The Clustering of Other Chronic Inflammatory Diseases in Inflammatory Bowel Disease: A Population-Based Study

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See editorial on page 1117.

Background & Aims: **We aimed to discern the relative risk for several chronic inflammatory conditions in patients with ulcerative colitis (UC) and Crohn's disease.** ***Methods:*** **We used the population-based University of Manitoba IBD Database that includes longitudinal files on all patients from all health system contacts identified by International Classification of Diseases, 9th revision, Clinical Modification codes for visit diagnosis. From the provincial database we extracted a control cohort matching the IBD patients 10:1 by age, sex, and geography. We considered a potential comorbid disease to be present if the patient had 5 or more health system contacts for that diagnosis. The comorbid disease period prevalence was analyzed separately for patients with UC and Crohn's disease and a prevalence ratio was calculated comparing the IBD populations with the matched cohort.** ***Results:*** **There were 8072 cases of IBD from 1984 to 2003, including UC (n = 3879) and Crohn's disease (n = 4193). There was a mean of approximately 16 person-years of coverage for both patients and control patients. Both UC and Crohn's disease patients had a significantly greater likelihood of having arthritis, asthma, bronchitis, psoriasis, and pericarditis than population controls. An increased risk for chronic renal disease and multiple sclerosis was noted in UC but not Crohn's disease patients. The most common nonintestinal comorbidities identified were arthritis and asthma.** ***Conclusions:*** **The finding of asthma as the most common comorbidity increased in Crohn's disease patients compared with the general population is novel. These may be diseases with common causes or complications of one disease that lead to the presentation with another. Studies such as this should encourage further research into the common triggers in the organ systems that lead to autoimmune diseases.**

IBDs such as Crohn's disease and ulcerative colitis (UC) are considered to be diseases of immune dysregulation, occurring in patients with the appropriate genetic predispositions. This paradigm is shared by a number of other immune-mediated diseases, some of which are categorized as autoimmune diseases,[1] under the presumption that the body's immune system is reacting against self. Whether or not the body is reacting against self or foreign antigens, there has been a clinical impression that the diseases cluster together.[1,2] A genome scan study showed nonrandom clustering of susceptibility loci of autoimmune diseases supporting the clinical impression that these diseases may cluster in individual patients.[3] There are a number of immune-mediated diseases known to be increased in IBD. These are the classic extraintestinal manifestations that include arthritis, ankylosing spondylitis, erythema nodosum, pyoderma gangrenosum, iritis, uveitis and other inflammatory ocular disorders, and primary sclerosing cholangitis. In a previous study, we reported the first assessment of these conditions (except for arthritis) in a North American population–based study.[4] We reported higher rates for several of these conditions and that 6% of IBD patients concomitantly have 1 of these disorders and .3% have as many as 2 or more.

By using similar methodology we have pursued a population-based study assessing for a number of other chronic inflammatory conditions in patients with IBD. We have created a matched control group of patients not affected with IBD to determine the relative risks for these conditions in IBD. The finding of an increased association of chronic inflammatory diseases with either form of IBD could suggest a common genetic predisposition, common causative triggers, or possibly the triggering of one inflammatory condition secondary to the treatment of a primary inflammatory condition.

Abbreviations used in this paper: CI, confidence interval; ICD-9-CM, International Classification of Diseases, 9th revision, Clinical Modification; OR, odds ratio; PR, prevalence ratio.

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Materials and Methods

Data Sources

Data for this study were derived from the Manitoba Health administrative databases. Manitoba Health provides universal health insurance for Manitoba residents that includes coverage for physician and hospital services. Manitoba Health maintains computerized records that are based on the use of health care services by individuals in the province, including admissions to hospitals and physician visits. For each physician service the patient's identification, the date of service, the diagnosis (3-digit, International Classification of Diseases, 9th revision, Clinical Modification [ICD-9-CM] code), and the service tariff code are entered into a physician-claims database. Similarly, after each hospitalization, Manitoba hospitals submit an abstract to Manitoba Health that includes the patient's identification, the dates of admission and discharge, the attending physicians, and up to 16 ICD-9-CM diagnoses. These hospital separation records constitute the hospital file. The accuracy of these administrative health data has been shown for a number of medical conditions.[5]

Manitoba Health also maintains a population registry that contains dates of insurance coverage, family information, and address for Manitoba residents. Death reports from Manitoba Vital Statistics are reviewed routinely and are used to update the population registry. Since 1984, the Manitoba Health population registry has maintained a unique personal health identification number that is included with each physician claim record and each hospital separation record.

We have used the Manitoba Health databases previously to create the University of Manitoba IBD database.[6] This database includes all persons with a physician claim or hospitalization for a diagnosis of Crohn's disease (ICD-9-CM code 555.xx) or UC (ICD-9-CM code 556.xx) since 1984. To improve the accuracy of case definition, persons residing in the province for at least 2 years were designated as having IBD only if they had at least 5 separate physician claims and/or hospitalizations. Persons residing in the province for less than 2 years were included in the IBD cohort if they had at least 3 separate physician claims and/or records. The accuracy of this case definition is high (sensitivity and specificity, $\simeq$90%) in comparison with both self-report and chart review.[5] The specificity of 90% refers to the specificity among those with at least 1 physician or hospital claim for a diagnosis of Crohn's disease or UC. Because the vast majority of the population of Manitoba (>1,000,000) have no claims for either IBD diagnosis, the specificity of our definition actually is much closer to 100% in the general population. Recently, this methodology has been reproduced in a population-based study in Manitoba creating a multiple sclerosis database. This study found that for patients within Manitoba having at least 5 health system contacts (or if a resident in the province for 2 years or less, having 3 health system contacts), the sensitivity was 93% and the specificity was 99% of truly having multiple sclerosis.[7]

Study design and analysis. We selected all patients within our IBD database from April 1, 1984, to March 31, 2003 (19 years of data accrual). The data included the following possible immune-mediated diseases that might have occurred before, concurrent with, or after any initial contacts for IBD: asthma, bronchitis, arthritis, thyroiditis, multiple sclerosis, neuropathy (including hereditary and idiopathic peripheral neuropathies), myasthenia gravis, chronic renal disease, psoriasis, and pericarditis (Table 1 lists the ICD-9-CM codes for these diseases). In assessing arthritis we included both degenerative and immune-mediated arthritis, recognizing the potential lack of precision with coding by physicians for arthritis. The classic arthritis associated with either UC or Crohn's disease is neither considered to be osteoarthritis nor rheumatoid arthritis; hence it is unknown which arthritis code physicians would use most typically. We compared the period prevalence and prevalence ratios for osteoarthritis (ICD-9-CM code 715) with rheumatoid arthritis (ICD-9-CM 714).

