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Original Articles

Primary Intestinal Lymphomas *

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Summary. The histology and immunohistology of twenty-seven malignant non-Hodgkin's lymphomas of the intestinal tract were studied. Nine of these cases were in the small intestine, ten in the ileocaecal region, two in the appendix and four in the large intestine. In one case, several locations in the gastrointestinal tract were involved. The so-called Kiel-Classification was applied. We have found thirteen lymphomas with low grade (lymphocytic, lymphoplasmacytic, centrocytic, centroblastic/centrocytic) and fourteen with high grade of malignancy (centroblastic, lymphoblastic, immunoblastic). For most of the lymphoplasmacytic and immunoblastic lymphomata a monoclonal pattern of intracellular immunoglobulin (IgM/kappa) was identified by the immunoperoxidase method. Tumour cells of lymphocytic, centrocytic, centroblastic/centrocytic, centroblastic and lymphoblastic lymphomas were always Ig-negative. The immunoperoxidase technique helped considerably in distinguishing between (monoclonal) malignant lymphomas and (polyclonal) lympho- or immunoproliferative processes.

Six out of twenty-seven malignant lymphomas had developed from immuno-inflammatory diseases of the gut. Four of these were complications of coeliac disease. One had developed from a "malabsorptive" dermatitis herpetiformis Duhring, and one from a complication of a long-standing ulcerative colitis. In two patients with coeliac sprue and "malabsorptive" dermatitis herpetiformis Duhring respectively the ulcerating small intestinal lymphomas were initially misinterpreted as "benigne ulcerative non-granulomatous jejunitis". The evidence from the literature summarized suggests strongly that the benign non-granulomatous jejunoileitis, lymphomatous ulcer, intestinal "pseudolymphoma" and malignant lymphoma, when associated with villous atrophy of adjacent mucosa and malabsorption symptoms, are all one condition, namely, malignant lymphoma.

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Introduction

The gastrointestinal tract is often afflicted by malignant lymphomas. Furthermore, it is the most frequent location of primary extranodal lymphomas (Dawson et al. 1961; Nasr et al. 1970; Freeman et al. 1972; Henry and Farrer-Brown 1977; Najman et al. 1977; Lewin et al. 1976, 1978; Al-Saleem et al. 1979; Isaacson et al. 1979).

Experimental investigations (Review: Osserman 1978; Haeney et al. 1979) and clinical observations have shown that patients with primary immunodeficiency syndromes and immunoinflammatory diseases ("immuno-proliferative reactions"; Damashek 1966) have a tendency to develop malignant, especially lymphoreticular neoplasms (Kersey et al. 1973a, b; Hess et al. 1975; Friedman and Fialkow 1976; Lennert et al. 1979). The following diseases and immunoinflammatory reactions occurring in and affecting the intestinal tract predispose to the development of lymphomas: *Mediterranean type of lymphoma* or *alpha-chain disease* (Ramot and Hulu 1975; Lewin et al. 1976; Galian et al. 1977; Haghighi et al. 1978; Nassar et al. 1978; Doe 1979), *selective IgA deficiency* (Eidelman 1976; Ross and Asquith 1979), *common variable (late-onset) hypogammaglobulinaemia* (Waldmann et al. 1972; Huizenga and Hermans 1972; Ament et al. 1973; Ament 1975; Hermans et al. 1976; Webster 1976), *coeliac disease* (Harris et al. 1967; Stockes and Holmes 1974; Holmes et al. 1976; Nisard et al. 1976; Freeman et al. 1977; Brandt et al. 1978; Isaacson and Wright 1978b, c; Cooper et al. 1978; Asquith and Haeney 1979), the so-called *"malabsorptive" dermatitis herpetiformis Duhring* (Alexander 1975; Gebbers et al. 1977; Freeman et al. 1977; Otto et al. 1979), *Crohn's disease* (Lee et al. 1977; Collins 1977), and *ulcerative colitis* (Sherlock et al. 1970; Nugent et al. 1972; Wagon-Feld et al. 1977; Otto et al. 1978).

Of the numerous hypotheses concerning the formal pathogenesis of intestinal lymphomas that of persistent antigen exposure is the only one considered here (Dutz et al. 1971; Schwartz 1972; Friedman and Fialkow 1976; Salomon 1978).

The original location of the immuno-inflammatory reaction is the local lympho-reticular tissue of the gut, the so-called "*gut-associated lymphoid tissue*". It should be kept in mind that the development and function of the intestinal lymphoid tissue is due to a permanent, but controlled stimulation by antigens (Porter and Knight 1977; Ruchti et al. 1980). The inner surface of the gut can be characterized as an immuno-biological marginal surface. Frequently a disturbance or break-down of gut-associated immuno-biological regulation causes a persistent over-stimulation of the local immune system. An *immunoproliferative disease* will develop a *plasma cell* dyscrasia (Osserman 1978), with the tendency for malignant transformation ("hyperplasiogenic neoplasia").

In the present study, twenty-seven intestinal non-Hodgkin's lymphomas are described. Six of them arose from long standing gluten-sensitive enteropathies, Duhring's disease, and from ulcerative colitis. Special emphasis has been laid on the discussion of differential and early diagnostic aspects.

Table 1. Locations of 27 malignant non-Hodgkin's lymphomas of the intestinal tract

Small bowel, jejunum	5	
Small bowel, ileium	4	
Terminal ileum and coecum	3	14
Caecum	3	
Caecum and vermiform appendix	4	
Vermiform appendix	2	
Ascending colon	2	
Sigmoid colon	2	
Stomach, small intestine and colon	1	

Material and Methods

Between 1974 and 1979 twenty-seven cases of primary intestinal non-Hodgkin's lymphomas were investigated. Only one case had been diagnosed preoperatively. The following diagnoses had prompted operation: bleeding ileocaecal tuberculosis, ileocaecal obstruction (Crohn's disease or carcinoma), Crohn's disease and appendicitis. In a fourty-one year old patient with a twenty year history of dermatitis herpetiformis Duhring, a malignant lymphoma located in the upper jejunum was first revealed at the postmortem examination (cf. Gebbers et al. 1977). In four patients who were known to suffer from coeliac disease, a tumour of the small intestine (lymphoma or sarcoma) had been suspected for many years after X-ray examination. One of these cases had undergone an emergency laparotomy for symptoms of an acute abdomen (due to perforation of the small intestine). Another fourty-year old male patient with a fourteen year history of ulcerative colitis had first undergone proctocolectomy because of a histologically verified carcinoma of the rectum. Complete histological investigation of the resected specimen revealed a coexistent malignant lymphoma in the upper sigmoid colon (cf. Otto et al. 1978).

The localization of the malignant lymphomas are listed in Table 1. The salient clinical data of the twenty-seven cases included in this report are summarized in Table 2.

Imprints were prepared from the resection specimens and stained by Pappenheim, PAS, alkaline and acid phosphatase (Lillie 1965). Subsequently the resected specimens were fixed in Bouin's solution for 4 to 6 h at room temperature. Paraffin wax specimens were cut at 4–6 μm and stained with haematoxylin and eosin, PAS, Giemsa and Gomori. Activity of alpha-naphthyl acetate esterase (Knowles and Holck 1978) was also demonstrated.

Immunohistochemistry

Immunoglobulins (all classes of heavy and light chains) and muraminidase (lysozyme) were demonstrated specifically by a modified immunoperoxidase sandwich method (peroxidase-antiperoxidase technique) described by Taylor and Mason (1974) using commercially obtained rabbit anti-human immunoglobulin antisera on serial sections 4–6 μm thick in each case. Details of the method have been described elsewhere (Gebbers and Otto 1978). In addition, control sections using normal rabbit serum or rabbit anti-human thyreoglobulin in place of the specific anti-human sera were included with each immunoperoxidase run and were uniformly negative.

IgA-, IgG-, and IgM-antisera as well as kappa- and lambda-antisera were obtained from Nordic Immunological Laboratories b.v., Tilburg, Netherlands, lysozyme from Medac, Hamburg, and the PAP immune complex was from Dakopatts A/S of Copenhagen.

For the quantitation of the plasma cell reaction, systematic counts of labelled immunocytes were made based on the method described by Brandtzaeg et al. (1974) in individually defined "mucosal tissue units" constituting a 6 μm thick and 500 μm wide block of tissue, including the mucosa at full height from the muscularis mucosae.

