Draft

Crohn's disease registries from Copenhagen (Denmark;  $n = 373$ ), Oslo (Norway,  $n = 232$ ), Toronto (Canada,  $n = 1,411$ ), New York (USA,  $n = 516$ ) and Chicago (U.S.A.,  $n = 2,600$ ) were included in this survey. Among these five data sets, two were population based (Copenhagen, Oslo) and three were from referral centers (medical: University of Chicago, The Mount Sinai Hospital New York; surgical: Mount Sinai Hospital Toronto).

#### *Age at Onset/Age at Diagnosis*

Age at Onset and Age at Diagnosis were highly correlated (Pearson's  $r = 0.97$ ). More data were available on Age at Diagnosis (median 82%, range 77–100%) than on Age at Onset (median 58%, 0–99.5%).

#### *Family History*

Data were available from four centers. First degree relatives with IBD were present in 17% (range 11–30%)

and other relatives with IBD in 11% (range 3–15%). The availability of family data varied between centers and countries and the accuracy of family data was generally unconfirmed.

#### *Location*

The New York draft collected data at four points in time: at diagnosis, during follow-up, at resection, and after resection. Most data were available only “at diagnosis” and “during follow-up.” About one-half of patients had undergone resection (median 55%, 15–56%). Although all registries had collected data on Location, it was impossible to compare data among centers for the following reasons: first, the anatomic sites documented differed among centers; second, different definitions were used for specific sites (e.g., some centers recorded ileocecal disease as ileocolonic disease, others as pure ileal disease); third, some registries had information only on the most recently involved sites of disease. It could be shown, however, that the extent of involvement present at time of diagnosis may progress (Toronto) or regress (Oslo) during follow-up.

#### *Behavior*

The New York draft requested data from three points in the course of disease. One center (Oslo) had collected data according to this protocol, another had data only at the time of surgery (Toronto). The proportion of patients with stricturing or penetrating disease was small at the time of diagnosis (10.2%) but increased in the population that underwent surgery (97% [Oslo] or 58% [Toronto]).

#### *Extraintestinal Manifestations*

All centers had information available sorted by gross organ involvement (i.e., joint, skin, eyes) without further disease specification (except Toronto). The proportions of patients with involvement of joints were 18% (11–33%), of skin 7% (5–19%), and of eyes 3% (0–9%).

#### **Validation of the Classification**

An internal validation was performed on the final classification prior to the presentation of the Working Party consensus in Vienna, September 1998. Populations from Europe [Copenhagen county, Denmark, n = 368 (14); and Oslo (Southeast Norway counties), Norway, n = 232 (15)] and North America [Olmsted county, Minnesota, n = 225 (16)] were classified using the three variables and 24 subgroups. The data shown are the percent-

age of the total number of patients from these populations with data available for classification (which is different among variables). Cross-table analyses were performed by chi-square testing to look for associations between the three variables in the CD populations. Correction for multiple testing was done by the Bonferroni-Holm procedure (17). To further tabulate the proportions of patients in each subgroup, data from CD registries were applied separately (surgical referral: Toronto, Canada; medical referral: New York, U.S.A.; see above).

## **RESULTS**

### **The Vienna Classification of Crohn's Disease**

At the final meeting it was decided to reduce the proposed variables and subgroups from the New York draft to allow for no more than 40 mutually exclusive subgroups. Upon evaluation of the data from the database trial it was finally agreed to define patients in terms of three variables giving a potential total of 24 subgroups (Table 1):

- Age at Diagnosis: below 40 years (A1), equal to or above 40 years (A2)
- Location: terminal ileum (L1), colon (L2), ileocolon (L3), upper GI (L4)
- Behavior: nonstricturing nonpenetrating (B1), stricturing (B2), penetrating (B3)

In order not to lose important information from the New York draft, however, it was agreed to collect those variables that would not be part of the classification in a separate section called “further data to be collected.” Besides patient identification data, this section finally included Gender (female/male), Ethnicity (caucasian/black/asian/other), Jewish (yes/no/partly), Family History of IBD (first degree relatives/other/none), Extraintestinal Manifestation (yes/no).

### **Operational Guidelines**

Age at Diagnosis was defined by the age when the diagnosis of CD was first definitively established by radiology, endoscopy, pathology, or surgery.

