Gut, 1963, **4**, 183

Ulcerative colitis in the United States Army in 1944

Follow-up with particular reference to mortality in cases and controls[1]

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EDITORIAL SYNOPSIS This paper compares the mortality of 525 men admitted to U.S. Army hospitals in 1944 with ulcerative colitis compared with 518 controls matched for age, race, and rank. The excess mortality in the ulcerative colitis group as compared with the control group was due to approximately equal proportions of deaths from ulcerative colitis (2·9%) and cancer of the caecum, colon, and rectum (3·2%). The mortality from ulcerative colitis occurred mainly in the first and immediately subsequent years after diagnosis while most of the deaths from cancer occurred in later years. A striking correlation is shown between bad prognosis and the extent of radiological involvement of the colon in 1944.

MATERIALS AND METHODS

SAMPLING Five hundred and twenty-five individuals were selected from among the admissions to Army hospitals[2] for ulcerative colitis during 1944. Those selected were the males with at least 90 days of Army service who had not already been admitted to an Army hospital at which a diagnosis of ulcerative colitis was made. The symptoms at the onset of the illness and at the reference point, *i.e.*, the date of admission to hospital, and clinical procedures carried out during the period in hospital have been described elsewhere (Acheson and Nefzger, 1963).

Controls were selected from a 0·1% sample of all males discharged from the Army to civil life during the interval between 1944 and 30 June 1947. They were matched individually to ulcerative colitis cases on the basis of age, race, and rank and were required to have been on active duty with the Army on the day when the matched case was admitted to hospital (Acheson and Nefzger, 1963).

FOLLOW-UP Follow-up data were obtained primarily from records under the jurisdiction of the Veterans Administration (Cohen, 1953). In previous studies the fact of death in groups similar to those described here has been obtained from the Veterans Administration with an accuracy which probably exceeds 94% (Beebe, 1961). When the fact of death had been ascertained death certificates, records of necropsies, and summaries of the terminal hospital illness were sought from the Veterans Administration and military records and from private sources when indicated. The follow-up of mortality extended to 31 December 1960 for both ulcerative colitis cases and their matched controls.

For ulcerative colitis cases, a complete history of service and admissions to Veterans Administration hospitals up to 31 December 1958 was sought by reviewing medical records. Dates of admission and discharge, final diagnoses, and surgical procedures were systematically recorded for each. Similar data were recorded for all cases admitted to private hospitals adequately documented in claims folders.

Because Veterans Administration records are not necessarily complete with regard to private medical care, such data were sought by postal questionnaire. However, of 480 men surviving at the time, a usable questionnaire was returned by only 301 (62.7%), and it was felt that little of value was added by this effort.

RESULTS

MORTALITY Among the 525 ulcerative colitis cases, there were 56 (10·7%) known deaths in the 17-year

[1]This study was financed under contract no. VAm-22734 with the Research Service, Department of Medicine and Surgery, U.S. Veterans Administration Central Office, Washington, 25 D.C., and is part of the programme developed by the NAS-NRC Committee on Veterans' Medical Problems at the request of the Veterans Administration and the Department of Defence.

[2]Basic punch-card rosters of admissions were provided by the Medical Statistics Division, Office of the Surgeon General.

interval ending on 31 December 1960 as compared with 26 (5·0%) among 518 matched controls ($P < 0·001$). The gross mortality rate in cases was, therefore, twice that of the controls. These results are shown in terms of life-table survival rates in Figure 1.

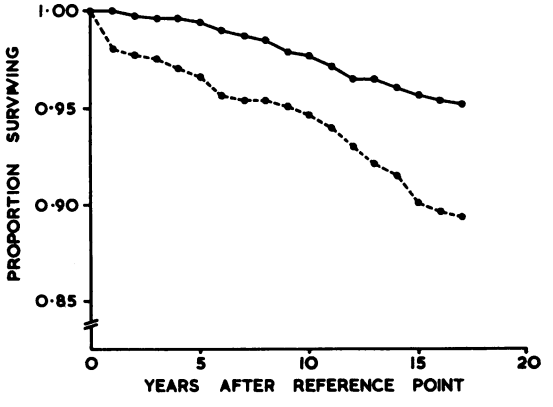

FIG. 1. *Survival after reference point for all ulcerative colitis cases (dashed line) and matched controls (solid line).*

MORTALITY ATTRIBUTED TO ULCERATIVE COLITIS Ulcerative colitis was given as the underlying cause of death in 15 of 56 deaths in cases (Table I) and was noted as present at death in 11 more. No such deaths were recorded in the control group. The 17-year mortality of 2·9% due to ulcerative colitis is shown in Fig. 2 in the form of a survival curve. Ulcerative colitis had its major effect on survival early, and indeed eight of the 15 deaths were within 12 months of admission to hospital for ulcerative colitis in 1944.

The immediate cause of death in the 15 cases was: peritonitis six, intestinal haemorrhage two, intestinal obstruction following ileostomy two, other and ill-defined causes five. Seven of the 15 deaths occurred within 30 days of an operation for ulcerative colitis.

