Histology of Crohn's syndrome

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EDITORIAL SYNOPSIS Three types of inflammatory reactions are described in an analysis of 61 patients diagnosed clinically as cases of Crohn's disease. The possibility of different aetiological factors is raised.

The term 'Crohn's syndrome' is preferred to that of Crohn's disease as this is a condition of unknown, single, or possibly multiple aetiology. There are a large number of synonyms, including terminal ileitis, regional ileitis, regional or segmented colitis. It affects ileum or colon, alone or in combination. The disease manifests itself by well-demarcated areas of thickened bowel, stenosis, often by adhesions, frequently by local lympho-adenopathy, and sometimes by fistulae. It frequently occurs in, but is not confined to, young adults. It is further characterized by a tendency to relapse and to take a chronic course but is seldom fatal.

MATERIAL AND METHODS

Sixty-one surgical specimens were available for study including 45 with lymph glands. In many cases the whole specimen was available and in the others numerous paraffin blocks. All cases were diagnosed on clinical, radiological, and macroscopic grounds as of Crohn's syndrome, the illness varying in duration from a few weeks to 10 years. Sections were stained routinely by haematoxylin and eosin and many with van Gieson, alcian blue, mucicarmine, periodic-acid Schiff, von Kossa, phosphotungstic acid haematoxylin, and Weigert reticulin. Frozen sections were also examined and stained with oil red O and Nile blue sulphate. All were examined under ordinary and polarized light.

In 24 cases the lesion was confined to the terminal ileum; the next most frequent sites were the terminal ileum and colon, in which lesions were found in 20 cases and in 15 the colon alone was affected. In only two cases did the lesion affect the ileum proximal to the terminal 2 feet, and then was within 6 feet of the ileo-caecal valve.

HISTOLOGICAL FEATURES

Figure 1 shows the general pattern of the inflammation. It is noted that all coats are affected, in particular the submucosa. The changes are similar in both the ileum and the colon.

TABLE I

Type of Inflammation	Intestine		Lymph Glands	
	%	No.	%	No.
Non-specific alone	21	13	100	45
Diffuse granulomatous	27	17	—	—
Focal granulomata	50	31	20	9
Schaumann bodies	10	6	9	4

The histological features fall into one of three types of inflammation, namely, non-specific, diffuse granulomatous, and focal granulomatous (Table I). The non-specific diffuse granulomatous inflammations may be grouped as the non-focal granuloma as distinct from focal granuloma.

NON-SPECIFIC INFLAMMATION This is present in every case and in 13 of the 61 (21%) it is the only finding. It is most prominent in the mucosa and submucosa, tending to be patchy rather than diffuse and with two components, cellular and fluid. Although the cellular exudate in itself is not specific, certain features are of value when the colon is affected in distinguishing it from ulcerative colitis, namely, the involvement of all coats, angular fissured ulcers, and prominent lymphoid tissue. The cellular component consists mainly of lymphocytes, some plasma cells, and scanty polymorphs. Eosinophils may be present but are inconspicuous. Polymorphs are most frequent in areas of mucosal ulceration and at the base of mucosal clefts. Histiocytes are scanty and giant cells are absent. The fluid component consists of lymph and serum produced from the engorged, distended capillaries and lymphatics, and associated is considerable activity of, and probably increase in, lymphoid follicles with prominent reticulum centres. These features produce the typical macroscopic cobblestone appearance of the mucosa. Superficial

FIG. 1. *Terminal ileum, showing the general pattern of inflammation. Haematoxylin and eosin $\times 4$.*

FIG. 2. *Mucosal ulcer with clefts. Haematoxylin and eosin $\times 24$.*

ulceration is common. In 25% of cases clefts or fissures are seen, often in relation to the overhanging edge of an ulcer (Fig. 2), and the clefts often terminate in a lymphoid follicle (Fig. 1). Occasionally they penetrate the muscle layer and even extend into the serosa, and are thought to be the basis of fistula formation. The superficial parts of the clefts are often lined by ingrowing columnar cells but the deeper parts are lined by inflammatory cells. The base or deepest angle frequently shows microabscesses. Fibrosis is seldom marked and dense collagen with disappearance of the cellular infiltration is never seen. The general thickening is due to the cellular infiltration and oedema rather than to fibrosis. Lymphatic and vascular block is not seen and there is no arteritis. There is no evidence of muscle or nerve fibre proliferation or hyperplasia. Ganglion cells are frequently conspicuous in both internal and external plexi but there is no definite increase or abnormality of these cells.

