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Corticosteroid or corticotrophin therapy in Crohn's disease (regional enteritis)

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SUMMARY Amongst 300 patients with Crohn's disease followed between 1944 and 1968, corticosteroids or corticotrophin was given to 124 patients, to 87 of them for more than 12 months. In the short-term assessment of 89 of these patients, 76% improved clinically within six months, but within 12 months 29% of these had relapsed. In the long term, the risk of operation each year for the patients treated with steroids was twice that of those not treated. There was a significantly increased mortality rate in the patients treated with steroids which in part was due to complications induced by this therapy for which no evidence of long-term benefit emerged from this study.

Initial reports suggested that therapy with corticotrophin (ACTH) might be beneficial in the treatment of Crohn's disease. Standley, Rosenberg, and Cleroux (1951) claimed excellent immediate responses in seven of the eight patients treated, discontinuing therapy after three or four weeks. Two of the patients remained symptomatically well over the following 12 months. They concluded that 'in cases resistant to the usual methods of treatment, maintenance therapy with corticotrophin or cortisone seems indicated to control symptoms'. Kirsner, Palmer, and Klotz (1952) treated four patients with severe chronic regional enteritis. They noted clinical improvement in three patients and considered 'the beneficial effect less pronounced than in ulcerative colitis'. Gray, Reifenstein, Benson, and Young (1951) were impressed by the dramatic effects in two patients and concluded that there was a good rationale for long-term maintenance therapy. A cautionary note was introduced by Sauer, Brown, and Dearing (1952) as the result of their study with ACTH in 12 patients. They wrote: 'the subjective improvement of these patients was not consistent enough to warrant any enthusiasm especially in view of the tendency towards remissions characteristic of regional enteritis with or without special types of treatment'.

More recently, Sparberg and Kirsner (1966) reported on long-term corticosteroid therapy for regional enteritis affecting the small intestine. Of 217 patients, 83 (38%) were so treated of whom 54 had had treatment for at least six months. In these 54 patients the initial response was considered excellent in 45 of the 58 courses, good in 11, and fair in two. At the end of six months, the response to these courses was considered excellent in 19, good in 10, fair in five, and poor in five, with 19 needing surgery. They commented: 'the response is variable and unpredictable'. Jones and Lennard-Jones (1966) reported on 30 patients treated with ACTH or prednisone and studied over 10 years. Twenty-two showed response, three going into remission, and 19 showing immediate improvement. However, follow up showed that eight subsequently underwent surgery and four had died. Seven still required treatment and three did not.

The lack of any conclusive reports as to the benefit of this type of therapy has not prevented its extensive use. Garlock (1967) commented that it was rare in his experience to encounter a patient with ileitis who had not been on steroid therapy. In his view, the use of steroid drugs

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should be considered as 'palliative conservative measures in preparation for the most desirable time for surgical intervention'. In this paper, we attempt to assess the short- and long-term effects of ACTH or corticosteroids and its place in therapy in regional enteritis.

Clinical Material and Methods

In general, steroid[1] therapy was administered: (1) for diffuse jejuno-ileitis in the absence of obstructive symptoms; (2) following re-operation for early recurrence, eg, 12-18 months after the initial operation; (3) for persistent disease activity (as indicated by low serum albumin levels, high serum seromucoids; Cooke, Fowler, Cox, Gaddie, and Meynell, 1958) and failure to attain clinical remission but with no indication for surgical resection; (4) to control diarrhoea, malaise, and disease activity in Crohn's colitis.

The type of therapy given is shown in Table I. The initial dosage of ACTH was 20 units twice a day intramuscularly, reducing after three to seven days to doses varying between 10 and 20 units daily. The initial dosage of oral corticosteroids was prednisone 10 mg tds or its equivalent, reducing to dosages between 5 and 15 mg daily or its equivalent. Any difference found between the results for ACTH and oral corticosteroids might lie in the effective dosage. The dosage of oral therapy was adjusted to a level which appeared to afford some control of symptoms whilst avoiding side effects, particularly that of water retention which the patients seemed particularly prone to develop at relatively low dosage.

