

THE UNIVERSITY OF CALGARY

Recurrence of Crohn's Disease following Surgery: Possible Risk Factors

by

Lloyd R Sutherland

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE

DEGREE OF

MSc

DEPARTMENT OF
MEDICAL SCIENCE

CALGARY, ALBERTA

JANUARY, 1989

© Lloyd R Sutherland, 1989



National Library
of Canada

Bibliothèque nationale
du Canada

Canadian Theses Service Service des thèses canadiennes

Ottawa, Canada
K1A 0N4

The author has granted an irrevocable non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of his/her thesis by any means and in any form or format, making this thesis available to interested persons.

The author retains ownership of the copyright in his/her thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without his/her permission.

L'auteur a accordé une licence irrévocable et non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de sa thèse de quelque manière et sous quelque forme que ce soit pour mettre des exemplaires de cette thèse à la disposition des personnes intéressées.

L'auteur conserve la propriété du droit d'auteur qui protège sa thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

ISBN 0-315-50395-5

THE UNIVERSITY OF CALGARY
FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Recurrence of Crohn's Disease Following Surgery: Possible Risk Factors", submitted by Dr. Lloyd R. Sutherland in partial fulfillment of the requirements for the degree of Master of Science.

Savitri Ramcharan

Supervisor: Dr. Savitri Ramcharan
Dept. of Community Health Sciences

H. Bryant

Dr. Heather Bryant, Examiner
Dept. of Community Health Sciences

G. Fick

Dr. Gordon Fick, Examiner
Dept. of Community Health Sciences

Kathryn J. Hannah

Dr. Kathryn J. Hannah, Examiner
Faculty of Nursing

Date: April 17, 1989

ABSTRACT

Crohn's disease, a chronic inflammatory condition which affects the gastrointestinal tract, often requires surgery for the control of symptoms. Recurrence of the disease following surgery is common. The objectives of this retrospective study were to 1) determine the rate of recurrence (defined as the need for a second resection) and 2) assess the impact of two previously reported risk factors for disease development, cigarette smoking and oral contraceptive use, on recurrence.

The charts of 258 consecutive patients who had undergone resection for Crohn's disease between 1966 and 1983 were abstracted for details of disease location and indication for surgery. Each patient received a questionnaire which queried additional surgery and use of cigarettes and oral contraceptives after surgery. One hundred and eighty patients (120 females, 60 males) responded. Mean followup was 8.6 years.

Eighty-four patients had a recurrence. Using life table analysis 5- and 10-year recurrence rates were 28% and 56% respectively. The odds ratio for smokers compared to non-smokers for recurrence within the first 5 years was 2.2 (CI₉₅ 1.1 - 4.3, P = 0.025). The 5- and 10- year recurrence rates amongst patients who smoked (36%, 70%) were significantly different from non-smokers (20%, 41%) (P = 0.001). Subsequent analysis demonstrated a difference in the 5- and 10- year recurrence rates between women who smoked (40%, 76%) and those who did not smoke (17%, 37%). When disease location and all recurrences were considered the increase in odds ratio in women was most evident in small bowel disease (odds

ratio 10.6), but the small sizes of the groups with ileocecal or colonic disease might have obscured the estimation of the effect. There was no support for the hypothesis that oral contraceptive users had an increased risk of recurrence compared to non-users. There was some evidence of an interaction between cigarette smoking and oral contraceptive use with modification of the smoking risk by oral contraceptive use. The possibility of a selection bias for oral contraceptive use cannot be excluded.

In conclusion, a retrospective analysis of a cohort of patients who had undergone resection for Crohn's disease revealed a recurrence rate of approximately 5% a year. Patients who smoked after surgery had an increased risk of recurrence compared to non-smokers. An interaction between oral contraceptive use and smoking was suggested.

ACKNOWLEDGEMENTS

I would like to thank Dr S Ramcharan, Chairman of my supervisory committee, who along with Dr H Bryant and Dr G Fick, provided generously of their time in assisting in the planning and execution of this research project. The support and encouragement of Dr Grant Gall, Director of the Intestinal Disease Research Unit, Dr Eldon Shaffer, Head, Division of Gastroenterology, and Dr Ed Love, Head, Department of Community Health Sciences, were most appreciated.

Funding for the project was provided by the Canadian Foundation of Ileitis and Colitis. The assistance of my research nurses, Nancy Racicot RN and Mary Crowther RN, in the collection of data is also gratefully acknowledged.

Finally I would like to thank my parents, Marie and Jed Sutherland, and a good friend, Dr Stan Giesbrecht, for their moral support and inspiration.

TABLE OF CONTENTS

	Page
Approval	ii
Abstract	iii
Acknowledgements	v
Table of Contents	vi
List of Tables	vii
List of Figures	viii
1. Introduction	1
2. Literature Review:	
A. Recurrence following surgery	4
B. Smoking and Crohn's disease	10
C. Oral contraceptives and Crohn's disease	16
D. Research Rationale	18
3. Objectives and hypotheses	19
4. Materials and methods	
A. Research design	21
B. Study definitions	22
C. Methods	23
D. Statistical methods	26
5. Results	
A. Study cohort	28
B. Sample characteristics	31

C. Recurrence following surgery	34
1. Influence of cigarette smoking	38
2. Influence of oral contraceptive use	57
3. Influence of smoking and oral contraceptives	61
6. Limitations of study	63
7. Discussion	64
References	70
Appendix 1 (Chart abstraction)	75
Appendix 2 (Covering letter)	77
Appendix 3 (Questionnaire for males)	78
Appendix 4 (Questionnaire for females)	83

LIST OF TABLES

TABLE 1		
	Description of the cohort	30
TABLE 2		
	Characteristics of responders and cohort	32
TABLE 3		
	Comparison of responders and non-responders	33
TABLE 4		
	Characteristics of patients with recurrence (Group 1) and those without recurrence (Group 2)	35
TABLE 5		
	Example of typical life table data	36
TABLE 6		
	Smoking among study patients in relation to disease milestones	39
TABLE 7		
	(a) Odds ratio for recurrence within 5 years	42
	(b) Odds ratio for recurrence following surgery	42
TABLE 8		
	Cigarettes smoked in the first year following surgery by recurrence: males and females	44
TABLE 9A		
	Odds ratio for recurrence within 5 years by smoking history and gender	46

TABLE 9B		
	Odds ratio for recurrence by smoking history and by gender	47
TABLE 10		
	Odds ratios for recurrence by smoking history and disease location	51,52
TABLE 11		
	Odds ratios for recurrence by gender, smoking and disease location	54
TABLE 12		
	Oral contraceptive use by 116 women, all ages	58
TABLE 13		
	Odds ratios for recurrence in oral contraceptive users 16-35 years of age by history of use	60
TABLE 14		
	Odds ratios for recurrence in women who smoked after surgery by oral contraceptive use	62

LIST OF FIGURES

FIGURE 1

Cumulative proportion of patients surviving
without recurrence for all study patients 37

FIGURE 2

Five year and 10 year cumulative recurrence
for smokers compared to non-smokers 43

FIGURE 3

Five and 10 year recurrence for women who smoked
compared to non-smokers following surgery 49

FIGURE 4

Five and 10 year recurrence for women who smoked
following surgery compared to women who quit 56

1. INTRODUCTION

Crohn's disease is a chronic inflammatory condition that can affect any part of the gastrointestinal tract from mouth to anus. Initially described by Crohn (1) in the 1930s as an acute inflammatory process limited to the terminal ileum, diagnosed in only a few patients, Crohn's disease has now become an important cause of gastrointestinal morbidity in the western world. Anatomically, patients with the disease may be divided into three groups: those in whom only the small bowel is effected, those in whom both small and large bowel are effected, and those in whom only the large bowel is effected. Although the etiology of the disease is unknown, current speculation suggests an interplay between infectious, environmental, genetic and immunologic factors.

Patients with Crohn's disease present with a variety of gastrointestinal symptoms. Generally diarrhea, abdominal pain and weight loss are predominant, but anorexia, fatigue and fever can also be significant symptom complaints. In the pediatric population failure to thrive or to commence puberty are important symptoms.

Prevalence rates for Crohn's disease vary from 20 - 106/100,000 population. Incidence rates have ranged between 1.3 - 7.3/100,000 population (2,3). Until recently the incidence of the disease appeared to be rising. Some of this increase probably reflected an increased awareness of the disease, and reclassification of patients who were originally thought to have ulcerative colitis as having Crohn's disease. The ready availability of gastroenterologists who have access to sophisticated diagnostic techniques may have also increased detection

striking increase in mortality, Crohn's disease has significant impact on society in terms of morbidity. This impact is magnified as the peak incidence occurs during the second and third decade of life. Thus patients with Crohn's disease, although they have a normal life expectancy (4), can be expected to utilize the health care system more often than the general population. For 1981-1982, Statistics Canada (5) reported 498 separations/100,000 population for patients in the diagnostic category of "non-infective enteritis and colitis" which would include Crohn's disease. The average hospital stay was 6.8 days.

Calkins et al (6) have examined the incidence of Crohn's disease from 1960 to 1979. Three surveys were performed (1960-1963, 1973, 1973-1979). They documented an increase in the age-adjusted rates for Crohn's disease over that period which appeared to occur between the first and second surveys and had stabilized by the time of the third survey.

Crohn's disease tends to occur in the countries of western Europe and Canada. It is uncommon in Asia, Africa and South America. The reasons for this geographic variability are not clear. In some cases the prevalence of infectious diarrhea may mask the presentation of Crohn's disease. The predominance of this disease in "westernized" countries may provide clues to etiology. For example, changes in diet and lifestyle, characteristic of western society, might increase the susceptibility of populations to develop Crohn's disease. Studies of immigrants in the United Kingdom have suggested that Crohn's disease is not rare, although more patients are seen with tuberculosis of the bowel than Crohn's disease (7).

The initial reports of Crohn's disease suggested that the disease was

more apt to occur in Jews (8,9) with a 2-4 fold increase in incidence. Crohn himself practiced at the Mount Sinai Hospital in New York and in his preliminary description of the disease, most of his patients were Jews. Subsequent studies have been criticized for both hospitalization and diagnostic bias. It is of interest that a recent analysis done in Israel (10) of native born Israelis has not documented this increased risk. This may be a reflection of the predominance of Ashkenazi Jews in America compared to the almost equal mix of Ashkenazi and Sephardic Jews in Israel. Differences in incidence could suggest an interaction between genetic and environmental factors in which a genetic predisposition allows an interaction with other environmental or infectious agents before the onset of Crohn's disease.

Typically Crohn's disease occurs in the second and third decades of life with a second smaller group of new cases presenting in the sixth and seventh decades. This bimodal variation in age distribution is not as marked as that seen in the other major inflammatory bowel disease, ulcerative colitis.

The influence of gender and socioeconomic status on the risk of developing Crohn's disease is not clear. In England and Northern Europe, female incidence rates seem to be 30% higher. In North America, which may be more ethnically diverse because of immigration, the increased risk among females is not as apparent (2). Although some studies have suggested that higher socioeconomic status is associated with increased risk of inflammatory bowel disease, level of education may be the more important variable.(2)

Treatment of Crohn's disease is difficult. Therapy with anti-inflammatory or immunosuppressant medications may be effective in controlling disease activity for a period of time (11-15). Nutritional therapy has its advocates as well (16,17). In the long term, however, most patients with Crohn's disease will come to surgical resection (18). The enthusiasm for extensive surgical resection has changed over the last decade. In the period from 1960-1980, the surgical approach stressed the importance of obtaining a complete resection of all involved bowel ("curative resection"). This was often pursued to the extent of ordering quick frozen sections of resection margins during surgery to ensure disease free margins. The inability of such resection to prevent recurrence led to a more conservative approach towards resecting only that part of the bowel responsible for current symptoms. A more conservative approach has been promoted by Alexander-Williams and Haynes (19) who suggest that strictureplasty in which the narrowed bowel segment is dilated rather than resected should be the procedure of choice for small bowel disease.

2. LITERATURE REVIEW:

A: RECURRENCE FOLLOWING SURGERY:

The definition of what constitutes a recurrence is controversial. Lennard-Jones and Stadler (20) have offered three definitions for recurrence: 1) recurrent symptoms of diarrhea, weight loss or pain, 2) recurrent symptoms with radiological or surgical evidence of recurrent disease and 3) further resection for Crohn's disease. In contrast, Korelitz (21) has defined recurrence as occurring

when objective signs re-appear, such as radiological abnormalities, subsequent to operation where all visible disease has been resected.

To date there have been several studies as to what factors predispose to recurrence. De Dombal and associates (22) reported in 1971 the results of a review of 168 patients who underwent primary resection for Crohn's disease at Leeds, UK from 1939 to 1968 inclusive. Although for most patients recurrence was defined as the need for a second operation, some patients were considered to have a recurrence based on symptoms plus radiologic evidence. The overall recurrence rate was 34.2%. The risk of recurrence was less in patients with disease confined to the large bowel compared to those with small bowel disease. Recurrence generally occurred proximal to the initial resection.

