INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

UMI

A Bell & Howell Information Company
300 North Zeeb Road, Ann Arbor MI 48106-1346 USA
313/761-4700 800/521-0600

THE PHARMACOEPIDEMIOLOGY OF CROHN'S DISEASE THERAPY IN SASKATCHEWAN

Pierre Geoffroy M.D., C.M.

Department of Epidemiology and Biostatistics
McGill University, Montreal

May 1997

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfilment of the requirements of the degree of Master of Science.

Acknowledgments

I wish to express my gratitude to my thesis director, Dr Lucien Abenhaim, for sharing his expertise with me. I thank Mr. Lorenz Luthe for his help with the SAS programming.

In particular, I thank my stepfather, John W. Dodds Ph.D., for his kind support, his insights, and his literary genius.

Finally, I thank Catherine Meunier for her gentle kindness and understanding.

Table of contents

List of tables

List of tables

List of tables

List of figures

Abstract

Crohn's disease is an inflammatory bowel disease associated with substantial morbidity. Complications arising from this disease affect many organ systems. In particular, hepatitis, pancreatitis, blood dyscrasias, and renal disease are believed to occur more frequently in patients with Crohn's disease. The incidence of these conditions is also believed to be increased by some of the medications used to treat Crohn's disease. Sulfasalazine as well as mesalamine have been associated with hepatitis, pancreatitis, renal disease, and blood dyscrasias. In addition to characterizing the demographics and severity of Crohn's disease in Saskatchewan, the purpose of this study was also to determine if, in patients with Crohn's disease, there is an increased risk of developing these adverse conditions associated with the medications used to treat this condition. Record linkage studies using large automated databases have proven useful in pharmacoepidemiology to determine the association between medications and longterm adverse effects. In this study 1 999 patients with Crohn's disease who met inclusion criteria, were identified in the Saskatchewan Healthcare datafiles. Sixty cases of hepatitis, 35 cases of pancreatitis, 33 cases of renal disease, and 27 cases of blood dyscrasia occurred in this dynamic cohort from January 1, 1980 to December 31, 1993. The incidence of the adverse conditions was not found to differ according to medication use, gender, or age category. However, the rate at which mesalamine, sulfasalazine, glucocorticoids, and 6-mercaptopurine were prescribed to patients who developed these conditions was elevated compared to that in patients who did not develope these conditions. Furthermore, hospitalization rates were also comparatively elevated in patients who developed the adverse conditions. It was concluded from this study that the use of the aforementioned medications was not associated with an elevated relative risk of developing the adverse conditions of interest in patients with Crohn's disease.

Résumé

La maladie de Crohn est une maladie inflammatoire de l'intestin associée à une morbidité substantielle. Les complications qui en résulte affectent plusieurs systèmes physiologiques. L'hépatite, la pancréatite, les dyscrasies sanguines et les maladies rénales en particulier sont des complications qui se manifestent plus fréquemment chez les patients atteints de la maladie de Crohn. La fréquence de ces complications semble augmenter avec l'utilisation de certains médicaments prescrits pour traiter la maladie de Crohn.

Des études fondées sur d'importantes bases de données se sont avérées utiles en pharmacoépidémiologie pour déterminer le lien qui extiste entre les médicaments et les effects secondaires à long terme. Un des but de cette étude était de déterminer si, chez les patients atteints de la maladie de Crohn, il y a un risque accru de développer ces complications associées aux médicaments utilisés pour traiter cette maladie.

Dans cette étude, 1999 patients atteints de la maladie de Crohn, qui répondaient aux critères d'inclusion, ont été répertoriés dans le fichier de données du département des soins de la santé en Saskatchewan. Soixante cas d'hépatite, 35 cas de pancréatite, 33 cas de maladies rénales et 27 cas de dyscrasis sanguines ont été rapportés dans ce groupe entre le 1er janvier 1980 et le 31 décembre 1993. La fréquence des complications rapportée ne différait pas selon l'utilisation de médicaments, le sexe ou les catégories d'âge. Cependant, la fréquence à laquelle la mésalamine, la sulfasalazine, les glucocorticoïdes et la 6-mercaptopurine avaient été prescrits aux patients qui ont souffert de complications était élevée par rapport à celle où les patients n'avaient pas eu de complications. De plus, le nombre d'hospitalisations était comparativement plus élevé chez les patients qui avaient souffert de complications.

Cette étude a donc démontré qu'on ne pouvait pas associer l'utilisation des médicaments mentionnés ci-dessus à un risque relatif élevé de développer les complications énumérées chez les patients atteints de la maladie de Crohn.

I. Introduction

Knowledge about the longterm effects of medications depends on systematic reporting and documentation of adverse events. Phase IV pharmaceutical studies, pharmacovigilance studies, and other pharmacoepidemiologic studies have begun to impact on our awareness of the long-term occurrence of adverse events from medications used. For anyone who has ever had to take medication, the need for this information is obvious. In this study, the adverse events occurring during therapy for Crohn's disease were examined. The events of interest were blood dyscrasias, hepatitis, pancreatitis, and renal disease. Of course, these illnesses occur normally in any population. What makes this study particularly challenging is that these illnesses appear to occur more frequently in people with Crohn's disease.

A clarification must be made at the onset. Throughout this document reference is made to the occurrence of blood dyscrasias, hepatitis, pancreatitis and renal disease as the occurrence of adverse events. While it is true that these events are adverse, the term 'adverse event' might seem to imply a cause and effect relationship between medication use and these events. This could be particularly misleading in so far as these conditions all occur spontaneously in the population and with increased frequency in patients with Crohn's disease. Therefore, the reader is advised that in this study the term adverse event was used to signify the occurrence of adverse conditions which may or may not be associated with the medications of interest in this study.

The pharmacotherapy of Crohn's disease, as will be seen in the literature review,

is varied. This study examined four classes of medications: sulfasalazine, mesalamine, glucocorticoids, and 6-mercaptopurine. The first two medications have, since shortly after their availability, been implicated with the development of severe adverse illnesses. However, this putative association has never been systematically examined. Glucocorticoids and 6-mercaptopurine are included in this study to examine their roles as potential covariates in the development of the adverse events of interest.

The emergence of large automated medicare databases, such as the Saskatchewan Health Care System databases, holds promise for continued progress in the area of pharmacoepidemiology. In this study, information about patients with Crohn's disease was gathered from this resource using record-linkage techniques. The emphasis of the study was to characterise the occurrence of adverse conditions in a dynamic cohort of patients with Crohn's disease, and to determine if the medications used to treat this condition are associated with these occurrences. The study is particularly important because it lays the groundwork by which other pharmacoepidemiologic studies, using the Saskatchewan Healthcare databases, can be carried out. Using a theoretical framework, the data in the Saskatchewan databases was accessed and the data restructured. In this way, each patient in the dynamic cohort could be followed through a fourteen year follow up period in which all prescriptions, for medication used to treat Crohn's disease, dispensed to every patient, were recorded. The timing of adverse events relative to the time of last medication use was then assessed and utilized to estimate measures of risk associated with the use of the medications for the treatment of Crohn's disease.

II. Study Objectives

The three main objectives of this study were:

1. To identify patients with Crohn's disease registered in the Saskatchewan Health Care databases and characterize the demographics of patients with this illness in Saskatchewan.

2. To characterize the use of medications for the treatment of Crohn's disease and to determine the severity of illness due to Crohn's disease in Saskatchewan using prescription rates as well as hospitalization rates.

3. To estimate the incidence rates of blood dyscrasia, hepatitis, pancreatitis, and renal disease in patients with Crohn's disease and to determine if these adverse events are associated with the use of sulfasalazine, mesalamine, glucocorticoids, and 6-mercaptopurine used in the treatment of Crohn's disease.

III. Literature Review

III.1.Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is comprised of two conditions, ulcerative colitis and Crohn's disease. These two conditions are often difficult to differentiate clinically and even pathologically. As many as 10% of cases may be misdiagnosed as being the other. The etiology of either disease has not been determined though hypotheses as to their nature abound. There is little doubt that these diseases are immunologically mediated and, while environmental and genetic factors appear to be implicated, an overall understanding of their role is still elusive. Several initiating factors in Crohn's disease and ulcerative colitis are currently being investigated. For instance, microbial pathogens, such as *Mycobacterium paratuberculosis* and *Listeria monocytogenes,* have been proposed as being implicated, based on several epidemiologic associations (Sartor, 1995). Unfortunately, treatment with antibacterials alone has been largely ineffective. An exception to this is the clinical response of some Crohn's disease patients to treatment with metronidazole, an antibiotic effective against many of the anaerobic bacteria found in large concentrations along the mucosa of inflammed intestines (Sutherland et al, 1991).

The importance of the role played by defective immunoregulation in the inflammatory process is increasingly supported by laboratory and clinical findings. Acceptance of these results is evidenced by a growing popularity in the medical literature

and the fact that they form the basis upon which medications presently are being developed. An imbalance between pro-inflammatory and anti-inflammatory molecules and immunoregulatory cells is believed to be at the root of the problem (Sartor, 1995). Present theories about the pathogenesis of IBD suggest an interaction between genetic susceptibility, such as defective genetic regulation of immunoresponsiveness (Van de Merwe et al, 1988), and exposure to putative environmental influences such as bacterial products, resulting in an improperly modulated immune reaction. Genetic susceptibility is supported by the greater occurrence of particular HLA haplotypes in patients with Crohn's disease and ulcerative colitis compared to people without these diseases (Toyoda et al, 1993). It is believed that local inflammation in the intestinal wall results from the disregulated immune response, which subsequently leads to tissue damage. The damaged mucosa then becomes more permiable to luminal bacterial products causing further immune mediated tissue damage.

Although the pathogenic cascade described above explains, in part, the mechanisms by which intestinal integrity is disturbed in IBD, it does not account for the differences in pathologic findings and clinical symptomatology between Crohn's disease and ulcerative colitis. Characteristically, lesions in Crohn's disease extend into the intestinal submucosa whereas the lesions in ulcerative colitis are more superficial. As a result of this deeper penetration, fistulas and abscesses are more commonly found in patients with Crohn's disease. In addition, the site of affliction varies between the two illnesses. In ulcerative colitis, lesions are limited to the colon and rectum while the entire length of the gut can be affected in Crohn's disease. The major symptoms of ulcerative

colitis are bloody diarrhea and abdominal pain whereas in Crohn's disease the symptoms depend greatly on the area of bowel affected. In general, fever and non-bloody diarrhea are more common in Crohn's disease. In both diseases, generalized fatigue with or without weight loss is often observed. Differentiating between Crohn's disease and ulcerative colitis can be difficult if based only on medical history and physical examination. Confirmation of the correctness of the diagnosis calls for radiologic, sigmoidoscopic or colonoscopic examination of the bowel. Biopsy of the bowel wall may also be necessary at times. In Crohn's disease the affected segments of the bowel wall are discontinuous, being separated by areas of normal bowel. In ulcerative colitis areas of inflammation of the bowel are continuous. Whereas the rectum is almost always affected in ulcerative colitis, it is seldom so in Crohn's disease.

III.2. Epidemiology of Crohn's Disease

Since its first description in 1932 by Crohn, Ginzburg and Oppenheimer (Crohn et al, 1932), there has been a steady rise in the number of cases reported. In particular, a remarkable rise in incidence was noted after Crohn's colitis (Crohn's disease of the colon only) was distinguished from ulcerative colitis in 1960; this is because 25% of patients with Crohn's disease present with colitis only and were incorrectly diagnosed as having ulcerative colitis. Hence, earlier misclassification of the disease probably accounts for a certain proportion of the reported increase in incidence. In addition, changes in the International Classification of Disease (ICD) classification codes for IBD have also

complicated the epidemiological efforts to estimate disease rates.

There are several noteworthy epidemiologic features to Crohn's Disease. The incidence of the disease has a bimodal distribution, occurring most often between the ages of 15 to 25 and between 50 to 80 years of age (Lashner, 1995). In general, women are affected 20% more than men. While the incidence of Crohn's disease increases with distance from the equator, rural populations are less affected than urban people (Lashner, 1995; Sonnenberg and Wasserman, 1991). Around the globe, variation in disease incidence is great, from a low of 0.08/100,000 pop. in Japan (Yoshida and Murata, 1990) to a high of 9.7 /100,000 population in the Netherlands (Shivananda et al, 1986). In the U.S. the reported incidence of Crohn's disease is 2 cases per 100 000 population (Glickman, 1987). Among migrant populations the incidence changes little, suggesting a minor causative role for environmental factors.

Although IBD is associated with fairly high morbidity, mortality due to the illness is not high and, consequently, the disease has a chronic nature. Therefore, its prevalence considerably exceeds its incidence. In the United States, mortality from Crohn's disease has been decreasing (Sonnenberg, 1986). Estimates of prevalence and incidence rates are based on the assumption that people with IBD seek medical attention. As such, rate calculations are based on hospital admissions and physician visits. Furthermore, because the course of the disease is variable, i.e., there may be long periods of remission either spontaneously or post treatment, it is not always clear who was included in the prevalence data assembly. Nevertheless, Crohn's disease was estimated to affect between 440 000 and 540 000 people in the United States in 1985 (Calkins and Mendeloff, 1986). In

Western Canada, Fedorak estimates the prevalence of Crohn's disease to be greater than 50/100 000 population (Fedorak, 1992).

Morbidity from Crohn's disease is difficult to estimate, in part because an indicator of morbidity is difficult to define and there is no standard measure. Hospitalizations due to a disease are often used as a proxy for morbidity. Applying this measure to the case of Crohn's disease, the National Hospital Discharge Survey from 1984 to 1987 showed that 26 630 men and 39 330 females with a primary diagnosis of Crohn's disease were discharged from hospital (Sonnenberg, 1990). Because a large percentage of people affected with Crohn's disease are young, the socioeconomic impact of the disease could be substantial. Unfortunately, there is a paucity of data in this regard.

III.3. Clinical Course and Prognosis of Inflammatory Bowel Disease

Commonly, extraintestinal manifestations of the disease will appear in the patient with IBD. In particular, the joints, skin, and eyes may be affected with arthritis, erythema nodosum and uveitis, respectively. What is more, these symptoms may appear prior to the onset of gastrointestinal signs and therefore the diagnosis of IBD may be delayed. In addition to the myriad nutritional and metabolic derangements variously encountered in IBD, hepatobiliary complications are not uncommon. Fatty liver, pericholangitis, sclerosing cholangitis and chronic active hepatitis and cirrhosis each may complicate the course of the disease (Glickman, 1987). However, hepatic complications are much rarer in patients with Crohn's disease than in patients with ulcerative colitis (Fedorak, 1992).

More specific to Crohn's disease is the formation of biliary lithiases as well as renal lithiases, the latter reportedly occurring in up to 30% of patients (Fedorak, 1992). Nephropathy, in part due to the increased incidence of renal stones, is observed in patients with Crohn's disease (Fedorak,1992). As a consequence of stone formation, pancreatitis can also result (Greenberger et al, 1987). Finally, hematological complications commonly arise in IBD, chiefly due to chronic blood loss through the gut wall and malnutrition. Megaloblastic and iron deficiency anemia are the most commonly encountered anemias in patients with Crohn's disease, but occasionally auto-immune hemolytic anemia is also found (Levine and Aust, 1987).

Patients with ulcerative colitis and Crohn's disease are usually plagued by recurrent, acute exacerbations of their condition which are of variable intensity and duration. Prior to the development of several effective treatments, acute, severe attacks of ulcerative colitis were associated with approximately a 5% mortality. In general, the prognosis for Crohn's disease is not as favourable as that for ulcerative colitis and its course is dependant upon the extent of involvement of the gastrointestinal tract. In patients with Crohn's disease limited to the colon, the prognosis is excellent. Accurate and up to date mortality data for IBD is sparse owing to the chronic nature of the disease and continuously evolving therapy. Furthermore, recording of deaths due to Crohn's disease and ulcerative colitis may be clouded by deaths that are due to complications of IBD rather than the disease itself. For instance, a death reported as secondary to hepatic failure may not indicate that the initial cause of the hepatic disease was an IBD.

III. 4. Treatment of Inflammatory Bowel Disease

There are two main strategies in the treatment of IBD: surgical and medical. Although surgery has an important role in the management of the patient with IBD, medical therapy is the focus of this thesis and as such will be the focus of this therapeutics review.

Once the disease has been correctly diagnosed, the treatment of inflammatory bowel disease can be multifaceted depending on the patient's clinical presentation. Therapy may be initiated in a doctor's office on an outpatient basis or may necessitate hospitalization. Reversal of metabolic and nutritional derangements, alleviation of pain and other presenting symptoms, are all to be considered. Following the physician's review of the case, the patient will be prescribed any of several classes of medication, each with a particular aim. Nutritional supplements, analgesics, and antidiarrheals, in addition to agents specifically designed to reverse the bowel inflammation, are commonly prescribed. Finally, once an acute exacerbation is over, long-term therapy to prevent recurrences might be instituted. Treatment is therefore highly individualized. Although surgical interventions can be necessary, the most common therapeutic modality for treatment of the acute exacerbation as well as for long-term control is medical.

A lack of understanding of the pathophysiology of Crohn's disease and ulcerative colitis, as well as the dearth of representative animal models has hindered the development of medical therapy. Nevertheless, there are several classes of drugs presently used in the treatment of Crohn's disease and some new ones, particularly the

immunomodulators, that are now undergoing clinical trials. The effectiveness of these drugs has been difficult to evaluate because the variability of disease presentation is so great and therefore precise therapeutic endpoints are difficult to define. The medications used to treat Crohn's disease and ulcerative colitis can be divided into four categories: antibiotics, steroidal and nonsteroidal antiinflammatory agents, combination antibiotic-antiinflammatory, and immunomodulator drugs. At present, it appears that the most effective drugs are sulfasalzine, 5-aminosalicylic acid derivatives, corticosteroids and metronidazole. The agents in the immunomodulator class are mainly 6-mercaptopurine, methotrexate, azathioprine and cyclosporine, but as of this date these have been used only sparingly in the treatment of Crohn's disease.

III.4.1. Antibiotics

Several antibiotics, individually and in combination, have been tried in the treatment of Crohn's disease. Their use was based on the hypothesis that bacterial overgrowths or imbalances play an important role in the pathophysiology of the disease. This belief is related to the similarity of IBD to recognized enteric infections. Generally, therapy with antibiotics is aimed at select groups of bacteria, namely, gram negative bacilli and anaerobic bacteria. Unfortunately, trials using antibiotics for treatment of IBD have generally yielded few positive results. As such, the use of antibiotics in the treatment of IBD remains empirical. Reviewed here are the few antibiotics still advocated for treatment of patients with IBD.

III.4.1.1. Metronidazole

Metronidazole is an imidazole derivative active against gram negative anaerobes. It is a unique antibiotic in many ways. Firstly, it is very effective against the spore-forming anaerobic bacteria *Clostridium difficile*. This organism is believed to be associated with a considerable proportion of relapses of ulcerative colitis. Therefore it is often prescribed, in combination with other drugs, in the initial management of patients presenting with a relapse of their disease (Griffin and Miner, 1995). Secondly, independent of its antibacterial effects, metronidazole may have antiinflammatory effects in IBD by interfering with the process of adhesion between white blood cells and endothelial cells. (Arndt, 1994). Given these attributes, a double blinded, placebo controlled trial has shown metronidazole to be therapeutic in mild to moderate Crohn's disease and as useful as sulfasalazine in another trial (Sutherland et al, 1991; Ursing et al, 1982).

III.4.1.2. Ciprofloxacin

Despite the lack of evidence from controlled trials, this quinalone antibiotic has gained acceptance in the treatment of IBD (Bitton and Peppercorn, 1995). Like metronidazole, it is also believed to have some antiinflammatory properties which may be useful against IBD (Wood, 1996).

III.4.2. Antiinflammatory Agents

There are several classes of drugs that fall into this category. For the purposes of this review, two categories of medications are classified under this heading: nonsteroidal antiinflammatory agents and glucocorticoids. Other drugs which also affect the normal function of inflammatory cells, such as immunosuppressive agents, will be discussed elsewhere.

III.4.2.1. NonsteroidalAntiinflammatory Drugs

III.4.2.1.1.Sulfasalazine

Initially developed for the treatment of rheumatoid arthritis in the 1930s, sulfasalazine was not commonly used for treatment of ulcerative colitis until nearly two decades later (Moertel and Bargen, 1959; Svartz, 1942, 1988). It was initially and successfully used in the treatment of acute exacerbations of ulcerative colitis and in 1965 its use in long-term maintenance therapy was advocated (Misiewicz et al, 1965; Summers et al, 1979). Sulfasalazine is a combination of 5-aminosalicylic acid, an anti-inflammatory, and sulfapyridine, an antibiotic, linked together by an azo-bond. The molecule is only 25% absorbed in the upper gastrointestinal tract as it makes its way down to the colon where gut bacteria split the molecule into 5-aminosalicylic acid and sulfapyridine (Schroder and Campbell, 1972). The latter can then be absorbed while the

former exerts local anti-inflammatory effects and is mostly excreted in the feces after acetylation by colonic bacteria. Sulfapyridine is acetylated in the liver and excreted in the urine. It is now known that sulfasalazine's effectiveness against the disease is due to the 5-aminosalicylic moiety (Azad Khan et al, 1977; Van Hees et al, 1980). Although a double effect of the drug might have been hypothesized i.e., antibacterial and antiinflammatory, sulfapyridine's role is to inhibit the absorption of the 5-aminosalicylic acid in the small intestine (Svartz, 1988). 5-Aminosalicylic acid is thus delivered to the colon where it exerts its therapeutic effects on the mucosa. Sulfasalazine is currently recommended primarily for use in patients with Crohn's disease of the colon (Hanauer, 1996)

III.4.2.1.2. 5 -Aminosalicylic acid

After it had been demonstrated that 5 - aminosalicylic acid was the active agent in sulfasalazine, and because several side effects of sulfasalazine were attributed to the sulfapyridine moiety, modifications of the 5 -aminosalicylic acid were introduced for use in the treatment of IBD.

