

## Progress report

# The place of surgery in Crohn's disease

In the early years after the recognition of regional enteritis by Crohn and his colleagues<sup>1</sup>, surgical treatment was considered curative and excision of the affected bowel the ideal treatment. During the next 10 years the high recurrence rate after surgery worried physicians and disillusioned surgeons and so Crohn's disease came to be regarded as something of a surgical enigma<sup>2</sup>.

The surgeon encounters Crohn's disease either as an acute emergency (often when the diagnosis has not been made before operation) or as a premeditated operation after the patient's condition has been carefully evaluated. The proportion of patients presenting as emergencies varies depending on whether the unit with the major interest in the disease is surgical or medical. In reports from surgical units approximately 20% of the patients reported have presented as acute emergencies<sup>3,4</sup>, whereas from medical units the proportion has been less than 10%<sup>5,6,7</sup>.

### Acute Ileitis

The clinical picture is often similar or identical to that of acute appendicitis and because of the dangers of neglecting acute appendicitis it is sometimes unsafe to make a confident preoperative diagnosis. The condition is usually diagnosed at laparotomy on the appearance of a thickened, inflamed terminal ileum.

Views on the correct management vary; the conservative view<sup>8,9,10,11</sup> is that nothing further should be done and the abdomen should be closed<sup>9,11,12,13</sup>. The results, however, do not support this conservative view. From centres with a large experience with acute ileitis a total of 93 patients were reported, 83 of whom had appendicectomy performed. Only two patients went on to develop fistula<sup>3,14,15</sup>. Studies of patients who have developed faecal fistulae after appendicectomy have shown that the majority arise from the adjacent terminal ileum<sup>3,14,15,16</sup> and it seems reasonable to assume that when a fistula occurs it is usually because of the laparotomy rather than the fact that the appendix was removed.

Is acute ileitis always due to Crohn's disease? Some patients initially diagnosed as having acute ileitis undoubtedly progress to the typical chronic Crohn's disease with recurrence and the characteristic histological features. However, it appears that over 90% of patients diagnosed as acute ileitis at laparotomy never manifest the signs of chronic Crohn's disease<sup>15</sup>. The typical findings of Crohn's disease may be absent, there may be no oedema of the mesentery and histological examination of excised appendices and regional nodes may not show the histological features of chronic Crohn's disease<sup>3</sup>. An interesting epidemiological study was reported among British troops in Port Said in 1956 which suggested that acute ileitis might be due to a bacterial or viral infection<sup>17</sup>.

As there is no way at laparotomy to distinguish the patients in whom the

disease is destined to become chronic there is, therefore, no indication for excision or bypass. There appears to be no significant danger in removing the appendix. However, appendectomy or lymph node biopsy is not indicated to provide a histological diagnosis or to elucidate the aetiology of Crohn's disease. The principal justification for appendectomy is that it would enable acute appendicitis to be excluded from the differential diagnosis in any future attack.

### Perforation

Free perforation into the peritoneal cavity is a rare complication of Crohn's disease. It is difficult to assess the true incidence as in some reports it is not possible to distinguish it from a rupture of a chronic intraabdominal abscess. In collected reports of 603 patients with chronic Crohn's disease, six have been reported with an acute free perforation<sup>3, 4, 14, 18, 19</sup> while of 65 patients with acute ileitis none were complicated by free perforation<sup>3, 4</sup>. In our experience of over 300 patients with chronic Crohn's disease we have seen six with an acute free perforation and three patients with peritonitis due to rupturing of a chronic intraabdominal abscess<sup>20</sup>. Our experience at Birmingham has been similar to that in other centres in that free perforation occurs during an acute exacerbation of chronic disease associated with distal obstruction due to stenosis<sup>21, 22</sup>. Free perforation can occur in patients who have had no previous operation and has so far been reported less commonly in patients who are on steroids than in those who are not.

The only report of perforation of colonic Crohn's disease was of one case where the perforation occurred at the splenic flexure<sup>23</sup>. Two instances have been reported of a perforation occurring in a bypassed loop of small bowel and in both of these there was distal obstruction<sup>20, 22</sup>. Treatment by simple closure and/or drainage has usually proved disastrous. Of 13 reported patients who were treated in this way, four died after the operation, one died immediately after a second operation for a re-perforation, and five needed early re-operation<sup>20, 21</sup>. The optimum treatment appears to be the primary excision of the perforated segment and all the distal diseased bowel.

### Elective Surgery for Crohn's Disease

In 1955 Kiefer<sup>24</sup>, reviewing the problem of recurrent Crohn's disease, felt that the place of surgery in Crohn's disease was in the management of its complications. The knowledge of the succeeding 15 years does not alter this view.

While recognizing that indications for surgery are almost always multiple this next section subdivides the subject and considers the place of surgery for bleeding, abscesses, fistulae and peri-anal complications, and the particular implications of Crohn's colitis.

