A search for seasonal variation in the onset and flares of ulcerative colitis and Crohn's disease in children and adolescents

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A SEARCH FOR SEASONAL VARIATION IN
UC & CROWN'S IN CHILDREN & ADOLESCENTS

COLLEEN S. THOMPSON BURSTEN

1981
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Signature of Author

April 24, 1981
Date
A Search for Seasonal Variation in the Onset and Flares of Ulcerative Colitis and Crohn's Disease in Children and Adolescents.

Joyce D. Gryboski, M.D.
Advisor

Colleen S. Thompson Bursten

A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the degree of Doctor of Medicine

1981
Introduction:

In inflammatory bowel disease, as in many diseases in which an exact etiology is still obscure, various investigators have turned to a study of the epidemiology of the disease in hopes of finding a clue to its cause, or to at least identify factors which exacerbate or ameliorate the disease (1-3). This thesis is designed to augment those studies by investigating the possibility of a seasonal peak in the onset of the disease or of its relapses in children. The much shorter lag time between onset of symptoms and diagnosis in children; an average of 8 months vs. 35 months (1,4), makes the former study possible. After a retrospective chart review involving the five year period 1974-1978 it was found that there is no significant seasonal peak to either the first onset of symptoms of Crohn's or ulcerative colitis or to the relapsing flares characteristic of these diseases.

Literature Review:

Since the establishment of ulcerative colitis as a diagnostic entity in 1875 and the description of Crohn's disease in 1932 much has been learned of the epidemiology of these diseases. Most of this work has been done in the past few decades and has revealed many interesting facts, some of which may provide clues as to the etiology of inflammatory bowel disease. The findings of these studies are summarized below.

Incidence:

The most striking feature in the studies of these diseases is that Crohn's disease, and perhaps also ulcerative colitis, is increasing in incidence. Mayberry, et al, in performing a retrospective study of the
incidence of Crohn's disease in Cardiff, Wales found a steady rise in incidence from 0.18 per 10^5 in the 1930's shortly after the first descriptions of Crohn's disease to 4.8 per 10^5 in the 1970's (5). Although it is true that Crohn's of the colon was not recognized until the 1940's, and that incidence rates prior to that time might be falsely lowered by misdiagnosis of those cases these authors point out that the increase was spread almost equally over increasing numbers of ileocecal, colonic, and small bowel cases and cannot be explained away by reclassification of colonic cases. Other studies in Britain, Scandinavia, central Europe, Israel and South Africa have also shown an increase in the incidence of Crohn's disease (6-17) (see Graph #1). In only one of these studies was the increase able to be accounted for by a lowered diagnostic threshold (11). Two other studies, one from Northern Ireland and one from Gloucester (18,19) found no increase in incidence, however, both of these studies were relatively short, 7 years and 4 years respectively, and with the large amount of scatter which can be expected in a relatively rare disease it is not surprising that they did not see an increase comparable to that of the other, longer studies.

For ulcerative colitis the data available is not as clear cut. Of five studies three show a rising trend (8,20,21), one quite dramatically (20) and two show essentially no change in the incidence of ulcerative colitis over the same time period during which marked increases were occurring in Crohn's disease (14,22) (see Graph #2). One of the studies which shows an increasing incidence involves only patients who were treated at the central hospitals in Finland (21), and it is possible that the slight increase seen reflects an increase in the percentage of patients referred to central
ULCERATIVE COLITIS

Graph #2

Annual Incidence per 100,000

1950 1960 1970

Oxford

Malmo

Tel-Aviv-Jafo

Norway

Finland
hospitals for treatment rather than a true increase in the disease. Of the remaining two studies which show a rise the study from Oxford (20) is the most dramatic and covers a defined population; however, the annual death rates for ulcerative colitis in England and Wales fell during the period of the study while death rates for Crohn's disease rose 2-fold (5), thus it is unlikely that the rising incidence found in the Oxford study reflects any national trends.