Type of Therapy	*No. of Patients*	*Percentage of Group Treated with Steroids*
ACTH only	40	32
Oral steroids only	32	26
Prednisone	22	
Hydrocortisone or cortisone	7	
Other	3	
Oral steroids and ACTH	44	35
Rectal administration only	8	6

Table I *Pattern of therapy administered to 124 patients*

Three hundred patients with Crohn's disease were followed by one of us between 1944 and 31 December 1968. There were 143 men and 157 women. Of these, 124 received steroid therapy; 91 of 249 patients with small bowel involvement and 33 of 51 with large bowel disease. A significantly greater proportion of men with small-intestinal involvement received steroid therapy than women, 51 out of 117 men compared with 40 out of 132 women ($P < 0.02$).

Thirty-six (29%) received therapy for less than one year, 23 (18%) for periods between one and two years, and 65 (52%) for more than two years. Therapy was continuous in 77% and intermittent in 23% of the patients. Forty-seven (38%) had continuous therapy for a mean period of 5·5 years (range 2-14·7 yr). Just over half of the 124 patients received their treatment within one year of diagnosis.

In 89 patients, treatment had been initiated under our own supervision and these patients formed the group on whom the short-term effects of therapy were assessed. Of these 89, 71 patients had steroid therapy for more than 12 months, 13 were treated between six and 12 months, and five had treatment for less than six months. In the remaining patients, treatment had been initiated elsewhere before referral.

Response to steroid therapy was assessed in the short term by the clinical, haematological, and biochemical changes produced and in the long term by the operation and mortality rates.

The optimum clinical response within six months following initiation of therapy was considered 'good' if the patient became symptom free, 'fair' if the patient gained at least 7 lb in weight and had some symptomatic improvement (eg, decreased bowel action or decreased pain), and as 'none' if no change in symptoms and signs was detected.

Biochemical response was assessed from changes in the serum levels of four measurements, albumin, globulin, seromucoids, and alkaline phosphatase. Haematological response was determined by changes also in four measurements, the serum levels of haemoglobin, iron, folic acid, and vitamin B_{12}. Response in these two groups of laboratory investigations were designated as 'good' if at least three measurements had returned to normal, 'fair' if two did so, and as 'none' if only one or none did so.

Improvement may have taken place at any time during the first six months and not necessarily been maintained. Further assessment determining the relapses at six and 12 months after initiation of therapy has been made in those 68 patients who had shown an initial good or fair response to steroid therapy. Relapse was deemed to have occurred if excisional or by-pass surgery had taken place or if the patient had returned to a state of health equal to or worse than that just before the commencement of therapy.

SHORT-TERM RESULTS

Short-term responses are shown in Table II, and it will be seen that only 24% failed to improve

Assessment	*Good*	*Fair*	*None*
Clinical	14 (15·7%)	54 (60·7%)	21 (23·6%)
Biochemical	25 (28·1%)	38 (42·7%)	26 (29·2%)
Haematological	5 (5·6%)	48 (53·9%)	36 (40·4%)

Table II *The clinical, biochemical, and haematological assessments of short-term response to steroid therapy in 89 patients*

[1]Steroid refers to either corticosteroids or corticotrophin (ACTH).

clinically within six months of initiation of therapy; 29% of the patients showed no biochemical improvement and 40% no haematological change. The subsequent relapse rate at six and 12 months of those patients who had improved clinically is shown in Table III. Twenty-one per cent had relapsed at six months and 29% by 12 months. Relapses occurred less frequently in those patients who had experienced a good short-term response to therapy than those who had a fair response. There was no significant difference in the relapse rate at 12 months between those with large bowel and those with small intestinal disease. A relatively greater proportion of patients receiving ACTH improved than those on oral corticosteroids alone. They also did better than those patients started on ACTH and maintained on oral corticosteroids (Table IV). None of the five patients treated for less than six months responded. As a group those who showed a good response received therapy significantly sooner than those who merely improved ($P < 0.01$) whilst those who merely improved had therapy earlier than those who failed to respond (Table IV).