#### ANAEMIA AND BLEEDING

Mucosal ulceration is an essential feature of the pathology of Crohn's disease so that intestinal blood loss is inevitable. Anaemia is common but severe, exanguinating bleeding is rare. The recognition of overt blood in the stool is dependent on the distance between the active lesion and the anus.

In a comprehensive haematological review of 300 patients it was found that at some time in the course of the history of the disease iron deficiency

occurred in 60% of patients, vitamin B<sub>12</sub> deficiency in 50%, and folic acid deficiency in 41%<sup>25</sup>.

Overt rectal bleeding is reported as occurring in between five and 15% of patients with predominantly small bowel disease<sup>6, 9, 13, 19, 26, 27</sup>. Reports differ about the incidence of bleeding when the large bowel is involved; some workers say it is common, some rare. Out of the total of 171 patients with Crohn's disease of the colon<sup>4, 28, 29, 30</sup>, 89 (52%) had overt rectal bleeding. However, in other series with a total of 102 patients<sup>31, 32, 33</sup>, only four patients (4%) were reported as having rectal bleeding and the rarity of bleeding was considered an important point of differentiation from ulcerative colitis.

Massive bleeding as the prime indication for surgical treatment of Crohn's disease is rare<sup>12</sup>. A total of 13 patients with massive bleeding from either ileum or colon can be found from a review of the literature<sup>2, 5, 19, 34, 35, 36</sup>, with an incidence—in the large series—of approximately 1%.

It must be remembered that massive bleeding in patients with Crohn's disease does not always necessarily come from the Crohn's disease itself but may come from a chronic duodenal ulcer<sup>38</sup>.

#### ABSCESS

The incidence of abscess formation is not easy to define but in some of the large series it appears that between 15 and 25% of patients have had excision or drainage of an abscess at some time<sup>5, 6, 13, 14</sup>. Two types of abscess appear to occur, those occurring spontaneously during the course of the disease and those following operative treatment.

Spontaneous abscess formation is common but the method of formation is not clearly understood, Schofield<sup>4</sup> considering that large lymph nodes may break down to form abscesses. However, the pathological changes in the lymph nodes in Crohn's disease are essentially those of non-caseative and non-suppurative inflammation so that node suppuration is probably a rare cause of abscess formation. It seems more likely that abscesses are the result of a slow penetration of the gut by ulceration. Many abscesses then find their way back into the gut, another organ, or the exterior and become fistulae.

Postoperative abscesses usually present early; however, it appears possible for abscesses to present months or even years later and still be a direct complication. Patients, whose operation was complicated by sepsis, have discharged a large pelvic abscess many years later without evidence of any recurrent bowel disease<sup>7, 37</sup>.

It appears that most, but not all, patients who have abdominal abscesses drained continue to have fistulae usually through the site of draining of the abscess<sup>10, 37</sup>.

#### *Treatment*

When an abscess presents at the surface or can be drained without rupture into the peritoneal cavity, simple drainage would appear to be the emergency treatment of choice, although it should be recognized that a fistula will almost always follow. If a deep intraabdominal abscess is encountered during the course of exploration for complicated chronic Crohn's disease it is usually possible to remove the abscess and affected bowel en masse. There may be occasions, however, when it would be wiser to drain the abscess and bypass the affected bowel.

## FISTULAE

Fistulae (excluding peri-anal fistulae) are due to the gradual transmural progression of ulceration preceded by a chronic inflammatory response that causes the adherence of serosal surfaces, the fistula becomes either internal or external, depending on whether the adhering serosa is visceral or parietal.

The relative incidence of internal and external fistulae are shown in Table I.

Series	Date of Communication	Percentage Incidence		
		Internal	External	Total
Van Patter <i>et al</i> <sup>27</sup>	1954	—	—	48
Crohn and Yarnis <sup>9</sup>	1958	—	—	42
Brown and Daffner <sup>38</sup>	1958	—	—	48
Colcock <sup>3</sup>	1964	18	17	35
Atwell <i>et al</i> <sup>3</sup>	1965	14	14	28
Schofield <sup>4</sup>	1965	12	19	31
Gjone <i>et al</i> <sup>18</sup>	1966	10	23	33
Koutny <sup>19</sup>	1968	20	21	41
Banks <i>et al</i> <sup>14</sup>	1969	—	—	31
Edwards <sup>13</sup>	1969	12	17	29
Williams <i>et al</i> <sup>9</sup>	1971	9	17	26

Table I Incidence of internal and external fistulae

However, the true incidence of internal fistulae is probably underestimated in most reports as the diagnosis often cannot be made until after surgical excision; even then it can be difficult.