There are now several formulations of 5 - aminosalicylic acid, commonly called mesalamine, which are currently being used in the treatment of IBD. Most of the differences in formulations are designed to enhance delivery to sites of inflammation and minimize systemic absorption. Thus rectal application is ideal in disease affecting predominantly the rectum and distal colon. As seen with sulfasalazine, binding

mesalamine to different carrier molecules can decrease absorption in the upper gastrointestinal tract, thereby delivering the bound molecule to lower parts of the gut where bacterial enzymes can split the molecule. Newer systems of delivery involve sophisticated coatings of mesalamine tablets which deliver the active compound to the desired area of the gastrointestinal tract before release. For instance, Asacol is a resin coated tablet that releases mesalamine in the alkaline milieu of the distal ileum and colon. Pentasa however, is mesalamine enclosed in a shell of ethyl-cellulose that allows water in to dissolve the mesalamine which then diffuses into the intestinal lumen. Another approach, introduced in Olsalazine, is the use of a mesalamine dimer that requires bacterial azo-reduction in the colon to release two active molecules of mesalamine.

The mechanism of mesalamine's action has not been completely elucidated. It is likely that the therapeutic effect is mediated through a combination of: free radical scavenging, thromboxane synthetase inhibition, diminished interleukin and cyclooxygenase production, and dimished immunoglobulin production by plasma cells (Greenfield et al., 1993; Hanauer 1996). As with sulfasalzine, mesalamine is used for treatment of mild to moderate Crohn's disease. However, sulfasalazine is considerably less expensive and therefore enjoys continued use.

III.4.2.2. Steroidal Antiinflammatories: Glucocorticoids

This group of medications which are derivatives of cortisol, can be given orally, parenterally, or rectally and are believed to be the most effective agents in the initial

treatment of Crohn's disease (Salomon et al, 1992). The use of these agents has greatly improved the prognosis of Crohn's disease (Jewell, 1989). Their action is unspecific for the disease, involving modulation of mediators of inflammation and of acute phase reactants. Since most cells have glucocorticoid receptors, the therapeutic effect of glucocorticoids is multifactorial and cannot be explained by a single mechanism. The local inflammatory response in Crohn's disease is characterized by a mixed cellular infiltrate composed of lymphocytes, plasma cells, macrophages, eosinophils, mast cells, and neutrophils (Von Herbay et al, 1990). The effect of glucocorticoids depends on the distribution of each cell type in the infiltrate but, in general, they decrease the overall inflammatory response of these cells. When used to treat Crohn's disease, glucococorticoids are initially given in high doses which are then gradually tapered to maintenance doses. Glucocorticoids are often combined with sulfasalazine or mesalamine, by which the capacity to induce remission is greatly enhanced.

III.4.2.3. Immunomodulators: 6-Mercaptopurine and Azathioprine

6-Mercaptopurine, as well as its parent compound azathioprine, is used mostly in cases resistant to conventional therapy. It is an immunomodulator which, in addition to its immunosuppressive effects, is used in the therapy of acute leukemias. It inhibits DNA and RNA production and as such has potential for serious toxicity, thus limiting its use. Nevertheless, this medication has been shown to be very effective, inducing remission in up to 60% of glucocorticoid - resistant patients with Crohn's disease (Fedorak, 1992).

Available since the early 1980s, this drug is increasingly used in the treatment of severe Crohn's disease.

III.5. Adverse Effects of Medications Used In the Treatment of Crohn's Disease

Crohn's disease can be quite debilitating for the patient. The medications used to treat this condition are, in most instances, very beneficial. Therefore, the use of medications which may have serious adverse effects has been de rigueur because a high benefit-to-risk ratio exists. The drugs used for the treatment of Crohn's disease can have serious adverse effects. Although many reports of patients suffering the side effects of medical therapy can be found in the literature, the true incidence of these events is not known. Drug monographs produced by pharmaceutical companies normally report all the adverse events encountered with a drug product. Unfortunately, this information is mostly gathered from phase I to III clinical studies in which therapy is maintained for limited periods of time. Treating physicians and their patients do not always report the occurrence of the adverse events during long treatment periods.

One of the difficulties in determining a cause and effect relationship between the medications used for the treatment of Crohn's disease and the occurrence of side effects is that many of the apparent side effects are simply complications of the disease itself. It is therefore of prime importance to determine precisely if there is increased occurrence of side effects when the medications are used. Although there are many undesirable effects associated with the medications described above, several, such as nausea, headache, or

skin rash, are quite nonspecific and can be associated with most medications. A glance through the Compendium of Pharmaceuticals and Specialties will confirm this statement (Canadian Pharmaceutical Association, 1995).

Of interest in the present study are the following events: pancreatitis, blood dyscrasias, hepatotoxicity, and nephrotoxicity. Judging from the number of cases reported in the medical literature, the incidence of these events, in association with the medications used to treat Crohn's disease, appears to be low. The medications associated with these events are primarily mesalamine, sulfasalazine and 6-mercaptopurine. Acquiring knowledge about the role played by these drugs in the etiology of the aforementioned events is made difficult by underreporting of events in patients on medications. Furthermore, estimating the incidence of these events is difficult because of the difficulty in establishing the extent of use of these medications.That is, there is often no common denominator with which to make comparisions. Most adverse events are reported alone or as a small group in a clinical report. A further difficulty is determining the period after the discontinuation of a medication that a patient is truly at risk of developing one of its adverse effects. Certain nonspecific adverse effects will stop soon upon stopping the medication, but others, such as hypersensitivity reactions may manifest themselves a fortnight later.

Non-serious side effects of the medications used to treat Crohn's disease are frequent. Sulfasalazine's use is limited by its numerous and reversible adverse effects such as nausea, headache, anorexia, and dyspepsia. These have been correlated with sulfapyridine blood levels and are reduced by lowering the dose of medication.

Sulfasalazine has also been associated with more serious reactions. These include hepatitis, pancreatitis, pneumonitis, pericarditis, and peripheral neuropathy (Caspi et al, 1992; Crowley et al, 1992; Das et al, 1973; Debongnie et al, 1994; Dwarakanath et al, 1992; Gabazza et al, 1992; Garau et al, 1994; Gremse et al, 1989; Hamadeh et al, 1992; Laasila et al, 1994; Pounder et al, 1975; Rubin, 1994; Shear et al, 1986; Sotolongo et al, 1978). Toxicity due to sulfapyridine may be related to acetylator phenotype which is genetically determined (Das et al., 1973; Schroder, 1972). In the liver, sulfapyridine is metabolized by acetylation and hydroxylation for transport to and excretion by the kidneys. Slow acetylators (mendelian recessive gene), who metabolize sulfapyridine more slowly, and thus have higher blood levels than rapid acetylators, have been shown to experience significantly more adverse events (Das et al, 1973).

It had been assumed that the major contributor to the adverse events encountered with sulfasalazine was the sulfapyridine moiety. This was essentially true, in the context of normal sulfasalazine therapy, but now, as the use of mesalamine is becoming more widespread, reports of serious adverse events with this drug are accumulating. Pancreatitis, hemolytic anemia, renal insufficiency, hepatitis, and myocarditis have all been reported during treatment with mesalamine (Abdullah et al, 1993; Agnholt et al,1989; Colombel et al, 1994; Debongnie and Dekoninck, 1994; Eckardt et al, 1991; Garcia-Diaz et al, 1995; Lankisch et al, 1995; McLeod et al, 1995; Novis et al, 1988; Petersen and Skovbjerg, 1995; Poldermans, 1988; Radke etal, 1993; Riley et al, 1992; Ruf-Ballauf et al, 1989; Sachedina et al, 1989; Thuluvath et al, 1994; Tromm et al, 1992; Witte et al, 1994). As noted earlier, the dose of sulfasalazine is limited by the adverse

effects of sulfapyridine, which concomitantly limits the dose, hence absorption, of 5-aminosalicylic acid. Following removal of the limiting factor, sulfapyridine, much higher doses of mesalamine are being given, with the likely consequence of significant systemic absorption. This may account for the increased toxicity of the 5-aminosalicylic acid moiety.

Various schemes have been proposed to classify adverse drug reactions. One classification system divides adverse drug reactions as those resulting from known pharmacological actions of a drug and the other group as those not expected on this basis (Davies, 1985). These are labelled type A and type B adverse drug reactions, respectively. To illustrate this classification, a well known vasodilatory drug, hydralazine, will be used as an example. As might be expected, this medication is used to lower blood pressure in hypertensive patients. It acts on vascular smooth muscle to promote vasodilatation. It is not surprising then that orthostatic hypotension i,e., rapid decreases in blood pressure upon changing position from the supine to standing position, occurs in patients using this drug. However, a lupus-like pericarditis can occur during use of hydralazine but is unexplainable pharmacologically. This adverse effect likely results from an unexpected immune reaction to the drug.

The mechanisms involved in the two types of drug reactions are as follows. Type A adverse drug reactions can occur in two ways based on the expected variety of responses to medications between individuals. For example, in a hypothetical group of one hundred hypertensive patients of the same age, weight, and gender, receiving the standard dose of hydralazine, only 5 may experience orthostatic hypotension but 85 have

significant improvement in their blood pressure. When the dose is increased by 30% perhaps 95 of the patients will have a favourable therapeutic response but 50% will experience dizziness upon standing. Thus there is a spectrum of responses, both therapeutic and adverse, that is dose-dependant but predictable. The differences in degrees of response may result from differences in the absorption and metabolism rates of the drug between patients. Alternatively, it may also be the consequence of unequal concentrations of drug sensitive receptors between patients. Nevertheless, type A adverse drug events can be explained on the basis of the pharmacology of the drug.

Type B adverse events are not the result of quantitative differences between individuals but, rather, represent qualitative irregularities of either medication or the person taking it. For example, a patient may become toxic following the ingestion of expired medication, because the decomposition products of the medication are toxic. On the otherhand, a patient's adverse reaction may be the result of a genetic abnormality: malignant hyperthermia results when certain anaesthetic agents are given to patients with a predisposing inherited autosomal dominant trait. Another commonly occurring example of type B reactions are immunolgically mediated allergic reactions. For example, angioedema following the use of the angiotensin converting enzyme inhibitor captopril.

Recognition of the above differences in mechanisms of adverse drug reactions has an important implication in pharmacovigilance and pharmacoepidemiology since adverse drug reactions may take many forms and may not be expected pharmacologically. Therefore, large healthcare databases in which are recorded patient diagnoses and prescriptions, such as the Saskatchewan databases, are useful tools in uncovering possible

associations between medications and adverse drug reactions.

III.6. Conceptual framework for the study

III.6.1. Special considerations in pharmacoepidemiologic studies

The determination of risk in pharmacoepidemiological studies requires special considerations regarding exposure time. Classically, in epidemiological studies, incidence rates can be calculated as the number of new cases of a disease occurring over a predefined period of time in a selected population (Kleinbaum et al, 1982). For example, a cohort of 1 000 patients with Crohn's disease are followed for ten years. During this time, fifty cases of hepatitis develop. If no patients are withdrawn during the follow up period, then 10 000 person years will have been accumulated and the incidence rate of pancreatitis in this cohort of patients would be 5/1 000 person years. In this example, the risk of developing hepatitis in the patients was assumed to be constant throughout the ten years. In pharmacoepidemiologic studies, where the risk of developing adverse drug reactions is of interest, it must be considered that risk varies according to time of exposure to the drug of interest. The risk of adverse events resulting from medication use changes once medication use is initiated and then stopped. (Miettinen and Caro, 1989). It also varies from one exposure period to another (Moride and Abenhaim , 1994). Risk of adverse events resulting from medication increases sometime after the start of medication use. Once a drug is discontinued, the risk of adverse events resulting from its use may

stay the same, may continue to increase, or may return toward pretreatment levels. Returning to the above example, the total amount of time on therapy with a medication for Crohn's disease could be calculated and the ratio of cases of hepatitis to this amount of person time on medication would yield the incidence of hepatitis per person time of medication use. Although this approach recognizes the need to consider exposure time, it does not differentiate between cases occurring during medication use or during time off medication. A diagrammatic representation of a twelve year dynamic cohort study in which timing of adverse events relative to medication use was considered is illustrated in Figure III.1. In this illustration patients entered the cohort upon diagnosis of a disease, in this case Crohn's disease, and medication use as well as events of interest, were recorded. The occurrence of adverse events could then be determined not only relative to total time of drug exposure, but also in relation to when medication was last used. Consequently, the incidence rate of adverse events occurring during treatment could then be compared to the rate during times when no medication was being taken. The relative risk of an adverse event associated with drug use is then taken as the ratio of the two incidence rates.

III.6.2. Hazard functions during and after medication use

The variability in risk relative to medication use can be conceptually described by hazard functions. Three types of hazard functions are depicted in Figure III.2 and III.3. According to the constant hazard model, sometime after the start of therapy, depending on the rapidity of a medication's toxic effects, a maximum risk of developing an adverse

effect is reached and maintained throughout the period of exposure. In the example shown, the risk gradually returns to, or near, baseline following discontinuation of the medication. An example of this type of hazard function is the risk of developing a *systemic lupus erythematosus-like syndrome* (SLE) during procainamide use (Bigger and Hoffman, 1985). The risk of developing this SLE-like syndrome remains constantly elevated throughout the course of therapy and gradually disappears after drug discontinuation. Other models, or non-constant hazard models, have also been used to describe the risk of adverse events associated with medications. For instance, the exponential hazard model best illustrates the risk of breast cancer during and following the use of hormonal preparations. In this situation, the pathogenic process is slowly initiated and the risk of an adverse event increases gradually with time. By contrast, the rapid rise in risk of an anaphylactic reaction following penicillin use, is best illustrated by the variable hazard function in Figure III.3. In this case, the risk of an adverse event rises sharply after the medication is taken and it returns rapidly to baseline shortly thereafter, despite continued use of the medication.

The period of time following discontinuation of the medication is also a period of potentially increased risk. The duration of this period of increased risk is dependent on the pathogenic process involved. Therefore, the overall period of time at excess risk of an adverse event is the time during which a patient is taking the medication of interest as well as for some length of time after drug discontinuation. The selection of excess risk time period designs in record linkage studies such as this one is a crucial part of pharmacoepidemiology (Miettinen and Caro, 1989; Moride and Abenhaim, 1994; Van

Staa et al, 1994). The rate of decrease in risk of developing an adverse event following discontinuation of medication depends on the natural history of the pathogenic process induced by the medication and how quickly it is reversed. In certain instances, this process may never be entirely undone and a permanent residual effect from exposure may remain.

The most appropriate post treatment time period is difficult to select and has been an area of controversy among epidemiologists. In their study of the use of nonsteroidal antiinflammatories and the risk of upper gastrointestinal bleeding, Van Staa et al demonstrated that the length of time selected for elevated post treatment risk significantly influenced the estimates of drug associated risks of adverse events (Van Staa et al, 1994). For his part, Shapiro has criticized record-linkage type pharmacoepidemiologic studies (Shapiro, 1989). He maintains that too long post treatment periods of excess risk are used, resulting in misclassification of cases and therefore compromising the validity of these studies. In the study at hand, the duration of this time period was largely selected based on some clinical reports of post medication toxicity. The rapid development of side effects, and therefore of pathogenic processes, has been previously documented for sulfasalazine and has been shown to vary according to acetylator phenotype (Das et al, 1973; Schroder and Evans, 1972; Sotolongo et al, 1978). However, the rate of decline in risk after discontinuation has not been studied. Approximately one month after discontinuation of sulfasalazine, patients with IBD who had developed a hepatitis while on this medication, had nearly completely returned to normal (Sotolongo et al, 1978). Similarly, mesalamine related adverse effects can appear

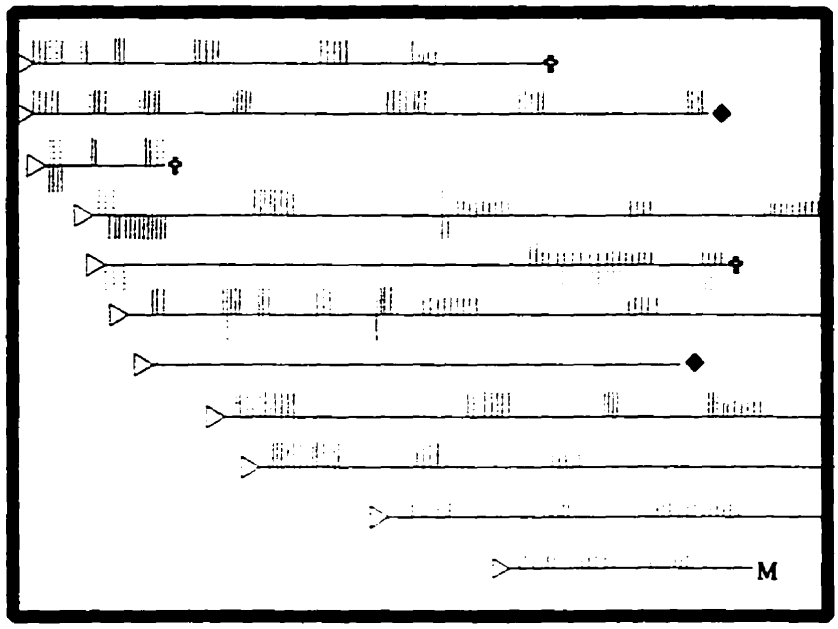
within 2 weeks of starting medication (Eckardt et al, 1991; Hanauer, 1993), and resolve shortly after stopping the medication (Eckardt et al, 1991). The pathogenic mechanisms by which the medications used to treat Crohn's disease induce adverse effects are not known well enough to determine how long the period of potentially increased risk after drug discontinuation is. This time window for post discontinuation effect must be reasonably long enough to capture adverse events truly resulting from medication effects yet not too long, to avoid exposure misclassification of adverse events, resulting in diminished precision and validity of the study (Miettinen and Caro, 1989; Van Staa et al, 1994).

In this study, several assumptions were made. A constant hazard model was employed in the design of this study. It was assumed that shortly after the initiation of therapy with one of the study medications the risk of an adverse event increases rapidly to a constant level. Once therapy is stopped the risk remains at this level for an additional thirty days, after which time it returns to baseline. A model of constant hazard was selected because it was believed that once a pathogenic process had been initiated for a particular adverse event, the risk of that adverse event had been set. That is, the risk of an adverse event was dependent on the development of a pathogenic process. Once the medication was removed, the pathogenic process gradually resolved. This would seem to be the case according to the reports alluded to above.

It was further assumed that the risk of an adverse event resulting from medication use returned to the same level with each repeated use. Although the work of Moride and Abenhaim on the risk associated with repeated uses of non-steroidal anti-inflammatories

might have suggested otherwise, there were no estimates that could be used to predict what that change in risk might have been with each repeated use of each particular medication in this study (Moride and Abenhaim, 1994). Therefore, no change in risk with each additional drug exposure was factored into this study.

Figure III.1. Diagrammatic representation of the 12 year follow up of a cohort of patients with Crohn's disease in Saskatchewan. Medications prescribed were recorded for each patient for the entire follow up period.



LEGEND

Mesalamine prescription

Sulfasalazine prescription

Glucocorticoid prescription

6-Mercaptopurine prescription

◆ Adverse event

✞ Death

M Moved from Saskatchewan

▷ Entry into the cohort

Figure III.2. Constant hazard function.