Location was defined as the maximum extent of disease involvement at any time before the first resection. Minimum involvement for a location was the presence of any aphthous lesion or ulceration. Mucosal erythema or edema would not suffice. For classification at least both a small bowel and a large bowel examination are required. The four mutually exclusive clusters of Location were: (L1) Terminal ileum: disease limited to the lower

**TABLE 1.** *The Vienna Classification of Crohn's Disease*

Age at diagnosis: <sup>1</sup>	A1, <40 years A2, ≥40 years
Location: <sup>2</sup>	L1, Terminal ileum <sup>3</sup> L2, Colon <sup>4</sup> L3, Ileocolon <sup>5</sup> L4, Upper GI <sup>6</sup>
Behavior:	B1, nonstricturing nonpenetrating <sup>7</sup> B2, Stricturing <sup>8</sup> B3, Penetrating <sup>9</sup>

Further data to be collected:

Patient's name: \_\_\_\_\_ Date of birth: \_\_\_/\_\_\_/\_\_\_

Sex: female / male

Ethnicity: Caucasian / Black / Asian / other: \_\_\_\_\_

Jewish: yes / no / partly

Family history of IBD: 1st degree relatives / other / none

Extraintestinal manifestation: yes / no

<sup>1</sup> The age when diagnosis of Crohn's disease was first definitively established by radiology, endoscopy, pathology or surgery.

<sup>2</sup> The maximum extent of disease involvement at any time before the first resection. Minimum involvement for a location is defined as any aphthous lesion or ulceration. Mucosal erythema and edema are insufficient. For classification at least both, a small bowel and a large bowel examination, are required.

<sup>3</sup> Disease limited to the terminal ileum (the lower third of the small bowel) with or without spill over into cecum.

<sup>4</sup> Any colonic location between cecum and rectum with no small bowel or upper gastrointestinal (GI) involvement.

<sup>5</sup> Disease of the terminal ileum with or without spill over into cecum and any location between ascending colon and rectum.

<sup>6</sup> Any disease location proximal to the terminal ileum (excluding the mouth) regardless of additional involvement of the terminal ileum or colon.

<sup>7</sup> Inflammatory disease which never has been complicated at any time in the course of disease.

<sup>8</sup> Stricturing disease is defined as the occurrence of constant luminal narrowing demonstrated by radiologic, endoscopic or surgical-pathologic methods with prestenotic dilatation or obstructive signs/symptoms without presence of penetrating disease at any time in the course of disease.

<sup>9</sup> Penetrating disease is defined as the occurrence of intraabdominal or perianal fistulas, inflammatory masses and/or abscesses at any time in the course of disease. Perianal ulcers are also included. Excluded are postoperative intraabdominal complications and perianal skin tags.

third of the small bowel with or without spill over into cecum; (L2) Colon: any colonic location between the cecum and rectum with no small bowel or upper gastrointestinal (GI) involvement; (L3) Ileocolon: disease of the terminal ileum and any location between the ascending colon and rectum; (L4) Upper GI: any disease location proximal to the terminal ileum (excluding the mouth) with or without additional involvement of terminal ileum or colon.

Since the most reliable data on complicated disease are available after resection from surgical or pathological reports, no specific limit in the course of disease was set to define Behavior. The term Nonstricturing Nonpenetrating Disease was reserved for uncomplicated inflammatory disease without evidence of stricturing or pen-

etrating disease. Stricturing Disease was defined as the occurrence of constant luminal narrowing demonstrated by radiologic, endoscopic, or surgical examination combined with prestenotic dilatation and/or obstructive signs or symptoms but without evidence of penetrating disease. Penetrating Disease was defined as the occurrence of intraabdominal or perianal fistulas, inflammatory masses, and/or abscesses at any time in the course of the disease. Although perianal ulcers were included in the definition, postoperative intraabdominal complications and perianal skin tags were excluded. Interventional success (e.g., by medical therapy) would not allow to downgrade Location or Behavior.

