

Primary lymphadenopathy complicating idiopathic steatorrhoea

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The association of abdominal lymphadenopathy and steatorrhoea has been extensively reviewed (Kent, 1964; Eidelman, Parkins, and Rubin, 1966) and there seems no doubt that a generalized reticulosarcoma or Hodgkin's disease with involvement of the bowel and/or abdominal nodes can cause steatorrhoea (Sleisenger, Almy, and Barr, 1953). Not only is this steatorrhoea a biochemical entity but it is also associated with the same histological jejunal villous atrophy seen in so-called idiopathic steatorrhoea. Leaving aside such cases there are undoubtedly others in which a primary lymphadenopathy appears as a late complication of idiopathic steatorrhoea (Best and Cook, 1961; Gough, Read, and Naish, 1962; Tonkin, 1963; Ross, 1965; Harris, Cooke, Thompson, and Waterhouse, 1967; Austad, Cornes, Gough, McCarthy, and Read, 1967). The development of this pathological entity, however, has not been adequately studied histologically and clearly only when it is more precisely defined will its clinical management be less empirical.

CASES STUDIED

The series includes seven cases in which a necropsy was performed and in four of these material obtained during life was also available. In one further case the only material was obtained at laparotomy. Recent exhaustive clinical reviews of this complication of steatorrhoea have stressed the changes in clinical pattern which herald the onset of the lymphadenopathy, and Harris *et al* (1967) have shown that early treatment may help to prevent the complication. It is only necessary here, therefore, to give a brief clinical summary, and in Table I the laparotomy and postmortem findings.

In cases 1, 2, 3, 4, and 7 there was a longstanding history and subsequent biochemical proof of steatorrhoea preceding the onset of lymphadenopathy. In cases 2, 4, and 7 a jejunal biopsy furnished additional evidence. In case 5, before a definite diagnosis of steatorrhoea, presumptive evidence of at least seven years' previous malabsorption was provided

by a multiple deficiency anaemia responding poorly to treatment (Whitehead, Carter, and Sharp, 1965) and a hypoproteinaemic oedema. Two years before the development of the lymphadenopathy a laparotomy showed no gross abnormality of the small bowel or mesenteric nodes. A similar anaemia, oedema, and osteomalacia were the features shown in case 6 for some 10 years before steatorrhoea was finally diagnosed. Although only found to have steatorrhoea one year before his death, case 8 had a long history of mild diarrhoea and was included because of the typical histological features seen in the tissue removed at laparotomy.

Table II summarizes the relevant findings in each case and this is accompanied by a more detailed description of the cases regarded as a whole.

PROGRESSIVE HYPERPLASIA

THE SMALL BOWEL In all cases the mucosa was in places of the flat type as seen with the dissecting microscope; elsewhere variations between this and a mucosa showing ridges and stunted, leaf-shaped villi were seen. Histologically all ranges of villous atrophy up to the subtotal type were present (Fig. 1). The picture was basically that seen in uncomplicated steatorrhoea except that the inflammatory infiltrate in the lamina propria tended to be denser. This was most marked in those cases showing mucosal ulcers, but in sites not ulcerated there was no extension of the infiltrate beyond the muscularis mucosa. In addition to lymphocytes the infiltrate is composed of large numbers of plasma cells sometimes containing Russell bodies and there are eosinophils, occasional histiocytes, and a proportion of cells having features of reticulum cells (Fig. 2). These have a blood monocyte-like nucleus, which often appears folded or is indented, and has a distinct nuclear membrane, an open chromatin pattern, and a definite nucleolus.

In the region of the ulcers the most obvious histological feature is the extension of the infiltrate beyond the lamina propria (Fig. 3). The ulcer base