Although they found that younger patients were more likely to have a recurrence than older people, part of this increased recurrence might have been simply due to a shorter followup period for older patients. Recurrence tended to occur either within the first two years following surgery or 5-15 years following surgery. Patients with early recurrence were more likely to give a short history of symptoms prior to surgery and had a poorer long-term prognosis compared to those with a late recurrence. The risk of repeat operation was found to be the same after a second or third operation as compared to the first.

Higgins and Allan (23) in 1980 reviewed the experience at Birmingham, UK in 227 patients with Crohn's disease involving the distal ileum. The year of surgery ranged from 1949 to 1978. They disputed the suggestion of De Dombal and colleagues that the age at the time of surgery influenced the

recurrence rate. Recurrence was defined as the need for a second surgery. By using life table analysis, they were also able to demonstrate that operative rates were similar after the first, second, and third operations. The 5- and 10- year recurrence rates were 17.6% and 36.0% respectively.

Greenstein et al (24) were among the first to stress the importance of using actuarial or life table analysis techniques in assessing recurrence rates. Comparison of this study of recurrence with other studies is difficult in that the definition of recurrence includes not only repeat surgery for Crohn's disease but also surgery for intra-abdominal procedures. In some cases recurrence was defined as symptoms with radiologic verification of disease activity. This tends to inflate the recurrence figures. Using life table analysis they suggested an 89% recurrence rate by 15 years after initial surgery. As well they demonstrated that recurrence was related to the number of previous surgeries with the percentage of patients having recurrence increasing from 37% after the first procedure to 60% after the fourth.

The National Cooperative Crohn's Disease Study (NCCDS) provided a wealth of information concerning clinical outcomes in patients with Crohn's Disease in the United States. The study is important as it involved over 500 patients drawn from 14 university centres scattered throughout the United States. Although the major focus of this study was the effectiveness of various medications in the treatment of Crohn's disease, one paper (25) dealt with issues of surgery and recurrence. This study defined recurrence as the need for a second operation. By 10 years after surgery, 50% of patients had required a second

resection for recurrent Crohn's disease. The NCCDS was unable to show a significant difference among patients following first resection compared to patients following second resections in terms of recurrence but the trend was towards an increased risk of recurrence for patients undergoing a second resection. Patients with ileocolonic disease had the shortest interval of time from onset of symptoms to surgery, followed by those with small bowel disease and colonic disease. The type of anti-inflammatory or immunosuppressant used did not have any effect on patients' need for surgery.

Farmer and associates (26-29) of the Cleveland Clinic (a major referral centre for inflammatory bowel disease in the United States) have written extensively on the importance of the clinical pattern (disease location, symptoms, complications) as predictors of outcome. They have described a long term follow-up (mean 11.5 years) of 361 patients with Crohn's disease at the Cleveland Clinic. They found a 3.9% annual reoperation rate for the first 8 years declining thereafter to 1.4%/year. In fact 85% of their patients with recurrence had been operated on again within 8 years following surgery. The Cleveland group felt that the disease location and indication for surgery were the primary predictors for recurrence. As well they prepared survival curves demonstrating that patients with ileocolonic disease have the highest recurrence rates but in fact there are no statistically significant differences between the recurrence curves.

Nugent et al (30) of the Lahey Clinic studied 44 patients with disease confined to the large intestine who underwent total colectomy for Crohn's disease. They found a very low recurrence rate defined as requiring a second operation (3

of 44) during a 13 year follow-up. The optimistic outlook for patients undergoing surgery for colonic Crohn's disease has not been shared by others. Steinberg and associates (31) reported a 33% recurrence rate (defined as need for second operation) following colectomy. Their group of patients was not strictly comparable to that described by the Lahey Clinic in that they included patients with who had ileocecal disease (38 of 73). As well the patients were younger and in many of the United Kingdom studies younger patients have had more recurrences. Korelitz and co-workers (32) also claimed that many patients with disease confined to the colon will eventually develop small bowel disease following surgery.

Hellers (33) has described the natural history of Crohn's disease in Stockholm. The recurrence rate (defined as need for second operation) was 30% at 5 years, 50% at 10 years, and 60% at 15 years. Patients with ileal and ileocolonic disease had the same recurrence rates, but patients with colonic disease alone had fewer recurrences.

Sachar et al (34) studied 93 patients who had undergone their first resection for Crohn's disease between 1964 and 1973. Variables studied included age, sex, anatomic location, operative procedure, preoperative duration of disease. Reflecting the approach of Greenstein and workers (24), recurrence was again defined as not only the need for a second procedure but also recurrent symptoms with radiologic evidence of new disease. They found no differences in recurrence rate (using life-table analysis) when age, sex, and anatomical distribution were considered. Patients who had symptoms more than 10 years prior to surgery had a statistically significant difference in recurrence rates (33%) than those who had

had symptoms less than 10 years (64%). They suggested that this might imply two forms of Crohn's disease, an indolent form which has a slower recurrence rate, and a more active form which has more severe symptoms and earlier recurrence.

Speranza et al (35) studied 90 patients who had had a curative resection for Crohn's disease with a mean follow-up of 9.3 years (range 1-22). This study is flawed by the variable range of followup, high selection bias of patients, and a definition of recurrence which includes "clinical or laboratory findings of reemergent (sic) disease". In contrast to Sachar et al (34) they found that patients who had symptoms for more than 5 years had a higher recurrence rate.

A recent report (36) matched 77 patients who had recurrence with 77 patients who did not have recurrence. Patients were matched by centre and length of follow-up. Recurrence was defined as need for surgery or recurrence of symptoms with objective evidence of recurrent disease. Mean follow-up was 3.7 years. The authors felt that age under 20 at either onset or time of surgery, female gender and absence of granuloma were factors which favoured recurrence.

To date, studies of factors which influence recurrence patterns have focused on disease location, indication for surgery and age of onset. When recurrence is defined as need for second operation, the above studies are in general agreement that the rate of recurrence is approximately 5% a year for the first 10 years. Disagreement exists amongst the various reviews as to the importance of disease location for recurrence.

Recently two lifestyle issues, smoking and use of oral contraceptives, have been claimed to be risk factors for development of Crohn's disease. If they are in fact risk factors, then it is appropriate to study their influence, if any, on patterns of recurrence.

B: SMOKING AND CROHN'S DISEASE:

The first study (37) of smoking as a risk factor for development of inflammatory bowel disease was carried out by Harries and co-workers. Although they were able to show that non-smoking was associated with an increased risk of developing ulcerative colitis, the incidence of smoking was no different for patients with Crohn's disease compared to controls. He found that 8% of patients with ulcerative colitis and 42% of patients with Crohn's disease were current smokers compared with 44% of his controls which were drawn from patients attending a fracture clinic. The controls were matched by age and sex, not social class. The problem with this study may have been that the matching of case to control was for the patients with ulcerative colitis not Crohn's disease. This might have influenced the results.

Logan et al (38) carried out a similar type of study design and executed a case-control study of 124 patients with ulcerative colitis. Each patient was matched with 2 controls drawn from the practice of the general practitioner currently treating the patient with ulcerative colitis. The relative risk (RR) with 95% confidence intervals (CI_{95}) for non-smokers compared to smokers for ulcerative colitis was 3.8 (CI_{95} 2.0 - 6.9) and appeared equally strong for non-smoking at the

time of disease onset (RR 6, CI₉₅ 2.9 - 12.3). For purposes of definition relative risk is defined as the ratio of the risk of disease amongst the exposed to the risk among the unexposed and 95% confidence intervals include the range of values for the variable of interest constructed so that the range has a 95% probability of including the true value of the variable. It should be pointed out that in the general medical community the terms, odds ratio and relative risk, are used interchangeably. Strictly speaking this only applies when the disease of interest is "rare". For the purposes of this literature review the term relative risk is used only if the authors of the study used that term.

Benoni and Nilsson (39) at about the same time reported on the proportion of smokers and non-smokers attending her clinic in Lund, Sweden. They reported that only 13% of patients with ulcerative colitis smoked compared with 47% of Crohn's patients. Approximately equal proportions of men and women smoked.

Sommerville et al (40) performed a case control study to ascertain the effect of smoking as a risk factor for Crohn's disease. Smoking was defined as smoking more than 5 cigarettes, 3 cigars, or 1/2 oz pipe tobacco weekly for at least one year. Of those who smoked, 97% smoked cigarettes and the subsequent analysis was confined to cigarette smokers alone. Age and sex matched controls were chosen from the same general practice list as the patients with Crohn's disease. Smoking was found to be a risk factor for Crohn's disease. Current smokers had a risk ratio of 3.5 (CI₉₅ 1.8 - 6.6) and smoking prior to disease onset was associated with a risk ratio of 4.8 (CI₉₅ 2.4 - 9.7).

In a case control study carried out in Milan, Italy, Franceschi and coworkers (41) compared 109 patients with Crohn's disease to 250 hospital based controls. They found that smoking was associated with a fourfold increase in risk of developing Crohn's disease. Subsequent analysis suggested that the effect of smoking was dose dependent with the chi-square test for trend highly significant at $P < 0.01$. The actual values for the odds ratios were as follows 2.3 (<15 cig/day), 7.1 (<15-24 cig/day) and 2.9 (>25 cig/day). In fact the confidence intervals for all ratios overlapped suggesting that this conclusion will require further study. The risk ratio rose by duration of smoking when smoking history was divided into two groups, <15 years and > 15 years. Finally they found that smoking as a risk factor for Crohn's disease was independent of sex with both men and women demonstrating equivalent increases in relative risk.

Lindberg et al (42) demonstrated an increased risk of developing Crohn's disease amongst smokers attending an inflammatory bowel disease clinic in Sweden. In their study the relative risk was doubled in smokers as compared to non-smokers. One hundred and forty-nine patients participated in the study and were matched with controls drawn from a general population register matched by age. This is one of the very few studies in which controls were drawn from the general population rather than from a hospital or clinic base. They divided smokers into two groups, those smoking < 10 cigarettes/day and those smoking > 10 cigarettes/day. No differences were detected when the sample was stratified by sex or amount of cigarettes smoked. One interesting point was that more women with Crohn's disease lived alone compared to controls. No information

was given as to whether those who lived alone were more apt to smoke.

Holdstock et al (43) have studied the effect of smoking on disease activity in patients with ulcerative colitis and Crohn's disease. They noted that patients with Crohn's disease who smoked reported more relapses compared to non-smokers. The study can be criticized as the authors did not define what a relapse was (i.e. symptomatic relapse, or need for surgery) and their conclusions were drawn by carrying out a large number of t-tests with no evidence of carrying out Bonferroni's adjustment. Duffy et al (44) have reported on 74 patients with Crohn's disease who were in remission prior to entry into the study. The outcome of interest was a change in the Crohn's Disease Activity Index (45), an index incorporating stool frequency, patient symptoms, patient weight and laboratory investigations. Patients were followed for 6 months with relapse defined as a Crohn's Disease Activity Index greater than 150. Although a relative risk of 1.6 (CI_{95} 1.1 - 2.2) was calculated in smokers for risk of relapse, the actual increase in Crohn's Disease Activity Index was not reported. Mean Crohn's Disease Activity Index scores for smokers and non-smokers remained less than 150 throughout the study.

In the United States, two studies of smoking and inflammatory bowel disease have been carried out. Hanauer et al (46) compared smoking habits in patients with ulcerative colitis, Crohn's disease and irritable bowel disease. The risk ratio for developing Crohn's disease amongst smokers was 3.4. They were unable to demonstrate increased risk ratios for ulcerative colitis amongst non-smokers. This study can be criticized for using patients with irritable bowel

syndrome (IBS) as the control group. Irritable bowel patients have a motility disorder of the intestines so cannot be defined as truly without disease. Patients with IBS often have complaints of cramps and diarrhea similar to patients with inflammatory bowel disease. If smoking is viewed as an appetite suppressant or mood relaxant, then both groups of patients might smoke for similar reasons. Calkins et al (47) found that patients with Crohn's disease were more apt to be current smokers than neighbourhood controls.

There has been one study of the incidence of inflammatory bowel disease in Mormons. Amongst other religious proscriptions, Mormons are forbidden to smoke. In a letter to the editor reporting on the results of a mail survey (50% response), Penny et al (48) found that the incidence of ulcerative colitis was higher in Mormons, (consistent with earlier reports) but that the incidence of Crohn's disease was the same as the general population and was not decreased.

Because of the concern that patients may alter their smoking habits after the onset of inflammatory bowel disease, Tobin and co-workers (49) studied smoking behaviours before the onset of symptoms. One hundred and fifty patients with Crohn's diseases were compared with 150 age and sex matched controls drawn from the patient lists of local general practitioners. Patients were sent a questionnaire which amongst other things asked for information about smoking habits. Patients were specifically asked if they had smoked at a certain age which was determined to be 6 months before the date given as relating to the onset of symptoms when the patients were first referred to the inflammatory clinic. They

found that smoking before the onset of symptoms was associated with a relative risk of 4.1 (CI₉₅ 2.0 - 8.7). They also demonstrated that after adjusting for sex, the relative risk was slightly higher in women (RR 3.1, CI₉₅ 1.6 -6.0) than men (RR 2.6, CI₉₅ 1.2 - 5.9). They were unable to demonstrate a dose dependent effect for increasing number of cigarettes smoked. The association between smoking and Crohn's disease was not influenced by site of disease or age of disease onset. A recent study reported by Smith et al (50) found that 78% of Crohn's disease patients surveyed at the University of Chicago stated that they had smoked prior to the onset of their symptoms but that only 33% were smoking at the time of the study.