TABLE I

NUMBER OF DEATHS AMONG ULCERATIVE COLITIS CASES AND MATCHED CONTROLS UP TO 31 DECEMBER 1960

Intervals	*Controls*	*Cases*		
		Ulcerative Colitis	*Cancer of Colon or Rectum*	*Other Causes*
1944-1945	0	9	1	2
1946-1950	5	4	3	5
1951-1955	11	0	5	5
1956-1960	10	2	8	12
Totals	26	15	17	24

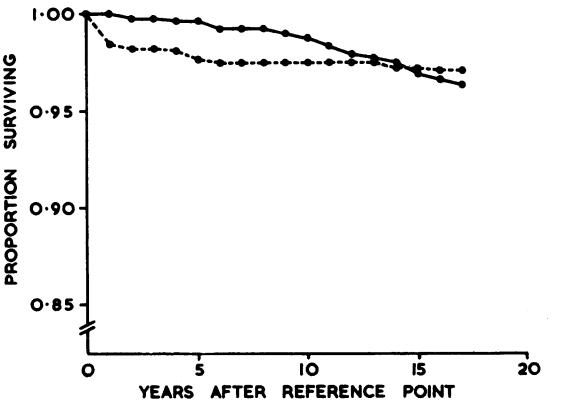

FIG. 2. *Survival after diagnosis of ulcerative colitis based on specific causes of death: ulcerative colitis (dashed line) and cancer of the colon or rectum (solid line).*

MORTALITY ATTRIBUTED TO CANCER OF LARGE BOWEL Seventeen deaths, all in the ulcerative colitis cases, were ascribed to carcinoma of the caecum, colon, or rectum. Of these, 15 men had a single primary tumour and two had two primary tumours. The sites of the 19 tumours were: rectum or recto-sigmoid junction, eight, descending or sigmoid colon three, transverse colon six, ascending colon one, and caecum one. The rectum (eight cases) and the whole of the remainder of the large bowel (11 cases) thus contribute approximately equal proportions of the tumours.

In 16 cases the diagnosis of carcinoma had been verified either by pathological examination of an operative specimen (13) or of necropsy material (three). In the remaining case the only available information was the death certificate which stated that the patient had died of 'peritonitis due to chronic ulcerative colitis and carcinoma of the caecum'.

In 16 of the 17 cases there was clear clinical evidence that ulcerative colitis had preceded the development of cancer. In one man who died in 1945, the onset of bloody diarrhoea was in 1937 before he entered the Army. He had further symptoms in 1943, but the first certain diagnosis of ulcerative colitis was made in 1944 when the sigmoidoscopic findings were typical of ulcerative colitis but the barium enema showed only redundancy of the colon. Intestinal obstruction developed in 1945 and at laparotomy peritoneal carcinomatosis from a primary lesion in the sigmoid colon was found. It is possible but unlikely that this man's whole illness had been due to carcinoma of the colon.

In all 16 cases in which either a surgical specimen is known to have been examined or a necropsy done, obvious macroscopic tumours were present. Five

patients presented clinically with intestinal obstruction, four with a colonic stricture or filling defect visible radiologically, and in three the initial diagnosis of cancer had been made by digital examination of the rectum. The remainder presented as follows:—Acute appendicitis with neoplastic infiltration of the appendix, one; tumour seen on sigmoidoscopy following recurrence of diarrhoea and bleeding, one. In two other cases the exact mode of presentation is unknown but inoperable carcinomata of the rectum with widespread metastases were found at laparotomy. With the possible exception of the case in which the death certificate was the only available source of information, none of the tumours were found unsuspected at operation or at necropsy.

In two men cancer developed after an operation on the colon. One had a caecostomy in 1948 and developed a carcinoma of the transverse colon in 1958. The other developed carcinoma of the rectum nine years after a subtotal colectomy.

The average age at death of the 17 men who died of colonic cancer was 36 years, the youngest being 23 and the oldest 49. Three were less than 30 years old, nine were in the fourth decade, and five were in the fifth decade. This supports the widely held view (Weckesser and Chinn, 1953; Bargen and Gage, 1960) that cancer following ulcerative colitis occurs at a younger age than does cancer of the large bowel not preceded by ulcerative colitis.

The interval between the first onset of symptoms of ulcerative colitis and the diagnosis of cancer was as follows: six to 10 years, four cases; 11 to 15 years, seven cases; 16 to 20 years, one case; 21 to 25 years, five cases.

The 17-year mortality of 3·4% due to cancer of the large bowel (Fig. 2) is almost identical with that from ulcerative colitis. However, the patterns of the survival curves are strikingly different, and this same difference is also seen in Table 1. The bulk of the mortality from ulcerative colitis is in the early years, while the bulk of the cancer mortality occurs later. It is noteworthy that the two survival curves crossed in the 15th year.