Results

The classification of the twenty-seven malignant non-Hodgkin's lymphomas in the intestinal tract is shown in Table 3. Thirteen lymphomas were of low-grade malignancy and fourteen high grade. In Fig. 1 the agecorrelated incidence rates

Table 2. Summary of clinical features

Case	Age	Sex	Duration of symptoms	Symptoms	Clinical diagnosis	Lymph nod	Histological diagnosis	Outcome
1	69	M	9 mo	Abdominal pain caecal obstruction	Carcinoma?	–	L., lymphocytic	Alive, 2 yr chemotherapy
2	39	M	5 mo	Abdominal pain diarrhoea bleeding	Carcinoma?	–	Immunocytoma	Alive, 1 yr chemotherapy
3	61	F	11 mo	Abdominal pain weight loss intestinal obstruction	?, Explorative laparotomy	–	Immunocytoma	Lost to follow-up
4	73	F	2 yr	Abdominal pain bleeding	Ileocoecal tuberculosis?	+	Immunocytoma	Lost to follow-up
5	67	M	1 yr	Abdominal pain	Carcinoma?	–	Immunocytoma	Alive, 4 yr chemotherapy
6	72	M	3 yr	Weight loss bleeding	Carcinoma?	–	Immunocytoma	Alive, 3 yr chemotherapy
7	61	F	9 mo	Abdominal pain	?, Explorative laparotomy	–	Immunocytoma	Lost to fllow-up
8	69	M	7 mo	Abdominal pain	Carcinoma	+	Immunocytoma	Lost to follow-up
9	51	F	3 yr	Abdominal pain weight loss	?, Small intestinal obstruction	+	L., centrocytic	Lost to follow-up
10	22	M	few days	Abdominal pain acute abdomen	Acute abdomen perforation	+	L., centrocytic	Died, peritonitis
11	70	F	few wk	Abdominal pain bleeding acute abdomen	Acute abdomen carcinoma?	–	L., centroblastic/ centrocytic	Died, peritonitis
12	62	F	2 yr	Abdominal pain weight loss bleeding	Carcinoma?	+	L., centroblastic/ centrocytic	Alive, 1 yr
13	64	M	9 mo	Abdominal pain	?, Explorative laparotomy	+	L., centroblastic/ centrocytic	Lost to follow-up
14	81	F	few days	Abdominal pain acute abdomen	Carcinoma	+	L., centroblastic	Died after operation
15	40	M	14 yr	Abdominal pain bleeding	Ulcerative colitis, carcinoma	–	Ulcerative colitis colitis-carcinoma L., lymphoblastic	Alive, 3 yr chemotherapy
16	7	M	few days	Abdominal pain	Appendicitis	+	L., lymphoblastic	Died 10 wk after operation with recurrence (ileum, mesenterium)

Table 2. Summary of clinical features

Case	Age	Sex	Duration of symptoms	Symptoms	Clinical diagnosis	Lymph nod	Histological diagnosis	Outcome
17	5	M	few wk	Abdominal pain bleeding	Ileocaecal tuberculosis?	+	L., lymphoblastic	Died 7 mo after operation with recurrence (diffuse)
18	12	M	few wk	Abdominal pain malabsorption	Ileocoecal obstruction, yersinia infect.?	+	L., lymphoblastic	Lost to follow-up
19	62	F	9 mo	Abdominal pain weight loss malabsorption	Lymphoma	+	L., lymphoblastic	Died 10 mo after operation and chemotherapy
20	11	M	few wk	Abdominal pain	Appendicitis	+	L., lymphoblastic	Lost to follow-up
21	7	M	few wk	Abdominal pain	Appendicitis	–	L., lymphoblastic	Alive, 1 yr chemotherapy
22	8	M	few days	Abdominal pain	Appendicitis	+	L., lymphoblastic	Died few wk after operation with recurrence
23	41	M	20 yr	Abdominal pain bleeding malabsorption	Gastric ulcer Crohn's disease lymphomat. ulcerat. dermatitis	+	L., immunoblastic	Died
24	27	F	sever. yr	Abdominal pain steatorrhoea	Coeliac sprue	+	L., immunoblastic	Died 1 yr after chemotherapy
25	34	F	sever. yr	Malabsorption weight loss	Coeliac sprue	–	L., immunoblastic	Alive, 2 yr chemotherapy
26	41	M	sever. yr	Abdominal pain weight loss malabsorption	Coeliac sprue	–	L., immunoblastic	Alive, 1 yr chemotherapy
27	33	M	sever. yr	Malabsorption weight loss acute abdomen	Coeliac sprue	–	L., immunoblastic	Alive, 2 yr chemotherapy

Table 3. Classification of 27 malignant non-Hodgkin's lymphomas (M.L.) of the intestinal tract, Kiel Classification

M.L., low grade of malignancy	13
Lymphocytic	1
Lympho-plasmacytic (Immunocytoma)	7
Centrocytic	2
Centroblastic/centrocytic	3
M.L., high grade of malignancy	14
Centroblastic	1
Lymphoblastic	8
Immunoblastic	5

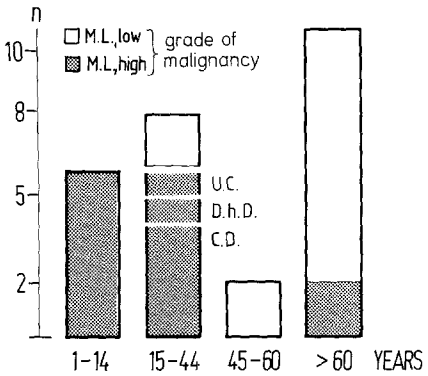

Fig. 1. Age-correlated incidence of 27 non-Hodgkin's lymphomas (M.L.) of the intestinal tract. U.C. lymphoma associated with ulcerative colitis, D.h.D. dermatitis herpetiformis Duhring, C.D. coeliac disease. Cases observed in the Institute of Pathology, University of Hamburg (1974–1979)

Table 4. Recent classifications of gastrointestinal lymphomas (cf. Isaacson et al. 1979)

	Plasmacytic	Lymphocyte derived	Histiocytic (Isaacson)	Histiocytic (Rappaport)	Others
Henry and Farrer-Brown (1977) Middlesex and Westminster Hospital, London	39%	55%	–	3%	3%
Lewin et al. (1978) Stanford University Medical Center	4%	20%	–	60%	16%
Isaacson et al. (1979) Wessex region of England	–	41%	50%[a]	–	9%

[a] 17% histiocytic lymphoma
33% malignant histiocytosis

of the lymphomas are presented (cf. Table 2) and it is evident that malignant lymphomas with a high grade of malignancy occur mainly in adolescence.

Six out of the twenty-seven malignant lymphomas had developed in the course of immuno-inflammatory diseases of the gut: four in the course of coeliac disease, one from a "malabsorptive" dermatitis herpetiformis, and one as complication of a long-standing ulcerative colitis.

Coeliac Disease-Associated Intestinal Lymphomas

Four out of one hundred and eighty-one patients with coeliac disease observed in a long follow-up study developed, after an average duration of disease of 21.7 years, malignant lymphomas situated in the proximal small intestine. Three of these lymphomas turned out to be immunoblastic lymphomas with monoclonal IgM/kappa-positive cytoplasmic inclusions, the fourth was an unclassified immunoblastic lymphoma.

The following findings seem to be remarkable in the immunoblastic lymphomas: the mucosal structure was altered considerably even after a strict diet

of gliadin withdrawal (Fig. 2). Finger-shaped mucosal villi could not be indentified. The villi were often club-like, swollen by vast infiltration of the stroma, in other parts the mucosa appeared atrophic. In a few cases erosive defects of the mucosa were found. Hyperplasia of the crypts did not exist. The stroma of the mucosa was interspised with lympho-plasmacytic infiltrates (Fig. 3). The plasmacellular compound was composed of IgA-, IgM- and IgG-cells, among which a disproportionate number of IgM-cells was conspicuous (cf. Fig. 13). Immunoblastic tumour-infiltration was found in all three lymphomas mainly in the deeper layers of the intestinal wall. To some extent however, it could not be distinguished from "reactive" lymphoplasmacytic infiltrations of the mucosal stroma (Fig. 2). The immunglobulin containing tumour cells were lysozyme-negative without exception.

In one case the lymphoblastic lymphoma and its development could be traced by mucosal biopsies over a period of four years. With a diet of gliadin withdrawal a remission lasting several years was first noticed. Four years before the patient had to undergo an emergency-laparotomy the intestinal biopsy specimens revealed conspicuous "lymphoreticular", often cord-like, infiltrates in the mucosal stroma (Fig. 4). This finding corresponded roughly with what Whitehead (1968) called "progressive lympho-reticular hyperplasia". At this stage, however a clear hyperregenerative transformation of the mucosa was never detected. The villi appeared rather atrophic. Nine months before the laparotomy, the clinical conditions began to worsen with attacks of spasmodic abdominal pain and steatorrhea. In the biopsy specimen from the small intestine (Fig. 5) wide-spread superficial ulceration was found with prominent dense foci of lympho-reticular inflammatory reactions (i.e. lymphomatous ulcer). This finding was interpreted as benign ulcerative non-granulomatous jejunitis. The patient developed an acute abdomen and had to undergo laparotomy. This revealed a segmental, 30 cm long induration of the small intestine with a local perforation situated about 20 cm distal from the duodenal-jejunal flexure. The histological section from the 70 cm long intestinal resection specimen showed ulcerations and a malignant lymphoma penetrating all layers of the intestinal wall. This was classified according to the criteria of the Kiel-Classification (Lennert et al. 1978) as unclassified lymphoblastic lymphoma (Fig. 6). The acid phosphatase reaction (imprint cytology) was negative. Immunohistochemistry showed negative staining of the tumour cells for all immunoglobulin classes and for lysozyme.

Dermatitis-Associated Intestinal Lymphoma

The case-history of this patient (fourty-three year old man with a twenty years long history of Duhring's disease) is summarized in Fig. 7 (cf. Gebbers et al. 1977). Numerous biopsy specimens from the small intestine, which had been taken in the years 1974 and 1975, revealed lymphomatous ulcerations (benign ulcerative non-granulomatous jejunitis), and lympho-reticular hyperplasia. Histology and immunocytochemistry of the autopsy specimen revealed a monoclonal IgM-immunoblastic lymphoma in the upper small intestine with involvement of the mesenteric, portal and parapancreatic lymph nodes.