Why should smoking predispose to Crohn's disease? There is a well defined genetic component to inflammatory bowel disease (51). Perhaps smoking is a causal factor which allows the expression of Crohn's disease and suppresses the manifestations of ulcerative colitis. There is some experimental evidence to suggest that smoking alters colonic mucus (52). Other authors have pointed out that smoking may have significant effects on the immune system. Gerrard and Hein (53) have noted that IgG, IgM, IgA levels are reduced in smokers while IgE levels are increased. Smoking may also reduce the ratio of T-helper-inducer to T-suppressor cells which again could have a significant effect on the host's ability to repel an infection. If there is an infectious component to the etiology of Crohn's disease, any agent which interferes with the body's defense mechanisms might influence development of disease.

C: ORAL CONTRACEPTIVES AND CROHN'S DISEASE:

In recent years, the use of oral contraceptives has been implicated as a risk factor for development of inflammatory bowel disease. The Royal College of General Practitioners' cohort study (54) reported that the incidence of Crohn's disease was 40% higher amongst users of oral contraceptives compared to non-users. This study also suggested that the incidence of ulcerative colitis among oral contraceptive users was twice that of non-users. Ramcharan et al (55) in a prospective study of the side effects of oral contraceptives suggested an association between the use of oral contraceptives and Crohn's disease.

Following the Royal College report a flurry of isolated case reports (56,57) described patients with symptoms of diarrhea associated with colonic pathology suggestive of inflammatory bowel disease which responded to withdrawal of oral contraceptives. Rhodes et al (58) suggested that the finding of an increased number of patients with Crohn's disease amongst users of oral contraceptives was due solely to an increase in colonic Crohn's disease. They studied 100 consecutive patients who were attending an inflammatory bowel disease clinic for follow-up in Birmingham, England. They compared the usage of oral contraceptives by women with Crohn's disease to that of women with ulcerative colitis. Adjustment was made for age and year of diagnosis. Sixty-three percent of women who had colonic Crohn's disease used oral contraceptives in the year prior to symptom development compared to 24% of women with small bowel disease. The authors of this study also reported that some women went into

remission after cessation of oral contraceptives. Patients who did not have non-caseating granulomata (often found in biopsies of patients with Crohn's disease) were more apt to respond to withdrawal of oral contraceptives than patients with granuloma. They hypothesized that oral contraceptives may produce a colonic disease, possibly ischemic in origin, which mimics Crohn's disease. Interestingly in contrast to the results of the Royal College survey only 9% of women with ulcerative colitis reported using oral contraceptives in the year prior to diagnosis.

While Rhodes dealt with cases attending a long term followup clinic, Lesko et al (59) were able to study patients who were newly diagnosed as having Crohn's disease. They studied 57 women admitted to hospital with Crohn's disease and 2189 controls with other conditions. The cases of Crohn's disease consisted of women admitted to hospital for their disease in whom the diagnosis had been made within the last 12 months. The control group consisted of women admitted to hospital for trauma or acute infection. Cases and controls were matched by decade. The relative risk for oral contraceptive users compared to non-users was 1.9 (CI₉₅ 1.0 - 3.5). The magnitude of the risk correlated with timing and duration of use. Within 4 years of discontinuation of contraceptive use, the relative risk declined to that of the non-users. The relative risk estimate for recent use that lasted for greater than 5 years was 8.0 (CI₉₅ 3.1 - 21.0).

This study can be criticized for being hospital based. Many patients with Crohn's disease would not be admitted to hospital within the first year of diagnosis and thus the sample is heavily weighted towards more severe cases and not representative of the spectrum of Crohn's disease. Unfortunately no attempt

was made to assess oral contraceptive use and disease location and thus an opportunity to reassess Rhodes's observation of an excess of colonic Crohn's among oral contraceptive users was lost.

Vessey et al (60) reported recently on development of inflammatory bowel disease within the Oxford Family Planning Association contraceptive study patients. They identified 49 women who developed inflammatory bowel disease (31 ulcerative colitis, 18 Crohn's disease) during the course of the cohort study. These investigators confirmed previous studies that smoking was associated with Crohn's disease. The incidence for both ulcerative colitis and Crohn's disease was nearly doubled among women currently using oral contraceptives compared to non-users. Adjustments for cigarette smoking (smoking history taken on entry into the cohort study) failed to demonstrate any interaction between smoking and oral contraceptive use.

D: RESEARCH RATIONALE:

A review of the literature reveals evidence implicating cigarette smoking as a risk factor for the development of Crohn's disease. Little has been done to assess the role of cigarette smoking after disease onset. The fragmentary reports to date have not used specific accepted measures to define the impact on recurrence. Since such information would have important implications for the management of patients with Crohn's disease, this study was undertaken to investigate the role of smoking on the recurrence of Crohn's disease following surgical resection. Moreover, there is no evidence to suggest that cigarette

smoking would be beneficial for patients with Crohn's disease. It was therefore decided that a one-tailed test of significance would be appropriate to assess the role of cigarette smoking on recurrence.

The evidence that oral contraceptive use is a risk factor for development of Crohn's disease is scanty. Nevertheless two well designed studies have documented an increased risk of Crohn's disease in oral contraceptive users. One study suggested that this effect was primarily in patients with colonic disease and inferred that the problem may be one of oral contraceptives provoking a colonic response which mimics Crohn's disease and disappears on withdrawal of oral contraceptives. Since physicians have a role to play in counselling patients on the use of oral contraceptives, this study was undertaken to assess the role of oral contraceptives on the recurrence of Crohn's disease following surgical resection. Since there were no studies to support a protective role for oral contraceptive use, a one-tailed test of significance for the hypothesis that oral contraceptive use would increase the risk of recurrence in Crohn's disease patients is appropriate.

3. OBJECTIVES:

1. To determine the surgical recurrence rate amongst patients with Crohn's disease following surgical resection at the Foothills Provincial Hospital between 1966 and 1983.

2. To determine what roles cigarette smoking and use of oral contraceptives have to play in determining the post-operative risk of recurrence (defined as need for a second resection) and the time of recurrence.

HYPOTHESES:

1. Cigarette smokers have a greater risk of recurrence (ie need for second operation) following surgery for Crohn's disease than non-smokers.
2. Users of oral contraceptives have a greater risk of recurrence (ie need for second operation) following surgery for Crohn's disease than non-users.
3. Users of oral contraceptives and cigarettes will have a greater risk of recurrence than one would expect based on the individual risks associated with the use of cigarettes and oral contraceptives alone.
4. Amongst those patients who have repeat resections
 - a) Cigarette smokers have a shorter time to recurrence than non-smokers.
 - b) Users of oral contraceptives have a shorter time to recurrence than non-users.
 - c) Smokers who use oral contraceptives, have a shorter time to recurrence than non-smokers who do not use oral contraceptives.

4. METHODS AND MATERIALS:

A: RESEARCH DESIGN:

This is a retrospective study of a cohort of patients who underwent surgery for Crohn's disease to ascertain the effects of smoking and oral contraceptive use on the likelihood of surgical recurrence. Patients who underwent two surgical resections were compared to those who had undergone only one resection. The study sample consists of all patients who underwent surgical resection for Crohn's disease at the Foothills Provincial Hospital between 1966 and 1983.

There are difficulties with any definition of recurrence, particularly when one considers the changing emphasis towards limited resections rather than curative resection. If recurrence is defined on the basis of symptoms it may be difficult to achieve agreement as to what symptoms reflect recurrence. Following surgery, many patients may have persistent diarrhea (particularly if the ileocecal valve has been resected). Some patients may never regain all the weight they lost prior to their surgical procedure.

If there is reliance on radiological evidence of recurrence other problems arise. It would be unethical to subject asymptomatic patients to a radiologic work-up simply to determine whether or not they have a recurrence. Again with limited resections, there may be evidence of disease on x-ray immediately following surgery making a diagnosis of recurrence difficult.

The need for a second operation would appear to be the most conservative approach to define recurrence. If the patient has undergone a curative resection, a second operation provides explicit evidence for recurrence. In patients who have undergone surgery without complete resection, the second operation may reflect not a recurrence but a worsening of disease, already present at the first operation. In such a study it is important to determine the indication for surgery, and to exclude patients who had surgery for reasons unrelated to recurrence, such as adhesions.

B: STUDY DEFINITIONS:

For the purposes of this paper the term "cohort" refers to all the patients who had surgery for Crohn's disease at the Foothills Hospital between 1966 and 1983. The term "sample" refers to those patients who returned questionnaires and were not excluded for any other reason, and on whom the study is based.

For the purpose of the study a recurrence is defined as having occurred if a repeat operation is required for control of an episode of Crohn's disease. If an operation was carried out solely for technical problems related to the ileostomy or as a planned re-anastomosis following a defunctioning procedure, then that operation was not considered to be a second surgery for Crohn's disease.

The definition for smoking was that of Logan and workers (38) with smoking defined as smoking more than 5 cigarettes per week for more than twelve

months. The definition of oral contraceptive use was that of Lesko and associates (59), namely use of oral contraceptives for more than 3 months.

Those patients who had a second surgery for Crohn's disease are classified as belonging to Group 1 and those who did not have a second surgery belong to Group 2.

C: METHODS:

The study was submitted to the Conjoint Ethics Committee of the University of Calgary Medical School and affiliated teaching hospitals and received ethical approval prior to initiation. The Medical Records Department of the Foothills Provincial Hospital was asked to search for all records of patients who underwent a surgical resection for Crohn's disease between 1966 (the year the hospital opened) and December 31, 1983. All charts coded with ICD-9 555 (Crohn's disease) were reviewed and abstracted onto a predesigned form (Appendix 1). Information to be gained from the chart review included demographic characteristics including address, telephone numbers, sex, date of birth, next of kin, surgeon and gastroenterologist. As well the indication for surgery, location of disease, type of surgery and extent of resection were noted. For each surgery performed at the Foothills Hospital a separate form was filled out (Appendix 1). The entire hospital record was carefully reviewed for references to surgery at other institutions.

The reliability of the search was confirmed by requesting the Department of Pathology to provide a list of all pathological reports of Crohn's

disease during that period. A random sample of these surgical reports was checked against the list of patients drawn from medical records.

Each patient was contacted initially by mail with a letter outlining the project (Appendix 2) and a questionnaire (males - Appendix 3, females - Appendix 4) using the most recent address according to the hospital chart. A self addressed stamped envelope was included to encourage ease of return. The patient questionnaire sought information as to when symptoms had first occurred, and when the diagnosis of Crohn's disease was made. As well the patient was asked to confirm the year of surgery as noted from the Foothills Hospital chart and was queried for details of surgery at any hospital other than the Foothills. If surgery had been performed elsewhere, the patient was asked to sign a release of information form so that the hospital could be contacted.

A specific set of questions inquired into the smoking history and use of oral contraceptives. Included with the questionnaire was a simple form which allowed the patient to report his/her smoking history in terms of quantity smoked and years in which smoking activity occurred. In addition to amount smoked, it was ascertained whether or not the patient smoked prior to: 1) onset of symptoms, 2) diagnosis, and 3) in the year prior to surgery. Finally the patient was asked if he/she smoked in the first year after surgical resection.

Similarly the use of oral contraceptives was also characterized in terms of duration of use and whether or not the patient used oral contraceptives prior to: 1) onset of symptoms, 2) diagnosis and 3) surgery. Contraceptive use after resection was also identified.

If no response was received from the patient after 3 weeks, an attempt was made to contact the patient either by phone or by contacting the next of kin as listed on the patient's chart. Patients were phoned at four different intervals, morning, afternoon, evening and weekend.

If we were able to contact the patient by phone we requested that the patient return the questionnaire and mailed an additional questionnaire if the patient stated that he/she had not received one. If we were unable to contact the patient by phone but had a new address from a next of kin or family doctor, then a new questionnaire was sent. For those individuals that we were unable to contact by phone and for whom no next of kin could be located, a final attempt was made to locate an address by contacting the national office for the Canadian Foundation for Ileitis and Colitis. Only two patients could be traced using the services of the Foundation.

Patients who were contacted by phone and who had not returned their questionnaire after 9 weeks received a hand-written letter requesting that the questionnaire be returned. Eleven patients responded to the handwritten letter and no further attempt was made to contact patients. All names on the list were followed using this program and by the end of 9 weeks if no questionnaire had been received then no further attempts were made to contact the patient. For those patients who responded and indicated that they had surgery at another institution, a request for discharge summary, operative and pathology reports was sent to that institution along with the release of information signed by the patient.