Clinical Response	*No. of Patients*	*Relapse Rate at*	
		Six Months	*Twelve Months*
Good	14	1 (7%)	1 (7%)
Fair	54	13 (24%)	19 (35%)
Combined improvement	68	14 (21%)	20 (29%)

Table III *The relapse rate at six months and at 12 months in the 68 patients showing improvement out of the 89 treated with steroid therapy in assessing short-term response*

Response	*No. of Patients*	*Treatment*			*Time from Diagnosis to Start of Therapy (mth)*		
		ACTH	*ACTH and Oral Steroids*	*Oral Steroids*	*Mean*	*SE*	*Range*
Good	14	8	4	2	19·14	9·44	0-106
Fair	54	28	17	9	56·17	10·22	0-280
None	21	1	8	12	91·33	20·54	0-307

Table IV *Short-term clinical response in relation to the type of therapy and to the time between diagnosis and initiation of therapy*

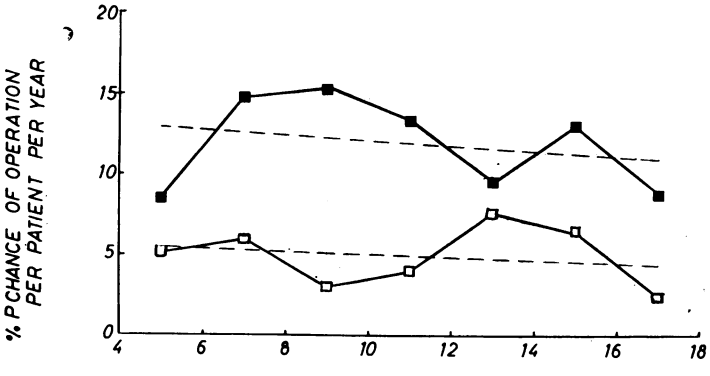

Fig. 1 *The risk of operation per year for the patients with small-intestinal involvement with steroid therapy (91 patients: ■) and without (185 patients: □).*

LONG-TERM RESULTS

Operation rates in the small intestine

All operations involving excisional or by-pass surgery were recorded from the time of diagnosis to 18 years later, together with the number of patients at risk in each year. Hence, the probability of any one patient having such an operation could be expressed as percentage chance of operation per patient per year. This was done for 249 patients with small-bowel involvement. Comparisons of the operation rates could thus be made between the 91 patients treated with steroids and the 158 not so treated with regard to the years at risk since diagnosis, for the years before the administration of steroids, and lastly, for years following the commencement of this therapy.

The mean number of operations per patient for the 91 patients treated with steroids and followed for a mean period of 11·8 years from diagnosis was 1·89 whilst for the 158 not so treated and followed for 12·5 years the mean number of operations was 1·38. When the operative rates for the two groups during the period of time between diagnosis and initiation of steroid therapy were compared, there was no significant difference, the operative rate per year for the steroid and non-steroid groups for each of the first two years being 51 and 45%, for the third and fourth 5 and 6%, and for the fifth and sixth years 10 and 5 % respectively.

The operation rates per patient per year for the years following diagnosis for the two groups are shown in Figure 1. The patients who received steroid therapy were not included in the calculations until therapy had been initiated. The slopes of the linear regression lines for the two groups do not significantly differ from zero ($P > 0.1$). (A similar result was reached using either Armitage's method for proportions or by weighted regression.) The mean percentage chance of operation per patient per year for the steroid treated group was 10·375 and for the untreated group 5·156; this difference is significant ($P < 0.05$). These results suggest that those who had received steroids had a significantly greater risk of having an operation at any time from four to 18 years after diagnosis. If all relevant operations are considered in addition to by-pass or excision, the patient treated with steroids had a 20% chance and those not treated 10% chance each year of surgical treatment. The difference was significant ($0.05 > P > 0.001$).

Operation rates in the large intestine

Operation rates were similarly determined from time of diagnosis to eight years later in 51 patients with large bowel disease and the rates of the 33 such patients who received corticosteroid therapy compared with those of the 18 patients who did not. The operative rate for these 51 patients with large bowel disease are shown in Fig. 2, and it will be seen that steroid therapy did not lessen the likelihood either of excision of the colon or of affecting the years since diagnosis at which it would be performed.

Mortality rates

Mortality rates were determined by reference to the Registrar General's life expectancy tables for 1951. Each patient was matched for age, sex, and years at risk from the onset of symptoms with a representative of the general population, and the expected mortality for the group determined for comparison with that which actually occurred (Prior, Fielding, Waterhouse, and Cooke, 1970). As it is not possible to assess mortality risk for those patients followed for less than one year the mortality rates were calculated in 295 patients only.