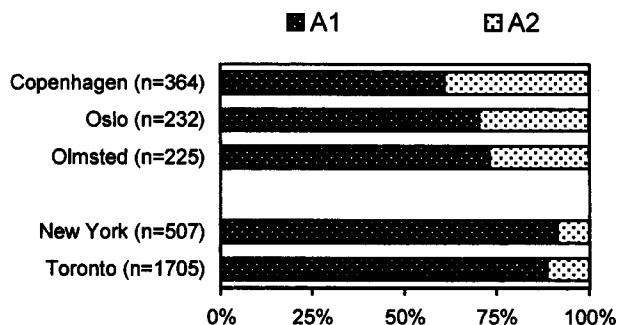
## Internal Validation

### *Distribution within Variables*

From the CD populations, 821 patients had data available on Age at Diagnosis: 69.9% were classified as A1 (below 40 years) and 30.1% as A2 (equal to or above 40 years). The specific allotment was different between Crohn's populations and referral databases ( $p < 0.001$ ) (Fig. 1). Appropriate assignment of patients to Location was possible in 791 individuals: 26.1% were classified as L1 (terminal ileum), 35.8% as L2 (colon), 23.3% as L3 (ileocolon), and 14.7% as L4 (upper GI). The ratio of L3 to L4 disease in Olmsted was inverse to the other populations under investigation and also to the referral databases (Fig. 2). Apart from referral registries, Behavior data were available from Oslo and Olmsted only ( $n = 401$ ). B1 (nonstricturing nonpenetrating) was found in 52.4%; B2 (stricturing) in 21.7% and B3 (penetrating) in 25.9% of the patients (Fig. 3). The higher number of B3-rated patients in the Olmsted county as compared with the Oslo population most likely reflects the differences in the median duration of follow-up between these populations (13.4 years versus 5.5 years).

### *Allocation to All Subgroups*

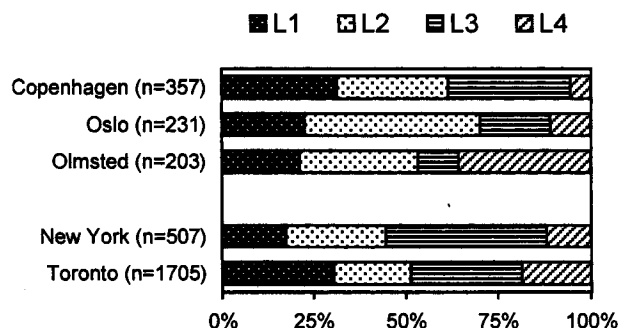
Patients ( $n = 401$ ) were allocated to all 24 subgroups as shown in Table 2. There was one subgroup (A1L2B2) that did not include any patient and another subgroup that indicated a cluster with 20.4% of all patients (A1L2B1). This observation could be due to the relatively low total number of patients in the study. Indeed, data available from the Toronto registry showed 1.3% of patients in the former subgroup (A1L2B2). The cluster (A1L2B1) filled with 9% (New York) and 15% (Toronto), respectively.



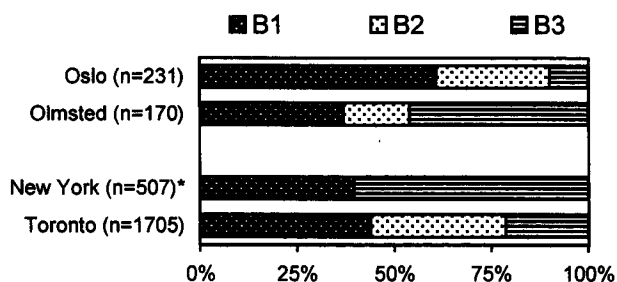
**FIG. 1.** Allocation of patients to the variable Age at Diagnosis. Crohn's populations from Europe (Copenhagen, Oslo) and North America (Olmsted) were classified by Age at Diagnosis (A1: below 40 years; A2: equal to or above 40 years). In these three populations, 69.9% were classified as A1 and 30.1% as A2. When compared with Crohn's patients from referral centers (medical: New York, U.S.A.; surgical: Toronto, Canada), the allotment was highly different. The data shown are the percentage of the total number of patients with data available for the classification.

#### Cross-Table Analyses

An association between the variables Age at Diagnosis and Location was found ( $p < 0.001$ ;  $n = 741$ ) (Table 3). The result showed the predominance of L2 (colon) in A2 patients (age at diagnosis equal to or above 40 years). A parallel association was demonstrated concerning the variables Behavior and Location ( $p < 0.001$ ;  $n = 401$ ) (Table 4). This demonstrated the predominance of L2 (colon) in the B1 (nonstricturing nonpenetrating) group and of L1 (terminal ileum) and L3 (ileocolon) in the B2 (stricturing) group. The third analysis between Age at Diagnosis and Behavior did not quite reach the level of significance ( $p = 0.091$ ;  $n = 401$ ) (Table 5).