D: STATISTICAL METHODS

Data obtained were analyzed using the computer software program BMDP: 1D for organization of data, 3D for analysis of continuous variable, 4F for preparation of frequency tables, odds ratios and stratified analysis, and 1L for preparation of life tables. The initial analysis was confined to comparison of the cohort and sample by individual variables. The percentage of patients in each group was compared in terms of sex ratio, disease location, indications for surgery and age at surgery. A similar comparison was made between responders and non-responders to assess the representativeness of the sample. Following that the sample was divided into two groups (Group 1 and 2) based on whether or not they had required a second surgery by December 31, 1987. BMDP3D was used to compare Group 1 and 2 in terms of continuous variables such as age, length of followup and duration of symptoms whereas BMDP4F was used for discrete variables such as sex, disease location and indication for surgery. Tests for significance using chi-square (Pearson's) were performed. Odds ratios for the variables of interest, smoking and oral contraceptive usage, were calculated. Since the time of interest was that following surgery the 2 major variables were the responses to the questions: 1)"Did you smoke in the first year after your operation for Crohn's disease?" and 2) "Did you take oral contraceptives after your operation for Crohn's disease?". In addition to odds ratios and significance testing, confidence intervals using the test-based method (61) were constructed.

Following the acceptance of the Hypothesis #1, (Cigarette smokers have a greater risk of recurrence (ie need for second operation) following surgery

for Crohn's disease than non-smokers) the data were further examined in an exploratory fashion to determine if any further comments could be made regarding the role of certain variables including sex and disease location as to their effect on smoking and recurrence.

Life table analysis has been used in the past by other investigators of gastrointestinal disease (62,63). BMDP1L was used to construct cumulative recurrence graphs for the entire sample and to further test Hypothesis #1. Although follow-up ranged from 4 to 25 yrs (Mean 10.3), the majority of patients had their surgery since 1977. Therefore all life table analysis was arbitrarily cut at 10 years (120 months). Differences between the two curves generated by the life-table analysis were assessed for statistical significance by calculation of two probabilities; the Generalized Savage (Mantel) which is a general assessment of differences between the two curves and the Generalized Wilcoxon (Breslow) which is more sensitive to changes in the early portion of the curve. Additional life tables were constructed to examine in a preliminary fashion the role of sex and disease location. As part of the life table analysis cumulative proportion with recurrence was calculated at fixed points (5 and 10 years). Confidence intervals were constructed for the differences in proportions (61) between the two groups.

Since Hypothesis #2 (users of oral contraceptives have a greater risk of recurrence (ie need for second operation) following surgery for Crohn's disease than non-users) was not supported, further statistical testing was not carried out.

5. RESULTS:

A: STUDY COHORT (Table 1):

Two hundred and seventy-four charts were identified as pertaining to patients who had surgery for Crohn's disease carried out at the Foothills Hospital between 1966 and 1983. On review, in 2 charts the pathologic diagnosis was not sufficiently clear to rule out ulcerative colitis or colitis indetermina (a pathologic diagnosis given when the features favouring a diagnosis of ulcerative colitis or Crohn's disease are present). Ten patients were noted to be dead from a review of their hospital records. One patient was excluded from the final analysis as she had at least two surgeries for Crohn's disease prior to 1966. As there could be significant temporal changes in terms of the surgical approach and standard of care for patients who had their initial surgery in the 1940s and 1950s, this patient was excluded.

Two hundred and sixty-one questionnaires were mailed out. One hundred and ninety-three questionnaires were returned giving an overall response of 70%. In 41 patients the questionnaire was returned as the address was not current. Seven were returned by other family members because of death. Of those patients with valid addresses (213) 90% responded. When operative reports were obtained on 3 other patients sufficient concern was raised as to the accuracy of the diagnosis of Crohn's disease that these patients were excluded. Four patients had 2 surgeries prior to 1966. Six patients had already had 2 resections for Crohn's disease at other hospitals prior to their surgery at the

Foothills Hospital. As the primary focus of this study was to examine the impact of smoking and oral contraceptive use on recurrence following the first or second surgery and since patients who have had numerous surgeries may have a higher risk of repeat surgery these patients were excluded.

In 6 patients details as to the exact date of surgery at other institutions could not be confirmed. They were included in the analysis for smoking and oral contraceptive use but excluded in the life table analysis as we could not confirm the exact date of surgery at the other institution. Six patients were excluded from the sample because they had their first surgery before age 15 (mean age 9.6, range 1-15 years), reflecting a period in time when the Foothills Hospital had an active pediatrics program. Since the activities of interest were smoking and using oral contraceptives, it was felt that these patients might not have sufficient opportunity for exposure to include in the analysis.

TABLE 1
Description of the cohort

Number identified by medical records	274
Number of deaths	10
Less patients in whom diagnosis of Crohn's disease could not be confirmed	2
Less patients who had both surgeries prior to 1966	1
Number sent a mailed questionnaire	261
Number who returned questionnaires	193
Number excluded after review	
Less patients in whom diagnosis of Crohn's disease could not be confirmed	3
Less patients who had both surgeries prior to 1966	4
Less patients who had two surgeries prior to surgery at the Foothills	6
Number for whom no current address available	41
Number returned (patient deceased)	7
Number contacted but did not return questionnaires	20
Number of patients in sample	180
Less patients less than 15 at first surgery	6

B: SAMPLE CHARACTERISTICS (Tables 2 and 3):

The analysis is based on 174 patients. Basic disease characteristics are noted in Table 2 with comparative data for the entire cohort displayed. The two groups appear to be comparable in terms of age at first surgery, gender, disease location, indication for surgery and number of days in hospital following surgery. No formal tests of significance were carried out.

Table 3 compares the characteristics of the 174 patients who responded with the 70 patients who did not respond either because of death, lack of current mailing address or refusal to respond. Both groups appear to be comparable in terms of disease location and indication for surgery. The group of non-responders included a higher proportion of men compared to the group of responders.

TABLE 2
 Characteristics of responders and cohort

	RESPONDERS	COHORT
Number of subjects	174(100%)	258(100%)
Age at first surgery	30.5	31
Gender (Males/Females) (Percent males)	58:116 33%	101:157 39%
Disease location		
Small intestine only	73(42%)	99(38%)
Ileocecal	83(48%)	134(52%)
Large intestine only	18(10%)	25(10%)
Surgical indication		
Intractability	64(37%)	93(36%)
Obstruction	34(20%)	46(18%)
Fistula	35(20%)	47(18%)
Abscess	14(8%)	18(7%)
Perforation	10(6%)	16(6%)
Stricture	13(7%)	16(6%)
Perianal disease	4(2%)	6(2%)
Megacolon	0(0%)	2(1%)
More than one indication	0(0%)	14(6%)
Days in hospital post surgery	15	16

TABLE 3

Comparison of responders and non-responders

	RESPONDERS	NON-RESPONDERS
Number of subjects	174* (100%)	78(100%)
Age at first surgery	30.5	34
Gender (Males/Females) (Percent males)	58:116 33%	38:40 49%**
Disease location		
Small intestine only	73(42%)	25(32%)
Ileocecal	83(48%)	46(59%)
Large intestine only	18(10%)	7(9%)
Surgical indication		
Intractability	64(37%)	25(32%)
Obstruction	34(20%)	12(15%)
Fistula	35(20%)	11(14%)
Abscess	14(8%)	4(5%)
Perforation	10(6%)	6(8%)
Stricture	13(7%)	3(4%)
Perianal disease	4(2%)	1(1%)
Megacolon	0(0%)	2(3%)
More than one indication	0(0%)	14(18%)
Days in hospital post surgery	16	15

* Excludes the 6 patients who could not be categorized as to the exact time of surgery

** P < 0.05

C: RECURRENCE FOLLOWING SURGERY (Table 4, Figure 1):

Of the 174 patients in the sample, 84 required a second operation for Crohn's disease by December 31, 1987. Those patients with recurrence (Group 1) are compared with those without recurrence (Group 2) in Table 4. For ease of comparison percentages for each variable of interest are offered. There were no major differences between the two groups in terms of sex ratio, indication for surgery and age at time of surgery and disease location.

In order to assess recurrence among the study population a life table of actuarial design was constructed for the sample as demonstrated in Table 5. For the sake of simplicity, the intervals are divided into 6 month periods. Patients that appear in the "withdrawn" column were not lost to followup but represent patients who reached the December 31, 1987 study termination date without recurrence.

Table 5 presents, in tabular form, the data derived from the life table for the entire sample. The results of the life table analysis are graphically presented in Figure 1. By 5 years, $28 \pm 3.5\%$ of the sample had required a second operation. This proportion rose to $56 \pm 4.9\%$ at the conclusion of ten years.

TABLE 4

Characteristics of patients with recurrence (Group 1) and those without recurrence (Group 2)

	Group 1	Group 2
Number of patients	84	90
Gender (Male/Female)	24:60	34:56
Percent male	29%	38%
Indication for surgery		
Intractability	37(44%)	27(30%)
Obstruction	13(15%)	21(23%)
Fistula	17(20%)	18(20%)
Abscess	4(5%)	10(11%)
Stricture	6(7%)	7(8%)
Perforation	3(4%)	7(8%)
Combination	4(5%)	0(0%)
Age at first surgery	30	31
Disease location		
Small intestine	29(35%)	44(49%)
Ileocecal	45(54%)	38(42%)
Large intestine	10(12%)	8(9%)

There are no significant differences between Group 1 and Group 2.

TABLE 5
EXAMPLE OF TYPICAL LIFE TABLE DATA

Month of Observation	Number			Proportion Recurred	Proportion Surviving	Cumulative proportion surviving to end of interval
	Entered*	Withdrawn	Recurrence			
0 - 6	168*	0	4	0.0237	0.9763	0.9763
6 - 12	164	0	8	0.0485	0.9515	0.9290
12 - 18	156	0	9	0.0573	0.9427	0.8757
18 - 24	147	0	2	0.0135	0.9865	0.8639
24 - 30	145	0	3	0.0205	0.9795	0.8462
30 - 36	142	0	3	0.0210	0.9790	0.8284
36 - 42	139	0	6	0.0429	0.9571	0.7929
42 - 48	133	1	5	0.0375	0.9625	0.7632
48 - 54	129	8	2	0.0161	0.9839	0.7509
54 - 60	119	4	5	0.0431	0.9569	0.7185
60 - 66	108	6	5	0.0472	0.9528	0.6846
66 - 72	97	7	2	0.0212	0.9788	0.6701
72 - 78	88	6	6	0.0698	0.9302	0.6234
78 - 84	76	7	3	0.0408	0.9592	0.5979
84 - 90	66	2	6	0.0909	0.9091	0.5436
90 - 96	58	7	2	0.0360	0.9640	0.5240
96 - 102	49	2	1	0.0204	0.9796	0.5133
102 - 108	46	3	2	0.0440	0.9560	0.4907
108 - 114	41	5	1	0.0253	0.9747	0.4783
114 - 120	35	5	3	0.0896	0.9104	0.4355

* Excludes 6 patients for which an exact time for surgery was not available

* Incomplete data available on 6 patients

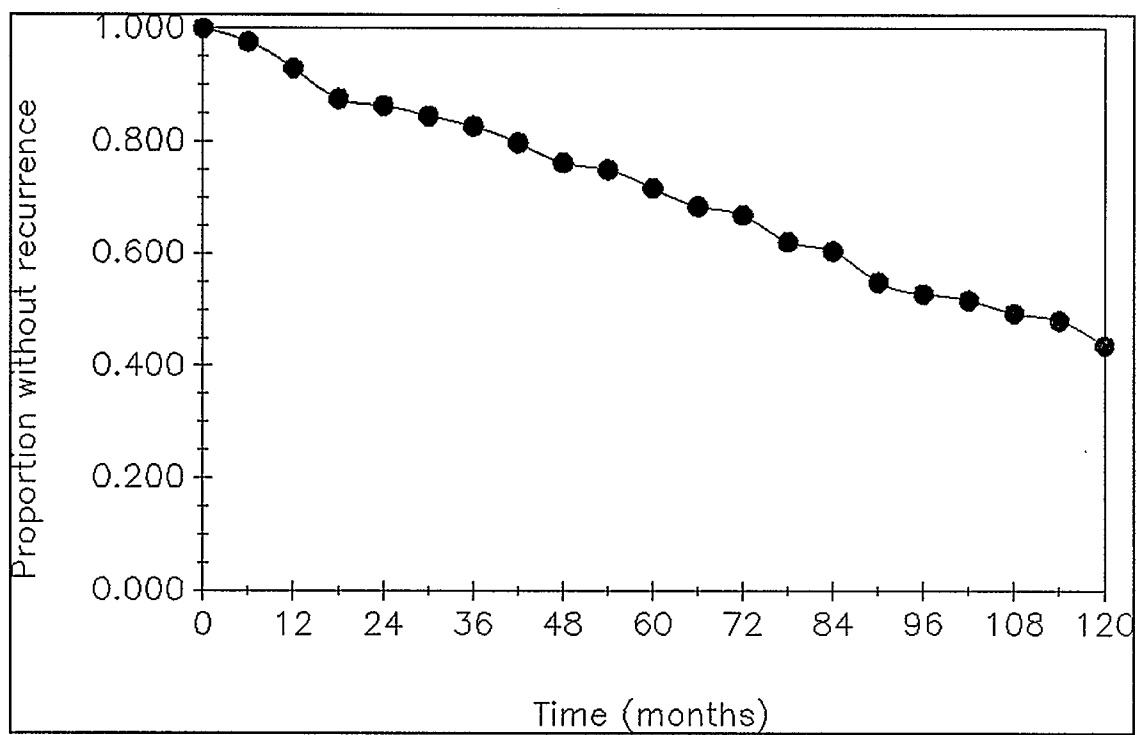


Figure 1 Cumulative proportion of patients surviving without recurrence for all study patients. 5 year proportion with recurrence = 28%, 10 year proportion with recurrence = 56%

1. Influence of cigarette smoking (Tables 6 - 11)

One hundred and twenty-three (71%) patients in the sample smoked at one point in their lifetime. The questionnaire separated the smoking history into various components related to the patient's Crohn's disease. Patients were asked if they had smoked: 1) before the onset of disease, 2) at the time of diagnosis, 3) prior to surgery, and 4) in the year after surgery. The details of their responses to these specific questions as to when they smoked in relation to disease milestones is given in Table 6. The questions are in fact in chronological order. It is of interest to note an apparent decline in smoking by Crohn's disease patients as they grew older. This trend was apparent in both sexes but less marked in women compared to men. The proportion of men who smoked following surgery was significantly less than the proportion of women who smoked following surgery. Although in the following tables data will be presented for each of these questions, it should be recognized that the key variable in terms of hypothesis testing relates to smoking after surgery.