TABLE I

SUMMARY OF CASES STUDIED

Case	Age (Years)	Sex	Minimum Duration of Steatorrhoea (Years)	Laparotomy	Principal Postmortem Findings
1 PM 918/60 SH 7193/60 Hosp. no. 217971	52	Male	5	One month before death Biopsy of enlarged mesenteric nodes	Bronchopneumonia, pulmonary emboli; thrombosis of inferior vena cava and leg veins; perforated ulcer of jejunum—peritonitis; simple gastric ulcers; enlarged mesenteric, para-aortic, cervical, and inguinal nodes
2 PM 821/65 Hosp. no. 227818	48	Male	9	—	Bronchopneumonia; generalized enlargement of lymph nodes; tumour deposits in lungs, liver, spleen, marrow, pericardium; no ulceration of bowel
3 PM 145/61 Hosp. no. 8680	58	Male	20	—	Bronchopneumonia, bronchiectasis, right pulmonary mycetoma (aspergillus ?); pulmonary emboli and infarcts, thrombosis of leg veins; ulcer of ileum; mesenteric lymph node enlargement; tumour infiltrates of liver, lungs, thoracic duct, and perirenal tissues
4 PM 146/64 SH 7414/62 7441/62 9303/63 Hosp. no. 332292	34	Male	Since childhood	Fifteen months before death—resection of jejunal ulcer, enlarged mesenteric nodes Two months before death further jejunal ulcers resected	Pulmonary emboli, thrombosis of leg veins; several jejunal and ileal ulcers; enlarged mesenteric lymph nodes
5 PM 302/62 SH 7008/61 Hosp. no. 298711	45	Female	7	Two years before death small bowel adhesions related to chronic salpingitis	Pulmonary emboli and infarcts; thrombosis of leg veins; pulmonary and internal genital tuberculosis; neoplastic ulcers of stomach, small and large bowel; enlarged mesenteric and paraaortic nodes; tumour infiltrates of skin, breasts, liver, and heart
6 PM 836/61 Hosp. no. 313623	64	Male	10	—	Osteomalacia and multiple fractures; bronchopneumonia and bronchiectasis; tentorial meningioma and cholelithiasis; early cirrhosis of liver and splenic enlargement; enlarged mesenteric, paraaortic and peripancreatic lymph nodes; tumour infiltration of marrow
7 SH 8073/66 10624/66 Hosp. no. 401443	47	Male	15	Resection of jejunal ulcer and enlarged mesenteric nodes	—
8 PM 609/67 SH 10052/66 Hosp. no. 241225	53	Male	1	Six months before death resection of jejunal ulcers and enlarged mesenteric lymph nodes	Bronchopneumonia, bronchiectasis, old myocardial infarct; several neoplastic small bowel ulcers; mesenteric lymph node enlargement

TABLE II

SUMMARY OF HISTOLOGICAL FINDINGS

Case No.	Small Bowel Mucosa	Year	Small Bowel Ulcers	Mesenteric Nodes	Other Nodes	Other Areas
1	Abnormal ¹	1960	Mainly sarcoma with foci of progressive hyperplasia remaining	As ulcers	Sarcoma	—
2	Abnormal	1965	—	Sarcoma	Sarcoma	Sarcoma
3	Abnormal	1961	Sarcoma	Mainly progressive hyperplasia with focal sarcoma	—	Sarcoma
4	Abnormal	1962 & 1963 & 1964	Progressive hyperplasia } Progressive hyperplasia with focal sarcoma	Progressive hyperplasia As ulcers	— —	— —
5	Abnormal	1961 & 1962	Sarcoma	{ Progressive hyperplasia with focal sarcoma	Paraaortic nodes non-specific hyperplasia	Sarcoma
6	Abnormal	1961	—	Progressive hyperplasia with focal sarcoma	Paraaortic nodes as mesenteric	Sarcoma
7	Abnormal	1965	Progressive hyperplasia with focal sarcoma	Progressive hyperplasia	—	—
8	Abnormal	1966 & 1967	Progressive hyperplasia	{ Progressive hyperplasia with focal sarcoma	—	—

¹Varying villous abnormality ranging to subtotal villous atrophy in one or all of biopsy, surgical and postmortem specimens.