Table 1. ICD-9-CM Codes for Diseases Assessed

Disease	ICD-9-CM codes
Asthma	493.xx
Bronchitis	491.xx
Arthritis	715.xx, 714.xx, 446.xx, 710.xx
Thyroiditis	245.xx
Multiple sclerosis	340.xx
Neuropathy	356.xx
Myasthenia gravis	358
Chronic renal disease	580.xx-583.xx
Psoriasis	691.xx
Pericarditis	420.xx, 423.1

Assessing renal diseases using administrative data is not simple. ICD-9-CM codes 580.xx include glomerulonephritis of various types, but ICD-9-CM 580.89 includes glomerulonephritis with interstitial (diffuse or focal) nephritis. ICD-9-CM code 581.x is for other glomerulonephritides that cause nephrotic syndrome and code 581.89 is for nephrotic syndrome associated with interstitial nephritis. ICD-9-CM code 582.x is for chronic glomerulonephritis (including 582.89 for chronic glomerulonephritis with interstitial nephritis) and code 583.x is for a variety of nephritides. Although it would be of great interest to attempt to differentiate renal diseases such as glomerulonephritis from interstitial nephritis, it may be unreliable to attempt this by using administrative data that rely on physician coding.

Between April 1, 1984, and March 31, 2003, there were 8072 patients who met the IBD case definition. Over time, 838 patients died and 756 patients moved out of the province. Manitoba Health lost track of 155 patients (these patients most likely moved out of the province as well). Tables 2 and 3 show a total of 8060 patients because 12 patients did not have matching controls. For Crohn's disease patients there were 16.39 $\pm$ 4.8 (SD) person-years of coverage. For UC patients there were 16.62 $\pm$ 4.53 (SD) person-years of coverage. The number of patients with IBD in Manitoba on March 31, 2003, was 6321.

Because the specificity of a single contact of any of these conditions is not known, we analyzed the data for having at

least 5 health system contacts. We chose this number because it proved to be associated with a sensitivity and specificity of approximately 90% for Crohn's disease and UC by self-report. By chart review, this administrative definition was associated with a sensitivity of approximately 90% for Crohn's disease and 75% for UC, and a specificity of approximately 90% for both Crohn's disease and UC. Five health system contacts also proved to be highly specific for a true diagnosis of multiple sclerosis in another population-based study conducted in Manitoba.[7] We present the data for both at least 1 health system contact and at least 5 health system contacts. The rationale for presenting the data for both 1 and 5 health system contacts is to show that the relationships are similar in both types of analysis. This reduces the likelihood that the associations found using the 5 contact rule are caused by greater medical contact and surveillance among those with IBD because the trend and magnitude of the associations are similar even at 1 contact. The 1 contact analysis is much more sensitive because it is highly unlikely that anyone with 1 of these conditions would go for a long period without any health system contacts, and also provides an upper limit for comorbidity period prevalence. However, all statistical analyses presented and conclusions made are based on data for at least 5 contacts. Our analysis was stratified for diagnosis of Crohn's disease vs UC and by sex and age.

Comparison With the General Population

A matched cohort design was used. Patients with IBD in the Manitoba IBD database (see earlier) were matched 1:10 to randomly selected members of the general population by age, sex, and postal area of residence. This control cohort was extracted from the population registry of Manitoba Health. Matched controls were selected based on the date of IBD diagnosis. Data on health system contacts were obtained through the patients' medical histories dating back to 1984 (the time at which personal health identification numbers were in use in the Manitoba Health system) and forward to 2003 for as long as the patient (IBD patient or control) remained alive and a resident of Manitoba. Hence, this is a clustering study. Period prevalence rates were calculated for the chronic diseases in Crohn's disease, UC, and control patients and prevalence ratios were calculated to determine the likelihood of having a chronic disease comorbidity in either Crohn's disease or UC compared with controls. This methodologic approach has been used by our group to study the associations of other disease entities with IBD patients.[8–10] For controls matched to the Crohn's disease cohort there were 15.91 $\pm$ 5.15 person-years of coverage. For controls matched to the UC cohort there were 15.99 $\pm$ 5.06 person-years of coverage. Hence, the follow-up periods were not significantly different between IBD patients and controls.

Comparisons between Crohn's disease and UC patients, between sexes and age groups (grouped by 0–19 y, 20–39 y, 40–59 y, and $\geq$60 y) and between IBD patients and the general population cohort yielded age-adjusted prevalence ratios (PRs). Mantel–Haenszel weights were used to calculate summary PRs based on age-specific estimates.

We also conducted an analysis whereby we determined if those patients with a chronic inflammatory disease had an increased risk for either Crohn's disease or UC. We compared the risk for either form of IBD in patients with chronic inflammatory diseases by sex and present the data for differences between women and men.

The construction of the University of Manitoba IBD Database and the use of it for clinical studies was approved by the University of Manitoba Research Ethics Board and by the Access and Confidentiality Committee of Manitoba Health (now referred to as Health Information Privacy Committee).

Results

There were 8072 patients with IBD who met our administrative definitions from April 1, 1984 to March 31, 2003. This included 4193 patients with Crohn's disease and 42,405 person-years of observation with disease and 31,365 person-years of observation without disease. There were 3879 patients with UC and 37,335 person-years of observation with disease and 31,904 person-years of observation without disease. There were 6 patients each with Crohn's disease and UC in whom age-matched, sex-matched, and geographically matched controls could not be identified.