Can fistulae arise spontaneously or do they always follow surgical intervention? Crohn and Yarnis<sup>9</sup> said that 'spontaneous fistulas to the abdominal wall without a previous laparotomy have not been observed'. Since then a total of 18 patients have been reported in whom fistulae either developed spontaneously or after the drainage of an abscess in patients who had no previous laparotomy<sup>3, 10, 19, 39</sup>.

As many fistulae occur after surgical intervention and frequently present through the scar, the surgeon tends to be blamed for causing the fistula. This blame is probably unjust for all the surgeon does is to provide a rough peritoneal surface to which the inflamed gut will adhere. Fistulae appear to be more common when the previous operation was 'exploratory' than when it was 'curative' (either excision or bypass)<sup>3</sup>.

Abdominal fistulae appear to be uncommon from Crohn's disease of the large bowel. In almost all the reported series of colonic Crohn's disease when external abdominal fistulae have occurred they have arisen from associated ileal disease<sup>26, 30, 31, 40</sup>.

The risk of developing a fistulae has been related to the severity of the disease<sup>13</sup> and also to the length of bowel involved<sup>40</sup>. From Table I it can be seen that the incidence of fistulae is less in the later reports than it was in series reported more than 10 years ago. It is possible that surgery is now being undertaken earlier before fistulae have a chance to develop. It seems likely also that the advent of steroid therapy has not increased the risk of fistula formation<sup>40</sup>.

*Treatment*

Fistulae arising immediately after resection are due to suture-line leakage rather than to continued disease activity and may heal spontaneously<sup>4</sup>. However, fistulae associated with active bowel disease only rarely close spontaneously. Simple local surgical treatment by curettage or simple suture is usually futile. The optimum form of treatment is excision en bloc of the actively diseased bowel from which the fistula is arising<sup>10, 13</sup>.

Immunosuppressive drugs such as azathioprine have been advocated in the treatment of patients with complex fistulae and successful closure without operation has been recorded<sup>39, 41, 42</sup>. However, the risks of long-term immunosuppressive therapy are usually greater than the risks of surgical resection and these drugs should not be looked upon as a substitute for surgical treatment of fistulae.

## ANAL LESIONS

The term 'anal lesion' is preferred to the more accurate pathological terminology of fissure or fistula as it is often difficult to differentiate these without thorough examination under anaesthesia<sup>43</sup>. A typical anal lesion is one or more indolent irregular ulcers with undermined edges and surrounding oedema. Fistulae also develop that also are often indolent and relatively painless. The reported incidence in different series is shown in Table II.

<i>Series</i>	<i>Date</i>	<i>Incidence (%)</i>
<i>Predominantly small bowel disease</i>		
Barber <i>et al</i> <sup>6</sup>	1962	11
Colcock and Vansart <sup>6</sup>	1962	18
Atwell <i>et al</i> <sup>3</sup>	1965	8.5
Schofield <sup>4</sup>	1965	14.3
Koutny <sup>19</sup>	1968	29
Banks <i>et al</i> <sup>14</sup>	1969	27
Edwards <sup>13</sup>	1969	12.5
Fielding <sup>44</sup>	1970	76
<i>Predominantly colonic Crohn's disease</i>		
Lockhart-Mummery and Morson <sup>45</sup>	1964	81
Schofield <sup>4</sup>	1965	43.7
Schofield and Fox <sup>46</sup>	1967	75
Farmer <i>et al</i> <sup>28</sup>	1968	50
Kyle <sup>47</sup>	1968	50
McGovern and Goulston <sup>32</sup>	1968	50
Fielding <sup>44</sup>	1970	93

Table II *Incidence of anal lesions*

The wide variation in the reported incidence can be seen although it is clear that anal lesions are much more common when the colon is involved than when the small bowel is involved. With distal colonic and rectal Crohn's disease the incidence of anal lesions approaches 100%. The incidence of abnormality is directly related to the care with which the area is examined. The very high incidence reported by Fielding includes the presence of hypertrophied skin tags; these were also found in 40% of a control series examined.

Anal fissures were present in 50% of those with small bowel disease, in 60% with large bowel disease, and in 4% of the control patients<sup>44</sup>.

The management of patients with Crohn's disease affecting the anal region presents a difficult problem, made easier only by the fact that the lesions are often not particularly painful. Most authors favour conservative management and suggest that ill considered intervention can exacerbate Crohn's lesions which will not heal<sup>14</sup>. Many believe that perineal wounds will not heal until the active proximal lesion is quiescent or excised. However, there is no published evidence to support this hypothesis<sup>2, 4, 45</sup>. Anal fistulae do not necessarily heal even after faecal diversion by ileostomy and furthermore fistulae can arise even after diversion<sup>48</sup>.

