

# The granuloma in Crohn's disease

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**SUMMARY** The number of granulomas in sections of bowel involved by Crohn's disease has been counted and related to length of previous history, treatment with steroids, site of involvement, and the subsequent course of the disease. It was found that a high content of granulomas predicted a good prognosis in the large bowel and anus, but was of no prognostic significance in the small bowel. A large regional variation in granuloma counts was observed from an average of 1 per section in the small bowel to 6 in the colon, 18 in the rectum, and 36 in the anus. Those patients with a long clinical history showed a low granuloma content. The findings are consistent with the view that the granuloma represents an adaptive mechanism for the removal or localisation of the causative agent of Crohn's disease.

Although Crohn's disease is usually described as a granulomatous disorder, granulomas are reported to be absent in 30-40% of cases (Morson and Dawson, 1972; Assarsson and Räf, 1974). Antonius *et al.* (1960) found no difference in the recurrence rate in patients with and without granulomas in bowel resected for Crohn's disease. Glass and Baker (1976) on the other hand, found that the presence of granulomas predicted a decreased chance of recurrence. Antonius *et al.* took 100 blocks from each of six patients with Crohn's disease who were reported on routine histology to have no granulomas, and found granulomas in three patients. To state that there are two groups of patients with Crohn's disease, those with and those without granulomas, is thus an oversimplification. This paper represents an attempt to relate a quantification of granulomas in bowel resected for Crohn's disease with the subsequent course of the disease.

## Methods

The patients included in this study were all the patients who had undergone primary surgery for Crohn's disease at St Mark's Hospital between 1955 and 1968 in whom a 10-year follow-up was available. The criteria used for a diagnosis of Crohn's disease were those described by Morson (1968). For each patient at least three, usually four, random sections from areas of resected bowel involved by Crohn's disease were inspected. The number of granulomas in each section was noted, together with the origin of the section (small intestine, colon, rectum, or anus). The patients' notes were then inspected. All

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patients with less than a 10-year follow-up were excluded, except from studies on the regional distribution of granulomas, and assessment of the effects of previous treatment with steroids. The 79 remaining patients were then divided into four groups:

1. Those patients with no evidence of recurrent Crohn's disease within 10 years after operation (47).
2. Those patients with radiological or biopsy evidence of recurrence of disease in parts of the bowel thought previously to be free of involvement, but in whom no further operation was performed (nine).
3. Those patients in whom recurrence necessitated further surgery (excision or resection). In these patients the sections of the operative specimens were analysed in the same way as the primary specimen (15).
4. Those patients in whom symptoms and signs (radiological or histological) of Crohn's disease persisted postoperatively for more than six months in areas known to have been diseased before operation (eight).

Those patients who had been administered steroids systemically within the 12 months preceding surgery were noted. The patients' assessment of the duration of previous symptoms was also noted.

## Results

Of the 79 patients in the study, 47 showed no recurrence within 10 years, a proportion which corresponds with recurrence rates for Crohn's disease or ileocolitis of 7-60% in other series (Baker, 1971; Burman *et al.*, 1971; de Dombal, *et al.*, 1971; Korelitz, *et al.*, 1972; Ritchie and

Table 1 *Number of granulomas per section in surgical specimens of Crohn's disease, related to subsequent disease course*

Group	Granulomas per section	Standard deviation	Number of specimens
No recurrence	13	19	47
Recurrence (no op.)	6.1	7.5	9
Recurrence (with op.)	4.4	8.3	15
Persistent disease	5.4	5.4	8
Persistent and recurrent disease	5.2	6.9	32

For no recurrence compared with the persistent/recurrent group as a whole, the likelihood of the difference in granulomas being due to chance is less than 1 in 100 ( $P < 0.01$ ).

Lockhart-Mummery, 1973; Steinberg, *et al.*, 1974). Fourteen patients had disease confined at primary surgery to the small bowel, 43 confined to the large bowel, and 22 had ileocolitis.