**Age Distribution:**

Of particular interest to this study, which concerns itself with children and adolescents, is the fact that many investigators have found that the rise in Crohn's disease is most marked in the younger age groups. Tresadern et al (19) found that the peak incidence of the disease was in 15-24 year olds with the most extensive disease in the younger patients. Norlen et al (9) found that the rising incidence of the disease was due mostly to an increase among 15-29 year olds. Gryboski and Spiro point out that of all patients seen at Yale-New Haven Hospital with Crohn's disease in 1955-65, 26% were less than 20 years old and 3% were less than 10. In the following 10 years more children with Crohn's disease were treated than children and adults combined for the previous decade and 11% of these children were less than 10 years old (4). Despite such increases all studies agree that children are at relatively low risk for Crohn's disease with an increased risk after adolescence. Brahme (14), Norlen (9), and Tresadern (19) showed a single peak incidence in early adulthood with lesser incidence thereafter. Other studies have shown a bimodal age distribution with peaks in the third and seventh decades (6,7,15,19). Yet other studies have shown essentially constant risk after the third decade (3,5,11).
For ulcerative colitis the data is less clear. There are suggestions from Gjone and Myren in Norway that ulcerative colitis is increasing especially much among children (23); however, the contradictions among the epidemiologic studies noted above suggest caution in drawing conclusions about world-wide trends. In general the age-specific incidence of ulcerative colitis parallels that of Crohn's disease with low incidence in childhood and a rise thereafter (3,8,20,22). Evans et al (20) found a bimodal distribution with peaks in the third and seventh decades. Gilat (22) found peaks among 15-25 year olds and 30-40 year olds. A single peak was seen by Myren et al (8) in 20-29 year olds and an even age distribution was found by Monk et al (3) in the United States.

Sex Distribution:

Much discussion has centered around whether there is any differential incidence between the sexes. For Crohn's disease 7 studies found a predominance of females (5,6,10,12-14,18), 6 found a predominance of males (3,7-9,15,19), and 2 studies found equal numbers for both sexes (11,20). Where differences were found they usually did not reach statistical significance.

For ulcerative colitis 3 studies showed a slight male predominance (8,21,22), 2 studies showed a slight female predominance (3,20), and one showed no difference (24). Once again most differences were not statistically significant.

Urban vs. Rural:

Monk et al found a predominance of inflammatory bowel disease among city dwellers, which could be explained at least in part by the tendency of Jews, who have a high incidence of the disease (see below), to live in
cities (3). Kyle in Aberdeen (6) and Humphreys in Northern Ireland (18) also found an increased incidence of Crohn's among urban populations despite a lack of significant numbers of Jews in their populations. However these results were not confirmed by Myren and Norlen in Norway and Central Sweden (8,9) where no such urban predominance was seen.

Studies of ulcerative colitis show an even distribution among rural and urban populations (8,20) except for the studies from Finland which offer contradictory evidence; the samplings from the central hospitals suggesting a greater incidence among the rural population whereas the more comprehensive but much shorter study involving all hospitals suggested a predominance among urban dwellers (21,24).

Level of Education:

Monk in Baltimore (3) also found that inflammatory bowel disease patients had a higher average level of education than controls. However Kyle in Aberdeen (6) found a relative dearth of white collar workers among Crohn's disease patients in his series and it remains to be shown if either of these findings will be borne out over the long run.

World Distribution:

Crohn's disease is most common in the British Isles, Sweden, Denmark and the United States (3,5,6,9-14,18,19); less common in Norway, Israel and South Africa (8,15,17), and rare to the point of being reportable elsewhere (26). Firm epidemiologic data for Australia is not available.

Ulcerative colitis is generally 2-10 times more common than Crohn's disease in most studies (3,8,15,20,22), but this ratio is diminishing as Crohn's disease becomes more common. In one study of patients under 20
years old the ratio of ulcerative colitis to Crohn's diminished from 1.92:1 in 1955-59 to 0.44:1 in 1970-74, thus making Crohn's more common than ulcerative colitis among the age group with whom we are most concerned in this thesis (25). Spatially ulcerative colitis is most common in the British Isles, United States and Sweden and less common in Finland, Norway and South Africa, with an intermediate rate in Israel. One study from the Hospital of the American University in Beirut suggests that ulcerative colitis in Arabs is not much less common than among western countries, although Crohn's among Arabs is vanishingly rare (26). Ulcerative colitis is also starting to be seen in third world countries both in Africa and in this hemisphere (27). Here at Yale-New Haven Hospital a boy from Brazil was recently treated by Dr. Gryboski in the Pediatric GI Clinic for severe ulcerative colitis.

Jews:

Jews have been shown in several studies to have up to five times the incidence of Crohn's disease and ulcerative colitis as the non-Jewish population (3,14,20). Although the validity of these results is not in question it is interesting to note that studies from Israel have shown the incidence of inflammatory bowel disease to be less than that found even among non-Jews in western countries, suggesting that race is not the only factor determining the high incidence of these disease among western Jews.