MORTALITY ATTRIBUTED TO OTHER CAUSES The overall mortality due to causes other than ulcerative colitis or cancer of the large bowel was almost identical in the two groups, there being 24 deaths among cases and 26 among controls (Table I and Fig. 3). This suggests that the degree of ascertainment of deaths was closely similar. By broad aetiological groups these deaths were distributed as follows:—Accidental, six cases, seven controls; malignant tumours other than of the colon or rectum, six cases, five controls; vascular disease, seven cases, 11 controls; and all other causes, five cases, three

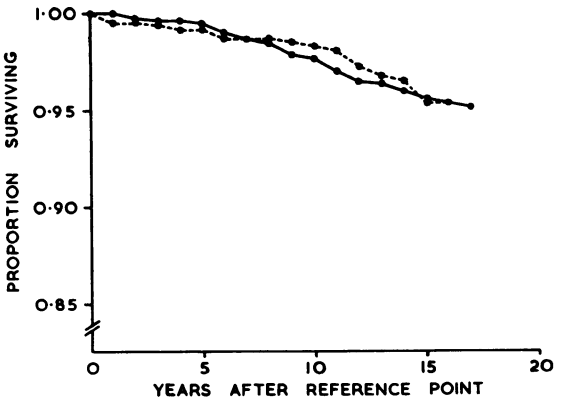

FIG. 3. *Survival after reference point based on all causes of death other than ulcerative colitis and cancer of the colon or rectum for all ulcerative colitis cases (dashed line) and matched controls (solid line).*

controls. The cancer deaths in the ulcerative colitis group were distributed as follows:—Carcinoma of the stomach, one; of the bile ducts, one; of the bronchus, one; malignant brain tumour, one; lymphatic leukaemia, one; and of unspecified site, one. Among controls, the distribution of cancer deaths was: carcinoma of the stomach, one; of the bronchus, one; of the testis, one; retroperitoneal sarcoma, one; and myeloid leukaemia, one. The excess of deaths ascribed to vascular disease in the control group was due to seven deaths from coronary heart disease, arteriosclerotic heart disease, etc., as opposed to two such deaths in the ulcerative colitis group. This difference is not significant ($P = >0{\cdot}05$).

OPERATIONS FOR ULCERATIVE COLITIS Sixty-five men (12·4%) are known to have had at least one abdominal operation other than exploratory laparotomy for ulcerative colitis or its complications, including cancer, since the reference point through 30 December 1958. Of these, 12 men had operations for carcinoma of the colon or rectum and 53 had operations for ulcerative colitis. Thirty-seven total colectomies and proctectomies are known to have been carried out and in three of these patients a diagnosis of cancer had been reached before surgery.

If patients in whom a diagnosis of cancer was made at or before operation are excluded there remain 47 men known to have had a permanent ileostomy performed during the interval since 1944. Seven of these had only an ileostomy performed, and six have since died. The remaining 40 had a procedure involving ileostomy with partial or complete removal of the large bowel, and only three of these have died. Of the 47 men, three died within 30 days

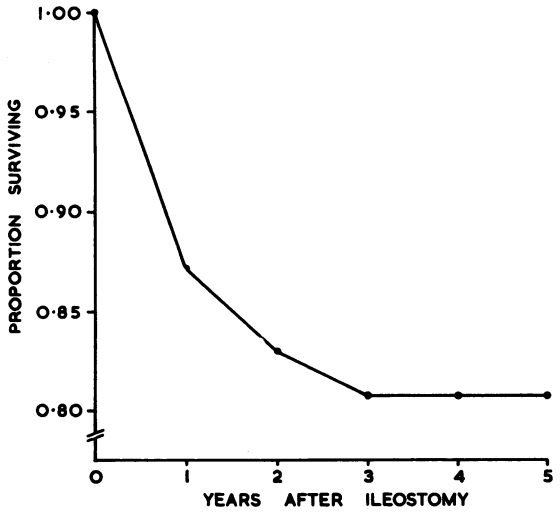

FIG. 4. *Survival after permanent ileostomy in 47 ulcerative colitis cases not known to have cancer of the colon or rectum at the time of surgery.*

of surgery and three more died within the first year. The remaining three deaths occurred in the second and third year. In total this material comprises over 350 completed man-years of observation of which almost all is for intervals of three or more years after surgery.

The survival curve following ileostomy is shown in Fig. 4 where it can be seen that the greatest loss (about 13%) is in the first year. Much of this is attributable to immediate post-operative deaths in desperately ill patients in whom an ileostomy without colectomy was done. After the first year the decline in survivors is slight, and there has been no further decline after the third year.

FACTORS WITH A BEARING ON PROGNOSIS Three groups of patients in whom the subsequent outcome has been unfavourable have been defined: (1) 15 men who have died of ulcerative colitis; (2) 19 men known to have suffered from cancer of the caecum, colon, or rectum (17 have died and have already been referred to); and (3) 45 other men who are known to have had colonic surgery or ileostomy for ulcerative colitis. Table III shows the distribution of these three groups of men separately and together, compared with the distribution of all cases, in terms of the extent of involvement of the colon indicated in the report of the barium enema performed during the reference period in hospital in 1944. One hundred and fourteen cases are excluded from Table III, among whom are nine in whom the radiologist's report indicated involvement of the right side or transverse portion of the colon only. None of these nine men subsequently died of ulcerative colitis or is known to have had colonic surgery or cancer of the large bowel. The other 105 were excluded because either barium enemas were not done or reports were not available.

Nine of the patients with a poor prognosis are among the 105 for whom a barium enema report was not available from the reference period in hospital. Four of these nine died during that admission and may have been too ill to examine radiologically. They were classed with the deaths due to ulcerative colitis. Of three others, who later developed cancer, one had a barium enema shortly before admission to hospital in 1944 which showed universal ulcerative colitis, and another showed universal colitis in 1946. The third man had a malignant polyp removed from the sigmoid in 1950 after an interval of freedom from symptoms, but is not known ever to have had a barium enema before the diagnosis of cancer.