#### *Quantification of granulomas in Crohn's disease*

The granuloma is a closely packed aggregate of cells, predominantly of the mononuclear phagocyte system (Turk, 1971). In tissue sections granulomas are usually easily identified in Crohn's disease, appearing as foci of eosinophilic epithelioid cells and macrophages, often accompanied by one or more giant cells. Sometimes several granulomas appeared to have coalesced, when the mass was counted as one granuloma. It was found that the four sections of involved bowel from any given patient tended to contain similar numbers of granulomas in each section. The average number of granulomas per section in the operative specimens of patients in the four groups is shown in Table 1. Patients with no recurrence within 10 years had significantly more granulomas per section than those patients whose disease persisted or recurred after surgery. This is in agreement with the results of Glass and Baker (1976), who found that absence of granulomas in Crohn's disease predicted an increased chance of recurrence.

Rather unexpectedly we noticed that there was a wide regional variation in the number of granulomas in involved bowel. Taking all the slides from involved small intestine as a group, the average number of granulomas per section was 1.1, compared with 6.1 in the colon, 18.26 in the rectum, and 36.1 in the anus (Fig. 1). This large difference in granulomas in different parts of the bowel could have accounted for the decreased number of granulomas in patients with a poor prognosis if this group had a higher loading of sections taken from proximal bowel. However, Fig. 2 shows that in each region of the bowel (except the ileum) the number of granulomas was lower in poor-prognosis groups. The number of

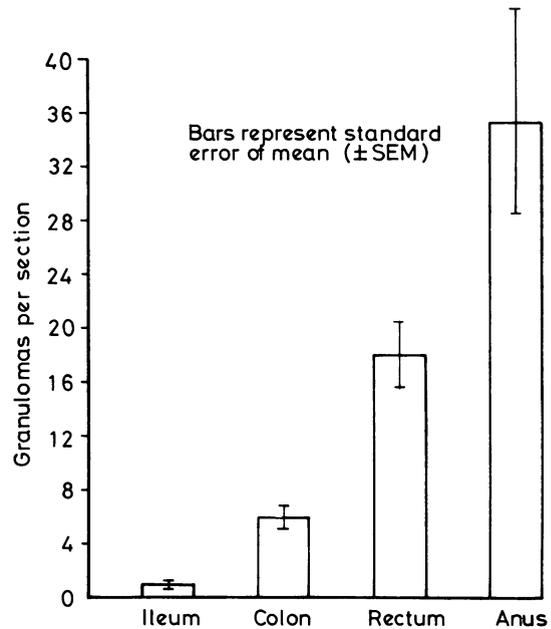


Fig. 1 *The average number of granulomas per section in bowel involved by Crohn's disease.*

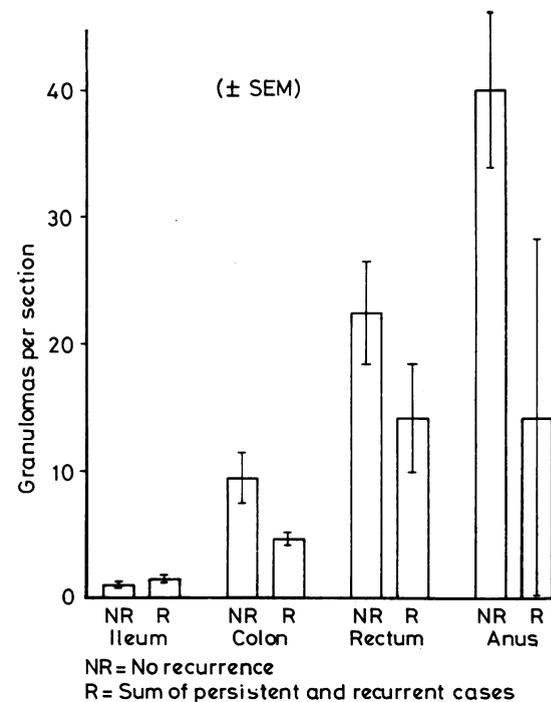


Fig. 2 *The number of granulomas in different regions of bowel involved by Crohn's disease, related to subsequent disease course.*

Table 2 Number of granulomas per section in surgical specimens of recurrent Crohn's disease

Origin of section	Granulomas (mean)	Standard deviation	No. of sections
Ileum	0.8	2	45
Colon	5	8.7	15
Rectum	0	—	5
Anus	4.3	4	3
Total	1.8	4.8	68

The chances of the sections of recurrences belonging to the same population as the persistence/recurrence primary excision specimen sections is less than 1 in 200 ( $P = <0.005$ ).