Colitis-Associated Intestinal Lymphoma

A proctocolectomy was carried out in a fourty year old male patient with a biopsy-verified colitis carcinoma, the case history of which had extended over roughly fourteen years before the operation (cf. Otto et al. 1978). Histological investigation of the resection specimen revealed a simultaneously existing malignant lymphoma situated in the sigmoid colon which was interpreted according to the Kiel-Classification as lymphoblastic lymphoma. Histologically, the

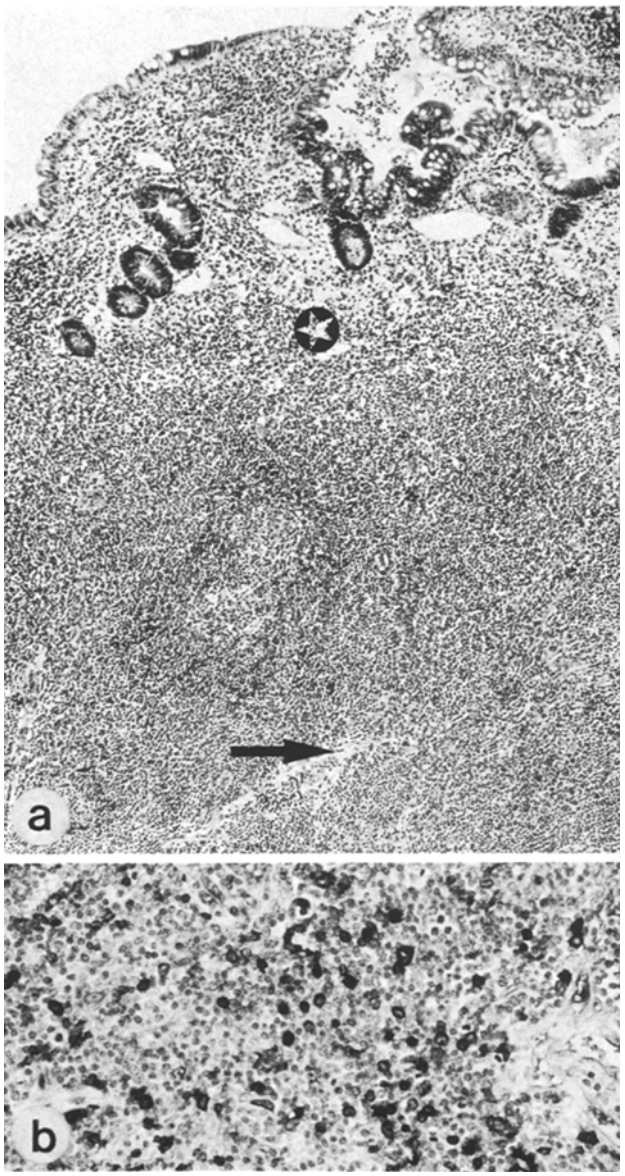

Fig. 2a, b. Immunoblastic lymphoma of the proximal small intestine after long-standing coeliac disease. IgM/kappa-positive (**b**). Irregular shaped villi with lymphoplasmacytic infiltration of the lamina propria. Area of tumour destroyed muscularis mucosae (asterix). Muscularis propria (arrow). **a** Haematoxylin & eosin, ×80, **b** Immunoperoxidase, anti-kappa, ×240 (J.No. 21 267/74; Institute of Pathology, University of Hamburg)

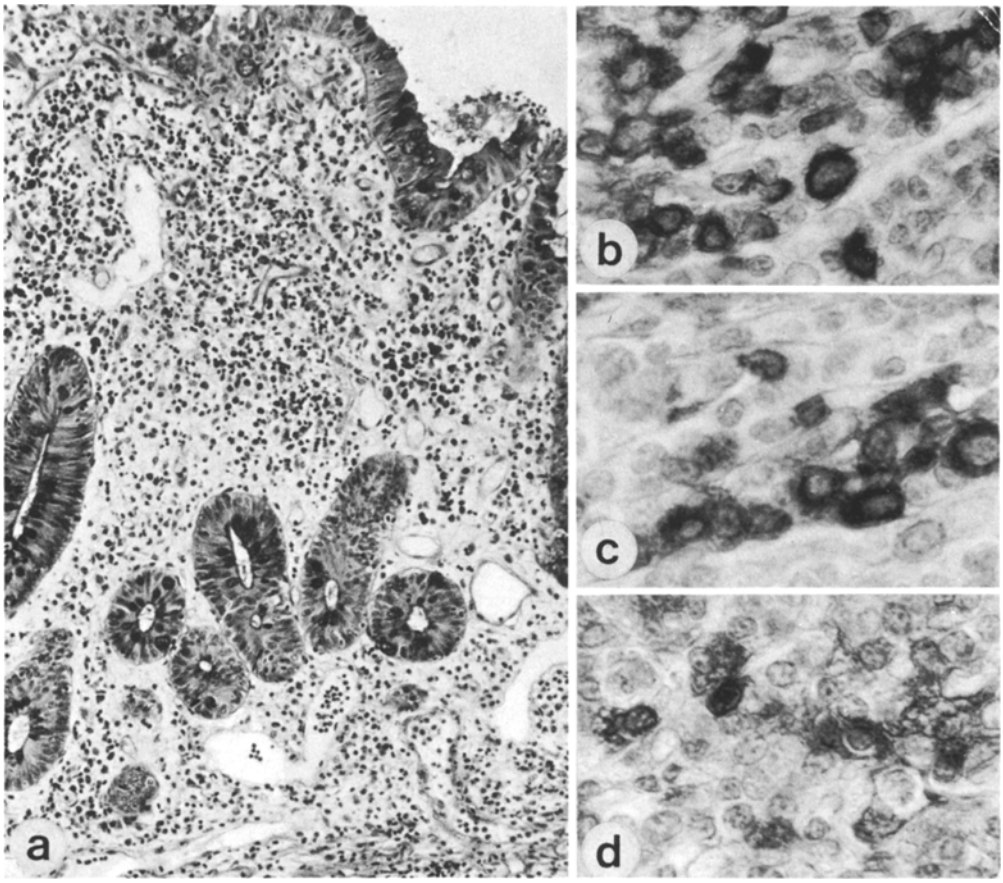

Fig. 3a–d. Same case as Fig. 2. Enlargement of the mucosal stroma by lymphoplasmacytic infiltration (**a**). Immunoperoxidase stains in many plasmacytoid cells. "Plasma cell dyscrasia" with marked disproportionate increase of IgM cells compared with that of IgA cells (cf. Fig. 13). a) PAS, ×320, b–d) Immunoperoxidase, anti-IgM, -IgA, and -IgG, ×820

lymphoma showed two typical differentiations. Focally cyto- and histological similarities to a malignant lymphoma of Burkitt's type could be seen (Fig. 8) with inclusion of histiocytic reticular cells and often a distinct activity of phagocytosis (starry-sky appearance). In the major part, however, the histological finding was that of a lymphoma of the unclassified sub-group, with loss of the starry-sky appearance (Fig. 9).

Intestinal Lymphomas Without Immuno-Inflammatory Diseases

Twenty-one lymphomas of the gut had developed without any immuno-inflammatory disease. The most frequent tumor types turned out to be lympho-plasmacytic and lymphoblastic lymphomas. All other patterns of differentiations of lymphoma (lymphocytic lymphomas and lymphomas of germinal-center cells) were rare.

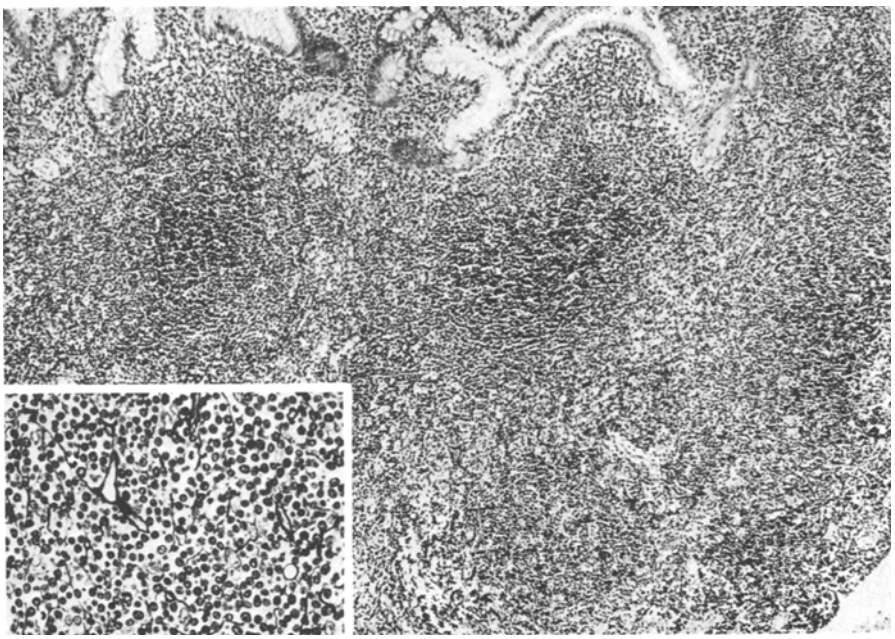

Fig. 4. Small intestinal biopsy specimen from the proximal jejunum showing villous irregularity without crypt hyperplasia. Dense lympho-reticular infiltrates in the lamina propria. PAS, ×80. Inset: Gomori, ×180 (J.No. 10 450/71; Institute of Pathology, University of Hamburg)