**FIG. 2.** Allocation of patients to the variable Location. Crohn's populations from Europe (Copenhagen, Oslo) and North America (Olmsted) were classified by Location (L1: terminal ileum; L2: colon; L3 ileocolon; L4: upper gastrointestinal). Altogether in these three populations, 26.1% were classified as L1, 35.8% as L2, 23.3% as L3, and 14.7% as L4. Different allotments exist between specific populations (Copenhagen, Olmsted) and between referral centers (medical: New York, U.S.A.; surgical: Toronto, Canada). The data shown are the percentage of the total number of patients with data available for the classification.



**FIG. 3.** Allocation of patients to the variable Behavior. Crohn's populations from Europe (Oslo) and North America (Olmsted) were classified by Behavior (B1: nonstricturing nonpenetrating; B2: stricturing; B3: penetrating). In these populations, B1 was found in 52.4%, B2 in 21.7%, and B3 in 25.9% of the patients. The allotments are highly different depending on the populations studied. The data shown are the percentage of the total number of patients with data available for the classification. \*No data available on B2.

#### DISCUSSION

There are currently no absolute gold standards for the diagnosis, differential diagnosis, and classification of inflammatory bowel diseases (12,18). Our Working Party has attempted to make further progress in the classification of patients with CD. The goals of this classification were to standardize the description of study populations in clinical trials and to aid in correlating putative etiologic (genetic or environmental) factors with particular clinical phenotypes. With these goals in mind, the Working Group sought a classification system based on well-defined clinical and pathologic variables containing a manageable number of possible subgroups. It became clear that achieving this goal would require compromises that ultimately led to the exclusion of potentially valuable classification variables from the current classification system.

Of the candidate variables from the New York draft, Age at Onset and Age at Diagnosis were thought to be relevant and reproducible. Since both of these variables were highly correlated and data were more reliable and more readily available on Age at Diagnosis, the Working Group decided to use only Age at Diagnosis in the final classification. The possibility was discussed to cut the population into three subgroups (below 20 years, 20 to 39 years, and 40 years and above). However, the incidence of CD peaks in the third decade of life, whereas after the age of 40 it shows a flat stable curve (14) or even a second peak (15,16). It was therefore finally agreed to bisect this variable at age 40. Another reason not to open a specific childhood subgroup was to limit the potential total (which would have increased to 36).

The discussion of the variable, Location, had focused on the question as to which of the four points in time is

**TABLE 2.** Allocation of patients to all 24 subgroups of the Vienna Classification

	A1			A2			Σ
	B1	B2	B3	B1	B2	B3	
L1	8.5	6.0	4.2	1.2	2.0	0.5	22.4
L2	20.4	0	5.0	11.5	0.2	2.7	39.9
L3	5.0	6.2	4.2	1.7	1.0	0.2	18.5
L4	2.5	4.2	7.5	1.5	2.0	1.5	19.2
Σ	36.4	16.5	20.9	16.0	5.2	5.0	100

Percent of the total population (n = 401) is shown.

the most relevant for disease classification (at diagnosis, during follow-up, at resection, or after surgery). The most consistent point in time for Location was felt to be at the time of diagnosis. However, many patients may not have had a complete diagnostic workup at the time of diagnosis. On the other hand, data on resection and even after resection are available only from one-half of patients and besides might reflect the influence of surgical intervention more than the underlying spontaneous phenotype of disease. The Working Party finally decided to classify Location as the maximum extent of disease involvement at any time before the first resection. From a practical point of view, it was thought that most patients with CD would have had a complete workup prior to having a resection. This would provide an accurate classification and also obviate the influence of the surgical intervention per se. For those patients who are not resected the maximum extent of disease at any time was regarded appropriate.

Disease Behavior was also considered to be an important variable to include in the classification. One suggestion was that perianal involvement reflects more a disease Behavior (i.e., penetrating) than a specific disease Location. It was therefore decided to classify perianal disease as part of the variable Behavior. The combination of perianal and intraabdominal fistulas as penetrating Behavior is probably the most substantial modification from previous classifications (which mostly used the term "perforating"). However, despite the clinical relevance of fistulas in CD, only few studies have focused on the pathobiology of fistula formation. No data are

available yet showing a pathogenetic or biologic difference between perianal and intraabdominal fistulas. This endorsed us to combine both types of fistulas as penetrating phenotype (B3). This combination has already become relevant in terms of therapy (i.e., immunosuppressives) and has been previously applied in clinical trials (19). We also intended to separate primary fistulous disease (independent from stricture formation) from the group with fistulas secondary to strictures. This was, however, omitted because no precise distinction had been found by testing it in a series of patients (Washington draft).