TABLE 6

Smoking among study patients in relation to disease milestones

	Total	Male	Female
	Number(%)	Number(%)	Number(%)
Total	174 (100%)	58 (100%)	116(100%)
Ever Smoked	123 (71%)	41 (71%)	82 (71%)
Smoked: before disease diagnosed	111 (63%)	36 (62%)	75 (65%)
at the time of diagnosis	97 (55%)	27 (47%)	70 (60%)
before first surgery	100 (57%)	30 (52%)	70 (60%)
after first surgery	89 (51%)	23 (40%)	66 (57%)*

* P < 0.05, chi-square test for significance

(information was missing on one patient in this group)

The first hypothesis to be tested was "Cigarette smokers have a greater risk of recurrence following surgery for Crohn's disease than non-smokers". A preliminary measure of the effect of smoking on recurrence was assessed by comparing the 5-year recurrence rates in those who smoked at any time in the year following surgery and in those who did not. The 5-year period was selected because it covered the maximum observation period contributed by the majority of the cohort. The odds ratio for recurrence was 2.2 (CI₉₅ 1.1 - 4.3) and the test for significance revealed a p value of 0.025 (Table 7a).

The risks associated with smoking at various times prior to and after surgery were also examined using an approximate measure based on all recurrences accumulated over the total observation period for the entire sample. This approach provided larger numbers in all of the categories. Odds ratios for recurrence amongst those who smoked 1) before diagnosis, 2) at the time of diagnosis, 3) before surgery and 4) in the first year after surgery, compared to non-smokers, were greater than 1.0 (Table 7b).

Since cigarette smoking after surgery was significantly associated with recurrence of disease (Table 7a) providing preliminary support for the hypothesis, a more definitive measure of smoking risk was obtained using life table analysis. As demonstrated in Figure 2, recurrence rates differed significantly between the two groups (Wilcoxon P = 0.007, Savage P = 0.002). At 5 years the proportion of smokers and non-smokers with recurrence was 36% and 20% respectively. By 10 years the proportions with recurrence rose to 70% and 41% respectively. The difference in proportions with recurrence between the two groups (with Confidence

Intervals) was 16% (2.4 - 29.6) at 5 years and 39% (14 - 54%) at 10 years.

If cigarette smoking has an important clinical effect on risk of recurrence, it is possible that the effect might be dose dependent. To assess this patients were grouped by the number of cigarettes smoked per day in the first year following surgery. The results are seen in Table 8. In this table only recurrences which occurred within the first five years following surgery are recorded. The table provides evidence for a dose related effect in women as compared to men since there is a tendency towards higher frequencies of recurrence with increasing number of cigarettes smoked per day.

TABLE 7

Table 7a: Odds ratios (95% confidence interval) for recurrence within the first 5 years following surgery in relation to smoking history*

	Recurrence		Odds ratio (CI ₉₅)
	Yes	No	
Smoked in the first year following surgery:			
Yes	32	57	2.2 (1.1 - 4.3) ^a
No	17	66	

Table 7b: Odds ratios for recurrence following surgery in relation to smoking history**

	Recurrence		Odds ratio	
	Yes	No		
Smoked:				
before diagnosis	Yes	59	52	1.7
	No	25	38	
at time of diagnosis	Yes	57	40	2.6
	No	27	50	
before first surgery	Yes	58	42	2.5
	No	26	48	
after first surgery	Yes	55	34	3.0
	No	29	55	

* Two patients did not respond

** One patient did not respond

^a p = 0.025

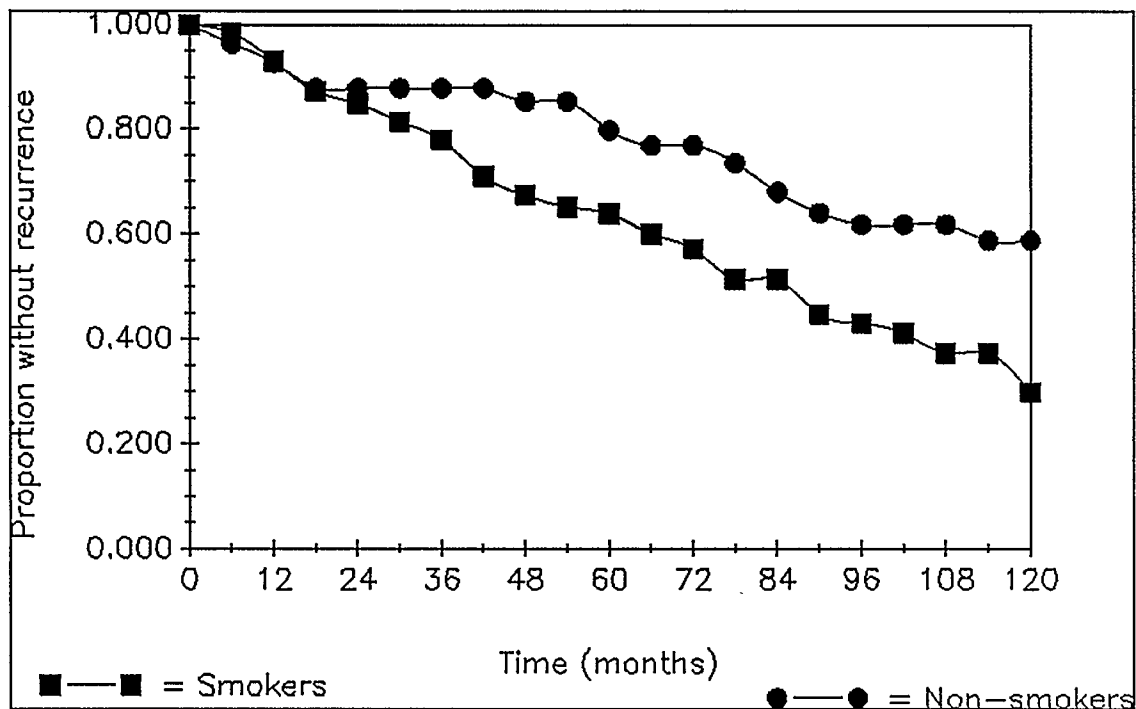


Figure 2 Five year and 10 year cumulative recurrence for smokers (36%, 70%) compared to non-smokers (29%, 41%). (Wilcoxin P = 0.007, Savage P = 0.002). Five year difference = 16%, (CI₉₅ 2.4 - 29.6); 10 year difference = 39% (CI₉₅ 14 - 54).

TABLE 8

Cigarettes smoked in the first year following surgery by recurrence:
males and females

a) females

Recurrence within 5 years

Number of cigarettes smoked/day	Yes	No
0	8(17%)	39(83%)
1 -10	3(25%)	9(75%)
11 - 20	10(40%)	15(60%)
21 - 30	11(42%)	15(58%)
31 - 50	1(50%)	1(50%)

B) males

Recurrence within 5 years

Number of cigarettes smoked/day	Yes	No
0	10(26%)	29(74%)
1 -10	2(40%)	3(60%)
11 - 20	3(27%)	8(73%)
21 - 30	2(29%)	7(71%)

Since Hypothesis #1 had been accepted it seemed appropriate to examine additional data generated by the analysis to gather some preliminary information as to what effect other variables might have on the relationship between smoking and recurrence. A greater proportion of males than females did not respond. It is not known if the non-responders would have differed by smoking or recurrence status. Therefore the next step of the analysis examined the associations between smoking and recurrence in males and females separately (Table 9A). The odds ratio for five year recurrence amongst women smokers was 2.8, (CI₉₅ 1.2 - 6.4). The odds ratio for recurrence within 5 years following surgery in men was 1.2 (CI₉₅ 0.2 - 6.1). The number of males within the study was small and the possibility of a Type II error is present.

Using the appropriate measure based on all recurrences over the entire follow-up period as described previously, the odds ratios for women are calculated to be greater than one for all smoking variables including smoking before diagnosis (Table 9B). This provides additional evidence to support a hypothesis that smoking is not only a risk factor for development of Crohn's disease but also for ongoing disease activity in women.

TABLE 9A

Odds ratios for recurrence within 5 years by smoking history and gender

		Recurrence		Odds Ratio (CI ₉₅)
		Yes	No	
Females				
<u>Smoked after surgery</u>				
	Yes	26	40	2.8 (1.2 - 6.4)
	No	9	40	
Males				
<u>Smoked after surgery</u>				
	Yes	6	17	1.2 (0.2 - 6.1)
	No	8	26	

TABLE 9B
Odds ratios for recurrence
by smoking history and by gender

Females

(b) Smoking status	Recurrence		Odds Ratio
	Yes	No	
<u>1) before diagnosis</u>			
Yes	46	29	3.0
No	14	27	
<u>2) at diagnosis</u>			
Yes	45	25	3.5
No	15	30	
<u>3) before surgery</u>			
Yes	44	26	3.2
No	16	31	
<u>4) after surgery</u>			
Yes	44	22	4.0
No	16	33	

Males

Smoking status	Recurrence		Odds Ratio
	Yes	No	
<u>1) before diagnosis</u>			
Yes	13	23	0.6
No	11	11	
<u>2) at diagnosis</u>			
Yes	12	15	1.3
No	12	19	
<u>3) before surgery</u>			
Yes	14	16	1.6
No	10	18	
<u>4) after surgery</u>			
Yes	11	12	1.5
No	13	22	

Life tables constructed for women demonstrate significant differences for females who smoked compared to non-smoking females (Figure 3). Among women who smoked after surgery, the proportion who required a second operation at 5 and 10 years was 40% and 76% respectively, compared to 17% and 37% for women who did not smoke. The differences between the cumulative proportion of women smokers versus non-smokers was 23% at 5 years (CI₉₅ 5.3 - 39.5%) and 39% (CI₉₅ 20-58%) at 10 years.

Not shown are similar life tables which were constructed for men. There were no differences in the curves for men who smoked compared to men who didn't smoke.

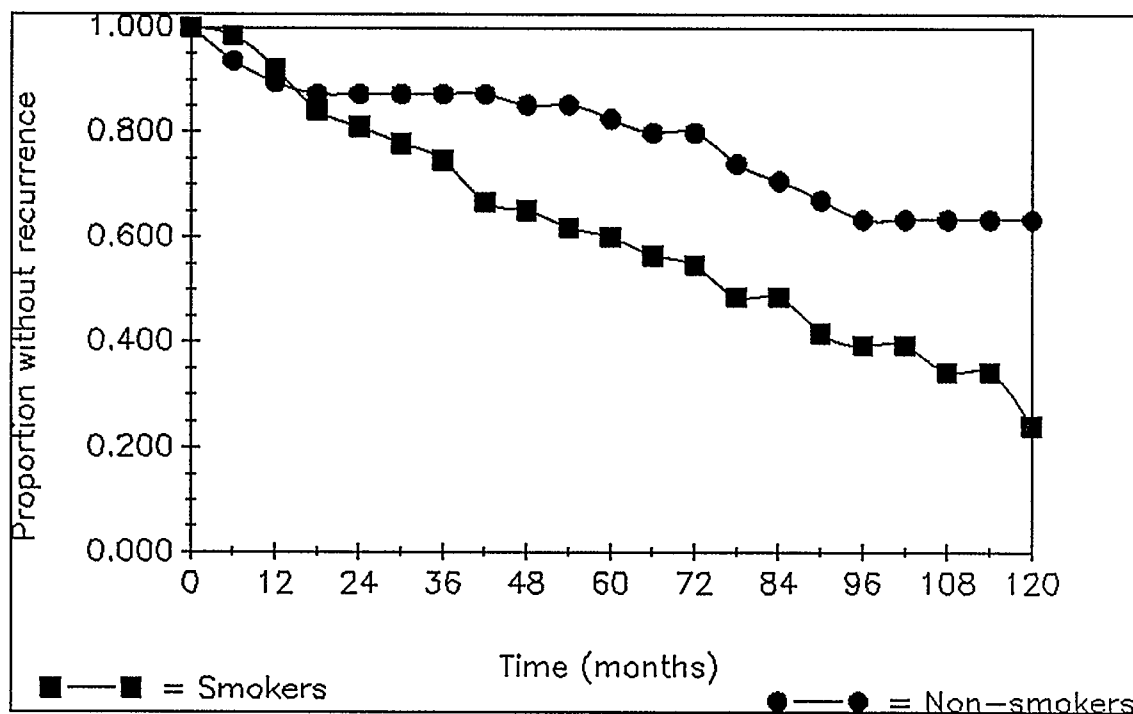


Figure 3 Five and 10 year recurrence for women who smoked (40%, 76%) compared to non-smokers (17%, 37%) following surgery. Five year difference = 23% (CI₉₅ 5.3 - 39.5); 10 year difference = 39% (CI₉₅ 20 - 58).