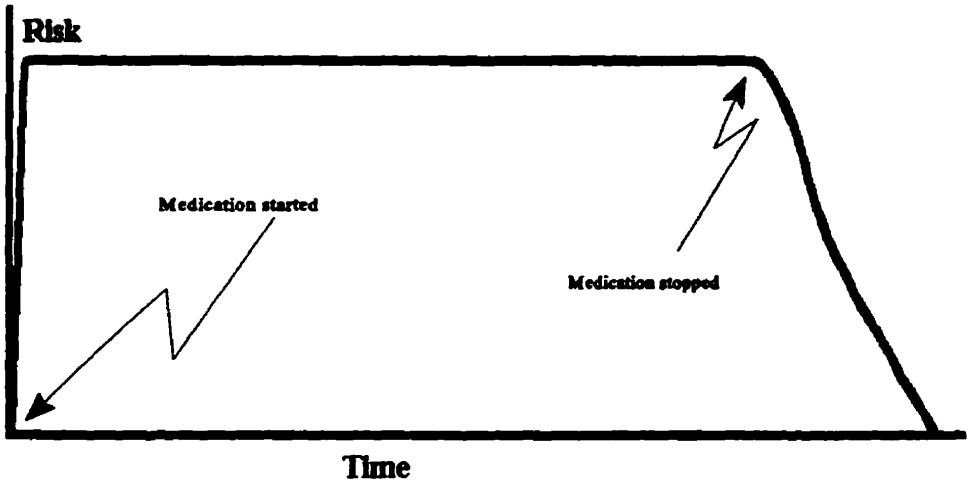
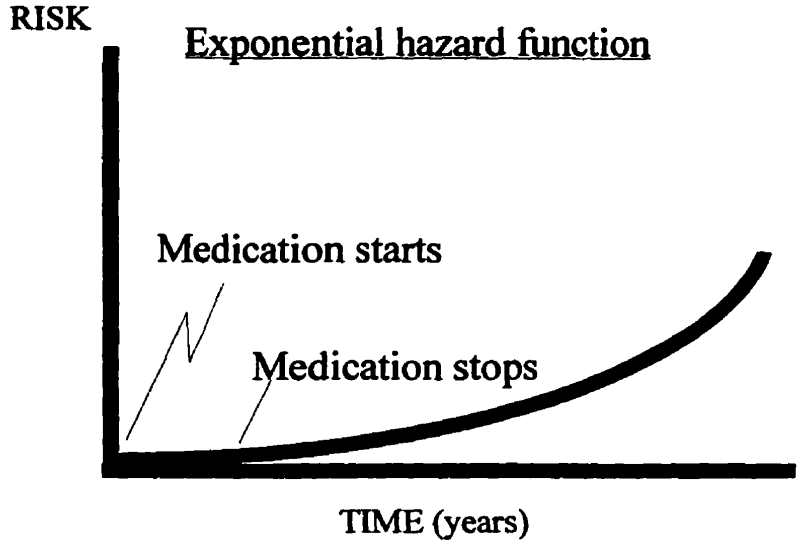
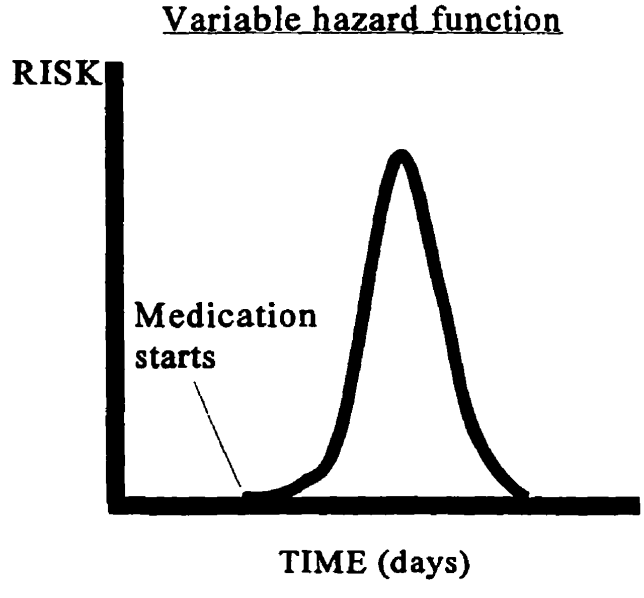


Figure III.3. Exponential and variable hazard functions.





IV. Methodology

All data were obtained from the four files of the Saskatchewan Health Services database that are described below. The data include entries made from January 1st, 1980 to December 31st, 1993. The information was made available through the Pharmacoepidemiology Unit, Laboratory and Disease Control Services, Saskatchewan Health. In order to maintain patient confidentiality, only the patient registration codes were obtained. In addition, only the data pertaining to inflammatory bowel disease were released to the investigator.

IV.1. The Saskatchewan Health Care System Databases

Saskatchewan has a population of about 1.1 million people. Residents of the province are registered with the Saskatchewan Department of Health and are entitled to receive health care benefits including free access to physicians and hospitals. Not included in the data are residents whose prescription costs are paid by other government agencies (members of the Royal Canadian Mounted Police and the Canadian Armed Forces, Registered Indians, Workers' Compensation Board Claimants, and beneficiaries of the Department of Veterans Affairs). Saskatchewan Health has had computerized data collection in various databases since 1963. Of interest in this study are the following four databases: the Health Insurance Registration File (HIRF), the Prescription Drug Plan (PDP), the Hospital Services Plan (HSP), and the Outpatient Physician Services Plan

(OPSP).

The information in the HIRF mainly consists of patient identifiers, such as the beneficiary registration number. It is through this file that a patient's eligibility for services offered by the health plan is verified. The PDP has been covering the cost of prescription medications for registered residents since 1975. Only prescriptions of medications listed on the province's formulary and prescribed by a physician licensed in Saskatchewan are recorded. From September 1975 to July 1987, and from January 1989 to present, pharmacists submitted claims to the PDP for reimbursement. In this way all eligible prescriptions filled were registered in the database. Unfortunately, from July 1 1987 to the end of 1988, the plan was changed and demands for reimbursement were filed on a family unit basis rather than on an individual basis. Thus, data captured during this period were incomplete and not used for this investigation.

The Saskatchewan drug formulary is under continuous review. Drugs are added or removed by overseeing expert committees. As of July 1993, the formulary listed 2125 drug products, including 487 different chemical entities. Although there are 389 interchangeable drug groups, not all generic formulations of a drug are necessarily on the list. Submissions are verified for claimant eligibility and for correctness of the information on the claim. Random checks for fraudulent claims are also performed on a weekly basis.

Data on all hospitalizations in Saskatchewan's approximately 134 hospitals is recorded in the HSP datafile. All hospital separations, i.e. when patients are discharged from the hospital, are documented. There are approximately 200,000 hospital separations

recorded yearly in Saskatchewan. In addition to admission and discharge dates, and services received while in hospital, with each hospital separation are also recorded the patient's primary and, when applicable, secondary diagnosis. Diagnostic coding uses the International Classification of Diseases (ICD) current at the time of coding. Prior to April 1, 1979, the ICDA-8 was in use. Since then, the four digit ICD-9 coding has been in use. Coding is carried out at the hospital. Accuracy and precision of coding are not systematically verified. While patients are hospitalized medications given to them are not recorded with the PDP. Consequently, medications received in hospital were not accounted for in this study.

The OPSP datafile contains information obtained from physicians' payment claims. For each patient visit a physician files a payment claim containing the patient's identifier and diagnosis. The diagnosis is recorded with the three digit ICD-9 code along with service codes, patient information (age, gender, HIRF number), and physician information (specialty, practice location, age, and gender). Due to the great number of physicians in Saskatchewan, and their wide geographic distribution throughout the province, it has not been feasible for Saskachewan Health to validate the diagnostic information on claims using information in patient charts.

IV.2. Demographics of the study population

The data received from Saskatchewan Health contained information on patients who had received at least one diagnosis of IBD. Diagnosis of Crohn's disease was

identified with the ICD code 555 in the HSP or OPSP datafiles. Patients eligible for this study were those who had received at least two diagnoses of Crohn's disease on two separate occasions by physicians (in the OPSP), or who had had at least one diagnosis of Crohn's disease, either as a primary or secondary separation diagnosis, in the hospital separation file. Two physician diagnoses as opposed to one hospital diagnosis were considered necessary because in a physician's office the diagnosis of Crohn's disease may not be confirmed until a second visit. In a hospital, due to the greater availability of diagnostic tools, such as radiologic studies and endoscopy, the diagnosis may be confirmed on the first visit. Date of entry into the cohort was the date on which the diagnosis of Crohn's disease was first made by a physician (in the OPSP) or the date of the admission to hospital in which the diagnosis of Crohn's disease was made. Entries into the datafiles regarding each patient were analysed from the time of entry into the study cohort, until the patient was censored (when a patient reached an endpoint of interest, died, was struck from the registry [for instance, because of moving from the province], or until the end of the study). Patients were only counted in the study group if they had more than one day between the day of diagnosis of Crohn's disease and censoring.

The age of the patients used in the study was that which was recorded on the date of registration into the Saskatchewan database (Index date). For the multivariate analysis, age was subdivided into two age categories, those less than 45 years and those greater than or equal to 45 years. Only patients 15 years old or more were included.

IV.3. Calculation of person time in the cohort and person time of drug exposure

For each patient, every single day from the time of entry into the cohort until study termination or censoring from the study, was counted as a person day in the cohort. Using the ID number of each patient, the PDP datafile was searched to obtain the type and date of every prescription for medications of interest listed in section IV.4.1, dispensed to a patient between the time of entry into, and exit from, the cohort.

Having so obtained all the information pertaining to medication use by each patient while in the cohort, the task of counting person time in the cohort and person time of drug exposure, was then undertaken.

Each prescription dispensed was counted as thirty days of medication use unless interrupted by another prescription, by withdrawal of the patient from the cohort, either following an adverse event, death, striking from the Saskatchewan Healthcare datafiles, or the end of the study period.

For each patient in the study, each day in the cohort was counted as either 'a day at baseline risk', or 'a day at excess risk' of developing an adverse event. Baseline risk is a day on which no medications are being taken. There are two types of days at excess risk of adverse effects. First, there is a day at risk while taking a medication, which is referred to as a 'treatment day'. The second type of days at excess risk are those days following discontinuation of a course of medication. Thirty days following drug discontinuation are counted in this category. These are called 'post-treatment days at risk'. In the analysis,

post treatment days were not analyzed separately. Instead, the statistical analysis was done either counting only treatment days or treatment days plus post treatment days.

A purpose of this study being the determination of risk of developing an adverse event as a result of exposure to particular medications, the incidence of adverse events during person-time of drug use, or for thirty days after drug discontinuation, was compared to that during person-time without drug use. The denominator used in calculating these incidences was person-time on or off a particular medication depending on whether the event occurred during a treatment, or post treatment day, or not. An example of how this was done is provided in Figure IV.1A. In this simplified case, a patient was diagnosed to have Crohn's disease on December 16. Three days later, on December 19, he started a course of glucocorticoids. He took one day of this medication before being dispensed mesalamine. He developed renal disease on January 13. Therefore, this patient was recorded to have had 3 drug free days, 1 day of glucocorticoids alone, and 25 days of mesalamine plus glucocorticoid before withdrawl from the cohort. The corresponding data entry are provided in Figure IV.1B. An actual, and slightly more complicated case, is depicted in Figure IV.2. In this instance, patient 5002546 received 59 prescriptions for sulfasalazine spread over more than nine years in the cohort. Table IV.1 reports the records of this patient if only the treatment days are counted. The total time spent in the cohort by this patient was 3245 days (see column marked SPAN). During this period the patient had 1698 days of sulfasalazine treatment days (see Totals of column SALAZIN) and 1547 drug free days (Totals of column DRUGFREE). In Table IV.2, post treatment days were added to the treatment days of

sulfasalazine. As a result, in row '283' of Table IV.2, the first line of data entry for patient 5002546, corresponding to the first prescription of sulfasalazine, the number of days of sulfasalazine increased by twenty-seven and the number of drug free days was consequently adjusted downward by twenty-seven days. In this instance, twenty-seven days represents the number of days elapsed between the end of the first prescription (03 AUG 84) and the dispensing of the second (29 SEP 84).Thus, when the post treatment period is interrupted by another prescription for the same drug, as is often the case for patient 5002546, then the count for post treatment days is stopped. If there was a prescription for a different drug during the post treatment period, then both would be accounted for. That is, the days would be counted as a combination treatment day for the new drug plus post treatment day of the first drug. Examples of this can be found in Figure IV.3. In this figure six patient scenarios are depicted. There are four thirty day periods labelled A, B, C, and D. In the first scenario (1), ASA is dispensed at point 'a' and an event occurs at point 'c'. In this instance, 21 days of mesalamine are credited to the total of person days of mesalamine for the cohort and an event was registered as having occurred on a sulfasalazine treatment day. In patient scenario 2, mesalamine is dispensed at 'a' and an event occurs 37 days later at 'd'. In this case the event occurred during a post treatment day since it occurred thirty-seven days after the prescription for mesalamine had been dispensed. Therefore, thirty treatment days were added to person days of mesalamine and seven days were added to mesalamine post treatment days. In the third patient scenario, mesalamine was again prescribed on the day of diagnosis. Fifteen days later, sulfasalazine was prescribed (point 'b') and an event occurred a week later at

point 'c', on a combination mesalamine-sulfasalazine treatment day. Fifteen mesalamine treatment days were tallied, as were seven days of combination mesalamine plus sulfasalazine treatment days. Scenario 4 is similar except that the event occurred 37 days following the initial prescription for mesalamine was dispensed. In this case 15 days of mesalamine treatment were counted as well as 15 days of mesalamine plus sulfasalzine and seven days of sulfasalazine alone. In the analysis including the post treatment days, the seven days of sulfasalazine alone were counted as seven sulfasalazine plus post treatment mesalamine days since mesalamine post treatment days extend into this time. Scenario 5 depicts a situation in which are recorded 15 treatment days of mesalamine use alone, 15 combination treatment days of mesalamine plus sulfasalazine, 15 combination treatment days of sulfasalazine plus post treatment mesalamine, 15 days of post sulfasalazine treatment days and 38 drug free days. The event occurred on a drug free day. Scenario 6 illustrates a situation in which an event occurred while a patient was on triple therapy. In this instance, 15 treatment days of mesalamine, 15 treatment days of mesalamine plus sulfasalazine, 22 treatment days of sulfasalazine, 7 combination treatment days of sulfasalazine plus glucocorticoids, and 7 treatment days of sulfasalazine plus glucocorticoids plus 6-mercaptopurine in combination were recorded before the event occurred. For every patient in the cohort, all treatment days alone or in combination, and all post treatment days alone or in combination, were identified in this way and added together for each medication.

IV.4. Medication use by Crohn's disease patients and indices of severity of illness

IV.4.1. Study medications

Four medications used to treat Crohn's disease were studied: sulfasalazine, 5-aminosalicylic acid (mesalamine), glucocorticoids, and 6-mercaptopurine. In the Saskatchewan Health Care drug formulary, these medications come in a variety of formulations and can be given via the oral, rectal, and intravenous routes. For the purposes of this pharmacoepidemiologic study, differences in formulations and routes of administration were not considered. Therefore, as listed below, the medications were only studied as four different groups. Although available from the PDP datafile, doses of drugs were not taken into account. The medications were identified with the following codes in the Saskatchewan Drug file:

1) Sulfasalazines:
    - Oral
        - 009 Sulfasalazine
        - 010 Olsalazine
    - Rectal
        - 052 Rectal Sulfasalazine

2) 5 - Aminosalisylic acids (mesalamine):
    - Oral
        - Enteric coated
            - 001 Asacol
            - 003 Salofalk
            - 004 Mesasal

Delayed release
002 Pentasa
Suppository
005 Rectal 5 - ASA

3) Glucocorticoids
006 Oral Prednisone
007 all other corticosteroids (betamethasone, hydrocortisone)
008 Rectal corticosteroids

4) Mercaptopurine:
051 6 - Mercaptopurine

There were, as discussed with the examples given in chapter IV.3, days on which more than one study medication was taken by a patient. For any such combination of drugs used on a given day, a different identification number was assigned. Therefore, each drug combination day was separately identified and added to the sum of all same combination days of all the other patients. Identification of drug combination days was important for the multivariate analysis such that the use of more than one drug on any day could be accounted for. The identification numbers for each of the combinations encountered in the study are listed in Table IV.3. In the datafile used for final statistical analysis of these drug combinations were further coded into a binary classification. For example, the treatment combination 'mesalamine plus glucocorticoid' was given the identification number '4' and was coded as 1-0-1-0-0 in the binary format. Returning to the example of patient 5002546, the method used to enter this medication related information is depicted in Table IV.4, which is a portion of the datafile used for the statistical analysis. In the observation lines 850 and 851, all the information pertaining to this patient for each drug or drug combination dispensed, is listed. In this case the patient,

who is male (Sex = 0)and less than 45 years old (Age = 0), had no events (coded as '0' under each of the columns for adverse events) while on sulfasalazine (Rx = 14). He accumulated 1698 sulfasalazine treatment days which are coded as '1' in the 'Sal' column. In observation line 851, one finds that this patient had a hepatitis while on a drug free day (Rx = 19), which was marked as a '1' in the column marked 'Hep'. When post treatment days were considered, these were coded in the same way for each patient in each drug or drug combination line. In Table IV.5 it can be noted that patient 5002546 had his hepatitis during a sulfasalazine post treatment day. The total number of days of sulfasalazine increased to 2301, and drug free days decreased to 944 when the 30 day post treatment period was considered. This patient had taken no other drugs for the treatment of Crohn's disease.

In another case discussed earlier, and shown in Figure IV.1a and 1b, the patient had three lines of coding in the final datafile. The first shows 3 drug free days (Rx = 19), followed by 25 days of mesalamine plus glucocorticoids in combination (Rx = 4) and, finally, one day of glucocorticoids alone (Rx =10). This system was used to classify all days in the cohort for each patient with Crohn's disease.

IV.4.2. Severity of illness indices: Prescription and hospitalization rates

Crohn's disease can affect different patients variably. Whereas some patients may suffer substantial morbidity from this inflammatory illness, others may suffer only a few bouts of abdominal pain and diarrhea throughout the course of their illness. It follows

then, that depending on the severity of their affliction, patients may have more or less medication prescribed to them, just as they may require more or less frequent hospitalizations. To compare the severity of illness in patients with Crohn's disease who did and those who did not suffer adverse events, prescription rates and hospitalization rates were calculated.

Prescription rates were achieved by counting all the prescriptions for each type of medication used for the treatment of Crohn's disease and dividing this sum by the number of person days in the cohort for all the patients in each adverse event category. Only the prescriptions dispensed prior to an adverse event were counted. In a similar fashion, hospitalization rates were calculated for patients in each adverse event group. Only those admissions which had a separation diagnosis of Crohn's disease or one of the adverse events were counted. The hospitalization rate for each group was calculated by dividing the total number of hospitalizations in each adverse event group by person days in the cohort for all the patients in each adverse event group. In this way, for example, hospitalization and prescription rates for patients who suffered a pancreatitis could be compared to that for Crohn's disease patients who never suffered a pancreatitis.

IV.5. Adverse events: Their incidence and their association with study medication use

IV.5.1. The adverse events

The events of interest were the occurrence of a blood dyscrasia, hepatitis,

pancreatitis and renal disease as defined by the following ICD-9 codes in the HSP or OPSP datafiles:

Blood Dyscrasia:

283 Acquired hemolytic anemia
284 Aplastic anemia
287 Purpura and other hemorrhagic conditions
288 Disease of white blood cells

Hepatitis:

570 Acute and subacute necrosis of the liver
571 Chronic liver disease and cirrhosis
572 Liver abscess and sequelae of chronic liver disease
573 Other disorders of the liver

Pancreatitis:

577 Disease of the pancreas

Renal disease:

580 Acute glomerulonephritis
581 Nephrotic syndrome
582 Chronic glomerulonephritis
583 Nephritis and nephropathy not specified as acute or chronic
584 Acute renal failure
585 Chronic renal failure
586 Renal failure, unspecified
587 Renal sclerosis, unspecified
588 Disorders resulting from impaired renal function.

General diagnostic terms were used, such as renal disease, to encompass several more specific conditions. Patients were removed from the study once they had had an adverse event of interest.

IV.5.2. Association between medication use and adverse events

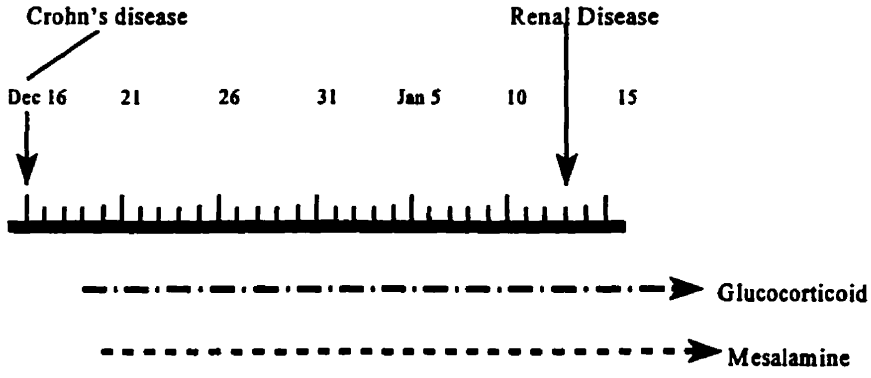
The occurrence of adverse effects was determined in relation to when medication was used and relative to total time of drug exposure. The number of events by gender, age category, and exposure history were calculated and expressed as rates per 100,000 person days. In the stratified statistical analyses relative risks were calculated to estimate the association between each variable and each adverse event. In this study, because the events of interest were rare, a Poisson regression model was used for the multivariate analysis. This type of regression model is ideally suited for cohort data with person-time denominators (EGRET reference manual, 1991). The Poisson regression model links a count, in this instance adverse events, and a rate multiplier variable with a set of covariates. It adjusts for the relative sizes of the risk populations in the various cells or covariate patterns. The rate multiplier used was person-time. The dependent variable was the number of each type of adverse event and the model was controlled for gender and age category. Incidence rates and relative risks were generated for each medication using concomitant drugs used as covariates in the model. The Newton-Raphson fitting algorithm was utilized with a maximum iteration number of twenty. All calculations were carried out separately for treatment days alone and then with post treatment days included. Test-based 95% confidence intervals were calculated throughout.

IV.6. Data manipulation and analysis tools.