Table II shows a striking correlation between a bad prognosis (as defined) and the degree of radiological involvement of the colon. Thus 47·1% of the cases with a bad prognosis had universal involvement as opposed to only 16·5% of all cases, while 15·7% of the bad cases had normal barium enemas as opposed to 47·2% of all cases. A goodness of fit test indicates ($P = < 0{\cdot}001$) that the 70 cases with

TABLE II

EXTENT OF COLONIC INVOLVEMENT BY BARIUM ENEMA DURING REFERENCE PERIOD IN HOSPITAL IN SELECTED GROUPS WITH POOR PROGNOSIS

Extent of Involvement	*Poor Prognosis Groups*				*All Ulcerative Colitis Cases*
	Cancer of Caecum, Colon, or Rectum	*Death Due to Ulcerative Colitis*	*Colonic Surgery*[1]	*Total*	
Universal	9 (56·2%)	5 (50%)	19 (43·2%)	33 (47·1%)	68 (16·5%)
Left side and transverse	2 (12·5%)	0	7 (15·9%)	9 (12·9%)	33 (8·0%)
Left side only	2 (12·5%)	2 (20·0%)	13 (29·5%)	17 (24·3%)	116 (28·2%)
Normal	3 (18·8%)	3 (30·0%)	5 (11·4%)	11 (15·7%)	194 (47·2%)
Totals	16 (100·0%)	10 (100·0%)	44 (100·0%)	70 (100·0%)	411 (99·9%)

[1]Excluding cases known to have cancer of the caecum, colon, or rectum and cases whose death was attributed to ulcerative colitis.

a bad prognosis do not represent a random selection from the whole group with respect to the extent of involvement of the colon. When the three individual bad prognostic groups are examined in Table III, the trend is seen to be present to a roughly equivalent extent in all three. There is a suggestion that those in whom the left side of the colon and the transverse colon were involved did worse than those in whom the left side was involved without the transverse colon, but this difference is not statistically significant ($P = < 0.05$).

To explore the possibility that symptoms provide an index to prognosis, the groups with a bad prognosis first were compared with all cases for each of 10 symptoms reported present at either the onset of the reference illness or reference point (Table III). All bad prognosis groups combined are significantly different from all other cases only in respect to the relative frequencies of cases with diarrhoea ($P = < 0.05$) and tenesmus ($P = < 0.03$). There are striking differences among the three bad prognosis groups, but when compared individually with all cases, only the colonic surgery group is statistically significant in respect to diarrhoea ($P = < 0.05$) and tenesmus ($P = < 0.01$). Eighteen (22·8%) of the 79 bad prognosis cases had both diarrhoea and tenesmus as compared with 70 (13·3%) in the total group of ulcerative colitis cases ($P = < 0.02$).

In Table IV is shown the number of certain specified symptoms reported at reference point or at onset of the reference episode in all cases and in the groups which have carried a bad prognosis. Table IVA shows the patients who had any one, two, or three of the following symptoms: diarrhoea, rectal bleeding, or abdominal pain. All bad prognostic groups combined show a trend in favour of more patients with combinations of these symptoms but

TABLE III

INDIVIDUAL SYMPTOMS AT ONSET OF REFERENCE ILLNESS OR AT REFERENCE POINT IN SELECTED GROUPS WITH POOR PROGNOSIS

Symptom	*Poor Prognosis Groups*				*All Ulcerative Colitis Cases*
	Cancer of Caecum, Colon, or Rectum	*Death Due to Ulcerative Colitis*	*Colonic Surgery*[1]	*Total*	
Diarrhoea	17 (89·5%)	13 (86·7%)	41 (91·1%)[2]	71 (89·9%)[2]	412 (78·5%)
Rectal bleeding	10 (52·6%)	10 (66·7%)	30 (66·7%)	50 (63·3%)	286 (54·5%)
Abdominal pain	11 (57·9%)	13 (86·7%)	34 (75·6%)	58 (73·4%)	370 (70·5%)
Fever	1 (5·3%)	0	4 (8·9%)	5 (6·3%)	59 (11·2%)
Weight loss	5 (26·3%)	6 (40·0%)	9 (20·0%)	20 (25·3%)	94 (17·9%)
Faecal incontinence	1 (5·3%)	0	1 (2·2%)	2 (2·5%)	3 (0·6%)
Tenesmus	3 (15·8%)	3 (20·0%)	14 (31·1%)[2]	20 (25·3%)[2]	84 (16·0%)
Vomiting	1 (5·3%)	1 (0·0%)	8 (17·8%)	10 (12·7%)	75 (14·3%)
Joint pain	0	0	1 (2·2%)	1 (1·3%)	10 (1·9%)
Constipation	0	0	1 (2·2%)	1 (1·3%)	25 (4·8%)

[1]Excluding patient known to have cancer of the caecum, colon, or rectum and patients whose death was attributed to ulcerative colitis.
[2]$P = < 0.05$.