Etiologic Implications:

Given the evidence condensed above it is clear that no single factor will explain the observed distribution of inflammatory bowel disease. The simplest etiologic hypothesis would have to include both an environmental
and a genetic component to account for what is known. That a genetic factor is present is amply demonstrated by the high incidence of inflammatory bowel disease in American and European Jews despite lifestyles similar to those of their compatriots. It is further supported by the well-known tendency of ulcerative colitis to run in families, and by the high incidence of ulcerative colitis found in relatives of Crohn’s disease patients (28). Further support for a genetic component is found in the fact that Black &/or Spanish-speaking Americans retain the low incidence rates of their ancestral countries (3,29).

The evidence for an environmental component is equally compelling. The rise in the incidence in Crohn’s disease has taken place within one or at most two generations and could not possibly be explained by genetic shifts (28,30). In Israel both factors are well displayed. The lower incidence of inflammatory bowel disease among Israeli Jews versus their American and European counterparts can most easily be explained by their different environments, whereas the relatively higher incidence of these diseases among Ashkenazi versus non-Ashkenazi Jews even in Israel suggests that genetic factors are still at work, although it is conceivable that this could be due to different lifestyles as well.

Many theories have been advanced as to what the relevant genetic and environmental factors might be, and these theories have been well reviewed by Fielding in 1970 (28), and Acheson in 1965 (31). In brief the genetic factor is most generally, and logically, thought to be an immunologic susceptibility to react to a stimulus with an inflammatory bowel disease type of picture. The environmental stimulus is generally thought to be either an infectious, antigenic, or dietary agent.
In favor of a dietary factor Rozen et al. (15) have pointed out that Israeli Jews eat more carbohydrates and fiber and less fat and meat than Americans, and that Ashkenazim eat more meat, eggs and milk than the non-Ashkenazim who enjoy a lesser incidence of inflammatory bowel disease. In a British study James and Gardner (32, 33) have found a statistically significant predominance of breakfast cereal eaters among Crohn's disease patients, with corn flakes, wheat, and porridge being specifically implicated. Milk proteins have also been thought by some to be possible etiologic agents in inflammatory bowel disease (31), and removal of milk products from the diet has been of benefit to some patients.

Another possibility is that the environmental factor is an antigenic stimulus in the bowel to which certain people have an anomalous reaction. This reaction could be mediated by a failure in the production of "symbodies", antibodies which normally mask antigens and therefore provide tolerance to certain antigenic stimuli (28). The increasing incidence could be explained by an increase in a bacterial or dietary antigen which in non-susceptible populations would be entirely innocuous.

Lastly, it is possible that an infectious agent is responsible; either bacterial, mycobacterial, or viral. The increase in incidence of Crohn's disease could be explained by the rise and spread of this infectious agent among susceptible populations, and the heretofore low incidence of Crohn's disease in Israel could be accounted for by the hypothesis that the agent was only recently introduced into the area and is now undergoing the same increase that it began earlier in Europe and the United States. Mitchell and Rees (34) showed in 1970 that there was an agent transmissible from Crohn's disease tissue which could elicit granuloma formation in the footpads of mice, but there has been no report since to indicate if this was
an infectious or merely antigenic agent. Other data which would support an infectious etiology would be a clustering of cases, as has indeed been found in Cardiff, in which patients with Crohn's disease were found to live mostly along the River Taft (2). However, a careful search for time-space clustering carried out in the Nottingham area failed to reveal any positive results (35), and mapping of cases found in other cities as well has failed to show any patterns (20). Seasonal variation in the onset of Crohn's disease or ulcerative colitis would also be evidence in favor of an infectious etiology since such agents often show this behavior. Cave and Freedman (36) found statistically significant seasonal variation in the month of onset of symptoms for Crohn's disease with peaks in January and July. They also found a less prominent, but still significant, variation for ulcerative colitis with a single peak in mid-winter. Mayberry et al (5) investigated seasonal variation in their patients with Crohn's disease, using the date of diagnosis rather than date of onset of symptoms for their study, and no seasonal variation was found. Evans et al (20) studied seasonal variation in the onset of symptoms in their series of ulcerative colitis patients and found no seasonal trends. This thesis then, is intended to help settle the issue of possible seasonal variation and thus clarify the evidence for or against an infectious etiology.

Methods:

To test the null hypothesis that there is no seasonal variation in either the onset or relapses of ulcerative colitis or Crohn's disease a retrospective chart review was performed involving the 5 year period from 1974 to 1978 when the review was begun. The chart review was limited to
only five years because the treatment of patients with inflammatory bowel disease, at least those followed in the Pediatric Gastroenterology Clinic, had remained fairly uniform during that period and therefore variations in management would not have to be taken into account as a factor which could influence the occurrence of relapsing flares. Aside from treatment there were no other variables which we felt could or need be eliminated.