Analysis of the data was carried out using a NEC Versa Pentium computer. Data manipulation and stratified analyses were performed using the SAS 6.10 statistical package for Windows. The multivariate analyses were conducted using EGRET statistical package version 0.19.6 for DOS.

Figure IV.1. The case of patient 5009288.

A) Schematic representation of medication use.



B) The corresponding data entries for each medication used by patient 5009288.

ID	Sex	Age	BD	Hep	Ren	Pan	Rx	Days	ASA	Sal	Str	6M	Free
.													
.													
5009288	0	0	0	0	0	0	19	3	0	0	0	0	1
5009288	0	0	0	0	1	0	4	25	1	0	1	0	0
5009288	0	0	0	0	0	0	10	1	0	0	1	0	0
.													
.													

Legend

BD = blood dyscrasia, Hep= hepatitis, Ren = renal disease, Pan = pancreatitis, Rx = medication code, Days = number of days of treatment on particular medication, ASA = mesalamine, Sal = sulfasalazine, Str = glucocorticoids, 6M = 6-mercaptopurine, Free = drug free days, 4 = mesalamine + glucocorticoid days, 10 = glucocorticoid treatment days, 19 = drug free days.

Figure IV.2. Schematic representation of time points for Patient 5002546.

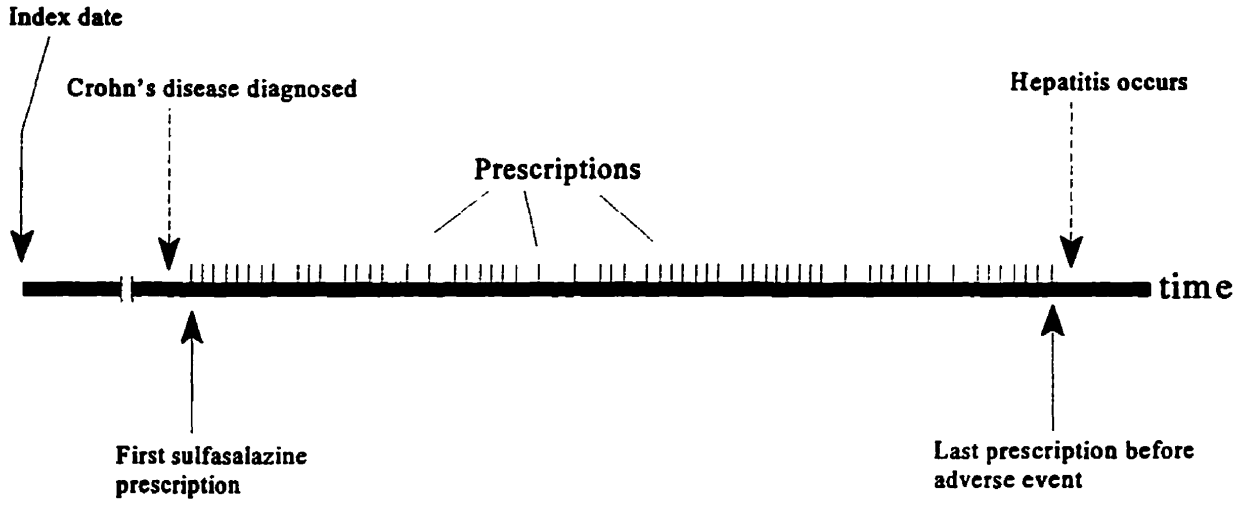
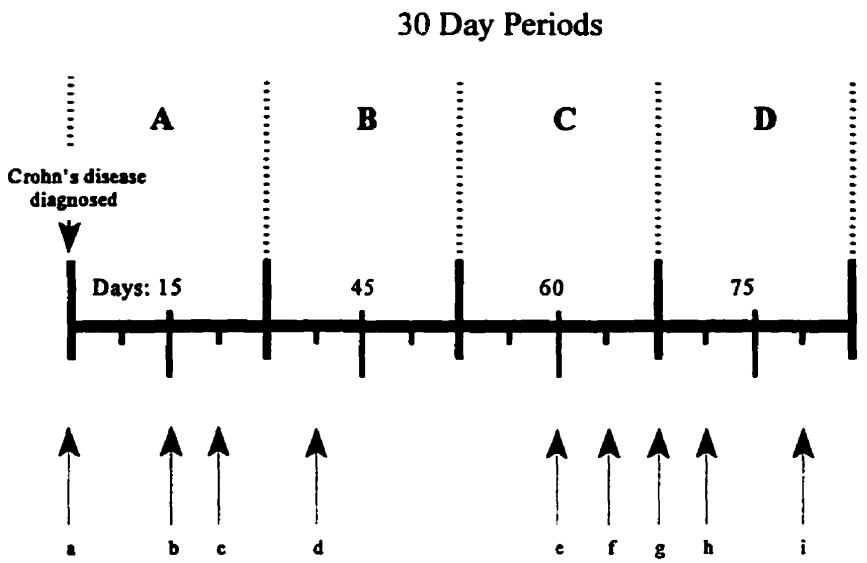


Figure IV.3. Six hypothetical scenarios of medication use in patients.



1	ASA		E						
2	ASA			E					
3	ASA	SAL	E						
4	ASA	SAL		E					
5	ASA	SAL							E
6	ASA	SAL			SAL	STR	M6	E	

Legend

ASA = mesalamine
SAL = sulfasalazine
STR = glucocorticoid
M6 = 6-mercaptopurine
E = adverse event

Table IV.1. Medication use data for patient # 5002546. Treatment days only are counted.

ID=5002546

OBS	ID	RXCOMB1	EVENTCAT	DATE	DATERX	RXCHANGE	DAYSRX	ASA_	ASA_STER	ASA_SALZ	ASA_MERC	ASA_STER_M	STEROID	STERSALZ	STER_6M	SALAZIN	MERC	DRUGFREE	DAYPRERX	DATE1	ADMIT	DATEDIAG	TERM	DAYS	SPAN
283	5002546	Salazine	Hepatitis	09JUN93	03AUG84	No	57	0	0	0	0	0	0	0	0	30	0	27	0	16JUL84	.	16JUL84	31DEC93	3455	3245
284	5002546	Salazine	Hepatitis	09JUN93	29SEP84	No	30	0	0	0	0	0	0	0	0	30	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
285	5002546	Salazine	Hepatitis	09JUN93	29OCT84	No	30	0	0	0	0	0	0	0	0	30	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
286	5002546	Salazine	Hepatitis	09JUN93	28NOV84	No	20	0	0	0	0	0	0	0	0	20	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
287	5002546	Salazine	Hepatitis	09JUN93	18DEC84	No	49	0	0	0	0	0	0	0	0	30	0	19	0	16JUL84	.	16JUL84	31DEC93	3455	3245
288	5002546	Salazine	Hepatitis	09JUN93	05FEB85	No	16	0	0	0	0	0	0	0	0	30	0	6	0	16JUL84	.	16JUL84	31DEC93	3455	3245
289	5002546	Salazine	Hepatitis	09JUN93	13MAR85	No	15	0	0	0	0	0	0	0	0	30	0	5	0	16JUL84	.	16JUL84	31DEC93	3455	3245
290	5002546	Salazine	Hepatitis	09JUN93	17APR85	No	17	0	0	0	0	0	0	0	0	30	0	7	0	16JUL84	.	16JUL84	31DEC93	3455	3245
291	5002546	Salazine	Hepatitis	09JUN93	24MAY85	No	32	0	0	0	0	0	0	0	0	30	0	2	0	16JUL84	.	16JUL84	31DEC93	3455	3245
292	5002546	Salazine	Hepatitis	09JUN93	25JUN85	No	35	0	0	0	0	0	0	0	0	30	0	5	0	16JUL84	.	16JUL84	31DEC93	3455	3245
293	5002546	Salazine	Hepatitis	09JUN93	30JUL85	No	37	0	0	0	0	0	0	0	0	30	0	7	0	16JUL84	.	16JUL84	31DEC93	3455	3245
294	5002546	Salazine	Hepatitis	09JUN93	05SEP85	No	36	0	0	0	0	0	0	0	0	30	0	6	0	16JUL84	.	16JUL84	31DEC93	3455	3245
295	5002546	Salazine	Hepatitis	09JUN93	11OCT85	No	36	0	0	0	0	0	0	0	0	30	0	6	0	16JUL84	.	16JUL84	31DEC93	3455	3245
296	5002546	Salazine	Hepatitis	09JUN93	16NOV85	No	35	0	0	0	0	0	0	0	0	30	0	5	0	16JUL84	.	16JUL84	31DEC93	3455	3245
297	5002546	Salazine	Hepatitis	09JUN93	21DEC85	No	35	0	0	0	0	0	0	0	0	30	0	5	0	16JUL84	.	16JUL84	31DEC93	3455	3245
298	5002546	Salazine	Hepatitis	09JUN93	25JAN86	No	35	0	0	0	0	0	0	0	0	30	0	5	0	16JUL84	.	16JUL84	31DEC93	3455	3245
299	5002546	Salazine	Hepatitis	09JUN93	01MAR86	No	34	0	0	0	0	0	0	0	0	30	0	4	0	16JUL84	.	16JUL84	31DEC93	3455	3245
300	5002546	Salazine	Hepatitis	09JUN93	04APR86	No	35	0	0	0	0	0	0	0	0	30	0	5	0	16JUL84	.	16JUL84	31DEC93	3455	3245
301	5002546	Salazine	Hepatitis	09JUN93	09MAY86	No	36	0	0	0	0	0	0	0	0	30	0	6	0	16JUL84	.	16JUL84	31DEC93	3455	3245
302	5002546	Salazine	Hepatitis	09JUN93	14JUN86	No	35	0	0	0	0	0	0	0	0	30	0	5	0	16JUL84	.	16JUL84	31DEC93	3455	3245
303	5002546	Salazine	Hepatitis	09JUN93	19JUL86	No	31	0	0	0	0	0	0	0	0	30	0	1	0	16JUL84	.	16JUL84	31DEC93	3455	3245
304	5002546	Salazine	Hepatitis	09JUN93	19AUG86	No	38	0	0	0	0	0	0	0	0	30	0	8	0	16JUL84	.	16JUL84	31DEC93	3455	3245
305	5002546	Salazine	Hepatitis	09JUN93	26SEP86	No	35	0	0	0	0	0	0	0	0	30	0	5	0	16JUL84	.	16JUL84	31DEC93	3455	3245
306	5002546	Salazine	Hepatitis	09JUN93	31OCT86	No	35	0	0	0	0	0	0	0	0	30	0	5	0	16JUL84	.	16JUL84	31DEC93	3455	3245
307	5002546	Salazine	Hepatitis	09JUN93	05DEC86	No	34	0	0	0	0	0	0	0	0	30	0	4	0	16JUL84	.	16JUL84	31DEC93	3455	3245
308	5002546	Salazine	Hepatitis	09JUN93	08JAN87	No	36	0	0	0	0	0	0	0	0	30	0	6	0	16JUL84	.	16JUL84	31DEC93	3455	3245
309	5002546	Salazine	Hepatitis	09JUN93	13FEB87	No	32	0	0	0	0	0	0	0	0	30	0	2	0	16JUL84	.	16JUL84	31DEC93	3455	3245
310	5002546	Salazine	Hepatitis	09JUN93	17MAR87	No	35	0	0	0	0	0	0	0	0	30	0	5	0	16JUL84	.	16JUL84	31DEC93	3455	3245
311	5002546	Salazine	Hepatitis	09JUN93	21APR87	No	35	0	0	0	0	0	0	0	0	30	0	5	0	16JUL84	.	16JUL84	31DEC93	3455	3245
312	5002546	Salazine	Hepatitis	09JUN93	26MAY87	No	35	0	0	0	0	0	0	0	0	30	0	5	0	16JUL84	.	16JUL84	31DEC93	3455	3245
313	5002546	Salazine	Hepatitis	09JUN93	30JUN87	No	835	0	0	0	0	0	0	0	0	30	0	805	0	16JUL84	.	16JUL84	31DEC93	3455	3245
314	5002546	Salazine	Hepatitis	09JUN93	12OCT89	No	8	0	0	0	0	0	0	0	0	8	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
315	5002546	Salazine	Hepatitis	09JUN93	20OCT89	No	50	0	0	0	0	0	0	0	0	30	0	20	0	16JUL84	.	16JUL84	31DEC93	3455	3245
316	5002546	Salazine	Hepatitis	09JUN93	09DEC89	No	47	0	0	0	0	0	0	0	0	30	0	17	0	16JUL84	.	16JUL84	31DEC93	3455	3245
317	5002546	Salazine	Hepatitis	09JUN93	25JAN90	No	47	0	0	0	0	0	0	0	0	30	0	17	0	16JUL84	.	16JUL84	31DEC93	3455	3245
318	5002546	Salazine	Hepatitis	09JUN93	13MAR90	No	37	0	0	0	0	0	0	0	0	30	0	7	0	16JUL84	.	16JUL84	31DEC93	3455	3245
319	5002546	Salazine	Hepatitis	09JUN93	19APR90	No	36	0	0	0	0	0	0	0	0	30	0	6	0	16JUL84	.	16JUL84	31DEC93	3455	3245
320	5002546	Salazine	Hepatitis	09JUN93	25MAY90	No	33	0	0	0	0	0	0	0	0	30	0	3	0	16JUL84	.	16JUL84	31DEC93	3455	3245
321	5002546	Salazine	Hepatitis	09JUN93	27JUN90	No	44	0	0	0	0	0	0	0	0	30	0	14	0	16JUL84	.	16JUL84	31DEC93	3455	3245
322	5002546	Salazine	Hepatitis	09JUN93	10AUG90	No	55	0	0	0	0	0	0	0	0	30	0	25	0	16JUL84	.	16JUL84	31DEC93	3455	3245
323	5002546	Salazine	Hepatitis	09JUN93	04OCT90	No	41	0	0	0	0	0	0	0	0	30	0	11	0	16JUL84	.	16JUL84	31DEC93	3455	3245
324	5002546	Salazine	Hepatitis	09JUN93	14NOV90	No	34	0	0	0	0	0	0	0	0	30	0	4	0	16JUL84	.	16JUL84	31DEC93	3455	3245
325	5002546	Salazine	Hepatitis	09JUN93	18DEC90	No	31	0	0	0	0	0	0	0	0	30	0	1	0	16JUL84	.	16JUL84	31DEC93	3455	3245
326	5002546	Salazine	Hepatitis	09JUN93	18JAN91	No	20	0	0	0	0	0	0	0	0	20	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
327	5002546	Salazine	Hepatitis	09JUN93	07FEB91	No	35	0	0	0	0	0	0	0	0	30	0	5	0	16JUL84	.	16JUL84	31DEC93	3455	3245
328	5002546	Salazine	Hepatitis	09JUN93	14MAR91	No	35	0	0	0	0	0	0	0	0	30	0	5	0	16JUL84	.	16JUL84	31DEC93	3455	3245
329	5002546	Salazine	Hepatitis	09JUN93	18APR91	No	32	0	0	0	0	0	0	0	0	30	0	2	0	16JUL84	.	16JUL84	31DEC93	3455	3245
330	5002546	Salazine	Hepatitis	09JUN93	20MAY91	No	66	0	0	0	0	0	0	0	0	30	0	36	0	16JUL84	.	16JUL84	31DEC93	3455	3245
331	5002546	Salazine	Hepatitis	09JUN93	25JUL91	No	50	0	0	0	0	0	0	0	0	30	0	20	0	16JUL84	.	16JUL84	31DEC93	3455	3245
332	5002546	Salazine	Hepatitis	09JUN93	13SEP91	No	62	0	0	0	0	0	0	0	0	30	0	32	0	16JUL84	.	16JUL84	31DEC93	3455	3245
333	5002546	Salazine	Hepatitis	09JUN93	14NOV91	No	103	0	0	0	0	0	0	0	0	30	0	73	0	16JUL84	.	16JUL84	31DEC93	3455	3245
334	5002546	Salazine	Hepatitis	09JUN93	25FEB92	No	43	0	0	0	0	0	0	0	0	30	0	13	0	16JUL84	.	16JUL84	31DEC93	3455	3245
335	5002546	Salazine	Hepatitis	09JUN93	08APR92	No	41	0	0	0	0	0	0	0	0	30	0	11	0	16JUL84	.	16JUL84	31DEC93	3455	3245
336	5002546	Salazine	Hepatitis	09JUN93	19MAY92	No	41	0	0	0	0	0	0	0	0	30	0	11	0	16JUL84	.	16JUL84	31DEC93	3455	3245
337	5002546	Salazine	Hepatitis	09JUN93	29JUN92	No	77	0	0	0	0	0	0	0	0	30	0	47	0	16JUL84	.	16JUL84	31DEC93	3455	3245
338	5002546	Salazine	Hepatitis	09JUN93	14SEP92	No	91	0	0	0	0	0	0	0	0	30	0	61	0	16JUL84	.	16JUL84	31DEC93	3455	3245
339	5002546	Salazine	Hepatitis	09JUN93	14DEC92	No	126	0	0	0	0	0	0	0	0	30	0	96	0	16JUL84	.	16JUL84	31DEC93	3455	3245
340	5002546	Salazine	Hepatitis	09JUN93	19APR93	No	64	0	0	0	0	0	0	0	0	30	0	34	0	16JUL84	.	16JUL84	31DEC93	3455	3245
					TOTAL:		3245	0	0	0	0	0	0	0	0	1698	0	1547	0						

Legend

RXCOMB1 = medication, DATE = date of event, DATERX = date prescription dispensed, DAYSRX = treatment days, DATE1= date of first physician diagnosis, ADMIT = date of hospital admission (if applicable), DATEDIAG = date of Crohn's disease diagnosis(date of entry into cohort), TERM = date of exit if no event occurs, DAYS = number of days in Saskatchewan database until censoring, SPAN = number of days in the cohort. Medication abbreviations used alone or in combinations: ASA = mesalamine, STER = ST = glucocorticoids, SALZ =SALAZIN = sulfasalazine, MERC = 6M = M = 6-mercaptopurine.

Table IV.2. Medication use data for patient # 5002546. Post treatment days included (See Table IV.1 for abbreviations).