#### COLONIC CROHN'S DISEASE

Crohn's disease can occur in the colon alone as well as in association with small bowel involvement<sup>31, 45, 49</sup>. When the disease predominantly affects the large bowel the symptomatology and indications for surgical treatment are different from those when the small bowel is affected. In colonic Crohn's disease the incidence of anal lesions and rectal bleeding is increased but the incidence of obstructive symptoms and of external fistulae is decreased.

Acute toxic dilatation, once thought to be peculiar to ulcerative colitis, has now been described in patients considered to have Crohn's disease of the colon. In some of the reported series the criteria for the diagnosis of Crohn's colitis would not satisfy all authorities<sup>28, 32</sup>. However, there are at least four published reports of patients with unequivocal Crohn's disease and acute dilatation<sup>23, 50</sup>.

As Crohn's disease of the colon is often segmental is local excision indicated? When the right side of the colon is involved in continuity with ileal disease a right hemicolectomy is the treatment of choice<sup>32</sup>. In view of the high risk of recurrence after segmental resections most authorities advocate managing colonic disease conservatively; when operation is imperative, radical excision with ileorectal anastomosis or total colectomy is considered the treatment of choice<sup>31, 32</sup>. There is, however, a high rate of recurrence even after ileorectal anastomosis<sup>8, 51</sup> or total colectomy and ileostomy<sup>52</sup>.

#### Surgical Technique

Three of the important technical questions facing the surgeon treating a patient with Crohn's disease are: (1) should the disease be bypassed or resected? (2) how much of the bowel should be resected? and (3) can bowel affected by Crohn's disease be 'rested' by bypass with the expectation of later successful reconnexion?

#### EXCISION VERSUS BYPASS

The early attempts at curative excision of Crohn's disease proved hazardous and in 1940 surgeons began to favour bypass as being a safer alternative<sup>53</sup>. Although many surgeons express preference for bypass with exclusion as opposed to a simple side-to-side bypass<sup>54</sup>, no conclusive evidence has been provided to prove its superiority. Improvement in postoperative management soon led to a substantial reduction in the risk of all operations and surgeons then found that the immediate results of excising the inflamed area were just as good, if not better, than those of bypass. As surgeons prefer to have 'the



disease in the bucket rather than in the patient' excision became the preferred method of treatment. When a panel considered this question in 1959, Dr Crohn was alone amongst the distinguished gathering in favouring bypass<sup>55</sup>.

In the past 10 years most of the reported series tended to favour excision. A comparison of the recurrence rates reported after bypass and excision is shown in Table III.

Series	Date	Bypass		Excision	
		No. of Patients	Recurrence (%)	No. of Patients	Recurrence (%)
Barber <i>et al</i> <sup>6</sup>	1962	15	40	75	16
Colcock <sup>2</sup>	1964	30	87	—	—
Atwell <i>et al</i> <sup>3</sup>	1965	39	92	145	50
Schofield <sup>4*</sup>	1965	18	89*†	49	18*†
Gjone <i>et al</i> <sup>18</sup>	1966	16	79	41	4
Fielding <i>et al</i> <sup>56</sup>	1971	25	80 44*†	89	48 26*†

Table III *Bypass versus excision*

\*At five years after the first operation.

†Significantly less after excision,  $P < 0.0005$ .

There are many limitations to such an analysis, one of the principal ones being that in most of the reports cited, bypass was the preferred treatment in the early part of the series whereas bypass was later reserved for the seriously ill patients, so prejudging the results in favour of excision. In few of the reports is the risk of recurrence related to the length of follow up. However, in the two series in which the recurrence rate is measured at five years there is a highly significant advantage in favour of the excision operation<sup>4, 56</sup>. Nevertheless other authors conclude that the type of initial operation did not affect the ultimate result<sup>14</sup>.

When Crohn's disease of the duodenum causes obstruction, bypass by gastrojejunostomy appears to be the treatment of choice<sup>2, 57</sup>.

#### HOW MUCH TO RESECT ?

Some surgeons believe that surgery has a place only in the treatment of the local complications of Crohn's disease and that there is no point in attempting to remove the whole of the affected gut<sup>58</sup>. Other surgeons, conscious of the high recurrence, particularly at the site of previous anastomoses, believe that a generous segment (30-60 cm) of normal gut should be removed on either side of the affected area<sup>59</sup>. Other surgeons, believing that Crohn's disease begins in the affected regional lymph nodes, try to excise all the enlarged mesenteric nodes, even if this means the sacrifice of a length of apparently normal gut<sup>8</sup>. There is no proof that any of these views is correct and so far there are no published data that allow us to compare the results of the various surgical philosophies. It is important to recognize that skip areas of ulceration of the mucosa can extend over long distances proximal to an area of the gut obviously affected by Crohn's disease on its serosal surface. Moreover, it has been shown that bowel, appearing to the surgeon to be macroscopically normal at operation, may contain microscopic mucosal abnormalities even in areas remote from any obvious active disease<sup>59</sup>. Some advocate immediate

frozen section examination of the line of section<sup>58,60</sup>. However, it is simpler, and probably of greater value, to observe the naked-eye appearance of the surface of the opened specimen to judge how far clear is the resection from gross mucosal disease<sup>3,61</sup>.