By using a disease diagnosis definition of only 1 health system contact, all other immune diseases studied were more common among patients with UC and Crohn's disease (Tables 2 and 3). However, using the stricter definition of 5 health system contacts rendered the diagnoses of thyroiditis, neuropathy, and myasthenia gravis not to be increased significantly in UC patients and for thyroiditis, multiple sclerosis, neuropathy, myasthenia gravis, and chronic renal disease not to be increased significantly in Crohn's disease patients. Both UC and Crohn's disease patients had a greater likelihood of having asthma or bronchitis, psoriasis, and pericarditis than population controls (Tables 2 and 3). All diseases were slightly more common in UC than Crohn's disease patients, but the differences in PRs between UC and Crohn's disease patients were not statistically significant. The PR of arthritis in UC (11.8%) and Crohn's disease (6.3%) patients and of asthma in both UC (7.9%) and Crohn's disease (7.1%) patients renders these diseases the most common nonintestinal comorbidity identified in our Manitoba studies.[4,8–10] Although arthritis is a widely recognized comorbidity in IBD, the finding of asthma as among the most common comorbidity that is increased significantly in Crohn's disease patients compared with the general population is novel.

Table 2. Prevalence and PRs of Comorbid Diagnoses in UC

	Single health contact			≥ 5 health contacts		
	Controls n = 38,674	UC cases n = 3873	UC PR (*95% CI*)	Controls	UC cases n = 3873	UC PR (*95% CI*)
Asthma	15.08%	21.17%	1.53 (1.41–1.66)	4.9%	7.88%	1.66 (1.46–1.88)
Bronchitis	4.34%	5.65%	1.33 (1.15–1.54)	.32%	.67%	2.10 (1.36–3.23)
Arthritis	24.8%	30.9%	1.47 (1.35–1.59)	8.35%	11.77%	1.55 (1.39–1.74)
Thyroiditis	1.16%	1.57%	1.37 (1.04–1.80)	.15%	.23%	1.58 (.79–3.2)
Multiple sclerosis	.76%	1.37%	1.81 (1.35–2.42)	.29%	.54%	1.90 (1.19–3.03)
Neuropathy	1.4%	2.40%	1.75 (1.39–2.18)	.12%	.18%	1.47 (.66–3.25)
Myasthenia gravis	.18%	.36%	2.2 (1.26–3.85)	.04%	.07%	1.66 (.49–5.65)
Chronic renal disease	.86%	1.52%	1.78 (1.35–2.35)	.16%	.39%	2.46 (1.40–4.35)
Psoriasis	6.23%	9.19%	1.53 (1.36–1.71)	1.04%	1.7%	1.65 (1.27–2.15)
Pericarditis	.55%	2.09%	1.46 (1.00–2.13)	.07%	.23%	3.33 (1.57–7.07)

The diagnosis of osteoarthritis occurred in 7.89% of all IBD patients combined compared with 6.13% of controls (PR, 1.37; 95% confidence interval [CI], 1.25–1.50). The diagnosis of rheumatoid arthritis occurred in 1.63% of all IBD patients combined compared with .93% of controls (PR, 1.76; 95% CI, 1.46–2.13).

Sex

Among those with significantly increased PRs in UC by 5 health system contacts, compared with controls there was a greater risk among women for bronchitis, arthritis, and chronic renal disease. There was a greater PR for multiple sclerosis among men. Of all increased risks when comparing by sex, multiple sclerosis was the only disease associated with a statistically significant difference in risk in 1 sex over the other ($P = .035$). There were similarly increased risks for asthma, psoriasis, and pericarditis by sex (Table 4). Among those with significantly increased PRs in Crohn's disease by 5 health system contacts, compared with controls there was a greater risk among women for bronchitis only. The increased risk was similar for women and men for asthma, arthritis, psoriasis, and pericarditis (Table 4).

Age

There were no definite trends in terms of age groups most likely to have concurrent chronic inflammatory diseases in Crohn's disease patients. However, in UC patients, the increased risk for multiple sclerosis was significant only in the 40- to 59-year age group (PR, 2.46; 95% CI, 1.31–4.64), the increased risk for chronic renal disease was significant only in the 20- to 39-year age group (PR, 3.70; 95% CI, 1.63–8.36), and the only significant risk for psoriasis was in the over 60-year age group (PR, 2.02; 95% CI 1.28–3.17).

The Risk for Having IBD Among Those With Chronic Inflammatory Diseases

We analyzed the data by assessing all patients with chronic inflammatory diseases for the likelihood of having either Crohn's disease or UC (Table 5). Patients with asthma, arthritis, or psoriasis had increased risks for having either Crohn's disease or UC, with comparably increased risks among men and women. Female patients with bronchitis (PR, 1.98; 95% CI, 1.23–3.19) had a significantly increased risk for Crohn's disease but men

Table 3. Prevalence and PRs for Comorbid Diagnoses in Crohn's Disease

	Single health contact			≥5 health contacts		
	Controls n = 41,815	CD cases n = 4187	CD PR (*95% CI*)	Controls n = 41,815	CD cases n = 4187	CD PR (*95% CI*)
Asthma	15.7%	19.9%	1.34 (1.24–1.46)	5.1%	7.09%	1.43 (1.26–1.62)
Bronchitis	3.38%	4.49%	1.36 (1.16–1.59)	.26%	.48%	1.86 (1.15–3.02)
Arthritis	20.1%	25.0%	1.43 (1.31–1.55)	6.32%	7.88%	1.24 (1.12–1.39)
Thyroiditis	1.29%	1.46%	1.13 (1.87–1.48)	.20%	.19%	.96 (.47–2.0)
Multiple sclerosis	.97%	1.62%	1.69 (1.31–2.19)	.37%	.41%	1.11 (.67–1.84)
Neuropathy	1.29%	2.34%	1.85 (1.48–2.30)	.13%	.10%	.74 (.27–2.05)
Myasthenia gravis	.15%	.57%	1.43 (.71–2.87)	0	.04%	0
Chronic renal disease	.78%	1.82%	2.37 (1.85–3.06)	.20%	.26%	1.34 (.72–2.52)
Psoriasis	6.28%	9.39%	1.55 (1.39–1.73)	1.07%	1.7%	1.59 (1.24–2.05)
Pericarditis	.45%	.88%	1.96 (1.38–2.78)	.06%	.19%	3.07 (1.39–6.78)

Table 4. Comparison by Sex of PRs for Crohn's Disease and UC Vs Controls for Selected Comorbidities Known to Be Increased Overall in Either or Both of the Diseases