ID=5002546

OBS	ID	RXCOMBI	EVENTCAT	DATE	DATERX	RXCHANGE	DAYSRX	ASA_	ASASTER	ASASALZ	ASAMERC	ASASTM	STEROID	STERSALZ	STERSTM	SALAZIN	MERC	DRUGFREE	DAYPRERX	DATE1	ADMIT	DATEDIAG	TERM	DAYS	SPAN
283	5002546	Salazine	Hepatitis	09JUN93	03AUG84	No	57	0	0	0	0	0	0	0	0	57	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
284	5002546	Salazine	Hepatitis	09JUN93	29SEP84	No	30	0	0	0	0	0	0	0	0	30	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
285	5002546	Salazine	Hepatitis	09JUN93	29OCT84	No	30	0	0	0	0	0	0	0	0	30	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
286	5002546	Salazine	Hepatitis	09JUN93	28NOV84	No	20	0	0	0	0	0	0	0	0	20	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
287	5002546	Salazine	Hepatitis	09JUN93	18DEC84	No	49	0	0	0	0	0	0	0	0	49	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
288	5002546	Salazine	Hepatitis	09JUN93	05FEB85	No	36	0	0	0	0	0	0	0	0	36	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
289	5002546	Salazine	Hepatitis	09JUN93	13MAR85	No	35	0	0	0	0	0	0	0	0	35	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
290	5002546	Salazine	Hepatitis	09JUN93	17APR85	No	37	0	0	0	0	0	0	0	0	37	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
291	5002546	Salazine	Hepatitis	09JUN93	24MAY85	No	32	0	0	0	0	0	0	0	0	32	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
292	5002546	Salazine	Hepatitis	09JUN93	25JUN85	No	35	0	0	0	0	0	0	0	0	35	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
293	5002546	Salazine	Hepatitis	09JUN93	30JUL85	No	37	0	0	0	0	0	0	0	0	37	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
294	5002546	Salazine	Hepatitis	09JUN93	05SEP85	No	36	0	0	0	0	0	0	0	0	36	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
295	5002546	Salazine	Hepatitis	09JUN93	11OCT85	No	36	0	0	0	0	0	0	0	0	36	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
296	5002546	Salazine	Hepatitis	09JUN93	16NOV85	No	35	0	0	0	0	0	0	0	0	35	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
297	5002546	Salazine	Hepatitis	09JUN93	21DEC85	No	35	0	0	0	0	0	0	0	0	35	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
298	5002546	Salazine	Hepatitis	09JUN93	25JAN86	No	35	0	0	0	0	0	0	0	0	35	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
299	5002546	Salazine	Hepatitis	09JUN93	01MAR86	No	34	0	0	0	0	0	0	0	0	34	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
300	5002546	Salazine	Hepatitis	09JUN93	04APR86	No	35	0	0	0	0	0	0	0	0	35	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
301	5002546	Salazine	Hepatitis	09JUN93	09MAY86	No	36	0	0	0	0	0	0	0	0	36	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
302	5002546	Salazine	Hepatitis	09JUN93	14JUN86	No	35	0	0	0	0	0	0	0	0	35	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
303	5002546	Salazine	Hepatitis	09JUN93	19JUL86	No	31	0	0	0	0	0	0	0	0	31	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
304	5002546	Salazine	Hepatitis	09JUN93	19AUG86	No	38	0	0	0	0	0	0	0	0	38	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
305	5002546	Salazine	Hepatitis	09JUN93	26SEP86	No	35	0	0	0	0	0	0	0	0	35	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
306	5002546	Salazine	Hepatitis	09JUN93	31OCT86	No	35	0	0	0	0	0	0	0	0	35	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
307	5002546	Salazine	Hepatitis	09JUN93	05DEC86	No	34	0	0	0	0	0	0	0	0	34	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
308	5002546	Salazine	Hepatitis	09JUN93	08JAN87	No	36	0	0	0	0	0	0	0	0	36	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
309	5002546	Salazine	Hepatitis	09JUN93	13FEB87	No	32	0	0	0	0	0	0	0	0	32	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
310	5002546	Salazine	Hepatitis	09JUN93	17MAR87	No	35	0	0	0	0	0	0	0	0	35	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
311	5002546	Salazine	Hepatitis	09JUN93	21APR87	No	35	0	0	0	0	0	0	0	0	35	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
312	5002546	Salazine	Hepatitis	09JUN93	26MAY87	No	35	0	0	0	0	0	0	0	0	35	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
313	5002546	Salazine	Hepatitis	09JUN93	30JUN87	No	835	0	0	0	0	0	0	0	0	60	0	775	0	16JUL84	.	16JUL84	31DEC93	3455	3245
314	5002546	Salazine	Hepatitis	09JUN93	12OCT89	No	8	0	0	0	0	0	0	0	0	8	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
315	5002546	Salazine	Hepatitis	09JUN93	20OCT89	No	50	0	0	0	0	0	0	0	0	50	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
316	5002546	Salazine	Hepatitis	09JUN93	09DEC89	No	47	0	0	0	0	0	0	0	0	47	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
317	5002546	Salazine	Hepatitis	09JUN93	25JAN90	No	47	0	0	0	0	0	0	0	0	47	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
318	5002546	Salazine	Hepatitis	09JUN93	13MAR90	No	37	0	0	0	0	0	0	0	0	37	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
319	5002546	Salazine	Hepatitis	09JUN93	19APR90	No	36	0	0	0	0	0	0	0	0	36	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
320	5002546	Salazine	Hepatitis	09JUN93	25MAY90	No	33	0	0	0	0	0	0	0	0	33	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
321	5002546	Salazine	Hepatitis	09JUN93	27JUN90	No	44	0	0	0	0	0	0	0	0	44	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
322	5002546	Salazine	Hepatitis	09JUN93	10AUG90	No	55	0	0	0	0	0	0	0	0	55	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
323	5002546	Salazine	Hepatitis	09JUN93	04OCT90	No	41	0	0	0	0	0	0	0	0	41	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
324	5002546	Salazine	Hepatitis	09JUN93	14NOV90	No	34	0	0	0	0	0	0	0	0	34	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
325	5002546	Salazine	Hepatitis	09JUN93	18DEC90	No	31	0	0	0	0	0	0	0	0	31	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
326	5002546	Salazine	Hepatitis	09JUN93	18JAN91	No	20	0	0	0	0	0	0	0	0	20	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
327	5002546	Salazine	Hepatitis	09JUN93	07FEB91	No	35	0	0	0	0	0	0	0	0	35	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
328	5002546	Salazine	Hepatitis	09JUN93	14MAR91	No	35	0	0	0	0	0	0	0	0	35	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
329	5002546	Salazine	Hepatitis	09JUN93	18APR91	No	32	0	0	0	0	0	0	0	0	32	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
330	5002546	Salazine	Hepatitis	09JUN93	20MAY91	No	66	0	0	0	0	0	0	0	0	60	0	6	0	16JUL84	.	16JUL84	31DEC93	3455	3245
331	5002546	Salazine	Hepatitis	09JUN93	25JUL91	No	50	0	0	0	0	0	0	0	0	50	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
332	5002546	Salazine	Hepatitis	09JUN93	13SEP91	No	62	0	0	0	0	0	0	0	0	60	0	2	0	16JUL84	.	16JUL84	31DEC93	3455	3245
333	5002546	Salazine	Hepatitis	09JUN93	14NOV91	No	103	0	0	0	0	0	0	0	0	60	0	43	0	16JUL84	.	16JUL84	31DEC93	3455	3245
334	5002546	Salazine	Hepatitis	09JUN93	25FEB92	No	43	0	0	0	0	0	0	0	0	43	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
335	5002546	Salazine	Hepatitis	09JUN93	08APR92	No	41	0	0	0	0	0	0	0	0	41	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
336	5002546	Salazine	Hepatitis	09JUN93	19MAY92	No	41	0	0	0	0	0	0	0	0	41	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
337	5002546	Salazine	Hepatitis	09JUN93	29JUN92	No	77	0	0	0	0	0	0	0	0	60	0	17	0	16JUL84	.	16JUL84	31DEC93	3455	3245
338	5002546	Salazine	Hepatitis	09JUN93	14SEP92	No	91	0	0	0	0	0	0	0	0	60	0	31	0	16JUL84	.	16JUL84	31DEC93	3455	3245
339	5002546	Salazine	Hepatitis	09JUN93	14DEC92	No	126	0	0	0	0	0	0	0	0	60	0	66	0	16JUL84	.	16JUL84	31DEC93	3455	3245
340	5002546	Salazine	Hepatitis	09JUN93	19APR93	No	64	0	0	0	0	0	0	0	0	60	0	4	0	16JUL84	.	16JUL84	31DEC93	3455	3245
341	5002546	Salazine	Hepatitis	09JUN93	22JUN93	No	0	0	0	0	0	0	0	0	0	0	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
342	5002546	Salazine	Hepatitis	09JUN93	28JUL93	No	0	0	0	0	0	0	0	0	0	0	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
343	5002546	Salazine	Hepatitis	09JUN93	23SEP93	No	0	0	0	0	0	0	0	0	0	0	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
344	5002546	Salazine	Hepatitis	09JUN93	07DEC93	No	0	0	0	0	0	0	0	0	0	0	0	0	0	16JUL84	.	16JUL84	31DEC93	3455	3245
					Total		3245	0	0	0	0	0	0	0	0	2301	0	944	0						

Table IV.3. Medication combinations used in the treatment of Crohn's disease. Each combination was given a number (Rx) and was coded for in the dataset used for statistical analysis.

		Dataset Coding				
Rx	**MEDICATIONS**	**ASA**	**Sal**	**Str**	**M6**	**Drug free**
1	mesalamine	1	0	0	0	0
2	rectal mesalamine	1	0	0	0	0
3	mesalamine + rectal mesalamine + 6-mercaptopurine	1	0	0	1	0
4	mesalamine + glucocorticoid	1	0	1	0	0
5	rectal mesalamine + glucocorticoid	1	0	1	0	0
6	mesalamine + sulfasalazine	1	1	0	0	0
7	mesalamine + rectal sulfasalazine	1	1	0	0	0
8	mesalamine + 6-mercaptopurine	1	0	0	1	0
9	mesalamine + glucocorticoid + 6-mercaptopurine	1	0	1	1	0
10	glucocorticoid	0	0	1	0	0
11	glucocorticoid + sulfasalazine	0	1	1	0	0
12	glucocorticoid + sulfasalazine + 6-mercaptopurine	0	1	1	1	0
13	glucocorticoid + 6-mercaptopurine	0	0	1	1	0
14	sulfasalazine	0	1	0	0	0
15	rectal sulfasalazine	0	1	0	0	0
16	sulfasalazine + 6-mercaptopurine	0	1	0	1	0
17	sulfasalazine + rectal sulfasalazine	0	1	0	0	0
18	6-mercaptopurine	0	0	0	1	0
19	no medication	0	0	0	0	1

Table IV.4. Sample of dataset used for statistical analysis. Treatment days only. Data for patient # 5002546 is highlighted (see Figure IV.1b for list of abbreviations).

Obs	ID	Sex	Age	BD	Hep	Ren	Pan	Rx	Days	ASA	Sal	Str	6M	Free
843	5002539	0	0	0	0	0	0	14	2292	0	1	0	0	0
844	5002539	0	0	0	0	0	0	19	2685	0	0	0	0	1
845	5002541	0	0	0	0	0	0	1	60	1	0	0	0	0
846	5002541	0	0	0	0	0	0	4	30	1	0	1	0	0
847	5002541	0	0	0	0	0	0	10	1087	0	0	1	0	0
848	5002541	0	0	0	0	0	0	19	1152	0	0	0	0	1
849	5002543	0	0	0	0	0	0	19	844	0	0	0	0	1
850	**5002546**	**0**	**0**	**0**	**0**	**0**	**0**	**14**	**1698**	**0**	**1**	**0**	**0**	**0**
851	**5002546**	**0**	**0**	**0**	**1**	**0**	**0**	**19**	**1547**	**0**	**0**	**0**	**0**	**1**
852	5002548	0	0	0	0	0	0	14	30	0	1	0	0	0
853	5002548	0	0	0	0	0	0	19	3699	0	0	0	0	1
854	5002549	0	0	0	0	0	0	19	303	0	0	0	0	1
855	5002551	0	0	0	0	0	0	1	264	1	0	0	0	0
856	5002551	0	0	0	0	0	0	4	97	1	0	1	0	0
857	5002551	0	0	0	0	0	0	8	195	1	0	0	1	0
858	5002551	0	0	0	0	0	0	9	52	1	0	1	1	0
859	5002551	0	0	0	0	0	0	10	118	0	0	1	0	0
860	5002551	0	0	0	0	0	0	18	98	0	0	0	1	0
861	5002551	0	0	0	0	0	0	19	865	0	0	0	0	1
862	5002559	0	0	0	0	0	0	1	1058	1	0	0	0	0
863	5002559	0	0	0	0	0	0	4	137	1	0	1	0	0
864	5002559	0	0	0	0	0	0	10	48	0	0	1	0	0
865	5002559	0	0	0	0	0	0	11	60	0	1	1	0	0
866	5002559	0	0	0	0	0	0	19	1849	0	0	0	0	1
867	5002565	0	0	0	0	0	0	19	3546	0	0	0	0	1
868	5002570	0	0	0	0	0	0	10	208	0	0	1	0	0
869	5002570	0	0	0	0	0	0	11	1552	0	1	1	0	0
870	5002570	0	0	0	0	0	0	14	407	0	1	0	0	0
871	5002570	0	0	0	0	0	0	19	1288	0	0	0	0	1
872	5002573	0	0	0	0	0	0	1	80	1	0	0	0	0
873	5002573	0	0	0	0	0	0	19	3557	0	0	0	0	1
874	5002576	0	0	0	0	0	0	1	90	1	0	0	0	0
875	5002576	0	0	0	0	0	0	10	30	0	0	1	0	0
876	5002576	0	0	0	0	0	0	14	120	0	1	0	0	0
877	5002576	0	0	0	0	0	0	19	3671	0	0	0	0	1
878	5002579	0	0	0	0	0	0	19	1993	0	0	0	0	1
879	5002588	0	0	0	0	0	0	10	62	0	0	1	0	0
880	5002588	0	0	0	0	0	0	11	503	0	1	1	0	0
881	5002588	0	0	0	0	0	0	14	620	0	1	0	0	0
882	5002588	0	0	0	0	0	0	19	3905	0	0	0	0	1
883	5002589	0	0	0	0	0	0	19	989	0	0	0	0	1
884	5002590	0	0	0	0	0	0	10	70	0	0	1	0	0
885	5002590	0	0	0	0	0	0	13	42	0	0	1	1	0
886	5002590	0	0	0	0	0	0	18	500	0	0	0	1	0
887	5002590	0	0	0	0	0	0	19	1707	0	0	0	0	1
888	5002591	0	0	0	0	0	0	1	452	1	0	0	0	0
889	5002591	0	0	0	0	0	0	4	140	1	0	1	0	0
890	5002591	0	0	0	0	0	0	10	296	0	0	1	0	0
891	5002591	0	0	0	0	0	0	19	3069	0	0	0	0	1
892	5002592	0	0	0	0	0	0	10	328	0	0	1	0	0

Table IV.5. Sample of dataset used for statistical analysis. Medication use includes post treatment time. Data for patient #5002546 is highlighted (See Figure IV.1b for abbreviations).

OBS	ID	Sex	Age	BD	Hep	Ren	Pan	Rx	Days	ASA	Sal	Str	6M	Free
829	5002539	0	0	0	0	0	0	14	3731	0	1	0	0	0
830	5002539	0	0	0	0	0	0	19	1246	0	0	0	0	1
831	5002541	0	0	0	0	0	0	1	70	1	0	0	0	0
832	5002541	0	0	0	0	0	0	4	60	1	0	1	0	0
833	5002541	0	0	0	0	0	0	10	1609	0	0	1	0	0
834	5002541	0	0	0	0	0	0	19	590	0	0	0	0	1
835	5002543	0	0	0	0	0	0	19	844	0	0	0	0	1
836	**5002546**	**0**	**0**	**0**	**1**	**0**	**0**	**14**	**2301**	**0**	**1**	**0**	**0**	**0**
837	**5002546**	**0**	**0**	**0**	**0**	**0**	**0**	**19**	**944**	**0**	**0**	**0**	**0**	**1**
838	5002548	0	0	0	0	0	0	14	30	0	1	0	0	0
839	5002548	0	0	0	0	0	0	19	3699	0	0	0	0	1
840	5002549	0	0	0	0	0	0	19	303	0	0	0	0	1
841	5002551	0	0	0	0	0	0	1	244	1	0	0	0	0
842	5002551	0	0	0	0	0	0	4	135	1	0	1	0	0
843	5002551	0	0	0	0	0	0	8	209	1	0	0	1	0
844	5002551	0	0	0	0	0	0	9	52	1	0	1	1	0
845	5002551	0	0	0	0	0	0	10	160	0	0	1	0	0
846	5002551	0	0	0	0	0	0	13	11	0	0	1	1	0
847	5002551	0	0	0	0	0	0	18	75	0	0	0	1	0
848	5002551	0	0	0	0	0	0	19	803	0	0	0	0	1
849	5002559	0	0	0	0	0	0	1	1752	1	0	0	0	0
850	5002559	0	0	0	0	0	0	4	227	1	0	1	0	0
851	5002559	0	0	0	0	0	0	10	24	0	0	1	0	0
852	5002559	0	0	0	0	0	0	11	70	0	1	1	0	0
853	5002559	0	0	0	0	0	0	19	1079	0	0	0	0	1
854	5002565	0	0	0	0	0	0	19	3546	0	0	0	0	1
855	5002570	0	0	0	0	0	0	10	41	0	0	1	0	0
856	5002570	0	0	0	0	0	0	11	2091	0	1	1	0	0
857	5002570	0	0	0	0	0	0	14	296	0	1	0	0	0
858	5002570	0	0	0	0	0	0	19	1027	0	0	0	0	1
859	5002573	0	0	0	0	0	0	1	110	1	0	0	0	0
860	5002573	0	0	0	0	0	0	19	3527	0	0	0	0	1
861	5002576	0	0	0	0	0	0	1	180	1	0	0	0	0
862	5002576	0	0	0	0	0	0	10	30	0	0	1	0	0
863	5002576	0	0	0	0	0	0	14	240	0	1	0	0	0
864	5002576	0	0	0	0	0	0	19	3461	0	0	0	0	1
865	5002579	0	0	0	0	0	0	19	1993	0	0	0	0	1
866	5002588	0	0	0	0	0	0	11	872	0	1	1	0	0
867	5002588	0	0	0	0	0	0	14	676	0	1	0	0	0
868	5002588	0	0	0	0	0	0	19	3542	0	0	0	0	1
869	5002589	0	0	0	0	0	0	19	989	0	0	0	0	1
870	5002590	0	0	0	0	0	0	10	117	0	0	1	0	0
871	5002590	0	0	0	0	0	0	13	47	0	0	1	1	0
872	5002590	0	0	0	0	0	0	18	595	0	0	0	1	0
873	5002590	0	0	0	0	0	0	19	1560	0	0	0	0	1
874	5002591	0	0	0	0	0	0	1	543	1	0	0	0	0
875	5002591	0	0	0	0	0	0	4	237	1	0	1	0	0
876	5002591	0	0	0	0	0	0	10	388	0	0	1	0	0
877	5002591	0	0	0	0	0	0	19	2789	0	0	0	0	1
878	5002592	0	0	0	0	0	0	10	354	0	0	1	0	0
879	5002592	0	0	0	0	0	0	11	214	0	1	1	0	0
880	5002592	0	0	0	0	0	0	12	26	0	1	1	1	0

V. Results

V.1 Patient demographics and person-time in the study

Recorded in the Saskatchewan Health databases were 10 797 patients with at least one diagnosis of inflammatory bowel disease, 10 389 of whom were 15 years old or more (Table V.1). Of these, there were 3 911 patients who, at least once, were given a diagnosis of Crohn's disease as recorded in the HSP or OPSP. There were 1 999 patients who met the criteria for inclusion into the study group. Among them were 1 116 female patients (55%) and 883 male patients (Table V.2). The average age of the patients meeting inclusion criteria, at entry into the Saskatchewan database (age at index), was 36.6 years (sd = 17.2). Age did not differ significantly between genders (Table V.2) . The youngest patient was 15 years old and the oldest was 94 years old (Figure V.1). There was a total of 4 748 639 person days recorded during the period of study (Table V.2). Fifty - five percent of these person days were attributed to female patients. The average length of stay in the cohort for all patients with Crohn's disease was 6.5 years (4 748 639 person days X 1y/365d X 1/1999 patients).

V.2. Medication use by patients withCrohn's disease in Saskatchewan

The amount of each medication dispensed to treat Crohn's disease, in treatment days, is listed in Table V.3. Together there were 27 928 prescriptions filled for

mesalamine, sulfasalazine, glucocorticoids, and 6-mercaptopurine. As mentioned earlier, this does not include medications given in hospital or in the period between July 1,1987 to December 31,1988. There was a total of 671 913 treatment days. Of these, over a third were sulfasalazine treatment days. Of all treatment days, 83 911 were days on which more than one medication for the treatment of Crohn's disease were taken.

Sulfasalazine was most often prescribed (9 615 prescriptions) but on a person-day in the cohort basis, there was little difference between how frequently it was prescribed compared to glucocorticoids (Table V.3). Overall, it was prescribed equally between genders but was prescribed more frequently in patients greater than 45 years of age (Table V.4). This difference between age groups was not observed with the other medications and was noted to be reversed in the case of 6-mercaptopurine where the younger age group had the medication prescribed significantly more often than the older age group. Male patients with Crohn's disease also tended to receive 6-mercaptopurine more frequently. Mesalamine and glucocorticoids were prescribed equally between genders. 6-Mercaptopurine was the least frequently prescribed of the medications. There were only 956 prescriptions for 6-mercaptopurine dispensed to all the patients in the cohort, nearly ten times less than for sulfasalazine overall (Table V.3).

V.3. Measures of severity of illness

V.3.1. Prescription rates

Generally, all the medications were prescribed less in patients who did not

suffer an adverse event than in those who did (Figure V.2, Table V.5, V.6). Patients who experienced an adverse event received almost twice as many prescriptions for drugs used to treat Crohn's disease as did patients who did not have an adverse event. Whereas sulfasalazine was prescribed most frequently to patients who later developed a blood dyscrasia, glucocorticoids and mesalamine were each most prescribed to patients who experienced a pancreatitis (Table V.5). Mesalamine was not at all used by patients who developed renal disease and only sparingly used in the other groups (Table V.5).

Twenty-three of the 155 patients (15%) who had an event had no prescriptions dispensed for any of the medications used to treat Crohn's disease (Table V.7). Among those patients who did not suffer a pancreatitis, hepatitis, blood dyscrasia, or renal disease, no medications were dispensed to 353, or 19.4% of them. In the entire cohort, 18.8% of the patients did not receive any medications.

V.3.2. Hospitalization rates

There were 4 118 total hospital admissions throughout the study among all Crohn's disease patients (Table V.8) for an overall admission rate of 86.8 per 100 000 pd. The rates were the same for males and females. However, patients aged over 45 years had a higher hospitalization rate than the younger patients (RR = 1.31, 95% CI = 1.23, 1.40).

When hospitalization rates were examined by adverse event group significant differences were noted (Table V.9). Whereas the overall admission rate was 86.7/100000pd, it shot up to 431.5 among patients who developed a pancreatitis.

Compared to the 'no event' group all adverse event groups had much higher hospitalization rates.

V.4. Incidence of adverse events.

V.4.1.Incidence of blood dyscrasia, hepatitis, pancreatitis, and renal disease according to age group and gender in patients with Crohn's disease.

The overall incidence of adverse events was 3.3/100000 person-days (Table V.10). In all, there were 155 patients who had an event and 1844 who did not (Table V.11). There were 60 cases of hepatitis, 35 cases of pancreatitis, 33 cases of renal disease, and 27 cases of blood dyscrasias. As shown in Table V.11, the average age (at the time of registration into the Saskatchewan database) of the patients who had an event of interest was significantly greater than that of the patients who did not have an adverse event (42.7 years, 95%CI = 39.7, 45.7 compared to 36.1 years 95% CI = 35.3, 36.9). Among those patients who had an event, on average, the eldest were those with renal disease, 52.9 years, and the youngest were those who had hepatitis (37.0 years). The incidence of hepatitis was nearly double that of any of the other condition (Table V.10). The incidence rate of adverse events was generally higher among the older age groups, particularly in pancreatitis and renal disease (Table V.12- V.15). There was no significant difference in incidence rates between genders for any of the adverse events. When multivariate analyses were used to adjust for gender and age category, no significant differences were

found in the analysis (Tables V.16-V.19). There was no significant change in the relative risks when post treatment days were also included in the analysis (Tables V.16 - V.19).