There is clearly a need for a prospective study in an attempt to determine whether there is any advantage in taking a generous portion of normal bowel on either side of the grossly diseased area.

#### CAN DEFUNCTED BOWEL BE SUCCESSFULLY USED AGAIN ?

As Crohn's disease may involve successive lengths of bowel, after each resection there is a danger that the patient may eventually 'run out' of normal gut and as active disease sometimes resolves in a bypassed segment, it is theoretically attractive to 'rest' an inflamed segment for later re-use. There are few reports of this theoretical ideal being achieved. Truelove and his colleagues<sup>62</sup> performed ileostomies on five patients with Crohn's disease. Four survivors had the ileostomy closed later; three with successful results. All three, however, needed excision of some diseased gut before the ileostomy could be closed, so that in none of them did the bypass enable the active disease to subside so that it could successfully be used again. Of 13 other patients with Crohn's colitis who had a defunctioning ileostomy, the radiological and biopsy appearance was returned towards normal in all and three were later re-united with two short-term successes.<sup>29</sup>

In three other series a total of 37 patients have had lengths of 'active' Crohn's disease defunctioned by bypass or exclusion and in none of these did the disease process settle sufficiently to allow the bowel to be used again in circuit<sup>32, 48, 63</sup>.

Continued disease in a bypassed loop may be dangerous<sup>2</sup>; two patients have died following a free perforation<sup>20,22</sup>.

### Results of Surgical Treatment

#### MORTALITY

It is difficult to measure the success of surgical treatment of Crohn's disease other than by surgical mortality and recurrence; even these measurements do not necessarily allow comparison of one series with another.

Not all series define 'operative mortality' though this is usually accepted as being death within one month per 100 operations. In those centres where desperate salvage surgery is usually attempted on all terminal patients with Crohn's disease the surgical mortality will be high and it may therefore be more accurate to compare the number of surgically treated patients who died of the disease.

It is necessary first to consider the overall mortality and the disease mortality. These figures should also be related to the length of follow up. The figures for four of the large series with a fully recorded long-term follow up are shown in Table IV.

It appears from these figures that, in patients with Crohn's disease followed for more than 10 years, approximately half the deaths occurring are due to the disease or its effects. The incidence of unrelated deaths is similar to the expected death rate according to life insurance tables<sup>65</sup> and so it may be said that Crohn's disease halves the patient's expectation of life.

The operative mortality can be calculated by dividing the number of deaths



Centre	Date	No. of Patients	Mean Follow-up (yr)	Total Dead		Died of Disease	
				No.	%	No.	%
Boston, USA <sup>14</sup>	1969	168	14.5	25	15	16	9.5
London <sup>13</sup>	1969	276	11*	48	17	> 24	8.7
Birmingham <sup>1</sup>	1971	300	13.7	54	18	25	8.3
Leeds <sup>64</sup>	1971	244	Range: 1-30	39	17	—	—

Table IV Mortality

\*Exact figure not given in the original paper.

occurring within one month of operation by the number of major therapeutic (as opposed to diagnostic) operations. Unfortunately not all series differentiate between major therapeutic operations such as resection or bypass and minor diagnostic operations such as laparotomy, appendicectomy, drainage of an abscess, or minor anal procedures.

The operative mortality compared with patient mortality is shown in Table V. The mortality figures from the different centres compare very closely, indicating a risk of approximately 5% attending each major operative procedure.

Centre	Date	No. of Patients Treated Surgically	No. of Major Operations	Surgical Deaths	Operative Mortality	Patient Mortality (%)
Rochester, USA <sup>27</sup>	1954	402	564	22	3.9	5.5
Boston, USA <sup>6</sup>	1960	304	346	6	1.7	2.0
Rochester, USA <sup>5</sup>	1962	257	325	8	2.4	3.1
Norway <sup>18</sup>	1966	72	57	4	7.0	5.5
London <sup>66</sup>	1967	73	91	5	5.5	6.8
Boston, USA <sup>14</sup>	1969	147	213	11	5.2	7.5
London <sup>13</sup>	1969	195	244	12	4.9	6.2
Birmingham <sup>7</sup>	1971	254	459	18	3.9	7.1
Leeds <sup>64</sup>	1971	244	415	24	5.7	9.9

Table V Mortality

#### RECURRENCE

The exact definition of recurrence presents some difficulties as recurrent symptoms such as diarrhoea or weight loss do not necessarily mean a recurrence of the active disease process but may be due to secondary disorders such as bile salt deficiency. The ratio of recurrent symptoms to the need for surgical treatment varies from 3 to 1 to 1.5 to 1<sup>3, 5, 6, 66, 27</sup>.