Once the time period and methods for the study had been decided charts were obtained through the Yale-New Haven Hospital Medical Records Research Department in one of two ways. First all charts of patients followed for inflammatory bowel disease in the Pediatric GI Clinic were called up by their unit numbers which were supplied by Dr. Gryboski. When the review of these charts was completed additional charts were obtained by having the research personnel call up pediatric patient charts by diagnosis for the time period in question until all traceable charts had been seen.

In reviewing the charts the data which we felt would be most helpful in determining when onset of symptoms or relapse had occurred was extracted and condensed onto a data sheet as shown in Figure I. Although the most important information was of course the symptoms directly related to the GI tract, other signs and symptoms known to be associated with inflammatory bowel disease were also recorded to clarify cases in which the GI symptoms might be ambiguous. Medications and operations were also recorded since they have obvious effects on the course of the disease.

All available data between Jan. 1974 and Dec. 1978 was recorded with the exception of that for patients who turned 21 during this period. For those patients data was collected only up to Dec. of the year before they turned 21. This was done to avoid biasing the data towards the first part
<table>
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<tr>
<th>Steroid meds, (type &amp; dose)</th>
<th>Jan</th>
<th>Feb</th>
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<td># of stools/day loose vs. formed</td>
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<td>GI complications (fistulae, obs. etc.)</td>
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<td>Other meds (Azulfidine, opiates, etc.)</td>
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<td>Albumin/globulin</td>
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<td>Level of Activity</td>
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<td>Temperature (fevers + or -)</td>
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<td>Arthralgias, rashes, pyoderma gangrenosum + or -</td>
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<td>Hospitalizations, operations, diag. tests or exams &amp; results</td>
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<td>&amp; Misc.</td>
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of the year as might have happened had we included these patients up to the moment of their 21st birthday.

Although for most patients the records were somewhat spotty with long gaps, sometimes of years, with no recorded visits or hospitalizations this was not felt to be a problem since for the few patients for whom the reason for the gaps was known it was good health that had kept them away, and even if for some patients the gaps represent times when they were treated elsewhere there is no reason to believe that this would bias our data toward any particular time of year. Thus all patients for whom data was available were included in the study even if the data covered only a few months during the years we were interested in.

Once the data was collected the months of onset of symptoms or of relapses were determined. For the first onset of symptoms this was very straightforward, however, for relapses this was much more complicated since exacerbations of symptoms occurred in many contexts. To simplify analysis the following definitions were used to separate what we felt to be true relapses of the disease from less important, but perhaps meaningful, increases in symptoms.

I. True relapses- Pt. asymptomatic off steroids for 3 months or longer before the recrudescence of GI symptoms lasting longer than 1 week and generally requiring that the patient be put back on medication.

II. Intermediate flares- Pt. asymptomatic greater than 1 month but less than 3 months off steroids before the reappearance of symptoms.

III. Tapering flares- recurrence of symptoms as steroid dose is tapered.

Just as for the onset of symptoms, flares were counted for the month in which the new symptoms were first noticed by the patient, not in the month
in which they were brought to the physician's attention and treated.

Once the frequency per month of onset of Crohn's and UC and their flares had been determined the $X^2$ test was applied to check for any significant deviation from the null hypothesis. The data for UC and Crohn's was analyzed separately and the $X^2$ test was applied to the data for onset of the disease, relapsing flares, intermediate flares, and tapering flares individually as well as to the combined data for all three types of flares. For onset of the disease, relapsing flares and intermediate flares the frequencies were not high enough to analyze the data by individual months since this would have given an expected frequency per month of less than two in which case the $X^2$ test is invalid. Therefore the frequencies were collapsed down to seasons with Winter = Dec.-Feb., Spring = Mar.-May, Summer = June-Aug., and Fall = Sep.-Nov., after which the expected frequencies were all greater than two and the $X^2$ test could be used. For tapering flares and the combined data for all flares the frequencies were high enough that the data could be analyzed by individual months so this data was not collapsed into seasons. (See Appendix 1 for details of $X^2$ test).