V.4.2. Incidence of adverse events according to the use of medications used to treat Crohn's disease

There were few adverse events that occurred during treatment days. Of the 27 cases of blood dyscrasias only 4 occurred during a treatment day with all study drugs combined, and 6 when post treatment days were included (Tables V.20, V.21). Of the 60 cases of hepatitis, only 4 occurred during a treatment day. This increased to 12 cases when post treatment days were included (Tables V.22, V.23). The number of cases of pancreatitis went from 6 to 8 when post treatment days were included, while renal disease went from 8 to 10 cases (Tables V.24 -V.27).

The incidence of adverse events was not significantly associated with any of the medications examined in this study when considering treatment days alone or with post treatment days included (Tables V.20-V.27). In these tables, the relative risk of an adverse event occurring during a day at excess risk (treatment day and post treatment day) was calculated from the ratio of incidence rate on a treatment day to the incidence rate of an adverse event during a non-treatment day. For example, in Table V.20, the relative risk of a blood dyscrasia occurring during a mesalamine treatment day, as opposed to a day when meslamine was not taken, is 2.0 (95% CI = 0.5, 8.4). Person days represent days of treatment with mesalamine (yes) and days with no mesalamine taken (no).

When adjustment was made for age group, gender, and concomitant medication use, using Poisson regression analysis, no significant associations between the use of drugs used for the treatment of Crohn's disease and the adverse events of interest were found (Table V.28 - V.31).

Table V.1. Patients in the Saskatchewan Healthcare datafiles meeting criteria for inclusion into the Crohn's disease cohort.

Condition	Patient number
Initial Saskatchewan database (all patients with at least one diagnosis of inflammatory bowel disease: ICD-9 code 555 & 556).	10 797
Aged 15 years or more.	10 389
Patients with at least one diagnosis of Crohn's disease (ICD code 555).	3 911
Patients with at least two diagnoses of Crohn's disease from physician visits, or, one hospital separation diagnosis of Crohn's disease.	1 999

Table V.2. Patient demograghics.

PATIENTS	N	Mean AGE (sd)*	95% C.I.	PERSON DAYS in the COHORT
All	1999	36.6 (17.3)	35.9, 38.1	4748639
female	1116	37 (17.5)	36.0, 38.0	2635132
male	883	36.1 (16.9)	35.0, 37.2	2113507

* age at index.

Figure V.1: Age distribution of patients with Crohn's disease at index date.

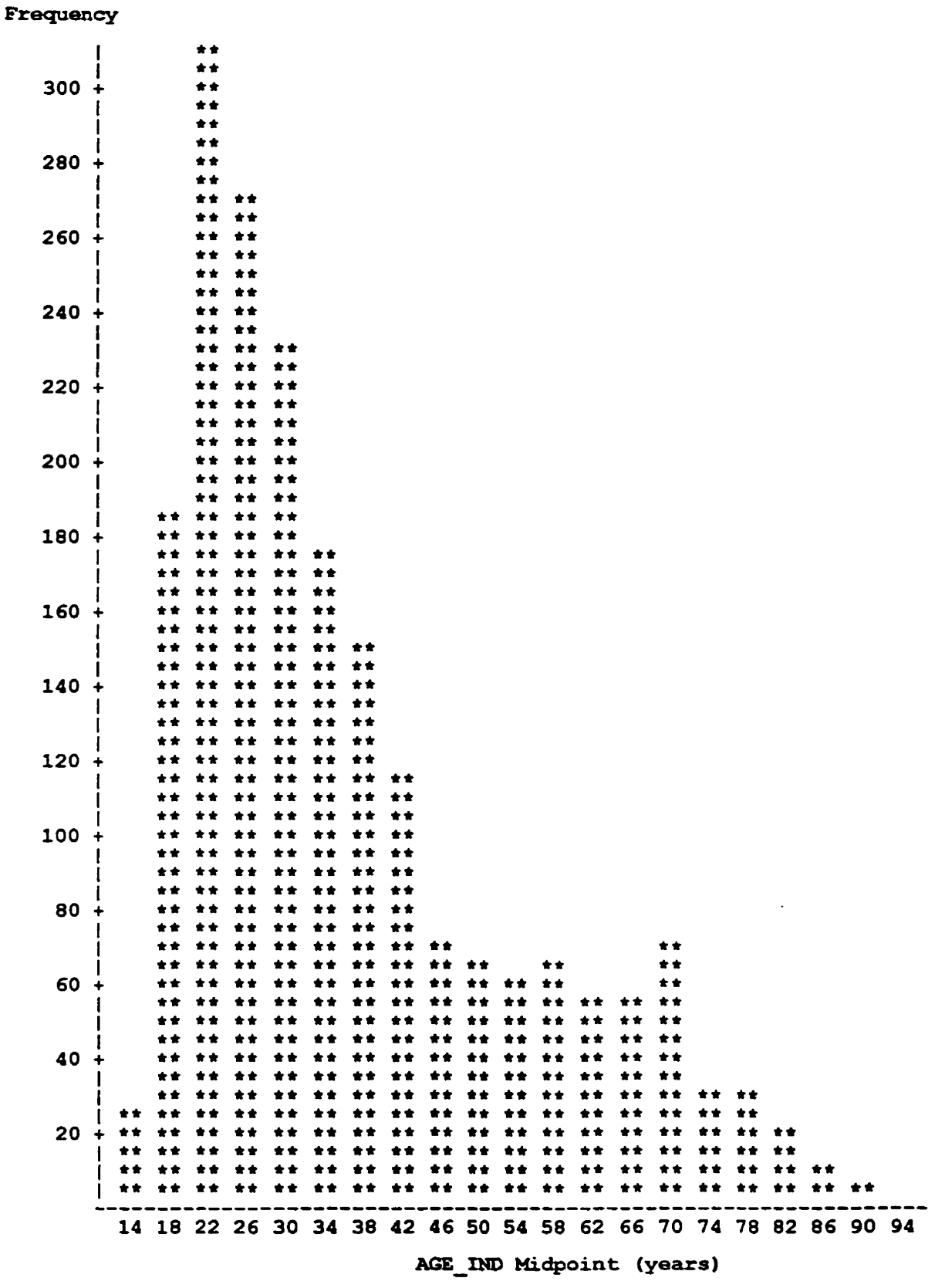


Table V.3. Overall number of prescriptions dispensed, days of treatment, and prescription rates for the entire cohort of patients with Crohn's disease.

MEDICATION	NUMBER OF PRESCRIPTIONS FOR MEDICATIONS TO TREAT CROHN'S DISEASE	TREATMENT DAYS	RATE OF PRESCRIPTIONS PER 1000 PERSON DAYS IN THE COHORT*
All	27 928	671 913	5.9
Mesalamine	7 883	183 970	1.7
Sulfasalazine	9 615	246 887	2.0
Glucocorticoid	9 474	222 087	2.0
6-mercaptopurine	956	18 969	0.20
Combination of more than one medication	n/a	83 911	n/a

* Based on 4 748 639 total person days in the cohort

Table V.4. Rate of medication prescription by gender and age category in all patients with Crohn's disease.

PROFILE	NUMBER OF PRESCRIPTIONS	PERSON DAYS in the cohort	PRESCRIPTION RATE per 1000 pd in the cohort	95% CI
Mesalamine				
female	4376	2635132	1.66	1.61, 1.71
male	3507	2113507	1.66	1.61, 1.72
<45	5962	3561152	1.68	1.64, 1.72
>/= 45	1921	1187487	1.62	1.15, 1.69
Sulfasalzine				
female	5415	2635132	2.06	2.01, 2.11
male	4200	2113507	1.99	1.93, 2.05
<45y	6736	3561152	1.9	1.86, 1.95
>/= 45	2879	1187487	2.42	2.33, 2.51
Glucocorticoid				
female	5151	2635132	1.95	1.90, 2.00
male	4323	2113507	2.04	1.98, 2.10
<45	7048	3561152	1.98	1.93, 2.03
>/= 45	2426	1187487	2.04	1.96, 2.12
6-Mercaptopurine				
female	419	2635132	0.16	0.15, 0.18
male	537	2113507	0.25	0.23, 0.27
<45y	814	3561152	0.23	0.21, 0.25
>/= 45	142	1187487	0.12	0.10, 0.14

Figure V.2. Prescription rate of each medication by adverse event.

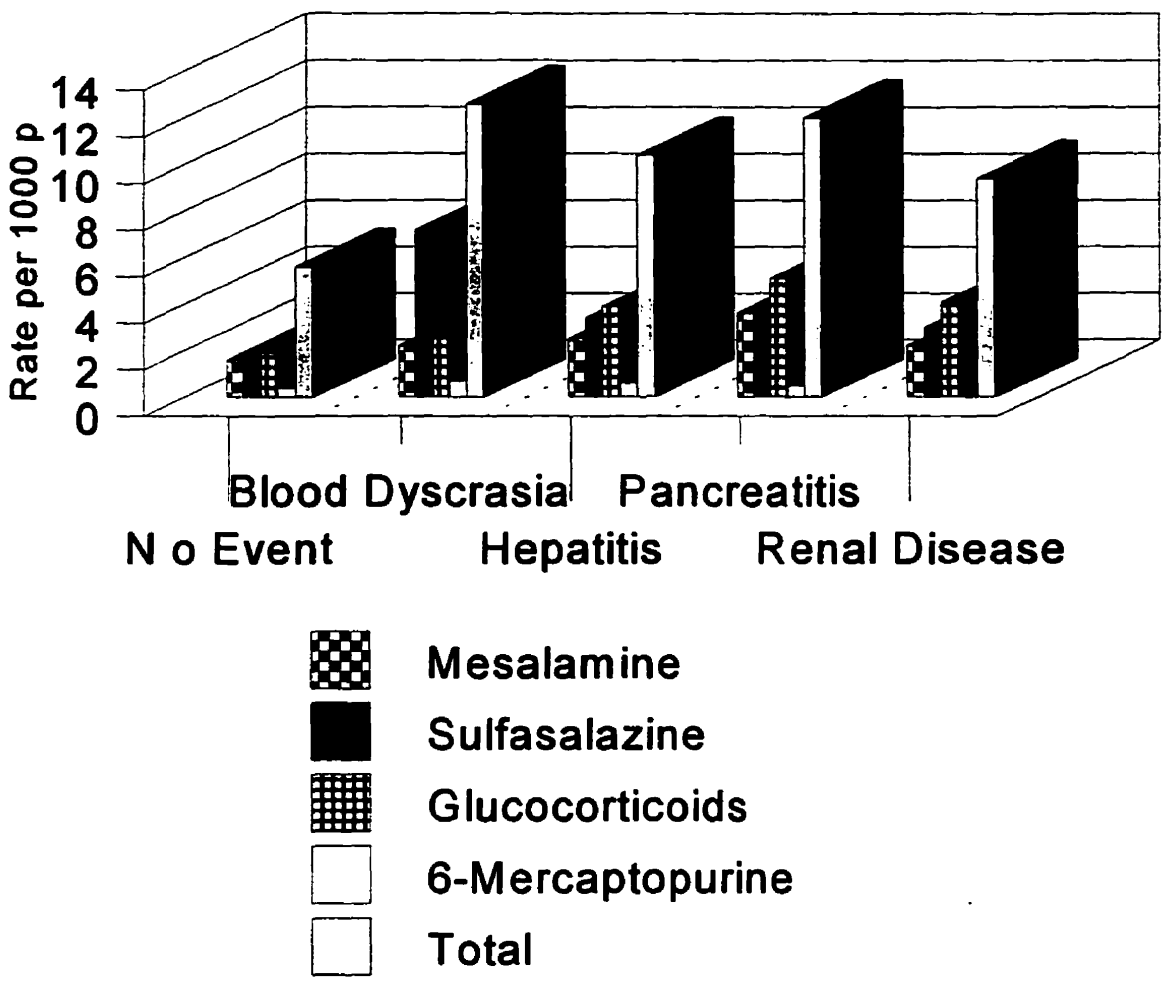


Table V.5. Prescription rates, by adverse event groups, for medications used to treat Crohn's disease.

PROFILE	TOTAL PRESCRIPTIONS for medications used tor treat Crohn's diaease	PERSON DAYS in the cohort	PRESCRIPTION RATE per 1000 pd in the cohort	95% CI
Mesalamine				
No Event	7247	4498240	1.6	1.5, 1.7
Blood Dyscrasia	120	54418	2.2	1.9, 2.6
Hepatitis	264	104791	2.5	2.2, 2.8
Pancreatitis	130	36621	3.6	3.0, 4.2
Renal disease	122	54569	2.2	1.9, 2.7
Sulfasalazine				
No Event	8595	4498240	1.9	1.8, 2.0
Blood Dyscrasia	391	54418	7.2	6.5, 7.9
Hepatitis	358	104791	3.4	3.1, 3.8
Pancreatitis	105	36621	2.9	2.4, 3.5
Renal disease	166	54569	3.0	2.6, 3.5
Glucocorticoids				
No Event	8523	4498240	1.9	1.8, 2.0
Blood Dyscrasia	137	54418	2.5	2.1, 3.0
Hepatitis	405	104791	3.9	3.5, 4.3
Pancreatitis	185	36621	5.1	4.4, 5.8
Renal disease	224	54569	4.1	3.6, 4.7
6-Mercaptopurine				
No Event	836	4498240	0.4	0.36, 0.42
Blood Dyscrasia	37	54418	0.7	0.5, 0.9
Hepatitis	64	104791	0.6	0.5, 0.8
Pancreatitis	19	36621	0.5	0.3, 0.8
Renal disease	0	54569	0.0	

Table V.6. Total prescriptions and prescription rates by disease category.

PROFILE	TOTAL PRESCRIPTIONS	PERSON-DAYS in the cohort	PRESCRIPTION RATE per 1000 pd in the cohort	95% CI
No Event	25 201	4 498 240	5.6	5.5, 5.7
Blood Dyscrasia	685	54 410	12.6	12.5, 12.7
Hepatitis	1091	104 791	10.4	10.3, 10.5
Pancreatitis	439	36 621	12.0	11.9, 12.1
Renal disease	512	54569	9.4	9.3, 9.5

Table V.7. Number of patients with Crohn's disease who never had any of the medications under study prescribed.

PROFILE	NUMBER WITHOUT PRESCRIPTIONS	PERCENTAGE OF EACH PROFILE GROUP
No Event	353	19.4
Blood dyscrasia	6	22.2
Hepatitis	10	16.7
Pancreatitis	3	8.6
Renal disease	4	12.6
Total	376	18.8

Table V.8.Hospital admission rates for all patients with Crohn's disease.

PROFILE	Total Admissions	Person Days in the cohort	Admission Rate per 100000 pd	Relative Risk	95% CI
ALL Patients	4118	4748639	86.8		
GENDER					
female	2304	2635132	87.4	Ref	
male	1814	2113507	85.9	0.98	0.92, 1.04
AGE CATEGORY					
<45	2863	3561152	80.4	ref	
>/=45	1255	1187487	105.7	1.31	1.23, 1.40

Table V.9. Hospital admission rates by adverse event category.

PROFILE	TOTAL ADMISSIONS	PERSON DAYS in the cohort	ADMISSION RATE per 100000 pd	95% CI
All Patients	4118	4748639	86.7	86.6, 86.8
No event	3543	4498240	78.8	78.7, 78.9
Blood Dyscrasia	119	54418	218.7	218.6, 218.9
Hepatitis	179	104791	170.8	170.6, 170.9
Pancreatitis	158	36621	431.5	431.3, 431.7
Renal disease	119	54569	331.7	331.5, 331.9

Table V.10. Incidence rates of adverse events in patients with Crohn's disease.

EVENT	NUMBER OF EVENTS	Person Days in the Cohort	RATE/100000pd	95% CI
All events	155	4748639	3.3	3.2, 3.4
Blood Dyscrasia	27	4748639	0.6	0.5, 0.7
Hepatitis	60	4748639	1.3	1.2, 1.4
Pancreatitis	35	4748639	0.7	0.6, 0.8
Renal disease	33	4748639	0.7	0.6, 0.8

Table V.11. Patient demograghics (age at index) according to adverse event category.

PATIENTS	N	Mean AGE	S.D.	C.I.
No Events	1844	36.1	17	35.3, 36.9
female	1031	36.6	17.3	35.5, 37.6
male	813	35.5	16.6	34.3, 36.6
All Events	155	42.7	18.9	39.7, 45.7
female	85	42.1	19.2	38.0, 46.3
male	70	43.5	18.8	39.0, 48.0
Blood dyscrasia	27	40.2	19.8	32.4, 48.0
female	18	37.8	18.1	28.8, 46.8
male	9	45.1	23	27.4, 62.8
Hepatitis	60	37	16.7	32.7, 41.3
female	27	36	16.1	29.7, 42.4
male	33	37.8	17.3	31.6, 43.9
Pancreatitis	35	44.9	17.1	39.0, 50.8
female	21	40.1	14.9	33.3, 46.9
male	14	52.1	18.2	41.6, 62.6
Renal disease	33	52.9	20.2	45.8, 60.1
female	19	57.1	21.6	46.7, 67.5
male	14	47.3	17.3	37.3, 57.3

Table V.12. Rate of blood dyscrasia by gender and age category in patients with Crohn's disease.

PROFILE	EVENTS	PERSON-DAYS in the cohort	RATE/ 100000 pd	Rel Risk	95% CI
GENDER					
female	18	2635132	0.68	1.6	0.72, 3.57
male	9	2113507	0.42		
AGE CATEGORY					
<45	17	3561152	0.48		
>/= 45	10	1187487	0.84	1.76	0.81, 3.85

Table V.13: Rate of hepatitis by gender and age category in patients with Crohn's disease.

PROFILE	EVENTS	PERSON-DAYS in the cohort	RATE/ 100000 pd	Rel Risk	95% CI
GENDER					
female	27	2635132	1.0	0.7	0.4, 1.1
male	33	2113507	1.6		
AGE CATEGORY					
<45	41	3561152	1.2		
>/= 45	19	1187487	1.6	1.4	0.8, 2.4

Table V.14. Rate of pancreatitis by gender and age category in patients with Crohn's disease.

PROFILE	EVENTS	PERSON-DAYS in the cohort	RATE/ 100000 pd	Rel Risk	95% CI
GENDER					
female	21	2635132	0.8	1.2	0.61, 2.37
male	14	2113507	0.7		
AGE CATEGORY					
<45	18	3561152	0.5		
>/= 45	17	1187487	1.4	2.83	1.46, 5.50

Table V.15. Rate of renal disease by gender and age category in patients with Crohn's disease

PROFILE	EVENTS	PERSON-DAYS in the cohort	RATE/ 100000 pd	Rel Risk	95% CI
GENDER					
female	19	2635132	0.7	1.09	0.6, 2.2
male	14	2113507	0.7		
AGE CATEGORY					
<45	9	3561152	0.3		
>/= 45	24	1187487	2.0	8.01	3.7, 17.2

Table V.16. Adjusted relative risks of blood dyscrasia according to age and gender.

PROFILE	TREATMENT DAYS			POST TREATMENT DAYS		
	Number of Events	Relative Risk	95% CI	Number of Events	Relative Risk	95% CI
GENDER						
Female	18	ref		18	ref	
Male	9	1.6	0.7, 3.6	9	1.6	0.7, 3.6
AGE CATEGORY						
<45	17	ref		17	ref	
>/=45	10	1.8	0.8, 3.8	10	1.7	0.8, 3.8

Table V.17: Adjusted relative risks of hepatitis according to age and gender.

PROFILE	TREATMENT DAYS			POST TREATMENT DAYS		
	Number of Events	Relative Risk	95% CI	Number of Events	Relative Risk	95% CI
GENDER						
Female	27	ref		27	ref	
Male	33	0.6	0.4, 1.1	33	0.6	0.4, 1.1
AGE CATEGORY						
<45	41	ref		41	ref	
>/=45	19	1.4	0.8, 2.5	19	1.4	0.8, 2.4

Table V.18: Adjusted relative risks of pancreatitis according to age and gender.

PROFILE	TREATMENT DAYS			POST TREATMENT DAYS		
	Number of Events	Relative Risk	95% CI	Number of Events	Relative Risk	95% CI
GENDER						
Female	21	ref		21	ref	
Male	14	1.1	0.6, 2.3	4	1.1	0.6, 2.3
AGE CATEGORY						
<45	18	ref		18	ref	
>/=45	17	2.8	1.5, 5.5	17	2.8	1.5, 5.4

Table V.19. Adjusted relative risks of renal disease according to age and gender.

PROFILE	TREATMENT DAYS			POST TREATMENT DAYS		
	Number of Events	Relative Risk	95% CI	Number of Events	Relative Risk	95% CI
GENDER						
Female	19	ref		19	ref	
Male	14	0.99	0.5, 2.0	14	1.0	0.5, 2.0
AGE CATEGORY						
<45	9	ref		9	ref	
>/=45	24	8.0	3.7, 17.3	24	8.1	3.7, 17.4

Table V.20. Incidence of blood dyscrasia according to exposure to different medications during treatment days.