The decision to relegate Gender, Ethnicity, Family History of IBD, and Extraintestinal Manifestations into the section Further Data To Be Collected was empirically done and based on the need to limit the total number of subgroups in the system. Family History of IBD was considered to be difficult to validate, as many patients were unaware of their family history and it was also difficult to confirm a positive family history. In addition this variable depends on the size of the individual family, the age of the patient, and can clearly change with the passage of time. A classification that included Extraintestinal Manifestations was considered as well but specific extraintestinal manifestations are too rare and fluctuate over time. When some manifestations would be lumped together (by organ, by relation to disease activity, or even as a single cluster) they would not further represent homogeneous groups.

The three variables of the Vienna classification might mimic different dimensions of disease. Classification by

**TABLE 3.** Cross-table analysis between Age at Diagnosis and Location

	A1	A2	Σ
L1	17.4	6.3	23.8
L2	21.6	15.1	36.7
L3	19.7	6.7	26.5
L4	9.0	4.1	13.1
Σ	67.7	32.3	100

p < 0.001 by the chi-square test.

**TABLE 4.** Cross-table analysis between Behavior and Location

	B1	B2	B3	Σ
L1	9.7	8.0	4.7	22.4
L2	31.9	0.2	7.7	39.9
L3	6.7	7.2	4.5	18.5
L4	4.0	6.2	9.0	19.2
Σ	52.4	21.7	25.9	100

p < 0.001 by the chi-square test.

**TABLE 5.** Cross-table analysis between Age at Diagnosis and Behavior

	A1	A2	Σ
B1	36.4	16.0	52.4
B2	16.5	5.2	21.7
B3	20.9	5.0	25.9
Σ	73.8	26.2	100

p = 0.091 by the chi-square test.

Age at Diagnosis (or onset) is used in a variety of monogenic inherited diseases. Early Age at Diagnosis is more often associated with major genetic abnormalities and complete loss of protein activity. Late onset of disease occurs in patients with minor mutations and residual activity. Thus, the variable Age at Diagnosis represents to some extent a genetic component of CD. Location, of course, delineates disease anatomy, another dimension, and Behavior describes the biology of disease with occurrence of specific pathological features.

In an effort to validate this classification, patients recorded in three well-defined populations and in two referral center databases were allocated among the 24 subgroups. The allocation proved feasible, with each of the 24 subgroups including some cases. Clusters with up to 20% of the total population were also present. To further clarify any relevance concerning the variables Age at Diagnosis and Behavior, the impact of each variable on Location was tested. Cross-table analyses showed that the A1 (age at diagnosis below 40 years) group has a distinct pattern of Location compared with the A2 group (age at diagnosis equal to or above 40 years). The same was shown for the different Behavior subtypes. We conclude both Age at Diagnosis and Behavior are associated with different disease locations and are therefore meaningful variables. The results of the internal validation confirm previous work (20), and demonstrate the consistency of these observations when accompanied by clear and specific definitions.

There are two potentially useful applications of this phenotypic classification. First, it could help to define the eligibility criteria for clinical trials and could serve to characterize more homogenous subgroups for statistical analysis and reporting. Standardized delineation of patient subgroups should facilitate the interpretation of a particular trial and the comparison with other trials. Second, correlations with biological markers (e.g., HLA haplotypes, cytokine polymorphisms, antineutrophil cytoplasmic antibodies, *antisaccharomyces cerevisiae* antibodies, etc.) and with environmental factors (e.g., smoking, diet, stress, childhood infections, etc.) could more clearly identify associations with specific disease

phenotypes. In case of a small study population, only one or two variables of the classification system might be applied in order to decrease the total of subgroups.

Whether the Vienna classification will have prognostic and therapeutic relevance remains to be determined. In other disease settings, phenotypic classification systems have proved useful. For instance, in patients with non-Hodgkin's lymphoma, the large number of potential disease subtypes appear to have a biologic basis with unique prognostic and therapeutic implications. Similarly, with solid tumors, the TNM classification system has both prognostic and therapeutic implications. It seems inevitable that with better understanding of etiologic mechanisms, future modifications to the Vienna classification will be required. In the interim, we encourage physicians worldwide to use this simple system for classification of all patients with Crohn's disease.

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