Sex	Comorbidity	Crohn's disease PR (*95% CI*)	UC PR (*95% CI*)
Female	Asthma	1.44 (1.23–1.69)	1.65 (1.4–1.95)
Male		1.40 (1.13–1.73)	1.67 (1.37–2.03)
Female	Bronchitis	2.21 (1.23–3.96)	2.32 (1.28–4.22)
Male		1.36 (.58–3.22)	1.88 (1.00–3.54)
Female	Arthritis	1.29 (1.10–1.50)	1.71 (1.48–1.98)
Male		1.39 (1.10–1.75)	1.33 (1.11–1.60)
Female	Multiple sclerosis	1.32 (.78–2.22)	1.52 (.83–2.80)
Male		.32 (.04–2.36)	2.84 (1.35–5.97)
Female	Chronic renal disease	1.31 (.56–3.06)	3.34 (1.31–8.49)
Male		1.39 (.55–3.54)	2.10 (1.02–4.32)
Female	Psoriasis	1.50 (1.08–2.09)	1.80 (1.26–2.56)
Male		1.74 (1.17–2.57)	1.51 (1.02–2.23)
Female	Pericarditis	.83 (.11–6.40)	3.99 (1.25–12.72)
Male		4.99 (2.02–12.34)	2.94 (1.08–7.95)

did not (PR, 1.32; 95% CI, .62–2.80). Both men and women with bronchitis had similar increased risks for UC. Men (PR, 3.67; 95% CI, 2.00–6.73), but not women (PR, .85; 95% CI, .13–5.56) with pericarditis had an increased risk for Crohn's disease whereas both men and women with pericarditis had similar increased risks for UC. Men with multiple sclerosis had an increased risk for having UC (PR, 2.42; 95% CI, 1.36–4.31) but women did not (PR, 1.45; 95% CI, .86–2.46). Both women (PR, 2.75; 95% CI, 1.37–5.51) and men (PR, 1.41; 95% CI, 1.05–3.46) with chronic renal diseases had increased risks for UC but this risk was greater among women.

When using the 5-claim definition for each diagnosis, 63% of chronic inflammatory diseases were diagnosed before IBD was diagnosed.

Discussion

A number of case reports and case series have suggested that the chronic inflammatory diseases we studied are increased in patients with IBD. A recent case-control study was performed at the Mayo Clinic.[11]

Table 5. The PRs (95% CIs) of Having IBD if a Person Has a Diagnosis of Other Chronic Inflammatory Disease

	Crohn's disease	UC
Asthma	1.38 (1.23–1.53)	1.56 (1.4–1.74)
Bronchitis	1.72 (1.15–2.58)	1.92 (1.35–2.73)
Arthritis	1.24 (1.11–1.38)	1.41 (1.28–1.54)
Multiple sclerosis	1.10 (.7–1.73)	1.75 (1.18–2.60)
Neuropathy	.76 (.9–1.95)	1.40 (.70–2.80)
Myasthenia gravis	[a]	1.57 (.55–4.48)
Chronic renal disease	1.30 (.75–2.27)	2.17 (1.38–3.42)
Pericarditis	2.59 (1.41–4.75)	2.75 (1.56–4.85)
Psoriasis	1.52 (1.22–1.89)	1.56 (1.24–1.95)
Thyroiditis	.85 (.42–1.74)	1.50 (.82–2.75)

[a]PR estimates not computed because of small cell sizes.

In that study, 243 patients with IBD presenting to the specialty clinic at Mayo Clinic were enrolled over an 8-month period. Controls were identified from outpatients seen at the Mayo Clinic who did not have IBD and were matched to IBD patients by age, sex, and geographic residence. This study found an increased prevalence of classic extraintestinal manifestations (40% vs 14%) and the odds ratio (OR) for being diagnosed with IBD and any of theses extraintestinal manifestations was 2.9 (95% CI, 1.9–4.2). A total of 10% of IBD patients had 1 or more autoimmune diseases compared with 19% of matched control patients. Having an IBD diagnosis conferred a lower risk for acquiring any autoimmune disease (OR, .4; 95% CI, .1–.96). The most common autoimmune disorder was autoimmune thyroid disease, however, there were fewer cases of autoimmune thyroid disease and systemic lupus erythematosus among IBD patients compared with control patients. Psoriasis and multiple sclerosis were no more common in IBD patients than in control patients.

The Mayo Clinic study differed from our study in several ways. The Mayo Clinic study was considerably smaller than the Manitoba study. The Manitoba study had the advantage of using population-based data, making it less likely we would have missed previously diagnosed autoimmune diseases. Also, the Mayo Clinic has a referral bias and control patients may have an increased prevalence of autoimmune disease. However, the Mayo Clinic study had the advantage of diagnosis confirmation. To enhance the likelihood of assessing true diagnoses of the comorbid diseases in question we have based our conclusions on a measure of 5 health system contacts. This has proven to be very specific in diagnosing Crohn's disease, UC, and multiple sclerosis in Manitoba.[6,7]

The Mayo Clinic study did assess for rheumatoid arthritis and systemic lupus erythematosus, but not os-

teoarthritis, a disorder considered more degenerative and less inflammatory in the classic sense. We assessed for both of these forms of arthritis and other connective tissue disorders because it is not clear how physicians would code diagnostically for the arthritis that occurs in IBD. Although we found a higher relative risk for the classically immune-mediated arthritis (rheumatoid arthritis) than osteoarthritis, we are not drawing any conclusions from this because of coding issues.

Arthritis long has been described as a common extraintestinal manifestation of IBD. Older studies suggested rates of 15%–20%, with higher rates in Crohn's disease than in UC patients.[10–12] A population-based study from Sweden reported a prevalence of peripheral arthritis in IBD patients of 10.6%, with a higher prevalence in UC than Crohn's disease patients.[13] Another study from a tertiary referral clinic reported prevalence rates of arthritis of 6%–10%, which is similar to our results, however, they did report a higher rate in Crohn's disease than UC patients.[14] We are reporting similar increased risks for arthritis between UC and Crohn's disease patients and among women vs men.

The Mayo Clinic study did not assess for chronic inflammatory pulmonary disease. By case series and some case-control studies a high prevalence of both subclinical pulmonary pathology and of respiratory symptoms has been identified among IBD patients.

Of 66 IBD patients presenting at a specialty clinic, 42% were reported to have at least 1 pulmonary function test abnormality compared with 3% of controls.[15] This study also found greater pulmonary function abnormalities in patients with active disease than those in remission. The abnormalities were independent of mesalamine use or disease diagnosis (Crohn's disease vs UC). None of these patients had respiratory symptoms.