It is perhaps most accurate to consider recurrence rate as the need for further surgical treatment but even this does not permit an accurate comparison of series, as in some centres patients are submitted to re-operation much sooner than in others. Some authorities believe that it is not worthwhile submitting a patient to more than three excision or bypass operations<sup>4, 24</sup>, while others believe in 'salvage surgery'<sup>67</sup>, and as many as 5-30% of patients have had four or more operations<sup>7, 14</sup>.

A 'league table' of the re-operation rate after resection was constructed by Lennard-Jones and Stalder<sup>66</sup> and is reproduced in Table VI.

Series	Date	No. of Patients	Length of Follow-up (yr)	Risk of Requiring Second Operation (%)
Crohn and Yarnis <sup>9</sup>	1958	62	1-25	27.4
Pollock <sup>68</sup>	1958	24	> 5	33
		11	> 10	45
Brown and Daffner <sup>38</sup>	1958	28	?	54
Gump <i>et al</i> <sup>15</sup>	1960	66	> 2	15.2
Colcock and Vansart <sup>6</sup>	1960	272	Up to 25	20.6
Barber <i>et al</i> <sup>5</sup>	1963	88	> 10	26.5
Atwell <i>et al</i> <sup>3</sup>	1965	133	Up to 20	25.6
Schofield <sup>4</sup>	1965	47	> 5	19.1
Lennard-Jones and Stalder <sup>66</sup>	1967	71	Up to 10	17.0

Table VI Recurrence

J. ALEXANDER WILLIAMS  
*Nutritional and Intestinal Unit,  
 General Hospital, Birmingham*

#### References

- <sup>1</sup>Crohn, B. B., Ginzberg, L., and Oppenheimer, G. D. (1932). Regional ileitis: a pathologic and clinical entity. *J. Amer. med. Ass.*, **99**, 1323-1329.
- <sup>2</sup>Colcock, B. P. (1964). Regional enteritis: a surgical enigma. *Surg. Clin. N. Amer.*, **44**, 779-784.
- <sup>3</sup>Atwell, J. D., Duthie, H. L., and Goligher, J. C. (1965). The out come of Crohn's disease. *Brit. J. Surg.*, **52**, 966-972.
- <sup>4</sup>Schofield, P. F. (1965). The natural history and treatment of Crohn's disease. *Ann. roy. Coll. Surg. (Engl.)*, **36**, 258-279.
- <sup>5</sup>Barber, K. W., Jr., Waugh, J. M., Behars, O. H., and Sauer, W. G. (1962). Indications for and the results of the surgical treatment of regional enteritis. *Ann. Surg.*, **156**, 472-482.
- <sup>6</sup>Colcock, B. P., and Vansant, J. H. (1960). Surgical treatment of regional enteritis. *New Engl. J. Med.*, **262**, 435-439.
- <sup>7</sup>Cooke, W. T. (1971). Personal communication.
- <sup>8</sup>Burman, J. H., Cooke, W. T., and Williams, J. A. (1971). The fate of ileorectal anastomosis in Crohn's disease. *Gut*, **12**, 432-436.
- <sup>9</sup>Crohn, B. B., and Yarnis, H. (1958). *Regional Enteritis*, 2nd ed. Grune and Stratton, New York.
- <sup>10</sup>Enker, W. E., and Block, G. E. (1969). The operative treatment of Crohn's disease complicated by fistulae. *Arch. Surg.*, **98**, 493-499.
- <sup>11</sup>Slaney, G. (1968). Crohn's disease. *Brit. med. J.*, **2**, 294-298.
- <sup>12</sup>Cattell, R. B. (1959). Panel discussion. Regional enteritis. *Gastroenterology*, **36**, 403-408.
- <sup>13</sup>Edwards, H. (1969). Crohn's disease, an enquiry into its nature and consequences. *Ann. roy. Coll. Surg. (Engl.)*, **44**, 121-139.
- <sup>14</sup>Banks, B. M., Zetzel, L., and Richter, H. S. (1969). Morbidity and mortality in regional enteritis. *Amer. J. dig. Dis.*, **14**, 369-379.
- <sup>15</sup>Gump, F. E., Lepore, M., and Barker, H. G. (1967). A revised concept of acute regional enteritis. *Ann. Surg.*, **166**, 942.
- <sup>16</sup>Marx, F. W., Jr. (1964). Incidental appendectomy with regional enteritis. *Arch. Surg.*, **88**, 546-551.
- <sup>17</sup>Cowan, D. J. (1958). Appendicitis and acute terminal ileitis during an outbreak of gastro-enteritis among British troops in Port Said. *Brit. med. J.*, **1**, 438-440.
- <sup>18</sup>Gjone, E., Orning, G. O. M., and Myren, J. (1966). Crohn's disease in Norway. *Gut*, **7**, 372-374.
- <sup>19</sup>Koutny, J. (1968). Experience clinique et chirurgicale dans 70 cas de maladie de Crohn. *Acta chir. belg.*, **10**, 981-1010.
- <sup>20</sup>Williams, J. A., and Cooke, W. T. (1971). Free perforation in Crohn's disease. (In preparation.)
- <sup>21</sup>Nasr, K., Morowitz, D. A., Anderson, J. G. D., and Kirsner, J. B. (1969). Free perforation in regional enteritis. *Gut*, **10**, 206-208.
- <sup>22</sup>Waye, J. D., and Lithgow, C. (1967). Small bowel perforation in regional enteritis. *Gastroenterology*, **53**, 625-629.
- <sup>23</sup>Javett, S. L., and Brooke, B. N. (1970). Acute dilatation of colon in Crohn's disease. *Lancet*, **2**, 126-128.
- <sup>24</sup>Kiefer, E. D. (1955). Recurrent regional ileitis. *Surg. Clin. N. Amer.*, **35**, 801-807.
- <sup>25</sup>Swan, C. H. J. (1969). M.D. Thesis. University of Birmingham.
- <sup>26</sup>Korelitz, B. I. (1967). Clinical course, late results and pathological nature of inflammatory disease of the colon initially sparing the rectum. *Gut*, **8**, 281-290.
- <sup>27</sup>Van Pater, W. N., Barga, J. A., Dockerty, M. E., Feldman, W. H., Mayo, W., and Waugh, J. M. (1954). Regional enteritis. *Gastroenterology*, **26**, 347-450.