The next analysis separated patients by disease location and smoking activities after surgery and is demonstrated in Table 10. Odds ratios are greater than one for all disease locations. For patients with small bowel disease the odds ratio for recurrence for smokers after surgery compared to non-smokers was of considerable magnitude (4.5), but for ileocecal disease the magnitude of the odds ratio was of a much lower degree (1.9). Even though the odds ratio for recurrence after surgery for disease confined to the large intestine was large (3.4), the small number of patients in this category made any characterization of the effect of smoking on colonic disease tentative.

TABLE 10
Odds ratios for recurrence
by smoking history and disease location

		Recurrence		Odds Ratio	
		Yes	No		
SI*	<u>smoking status</u>				
	<u>before diagnosis</u>				
	Yes	24	26	3.1	
	No	5	18		
	<u>at diagnosis</u>				
	Yes	22	18	4.3	
	No	7	26		
	<u>before surgery</u>				
	Yes	22	18	4.3	
	No	7	26		
	<u>after surgery</u>				
	Yes	20	14	4.5	
	No	9	30		
	ILC*	<u>before diagnosis</u>			
		Yes	27	20	1.3
		No	18	18	
<u>at diagnosis</u>					
Yes		27	17	1.8	
No		18	21		
<u>before surgery</u>					
Yes		29	20	1.6	
No		16	18		
<u>after surgery</u>					
Yes		28	17	1.9	
No		17	20		

TABLE 10 (continued)
Odds ratios for recurrence
by smoking history and disease location

LB*		Recurrence		Odds Ratio
		Yes	No	
	<u>smoking status</u>			
	<u>before diagnosis</u>			
	Yes	8	6	1.3
	No	2	2	
	<u>at diagnosis</u>			
	Yes	8	5	2.2
	No	2	3	
	<u>before surgery</u>			
	Yes	7	4	2.1
	No	3	4	
	<u>after surgery</u>			
	Yes	7	3	3.4
	No	3	5	

* SI = Small Intestine, ILC = Ileocecal, LB = Large Intestine

Table 11 displays the data for smoking and recurrence in patients grouped by sex and disease location. The odds ratios for women are greater than one for all disease locations. The high odds ratio (9.2) for recurrence of small bowel disease amongst women who smoked after surgery suggests a particularly strong smoking effect on small bowel disease. The effects of cigarette smoking on recurrence of disease at specific sites in men are necessarily inconclusive because of small numbers of patients in the subgroups.

TABLE 11

Odds ratios for recurrence
by gender, smoking and disease location

<u>Location*</u>	<u>Smoked after surgery</u>	<u>Recurrence</u>		<u>Odds Ratio</u>
		Yes	No	
WOMEN				
SI	Yes	16	8	9.2
	No	3	16	
ILC	Yes	23	11	2.6
	No	11	14	
LB	Yes	5	3	2.2
	No	2	3	
MEN				
SI	Yes	4	6	3.2
	No	3	16	
ILC	Yes	5	6	0.8
	No	6	6	
LB	Yes	2	0	
	No	1	2	

* SI = Small Intestine, ILC = Ileocecal, LB = Large Intestine

If cigarette smoking carries a risk for recurrence, it would be of interest for patient education to demonstrate that smokers who quit after surgery have less recurrence than patients who continue to smoke. Women who smoked before their first surgery were separated into two groups, those who continued to smoke following surgery (62 patients) and those who ceased smoking (5 patients). A life table was calculated and the results are presented graphically in Figure 4. Inferences from this graph should be made with caution as one group (those that quit) is very small. A larger number of patients in the quitting group would be necessary to draw any valid conclusions.

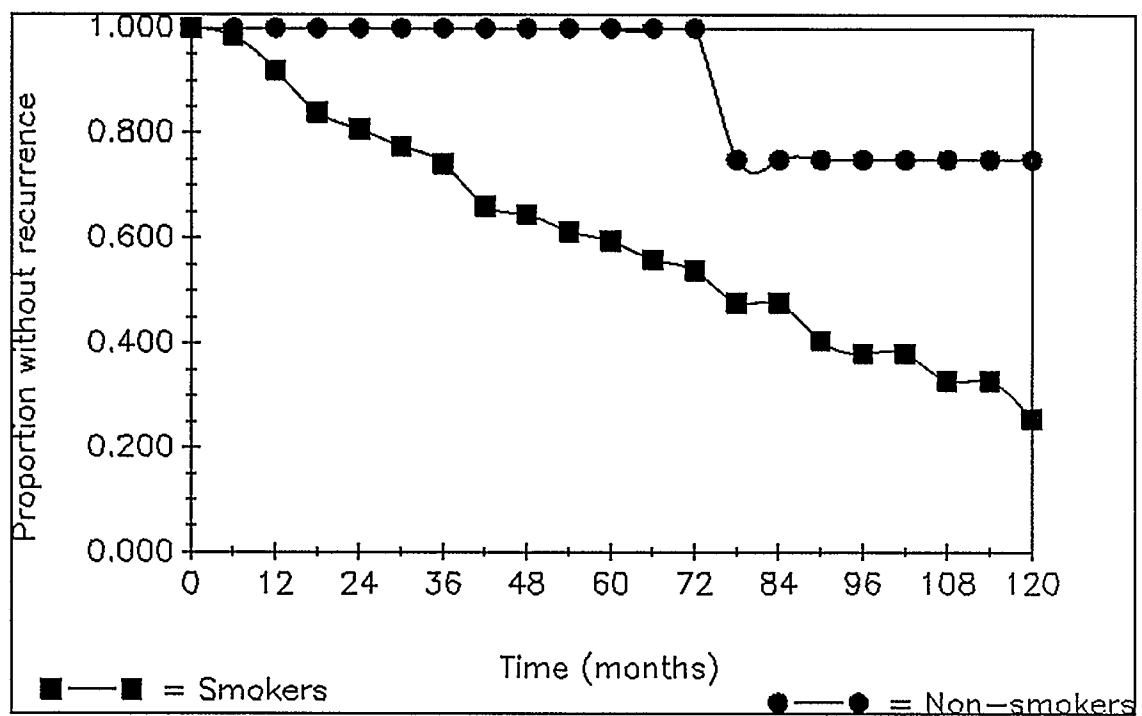


Figure 4 Five and 10 year recurrence for women who smoked following surgery (41%, 74%) compared to women who quit smoking (0, 25%). Note that one group contains only 5 patients.

To test Hypothesis #4 "Amongst those who have repeat resections, cigarette smokers have a shorter time to recurrence than non-smokers", all patients with recurrence were grouped and the average time to surgery for smokers as compared to non-smokers was calculated. The mean time to recurrence for smokers was 58.4 ± 52.4 months compared to 47.9 ± 39.1 months for non-smokers. These differences are not significant ($P = 0.459$). Mean time to recurrence is a rather crude measurement and the standard deviations were large.

2. Influence of oral contraceptive use (Tables 12,13).

The second hypothesis dealt with the effect of oral contraceptive use on recurrence and stated "Users of oral contraceptives have a greater risk of recurrence following surgery for Crohn's disease than non-users". Seventy percent of the 116 women in the sample used oral contraceptives (OCP) at some time. The breakdown of their usage is demonstrated in Table 12. Respondents were asked to characterize their OCP usage in relation to their disease. Specific variables were created for the use of OCP's: 1) prior to disease onset, 2) at time of diagnosis, 3) before surgery, and 4) after surgery. Many of the women in the sample were over age 45 at the time of the first surgery and at that time were either approaching menopause or may have already had sterilization. In fact no patient over age 36 took oral contraceptives after surgery. Therefore the analysis is confined to women who were less than age 35 at the time of first surgery.

TABLE 12

Oral contraceptive use by 116 women, all ages

	Number responding	Yes
Ever used oral contraceptives	115/116	80 (70%)
Used before disease diagnosed	115/116	62 (54%)
Used at the time of diagnosis	115/116	37 (32%)
Used before first surgery	114/116	26 (23%)
Used after first surgery	115/116	37 (32%)

Oral contraceptive use by women, ages 16-35

	Number responding	Yes
Ever used oral contraceptives	87/87	71 (82%)
Used before disease diagnosed	87/87	53 (61%)
Used at the time of diagnosis	87/87	32 (37%)
Used before first surgery	86/87	24 (28%)
Used after first surgery	87/87	36 (41%)

Construction of 2 x 2 tables for recurrence based on oral contraceptive use at the time of surgery were prepared. Risk ratios are presented in Table 13. The variable of interest for hypothesis testing is for OCP use following surgery. There was no support for the hypothesis that women who use OCP have a greater risk of recurrence than non-users since the odds ratio for recurrence in women who used OCP following surgery compared to non-users was not greater than unity.

Since there was no support for the hypothesis, one could argue that no additional analysis should be carried out. It would be unfortunate, however, not to take the opportunity to examine the data in a preliminary fashion in order to generate new hypotheses for future studies. As can be seen in Table 13 the odds ratios for recurrence in oral contraceptive users were all less than one. Since Hypothesis #2 was not accepted, calculation of time to surgery for oral contraceptive users compared to non-oral contraceptive users was not performed (Hypothesis #4).

TABLE 13

Odds ratios for recurrence in oral contraceptive users 16-35 years of age by history of use

Used oral contraceptives:	Recurrence		Odds ratio
	Yes	No	
before diagnosis	Yes	24	0.6
	No	29	
at the time of diagnosis	Yes	20	0.4
	No	14	
before first surgery	Yes	12	0.6
	No	20	
after first surgery	Yes	32	0.4
	No	23	

3. Influence of cigarette smoking and oral contraceptive use (Table 14).

With hypothesis #1 supported but hypothesis #2 rejected, there was some question as to whether or not to test hypothesis #3 which stated that oral contraceptive use might have an interaction effect on the risk associated with cigarette smoking, based on a multiplicative model. The data provided evidence indicating that the effect of cigarette smoking was evident in women. Since others have also found that the risk from cigarette smoking for development of Crohn's disease was increased in women, further exploratory analysis of the data was carried out.

Two by two tables (Table 14) were constructed separating women age 16 to 35 into 2 groups based on their use of oral contraceptives following surgery. As can be seen the odds ratio for recurrence in women who smoked after surgery is more than three times higher in oral contraceptive users compared to non-users. This non-uniformity of the odds ratio over oral contraceptive strata suggests interaction on a multiplicative scale.

TABLE 14

Odds ratios for recurrence in women who smoked
after surgery by oral contraceptive use

Used oral contraceptives:

		Recurrence		Odds ratio
		Yes	No	
Smoked after surgery	Yes	12	9	12.7
	No	1	14	

Did not use oral contraceptives:

		Recurrence		Odds ratio
		Yes	No	
Smoked after surgery	Yes	21	7	3.7
	No	10	13	

6: LIMITATIONS OF THE STUDY:

The overall response rate was 70% and of those patients who were alive and had valid addresses, over 90% responded. There are no apparent important differences between the responders and the non-responders except that there was a larger proportion of males in the non-responder category than women. Since smoking and recurrence rates in male responders might differ from those in male non-responders, the data were analyzed separately for males and females.

The study is a retrospective study which relies heavily on patient recall of surgery, cigarette smoking and oral contraceptive use. It seems unlikely, however, that patients would have difficulty in recalling whether or not they had a second operation for their Crohn's disease. Moreover, the surgical dates provided by the subjects were confirmed against hospital records and the 6 cases for which the actual date of surgery was not available were excluded from the life table analysis. Since the study is based on only one hospital, the possibility of inter-hospital differences does not arise.

The ability of patients to confirm smoking history and oral contraceptive history is less clear. We had no opportunity of validating the patient's recall of such life style issues. Since the questionnaire was clearly designed to ascertain smoking and oral contraceptive usage, it is possible those subjects who had recurrence may have been biased towards over- or underestimating the amount of cigarettes smoked and oral contraceptives used. We made no attempt to determine the type of cigarette and oral contraceptive used and thus are unable to stratify on the basis of nicotine or estrogen content.