Results:

A total of 76 patients were found who had diagnoses of ulcerative colitis or Crohn's disease confirmed by sigmoidoscopy, rectal biopsy, x-ray findings or surgical pathology. Of these 38 had Crohn's disease and 38 had ulcerative colitis. 57 of the patients were followed by Dr. Grycoski in the Pediatric GI Clinic, and the remaining 19 were followed by an assortment of other physicians associated with Yale-New Haven Hospital. 22 patients had their first presentation within the study period, 13 with ulcerative
colitis and 9 with Crohn's disease. A total of 74 flares of all types occurred among ulcerative colitis patients during the study period, and 74 occurred among the Crohn's patients. (Similarities in numbers are coincidental). The distributions of those flares and new onsets are as shown in Figures 2, 3 & 4.

The $X^2$ test applied to the data for new onset, relapsing flares, and intermediate flares by season showed no significant seasonal variation for any of these either for Crohn's patients or ulcerative colitis patients ($p > 0.05$). The $X^2$ test applied to the data for tapering flares and the combined data for all flares by month yielded similar results ($p > 0.05$) for both Crohn's and ulcerative colitis patients. See Table 1.

Discussion:

These results, which show no seasonal variation, do not support an infectious etiology. However neither do they rule it out, nor do they support or deny any of the other etiologic possibilities. This particular study is hampered by small numbers of patients; 76 patients total, 38 each for UC and Crohn's, and only 22 with new onset; whereas the other studies available had at least 200 patients in each category (36), or more (20), and must be regarded as being much more significant than the results presented here. Of these two studies which looked at month of onset, only the one by Cave and Freedman (36) included Crohn's disease patients, and it was among these patients that the most striking seasonal variation was found. The seasonal peak that they found for ulcerative colitis patients was very small, although still statistically significant, and may not be in such opposition to the findings of Evans et al (20) in Oxford where no
Figure 2

Crohn’s Disease

New Onset

Type I

Type II

Type III

Figure 2
Ulcerative Colitis

Figure 3
Figure 4

Crohn's Disease

Ulcerative Colitis

Figure 4
### Crohn's Disease:

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<th>$X^2$</th>
<th>$p$</th>
<th>$X^2$ for $\alpha = 0.05$</th>
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<td>4.77</td>
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<td>6.41</td>
<td>$p &gt; 0.05$</td>
<td>19.67</td>
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### Ulcerative Colitis:

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<td>2.69</td>
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<tr>
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<td>11</td>
<td>12.58</td>
<td>$p &gt; 0.05$</td>
<td>19.67</td>
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Table 1
seasonal peak was seen for ulcerative colitis. Until the results of these papers can be confirmed or denied by another equally large series the issue of seasonal variation will remain an open one.

The study of the seasonal distribution of flares of ulcerative colitis and Crohn's disease is unique to this thesis. Acheson in 1965 (31) maintained that flares of inflammatory bowel disease often follow upper respiratory infections, which if true should lead to a preponderance of flares occurring in winter and spring. Other infections which might trigger flares could also be expected to leave a characteristic pattern in their seasonal incidence. It has also often been said, at least for ulcerative colitis, that psychological factors play an important role in the remissions and relapses of the disease. In the life of a child or adolescent, with each season marked by special events and stresses; i.e. start of school, holidays, summer vacation; a strong psychological factor in the initiation of flares could be expected to lead to a seasonal variation in their occurrence. Other environmental factors may lead to a seasonal variability as well, as demonstrated by the autumn trough and winter peak in the incidence of perforated ulcers following the holiday excesses (36). That no such variation was found can mean either that 1) intercurrent infections, seasonal changes in diet, or psychological stresses have no effect upon flares of inflammatory bowel disease, or 2) the numbers of patients and patient flares which we were able to collect are insufficient to show a seasonal variation which may have become obvious were greater numbers available. It is also possible that many factors play a role in the initiation of flares, and that some or many of them may have led to a seasonal peak if operating alone, but that together their peaks and troughs overlap to produce a nearly constant incidence. Such speculations must await a more definitive study involving much greater numbers of patients than were available at Yale-New Haven Hospital alone.
Appendix 1:

Chi-squared ($X^2$) test:

$$X^2 = \sum_{a=1}^{n} \frac{(f_{\text{observed}} - f_{\text{expected}})^2}{f_{\text{expected}}}$$

Where $n$ = number of time periods
$f$ = frequency

$X^2$ values for various values of $p$ can be found in statistical tables.

$X^2$ for $p = 0.05$ is 7.81 \hspace{1cm} df = 3
$X^2$ for $p = 0.05$ is 19.67 \hspace{1cm} df = 11

Where $p$ = probability of the observed variation arising by chance
$df$ = degrees of freedom = $n-1$
Bibliography:


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