There was a significant increase in the number of deaths in patients with regional enteritis who were less than 40 years old at onset compared with the expected frequency (Table V). There was also a significantly greater number of deaths in the steroid-treated group compared with the untreated group (P < 0·001). There was no significant difference between the patients treated with steroids and those not treated who died in respect of age at diagnosis, length of follow up, and age at death. In men under the age of 40, the increased mortality observed was due to the deaths in the steroid-treated patients. It is of interest that of a group of 47 patients treated continuously for two to 14 years, the mortality rate of the 26 men was significantly more than expected (observed 6: expected 1·19; P < 0·001) whilst the mortality rate of the 21 women was not significantly different from that expected. Of the six deaths amongst the 26 men continuously treated for more than two years, two had cancer, one had chronic progressive jejunoileitis, and in the remaining three death was related to steroid administration. An increased mortality rate was also noted in the women under the age of 40 not treated with steroids. The numbers were insufficient to allow such comparisons of the mortality rates of patients with only the large bowel affected.

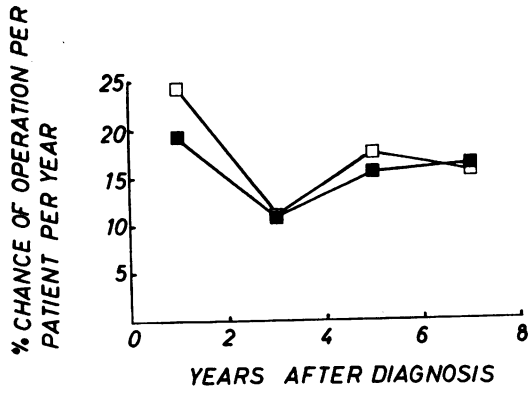

Fig. 2 *The risk of operation per year for patients with Crohn's colitis with steroid therapy (33 patients: ■) and without (18 patients: □).*

Group	No. of Patients	Deaths		Probability
		Expected	Observed	
1944-1968	295	25·66	53	<0·001
Men	142	15·30	34	<0·001
Women	153	10·36	19	<0·01
Onset < 40 years	219	6·679	29	<0·000000
<25 years	117	2·65	14	<0·001
25-39 years	102	3·97	15	<0·001
Men	99	3·635	18	<0·000000
Women	120	2·944	11	<0·000250
Onset > 40 years	76	19·079	24	0·155 (NS)
Men	39	11·665	16	0·132366 (NS)
Women	37	7·414	8	0·4627 (NS)
Steroid 1944-1968	121	6·35	24	<0·001
Men	64	3·86	19	<0·001
Women	57	2·49	5	>0·1 (NS)
Onset < 40 years	99	2·446	15	<0·000000
Men	51	1·482	12	<0·000000
Women	48	0·963	3	0·07623 (NS)
Onset > 40 years	22	3·907	9	<0·018
Men	13	2·378	7	<0·011073
Women	9	1·529	2	0·451833 (NS)
Non-steroid 1944-1968	174	19·31	29	<0·02
Men	77	11·441	15	>0·25 (NS)
Women	97	7·86	14	>0·012
Onset < 40 years	120	4·133	14	<0·000107
Men	48	2·153	6	<0·022740
Women	72	1·981	8	<0·001033
Onset > 40 years	54	15·10	15	0·544 (NS)
Men	27	9·287	9	0·581515 (NS)
Women	27	5·885	6	0·535676 (NS)

Table V *Comparison of observed and expected numbers of deaths by the Poisson distribution by treatment, age, and sex based on 1951 life tables*

CAUSE OF DEATH IN PATIENTS TREATED WITH STEROIDS

Twenty-four of the 124 patients treated with steroids died, a mortality approximately four times that expected in the normal population and two and a half times that experienced in patients not treated. The ready explanation for this finding might be that the more seriously ill patients had been put on steroids and therefore had unduly weighted the statistics. Such a suggestion cannot easily be refuted. However, the mortality of those 53 patients with onset of symptoms before 1951 and not treated with steroids was not significantly increased over the expected mortality (P = 0·07), and, amongst these, seen at the time when steroids were not available and electrolyte depletion was not so well understood, there were many seriously ill patients, often

with diffuse involvement, who are now well. The difficulties, however, of such retrospective comparisons are well exemplified by two of our cases (122 and 285).