DIFFUSE GRANULOMATOUS INFLAMMATION This type is always accompanied by non-specific inflammation. In 17 of 61 cases (27%) it is present in the absence of focal granuloma. As in the non-specific type it is most marked in the submucosa but may involve the muscle and serosa. The features which distinguish it from non-specific inflammation are the presence of giant cells and histiocytes, the former consisting of foreign body type, multinucleate giant cells (Fig. 3), with very occasional giant cells of the Langhans type. There was no evidence that these

FIG. 3. Diffuse granulomatous inflammation. Haematoxylin and eosin $\times 150$.

cells arise from muscle or nerve cells. Some giant cells show small vacuoles. It was not possible to demonstrate foreign bodies, talc, vegetable fibres, Schaumann bodies, mucin, fats, or fatty acids. The histiocytes have the appearance of mononuclear epithelioid cells. It is stressed that there are no focal aggregates of epithelioid cells and the features are those of an admixture: a diffuse infiltration of epithelioid cells, non-specific inflammatory cells, and scattered foreign body giant cells.

FOCAL GRANULOMA These are present in 50% of the cases. They consist of compact focal aggregates of epithelioid cells with peripheral Langhans type giant cells, an outer poorly demarcated rim of lymphocytes, and no caseation (Fig. 4). These features are indistinguishable from those of sarcoid granuloma or non-caseating tubercle. Some foci show central hyalinized connective tissue which is easily distinguished from caseation by the presence of intact and thickened reticulin. There is always associated non-specific inflammation with scattered lymphocytes, lymphoid hyperplasia, oedema, mucosal ulceration, and clefts. As a result of the oedema the epithelioid cells may become less tightly packed but away from the submucosa, particularly in the serosa, they show their true features. As in the other types of inflammation, focal granuloma may be found in any layer but are most frequent in the submucosa. They occur singly or in groups. Care must be taken to avoid confusing the active reticulum cell centres of lymph follicles with focal granuloma. They are not particularly related to lymphoid follicles or lymphatics and no blockage of the latter was seen. They are also not related to arterioles and endarteritis is inconspicuous.

Schaumann bodies are seen in 10% of cases with focal granulomata but not in the other types of inflammation. They are indistinguishable from those seen in the draining lymph glands. There are two components, birefringent crystals and basophilic conchoidal bodies. The crystals are sharply angulated, brilliantly birefringent particles occurring initially singly in epithelioid cells. Aggregated collections are common and are then often found in giant cells of the Langhans or foreign body type (Fig. 5). The aggregated forms are often coated with basophilic material and so form a mulberry-shaped Schaumann body (Fig. 6). The basophilic body may be found without crystals, when it is described as a shell-like conchoidal body. The crystals are easily distinguishable from talc, with which they may be confused, by their solubility in dilute (5%) mineral acids, and their refractive index lies between 1.603 and 1.613. Asteroid bodies and fatty acid crystals were not found.

FIG. 4. *Focal granulomata. Haematoxylin and eosin $\times 350$.*

FIG. 5

FIG. 5. *Aggregate crystals of Schaumann bodies. Haematoxylin and eosin $\times 400$ (polarized).*

FIG. 6

FIG. 6. *Schaumann bodies. Haematoxylin and eosin $\times 210$ (polarized).*

FIG. 7. Focal granuloma in lymph gland. Haematoxylin and eosin $\times 140$.