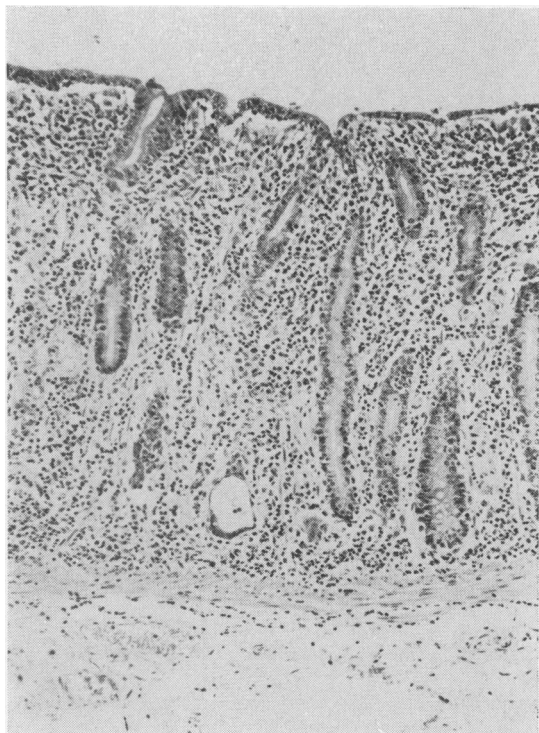


FIG. 1. Jejunal mucosa of flat type (case 7) showing absence of villi. There is a dense inflammatory infiltrate in the lamina propria (haematoxylin and eosin $\times 100$).

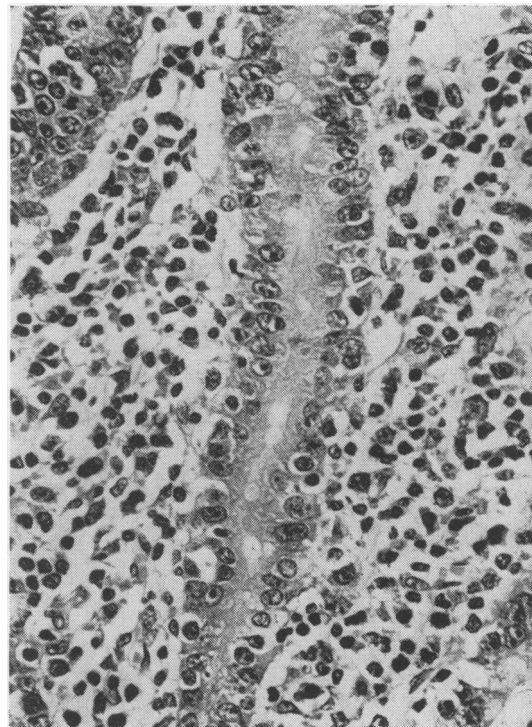


FIG. 2. Jejunal mucosa (case 7) showing that the infiltrate in the lamina propria contains reticulum cells which are occasionally abnormal (haematoxylin and eosin $\times 300$).

is composed of necrotic debris and necrosis is often also seen in the deeper infiltrate which involves not only the submucosa but also the muscularis proper. Occasionally the necrosis is associated with thrombi in nearby small vessels. At this stage the infiltrate is considerably denser than it is elsewhere and the reticulum cells increase in number at the expense of the other cell types (Fig. 4). They show an increasing pleomorphism and hyperchromasia with occasional mitotic figures and binucleate forms. They correspond to the cell designated as a pro-histiocyte by Robb-Smith (1938). The serosa in relation to the ulcers is frequently covered by a zone of granulation tissue and organizing fibrin and an exact demarcation between this and the outer zone of cellular infiltrate is impossible.

LYMPH NODES In the earliest stages of lymph node enlargement (Fig. 5) follicles are increased in number and are widely spaced, frequently showing germinal centres. The sinuses are dilated and contain occasional cells of the type found in the medulla, together with a few foamy histiocytes. The sinus endothelial cells are plump and between the sinuses

and the follicles the medulla contains a mixture of cells identical to those seen in the bowel (Fig. 6).

As the condition progresses abnormal reticulum cells increase in number and other cell types decrease. As this occurs the medulla comes to occupy more of the node, the sinuses become obliterated, and the follicles less distinct, often losing their germinal centres (Fig. 7).

SARCOMA STAGE

THE SMALL BOWEL Between the stage of sarcoma and progressive hyperplasia stages of transition are seen and some areas of progressive hyperplasia may persist even when the sarcoma is advanced. The abnormal reticulum cells gradually appear in more or less homogenous sheets (Fig. 8) and the tumour in each case shows the same type of histological variation as reticulosarcomas arising elsewhere. Whilst some are well differentiated and produce easily demonstrated fibres (Fig. 9), others are more anaplastic and form scanty reticulum.