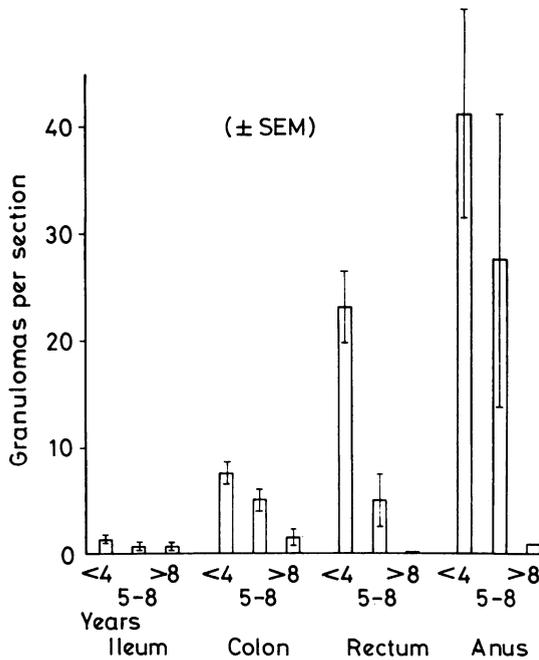


Fig. 3 The relationship between duration of previous symptoms and the number of granulomas in bowel excised for Crohn's disease.

granulomas per section in the terminal ileum of patients with disease confined to the ileum and in those with ileocolitis were calculated. It was found that in ileal Crohn's there was a mean of 0.6 granulomas per section, while in ileocolitis sections of ileum contained an average of 3.7 granulomas ( $P < 0.05$ ).

HISTOLOGICAL CHANGES AT RECURRENCE

Table 2 shows the average number of granulomas counted in specimens of recurrent disease. Compared with the average of primary resections or excisions, recurrent disease contains fewer granulomas. Recurrences also tended to repeat the pattern of the original specimen. If the number of granu-

lomas in the original specimen was lower than average, then the number in the recurrence was also likely to be low. This pattern was observed in 12 out of 13 pairs of specimens.

DURATION OF SYMPTOMS BEFORE SURGERY

All patients undergoing primary surgery, irrespective of subsequent course, were divided into three groups: those with symptoms for four years or less preceding surgery; those with symptoms for between four and eight years; and those with symptoms for more than eight years. Figure 3 shows that there is a significant relationship between duration of symptoms and the number of granulomas in subsequently removed bowel.

EFFECT OF STEROIDS ON GRANULOMAS

Systemic steroids were administered to some patients in the 12 months preceding surgery. In these the number of granulomas in all regions of the bowel was slightly reduced (Fig. 4) compared with patients not treated with steroids, but the difference did not reach statistical significance. Steroids have diverse effects on macrophage and lymphocyte function (Rinehart *et al.*, 1975) and have been shown to suppress granuloma formation (see Warren, 1976).