LYMPH GLANDS All the glands examined show non-specific reactive hyperplasia, enlarged follicles with prominent reticulum centres, littoral cell hyperplasia, and prominent sinusoids distended with faintly eosinophilic lymph. Diffuse granulomatous inflammation is not found. In nine cases (20%) focal granulomata are present, indistinguishable from those described in the intestines (Fig. 7). These are never very numerous and are scattered at random with no particular relationship to the gland architecture. Of these nine cases with focal granulomata, four show similar Schaumann bodies to those described above but they are not seen in the absence of focal granulomata.

DISCUSSION

It is important to realize that this condition is a syndrome and as such the histological diagnosis is partly dependent on clinical and macroscopic appearances. It is further noted that the three histological types are indistinguishable in ileum and colon.

When focal, sarcoid-like, granuloma are present (50%) the diagnosis is rarely in doubt. Similarly

those cases (27%) with diffuse granulomatous inflammation present no real difficulty. The most confusion is accounted for by the cases with non-specific inflammation (21%). This is especially so when the colon alone is affected, when the condition has to be distinguished from segmental ulcerative colitis. In ulcerative colitis the inflammation is usually superficial, involving only the mucosa, except in acute cases when there is extensive purulent inflammation and necrosis (Lockhart-Mummery and Morson, 1960). Ulcers and clefts are common and the latter can be distinguished from diverticula by their superficial situation, their relationship to ulcers, and part mucosal lining. Hadfield (1939) considered ulceration to be secondary to underlying lymphoid hyperplasia but this could not be confirmed. The only possible association is that the clefts often terminate in lymph follicles. The presence of these ulcers and clefts, together with the unusual combination of lymphocytic proliferation and oedema with relative paucity of polymorphs, is of considerable diagnostic value, and, when combined with the gross appearances, then the diagnosis is certain. The clefts may be the result of traumatic tearing of the oedematous, cellular, bulging mucosa, but this is unlikely, as they are not more common in the colon than in the ileum. They may result from uncoordinated muscle contractions or spasm. Meyer (1960) described focal hypertrophy of the muscularis mucosa, but this feature was not seen. Barbour and Stokes (1936) and Davis, Dockerty, and Mayo (1955) incriminate involvement and increase of nerve cells, and Antonius, Gump, Lattes, and Lepore (1960) described 'neuromatous' lesions; these findings could not be confirmed. However, the absence of anatomical changes does not disprove a functional disturbance.

Considerable interest has been centred on the two types of giant cells, foreign body cells and Langhans. To explain the foreign body type, various exogenous particles have been considered, *e.g.*, food particles (Crohn, Ginzburg, and Oppenheimer, 1932; Ginzburg and Oppenheimer, 1933) and talc (Reichert and Mathes, 1936) but these could not be demonstrated in the present series. In those patients with previous operations glove powder was looked for but was not found. Homans and Hass (1933) and Warren and Sommers (1954) suggested that they were a reaction to lipids and fats, but this could not be confirmed. Displaced mucins free in the tissues were sought for, as the author has seen a similar foreign body type granulomatous reaction in diverticulitis and cholecystitis but again the results were negative. It is, however, possible that the reaction could occur to altered mucin which has lost its staining properties. Even more interest has been

centred on the Langhan type giant cells and associated epithelioid cell, focal granuloma. This feature was present in 50% of this series as compared to 37% of 363 cases described by Van Patter, Bargen, Dockerty, Feldman, Mayo, and Waugh (1954) and 83% of 120 cases of Warren and Sommers (1948). The latter figure may be higher as a result of including cases now classified as diffuse granuloma. As shown above, in 10% of focal granuloma cases Schaumann bodies are present. These were never numerous and were most frequent where there is involvement of skin, either by fistulae of the abdominal wall or the anus. It does not appear to have been previously recognized that the constituent crystals and conchoidal bodies are identical in appearance and properties with those described in sarcoidosis, chronic beryllium disease, and tuberculosis (Jones Williams, 1960). Warren and Sommers (1948) found birefringent crystals in 4% of 120 cases but did not distinguish them from talc; Foss and Barnes (1951) mention, but do not identify, refractile bodies in giant cells; Moschowitz and Wilensky (1923) in their case 1 showed laminated refractile bodies which, from the photographs, could well be a broken-up conchoidal body. It is interesting to compare the relative incidence of Schaumann bodies in Crohn's syndrome, sarcoidosis, and tuberculosis (Table II). However, the similar incidence to that in tuberculosis does not warrant a conclusion of similar aetiology. Many investigators have searched for tubercle bacilli but with uniformly negative results.