- <sup>18</sup>Farmer, R. G., Hawk, W. A., and Turnbull, R. B., Jr. (1968). Regional enteritis of the colon. A clinical and pathologic comparison with ulcerative colitis. *Amer. J. dig. Dis.*, **13**, 501-514.
- <sup>19</sup>Oberhelman, H. A., Jr., Kohatsu, S., Taylor, K. B., and Kivel, R. M. (1968). Diverting ileostomy in the surgical management of Crohn's disease of the colon. *Amer. J. Surg.*, **115**, 231-240.
- <sup>20</sup>Schmidt, G. T., Lennard-Jones, J. E., Morson, B. C., and Young, A. C. (1968). Crohn's disease of the colon and its distinction from diverticulitis. *Gut*, **9**, 7-21.
- <sup>21</sup>Lindner, A. E., Marshak, R. H., Wolf, B. S., and Janowitz, H. D. (1963). Granulomatous colitis: a clinical study. *New Engl. J. med.*, **269**, 379-385.
- <sup>22</sup>McGovern, V. J., and Goulston, S. J. M. (1968). Crohn's disease of the colon. *Gut*, **9**, 164-176.
- <sup>23</sup>Snellman, B., and Westerholm, P. (1967). Crohn's disease of the colon and rectum. *Dis. Colon Rect.*, **9**, 427-433.
- <sup>24</sup>Brown, P. W. (1957). Massive recurring bleeding in regional enteritis. *Minn. Med.*, **40**, 847-848.
- <sup>25</sup>Goldstein, M. J., Schachter, H., and Kirsner, J. B. (1958). Surgery and clinical progression in patients with Crohn's disease of the small and large intestine. *Amer. J. Surg.*, **115**, 376-384.
- <sup>26</sup>Williams, J. A., Swan, C. H. J., and Cooke, W. T. (1911). Bleeding as an indication for surgery in Crohn's disease. (In preparation.)
- <sup>27</sup>Goldstein, M. J., Nasr, K., Singer, H. C., Anderson, J. G. D., and Kirsner, J. B. (1969). Osteomyelitis complicating regional enteritis. *Gut*, **10**, 264-266.
- <sup>28</sup>Brown, C., and Daffner, J. E. (1958). Regional enteritis II. Results of medical and surgical treatment in one hundred patients. *Ann. intern. Med.*, **49**, 595-606.
- <sup>29</sup>Williams, J. A., Fielding, J. F., and Cooke, W. T. (1971). Fistulae in Crohn's disease. (In preparation.)
- <sup>30</sup>Eade, M. N., Cooke, W. T., and Williams, J. A. (1971). The interrelationship of clinical and haematological features of Crohn's disease: *Surg. Gynec. Obstet.*, In press.
- <sup>31</sup>Brooke, B. N., Javett, S. L., and Davison, O. W. (1970). Further experience with azathioprine for Crohn's disease. *Lancet*, **2**, 1050-1053.
- <sup>32</sup>Jones, F. A., Brown, P., Lennard-Jones, J. E., Jones, J. H., and Milton-Thomas, G. J. (1969). Azathioprine for Crohn's disease. *Lancet*, **2**, 795.
- <sup>33</sup>Morson, E. C., and Lockhart-Mummery, H. E. (1959). Anal lesions in Crohn's disease. *Lancet*, **2**, 1122-1123.
- <sup>34</sup>Fielding, J. F. (1970). Crohn's disease. M.D. Thesis, University of Cork.
- <sup>35</sup>Lockhart-Mummery, H. E., and Morson, B. C. (1964). Crohn's disease of the large intestine. *Gut*, **5**, 493-509.
- <sup>36</sup>Schofield, P. F., and Fox, H. (1967). The diagnosis of Crohn's disease of the colon. *Brit. J. Surg.*, **54**, 307-311.
- <sup>37</sup>Kyle, J. (1968). Fistula formation in regional enteritis. In Abstracts of *VIIIth International Congress of Gastroenterology*, Prague.