DRUG CATEGORY	EVENTS	PERSON DAYS at risk	RATE/ 100000 pd	Rel Risk	95% CI
Mesalamine					
yes	2	183970	1.1	2.0	0.5, 8.4
no	25	4564669	0.6		
Sulfasalazine					
yes	1	246887	0.4	0.7	0.1, 5.2
no	26	4501752	0.6		
Glucocorticoids					
yes	1	222087	0.5	0.8	0.1, 5.8
no	26	4526552	0.6		
Mercaptopurine					
yes	1	18969	5.3	9.6	1.3, 70.7
no	26	4729670	0.6		
Combined					
drug	4	587605	0.9	1.2	0.4, 3.6
no drug	23	4161034	0.6		

Table V.21. Incidence of blood dyscrasia according to exposure to different medications during treatment days and post treatment days.

DRUG CATEGORY	EVENTS	PERSON DAYS at risk	RATE/ 100000 pd	Rel Risk	95% CI
Mesalamine					
yes	3	256003	1.2	2.2	0.7, 7.3
no	24	4493813	0.5		
Sulfasalazine					
yes	2	365762	0.6	1.0	0.2, 4.1
no	25	4384054	0.6		
Glucocorticoids					
yes	1	328242	0.3	0.5	0.1, 3.8
no	26	4421574	0.6		
Mercaptopurine					
yes	1	23514	4.3	7.7	1.1, 57.0
no	26	4726302	0.6		
Combined					
drug	6	827174	0.7	1.4	0.6, 3.3
no drug	21	3922642	0.5		

Table V.22. Incidence of hepatitis according to exposure to different medications during treatment days.

DRUG CATEGORY	EVENTS	PERSON DAYS at risk	RATE/ 100000 pd	Rel Risk	95% CI
Mesalamine					
yes	1	183970	0.5	0.42	0.1, 3.0
no	59	4564669	1.3		
Sulfasalazine					
yes	2	246887	0.8	0.62	0.2, 2.6
no	58	4501752	1.3		
Glucocorticoids					
yes	2	222087	0.9	0.7	0.2, 2.9
no	58	4526552	1.3		
Mercaptopurine					
yes	0	18969	0.0	-	-
no	60	4729670	1.3		
Combined					
drug	4	587605	0.7	0.5	0.2, 1.4
no drug	56	4161034	1.4		

Table V.23. Incidence of hepatitis according to exposure to different medications during treatment days plus post treatment days.

DRUG CATEGORY	EVENTS	PERSON DAYS at risk	RATE/ 100000 pd	Rel Risk	95% CI
Mesalamine					
yes	3	256003	1.2	0.9	0.3, 3.0
no	57	4493813	1.3		
Sulfasalazine					
yes	6	365762	1.6	1.3	0.6, 3.2
no	54	4384054	1.2		
Glucocorticoids					
yes	7	328242	2.1	1.7	0.8, 4.0
no	53	4421574	1.2		
Mercaptopurine					
yes	0	23514	0	0	
no	60	4726302	1.3		
Combined					
drug	12	827174	1.5	1.2	0.6, 2.3
no drug	48	3922642	1.2		0.4, 1.6

Table V.24. Incidence of pancreatitis according to exposure to different medications during treatment days.

DRUG CATEGORY	EVENTS	PERSON DAYS at risk	RATE/ 100000 pd	Rel Risk	95% CI
Mesalamine					
yes	1	183970	0.5	0.7	0.1, 5.3
no	34	4564669	0.7		
Sulfasalazine					
yes	2	246887	0.8	1.1	0.3, 4.6
no	33	4501752	0.7		
Glucocorticoids					
yes	4	222087	1.8	2.6	0.1, 2.6
no	31	4526552	0.7		
Mercaptopurine					
yes	0	18969	0.0		
no	35	4729670	0.7		
Combined					
drug	4	587605	0.7	0.9	0.3, 2.6
no drug	31	4161034	0.7		

Table V.25. Incidence of pancreatitis according to exposure to different medications during treatment and post treatment days.

DRUG CATEGORY	EVENTS	PERSON DAYS at risk	RATE/ 100000 pd	Rel Risk	95% CI
Mesalamine					
yes	2	256003	0.8	1.1	0.3, 4.4
no	33	4493813	0.7		
Sulfasalazine					
yes	3	365762	0.8	1.1	0.3, 3.7
no	32	4384054	0.7		
Glucocorticoids					
yes	4	328242	1.2	1.7	0.6, 4.9
no	31	4421574	0.7		
Mercaptopurine					
yes	0	23514	0.0		
no	35	4726302	0.7		
Combined					
drug	6	827174	0.7	1.0	0.4, 2.4
no drug	29	3922642	0.7		

Table V.26: Incidence of renal disease according to exposure to different medications during treatment days.

DRUG CATEGORY	EVENTS	PERSON DAYS at risk	RATE/ 100000 pd	Rel Risk	95% CI
Mesalamine					
yes	4	183970	2.2	3.4	1.2, 9.7
no	29	4564669	0.6		
Sulfasalazine					
yes	0	246887	0.0		
no	33	4501752	0.7		
Glucocorticoids					
yes	5	222087	2.3	3.6	1.4, 9.4
no	28	4526552	0.6		
Mercaptopurine					
yes	0	18969	0.0		
no	33	4729670	0.7		
Combined					
drug	8	587605	1.4	2.5	1.0, 5.0
no drug	25	4161034	0.6		

Table V.27.Incidence of renal disease according to exposure to different medications during treatment days plus post treatment days.

DRUG CATEGORY	EVENTS	PERSON DAYS at risk	RATE/ 100000 pd	Rel Risk	95% CI
Mesalamine					
yes	5	256003	2.0	3.1	1.2, 8.1
no	28	4493813	0.6		
Sulfasalazine					
yes	0	365762	0.0		
no	33	4384054	0.8		
Glucocorticoids					
yes	6	328242	1.8	3.0	1.2, 7.3
no	27	4421574	0.6		
Mercaptopurine					
yes	0	23514	0.0		
no	33	4726302	0.7		
Combined					
drug	10	827174	1.2	2.0	1.0, 4.3
no drug	23	3922642	0.6		

Table V.28. Adjusted relative risk of blood dyscrasia according to medication use with and without post treatment days included.

	TREATMENT DAYS			POST TREATMENT DAYS		
MEDICATION	**Number of Events**	**Relative Risk**	**95% CI**	**Number of Events**	**Relative Risk**	**95% CI**
Mesalamine						
Yes	2	1.7	0.4, 7.5	3	2.1	0.6, 7.2
No	25	ref		24	ref	
Sulfa-salazine						
Yes	1	0.8	1.0, 5.6	2	1.1	0.3, 4.8
No	26	ref		25	ref	
gluco-corticoid						
Yes	1	0.7	0.9, 5.4	1	0.4	0.1, 3.3
No	26	ref		26	ref	
6-merc-aptopurine						
Yes	1	9.0	1.2, 74.9	1	7.5	1.0, 58.9
No	26	ref		26	ref	

Table V.29: Adjusted relative risk of hepatitis according to medication use with and without post treatment days included.

	TREATMENT DAYS			POST TREATMENT DAYS		
MEDICATION	**Number of Events**	**Relative Risk**	**95% CI**	**Number of Events**	**Relative Risk**	**95% CI**
Mesalamine						
Yes	1	0.42	0.06, 3.0	3	0.88	0.27, 2.85
No	59	ref		57	ref	
Sulfa-salazine						
Yes	2	0.63	0.15, 2.60	6	1.18	0.49, 2.83
No	58	ref		54	ref	
gluco-corticoid						
Yes	2	0.79	0.19, 3.29	7	1.76	0.77, 3.99
No	58	ref		53	ref	
6-merc-aptopurine						
Yes	0	n/c*			n/c	
No	60	ref		60	ref	

Table V.30. Adjusted relative risk of pancreatitis according to medication use with and without post treatment days included.

	TREATMENT DAYS			POST TREATMENT DAYS		
MEDICATION	**Number of Events**	**Relative Risk**	**95% CI**	**Number of Events**	**Relative Risk**	**95% CI**
Mesalamine						
Yes	1	0.6	0.1, 4.7	2	1.0	0.2, 4.2
No	34	ref		33	ref	
Sulfa-salazine						
Yes	2	0.8	0.2, 3.5	3	0.9	0.3, 3.2
No	33	ref		32	ref	
Gluco-corticoid						
Yes	4	2.8	1.0, 8.2	4	1.8	0.6, 5.1
No	31	ref		31	ref	
6-merc-aptopurine						
Yes	0	n/c*		0	n/c	
No	35	ref		35	ref	

Table V.31. Adjusted relative risk of renal disease according to medication use with and without post treatment days included.

	TREATMENT DAYS			POST TREATMENT DAYS		
MEDICATION	**Number of Events**	**Relative Risk**	**95% CI**	**Number of Events**	**Relative Risk**	**95% CI**
Mesalamine						
Yes	4	2.9	1.0, 8.5	5	2.8	1.1, 7.4
No	29	ref		28	ref	
Sulfa-salazine						
Yes	0	n/c*		0	n/c	
No	33	ref		33	ref	
Gluco-corticoid						
Yes	5	3.2	1.2, 8.5	6	2.7	1.08, 6.5
No	28	ref		27	ref	
6-merc-aptopurine						
Yes	0	n/c		0	n/c	
No	33	ref		33	ref	

VI. Discussion

In addition to describing certain demographic features of Crohn's disease in Saskatchewan, this study aimed to determine whether four conditions, viz., blood dyscrasias, hepatitis, pancreatitis, and renal disease, were associated with the use of the medications given to treat patients with Crohn's disease. There have been reports in the past of patients developing these conditions while taking sulfasalazine and mesalamine. To date there has been no systematic investigation to confirm the association between medications used to treat Crohn's disease and the above conditions. In this observational study the incidences of blood dyscrasias, hepatitis, pancreatitis, and renal disease were determined in a cohort of patients with Crohn's disease registered in the Saskatchewan Heathcare databases. The exposure of these patients to sulfasalazine, mesalamine, glucocorticoids, and 6 - mercaptopurine was estimated, as were their rates of hospitalization.

The epidemiological techniques utilized in this study deserve emphasis. Although complex, the methods employed allowed each day, for each patient in the cohort, to be completely characterized with respect to the dispensing of four medications used to treat Crohn's disease. With the exception of an eighteen month lacune in recording of prescriptions dispensed in the Saskatchewan datafiles, everyday of medication use, whether it be of single or multiple drug use, was tabulated for all the patients entering the cohort over a fourteen year period. In addition to accurately quantifying the exposure to each medication by patients in the cohort, it was possible, for each patient who

experienced an adverse event, to determine which medications the patient had taken in the sixty days (30 treatment days plus 30 post treatment days) prior to the adverse event. In this way the temporal relationship between the occurrence of adverse events and current medication use was established. The incidence of events occurring during periods of excess risk (treatment and post treatment days) could then be directly compared to the incidence of events occurring during periods of low risk (drug free days). As a result, a more precise assessment of the association between medication use and adverse events could be achieved.

Measurement of person time was an integral part of the methodology utilized in this study. Person time at excess risk (treatment and post treatment days) was used as the common denominator for determining the relative risk of adverse events during drug use. This methodology distinguishes this study from more classical epidemiologic studies in which only previous history of exposure is the basis for estimates of risk. Differentiating between time at excess risk and time not at excess risk permits a more valid estimate of the relative risk of adverse events related to medication use since the measure of incidence rates can be calculated for time at excess risk only. In this way, patients who did not suffer an adverse event are compared to those who did suffer an adverse event on the basis of what is truly of interest, ie., timing of exposure to the drug of interest.

With respect to the demographic data, although the observed peak age of onset is in the third decade of life, a bimodal distribution of onset, as is documented in the literature review, was not discernable in this study (Figure V.1). Failure to observe this in the present study may be explained by the fact that when recording of cases in the

Saskatchewan databases started after 1980, there were already many individuals of all ages who may already have had the diagnosis of Crohn's disease. Hence, the age distribution observed is not only of incident cases but also of prevalent cases. However, it is noteworthy that at least one other study has failed to observe a bimodal distribution in the incidence of Crohn's disease (Hellers, 1979).

A slightly greater than 10 % preponderance of women with Crohn's disease was found in this study (Table V.2). This is not inconsistent with published data (Lashner, 1995). Women also had 10% more person days in the cohort. This suggests that the rate of censoring from the study was equal for both genders.

Although there was a large number of patients recorded in the database who had at least one diagnosis of inflammatory bowel disease, less than 20 percent met the inclusion criteria for entrance into the study group of Crohn's disease (Table V.1). Of these, fewer than 8 percent (155/1 999) had an event of interest, namely, a blood dyscrasia, a hepatitis, a pancreatitis, or renal disease (Table V.11). Even though Poisson regression analysis, which is specifically designed to handle rare events, was used, the relatively small number of patients experiencing adverse events was detrimental to the power of this study because of the limited number of cases per cell. As a result, not all permutations could be tested in the regression analysis. For instance, there was only one pancreatitis that occurred during mesalamine use (Table V.24). Many of the analyses with 6-mercaptopurine were nonconvergent as a result of the paucity of cases occurring during treatment with this medication.

Despite the relatively small number of actual Crohn's disease patients studied,

there was a very high number of person-days that could be used for analysis. Unfortunately, over 80 percent of the 4.7 million person days were medication free days (Table V.3). In considering the high number of drug free days recorded, one must be mindful that there is an 18 month gap from July 1987 to December 1988 when prescriptions were not recorded but person-days were counted. It is equally notable that nearly 20% of the patients studied never had one of the study medications dispensed for the treatment of Crohn's disease (Table V.7). Very few patients who truly have Crohn's disease will not need these medications during the course of their illness. Although a number of these patients may have had surgery to treat their illness, this is very unlikely to account for this high percentage of patients not treated with medication. Few patients with Crohn's disease are treated initially with surgery. Medical therapy is the first line of treatment except in complicated cases such as bowel obstruction. Furthermore, unlike the case for ulcerative colitis, surgery usually is not curative in Crohn's disease and patients may still require medication afterwards. Nevertheless, if the natural history of the disease is altered by surgery, then patients in the cohort who underwent bowel surgery might best have been censored from the study at that time.

Some patients received medical therapy while hospitalized (recall that medications given in hospital were not recorded in the Saskatchewan prescription database). Although this would probably not account for a significant amount of medication used overall, it would have been important to know if an adverse event occurred during medical therapy in hospital.

The large number of patients with Crohn's disease who were enrolled in the study

but never received any medications for this illness raises the possibility that patients were misclassified as having had Crohn's disease. To correct this, it might have been necessary to include as an additional inclusion criteria, the presence of at least one prescription for a medication used in the treatment of Crohn's disease. This might have helped to confirm the diagnosis of Crohn's disease. The criteria used for entry into the study cohort were perhaps too sensitive and the addition of this proposed inclusion criteria would have increased their overall specificity.

Misclassification of patients in large medicare databases such the Saskatchewan Healthcare databases is of concern for another reason. In the Outpatient Physician Services Plan the diagnosis of a patient is entered in the database based solely on the diagnostic code submitted by the treating physician. These codes are entered on the billing slips used by the physicians being reimbursed by medicare. The code entered does not always correctly identify the patient's condition. A physician may write the code for Crohn's disease on the slip because this is a possible diagnosis for a patient who presents with bloody stools and abdominal cramping. In a certain percentage of patients, the symptoms represented another illness which was self-limiting and resolved with time. Unfortunately, the diagnosis will remain in the datafile. Verification of patient charts would be necessary to validate diagnostic information from physicians. In this study, in an attempt to curb this problem, the inclusion criteria included the necessity of at least two physician diagnoses of Crohn's disease. However, this may not have been enough to prevent this type of patient misclassification. Although hospital separation data are not validated either, the reliability of the diagnoses is generally better in these records

because the diagnosis is obtained directly from patient charts.

Hospitalization rates were measured for each adverse event group of patients in the cohort. In all instances, the relative risk of hospitalization in patients who had an adverse event was greater than that in those patients who did not have an event of interest (Table V.9). There are several possible explanations for this. First of all, only hospitalizations related to Crohn's disease and its complications were counted. The conditions under investigation in this study are themselves reported complications of Crohn's disease. It is therefore possible that the patients who eventually developed a blood dyscrasia, hepatitis, pancreatitis, or renal disease did so because they were more affected by their disease than the other members of the cohort (as discussed below, this is also reflected by an increased prescription rate in patients who developed adverse events). If these individuals were indeed sicker, then it might be expected that they would have been hospitalized more often. Therefore, hospitalization rates in patients with Crohn's disease might serve as an index of severity of illness. If that was the case, then one could argue that the adverse events in this study occurred as a result of more severe illness. This explanation is supported by the observation that the prescription rate of many of the medications was higher among the patients who had an adverse event. The absence of an association between the use of the medications used to treat Crohn's disease with the adverse events of interest, combined with the higher prescription rate and hospitalization rates in patients who had an adverse event , suggests that they were sicker, and hence at greater baseline risk of developing an adverse event. To verify the hypothesis that adverse events are associated with more severe Crohn's disease, one could have compared the

incidence of bowel surgery in patients in the cohort who did and did not have adverse events. Surgery in Crohn's disease is reserved for more severe and medically less responsive disease. If this hypothesis is true, adverse events would have been found to occur more frequently in patients who underwent bowel surgery. In any event, both the number of hospitalizations and the presence of bowel surgery for each patient in the cohort should have been included in the multivariate analysis as proxies for severity of illness. At the very least, in this way the possibility that severity of illness was a confounding variable associated with the risk of adverse events could have been tested. Another explanation for the increased hospitalization rate in patients who suffered adverse events might not be severity of illness but, rather, their more advanced age. As shown in Table V.11, those patients who suffered adverse events were older than those who did not. Consistent with this argument is the fact that the rate of admission to hospital was greater in the older age group (Table V.8). It is possible that patients who got admitted because of their disease did so not because their disease was more severe but because they were older. Older patients may be weakened more significantly by their disease and therefore necessitate admission on that basis. This is supported by the finding that, in the mulitvariate analyses, age category was generally not found to be a determinant of adverse event risk (Table V.16 -V.19). Although in some of these analyses age was associated with a relative risk greater than 1, the 95% CI are to large to conclude a relationship between age and the occurrence of adverse events.

In contradistinction to the information regarding diagnoses, information about prescriptions is more reliable in the Saskatchewan databases because there is a record of

the medication being dispensed. However, this does not necessarily equate with actually taking the medication since compliance was not verified. Potentially only the sickest patients regularly took their medications, placing them at even greater risk of an adverse event, especially if complications of Crohn's disease arise more often in patients more severely affected by their illness. In this regard, it is interesting to note that although some medications, such as sulfasalazine, were prescribed at a higher rate in patients who suffered an event, users of this medication were not found to be at increased risk of developing one of these events (Table V.5, Figure V.2, Table V.28 - 31). For example, the overall sulfasalazine prescription rate in patients who had no events under study was 1.9 (95% CI = 1.8, 2.0), and it was 7.2 (95% CI = 6.5, 7.9) in those patients who had a blood dyscrasia (Table V.5). However, the relative risk of developing a blood dyscrasia in patients using sulfasalazine was 0.8 (95% CI = 0.1, 5.6) (Table V.28).

That sulfasalazine was the most prescribed medication is not entirely unexpected since the use of mesalamine did not become popular until after 1985. It might have been useful to add another covariate to the analysis to account for this. That is, the patients in the cohort could have been further subdivided into two groups, those entering the cohort before and after 1985. However, with the few events recorded in this study, it is unlikely that this would have made any difference in the analysis.

As previously mentioned, the low number of events occurring in patients in this study limited the power of the statistical analysis. For instance, because there was only one patient who developed a blood dyscrasia while taking sulfasalazine, this event was too rare for adequate statistical analysis (Table V.28). This is reflected by the wide

confidence intervals found with nearly all the relative risks obtained in the analysis of association between medication use and the occurrence of events. The low incidence rates of endpoints of interest have compromised the conclusions that can be derived from the statistical analyses. As such, one must be cautious in concluding that there is no increased risk of developing blood dyscrasias, hepatitis, pancreatitis, or renal disease in Crohn's disease patients treated with sulfasalazine and mesalamine alone or in combination with other medications such as glucocorticoids or 6-mercaptopurine. For 6-mercaptopurine this is not surprising, given the low utilization rate by patients in the study. The utilization of this medication reflects its recent addition to the list of drugs used to treat Crohn's disease. Immunomodulatory therapy in Crohn's disease is still in its early stages and the longterm incidence of adverse events related to the use of these drugs will only be accurately evaluated after further use.