A brother and sister, respectively aged 16 and 14 at the onset of their disorders, each had diffuse jejuno-ileitis and identical radiological appearances. Clinically, at onset the girl was more severely ill than the boy. She was treated with bed rest for nearly 12 months, needing laparotomy and by-pass at the age of 19, and gastrectomy for peptic ulcer at 21. She had had two children when she was 24 and 26, had completed a teacher's training course at 31, and is now aged 35 and teaching. Her brother failed to respond adequately to bed rest and found it difficult to accept restriction of his activities. He was treated with ACTH which enabled him to lead a more normal life but at no time did he lose the abdominal symptoms or hypoproteinaemia. He needed vagotomy and pyloroplasty for peptic ulcer at age 21. He died, aged 24, of carcinoma of the small intestine and histological evidence of active Crohn's disease.

Such examples make us reluctant to accept without reservation the ready explanation for the increased mortality amongst the steroid-treated patients.

In Table VI the causes of death of the 24 patients treated with steroids are listed, together with an assessment as to whether or not steroid therapy contributed to the fatal outcome. Four patients died as a consequence of malignant hypertension having been on ACTH (10 units daily) for nine months, one year, two years, and 10 years respectively. Two further patients in the series, both women, developed malignant hypertension after ACTH administration for six and three years respectively. With the curtailment and then eventual withdrawal of ACTH and the administration of hypotensive drugs for a short period, both became normotensive and have not so far manifested any more serious complications. Three patients developed haemorrhagic complications best described as thrombotic thrombocythaemia and died with uncontrollable haemorrhage from the bowel. Neither of these two complications was encountered in the patients not treated with steroids.

One patient (108) died after operation for gastrointestinal bleeding from a gastric ulcer on the greater curvature and it seems reasonable to attribute an ulcer at this site to steroid therapy. Lung abscess and monilia infection caused the death of case 64; these are accepted complications of long-term steroid therapy. Case 25, who perforated when not on steroids, developed postoperative adrenal failure. Lastly it could be argued as to the validity of including case 76, who had retention enemas daily for two months and was given massive hydrocortisone cover parenterally for two weeks following operation. He died of tuberculous bronchopneumonia; review of the preoperative chest films showed apparently healed tuberculosis of long standing. There was also a marked fall in blood pressure which responded to intravenous hydrocortisone so that mild adrenal failure was also present. If these 12 patients are considered as steroid-related deaths and excluded, then the mortality rate of the 124 treated patients shows no significant difference from those who did not receive steroids.

Case No.	*Sex*	*Age at Death*	*Cause of Death*	*Death Related to Steroid Therapy*
87	M	24	Malignant hypertension	Yes
30	M	24	Malignant hypertension	Yes
54	M	59	Malignant hypertension	Yes
9	M	28	Malignant hypertension	Yes
123	F	37	Haemorrhagic thrombocythaemia	Yes
3	M	29	Haemorrhagic thrombocythaemia	Yes
59	M	25	Haemorrhagic thrombocythaemia	Yes
76	M	49	Tuberculous bronchopneumonia	Yes
64	M	58	Moniliasis, lung abscess	Yes
108	M	49	Gastric ulcer, melaena	Yes
25	M	32	Postoperative adrenal failure	Probable
39	M	35	Postoperative adrenal failure	Probable
60	M	42	Amyloid	No
106	M	65	Amyloid	No
4	F	43	Chronic progressive disease	No
20	M	26	Chronic progressive disease	No
52	M	59	Chronic progressive disease	No
112	M	47	Carcinoma: ampulla of Vater	No
108	M	88	Haematemesis, gastric ulcer, BTZ	No
122	M	24	Carcinoma: small intestine	No
47	M	43	Cerebral haemorrhage	No
103	F	61	Intestinal insufficiency	No
113	F	72	Cerebral atherosclerosis	No
94	F	36	Pyaemia, postoperative sepsis	No

Table VI *Causes of death in 24 patients treated with steroids and possible contributory role played by steroids*

Discussion

The difficulties of control and of prospective study in regional enteritis are well known. The studies on which this paper has been based are the result of recording as many factors as possible over the past 25 years in order to establish the life history of the disease whilst searching for the basis of an adequate programme for prospective trials. Though these observations have been made on the patients under the clinical care of one man, the study still has the defects inherent in any retrospective analysis with the added clinical bias of the physician in charge. Nevertheless, such analyses, as Feinstein and Spitz (1969) point out, allow conclusions to be drawn which in themselves may serve the starting point for future programmed studies.