LYMPH NODES As the number of abnormal reti-

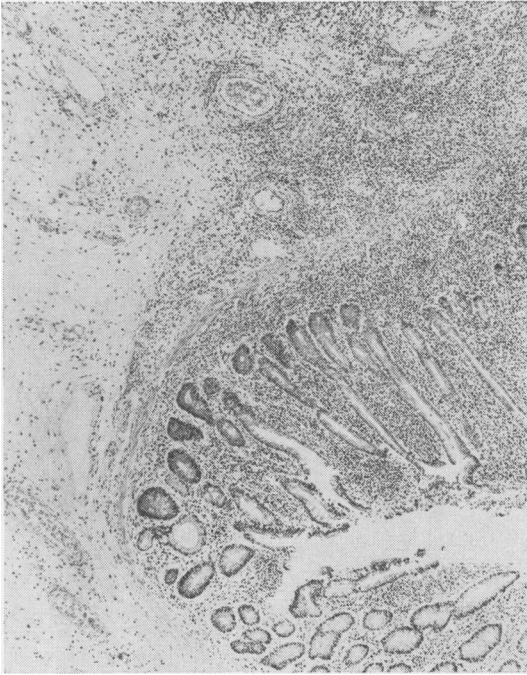


FIG. 3.

FIG. 3. *Jejunal mucosa (case 8). The infiltrate can be seen penetrating the muscularis mucosa (haematoxylin and eosin $\times 40$).*

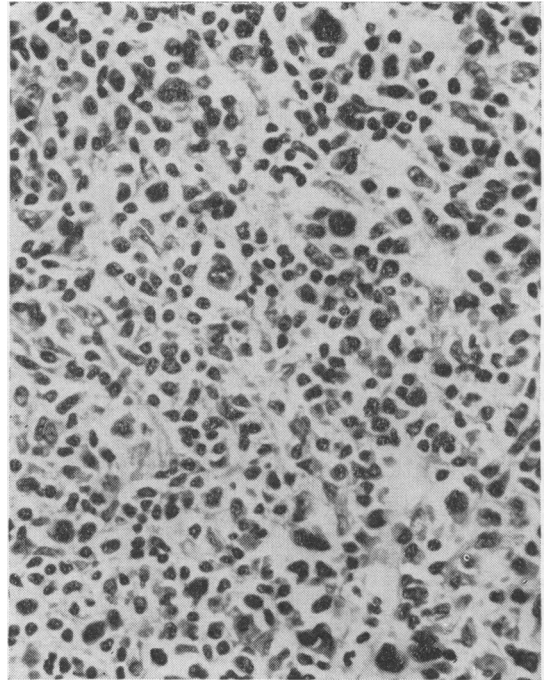


FIG. 4.

FIG. 4. *Jejunal mucosa (case 8). The infiltrate where the muscularis mucosa has been breached. Note the increased number and abnormality of reticulum cells and compare with Fig. 2 (haematoxylin and eosin $\times 300$).*

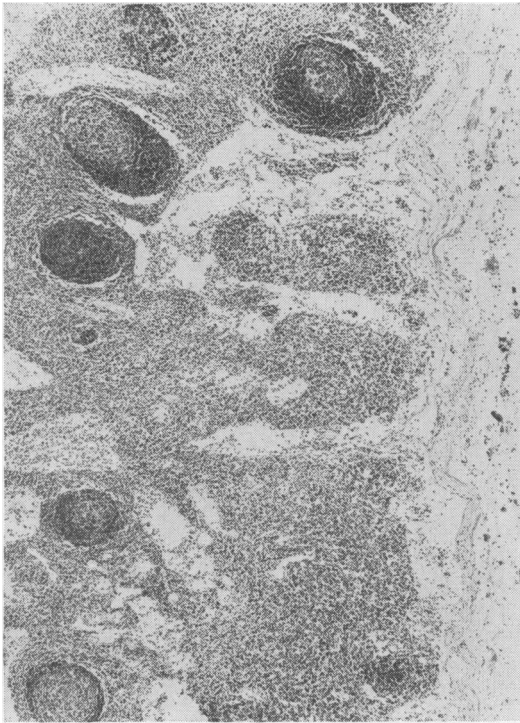


FIG. 5.