TABLE II

PERCENTAGE INCIDENCE OF SCHAUMANN BODIES

Condition	%
Crohn's syndrome with focal granuloma	10
Sarcoid	88
Chronic beryllium disease	62
Tuberculosis	6

The non-caseating epithelioid granulomata and inclusion bodies are considered to be indistinguishable from those found in sarcoidosis. This is not in agreement with Cornes and Stecher (1961) who have attempted to differentiate the two, although identification does not denote a common aetiology. There is general agreement that, clinically, the two conditions are distinct. Crohn's syndrome is not associated with the other stigmata of sarcoidosis and in sarcoidosis intestinal involvement is extremely rare (Longcope and Freiman, 1952). There is, however, an interesting exception to the clinical distinction, that of similar negative Mantoux reactors, in sarcoidosis about 60 to 70%. Jones Williams (1963) found in Crohn's syndrome 67%

to be negative, a similar figure to that of Phear (1958) and Blackburn, Hadfield, and Hunt (1939), and further showed that most of the cases with focal granuloma are negative reactors while the diffuse granuloma and non-specific cases show a mixed picture.

Consideration of the three histological types of inflammation fails to show that they are stages in a single process. There is no correlation of type with length of history nor is there any constant occurrence of type at the junction of normal and diseased bowel. Definite proof that one type succeeds another can only be obtained by serial biopsies over a period of time, and a few included in this series are inconclusive. Previous workers have differed in their views: Schepers (1945), Foss and Barnes (1951), and Meyer (1960) support non-granulomatous as the primary phases, while Hadfield (1939), Van Patter *et al.* (1954), Warren and Sommers (1954), and Ammann and Bockus (1961) support primary focal granuloma. From the present investigations it is therefore suggested that the three described types may not be related. It is thought that (a) non-specific and (b) diffuse granulomatous cases may be joined together as the non-focal granuloma group as distinct from that of (c) focal granuloma. This is supported by the fact that a mixture of (a) and (b) is not infrequent in other inflammatory-intestinal diseases, such as diverticulitis, cholecystitis, and peptic ulceration. There is further support from the Mantoux reactions in that (c) cases are usually Mantoux negative while (a) and (b) cases may be positive or negative. It can therefore be postulated that (a) and (b) may have a different cause to (c). It is felt that this would considerably assist in the search for aetiological agents, which search should take full cognisance of the underlying histology in otherwise identical clinical and macroscopic cases.

SUMMARY

This study is based on 61 cases with a clinical and macroscopic diagnosis of Crohn's syndrome affecting ileum and/or colon.

Three types of inflammation are described, mainly involving but not confined to the mucosa and sub-mucosa, and histologically identical in the ileum and colon. Non-specific inflammation, found in all cases and the only finding in 21%, is characterized by chronic inflammatory cells, prominent oedema, superficial ulceration, and fissures. Diffuse granulomatous inflammation was present in 27% of cases, showing scattered histocytes, foreign body type giant cells but no particular foreign materials, and always admixed with the non-focal type. Focal granulomatous inflammation was present in 50% of cases

and in 10% was associated with Schaumann bodies, both features being identical with those found in sarcoidosis. It is postulated that the two first types of inflammation should be grouped as cases of non-focal granuloma as distinct from those with focal granuloma. Such a division may assist in the future search for aetiological agents.

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