TABLE IV

SYMPTOMS AT ONSET OF REFERENCE ILLNESS OR AT REFERENCE POINT IN SELECTED GROUPS WITH POOR PROGNOSIS

Number of Symptoms[1] [2]	*Poor Prognosis Groups*				*All Ulcerative Colitis Cases*
	Cancer of Caecum, Colon, or Rectum	*Death Due to Ulcerative Colitis*	*Colonic Surgery*	*Total*	
A *Diarrhoea, rectal bleeding, and abdominal pain*					
None	1 (5·3%)	0	0	1 (1·3%)	30 (5·7%)
One	3 (15·8%)	2 (13·3%)	6 (13·3%)	11 (13·9%)	107 (20·4%)
Two	10 (52·6%)	5 (33·3%)	18 (40·0%)	33 (41·8%)	203 (38·7%)
Three	5 (26·3%)	8 (53·3%)	21 (46·7%)	34 (43·0%)	185 (35·2%)
Totals	19 (100·0%)	15 (99·9%)	45 (100·0%)	79 (100·0%)	525 (100·0%)
B *Fever, weight loss, faecal incontinence, tenesmus, and vomiting*					
None	10 (52·6%)	7 (46·7%)	18 (40·0%)	35 (44·3%)	280 (53·3%)
Any one	8 (42·1%)	6 (40·0%)	19 (42·2%)	33 (41·8%)	185 (35·2%)
More than one	1 (5·3%)	2 (13·3%)	8 17·8%)	11 (13·9%)	60 (11·4%)
Totals	19 (100·0%)	15 (100·0%)	45 (100·0%)	79 (100·0%)	525 (99·9%)

[1]Diarrhoea, rectal bleeding, or abdominal pain.
[2]Fever, weight loss, faecal incontinence, tenesmus, or vomiting.

this is not significant (P = > 0·05). Examination of the subgroup shows that the cancer cases do not contribute to this trend. All of the trend is contributed by the patients who died, or who had colonic surgery, but when these are combined the effect still is not significant (P = > 0·05).

Table IVB shows the distribution of cases with none, any one, or any two of five additional symptoms which are regarded as indicative of a severe reference illness: these are fever, weight loss, faecal incontinence, tenesmus, and vomiting. The same effect is seen as was demonstrated in Table IIa, namely, that when the combined bad prognostic groups are examined they show a slight trend in favour of more of these symptoms when compared with all the material, but that the whole of this effect is in the groups of patients who died or who had surgery, and none of it is in the cancer group. Again, neither of these distributions is significantly different from that of all cases.

Table V shows the distributions of the bad prognostic groups in terms of the length of the reference period in hospital. The combined bad prognostic groups tended to have a longer period in hospital than the remainder. The goodness of fit test for the groups is significant (P = < 0·02) in spite of the influence of the seven deaths due to ulcerative colitis during the reference period in hospital. The distribution of cases later subjected to surgery is significantly different from that of all cases (P = < 0·001). The distribution of cases in which cancer developed cannot be tested because of extremely small numbers.

Table VI shows the bad prognostic groups distributed by the year of onset of the first symptoms of ulcerative colitis. In a chronic disease such as ulcerative colitis where the onset may be gradual, this date is clearly open to wide errors, and in a service population additional error may be introduced by considerations relating to compensation. When the three groups carrying a poor prognosis were considered together no definite trend was observed (P = > 0·05). Considered separately, the most distinctive trend is seen in the colonic surgery group in which the highest proportions are from groups with earlier onset. Among deaths from ulcerative colitis this trend is reversed. A surprising finding is that three of 18 men with an onset before 1930 subsequently developed cancer, whereas none died of ulcerative colitis or had colonic surgery.

An attempt was made to distinguish the effects of age at onset and year of onset on the risk of cancer. Because the vast majority of the men who dated the onset of their illness in 1940 or afterwards were 20 years old at that time, a meaningful age comparison was not possible for this group. However, there were 86 men whose date of first symptoms was before 1940. Of these, 42 were under 20 years of age at that time and 44 were 20 or over. Five of the 42 (11·9%) as opposed to two of the 44 (4·5%) are

TABLE V

LENGTH OF REFERENCE PERIOD IN HOSPITAL FOR SELECTED GROUPS WITH POOR PROGNOSIS

Length of Stay (mth.)	*Poor Prognosis Groups*				*All Ulcerative Colitis Cases*
	Cancer of Caecum, Colon, or Rectum	*Death Due to Ulcerative Colitis*	*Colonic Surgery*	*Total*	
<1	4 (21·0%)	2[1] (13·3%)	1 (2·2%)	7 (8·9%)	82 (15·6%)
1-3	10 (52·6%)	8[2] (53·3%)	19 (42·2%)	37 (46·8%)	284 (54·1%)
>3	5 (26·3%)	5[3] (33·3%)	25 (55·6%)	35 (44·3%)	159 (30·3%)
Totals	19 (99·9%)	15 (99·9%)	45 (100·0%)	79 (100·0%)	525 (100·0%)

[1]One died during reference period in hospital, [2]four died during reference period in hospital, [3]two died during reference period in hospital.