7: DISCUSSION:

Crohn's disease is a chronic inflammatory condition characterized by remissions and recurrences. To date studies of recurrence have focused on the role of disease location and duration of symptoms. Medical therapy has been shown to have no role to play in either prophylaxis or prevention of recurrence. This study attempts to ascertain whether or not two "life style" issues, smoking and use of oral contraceptives, have an impact on recurrence. Holdstock et al (43) suggested that cigarette smoking may have a role to play in frequency of clinical recurrences. Rhodes and associates (58) reported that some women achieved remission with cessation of contraceptive use.

Before turning to an examination of the hypotheses and results, a few comments as to the generalizability of this study in relationship to other studies in the literature are in order. In this study the cumulative recurrence rate was 28% at five years and 56% at ten years. This is in general agreement with previous work by Lock et al (27) and somewhat lower than that of Greenstein and co-workers (24) who used a broader definition of recurrence which included recurrence of symptoms confirmed by radiology. The National Cooperative Crohn's Disease Study (25) reported a 50% recurrence rate by 10 years.

Seventy-one percent of patients in the study smoked at one time in their lives. These percentages are in agreement with that of Sommerville et al(40) as 73% of patients with Crohn's disease in his sample smoked. In this study by the time of surgery 45% of men and 57% of women were smoking. Few patients who smoked before surgery quit smoking following surgery. Evaluation of the data

supports the initial hypotheses that smokers would be more apt to require a second surgery than non-smokers. This hypothesis is supported by the calculation of odds ratios and preparation of life tables. The calculated odds ratio for recurrence in smokers compared to non-smokers was 2.2. The confidence interval (1.1 - 4.3) is reasonably narrow for a clinical study and would require the addition of many more patients to acquire more precision. Evidence from further analysis of the data suggests that not only is cigarette smoking a risk factor for recurrence but that the effect may be dose dependent.

An unexpected finding was the suggestion of an interaction between oral contraceptive use and smoking as a risk factor for recurrence. This is not the first time that gender differences in relation to cigarette smoking as a risk factor for Crohn's disease have been reported. Benoni and Nilsson (64) also found that smoking as a risk factor for development of Crohn's disease appeared to be more important in women than in men. She hypothesized that oral contraceptive usage might explain this but in this study some evidence has been presented which does not support this theory. It is important to note that the evidence of possible interaction is based on small groups of patients. Minor errors in classifying patients as to their oral contraceptive use (possible in a retrospective study) would have a major effect in the calculation of the odds ratios and confidence intervals.

The initial hypothesis did not include any suggestion that the effect of cigarette smoking after surgery would be limited to any specific gastrointestinal site. In reviewing the analysis of subgroups stratified by disease location, however, there is some suggestion that the effect might be site specific. These data should

be interpreted cautiously as the large intestine group was particularly sparse in this study. There is no evidence in the literature to suggest why smoking should have an effect primarily on the small bowel. In fact in the study of Sommerville et al(40) of smoking as a risk factor for development of Crohn's disease, only ileocecal and large bowel disease were associated with smoking. Since there is little understanding of the actual pathophysiology involved in Crohn's disease, one could indulge in a variety of speculations as to why the effect on small bowel was detected. Investigators in the past have speculated that the condition that we know as Crohn's disease may represent a variety of diseases which evoke similar responses from the gut. The finding of a site specific risk factor would add credence to this theory. Another possibility would be that the putative toxic substance in cigarette smoke becomes attenuated or diluted as it passes through the gastrointestinal tract and no longer is toxic by the time it reaches the large intestine. This might be analogous to that suggested for bladder cancer in which a substance from cigarette smoke is absorbed into the systemic circulation and concentrated in the urine.

It is important to consider alternative explanations for the finding of increased recurrence amongst smokers. One possibility is that the association arose by chance. Potential safeguards against this explanation include 1) the hypothesis was clearly stated in advance and 2) the significance testing suggests that the probability that this was a chance finding is low. The study population is similar to other published studies with similar 5 and 10 year cumulative recurrences and generally identical distribution by disease location.

Another explanation for the finding would be that cigarette smoking is not a risk factor per se but rather is a marker for severe disease. In this scenario patients with Crohn's disease smoke because it relaxes them and suppresses their appetite which in turn might reduce abdominal pain. This is a more difficult hypothesis to reject since the odds ratios for smokers are generally consistent across gender and disease location. However, the confidence intervals are only narrow for women with small bowel disease although a larger study with more patients might identify other groups of patients. The preliminary data presented which suggests a dose related effect would also argue against this hypothesis.

Finally, with respect to smoking one should consider whether or not the difference found in cumulative recurrence between smokers and non-smokers is clinically significant. In the general analysis there was a difference of 16% between the cumulative proportions at 5 years which rose to 41% at 10 years. Confidence intervals for these differences while still demonstrating statistical significance suggest that the effect of stopping smoking following surgery might be as minimal as 2% or as high as 50-60%. A prospective clinical trial might answer some of the questions as to clinical relevance but ethically it would be difficult to justify a study in which a group of patients were encouraged to continue smoking. As well many patients who are told to stop smoking are unable to do so. In this study only 5 women could be identified as having stopped smoking after surgery.

There was little support for the hypothesis that oral contraceptive use by itself increased the risk of recurrence or shortened the time to recurrence.

Analysis of the findings suggest in fact that a lower risk of recurrence for women taking oral contraceptives was possible. There was evidence for an interaction between cigarette smoking and oral contraceptive use with oral contraceptive use altering the risk related to cigarette smoking. This study was not designed to examine this possibility and any inferences from this data should be interpreted with caution.

The most likely explanation for the unexpected finding that oral contraceptive use appeared to be protective is that of selection bias. Oral contraceptives could appear to be protective if 1) women who recently had surgery were feeling well and wished to avoid pregnancy by taking oral contraceptives or 2) women who were not well following surgery did not receive oral contraceptives as their physician did not wish to further complicate their management. Alternative explanations against a selection bias would be that women who feel well are less likely to take oral contraceptives and more likely to begin a family. Ill patients may take oral contraceptives to prevent complicating their disease with a pregnancy. To evaluate this further a second study with a new questionnaire to assess possible reasons for using oral contraceptives could be carried out.

In conclusion, a retrospective study of a cohort of patients who underwent surgery for Crohn's disease suggests that the risk of recurrence, defined as the need for second surgery, is increased in women who smoke. The effect in women is most apparent in those who have disease confined to the small intestine. Using life table analysis it was possible to confirm the hypothesis that patients who smoked after surgery had an increased risk of recurrence compared

to non-smokers.

No support could be demonstrated for the hypothesis that oral contraceptive use had a deleterious effect on recurrence rates. An interaction between smoking and oral contraceptive use was suggested. Additional studies to examine the hypothesis that oral contraceptive use is protective or represents a marker for benign disease should be carried out.

Treatment of Crohn's disease remains a complex challenge for the physician. In addition to considering therapeutic options it would appear that physicians should consider the impact of smoking on disease activity when treating patients.

REFERENCES

1. Crohn BIB, Ginzburg L, Oppenheimer GD. Regional Ileitis: A pathological and clinical entity. *JAMA* 1932;99:1323-1329.
2. Calkins BM, Mendeloff AL. Epidemiology of inflammatory bowel disease. *Epidemiol Rev* 1986;8:60-91.
3. Sandler RS, Golden AL. Epidemiology of Crohn's disease. *J Clin Gastroenterol* 1986;2:160-165.
4. Binder V, Hendriksen C, Kreiner S. Prognosis in Crohn's disease-based on results from a regional patient group from the county of Copenhagen. *Gut* 1985;26:146.
5. Hospital Morbidity 1981-1982, 1982-1983. In: *Catalogue 82-206 Annual*. Ottawa: Statistics Canada, 1983:Table 2.
6. Calkins BM, Lilienfeld DE, Mendeloff AL, Gerland CF. Trend in the incidence of ulcerative colitis and Crohn's disease. *Dig Dis Sci* 1984;29:913-920.
7. Walker-Smith JA, Benfield GFA, Montgomery RD, et al. Chronic inflammatory bowel disease immigrants in the United Kingdom. In: McConnell R, Rozen P, Langman M, Gilat T, eds *Frontiers in Gastrointestinal Research: The Genetics and Epidemiology of Inflammatory Bowel Disease*. Basel: Karger, 1986:118-134.
8. Acheson ED. The distribution of ulcerative colitis and regional enteritis in United States veterans with particular reference to the Jewish religion. *Gut* 1960;1:291-293.
9. Monk M, Mendeloff AL, Siegel CI, Lilienfeld A. An epidemiological study of ulcerative colitis and regional enteritis among adults in Baltimore: I. Hospital incidence and prevalence, 1960-1963. *Gastroenterology* 1967;53:198-210.
10. Gilat T, Ribak J, Benaroya Y, Zemishlany Z, Weissman I. Ulcerative colitis in the Jewish population of Tel-Aviv-Jafo I. *Epidemiology. Gastroenterology* 1974;66:335-342.
11. Summers RW, Switz DM, Sessions JT Jr, et al. National Co-operative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979;77:847-869.
12. Van Hees PAM, Van Lier HJJ, van Elteren PH, et al. Effect of sulphasalazine in patients with active Crohn's disease: A controlled double-blind study. *Gut* 1981;22:404-409.

13. Present DH, Korelitz BI, Wisch N, et al. Treatment of Crohn's disease with 6-mercaptopurine: a long-term randomized double-blind study. *N Engl J Med* 1980;302:981-987.
14. Ursing B, Alm T, Barany F, et al. A comparative study of metronidazole and sulfasalazine for active Crohn's disease. The cooperative Crohn's study in Sweden. *Gastroenterology* 1982;83:550.
15. Vessey M, Jewell D, Smith A, Yeates D, McPherson K. Chronic inflammatory bowel disease, cigarette smoking, and use of oral contraceptives: findings in a large cohort study of women of childbearing age. *Br Med J* 1986;292:1101-1103.
16. Clark ML. Role of nutrition in inflammatory bowel disease: An overview. *Gut* 1986;27 S1:72-75.
17. Harries AD, Jones LA, Danis V, et al. Controlled trial of supplemented oral nutrition in Crohn's disease. *Lancet* 1983;1(8330):887-890.
18. Fielding JF, Cooke WT, Alexander-Williams J. The incidence of recurrence in Crohn's disease. *Surg Gynecol Obstet* 1972;134:467-469.
19. Alexander-Williams J, Haynes IG. Conservative operations for Crohn's disease of the small bowel. *World J Surg* 1985;9:945-950.
20. Lennard-Jones JE, Stadler GA. Prognosis after resection of chronic regional ileitis. *Gut* 1967;8:332-336.
21. Korelitz BI. Therapy of inflammatory bowel disease, including use of immunosuppressant agents. In: Farmer RG, ed *Clinics in Gastroenterology*. London: W.B. Saunders Company, 1980:331-349.
22. De Dombal FT, Burton I, Goligher JC. Recurrence of Crohn's disease after primary excisional surgery. *Gut* 1971;12:519-527.
23. Higgins CS, Allan RN. Crohn's disease of the terminal ileum. *Gut* 1980;21:993-940.
24. Greenstein AJ, Sachar DB, Pasternack BS. Reoperation and recurrence in Crohn's colitis and ileocolitis. *N Engl J Med* 1975;293:685-690.
25. Mekhjian HS, Sweitz DM, Watts HD, Deren JJ, Katon RM, Beman FM. National Cooperative Crohn's Disease Study: factors determining recurrence of Crohn's disease after surgery. *Gastroenterology* 1979;77:907-913.
26. Farmer RG, Hawk WA, Turnbull RB Jr. Clinical patterns in Crohn's disease: A statistical study of 615 cases. *Gastroenterology* 1975;68:627-635.

27. Lock MR, Farmer RG, Fazio VW. Recurrence and reoperation for Crohn's disease. *N Engl J Med* 1981;304:1586-1588.
28. Farmer RG, Whelan G, Fazio VW. Long-term follow-up of patients with Crohn's disease. *Gastroenterology* 1985;88:1818-1825.
29. Whelan G, Farmer RG, Fazio VW, Goormastic M. Recurrence after surgery in Crohn's disease. Relationship to location of disease (clinical pattern) and surgical indication. *Gastroenterology* 1985;88:1826-1833.
30. Nugent FW, Veidenheimer MC, Meissner WA, Haggitt RC. Prognosis after colonic resection for Crohn's disease of the colon. *Gastroenterology* 1973;65:398-402.
31. Rampton DS, Sladen GE. Relapse of ulcerative proctocolitis during treatment with non-steroidal anti-inflammatory drugs. *Postgraduate Medicine* 1981;57:297-299.
32. Korelitz BI, Present DH, Alpert LI, Marshak RH, Janowitz HD. Recurrent regional ileitis after ileostomy and colectomy for granulomatous colitis. *N Engl J Med* 1972;287:110-115.
33. Hellers G. Crohn's Disease in Stockholm County. *Act Chir Scandinavia* 1979;Supp 490.
34. Sachar DB, Wolfson DM, Greenstein AJ, Goldberg J, Styczynski R, Janowitz HD. Risk factors for post-operative recurrence of Crohn's disease. *Gastroenterology* 1983;85:917-921.
35. Speranza V, Simi M, Leardi S, Del Papa M. Recurrence of Crohn's disease after resection. Are there any risk factors?. *J Clin Gastroenterol* 1986;8:640-646.
36. Softley A, Myren J, Clamp SE, Bouchier AD, Watkinson G, DeDombal FT. Factors affecting recurrence after surgery for Crohn's disease. *Scand J Gastroentol* 1988;23 (supp 144):31-34.
37. Harries AD, Baird A, Rhodes J. Non-smoking: a feature of ulcerative colitis. *Br Med J* 1982;284:706.
38. Logan RFA, Edmond M, Somerville KW, Langman MJS. Smoking and ulcerative colitis. *Br Med J* 1984;288:1307.
39. Rampton DS, McNeil NI, Sarnar M. Analgesic ingestion and other factors preceding relapse in ulcerative colitis. *Gut* 1983;24:187-189.
40. Somerville KW, Logan RFA, Edmond M, Langman MJS. Smoking and Crohn's disease. *Br Med J* 1984;289:954-956.