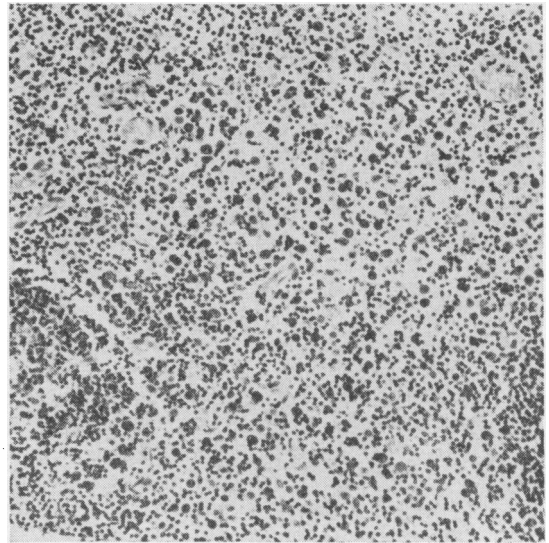


FIG. 6.

FIG. 5. *Mesenteric lymph node (case 8). The follicles have germinal centres, there are dilated sinuses, and the medulla is cellular (haematoxylin and eosin $\times 35$).*

FIG. 6. *Same lymph node as in Fig. 5 to show abnormal reticulum cells in the medulla. At upper left and right the edges of follicles can be seen (haematoxylin and eosin $\times 120$).*

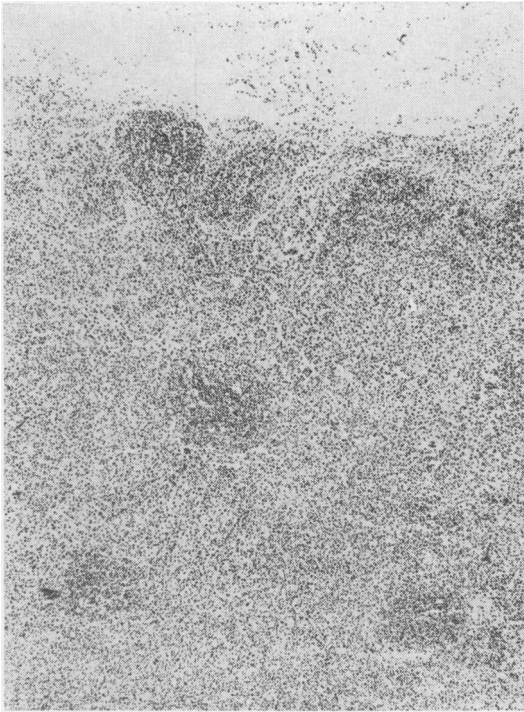


FIG. 7.

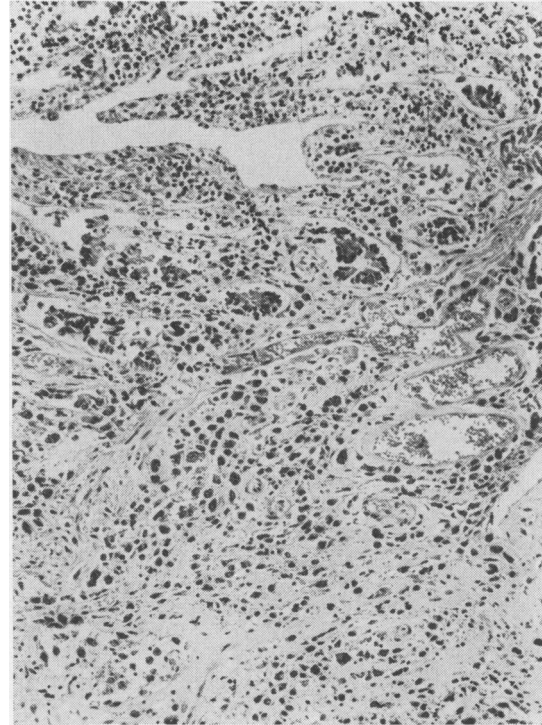


FIG. 8.

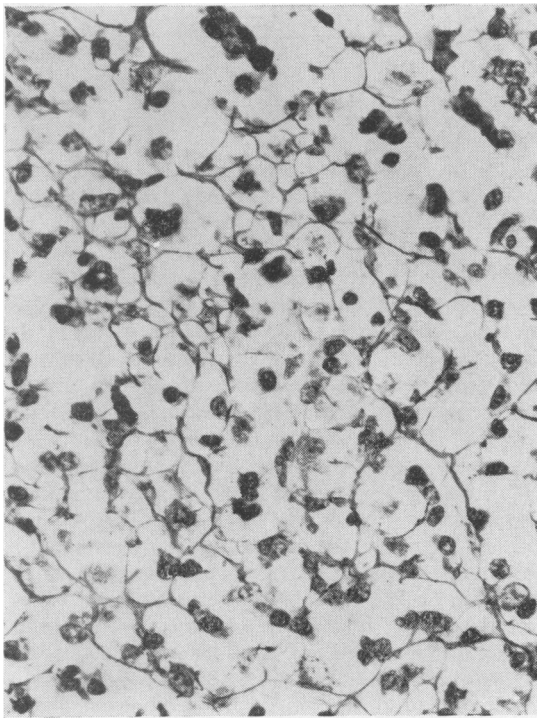


FIG. 9.