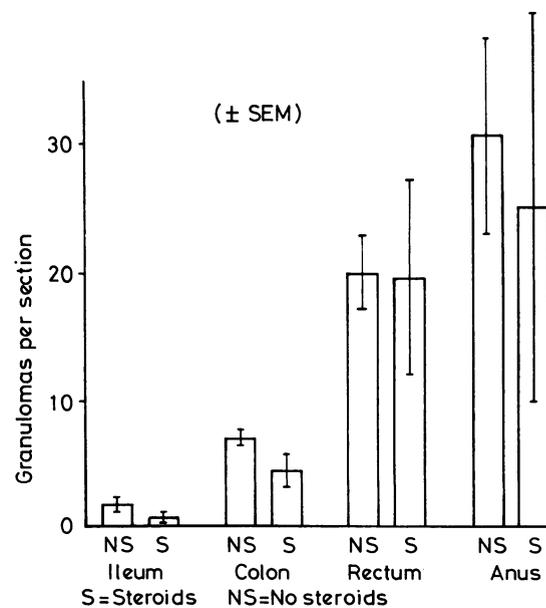


Fig. 4 The effect of steroids on the number of granulomas in bowel involved by Crohn's disease.

## Discussion

The significance of the granuloma in Crohn's disease is not clear. It is generally assumed to represent a response to the aetiological agent (Warren and Sommers, 1948; Golde, 1968; Mitchell *et al.*, 1976). It is conceivable that it follows mucosal ulceration with resulting penetration of bowel contents into tissues. Recently, Ward (1977) has suggested a third possibility—namely, that a macrophage defect prevents complete degradation of ingested material.

When present, the granuloma is a useful histological marker for Crohn's disease, since it is not seen in the major differential diagnoses of inflammatory bowel disease. Even in the 30% of cases in which granulomas are absent, however, the other features of Crohn's disease are sufficiently characteristic to allow a diagnosis in the majority of cases. The disease shows a predictable histological appearance, with mural thickening and transmural inflammation, submucosal lymphoid aggregates, and fissuring ulceration (Morson, 1968). Superimposed on these features is a histocytic infiltrate which shows a spectrum from diffuse, with no granuloma formation, through 'microgranulomas' (Morson, 1971; Rotterdam *et al.*, 1977) with collections of histiocytes too loosely aggregated to be definitively identified as granulomas, to an infiltrate in which granulomas are a dominant feature.

Glass and Baker (1976) divided patients into two groups: those with and those without granulomas. They found that the presence of granulomas conferred an improved prognosis. The present results are broadly in agreement with their findings. However, granulomas in Crohn's disease represent a continuous spectrum, between those patients in whom none are seen even on inspection of many sections, through those in whom a small sample shows no granulomas but more sections reveal their presence, to those patients in whom granulomas appear in large numbers. The results presented here show that the finding of a small number of granulomas does not lift the patient into a significantly better prognosis group in comparison with a patient in whom none was found.

It is unlikely that the granulomas of Crohn's disease arise as a reaction to the introduction of bowel luminal contents into the tissues secondary to mucosal ulceration. Granulomas are only rarely seen in other ulcerative diseases of the bowel—for example, ulcerative colitis and ischaemia. In diverticulitis, giant cells are often seen in the inflammatory infiltrate lining ulcerated surfaces, but they usually can be seen to contain faecal debris, and true granuloma formation is not a

feature. Further, in Crohn's disease granulomas are often seen in non-ulcerated bowel wall, and no luminal debris can be identified.

The findings of this study do not support the suggestion made by Ward (1977) that the granulomatous inflammation of Crohn's disease is a result of some defect in degradation by macrophages of foreign material penetrating from the bowel lumen through normal mucosa. If this were the case, then a granuloma count, as a quantitative measure of granulomatous inflammation, would be expected to be higher in those patients with a more severe macrophage defect. Patients with more granulomas should then have a worse prognosis than those with fewer. In fact, this study shows that high numbers of granulomas confer an improved prognosis.

By exclusion, the most likely explanation for the presence of granulomas in Crohn's disease is that they are a response of normal tissues to the aetiological agent of Crohn's disease. To elicit granuloma formation an agent must have certain predictable properties. The most important of these is resistance to degradation. This property alone is not sufficient to lead to granuloma formation. The injection of carbon particles into tissues, for instance, may lead to a transient mild inflammation, but, after ingestion by macrophages, the macrophages randomly leave the implantation site without granuloma formation. If on the other hand the insoluble material is either directly damaging to macrophages—for example, silica, streptococcal cell walls—or if the agent stimulates the immune system—for example, mycobacteria, beryllium—then granulomatous inflammation will result.