The effect of steroid therapy in bringing about an improvement in symptoms and the restoration of normal haematological values together with normal levels of seromucoids can be readily documented and was evaluated objectively when assessing the short-term response in this study. There appeared to be no doubt that restoration of apparently normal health in certain patients was directly attributable to the use of steroid

therapy. Even in those patients in whom death was attributable to the use of steroids, the quality of life was often immeasurably improved. Thus, case 30, aged 20, was enabled to work as a carpenter and provide a home for a wife and family until stricken with malignant hypertension. Without such domestic and economic pressure conservative therapy might have allowed the disease to burn out leaving a healthy patient able to lead a normal working life. Case 77 was first seen with an abdominal mass after intestinal resection 12 months previously. Radiological examination demonstrated considerable ileal involvement in the pre-anastomotic area. At the request of the surgeon, steroid therapy was started, resulting in great clinical improvement, return to apparent radiological normality, and normal laboratory findings. After six years' apparent good health the therapy was stopped. Within 12 months recurrence had occurred necessitating two operations, including the establishment of an ileostomy (Fig. 3). This pattern of containment and even regression of the disorder has been noted many times. Normal economic life has been made possible but recurrence following cessation of therapy was seen on many occasions.

It is, however, difficult to avoid the conclusion that steroid therapy was partly responsible for the significantly increased mortality rate amongst men, particularly when the onset of symptoms was before the age of 40. On the other hand, the only significant increase in mortality rate amongst women was in those under 40 and not treated with steroids; six of the eight deaths which occurred in this group were directly related to the disease. It is possible, therefore, to attribute the significantly lower mortality rate in the treated women with onset under 40 to steroids. In the men and women in whom the onset was after the age of 40, there was no significant increase in the mortality rate and it would be difficult therefore to demonstrate the efficacy of steroid therapy in this group.

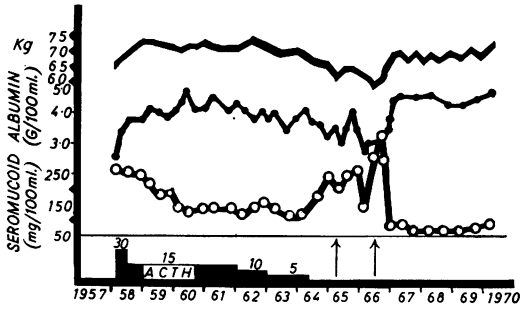

Fig. 3 *The return to normality of serum albumin (N > 3·8 g/100 ml) and serum seromucoids (N < 150 mg/100 ml) and weight gain with ACTH. There is a gradual regression with diminishing dosage and eventual relapse leading to further resection (left-hand arrow) and ileostomy and colectomy (right-hand arrow). The patient has remained well and working between 1967 and 1970.*

Our own experience leads us to recognize that serious complications may follow steroid therapy leading to the death of the patient. Even so recognition that serious complications occur did not prevent their occurrence. However, the ability of steroid therapy to promote restoration of clinical well being and normal laboratory findings ensures a place in therapy. In our view, steroid therapy had a beneficial effect in controlling symptoms and signs in a patient in whom treatment would otherwise entail a prolonged period of conservative therapy and restricted activities. How such therapy leads to an increase in both the number and chance of operations remains to be answered. In both groups, steroid treated and those not treated, the indications for surgical therapy were the same: enteroenteric and other fistula, recurrent intestinal obstruction, and diagnostic laparotomy to ascertain the exact extent of the disease. Resection in both groups has been limited to excision of the smallest length of intestine necessary to remove the obstruction, fistula, and other complications. Steroid therapy may well suppress the exudative aspect of the disorder and allow the reparative fibrosing processes of the individual time to act.

In conclusion, some unexpected findings have emerged from this study: the increased mortality and the increased probability of operation for by-pass or resection in steroid-treated patients. Whilst there was no significant difference between men and women with regard to operation rate, the mortality rate for 153 women was significantly less than the mortality rate for 142 men. Much of this difference was attributable to the 11 deaths due to steroid therapy in men in contrast to one only due to this cause in women. Whether this indicates that Crohn's disease is a milder disorder in women than in men will need a larger series of observations to determine. In our hands treatment with steroids carried significant risk, and evidence of long-term benefit in this disorder has not been forthcoming.

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