A case-control study of 82 patients with IBD reported 57% had pulmonary abnormalities including both ventilatory and diffusing capacity abnormalities.[16] In another case-control study of 44 patients with IBD and no respiratory symptoms, 20% were found to have an obstructive and/or restrictive ventilatory defect compared with 5% of controls ($P < .05$).[17] The most recent case-control study of 64 patients with IBD presenting to a hospital clinic compared with 1346 healthy controls drawn from the electoral register found that after adjustment for age, sex, and smoking, IBD patients were more likely to have symptoms of breathlessness (OR, 3.4; 95% CI, 2.0–6.0), sputum production (OR, 2.5; 95% CI, 1.2–5.0), and cough (OR, 1.8; 95% CI, 1.0–3.4).[18]

In uncontrolled studies, pulmonary function abnormalities have been reported in up to 55% of IBD patients, of which 29% had ventilatory defects and 35% had diffusion abnormalities.[19] One study assessed high-resolution lung computed tomography scans and 53% of IBD patients had respiratory symptoms, however, ventilatory and computed tomography scan abnormalities also were seen in asymptomatic patients.[20] Elsewhere, in IBD patients with respiratory symptoms, air trapping was the most common computed tomographic abnormality identified.[21]

A number of clinical lung disorders have been associated with IBD but whether the incidence of these conditions is increased in IBD has not been proven previously. Chronic bronchitis, chronic bronchiolitis, bronchiectasis, benign organizing obstructive pneumonitis, interstitial lung disease, subglottic stenosis, and necrobiotic nodules all have been described, but the true frequency of these conditions in IBD is unknown.[22,23]

Pulmonary granulomatous inflammation also has been reported in Crohn's disease in a case series.[24] In this series from the Mayo Clinic 11 of 3626 Crohn's disease patients seen at the clinic over a 7-year period had lung biopsy results available. Hence, this rate of .1% represents a prevalence of only those with lung biopsy examinations and not all patients with pulmonary disease.

We found that airway disease was the most common autoimmune or chronic inflammatory disease we assessed in patients with Crohn's disease and the second most common in UC patients. A prevalence of asthma in 7.1%–7.8% of patients with UC and Crohn's disease was higher than any of the classic extraintestinal diseases we assessed in a previous study (that study excluded arthritis).[4] Because airway disease is the most common pulmonary abnormality reported in IBD we chose to assess for the prevalence of 2 common airway diseases: asthma and bronchitis.

Although there was no statistically significant difference in PR by sex for asthma, there was a greater PR in women with both Crohn's disease and UC. Elsewhere, it has been reported that women had a greater percentage of pulmonary comorbidities than men.[23] In our study the increased risk for asthma was evident for both diseases across all ages, however, bronchitis mostly was evident among older adults. Although the increase of asthma in general has been of great interest and uncertain cause, it is noteworthy that the prevalence is even greater among patients with IBD.

Having found a significant association between these 2 major airway diseases and both UC and Crohn's disease, it is interesting to speculate on the pathogenesis. Embryologically the bowel and bronchial tree share similar origins. Hence, there may be anatomic or, more likely, immunologic predispositions shared by both organ systems. Crohn's disease patients are more likely to be

smokers and this is true in Manitoba as well (Bernstein, unpublished data). However, patients with UC are more likely to be ex-smokers or nonsmokers, so smoking does not likely account for the association in UC. Finally, because our study used administrative data that relied on health system contacts, it is possible that because IBD patients attend medical care more than the general population,[25] they might be more likely to present for non–IBD-related complaints. However, health care use data from Manitoba have shown that IBD patients have more overall outpatient visits and hospitalizations than a matched cohort from the general population, but do not have more non–gastrointestinal-related visits than the general population.[25] Furthermore, we found similar trends when assessing associations by even 1 health system contact (and it is unlikely that a patient would have only 1 health system contact if he or she truly had a chronic pulmonary condition). It is unclear what role medications may have in inducing, for instance, interstitial lung disease, however, sulfasalazine, which has been associated with benign organizing obstructive pneumonitis or pulmonary infiltrates and eosinophilia, is used with decreasing frequency.[21] Mesalamine is prescribed widely in both UC and Crohn's disease and also has been associated with lung disease.[26–29]

Multiple sclerosis has been suggested to be associated with IBD in small series,[30–33] but a definitive association has never been proven. These reports have included surveys of disease-specific societies and chart reviews from specialty clinics, but overall no population-based data have suggested a true association of IBD and multiple sclerosis within the same patient or diagnoses of these diseases in different patients within the same family. One population-based study using small samples of both multiple sclerosis and IBD patients suggested an association between the 2, but it was not statistically significant.[34] Because of the similar clinical patterns of disease (intermittent flaring or chronically progressive) for both IBD and multiple sclerosis and similar aberrant immunologic responses and even altered intestinal permeability in Crohn's disease and multiple sclerosis,[35] there has been some justification for considering that these case-series associations might be true. By using a more stringent criterion of requiring 5 health system contacts for a diagnosis of multiple sclerosis, and a case definition that has been validated in Manitoba,[7] our data have confirmed a significant association of multiple sclerosis and UC within the same patient, but not for Crohn's disease. Furthermore, a statistically significant increased relative risk is confined to men. Although more women than men have multiple sclerosis, there seems to be an increased risk for men among patients who also have UC. The only age group in whom the risk for multiple sclerosis proved to be increased significantly was for those aged 40–59 years. Because the association was statistically significant in a specific demographic group (men of a certain age with UC), it also is possible that this could be a chance observation.

Because of the potential association of IBD with multiple sclerosis and the sporadic reports of neuropathies associated with IBD such as optic neuritis,[36] peripheral neuropathies,[37–40] and sensorineural hearing loss,[41,42] and because one form of Crohn's disease is known to be associated with neuropathy (Melkersson–Rosenthal syndrome),[43] we assessed whether neuropathy is associated with IBD. The ICD-9-CM coding of neuropathy includes non–immune-mediated neuropathies that might affect patients with IBD such as nutritional deficiencies and drug toxicity (particularly toxicity associated with metronidazole).[44] Despite this, using 5 health system contacts there was no association of neuropathy with either UC or Crohn's disease. There has been 1 report of an association with Crohn's disease and myasthenia gravis.[45] In the Mayo clinic study they found no cases of myasthenia gravis in their IBD patients but 1 patient had a family member with myasthenia gravis.[11] We did not find an association between myasthenia gravis and either form of IBD. Hence, we believe that the association of IBD and autoimmune neurologic disease is weak and confined to men with UC having an increased risk for multiple sclerosis.