- <sup>38</sup>Burman, J. H., Thompson, H., Cooke, W. T., and Williams, J. A. (1971). The effects of diversion of intestinal contents on the progress of Crohn's disease of the large bowel. *Gut*, **12**, 11-15.
- <sup>39</sup>Goligher, J. C. (1967). *Surgery of the Anus, Rectum and Colon*, p. 974. Baillière, Tindall, and Cassell, London.
- <sup>40</sup>Schachter, H., Goldstein, M. J., and Kirsner, J. B. (1967). Toxic dilatation complicating Crohn's disease of the colon. *Gastroenterology*, **53**, 136-142.
- <sup>41</sup>Baker, W. N. W., Lockhart-Mummery, H. E., and Morson, E. C. (1971). Ileo-rectal anastomosis for colonic Crohn's disease. *Gut*, in press.
- <sup>42</sup>Fielding, J. F., Burman, J. H., Cooke, W. T., and Williams, J. A. (1971). Recurrent ileitis after total colectomy and ileostomy for Crohn's disease. (In preparation.)
- <sup>43</sup>Garlock, J. H., and Crohn, B. B. (1945). An appraisal of the results of surgery in treatment of regional ileitis. *J. Amer. med. Ass.*, **127**, 205-208.
- <sup>44</sup>Garlock, J. H., Crohn, B. B., Klein, S. H., and Yarnis, H. (1951). An appraisal of the long-term results of surgical treatment of regional ileitis. *Gastroenterology*, **19**, 414-423.
- <sup>45</sup>Crohn, B. B. (1959). Panel discussion. Regional enteritis. *Gastroenterology*, **36**, 398-408.
- <sup>46</sup>Fielding, J. F., Williams, J. A., and Cooke, W. T. (1971). Does by-pass surgery have a place in the treatment of ileal Crohn's disease. (In preparation.)
- <sup>47</sup>Fielding, J. F., Toye, D. K. M., Beton, D. C., and Cooke, W. T. (1970). Crohn's disease of the stomach and duodenum. *Gut*, **11**, 1001-1006.
- <sup>48</sup>Waugh, J. M. (1962). Cited by Barber *et al* (1962).<sup>5</sup>
- <sup>49</sup>Shiner, M., and Drury, R. A. B. (1962). Abnormalities of the small intestinal mucosa in Crohn's disease (Regional enteritis). *Amer. J. dig. Dis.*, **7**, 744-759.
- <sup>50</sup>Edwards, H. (1964). Treatment of regional enteritis. *J. roy. Coll. Surg. (Edinb.)*, **9**, 115-127b.
- <sup>51</sup>Turnbull, R. E. (1969). A symposium on Crohn's disease. Midland Society of Gastroenterology.
- <sup>52</sup>Truelove, S. C., Ellis, H., and Webster, C. U. (1965). Place of a double-barrelled ileostomy in ulcerative colitis and Crohn's disease of the colon; a preliminary report. *Brit. med. J.*, **1**, 150-153.
- <sup>53</sup>Jones, J. H., Lennard-Jones, J. E., and Lockhart-Mummery, H. E. (1966). Experience in the treatment of Crohn's disease of the large intestine. *Gut*, **7**, 448-452.
- <sup>54</sup>de Dombal, T. (1971). Personal communication.
- <sup>55</sup>Prior, P., Fielding, J. F., Waterhouse, J. A., and Cooke, W. T. (1970). Mortality in Crohn's disease. *Lancet*, **1**, 1135-1137.
- <sup>56</sup>Lennard-Jones, J. E., and Stalder, G. A. (1967). Prognosis after resection of chronic regional ileitis. *Gut*, **8**, 332-336.
- <sup>57</sup>Bowers, R. F. (1966). Is radical surgery valid for hopeless or near hopeless regional ileitis? *Amer. Surg.*, **32**, 829-833.
- <sup>58</sup>Pollock, A. V. (1958). Crohn's disease. *Brit. J. Surg.*, **46**, 193-206.