TABLE VI

FIRST ONSET OF SYMPTOMS IN SELECTED GROUPS WITH POOR PROGNOSIS

Year of Onset	*Poor Prognosis Groups*				*All Ulcerative Colitis Cases*
	Cancer of Caecum, Colon, or Rectum	*Death Due to Ulcerative Colitis*	*Colonic Surgery*	*Total*	
Before 1930	3 (15·8%)	0	0	3 (3.8%)	18 (3·6%)
1930-1939	4 (21·1%)	1 (6·7%)	10 (22·2%)	15 (19·0%)	68 (13·5%)
1940-1942	2 (10·5%)	2 (13·3%)	12 (26·7%)	16 (20·3%)	116 (23·1%)
1943	5 (26·3%)	4 (26·7%)	13 (28·9%)	22 (27·8%)	142 (28·3%)
1944	5 (26·3%)	8 (53·3%)	10 (22·2%)	23 (29·1%)	158 (31·5%)
Totals	19 (100·0%)	15 (100·0%)	45 (100·0%)	79 (100·0 %)	502[1] (100·0%)

[11]Twenty-three are unknown.

known to have developed cancer, which suggests that age at onset influences the risk of cancer independently of the duration of illness. This difference is not statistically significant.

PROGNOSIS IN JEWS AND OFFICERS In an epidemiological analysis of the data published elsewhere Jews and officers were found to have about twice the risk of developing ulcerative colitis as others (Acheson and Nefzger, 1963). To determine whether these groups also were more liable to a bad prognosis, counts were made of the number of Jews and of officers who died of ulcerative colitis, developed cancer, or were known to have been subjected to colonic surgery. There were no significant differences.

DISCUSSION

A vast literature concerning the mortality and natural history of ulcerative colitis already exists and has recently been reviewed by Texter (1957). Unfortunately in much of this material, with the exception of the series of Rice-Oxley and Truelove (1950), freshly diagnosed cases have not been distinguished from cases of many years' standing.

Cancer of the large bowel as a complication of ulcerative colitis has also been reported widely. The literature has been collected and reviewed by Goldgraber, Humphreys, Kirsner, and Palmer (1958) and Slaney and Brooke (1959). With the exception of the material from the Mayo Clinic (Sloan, Bargen, and Gage, 1950; Bargen, Sauer, Sloan, and Gage, 1954) estimates of the risk of cancer may have been misleading because they have not taken into account the number of man-years' exposure since the diagnosis or onset of ulcerative colitis. The wide fluctuations in the proportions of cases of cancer reported have reflected the varied means of selection of the material and differing degrees of success in following the patients. As might be expected the figures from hospital series reported by surgeons (Bacon, Ouyang, Carroll, Cates, Villalba, and McGregor, 1956; Slaney and Brooke, 1959) have been higher than those reported by physicians (Flood, Lepore, Hiatt, and Karush, 1956; Rice-Oxley and Truelove, 1950).

One striking feature demonstrated by the study reported here has been the relatively favourable mortality experience of the group of men with ulcerative colitis as compared with civilian hospital cases. Figure 1 shows that 89·4% of 525 men were alive 17 years after the reference period in hospital as compared with 95·2% of their controls matched for age, race, and rank. The risk of dying over this interval was therefore twice as high in the ulcerative colitis group as in the controls. In the series of Sloan, Bargen, and Gage (1950) of 2,000 cases of ulcerative colitis treated at the Mayo Clinic, 60% of the ulcerative colitis patients were alive after 17 years, as compared with an expected survival of 85% derived from United States life tables for persons of similar age. The risk of death over 17 years in the Mayo Clinic was thus more than three and a half times that expected. Apart from the obvious difference in sex composition between our cases and the Mayo Clinic series, Sloan, Bargen, and Gage's material differs from ours in that it is not derived from any definable population and contains an admixture of severe cases referred from other centres because of difficulties in diagnosis or management.

Both Sloan *et al.* (1950) and Rice-Oxley and Truelove (1950) have shown that the mortality in ulcerative colitis is higher in the first year after diagnosis than in subsequent years. This is borne out in our material (Fig. 2 and Table I) in that eight of the 15 deaths ascribed to ulcerative colitis occurred within the first year of diagnosis, giving a mortality rate of 1·5%. This figure is very much lower than that given by Rice-Oxley and Truelove (21·7%) or by Sloan *et al.* (9%). Differences in age and sex distribution between the series are unlikely to account for this (Rice-Oxley and Truelove, 1950). It may be due to the fact that our material was obtained from a closed community where in time of war milder cases of ulcerative colitis were admitted to hospital as part of the campaign against dysentery. This is borne out by Table II which shows that only 16·5% of our cases were found to have universal involvement of the colon during the reference illness as compared with 44·4% reported by Sloan *et al.* (1950). The lower mortality rate in our series might also be due either to a failure of ascertainment of death or to dilution of our material with other conditions misdiagnosed as ulcerative colitis and having a better prognosis. There is good reason to believe that ascertainment of death was almost complete (Beebe, 1961). Details of the diagnostic criteria and of the standard of investigation, together with case reports selected at random, have been published elsewhere (Acheson and Nefzger, 1963). It was concluded that although some dilution of the material with cases of dysentery and the irritable colon syndrome may have occurred, the bulk of the 525 men were suffering from ulcerative colitis in 1944.

The 17-year mortality rate from cancer of the colon or rectum in the ulcerative colitis cases was 3·4% as opposed to 0·0% in the matched controls. This finding confirms in a controlled series the widespread view that malignant change is an important complication of ulcerative colitis (Bargen, 1928; Slaney, and Brooke, 1959). With the exception of two cases the diagnosis of cancer was well

substantiated by macroscopic and microscopic examination either of a surgical specimen or at necropsy. In this series the highly significant excess mortality from cancer is not due either to confusion of the original condition with cancer nor to diagnoses of cancer based on dubious histological changes alone. The mortality from other types of cancer was closely similar in the two groups, suggesting that there was no greater tendency to ascribe the primary site of widespread cancer of inderterminate origin to the colon in cases than in controls. It is worth noting that if the cases were diluted with persons suffering from conditions other than ulcerative colitis our estimate of the risk of death from cancer of the large bowel must be erroneously low.