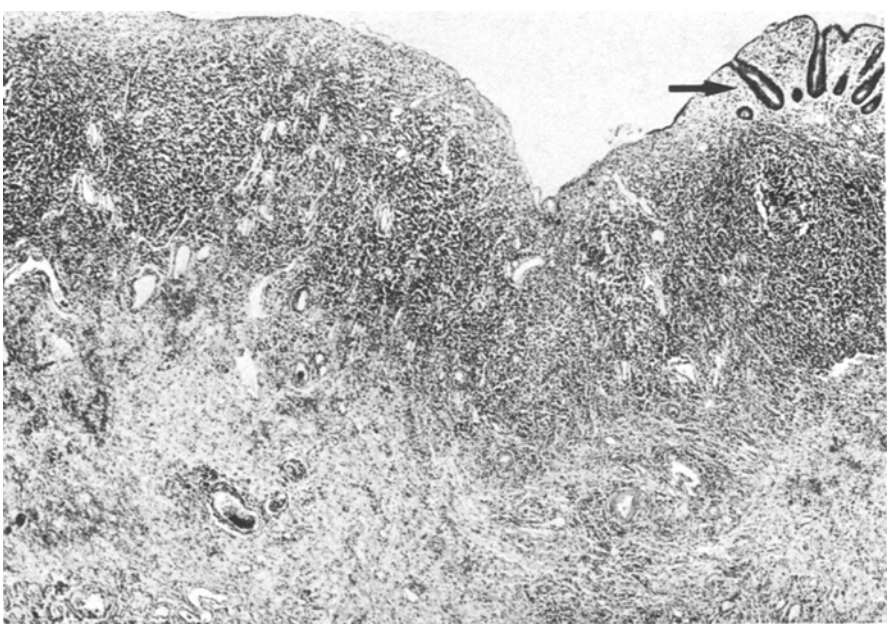

Fig. 5. Peroral jejunal biopsy specimen showing a "lymphomatous ulcer" with atrophic "flat" mucosa (arrow). Dense lympho-reticular infiltrate in the ulcer ground (same patient as Fig. 4). PAS, ×120 (J.No. 2 388/75; Institute of Pathology, University of Hamburg)

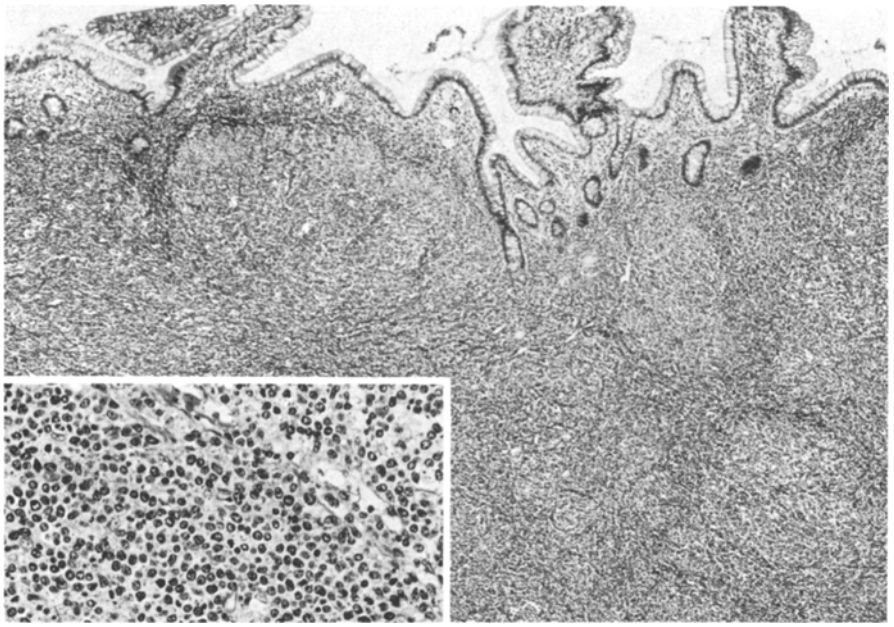

Fig. 6. Jejunal mucosa from resection specimen (same case as Figs. 4 and 5). Malignant lymphoma of the jejunum after long-standing coeliac disease, lymphoblastic type, unclassified. Haematoxylin & eosin, ×80. Inset: ×120 (J.No. 14 711/75; Institute of Pathology, University of Hamburg)

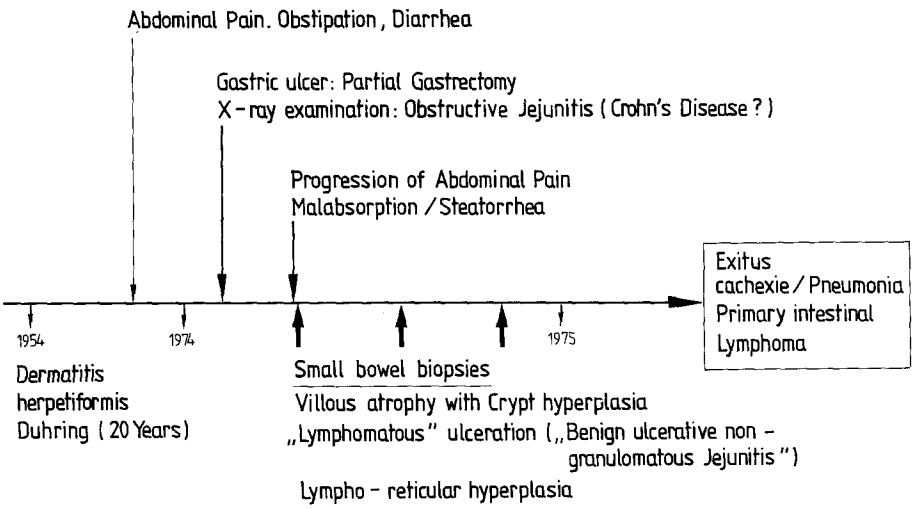

Fig. 7. "Malabsorptive" dermatitis herpetiformis Duhring associated with small-intestinal lymphoma. Schematic illustration of the case history. Multiple biopsies from the small intestine revealed repeatedly only atrophy of the mucosa, partly with a "lymphomatous ulceration", partly with "lymphoreticular hyperplasia" (S.No. 792/75; Institute of Pathology, University of Hamburg)

Fig. 8. Long-standing ulcerative colitis with malignant lymphoma of lymphoblastic type. Variable differentiation (cf. Fig. 9) with a focal "starry-sky" appearance (Burkitt's type). PAS, ×220. Inset: ×480 (J.No. 33 019/77; Institute of Pathology, University of Hamburg)

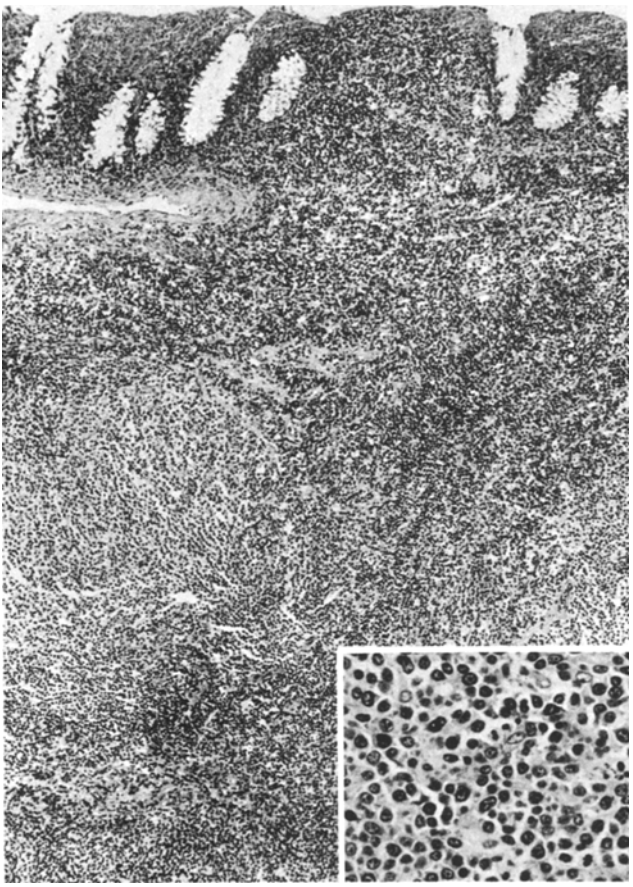

Fig. 9. Ulcerative colitis with malignant lymphoma of lymphoblastic type (same case as Fig. 8). In this part: lymphoblastic lymphoma of unclassified type. PAS, ×80. Inset: ×320

Lympho-Plasmacytic Lymphomas. Seven cases were classified as lympho-plasmacytic lymphomas (immunocytomas). These were confined to the caecum and to the caecum and appendix respectively. In two cases, apart from lymphocytic and plasmacellular differentiation, a large number of immunoblasts, centroblasts and centrocytes were found. Accordingly these lymphomas can be classified as polymorphic-type immunocytomas. The plasmacytic tumour cells contained PAS-positive cytoplasmatic inclusion bodies (Russell bodies) remakably often. In this phenotype, they were similar to the so-called Mott cells. In some parts of the sections, a large number of mature plasma cells could be identified. The histological picture of these tumours resembled, in some parts at least, mature plasmocytomas, which frequently seem to be localized in the caecal region (Douglas et al. 1971; Schweers et al. 1976; Henry and Farrer-Brown 1977). In all cases of immunocytomas, the cytoplasm contained IgM/kappa (Fig. 10). We could identify so-called epitheloid cell clusters in several instances (Fig. 11).