FIG. 7. Mesenteric lymph node from case 4 (necropsy 1964). The follicles have lost their germinal centres and the medulla is extremely cellular with a high abnormal reticulum cell component (haematoxylin and eosin $\times 35$).

FIG. 8. Jejunal mucosa (case 5) showing sarcomatous change (top) merging with autolysed mucosa (below). The muscularis mucosa runs diagonally top right to bottom left (haematoxylin and eosin $\times 100$).

FIG. 9. Pericellular reticulin production by sarcoma in lymph node (case 5) (Robb-Smith reticulin $\times 370$).

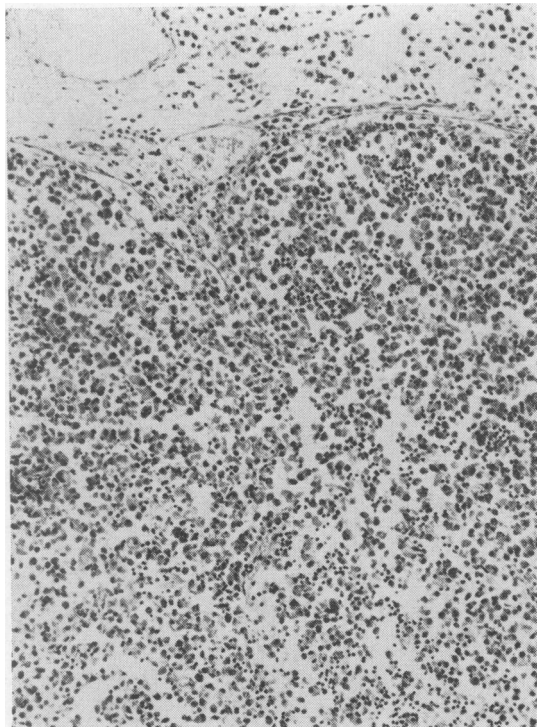


FIG. 10.

FIG. 10. Mesenteric lymph node (case 2). The abnormal reticulum cells have all but filled the node, small groups of lymphocytes remain. Note capsular invasion (haematoxylin and eosin $\times 100$).

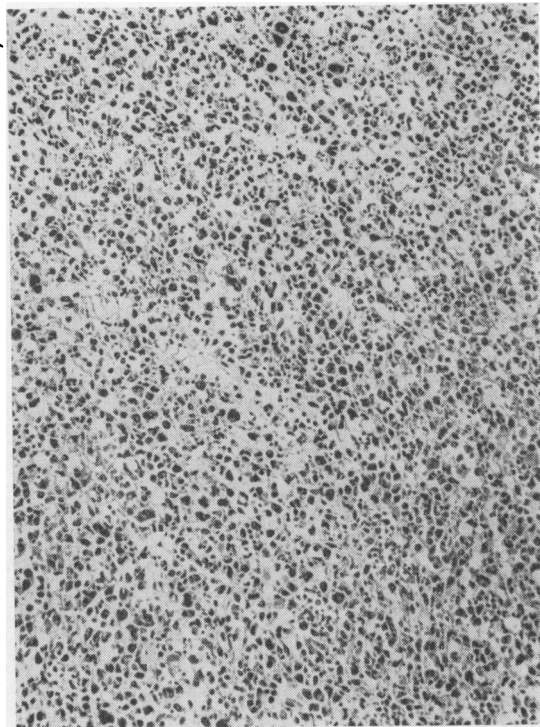


FIG. 11.

FIG. 11. Mesenteric lymph node (case 5). Diffuse abnormal reticulum cell proliferation (haematoxylin and eosin $\times 100$).

culum cells increases in the medulla, reticulin is produced concomitantly and produces abnormal skeins of fibres in the interfollicular areas and gradually as diffuse sarcoma supervenes the normal pattern of reticulin is replaced by a diffuse network. Other types of cells gradually disappear (Fig. 10) and the sarcoma begins to penetrate the capsule. Areas of progressive hyperplasia persist for a time as in the bowel but gradually a uniform picture of reticulum cell sarcoma is produced (Fig. 11).