The patterns of mortality from ulcerative colitis and from cancer of the colon amongst the cases are compared in Figure 2. At the end of 17 years the cumulative risk of dying from either of these two conditions had been almost identical. We know of two additional patients with cancer of the large bowel who were living on 31 December 1960. There may be others about whom we have no record, but if the five-year fatality rate for cancer complicating ulcerative colitis is 80% or more, as is reported by Slaney and Brooke (1959) in a series collected widely from the literature, the number living cannot be large. The bulk of the deaths from ulcerative colitis occurred in the first few years and the bulk of the cancer deaths have occurred more than 10 years after the reference point. If the present trends continue death from cancer of the colon will in future be a greater risk for these men than death from ulcerative colitis.

The close similarity between the survival curves for deaths from all other causes in cases and controls provides reassuring evidence that ascertainment of death was similar in the two groups. It also suggests that there is no other common fatal disease associated with ulcerative colitis. The tendency of patients with ulcerative colitis to die less frequently of coronary heart disease than controls is interesting although it does not reach conventional limits of statistical significance.

Fifty-three men (10·1%) are known to have had colonic surgery for ulcerative colitis or its complications. This figure is an underestimate because some operations may have been carried out in private hospitals without our knowledge. However, because we learned of only three such additional operations from 301 questionnaires we believe the error is small. The overall mortality following permanent ileostomy was 19·2%. As ascertainment of death was complete but ascertainment of operations was incomplete, this figure is biased and is necessarily too high; when the cases in which ileostomy alone was performed are excluded the mortality falls to 7·5% which is highly creditable, particularly as it represents the efforts of general surgeons in many centres, and the material contains both emergency and elective procedures.

Tables II to VI show attempts to identify features of the 1944 illness which have subsequently proved to indicate a poor prognosis. The most striking of these (Table II) is the correlation between the degree of radiological involvement of the colon and an unfavourable outcome. Of 68 men in whom universal ulcerative colitis was demonstrated radiologically during the reference illness in 1944, 33 (48·5%) have either died of ulcerative colitis or have developed cancer of the colon or had colonic surgery. This compares with 26 (17·5%) of 149 men who had partial radiological involvement, and 11 (5·7%) of 194 men whose barium enemas were reported as normal. This trend is also seen in each of the three individual groups with a poor outcome. Of 19 men who are known to have developed cancer of the large bowel, 11 were reported to have universal colitis at some stage in their illness.

As diarrhoea is usually evidence of extension of the disease process from the rectum into the colon, it is not surprising that the presence of this symptom during the reference illness denoted a poorer prognosis than did its absence (Table III). If faecal incontinence is excluded from consideration because of its extreme rarity, tenesmus seemed to be the most unfavourable individual symptom. Apart from the combination of diarrhoea and tenesmus, no combination of symptoms studied seemed to be of prognostic significance although slight trends were demonstrated (Table IV). Table V shows that there was a significant correlation between the length of the reference illness in 1944 and the subsequent prognosis.

In Table VI the cases are distributed according to their reported year of first onset of symptoms. In spite of the fact that all men on whom a diagnosis of ulcerative colitis had been made in the Army before 1944 had been excluded from the study, 202 of the men had first experienced diarrhoea or rectal bleeding before 1943. In many of these the early symptoms had been attributed correctly or incorrectly to gastroenteritis, enteritis, or haemorrhoids. This underlines the difficulties in dating the clinical onset of ulcerative colitis accurately. Although the trends in Table VI are not statistically significant they suggest that death from ulcerative colitis tends to occur early in the disease but that cancer develops late. This adds some additional weight to the patterns of mortality seen in Fig. 2 where the date of diagnosis is assumed to be the date of first exposure.

Bargen and his colleagues (1954) and Rosenqvist, Largercrantz, Öhrling, and Edling (1959) have suggested that the age at onset of ulcerative colitis is an important factor in determining the risk of cancer. However, neither has demonstrated that this is independent of duration of the illness. The evidence in this material is inconclusive but tends to support an independent effect related to age of onset.

Much has been written about the clinical type of ulcerative colitis which precedes the development of cancer of the large bowel. Although there is no doubt that cancer may develop in patients with chronic continuous or intermittent symptoms (Goldgraber *et al.*, 1958), Svartz and Ernberg (1949), Rosenqvist and his colleagues (1959) have stressed that it may also develop frequently in persons with quiescent colitis who have had freedom of symptoms for many years. Of the 17 men who died of cancer in this series, 13 are known to have been readmitted to hospital on at least one further occasion for ulcerative colitis after discharge from the Army before the diagnosis of cancer and seven had been readmitted four or more times. Two others in whom we have no record of a readmission stated that they had suffered continuous symptoms in the interim. Of the remaining two, one had two short episodes of symptoms between 1944 and the diagnosis of cancer in 1958 but the other appears to have been entirely well in the interim. In this series death from cancer seems to have occurred rarely in persons who have had a single attack of ulcerative colitis and have been free of symptoms subsequently. This suggestion is borne out by the disability ratings of these men three years after the reference point. Of the 15 men in whom cancer had not already been diagnosed three years after the reference point, 13 are known to have had a disability rating for ulcerative colitis at this time and in nine it was 50% or more. The other two men were receiving officers' retirement pay and were not eligible for a disability rating.