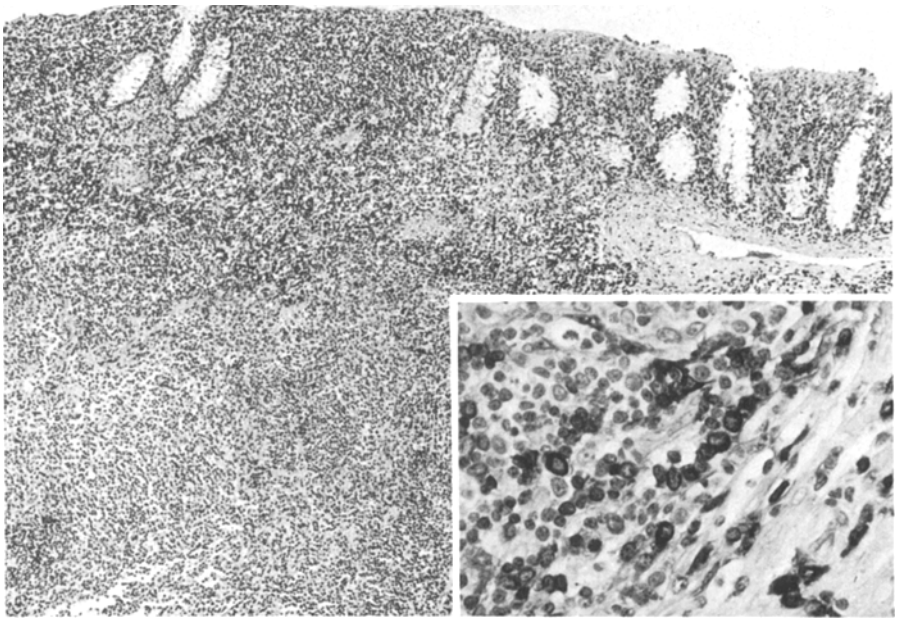

Fig. 10. Malignant lymphoma (cecum) with lympho-plasmacytic differentiation. Haematoxylin & eosin, ×80. Inset: Immunoperoxidase technique showing numerous tumour cells with kappa-chains. Immunoperoxidase, anti-kappa, ×320 (J. No. 33 109/78; Institute of Pathology, University of Hamburg)

Lymphoblastic Lymphomas. Eight cases in our series were classified as lymphoblastic lymphomas. These tumours were diffuse and composed of monomorphic undifferentiated lymphoid cells. These cells were relatively small or of medium-size. The nuclear chromatin was condensed, both at the nuclear membrane and around the nucleoli. The cytoplasm appeared scanty and basophilic.

Of the eight lymphoblastic lymphomas, we found three of Burkitt's type, the other five were classified as so-called unclassified lymphoblastic lymphomas (Fig. 12). We have not detected a lymphoblastic lymphoma of convoluted cell type in our series. Immunohistochemistry showed negative staining of the tumour cells for all immunoglobulin classes and for lysozyme. Alpha-naphthyl acetate esterase (Knowles and Holck 1978) also gave negative staining.

Lymphomas of Germinal-Center Cells. Six out of the twenty-seven intestinal lymphomas belonged to the group of lymphomas of germinal center cells. Two of these six were of centrocytic, one of centroblastic differentiation and the remaining three of centrocytic/centroblastic type. All centrocytic and centroblastic lymphomas were diffusely spread, both in the bowel wall and in the associated lymph nodes. Two of the three centroblastic/centrocytic lymphomas were nodular and the third diffuse. In accordance with Isaacson et al. (1979) our immunohistochemical studies showed negative staining of the tumour cells, but revealed the presence of scattered reactive plasma cells containing all three main classes of immunoglobulins.

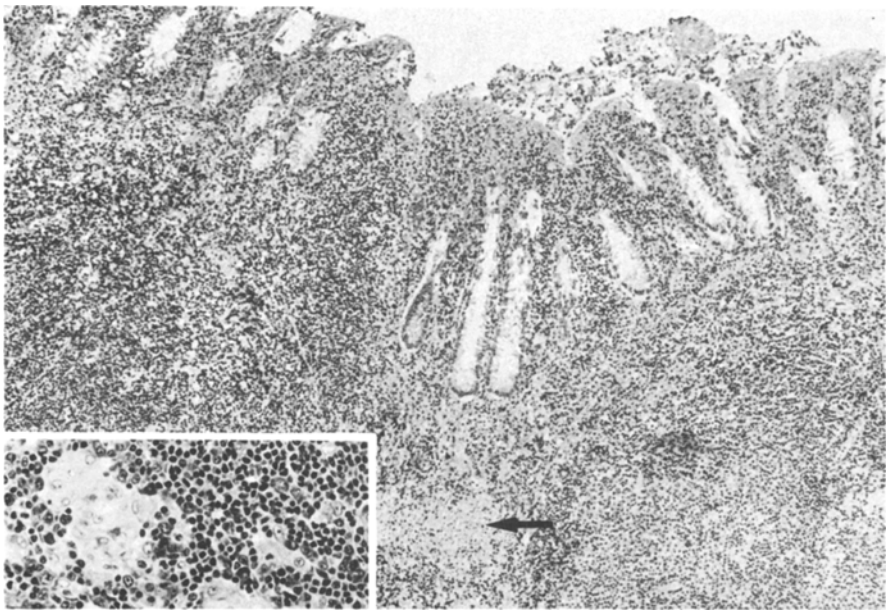

Fig. 11. Lympho-plasmacytic lymphoma of the caecum with epitheloid-cell clusters (arrow). Inset: Higher magnification of epitheloid-cell clusters. Haematoxylin & eosin, ×100. Inset: ×220 (J.No. 9 808/79; Institute of Pathology, University of Hamubrg)

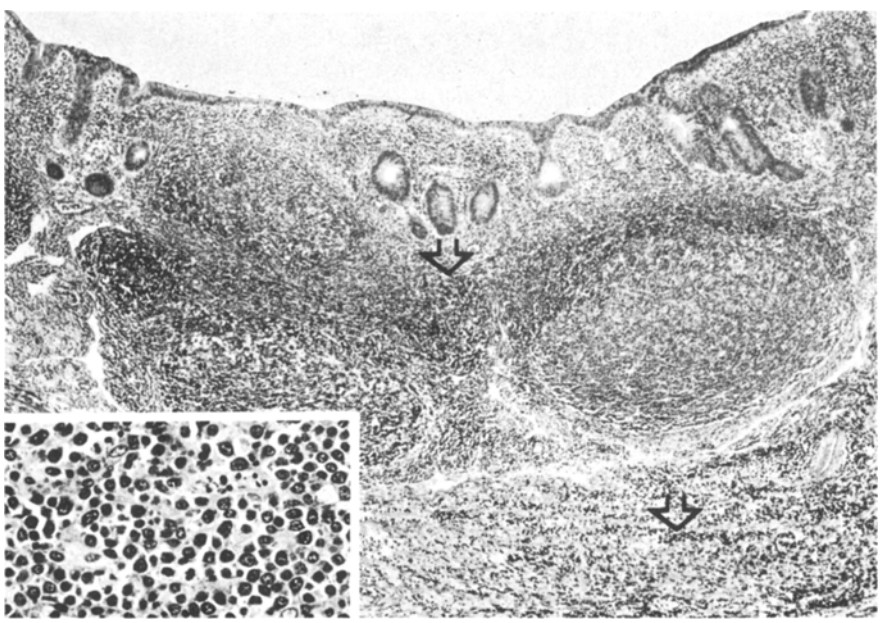

Fig. 12. Malignant lymphoma of the vermiform appendix: Lymphoblastic lymphoma, unclassified subtype. Tumour infiltration of the deeper layers and beginning infiltration of the follicles (arrows). PAS, ×80. Inset: ×220 (J.No. 13 465/79; Institute of Pathology, University of Hamburg)

Discussion

Between 1974 and 1979 twenty-seven non-Hodgkin's lymphomas of the intestinal tract (excluding the stomach) were investigated. Malignant lymphomas, although very rare compared with cancer, are the second most frequent tumor of the gastrointestinal tract.

A classification of malignant lymphomas by a etiology is not yet possible. The numerous different classifications (Rappaport 1966; Lukes and Collins 1974–1977; Dorfman 1977; Lennert et al. 1978) have provoked a somewhat confusing histomorphologic terminology. In addition, considerable difficulties have arisen in the differentiation of malignant lymphomas from reactive lympho- and immuno-proliferative processes (Goulston et al. 1965; Whitehead 1968; Sherlock et al. 1970; Lewin et al. 1976; Freeman et al. 1977; Nassar et al. 1978; Isaacson and Wright 1978b). The observation frequently found in literature, that lymphomas situated in the proximal part of the gastrointestinal tract tend to have a better prognosis than those in the distal part, is probably based less upon their localisation and more upon their type and grade of histologic differentiation.