Sarcoma of mesenteric nodes can develop independently of that in the bowel and vice versa. Once this stage is reached in either site sarcoma may be found in other nodes and in other organs. Whether other nodes are involved by metastases or go through a stage of hyperplasia is not known. Progressive hyperplasia with focal sarcoma was seen with regularity only in the mesenteric nodes and only in one case (case 6) in other abdominal nodes (the paraaortic nodes). On the evidence, as with other generalized lymph node malignancies, both metastases and a multifocal origin are probable.

DISCUSSION

In previously published cases of a lymphadenopathy complicating steatorrhoea it has been described variously as Hodgkin's disease, lymphosarcoma, or reticulosarcoma. In this study the course of progressive hyperplasia turning into malignancy is shown to be a characteristic and definite entity ending as it does in a reticulum cell sarcoma. In the stage of progressive hyperplasia it is easy to see its superficial resemblance to Hodgkin's disease. Apart from the fact that Hodgkin's disease seldom involves the gastrointestinal tract, the intimate morphology of the lymphadenopathy associated with steatorrhoea is quite distinct from Hodgkin's disease. Even in the cellular phase of Hodgkin's disease the normal architecture of the node is obscured by the cellular proliferation in which reticulum cells, including Sternberg-Reed cells, lymphoid cells, fibroblasts and eosinophils predominate whereas cells of the histiocyte series are inconspicuous; in the steatorrhoea lymphadenopathy the architectural landmarks of the node are main-

tained until sarcomatous change develops, the predominant cell is of the histiocyte or prohistiocyte type, and fibrosis does not occur although there usually is an increase in reticulin. Robb-Smith (1938) described this type of progressive hyperplasia as 'prohistiocytic fibrillary reticulosis' and in 1964 emphasized its association with steatorrhoea. However it would seem simpler to designate this form of lymphoreticular proliferation as the steatorrhoea lymphadenopathy.

It is equally clear how in some of these cases a histological diagnosis of lymphosarcoma could be reached. This is true especially when the cells are of fairly uniform type and fibre production is not marked. In our material fibre production has always been a feature even in the more pleomorphic and anaplastic tumours.

Why this complication occurs is not known but it may be in the nature of an autoimmune response which goes on to irreversible malignancy. In this respect the condition may be compared with the reticuloses which complicate a percentage of cases of Hashimoto's disease (Cox, 1964). There is in fact some serological evidence (Malik, Watson, Murray, and Cruickshank, 1964) that the lesion of idiopathic steatorrhoea is autoimmune in origin and the glandular atrophy with a lymphocytic and plasma cell infiltrate are typical of the lesions seen in other autoimmune diseases. The change can affect the small bowel, lymph nodes, or both, and once sarcoma has supervened infiltration of other organs may appear. It is obvious, therefore, that repeated small bowel biopsies will not necessarily help in the early diagnosis of the condition but if abnormal reticulum cells and numerous eosinophils are seen in an otherwise typical small bowel biopsy in steatorrhoea then the condition should be suspected.

If the complication is suspected due to a change in the clinical picture of the steatorrhoea patient, and if radiographic investigation is negative, a diagnostic laparotomy is probably indicated. Because the whole small intestine is potentially involved it would seem that surgical resection of the local lesions and lymph nodes which has been advocated (*Lancet*, 1964) is not a rational procedure. Whether radiotherapy and/or cytotoxic drugs should be recommended, and at what stage they should be used, are problems which will only be solved when the

entity as a specific complication of steatorrhoea is better recognized and experienced.

SUMMARY

Idiopathic steatorrhoea is sometimes complicated by a lymphadenopathy. The development of this lymphadenopathy as a progressive hyperplasia which becomes reticulosarcoma has been studied and described in eight cases. It is concluded that the lymphadenopathy of steatorrhoea is a specific histological entity which could be called 'steatorrhoea lymphadenopathy'.

During the preparation of this paper I have been fortunate to have the advice and helpful criticism of Dr A. H. T. Robb-Smith to whom I am indebted. For allowing access to the case records I would also like to express my thanks to those physicians and surgeons of the Radcliffe Infirmary who were responsible for the patients' care.

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