Glomerulonephritis has been associated with IBD in case reports but uncommonly.[46–48] Interstitial nephritis also has been reported; however, some of these reports have implicated mesalamine as the culprit.[47,49–53] There has been some debate as to whether the association between mesalamine use and interstitial nephritis is sufficiently robust to warrant renal function surveillance in users and a recent study in a large series suggested no association.[54] A population-based study of renal disease in IBD patients was performed in the United Kingdom by using the General Practice Research Database, which includes approximately 6% of the total registered population of England and Wales (approximately 5,000,000 adults and 37,984 patients with IBD).[54] The study population was divided into 3 cohorts: IBD patients using mesalamine, IBD patients without a history of mesalamine use, and sulphasalazine users with rheumatoid arthritis. The patients were matched by calendar time, medical practice, age, and sex to controls who had neither IBD nor mesalamine use. The incidence of renal disease in the cohort of IBD patients using mesalamine was .17/100 patient-years and in the cohort of IBD patients not using mesalamine was .25/100 patient-years

and in the reference cohort was .08/100 patient-years. The risk for renal disease was higher in Crohn's disease than UC patients (Crohn's disease OR 3.1; 95% CI, 2.11–4.56; and UC OR, 1.76; 95% CI, 1.26–2.45). Compared with the non-IBD/no mesalamine use cohort the relative risk for renal disease in the IBD cohort using mesalamine was 2.29 (95% CI, 1.78–2.94), and the relative risk in the IBD cohort not using mesalamine was 3.58 (95% CI, 2.43–5.27). Mesalamine did not prove to be associated with an increased risk for renal disease (adjusted OR, 1.14; 95% CI, .73–1.8). Overall, this study did not find an association between mesalamine use and renal disease, however, there was an increased risk for simply having IBD and having renal disease. In our study we found a statistically significant increased risk for renal disease in UC but not in Crohn's disease patients, with a greater increased risk among women compared with men. We could not distinguish whether the renal disease was necessarily a glomerular or tubular disease, nor could we distinguish whether patients were using mesalamine or not.

There have been reports of high rates of psoriasis in IBD and conversely high rates of colitis in patients with psoriasis and no gastrointestinal complaints, enhancing the likelihood that there is a link (perhaps immunologically) between psoriasis and IBD.[55–59] Psoriasis has been reported in 1.4% of patients with Crohn's disease and .8% of patients with UC presenting to a specialty clinic in the United Kingdom.[59] In our study we found a significantly increased PR of psoriasis in IBD patients, and at 1.7% psoriasis is as common in IBD patients as pyoderma gangrenosum.[2] The increased PR of psoriasis in IBD was similar among women and men.

Although there are relatively few case reports of thyroid disease in association with IBD,[59–62] there is a case-control study from a specialty referral clinic in the United Kingdom reporting a prevalence of autoimmune thyroid disease of 2.4% in Crohn's disease and .8% in UC patients, which is considerably higher than what we report in our population-based study.[59] We did not find an increased risk for thyroid disease overall; however, there was an increased risk in patients with UC between the ages of 40 and 59 years.

Pericarditis rarely has been reported in association with IBD.[63–68] It did not get mentioned in a recent review of rare extraintestinal manifestations of IBD.[69] Although the PR was increased in both UC and Crohn's disease patients over the general population, the actual prevalence of the condition was quite low.

Our study is an important addition to the IBD literature. It is a large population-based study that has assessed the comorbidity of several important immune-mediated diseases and we are reporting that a number of these conditions are increased significantly in both UC and Crohn's disease patients. Although there are limitations in using administrative data, we hope we have overcome the main problem of lacking chart-validated diagnoses in all patients by reporting associations for diagnoses made based on at least 5 health system contacts. Are there any practical implications of these findings? First, a link between these diseases and IBD may stimulate research pursuing the link of these organ systems on an immune basis. More practically, these data reinforce that respiratory complaints in patients with IBD should be taken seriously and, at the least, standard pulmonary function tests should be performed. However, routine pulmonary function testing cannot be recommended at this time. Paresthesias and nonfocal or focal neurologic complaints should be heeded and not necessarily attributed to concurrent drug use such as metronidazole. If there are objective abnormalities, brain imaging with a computed tomography scan should be considered. The finding of peripheral neuropathy does not necessarily implicate nutritional deficiencies. Although an increased prevalence of renal disease in UC patients was identified, we could not distinguish what role drugs may have played in those patients with renal disease. Hence, the role of routine renal function monitoring in all patients with IBD still remains to be proven. Our clinical study supports the genome scan study, which suggested that chronic immune diseases genetically cluster together.[3] Whether the association of chronic inflammatory diseases in IBD relates to shared genes, shared causative triggers, or consequences of disease manifestations or treatments is unknown at this time. The finding of an increased risk for either Crohn's disease or UC in patients with diagnoses of other chronic inflammatory diseases, and the finding that 63% had their chronic inflammatory disease diagnoses antedating their IBD diagnoses, potentially lends support to the common-cause hypothesis. Our study should encourage further research into the common triggers in the organ systems that lead to autoimmune diseases.

References

1. Davidson A, Diamond B. Autoimmune disease. N Engl J Med 2001;345:340–350.
2. Ginn LR, Lin JP, Plotz PH, et al. Familial autoimmunity in pedigrees of idiopathic inflammatory myopathy patients suggests common genetic risk factors for many autoimmune diseases. Arthritis Rheum 1998;41:400–405.
3. Becker KG, Simon RM, Bailey-Wilson JE, et al. Clustering of non-major histocompatibility complex susceptibility candidate loci in human autoimmune diseases. Proc Natl Acad Sci U S A 1998; 95:9979–9984.

4. Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. Am J Gastroenterol 2001;96:1116–1122.
5. Roos LL, Mustard CA, Nicol JP. Registries and administrative data: organization and accuracy. Med Care 1993;31:201–212.
6. Bernstein CN, Blanchard JF, Rawsthorne P, Wajda A. The epidemiology of Crohn's disease and ulcerative colitis in a central Canadian province: a population-based study. Am J Epidemiol 1999;149:916–924.
7. Elliott LJ, Yu N, Melanson M, Green C, Blanchard J. Application of a validated method using medical claims data to demonstrate very high prevalence and incidence of multiple sclerosis in a Canadian province. Am J Epidemiol 2004;159:S59.
8. Bernstein CN, Blanchard JF, Leslie WD, Wajda A, Yu N. The incidence of fractures among patients with IBD: a population-based study. Ann Intern Med 2000;133:795–799.
9. Bernstein CN, Blanchard JF, Houston D, Wajda A. The incidence of venous thromboembolic disease among patients with IBD: a population-based study. Thromb Haemost 2001;85:430–434.
10. Bernstein CN, Kliewer E, Wajda A, Blanchard JF. The incidence of cancer among patients with IBD: a population-based study. Cancer 2001;91:854–862.
11. Ricart E, III, Tremaine W, Harmsen WS, Zinsmeister AR, Sandborn WJ. Autoimmune disorders and extraintestinal manifestations in first degree familial and sporadic inflammatory bowel disease: a case-control study. Inflamm Bowel Dis 2004;10:207–214.
12. Haslock I, Wright V. The musculoskeletal complications of Crohn's disease. Medicine 1973;52:217–225.
13. Salvarani C, Vlachonikolis IG, van der Heijde DM, Fornaciari G, Macchioni P, Beltrami M, Olivieri I, de Gennaro F, Politi P, Stockbrugger RW, Russel MG, on behalf of the European Collaborative IBD Study Group. Musculoskeletal manifestations in a population-based cohort of inflammatory bowel disease patients. Scand J Gastroenterol 2001;36:1307–1313.
14. Orchard TR, Wordworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. Gut 1998;42:387–391.
15. Herrlinger KR, Noftz MK, Dalhoff K, Ludwig D, Stange EF, Fellerman K. Alterations in pulmonary function in inflammatory bowel disease are frequent and persist during remission. Am J Gastroenterol 2002;97:377–381.
16. Kuzela L, Vavreka A, Prikazska M, Drugda B, Hronec J, Senkova A, Drugdova M, Oltman M, Novotna T, Brezina M, Kratky A, Kristufek P. Pulmonary complications in patients with inflammatory bowel disease. Hepatogastroenterology 1999;46:1714–1719.
17. Dierkes-Globisch A, Mohr H-H. Pulmonary abnormalities in respiratory asymptomatic patients with inflammatory bowel disease. Eur J Int Med 2002;13:385–388.
18. Birring SS, Morgan AJ, Prudon B, McKeever TM, Lewis SA, Falconer Smith JF, Robinson RJ, Britton JR, Pavord ID. Respiratory symptoms in patients with treated hypothyroidism and inflammatory bowel disease. Thorax 2003;58:533–536.
19. Godet PG, Cowie R, Woodman RC, et al. Pulmonary function abnormalities in patients with ulcerative colitis. Am J Gastroenterol 1997;92:7.
20. Songur N, Songur Y, Tuzun M, Dogan I, Tuzun D, Ensari A, Hekimoglu B. Pulmonary function tests and high-resolution CT in the detection of pulmonary involvement in inflammatory bowel disease. J Clin Gastroenterol 2003;37:292–298.
21. Mahadeva R, Walsh G, Flower CDR, Shneerson JM. Clinical and radiological characteristics of lung disease in inflammatory bowel disease. Eur Respir J 2000;15:41–48.
22. Fireman Z, Osipov A, Kivity S, Kopelman Y, Sternberg A, Lazarov E, Fireman E. The use of induced sputum in the assessment of pulmonary involvement in Crohn's disease. Am J Gastroenterol 2000;95:730–734.
23. Storch I, Sachar D, Katz S. Pulmonary manifestations of inflammatory bowel disease. Inflamm Bowel Dis 2003;9:104–115.
24. Camus P, Piard F, Ashcroft T, et al. The lung in inflammatory bowel disease. Medicine (Baltimore) 1993;72:151–183.
25. Casey MB, Tazelaar HD, Myers JL, Hunninghake GW, Kakar S, Kalra SX, Ashton R, Colby TV. Noninfectious lung pathology inpatients with Crohn's disease. Am J Surg Pathol 2003;27:213–219.
26. Bernstein CN, Blanchard JF. Disease-related health care utilization is higher in Crohn's disease than ulcerative colitis. Gastroenterology 1999;116:A668.
27. Parry SD, Barbatzas C, Peel ET, et al. Sulfasalazine and lung toxicity. Eur Respir J 2002;19:756–764.
28. Bitton A, Peppercorn MA, Hanrahan JP, et al. Mesalamine-induced lung toxicity. Am J Gastroenterol 1996;91:1039–1040.
29. Sviri S, Gafanaovich I, Kramer MR, et al. Mesalamine-induced hypersensitivity pneumonitis. A case report and review of the literature. J Clin Gastroenterol 1997;24:34–36.
30. Camus P, Colby TV. The lung in inflammatory bowel disease. Eur Respir J 2000;15:5–10.
31. Rang EH, Brooke BN, Herman-Taylor J. Association of ulcerative colitis with multiple sclerosis (letter). Lancet 1982;2:555.
32. Purman J, Arendt G, Cleveland S, et al. Association of Crohn's disease and multiple sclerosis. J Clin Gastroenterol 1992;14:43–46.
33. Minuk GY, Lewkonia RM. Possible familial association of multiple sclerosis and inflammatory bowel disease. N Engl J Med 1986;314:586.
34. Sadovnik AD, Paty DW, Yannakoulias G. Concurrence of multiple sclerosis and inflammatory bowel disease. N Engl J Med 1989;321:762–763.
35. Kimura K, Hunter SF, Thollander MS, Loftus EV Jr, Melton LJ III, OBrien PC, Rodriguez M, Phillips SF. Concurrence of inflammatory bowel disease and multiple sclerosis. Mayo Clin Proc 2000;75:802–806.
36. Yacyshyn B, Meddings J, Sadowski D, Bowen-Yacyshyn MB. Multiple sclerosis patients have peripheral blood CD45RO+ B cells and increased intestinal permeability. Dig Dis Sci 1996;41:2493–2498.
37. Sedwick LA, Klingele TG, Burde RM, Behrens MM. Optic neuritis in inflammatory bowel disease. J Clin Neuroopthalmol 1984;4:3–6.
38. Zimmerman J, Steiner I, Gavish D, et al. Guillain-Barre syndrome: a possible extraintestinal manifestation of ulcerative colitis. J Clin Gastroenterol 1985;7:301–303.
39. Nemni R, Fazio R, Corbo M, et al. Peripheral neuropathy associated with Crohn's disease. Neurology 1987;37:1414–1417.
40. Humbert P, Monnier G, Billerey C, et al. Polyneuropathy an unusual extraintestinal manifestation of Crohn's disease. Acta Neurol Scand 1989;80:301–306.
41. Lossos A, River Y, Eliakim R, Steiner I. Neurologic aspects of inflammatory bowel disease. Neurology 1995;45:416–421.
42. Summers RW, Harker L. Ulcerative colitis and sensorineural hearing loss: is there a relationship? J Clin Gastroenterol 1982;4:251–252.
43. Bachmeyer C, Leclerc-Landgraf N, Laurette F, Coutarel P, Cadranel J-F, Medioni J, Dhote R, Mouget-Martin M. Acute sensorineural hearing loss associated with Crohn's disease. Am J Gastroenterol 1998;93:2565–2567.
44. Ilnyckyj A, Aldor TAM, Warrington R, Bernstein CN. Crohn's disease and the Melkersson-Rosenthal syndrome. Can J Gastroenterol 1999;13:152–154.
45. Duffy LF, Daum F, Fisher SE, et al. Peripheral neuropathy in Crohn's disease patients treated with metronidazole. Gastroenterology 1985;88:681–684.