A review of the literature shows that non-gastric malignant lymphomas are located predominantly in the small intestine. Lewin et al. (1978) report that the terminal ileum and ileocoecal region are the commonest location. In contrast carcinomas are known to occur mostly in the large intestine. Hess et al. (1975) have pointed out that the high incidence of carcinoma in the large intestine might correlate with the longer duration of exposure to and the higher concentrations of carcinogenic agents in the intestinal contents. Clinical observations and experimental investigations have indicated that the genesis of intestinal lymphomas is very probably favoured by chronic and persistent exposure to antigens. Viral exposure seems to play an important role in this process. Numerous experimental investigations have shown the great affinity of oncogenic viruses to lympho-reticular tissues. The relatively high incidence of lympho-reticular tumours in primary defet-immunopathies could also be caused by a higher susceptibility to oncogenic viruses (Schwartz 1972; Kersey et al. 1973a, b; Ament et al. 1973; Ament 1975; Hess et al. 1975; Friedman and Fialkow 1976; Talal 1977; Osserman 1978). The theory of viral tumor induction is supported by the extremely high incidence of Epstein-Barr viruses in African Burkitt's lymphoma (Review: Lennert et al. 1979). Immunological investigations by means of different methods have made it evident that the complex interaction of T- and B-lymphocytes is disturbed in Burkitt's lymphoma, Sjögren's disease, "malabsorptive" dermatitis herpetiformis, coeliac disease and in chronic inflammatory bowel disease (Waldmann et al. 1972 and 1974; Brandtzaeg et al. 1974; Jewell and Hodgson 1976; Webster 1976; Whitemeyer et al. 1976; Gebbers et al. 1977; Ferson et al. 1979). The high incidence of neoplastic diseases in animals under immunosuppressive therapy (Krueger 1972) seemingly supports this theory. We are of the opinion that the immunological surveillance is not effective to the same extent in the different tissues (cf. Hess et al. 1975).

Immunohomoiostasis is preserved by a controlled proliferation and functional interaction of immuno-competent cells (Damashek 1966; Porter and Knight 1977; Ruchti et al. 1979). The preservation of this immunohomoiostasis depends significantly upon the function of the gut-associated lymphoid tissue. The inner surface of the gut has been estimated at 200 to 300 m^2. This surface, containing the great variety of microorganisms, food antigens and oncogenic agents, is an important immunobiological border membrane. It has been estimated that about 90% of all immunoglobulins produced in the organism are directed against intestinal antigens (Ruchti et al. 1979). The production of these antibodies can best be understood by keeping in mind the theory of a physiological controlled antigen reception by the enterocytic epithelium. Experimental investigations have shown

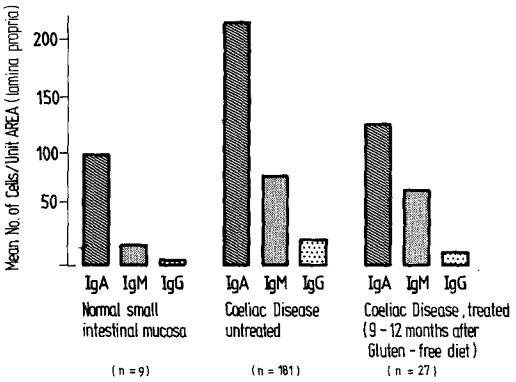

Fig. 13. Average numbers of IgA-, IgM-, and IgG-containing plasma cells per unit area of the lamina propria of control subjects ($n=9$), untreated coeliac disease ($n=181$) and treated coeliac disease ($n=27$)

that the physiological antigen absorption takes place in special lympho-epithelial areas of the mucosa, especially in Peyer's patches in the terminal ileum and in the solitary follicles in the appendix and in the rectum (Owen 1977; Thiery 1978).

Many facts indicate that the antigens which have passed the lympho-epithelial tissue can provoke a humoral reaction in the lamina propria (Ogra and Karzon 1969; Pierce and Gowans 1975; Tomasi 1976; Keren et al. 1978; Lancet Editorial 1979). Proliferation of the lymphatic B-cells and their differentiation into mature plasma cells is, apart from antigen stimulation, subordinated to an interaction with the T-lymphocytes (Parrott and Ferguson 1974; Rose et al. 1976; Parrott 1976). Intestinal T-lymphocytes regulate humoral immune reactions. Stimulated T-cells of the intestinal mucous membrane suppress IgM, IgE and IgG synthesis, but enhance IgA synthesis (Elson et al. 1979). Dependence of IgA production on helper T-cells is supported by the observations that nude mice have reduced IgA titers and that patients with T-cell defects also show an IgA deficiency (Tomasi 1976). The intestine thus possesses a special T-cell population with IgG and IgM suppressor cells and IgA helper cells.

In many cases, the failure of immuno-biological regulatory mechanisms associated with the intestine leads to a persistent overstimulation of the local immune system, i.e., to an immuno-inflammatory ailment. Ulcerative colitis and Crohn's disease represent the almost classical examples of an immuno-inflammatory disease with pronounced plasma cell dyscrasia (Brandtzaeg et al. 1974; Gebbers and Otto 1978). Furthermore Hodgson et al. (1978) have provided evidence for a reduction of suppressor T-cell activity in patients with Crohn's disease and ulcerative colitis.

The local immune reactions in coeliac disease have been investigated in detail by several researchers (Asquith and Haeney 1979). Coeliac disease is characterized by a persistent intolerance of the intestinal mucous membrane to gliadine. The typical, but not pathognomonic finding seen in the intestinal mucous membrane is a subtotal atrophy of the villi with hyperplasia of the crypts and a sometimes massive cell infiltration of the stroma of the mucous membrane. In particular, the plasma cells are abnormally increased in number (Fig. 13). Here our immuno-histological investigations have indicated a disproportionately strong increase of IgM- and IgG-cells compared to the increase of IgA-cells. During a diet free of gliadin, the number of plasma cells is reduced, but nevertheless remains well above normal. In particular, the number of IgM-cells remains elevated. This is interesting because intestinal lymphomas, which may occur as a complication during coeliac disease, are often immunoblastic lymphomas having a monoclonal IgM/kappa-synthesis. In addition, it was found

that T-lymphocytes are likewise reduced during coeliac disease and that cellular immunity is disturbed (Holmes et al. 1976; Scott and Losowsky 1976; O'Donoghue et al. 1976; Asquith and Haeney 1979).

Immunocytomas and immunoblastic lymphomas occur increasingly, but not exclusively, during immuno-proliferative disorders. Similar lymphomas also develop during the graft-versus-host-reaction, where a progressive generation of malignant lymphomas of high malignancy from those of low malignancy has been observed (Review: Lennert et al. 1979). The development of malignant lymphomas during immunoproliferating disorders and during graft-versus-host-reactions can possibly be traced to the same basic mechanism, insufficient control of the stimulation of B-lymphocytes by T-cells. It is not clear why the immunocytomas and immunoblastic lymphomas are primarily monoclonal IgM-lymphomas. Taking into consideration the immunogenetic findings, a defect of T-suppressor cells specifically associated with IgM may be assumed.

About 7% of patients with coeliac disease are likely to develop malignant tumors (cf. Asquith and Haeney 1979). Part from lymphomas, there is also an increased occurrence of gastro-intestinal carcinomas (Huizenga and Hermans 1972). Certain restrictions in cellular immune function are nowadays also blamed for the development of coeliac-associated carcinomas.

Coeliac-associated intestinal lymphomas are thought to develop via so-called progressive lymphoreticular hyperplasia, which is followed by manifest lymphomas after a period of months or years (Whitehead 1968). Histologically, progressive lympho-reticular hyperplasia is characterized by dense plasmacellular infiltrations of the mucous membrane, and of the associated regional lymph nodes. The plasma cells contain immunoglobulins of all main classes but a pronounced plasmacellular dyscrasia occurs in favour of the IgM-cells. Biopsy detection of this "pre-sarcomatic" phase is practically impossible. Electron microscopy indicates certain cytological and nuclear abnormalities especially in histiocytic cell forms. However, in our opinion, these do not represent reliable diagnostic criteria. The real nature of this progressive hyperplasia and the causes that ultimately lead to the transformation to monoclonal malignancy are unknown (Friedman and Fialkow 1976; Levy et al. 1977).

So-called chronic ulcerative non-granulomatous jejunoileitis is an additional serious complication of coeliac disease and malabsorptive dermatitis herpetiformis (Goulston et al. 1965; Bayless et al. 1967; Jeffries et al. 1968; Klaeveman et al. 1975; Freeman et al. 1977; Gebbers et al. 1977; Isaacson and Wright 1978b, c). It frequently appears in conjunction with Whitehead's progressive hyperplasia. The infiltration of the lamina propria consists of lymphohistiocytic cells (lymphomatous ulcer). Whitehead (1968) described an infiltration consisting of abnormal prohistiocytes. According to more recent investigations (cf. Freeman et al. 1977; Isaacson and Wright 1978b), progressive lympho-reticular hyperplasia and chronic ulcerative non-granulomatous jejunoileitis (lymphomatous ulceration) are developmental stages or special forms of intestinal lymphomas. Lymphomatous ulcerations, frequently mistakenly interpreted as benign ulcerative non-granulomatous jejunoileitis, must especially be considered as manifest ulcerated lymphomas of the intestinal tract.