The results of this study are consistent with the view that the granulomas of Crohn's disease form as a response to a poorly soluble antigenic agent. Patients with many granulomas show a good prognosis, while the disease tends to recur in those with poor granuloma formation. By analogy with leprosy, the tuberculoid variety, with granuloma formation, is associated with a higher degree of cell-mediated immunity, and better clinical outlook than the lepromatous form, in which granulomas are not seen. In tuberculosis, too, cell-mediated immunity has been shown both in animals and man to be important in resistance, and low resistance is associated with lack of granuloma formation in response to the organism. Experimentally, Boros and Warren (1971) have shown, using Schistosome eggs, that for antigenic, but not for non-antigenic materials, the cellular immune system converts poor into strong granuloma formation. Assuming, therefore, that the material causing granuloma formation is the same in all cases of Crohn's disease, and also

assuming normal macrophage function, the results of this study suggest by analogy that the immune system is responsible for converting a diffuse chronic inflammatory reaction into a granulomatous reaction, and this in turn suggests the presence of a poorly degradable antigenic agent, the localisation or elimination of which is improved by granuloma formation.

A large regional variation in granuloma counts was observed, from an average of 1.1 in sections of small bowel involved by Crohn's disease, to 36.1 in the anus. The explanation for this is not clear. It may be due to environmental differences—there may be an increasing concentration of granuloma-forming material distally, but, if this were so, Crohn's disease would be expected to occur more commonly in the same distribution. Alternatively, the difference may be due to differences in tissue susceptibility. The tissue response to the causative agent may be less effective in the terminal ileum than in the distal bowel. The finding of fewer granulomas in the terminal ileum could then reflect this inadequate tissue response and account for the higher incidence of Crohn's disease in the terminal ileum than elsewhere (Morson and Dawson, 1972). This suggestion is rendered less likely by the observation that the anus, as probably the second commonest site of involvement by Crohn's disease (Colcock, 1973) has the highest content of granulomas.

Our last suggestion is that ileal Crohn's disease comes to surgery later in the disease course than more distal disease. We have already noted (Fig. 3) that patients with a longer period of symptoms before surgery had reduced numbers of granulomas in the excised bowel wall. This is in agreement with the observations of earlier workers who noted that the granuloma was among the earliest histological abnormalities, often preceding ulceration (Hadfield, 1939; Warren and Sommers, 1948; Rappaport *et al.*, 1951). When ulceration supervenes granulomas were found to become less common or disappear altogether. The explanation for the reduced granuloma content of operative specimens of proximal bowel compared with distal bowel may then be that proximal disease necessitates surgery later in its course than distal disease. The reason for this may be that the luminal contents of the terminal ileum are still fluid, and a greater degree of obstruction may be necessary before surgery is needed for obstructive disease. In the distal bowel, the more solid bowel contents may lead to earlier obstruction. The situation may be analogous to caecal carcinoma, which classically remains occult longer than more distal tumours. Distal Crohn's disease would also seem more likely to cause diarrhoea earlier than

small intestinal Crohn's disease. The suggestion that ileal disease comes to surgery late would fit with the rigid 'hose pipe' stricture of the terminal ileum found at operation—such advanced fibrous narrowing is rarely found in the colon. We found that patients with disease confined to the ileum had significantly fewer granulomas than those in whom the colon was also involved. This is compatible with the suggestion that ileal disease has less granulomas due to later surgery, since the colonic disease would cause an earlier excision of diseased ileum, with a correspondingly increased ileal granuloma content.

A suggested course of events would be that some poorly degradable antigenic agent gains access to the bowel wall, and that the granuloma is an adaptation for the improved elimination of the agent. Early in the disease a well-marked granulomatous response thus suggests an effective host response. Poor granuloma formation on the other hand suggests poor resistance, as evidenced by persistence or recurrence of disease. Later in the disease process fewer granulomas may reflect either a continued poor response, with the same prognostic implications, or the late, resolving stage of an effective response.

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