Although the results of this study do not support the published reports that there is an increased risk of developing blood dyscrasias, hepatitis, pancreatitis, and renal disease with the use of sulfasalazine, mesalamine, glucocorticoids, and 6 - mercaptopurine in patients with Crohn's disease, the methods described herein nevertheless represent important pharmacoepidemiological tools. With the growing number of large automated patient databases available for analysis, these methods can be applied to test many putative drug-related adverse events. Several features of this study could be improved upon. Some of these, such as the inclusion of surgery as confounding variable in the multivariate analysis have already been discussed. The relatively small number of adverse events occurring during the study has also been alluded to. In order to improve upon this,

an approach might have been to do the analysis on all patients who had been diagnosed with inflammatory bowel disease (IBD). Even though the pathological processes in ulcerative colitis are not identical to those in Crohn's disease, medical treatment is nearly the same in the two diseases. Using all the patients with IBD the power of this study to detect an increase in relative risk of adverse events occurring with the medications under study would have been improved. Another potentially interesting variable might be acetylator phenotype. For reasons discussed in the literature review, this could be an important determinant of adverse events since slow acetylators would be expected to have higher and potentially more toxic, concentrations of the medications in their circulation, thereby predisposing to adverse reactions. Were the information available, this might have been an important covariate in this analysis. Certainly, as more acetylator phenotyping is carried out in various populations, we may discover that acetylator phenotype is an important determinant of adverse event occurrence.

VII.Summary and Conclusions

This study was designed to determine the association between the development of blood dyscrasias, hepatitis, pancreatitis, and renal disease in patients with Crohn's disease, with medications utilized to treat Crohn's disease. With this goal in mind, a record-linkage pharmacoepidemiologic study was undertaken. A dynamic cohort of patients with Crohn's disease was identified in the Saskatchewan Healthcare datafiles. For a fourteen year period, the incidence of each type of adverse event was calculated using person days of treatment with sulfasalazine, mesalamine glucocorticoids and 6-mercaptopurine as a common denominator.

The study also permitted a demographic profile of Crohn's disease in Saskatchewan to be obtained. Incidence rates of each of the adverse events of interest were computed, as were prescription and hospitalization rates. The relative risk of adverse events was determined but multivariate analysis, using Poisson regression, failed to establish an association between the use of the above study medications and the development of blood dyscrasias, hepatitis, pancreatitis, and renal disease. The following conclusions were drawn from this study:

1. Prescription rates of mesalamine, sulfasalazine, and glucocorticoids were greater in patients with Crohn's disease who developed blood dyscrasia, hepatitis, pancreatitis, and renal disease than in those who did not.
2. Hospitalization rates were higher for Crohn's disease patients who suffered adverse

events than in those patients who did not have an adverse event.

3. The use of sulfasalazine, mesalamine, glucocorticoids, and 6-mercaptopurine to treat Crohn's disease was not associated with an increased relative risk of developing hepatitis, pancreatitis, renal disease, or blood dyscrasia.

4. Record linkage studies can be powerful tools for pharmacovigilance but the accuracy of the data in large automated healthcare databases remains to be determined as misclassification of patients may be difficult to control.

5. The Saskatchewan Healthcare datafiles constitute a useful resource for conducting pharmacoepidemiological studies.

VIII. References

Abdullah, A.M., Scott, R.B., Martin,S.R. Acute pancreatitis secondary to 5-aminosalicylic acid in a child with ulcerative colitis. J Ped Gastroenterol 1993; 17: 441-444.

Angholt J., Sorenson, H.T., Rasmussen, S.N., et al. Cardiac hypersensitivity to 5 - aminosalicylic acid. Lancet 1995; 1: 1135.

Arndt, H., Palitzch, K.D., et al. Metronidazole inhibits leukocyte-endothelial cell adhesion in rat mesenteric venules. Gastroenterology 1994; 106: 1271- 1276.

Azad Khan, A. K., Piris, J, Truelove, S.C. An experiment to determine the active therapeutic moiety of sulphasalazine. Lancet 1977; 2: 892 - 895.

Behrens, R., Ruder, H. Chronic inflammatory intestinal disease and nephritis. Klinische Padiatrie 1992; 204: 61-64.

Bigger, J.T.. Hoffman, B.F. Antiarrhythmic Drugs. ch 31. In: The Pharmacological Basis of Therapeutics. A. Goodman Gilman et al., eds. 7th ed. 1985. MacMillan Publishing Co. New York.

Bitton, A. Peppercorn, M.A. Medical management of specific clinical presentations. Gastroenterol Clin N A 1995; 24: 541-557.

Calkins, B.M., Mendeloff, A.I. Epidemiology of inflammatory bowel disease. Epidemiology Rev 1986; 8: 60 - 91.

Canadian Pharmaceutical Association. Compendium of Pharmaceuticals and Specialties. Thirteenth edition, 1995. Ottawa.

Caspi, D. Fuchs, D., Yaron, M. Sulphasalzine induced hepatitis in juvenile rheumatoid arthritis. Ann Rheum Dis 1992; 51: 275-276.

Colombel, J-F, Brabant, G., et al. Renal insufficiency in infant: side-effect of prenatal exposure to mesalazine? Lancet 1994; 344: 620-621.

Crohn, B.B., Ginzburg, L., Oppenheimer, G.D. Regional ileitis: a pathologic and clinical entity. J Am Med Assoc 1932; 99: 1323-1329.

Crowley, J., Situnayake, R.D. Sulphasalazine induced hepatitis in adult Still's disease. Ann Rheum Dis 1992; 51: 1264-1265.

Das, K.M., Eastwood, M.A., McManus, J.P.A. et al. Salicylazosulfapyridine: Adverse reactions and relation to drug metabolism. N Engl J Med 1973; 289: 491-495.

Davies, D.M. Pathogenesis of adverse drug reactions. ch 2 In: Textbook of Adverse Drug Reactions. Davies, D.M. ed. 1985. Oxford University Press, Toronto.

Debongnie, J.C., Dekoninck, X. Sulfasalazine, 5-ASA and acute pancreatitis in Crohn's disease. J Clin Gastroenterol 1994; 19: 348-349.

Dwarakanath, A.D., Michael, J., Allan, R.N. Sulphasalzine induced renal failure. Gut 1992; 33: 1006-1007.

Eckardt, V.F., Kanzler, G. et al. Pancreatitis associated with 5-aminosalicylic acid. Dtsch Med Wschr 1991; 116: 540 - 542.

Fedorak, R.N., Thomson, A.B.R.: L'intestin grêle. ch 7. In: Principes fondamentaux de gastro-entérologie. Archambault, A., Thompson, A.B.R., and Shaffer, E.A. eds. 1992. Published by the Canadian Association of Gastroenterology.

Gabazza, E.C., Taguchi, O., et al. Pulmonary infiltrates and skin pigmentation associated with sulfasalazine. Am J Gastroenterol 1992; 87: 1654-1657.

Garau, P., Orenstein, S.R. et al. Pancreatitis associated with olsalazine and sulfasalazine in children with ulcerative colitis. J Ped Gastroenterol Nutr 1994; 18: 481-485.

Garcia-Diaz, M., Nevado, L., et al. Acute renal failure associated with 5-aminosalicylic acid in inflammatory bowel disease. Gastroenterologia Hepatologia 1995; 18: 18-21.

Glickman, R.M. Inflammatory Bowel Disease, ch 238. In: Harrison's Principles of Internal Medicine. Braunwald, E., Isselbacher, K.J. et al eds. 1987. 11th edition, McGraw - Hill Book Company, New York.

Greenberger, N.J, Toskes, P.P., Isselbacher, K.J. Diseases of the Pancreas. ch 255. In: Harrison's Principles of Internal Medicine. Braunwald, E., Isselbacher, K.J. et al eds. 1987. 11th edition, McGraw - Hill Book Company, New York.

Greenfield, S.M., Punchard, N.A., et al. Review article: The mode of action of the aminosalicylates in inflammatory bowel disease. Aliment Pharmacol Ther 1993; 7: 369 - 383

Gremse, D.A., Bancroft, J., Moyer, M.S. Sulfasalazine hypersensitivity with hepatotoxicity, thrombocytopenia and erythroid hyperplasia. J Pediatric Gastroenterol Nutr 1989; 9: 261-263.

Griffin, M.G., Miner, Jr, P.B. Conventinal drug therapy in inflammatory bowel disease. Gastroenterology Clin NA 1995; 24: 509-521.

Hamadeh, M.A., Atkinson, J. Smith, L.J. Sulfasalazine-induced pulmonary disease. Chest 1992; 101: 1033-1037.

Hanauer, S.B.. Inflammatory Bowel Disease. N Engl J Med 1996; 334: 841-848.

Hellers, G. Crohn's disease in Stockholm county 1955-1974. A study of epidemiology, results of surgical treatment and longterm prognosis. Scan J Gastroenterol 1979; 490 (suppl): 5-80.

Jewell, D.P. Corticosteroids for the management of ulcerative colitis and Crohn's disease. Gastroenterol Clin North Am 1989; 18: 21-34.

Kleinbaum, D.G., Kupper, L.L, Morgenstern, H. Epidemiologic Research: Principles and Quatitative methods. 1982. Van Nostrand Reinhold, New York.

Laasila, K. Leirisalo-Repo, M. Side effects of sulphasalazine in patients with rheumatic diseases or inflammatory bowel disease. Scand J Rheum 1994; 23: 338-340.

Lankisch, P.G., Droge, M. Gottesleben, F. Drug induced acute pancreatitis: incidence and severity. Gut 1995; 37: 565-567.

Lashner, B.A. Epidemiology of inflammatory bowel disease. Gastroenterol Clin N A 1995; 24: 467-473.

Levine, B.A., Aust, J.B. Surgical Disorders of the Small Intestine. ch 24. In: Essentials of Surgery. D.C. Sabiston ed. 1987. W.B. Saunders Co., Toronto.

McLeod, R.S, Wolff, B.G., et al. Prophylactic mesalamine treatment decreases postoperative recurrence of Crohn's disease. Gastroenterology 1995; 109: 404-413.

Miettinen, O.S., Caro, J.J. Principles of nonexperimental assessment of excess risk, with special reference to adverse drug reactions. J Clin Epidemiol 1989; 42: 325-331.

Misiewicz, J.J., Lennard-Jones, J.E. et al. Controlled trial of sulphasalazine in maintenance therapy for ulcerative colitis. Lancet 1965; 1:185 - 188.

Moertel, C.G., Bargen, J.A. A critical analysis of the use of salicylazosulfapyridine in chronic ulcerative colitis. Ann Intern Med 1959; 51: 879 - 889.

Moride, Y., Abenhaim, L. Evidence of the depletion of susceptibles effect in non-experimental pharmacoepidemiologic research. J Clin Epidemiol 1994; 47: 731-737.

Novis B.H., Korzets, Z., Chen, P., et al. Nephrotic syndrome after treatment with 5 - aminosalicylic acid. Br Med J 1988; 1: 1442.

Petersen, H.H., Skovbjerg, H. Acute pancreatitis-induced by 5-aminosalicylic acid or an extraintestinal manifestation of ulcerative colitis? Ugeskrift for Laeger 1995; 157: 5400-5401.

Poldermans, D., van Blankenstein, M. Pancreatitis induced by disodium azodisalicylate. Am J Gastroenterol 1988; 83: 578-580.

Pounder, R.E., Craven E.R., Henthorn, J.S. et al. Red cell abnormalities associated with sulphasalazine maintenance therapy for ulcerative colitis. Gut 1975; 16:181-185.

Radke, M., Bartolomaeus, G. et al. Acute pancreatitis in Crohn's disease due to 5-ASA therapy. J Ped Gastroenterol Nutr 1993; 16: 337-339.

Rao, S.S., Cann, P.A., Holdsworth, C.D. Clinical experience of the tolerance of mesalazine and olsalazine in patients intolerant of sulphasalazine. Scand J Gastroenterol 1987; 22: 332-336.

Riley, S.A., Lloyd, D.R., Main, V. Tests of renal function in patients with quiescent colitis: effects of drug treatment. Gut 1992; 33: 1348-1352.

Rubin, R. Sulfasalazine-induced fulminant hepatic failure and necrotizing pancreatitis. Am J Gastroenterol 1994; 89: 789-791.

Ruf-Ballauf, W. Hofstadter, F., Krentz, K. Acute interstitial nephritis caused by 5 - aminosalicylic acid. Internist 1989; 30: 262 -264.

Sachar, D.B.. Maintenance Therapy in Ulcerative Colitis and Crohn's Disease. J Clin Gastrenterol 1995; 20: 117-22

Sachedina, B., Saibil, F., Cohen, L.B., et al. Acute pancreatitis due to 5-aminosalicylate. Ann Intern Med 1989; 110: 490-492.

Salomon, P., Kornbluth, A.A., et al. How effective are current drugs Crohn's disease? A meta-analysis. J Gastroenterol 1992; 14: 211-215.

Sartor, R.B. Current concepts of the etiology and pathogenesis of Ulcerative Colitis and Crohn's Disease. Gastroenterol Clin N Amer 1995; 24: 475-507.

Schroder, H., and Price Evans, D.A. Acetylator phenotype and adverse effects of sulphasalzine in healthy subjects. Gut 1972; 13:278-284.

Schroder, H., Campbell, D.E.S.. Absorption, metabolism, and excretion of salicylazosulfapyridine in man. Clin Pharmacol Ther 1972; 13: 539-551.

Shapiro, S. The role of automated record linkage in the postmarketing surveillance of drug safety: A critique. Clin Pharmacol Ther 1989; 46: 371-330.

Shivananda, S., Weterman, I.T., Pena, A.S. Epidemiology of inflammatory bowel disease in the Netherlands. Front Gastrointest Res 1986; 11: 54-57.

Shear, N.H., Spielberg, S.P., Grant, D.M., et al. Differences in metabolism of sulfonamides predisposing to idiosyncratic toxicity. Ann Intern Med 1986; 105: 179-184.

Sonnenberg, A. Mortality from Crohn's disease and ulcerative colitis in England-Wales and the U.S. from 1950 to 1983. Dis Colon Rectum 1986; 29: 624-629.

Sonnenberg, A. Hospital discharges for inflammatory bowel disease. Time trends from England and the United States. Dig Dis Sci 1990; 35: 375-381.

Sonnenberg, A., Wasserman, I.H. Epidemiology of inflammatory bowel disease among US military veterans. Gastroenterology 1991; 101: 122-130.

Sotolongo, R.P., Neefe, L.I., Rudzki, C., et al. Hypersensitivity reaction to sulfasalazine with severe hepatotoxicity. Gastroenterology 1978; 75: 95-99.

Summers, R.W., Switz, D.M., et al. National cooperative Crohn's disease study: Results of drug treatment. Gastroenterology 1979; 77: 847-869.

Sutherland, L., Singleton, J., et al. Double-blind, placebo controlled trial of metronidazole in Crohn's disease. Gut 1991; 32: 1071-1075.

Svartz, N. Salazopyrin, a new sulfanilamide preparation. Acta Med Scand 1942; 110: 577-598.

Svartz, N. Sulfasalazine. II. Some notes on the discovery and development of salazopyrin. Am J Gastroenterol 1988; 83: 497 - 503.

Thuluvath, P.J., Ninkovic, M., et al. Mesalazine induced interstitial nephritis. Gut 1994; 35: 1493-1496.

Toyoda, H., Wang, S-J., et al. Distinct association of HLA Class II genes with inflammatory bowel disease. Gastroenterology 1993; 104: 741-748.

Trumm, A., Huppe, D., et al. Acute pancreatitis complicating Crohn's disease: mere coincidence or causality? Gut 1992; 33: 1289-1291.

Ursing, B. Alm, T. et al. A comparative study of metronidazole and sulfasalazine for active Crohn's disease: the Cooperative Crohn's Disease Study in Sweden. II. Result. Gastroenterology 1982; 83: 550-562.

Van de Merwe, J.P., Schroder, A.M., et al. The obligate anaerobic faecal flora of patients with Crohn's disease and their first-degree relatives. Scand J Gastroenterol 1988; 23: 1125-1131.

Van Hees, P.A, Bakker, J.H., van Tongeren, J.H. Effect of sulphapyridine, 5-aminosalicylic acid, and placebo in patients with idiopathic proctitis: A study to determine the active therapeutic moiety of sulfasalazine. Gut 1980; 21: 632-635.

Van Staa, T-P, Abenhaim, L., Leufkens, H. A study of the effects of exposure misclassification due to the time-window design in pharmacoepidemiologic studies. J Clin Epidemiol 1994; 47: 183-189.

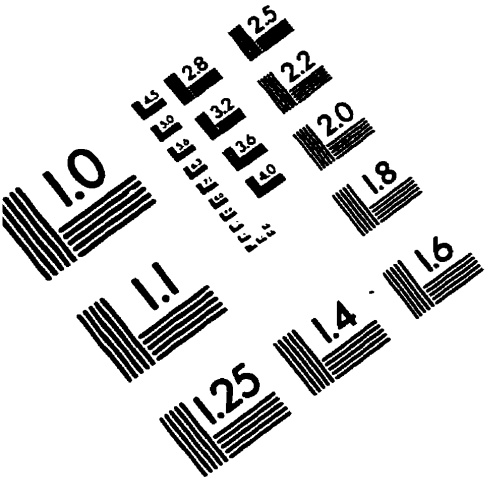
Von Herbay, A., Gebbers, J-O., Otto, H.F. Immunopathology of ulcerative colitis: a review. Hepato-Gastroenterology 1990; 37: 99-107.

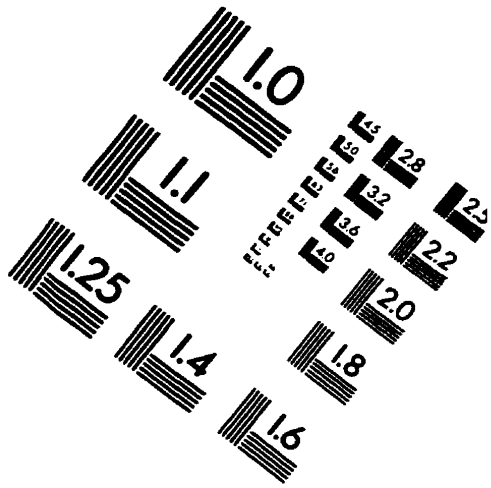
Witte, T., Olbricht, C.J., Koch, K.M. Interstitial nephritis associated with 5-aminosalicylic acid. Nephron 1994; 67: 481-482.

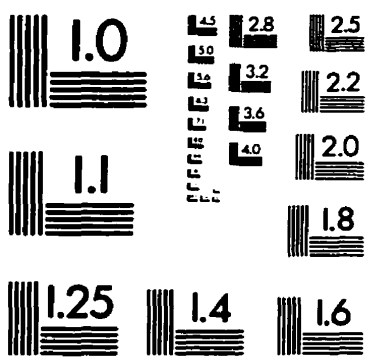
Wood A.J.J. Inflammatory bowel disease. N Engl J Med 1996; 334: 841-848.

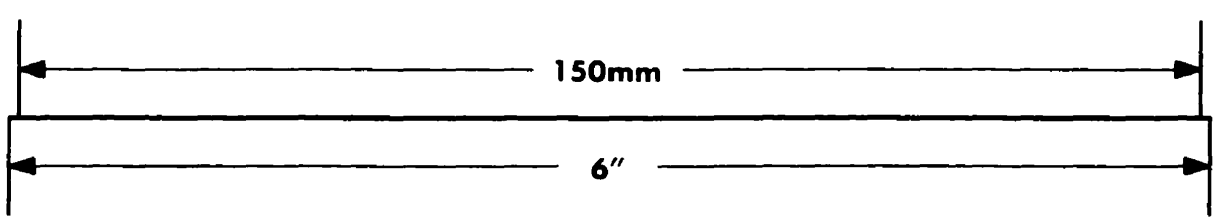
Yoshida, Y., Murata, Y. Inflammatory bowel disease in Japan: studies of epidemiology and etiopathogenesis. Med Clin N A 1990; 74: 67-90.

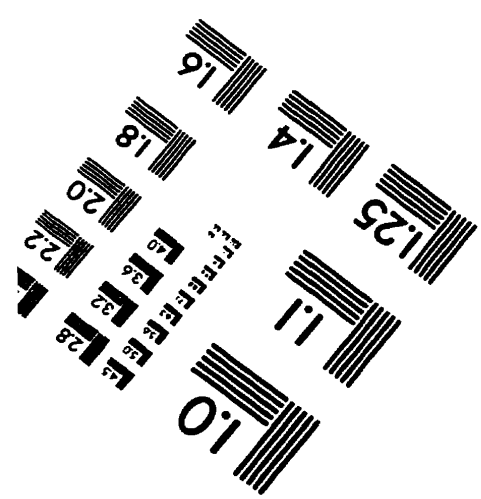
IMAGE EVALUATION
TEST TARGET (QA-3)

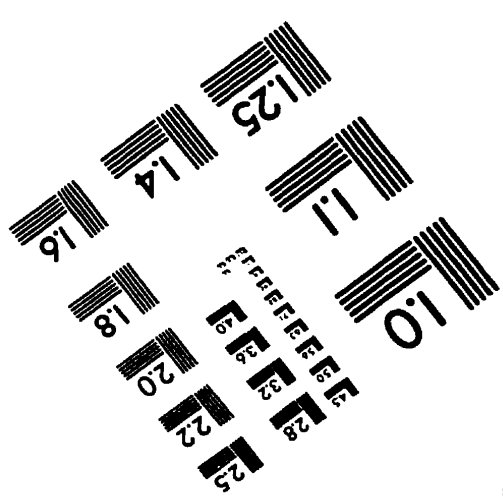












APPLIED IMAGE, Inc
1653 East Main Street
Rochester, NY 14609 USA
Phone: 716/482-0300
Fax: 716/288-5989