The 17-year death rate from cancer of the large bowel in this series (3·6%) is too low to justify the widespread employment of total colectomy as a preventive measure. However, the higher death rate from cancer in the 68 men shown to have universal colitis in 1944 (13·2%) (Table II), particularly when the increased death rate from ulcerative colitis itself in this group is considered (7·4%), may suggest that colectomy could be employed on a wider scale in persons with universal colitis. To be advantageous it would have to be shown that the mortality due to total colectomy and permanent ileostomy for universal colitis over a comparable period was substantially less than 20%.

CONCLUSIONS

The mortality during the period 1944-60 of 525 men admitted to U.S. Army hospitals in 1944 with ulcerative colitis has been compared with the mortality of 518 controls matched for age, race, and rank. There was a twofold difference between the mortality from all causes in the ulcerative colitis group (10·7%) and that in the control group (4·8%). The excess mortality among the cases was due to approximately equal proportions of deaths from ulcerative colitis (2·9%) and cancer of the caecum, colon, and rectum (3·2%). No death from either of these causes has so far been reported from the control group. The favourable mortality experience of the ulcerative colitis cases described here as compared with that reported in the literature is thought to be due to the fact that this material is more representative of ulcerative colitis of all degrees of severity as it occurs in a population than are series of civilian hospital cases.

The bulk of the mortality from ulcerative colitis occurred in the first and immediately subsequent years after diagnosis: most of the deaths from cancer occurred in the later years. If the present trends continue death from cancer of the large bowel will in future be a greater hazard to these men than will death from ulcerative colitis.

Sixty-five men (12·4%) are known to have had surgery for ulcerative colitis or its complications, including cancer between the reference point and 30 December 1958. A survival curve following permanent ileostomy is shown. Most of the deaths occurred in the first year and none occurred in the fourth, fifth, or subsequent years.

Three groups of patients in whom the subsequent outcome has been unfavourable have been defined and in an effort to identify prognostic factors these have been compared with the remainder in terms of selected features of the 1944 illness. A striking correlation is shown between a bad prognosis and the degree of radiological involvement of the colon in 1944: those with universal colitis fared worst, and those with normal radiological appearances did best. Where individual symptoms in 1944 were considered, those patients who had diarrhoea and tenesmus were found to have done worse than those without these symptoms. The subsequent outcome was also correlated with the length of stay in hospital in 1944.

Although the number of cancer deaths is small, the results support the view that the risk of dying of cancer of the large bowel increases with the duration of ulcerative colitis; that cancer occurs in younger people as a complication of ulcerative colitis than in persons without this complaint; that it develops

comparatively rarely in persons who have been asymptomatic for long periods; and that it occurs more frequently in those with universal ulcerative colitis than in others.

In addition to the willing cooperation of many records management people in the U.S. Veterans Administration and Department of Defense, the execution of this study has drawn upon the cooperation of many people throughout the staff of the National Research Council Follow-up Agency in both Washington D.C. and St. Louis, Missouri. The help of all is gratefully recorded with special thanks to Miss Vivian A. Heidenblut for supervision of abstracting from the records, Mr. A. H. Simon for technical supervision of all aspects of the work, and to Miss Imelda F. Murray for supervision of all mechanical processing.

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Methods and techniques

The application of the Holter valve to the treatment of resistant ascites

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An operative procedure has been devised for the drainage of resistant ascites (Smith, 1962; Smith, Preshaw, and Bisset, 1962): the method derives from the principle of the Spitz-Holter procedure for hydrocephalus, in which cerebrospinal fluid drains from the lateral ventricles via a catheter, passes through the Holter valve, and enters the circulation through another catheter. In the management of resistant ascites the 'ventricular' catheter is inserted over a stylet into the peritoneum exposed through a low paramedian incision. The catheter is connected to the upper end of the Holter valve, which has multiple chambers with reed valves, works at the low pressure of 15 mm. H_2O, is unidirectional and is specially siliconed, as is the catheter tubing used in the entire procedure. To the other end of the Holter valve is attached the venous catheter, which is inserted into any suitable adjacent systemic vein.

Ascitic fluid is in a state of dynamic turnover and the use of this procedure merely speeds the return to the circulation of excess fluid and protein in the peritoneal cavity. Most cases so treated have required maintenance diuretic therapy. There are certain disadvantages in the procedure: infection must not be introduced to the drainage system or a bacteraemia will result. The system may become occluded by fibrin or thrombus, and may occasionally drain a loculus rather than the main peritoneal cavity. It is not suitable for cases of ascites associated with cardiac lesions.

Advantages are that it is a simple operation in unfit subjects and loss of protein from the body is avoided. Liver function has been shown to improve following this procedure and no serious encephalopathic signs have been observed. An occluded valve may be replaced by another. In some instances the method may serve to prepare a patient with both portal hypertension and ascites for a more complicated procedure.

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