41. Franceschi S, Panza E, LaVecchia C, Parazzini F, Decarli A, Porro GB. Nonspecific inflammatory bowel disease and smoking. *Am J Epidemiol* 1987;125:445-452.
42. Lindberg E, Tysk C, Andersson K, Järnerot G. Smoking and inflammatory bowel disease, a case control study. *Gut* 1988;29:352-357.
43. Holdstock G, Savage D, Harman M, Wright R. Should patients with inflammatory bowel disease smoke?. *Br Med J* 1984;288:362-362.
44. Duffy LC, Zielezny M, Marshall J, Byers T, Weiser M, Graham S. Cigarette smoking and risk of clinical relapse in ulcerative colitis and Crohn's disease (abstr). Presented at the 1988 Annual Meeting of the Society for Epidemiological Research, Vancouver, British Columbia, Canada.
45. Tedesco FJ, Volpicelli NA, Moore FS, . Estrogen and progesterone associated colitis: A disorder with clinical and endoscopic features mimicking Crohn's colitis. *Gastro Endo* 1982;28:247-249.
46. Hanauer SB, Silverstein MD, Evans AA, Kirsner JB. A case control study of smoking in inflammatory bowel disease compared to the irritable bowel syndrome (abstr). *Clin Res* 1984;32:223A.
47. Calkins B, Lilienfeld A, Mendeloff A, Garland F. Some factors in ulcerative colitis and Crohn's disease in Baltimore (abstr). *Am J of Epidemiology* 1984;120:498.
48. Penny WJ, Penny E, Mayberry JF, et al. Mormons, smoking, and ulcerative colitis. *Lancet* 1983;2:1315.
49. Tobin NV, Logan RFA, Langman MJS, McConnell RB, Gilmore IT. Cigarette smoking and inflammatory bowel disease. *Gastroenterology* 1987;93:316-321.
50. Smith MB, Lashner BA, Hanauer SB. Smoking and inflammatory bowel disease in families. *Am J Gastroenterol* 1988;83:407-409.
51. Farmer RG, Michener WM, Mortimer EA. Studies of family history among patients with inflammatory bowel disease. *Clin Gastroenterol* 1980;9:271-280.
52. Cope GF, Heatley RV, Kelleher J. Smoking and colonic mucus in ulcerative colitis. *Br Med J* 1986;293:481.
53. Gerrard JW, Hein DC. Immunoglobulin levels in smokers and non-smokers. *Ann Allerg* 1980;44:261-262.
54. Royal college of general practitioners: Oral Contraceptives and Health. An interim report from the oral contraceptive study of the Royal college of general practitioners. New York: Pitman Medical, 1974.

55. Ramcharan S, Pellegrin FA, Ray F, Hsu J-P. The Walnut Creek Contraceptive Drug Study: A prospective study of the side effects of oral contraceptives. US Government Printing Office Publication No. (NIH) 81-564,1981;Volume 3.
56. Bernardino ME, Lawson TL. Discrete colonic ulcers associated with oral contraceptives. *Dig Dis Sci* 1976;21:503-506.
57. Camilleri M, Schafner K, Chadwick VS, Hodgson HJ, Weinbren K. Periportal sinusoidal dilatation, inflammatory bowel disease and the contraceptive pill. *Gastroenterology* 1981;80:810-815.
58. Rhodes JM, Cickel R, Allan RN, Hawker PC, Dawson J, Elias E. Colonic Crohn's disease and use of oral contraception. *Br Med J* 1984;288:595-596.
59. Lesko SM, Kaufman DW, Rosenberg L, et al. Evidence for an increased risk of Crohn's disease in oral contraceptive users. *Gastroenterology* 1985;89:1046-1049.
60. Vessey M, Jewell D, Smith A, Yeates D, McPherson K. Chronic inflammatory bowel disease, cigarette smoking, and use of oral contraceptives: findings in a large cohort study of women of childbearing age. *Br Med J* 1986;292:1101-1103.
61. Rosner B. *Fundamentals of Biostatistics*. Boston:Duxbury Press, 1986:319-322.
62. Anderson RP, Bonchek LI, Grunkemeier GL, Lambert LE, Starr A. The analysis and presentation of surgical results by actuarial methods. *J of Surg Res* 1974;16:224-230.
63. Devroede G, Taylor WF. On calculating cancer risk and survival of ulcerative colitis patients with the life table method. *Gastroenterology* 1976;71:505-509.
64. Benoni C, Nilsson A. Smoking habits in patients with inflammatory bowel disease. A case-control study. *Scand J Gastroentol* 1987;22:1130-1136.

APPENDIX 1
USED FOR CHART ABSTRACTION

1. NAME: _____
(LAST) (FIRST) (MIDDLE)

2. MAIDEN NAME: _____
(IF APPLICABLE)

3. PHONE: _____
(WORK) (RESIDENCE)

4. ADDRESS: _____

5. FOOTHILLS NUMBER: _____

6. NEXT OF KIN: _____

Phone # _____

7. SURGEON: _____ 8. GASTRO: _____

9. FAMILY MD: _____

10. DATE OF INFORMATION: _____

11. SEX: _____ 12. DOB:YY/MM/DD _____

13. YEAR OF SURGERY: _____

APPENDIX 1
USED FOR CHART ABSTRACTION

1. NAME: _____
(LAST) (FIRST) (MIDDLE)

2. MAIDEN NAME: _____
(IF APPLICABLE)

3. PHONE: _____
(WORK) (RESIDENCE)

4. ADDRESS: _____

5. FOOTHILLS NUMBER: _____

6. NEXT OF KIN: _____

- Phone # _____

7. SURGEON: _____
8. GASTRO: _____

9. FAMILY MD: _____

10. DATE OF INFORMATION: _____

11. SEX: _____
12. DOB:YY/MM/DD _____

13. YEAR OF SURGERY: _____

DETAILS OF SURGERY (_ OF _)

14. DATE OF SURGERY: _____

15. INDICATION FOR SURGERY:

OBSTRUCTION _____ PERFORATION _____

ABSCESS _____ FISTULA _____

INTRACTABLE _____ MEGACOLON _____

PERIANAL _____ OTHER _____

16. LOCATION OF DISEASE:

DUODENAL _____ RT COLON _____ ILEOCECAL _____

JEJUNUM _____ LT COLON _____ PANCOLON _____

ILEUM _____ RECTUM _____

17. TYPE OF SURGERY:

BYPASS _____ RESECTION _____

18. EMERGENCY/ELECTIVE ??

EMERGENCY _____ ELECTIVE _____

19. RESECTION:

COMPLETE _____ PARTIAL _____

20. LENGTH RESECTED: _____ CM

POST-OP CHARACTERISTICS:

21. DAYS IN HOSPITAL AFTER SURGERY _____

22. NEED FOR A SECOND OR (WITHIN 30 DAYS): YES NO

23. DEATH: YES NO

APPENDIX 2
COVERING LETTER

Dear _____

The Intestinal Disease Research Unit at the University of Calgary is currently following up patients who have had surgery for their Crohn's disease at the Foothills Hospital. Our records show that you were operated on for your Crohn's disease at the Foothill Hospital in _____. Dr. _____, who was involved in your care at that time, has given us permission to contact you. We enclose a questionnaire that will only take a few minutes of your time to complete and return to us.

All information received will be kept confidential. If you wish, a copy of the paper which will summarize the results of the study will be made available to you.

If you have any questions regarding the study please do not hesitate to contact me at 220-4500.

Yours truly,

Lloyd R, Sutherland MDCM, FRCP(C), FACP
Associate Professor of Medicine

APPENDIX 3

QUESTIONNAIRE FOR MALES

SECTION A: DEMOGRAPHIC AND SURGICAL INFORMATION

1. NAME: _____
(LAST) (FIRST) (MIDDLE)

3. ADDRESS: _____

3. PHONE: _____ (WORK) _____ (RESIDENCE)

4. Please confirm that you had an operation at the Foothills Hospital for Crohn's disease in _____

YES

NO

5. What year did you have your first symptoms of Crohn's disease?

19____ CAN'T REMEMBER

6. In what year was your Crohn's disease diagnosed?

19____ CAN'T REMEMBER

7. Was this the first operation you had for Crohn's Disease?

YES

NO

If YES, go to Question 9, if NO go to Question 8.

8. Where did you have your first operation, and in what year?

PLACE _____

YEAR _____

May we contact that hospital for your records?

YES

NO

9. Since your operation in _____ have you had any other operations for Crohn's disease

YES

NO

If YES, go to Question 8, if NO, go to Section B

10. Please list the place and years you have had additional surgery for Crohn's disease.

PLACE _____

YEAR _____

PLACE _____

YEAR _____

May we contact the hospital to obtain the records of these operations?

YES

NO

of I _____ authorize the release
(Your name)
my medical records to Dr. Lloyd R, Sutherland at the University of
Calgary.

(Signature)

(Witness)

(Date)

Would you like your name to be placed on the mailing list of the Intestinal
Disease Research Unit to be informed as to upcoming studies?

YES

NO

SECTION B: (MALES)

B-1. Have you ever smoked? For the purpose of this study, smoking is defined a smoking more than 5 cigarettes a week for more than a year.

YES

NO

If Yes, please answer the rest of the "B" questions. If No, thank you for your cooperation. Please return the completed questionnaire in the stamped envelope as soon as possible.

B-2. Did you smoke before your Crohn's disease was diagnosed?

YES

NO

B-3. Did you smoke at the time your Crohn's disease was diagnosed?

YES

NO

B-4. Did you smoke at anytime in the year prior to your first operation for Crohn's disease?

YES

NO

B-5. Did you smoke at anytime in the first year after you had your first operation for Crohn's disease?

YES

NO

Please indicate to the best of your memory your smoking history by placing an x in the appropriate box

Cigarettes smoked each day

Average number of cigarettes smoked each day

YEAR	0	1 - 10	11 - 20	21-30	31-50
1965					
1966					
1967					
1968					
1969					
1970					
1971					
1972					
1973					
1974					
1975					
1976					
1977					
1978					
1979					
1980					
1981					
1982					
1983					
1984					
1985					
1986					
1987					

APPENDIX 4

QUESTIONNAIRE FOR FEMALES

SECTION A: DEMOGRAPHIC AND SURGICAL INFORMATION

1. NAME: _____
(LAST) (FIRST) (MIDDLE)

2. MAIDEN NAME: _____
(IF APPLICABLE)

3. ADDRESS: _____

3. PHONE: _____ (WORK) _____ (RESIDENCE)

4. Please confirm that you had an operation at the Foothills Hospital for Crohn's disease in _____

YES

NO

5. What year did you have your first symptoms of Crohn's disease?

19____

CAN'T REMEMBER

6. In what year was your Crohn's disease diagnosed?

19____

CAN'T REMEMBER

7. Was this the first operation you had for Crohn's Disease?

YES

NO

If YES, go to Question 9, if NO go to Question 8.

8. Where did you have your first operation, and in what year?

PLACE _____

YEAR _____

May we contact that hospital for your records?

YES

NO

9. Since your operation in _____ have you had any other operations for Crohn's disease

YES

NO

If YES, go to Question 8, if NO, go to Section B

10. Please list the place and years you have had additional surgery for Crohn's disease.

PLACE _____

YEAR _____

PLACE _____

YEAR _____

May we contact the hospital to obtain the records of these operations?

YES

NO

of I _____ authorize the release
(Your name)
my medical records to Dr. Lloyd R, Sutherland at the University of
Calgary.

(Signature)

(Witness)

(Date)

Would you like your name to be placed on the mailing list of the Intestinal
Disease Research Unit to be informed as to upcoming studies?

YES

NO

SECTION B:

B-1. Have you ever smoked? For the purpose of this study, smoking is defined a smoking more than 5 cigarettes a week for more than a year.

YES

NO

If Yes, please answer the rest of the "B" questions. If No, thank you for your cooperation. Please return the completed questionnaire in the stamped envelope as soon as possible.

B-2. Did you smoke before your Crohn's disease was diagnosed?

YES

NO

B-3. Did you smoke at the time your Crohn's disease was diagnosed?

YES

NO

B-4. Did you smoke at anytime in the year prior to your first operation for Crohn's disease?

YES

NO

B-5. Did you smoke at anytime in the first year after you had your first operation for Crohn's disease?

YES

NO