46. Finnie IA, Shields R, Sutton R, Donnelly R, Morris AI. Crohn's disease and myasthenia gravis: a possible role for thymectomy. Gut 1994;35:278–279.
47. Wilcox GM, Aretz HT, Roy MA, Roche JK. Glomerulonephritis associated with inflammatory bowel disease. Gastroenterology 1990;98:786–791.
48. Pardi DS, Tremaine WJ, Sandborn WJ, McCarthy JT. Renal and urologic complications of inflammatory bowel disease. Am J Gastroenterol 1998;93:504–514.
49. Shaer AJ, Stewart LR, Cheek DE, Hurray D, Self SE. IgA antiglomerular basement membrane nephritis associated with Crohn's disease: a case report and review of glomerulonephritis in inflammatory bowel disease. Am J Kidney Dis 2003;41:1097–1109.
50. World MJ, Stevens PE, Ashton MA, et al. Mesalazine-associated interstitial nephritis. Nephrol Dial Transplant 1996;11:614–621.
51. Popoola J, Muller AF, Pollock L, et al. Late onset interstitial nephritis associated with mesalazine treatment. BMJ 1998;317:795–797.
52. DeBroe ME, Stolear JC, Nouwen EJ, et al. 5-Aminosalicylic acid and chronic tubulointerstitial nephritis in patients with chronic inflammatory bowel disease: is there a link? Nephrol Dial Transplant 1997;12:1839–1841.
53. Ransford RAJ, Langman MJS. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. Gut 2002;51:536–539.
54. Elseviers MM, D'Haens G, Lerebours E, Plane C, Stolear JC, Riegler G, Capasso G, Van Outryve M, Mishevska-Mukaetova P, Djuranovic S, Pelckmans P, De Broe ME, 5-ASA Study Group. Renal impairment in patients with inflammatory bowel disease: association with aminosalicylate therapy? Clin Nephrol 2004;61:83–89.
55. Van Staa TP, Travis S, Leufkens HG, Logan RF. 5-aminosalicylic acids and the risk of renal disease: a large British epidemiologic study. Gastroenterology 2004;126:1733–1739.
56. Yates VM, Watkinson G, Kelman A. Further evidence for an association between psoriasis, Crohn's disease and ulcerative colitis. Br J Dermatol 1982;105:323–330.
57. Lee FI, Bellary SV, Francis C. Increased occurrence of psoriasis in patients with Crohn's disease. Am J Gastroenterol 1990;85:962–963.
58. Scarpa R, Manguso F, D'Arienzo A, D'Armiento FP, Astarita C, Mazzacca G, Ayala F. Microscopic inflammatory changes in colon of patients with both active psoriasis and psoriatic arthritis without bowel symptoms. J Rheumatol 2000;27:1241–1246.
59. Najarian DJ, Gottlieb AB, Connections between psoriasis and Crohn's disease. J Am Acad Dermatol 2003;48:805–821.
60. Snook JA, de Silva HJ, Jewell DP. The association of autoimmune disorders with inflammatory bowel disease. QJM 1989;72:835–840.
61. Bonapace ES, Srinivasan R. Simultaneous occurrence of inflammatory bowel disease and thyroid disease. Am J Gastroenterol 2001;86:1925–1926.
62. Shah SA, Peppercorn MA, Palotta JA. Autoimmune (Hashimoto's) thyroiditis associated with Crohn's disease. J Clin Gastroenterol 1998;26:117–120.
63. Triantafillidis JK, Cherakakis P, Zervakakis A, et al. Coexistence of hyperthyroidism and ulcerative colitis: report of 4 cases and a review of the literature. Ital J Gastroenterol 1992;24:494–497.
64. Mukhopadhyay D, Nasr K, Grossma BJ, Kirsner JB. Pericarditis associated with inflammatory bowel disease. JAMA 1970;211:1540–1542.
65. Rheingold OJ. Inflammatory bowel disease and pericarditis. Ann Intern Med 1975;21:760–763.
66. Patwardan RV, Heilpern RJ, Brewstere AC, Darrah JJ. Pleuropericarditis an extraintestinal complication of inflammatory bowel disease. Arch Intern Med 1983;143:94–96.
67. Hoffmann RM, Kruis W. Rare extraintestinal manifestations of inflammatory bowel disease. Inflamm Bowel Dis 2004;10:140–147.
68. Farmer RG, Hawk W, Turnbull RB. Clinical patterns in Crohn's disease: a statistical study of 615 cases. Gastroenterology 1975;68:627–635.
69. Greenstein AJ, Janowitz HD, Sachar DB. The extra-intestinal complications of Crohn's disease and ulcerative colitis. A study of 700 patients. Medicine 1976;55:401–412.

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