Mainly because of these ulcerated lymphomas, which frequently display

only a short history, discussions concerning the nature of the relationship between coeliac disease and lymphomas have again been revived. Does the malabsorption syndrome lead to a disposition for the development of malignant lymphomas? Or is malabsorption the first clinical symptom of malignant lymphoma (primary intestinal lymphoma with malabsorption)? This question is still the subject of controversy (Isaacson and Wright 1978b, c; Cooper et al. 1978). The association of malignant lymphoma of the small intestine with malabsorption syndrome has been known for some time (cf. Isaacson and Wright 1978b). Lymphomas associated with coeliac disease develop after an average latency period of 21 to 26 years (Holmes et al. 1976). Among ulcerated lymphomas with malabsorption, having a remarkably abdominal symptomatology. Isaacson and Wright (1978a–c) found lymphomas of almost exclusively histiocytic origin. A distinction must be made here between malignant histiocytosis of the intestine, diffuse pleomorphic lymphomas associated with villous atrophy and ulceration of small intestine, and histiocytic lymphomas. The immunohistological findings of Isaacson and his co-workers are interesting: In all cases large numbers of malignant histiocytic cells were shown to contain all major classes of immunoglobulin heavy chains, and both light chains, the C3 component of complement and lysozyme. In contrast to histiocytic lymphomas, the histiocytes from malignant histiocytosis of the intestine contained easily demonstrable alpha$_1$-antitrypsin. This lymphoma group is thus clearly distinguishable by immuno-histological methods from the immunoblastic lymphomas of the Kiel-Classification. The intracytoplasmic detection of the various kinds of immunoglobulins in a tumour may result from pronounced phagocytotic activities of the tumour cells. Histiogenetically these presumably are tumours of histiocytic cell forms or rather tumours of the mononuclear phagocyte system, i.e., tumours originating from intestinal histiocytes and macrophages (Isaacson and Wright 1978; Isaacson et al. 1978). Such a distinction among tumours has not been detected in our studies.

It is remarkable that recent classifications of primary gastro-intestinal lymphomas have been contradictory (Table 4). Using Rappaport's classification (1966), the Stanford group found that diffuse histiocytic lymphoma was the most common histological type and constituted 60% of 117 cases (Lewin et al. 1978). Henry and Farrer-Brown (1977), in a morphological analysis of 125 cases, classified 51% as lymphocytic in origin and 30% as plasmacytic. Isaacson et al. (1978) examined 66 cases and found that histiocytic lymphomas accounted for 50% and lymphocyte-derived lymphomas for 41%. These discrepant results cannot be explained on the basis of methodology or epidemiology. In addition, there is variation in the frequency of certain types of intestinal lymphoma. This holds, for example, for the Mediterranean type of intestinal lymphoma (alpha chain disease). According to Lennert et al. (1979) an increased number of centroblastic lymphomas occur in the Mediterranean area. This group of lymphomas is supposed to constitute more than 50% of all gastrointestinal lymphomas.

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References

Alexander JOD (1975) Dermatitis herpetiformis. In: Rook A (ed) Major problems in dermatology, vol 4. W.B. Saunders Comp Ltd, London Philadelphia Toronto

Al-Saleem T, Zardawi IM (1979) Primary lymphomas of the small intestine in Iraq: A pathological study of 145 cases. Histopathology 3:89–106

Ament ME (1975) Immunodeficiency syndromes and gastrointestinal disease. Ped Clin N Amer 22:807–825

Ament ME, Ochs HD, Davis SD (1973) Structure and function of the gastrointestinal tract in primary immunodeficiency syndromes: A study of 39 patients. Medicine 52:227–248

Asquith P, Haeney MR (1979) Coeliac disease. In: Asquith P (ed) Immunology of the gastrointestinal tract. Churchill Livingstone, Edinburgh London New York, p 66

Bayless TM, Kapelowitz RF, Shelley WM, Ballinger WF, Hendrix TR (1967) Intestinal ulceration – complication of celiac disease. New Engl J Med 276:996–1102

Brandtzaeg P, Baklien K, Fausa O, Hoel PS (1974) Immunohistochemical characterization of local immunoglobulin formation in ulcerative colitis. Gastroenterology 66:1123–1136

Brandt L, Hagander B, Nordén A, Stenstam M (1978) Lymphoma of the small intestine in adult coeliac disease. Acta Med Scand 204:467–470

Collins WJ (1977) Maligant lymphoma complicating regional enteritis. Case report and review of the literature. Amer J Gastroenterol 68:177–181

Cooper BT, Holmes GKT, Cooke WT (1978) Intestinal mymphoma associated with malabsorption. Lancet I, 387

Damashek W (1966) Immunocytes and immunoproliferative disorders. In: Wolstenholme GEW, and Porter R (eds) The thymus: Experimental and clinical studies. Ciba Foundation Symposium. J. & A. Churchill Ltd, London, p 399

Dawson IMP, Cornes JS, Morson BC (1961) Primary malignant lymphoid tumours of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. Brit J Surg 40:80–89

Doe WF (1979) Alpha heavy chain disease and related small-intestinal lymphomas. In: Asquith P (ed), Immunology of the gastrointestinal tract. Churchill Livingstone, Edinburgh London New York, p 306

Dorfman RF (1977) Pathology of the non-Hodgkin's lymphomas: New classifications. Cancer Treat Rep 61:945–951

Douglass HO, Sika JV, LeVeen HH (1971) Plasmocytoma: A not so rare tumor of the small intestine. Cancer 28:456–460

Dutz W, Asvadi S, Sadri S, Kohout E (1971) Intestinal lymphoma and sprue: A systematic approach. Gut 12:804–810

Eidelman S (1976) Intestinal lesions in immune deficiency. Hum Pathol 7:427–434

Elson CO, Heck JA, Strober W (1979) T-cell regulation of murine IgA synthesis. J Exp Med 149:632–6643

Ferson M, Edwards A, Lind A, Milton GW, Hersey P (1979) Low natural killer-cell activity and immunoglobulin levels associated with smoking in human subjects. Int J Cancer 23:603–609

Freeman HJ, Weinstein WM, Shnitka TK, Piercey JRA, Wensel RH (1977) Primary abdominal lymphoma. Presenting manifestation of celiac sprue or complicating dermatitis herpetiformis. Am J Med 63:585–594

Friedman JM, Fialkow PhJ (1976) Cell marker studies of human tumorigenesis. Transplant Rev 28:17–33

Galian A, Lecestre MJ, Scotto J, Bognel C, Matuchansky C, Rambaud JC (1977) Pathological study of alpha-chain disease, with special emphasis on evolution. Cancer 39:2081–2101

Gebbers J-O, Otto HF (1978) Evidence for local immune complexes in ulcerative colitis. Acta Gastroenterol Belg 41:329–350

Gebbers J-O, Otto HF, Müller-Wieland K (1977) Immunoblastisches Sarkom („Retikulumzellsarkom") des Gastrointestinaltraktes bei Dermatitis herptiformis Duhring. Dtsch Med Wochenschr 102:242–247

Goulston KJ, Skyring AP, McGovern VJ (1965) Ulcerative jejunitis associated with malabsorption. Aust Ann Med 14:57–64

Haeney MR, Ferguson R, Asquith P (1979) Animal models for coeliac disease and inflammatory

bowel disease. In: Asquith P (ed) Immunology of the gastrointestinal tract. Churchill Livingstone, Edinburgh London New York, p 129
Haghighi P, Kharazmi A, Gerami C, Haghshenass M, Abadi P, Omidi H, Mostafavi N (1978) Primary upper small-intestinal lymphoma and alpha-chain disease. Report of 10 cases emphasizing pathological aspects. Am J Surg Pathol 2:147–157
Harris OD, Cooke WT, Thompson H, Waterhouse JAH (1967) Malignancy in adult coeliac disease and idiopathic steatorrhoea. Am J Med 42:899–912
Henry K, Farrer-Brown G (1977) Primary lymphomas of the gastro-intestinal tract. I. Plasma cell tumours. Histopathology 1:53–76
Hermans PE, Diaz-Buxo JA, Stobo JD (1976) Idiopathic late-onset immunoglobulin deficiency: clinical observation in 50 patients. Am J Med 61:221–237
Hess MW, Zimmermann A, Brun del Re G, Cottier H (1975) Immunologische Aspekte gastrointestinaler Neoplasien. Schweiz Med Wochenschr 105:570–575
Hodgson HJF, Wands JR, Isselbacher KJ (1978) Decreased suppressor cell activity in inflammatory bowel disease. Clin Exp Immunol 32:451–458
Holmes GKT, Stokes PL, Sorahan TM, Prior P, Waterhouse JAH, Cooke WT (1976) Coeliac disease, gluten-free diet and malignancy. Gut 17:612–619
Huizenga KA, Hermans PE (1972) Association of gastric carcinoma with idiopathic late-onset immunoglobulin deficiency. Ann Intern Med 76:605–609
Isaacson P (1978a) Middle East lymphoma and α-chain disease. Animmunohistochemical study. Am J Surg Pathol 3:431–441
Isaacson P, Wright DH (1978a) Origin of intestinal lymphomas. Lancet I:984–985
Isaacson P, Wright DH (1978b) Malignant histiocytosis of the intestine. Its relationship to malabsorption and ulcerative jejunitis. Hum Pathol 9:661–677
Isaacson P, Wright DH (1978c) Intestinal lymphoma associated with malabsorption. Lancet I:67–70
Isaacson P, Wright DH, Judd MA, Mepham BL (1979) Primary gastrointestinal lymphomas. A classification of 66 cases. Cancer 43:1805–1819
Jeffries GH, Steinberg H, Sleisenger MH (1968) Chronic ulcerative (nongranulomatous) jejunitis. Am J Med 44:47–59
Jewell DP, Hodgson HJF (1976) Autoimmune and inflammatory diseases of the gastrointestinal tract. In: Ferguson A, and MacSween RNM (eds) Immunological aspects of the liver and gastrointestinal tract. MTP Press Ltd, Lancaster, p 203
Keren DF, Holt PS, Collins HH, Gemski P, Formal SB (1978) The role of Peyer's patches in the local response of rabbit ileum to live bacteria. J Immunol 120:1892–1897
Kersey JH, Spector BD, Good RA (1973a) Primary immunodeficiency diseases and cancer: The immunodeficiency-cancer registry. Int J Cancer 12:333–347
Kersey JH, Spector, Good RA (1973b) Immunodeficiency and cancer. Adv Cancer Res 18:211–230
Klaeveman HL, Gebhard RL, Sessoms C, Strober W (1975) In vitro studies of ulcerative ileojejunitis. Gastroenterology 68:572–582
Knowles DM, Holck S (1978) Tissue localization of T-lymphocytes by the histochemical demonstration of acid α-naphthyl acetate esterase. Lab Invest 39:70–76
Krueger GRF (1972) Chronic immunosuppression and lymphomagenesis in man and mice. Nat Cancer Inst Monograph 35:183–190
Lancet-Editorial (1979) Gut reaction to antigen. Lancet I:763
Lee GB, Smith PM, Seal RME (1977) Lymphosarcoma in Crohn's disease. Report of a case. Dis Colon Rectum 20:351–354
Lennert K, Mohri N, Stein H, Kaiserling E, Müller-Hermelink HK (1978) Malignant lymphomas other than Hodgkin's disease. In: Uehlinger E (ed) Handbuch der speziellen pathologischen Anatomie und Histologie, Bd I/3 B. Springer, Berlin Heidelberg New York
Lennert K, Knecht H, Burkert M (1979) Vorstadien maligner Lymphome. Verh Dtsch Ges Pathol 63:170–196
Levy R, Warnke R, Dorfman RF, Haimovich J (1977) The monoclonality of human B-cell lymphomas. J Exp Med 145:1014–1028
Lewin KJ, Kahn LB, Novis BH (1976) Primary intestinal lymphoma of "Western" and "Mediterranean" type, alpha chain disease and massive plasma cell infiltration. A comparative study of 37 cases. Cancer 38:2511–2528

Lewin KJ, Ranchod M, Dorfman RF (1978) Lymphomas of the gastrointestinal tract. A study of 117 cases presenting with gastrointestinal disease. Cancer 42:693–707

Lillie RD (1965) Histopathologic technic and practical histochemistry, 3rd edn. McGraw-Hill, New York

Lukes RJ, Collins RD (1974) Immunologic characterization of human malignant lymphomas. Cancer 34:1488–1503

Lukes RJ, Collins RD (1975) New approaches to the classification of the lymphomata. Br J Cancer 31:(Suppl), 1–28

Lukes RJ, Collins RD (1977) Lukes-Collins classification and its significance. Cancer Treat Rep 61:971–979

MacLaurin BP, Cooke WT, Ling NR (1971) Impaired lymphocyte reactivity against tumour cells in patients with coeliac disease. Gut 12:794–800

Najman A, Gorin N-C, Barranger Ch, Duhamel G (1977) Les localisation digestives des lymphomes non hodgkiniens. 31 cas. Nouv Presse Med 6:3515–3519

Nasr K, Haghighi P, Bakhshandeh K, Haghshenas M (1970) Primary lymphoma of the upper small intestine. Gut 11:673–678

Nassar VH, Salem PhA, Shahid MJ, Alami SY, Balikian JB, Salem AA, Nasrallah SM (1978) "Mediterranean abdominal lymphoma" or immunoproliferative small intestinal disease. Part II: Pathological aspects. Cancer 41:1340–1354

Nisard A, Lecharpentier Y, Louvel A, Galian A, Bleichner G, Boisson J, Rambaud JC (1976) Etude anatomo-pathologique d'un lymphome malin compliquant une maladie coeliaque de d'adulte. Arch Fr Mal App Dig 65:295–305

Nugent FW, Zuberi S, Bulan MB, Legg MA (1972) Colonic lymphoma in ulcerative colitis: Report of four cases. Lahey Clin Found Bull 21:104–111

O'Donoghue DP, Lancaster-Smith M, Laviniere P, Kumar PJ (1976) T cell depletion in untreated adult coeliac disease. Gut 17:328–331

Ogra PL, Karzon DT (1969) Distribution of poliovirus antibody in serum, nasopharynx and alimentary tract following segmental immunisation of lower alimentary tract with poli vaccine. J Immunol 102:1423–1431

Osserman EF (1978) Multiple myeloma and related plasma cell dyscrasias. In: Samter M (ed) Immunological diseases, 3rd edn, vol I. Little, Brown & Co, Baltimore, p 499

Otto HF, Gebbers J-O, Matthaes P, Müller-Wieland K (1978) Malignes Lymphom and multitope Karzinome des Dickdarms als Komplikation einer langjährigen Colitis ulcerosa. Inn Med 5:189–195

Otto HF, Sack I, Gebbers J-O, Schulz KH, Müller-Wieland K (1979) Über die "malabsorptive" Dermatitis herpetiformis Duhring. Eine katamnestische Studie unter besonderer Berücksichtigung dünndarmbioptischer Befunde. Virchows Arch A Path Anat and Histol 383:195–206

Owen RL (1977) Sequential uptake of horseradish peroxidase by lymphoid follicle epithelium of Peyer's patches in the normal unobstructed mouse intestine: An ultrastructural study. Gastroenterology 72:440–451

Parrott DMV (1976) The gut as a lymphoid organ. Clinics in Gastroenterology 5:211–228

Parrott DMV, Ferguson A (1974) Selective migration of lymphoblasts within the small intestine. Immunology 26:571–579

Pierce NF, Gowans JL (1976) Cellular kinetics of the intestinal immune response to cholera toxoid in rats. J Exp Med 142:1550–1557

Porter R, Knight J (eds) (1977) Immunology of the gut. Elsevier, Excerpta Medica, North-Holland, Amsterdam Oxford New York

Ramot B, Hulu N (1975) Primary intestinal lymphoma and its relation to alpha chain disease. Br J Cancer 31: (Suppl) 343–349

Rappaport H (1966) Tumors of the hematopoietic system. In: Atlas of Tumor Pathology, Sect 3, Fasc 8. Armed Forces Institute of Pathology, Washington, DC

Rose ML, Parrott DMV, Bruce RG (1976) Migration of lymphoblasts to the small intestine. II. Divergent migration of mesenteric and peripheral immunoblasts to sites of inflammation in the mouse. Cell Immunol 27:36–43

Ross IN, Asquith P (1979) Primary immune deficiency. In: Asquith P (ed) Immunology of the gastrointestinal tract. Churchill Livingstone, Edinburgh London New York, p 152

Ruchti C, Luscieti P, Laissue J, Schaffner Th, Hess MW, Cottier H (1979) Funktionelle Morphologie des intestinalen Immunsystems. Z Gastroenterol, Verh-Bd 14:16–24

Salmon SE (1978) Neoplastic proliferation and natural history of B-cell neoplasia. In: Mathé G, Seligman M, Tubiana M (eds) Lymphoid neoplasias. I. Classification, categorization, natural history. Recent Results in Cancer Research, Bd 64:277–283. Springer, Berlin Heidelberg New York

Schwartz RS (1972) Immunoregulation, oncogenic viruses, and malignant lymphomas. Lancet I:1266–1269

Schweers CA, Shaw MT, Nordquist RE, Rose DD, Kell Th (1976) Solitary cecal plasmocytoma. Electron microscopic, immunologic, and cytochemical studies. Cancer 37:2220–2223

Scott BB, Losowsky MS (1976) Depressed cell-mediated immunity in coeliac disease. Gut 17:900–905

Sherlock P, Winawer SJ, Goldstein MJ, Bragg DG (1970) Malignant lymphoma of the gastrointestinal tract. Prog Gastroenterol 2:367–391

Stokes PL, Holmes GKT (1974) Malignancy. Clin in Gastroenterol 3:159–170

Swarbrick ET, Stockes CR, Soothill JF (1979) Absorption of antigens after oral immunisation and the simultaneous induction of specific systemic tolerance. Gut 20:121–125

Talal N (1977) Immunologic and viral factors in autoimmune diseases. Med Clin N Am 61:205–215

Taylor CR, Mason DY (1974) The immunohistological detection of intracellular immunoglobulin in formalin-paraffin sections from multiple myeloma and related conditions using the immunoperoxidase technique. Clin Exp Immunol 18:417–429

Thiery G (1978) L'appendice du lapin: Un modèle d'appareil immunitaire appliqué à l'étude de l'immunité épithéliale. Ann Immunol (Inst Pasteur) 129 C: 503–522

Tomasi TB (1976) The immune system of secretion. Prentice Hall, Englewood Cliffs NJ

Wagonfeld JB, Platz ChE, Fishman FL, Sibley R, Kirsner JB (1977) Multicentric colonic lymphoma complicating ulcerative colitis. Am J Dig Dis 22:502–508

Waldmann TA, Durm M, Broder S, Blackman M, Blaese RM, Strober W (1974) Role of suppressor T cells in pathogenesis of common variable hypogammaglobulinaemia. Lancet II:609–613

Waldmann TA, Stober W, Blaese RM (1972) Immunodeficiency disease and malignancy. Ann Intern Med 77:605–628

Webster ADB (1976) The gut and immunodeficiency disorders. Clin Gastroenterol 5:323–340

Whitehead R (1968) Primary lymphadenopathy complicating idiopathic steatorrhoea. Gut 9:569–575

Whitemeyer SB, Bankhurst AD, Williams RC (1976) Studies on the suppression of normal B-cell maturation by peripheral blood cells from patients with acquired hypogammaglobulinaemia and from normal neonates. Clin Exp Immunol 6:312–317

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