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PRIMARY INTESTINAL LYMPHOMA AND ITS RELATION TO ALPHA HEAVY CHAIN DISEASE

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Summary.—Primary intestinal lymphoma in young adults is a disease that occurs mainly in underprivileged populations. There is evidence that in some cases this disease evolves from a benign lymphoplasmocytic infiltration of the gut with α heavy chain. More studies are needed on the effect of environmental and genetic factors on the evolution of this disease. The role of oncogenic viruses in the development of intestinal lymphoma with malabsorption is an open question. Regional studies on the entity of intestinal lymphoma with malabsorption and its relationship to childhood lymphoma in the same populations are warranted.

LYMPHOMA of the small intestine can occur as a late manifestation of a disseminated disease or, far less frequently, as a primary lesion originating in the small intestine or mesenteric lymph nodes (Rosenberg *et al.*, 1961; Gough, Read and Naish, 1962). Solitary lymphoma of the gut occurs more commonly in the terminal ileum, predominantly in young children, whereas diffuse or multifocal lymphoma occurs usually in the proximal small intestine in the older age groups. Malabsorption is a rare manifestation of this condition in Western countries (Sleisenger, Almy and Barr, 1953; Skrimshire, 1955). However, the syndrome of malabsorption among underprivileged populations in primary intestinal lymphoma is not rare (Ramot, Shahin and Bubis, 1965; Eidelmann, Parkins and Rubin, 1966; Dutz *et al.*, 1971; Novis *et al.*, 1971).

This subject has been reviewed recently (Ramot, 1971; Ramot and Many, 1972). This presentation is an extension of previously published data on the clinical manifestations and course of intestinal lymphoma, and its relationship to α heavy chain disease, as described by Seligmann, Mihaesco (1968).

Primary lymphoma of the intestine in Western countries

This disease usually affects individuals over the age of 50, with a female : male ratio of 1 : 3. The history of malabsorption, when present, varies from several months to many years. In some patients lesions indistinguishable from coeliac disease are observed on intestinal biopsy (Austad *et al.*, 1967; Brunt, Sircus and MacLean, 1969).

The diagnosis of intestinal lymphoma is considered when patients with coeliac disease start losing weight, become febrile and cease to respond to a gluten-free diet. Peripheral adenopathy, splenomegaly or abdominal masses are rarely palpable on physical examination. An exploratory laparotomy reveals a lymphoma of the gut or mesenteric lymph nodes.

The association between coeliac disease and intestinal lymphoma in the Western world has been well established (Gough *et al.*, 1962; Harris *et al.*, 1967).

Intestinal lymphoma in Israel

In Israel the disease is relatively common among Arabs and first and second generation Jewish immigrants from Mid Eastern and North African countries. It is virtually non-existent among Jews of European origin (Ramot *et al.*, 1965; Eidelmann *et al.*, 1966). Shani *et al.* (1969) have shown that the remarkable ethnic incidence occurs not only in primary intestinal lymphoma but also in

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abdominal localization of lymphoma in general. About 50% of the cases of primary intestinal lymphoma in Israel were Arabs and the rest Jews, mainly from North African countries. Patients sought medical advice because of weight loss, abdominal pain and diarrhoea. This preceded hospitalization by months or even a number of years. Palpable masses were found on examination in more than 50% of the cases. Pitting oedema and clubbing of the fingers were frequent findings. The spleen was usually not enlarged, despite the presence of large abdominal masses.

The pathological findings in 22 cases diagnosed in Israel were reported by Rappaport *et al.* (1972). In about 25% of them a massive lymphoplasmocytic infiltration of the intestine was found and associated α heavy chain demonstrated in the serum of those tested.

Two cases with α heavy chain, not included in the former series and followed for 2 years, are discussed briefly as they illustrate the evolution of the disease.

Case 1.—A 30-year old Arab was hospitalized 2 years previously because of diarrhoea, abdominal pain and loss of 10 kg in weight. A malabsorption syndrome was diagnosed on clinical and laboratory investigation. Alpha heavy chain, αI Type, was found in the serum (Fig. 1). X-ray of the intestine showed an abnormal mucosal pattern with signs of pressure, suggestive of intestinal lymphoma. A duodenal biopsy revealed complete villous atrophy with preservation of the columnar epithelium and severe lymphoplasmocytic infiltration of the mucosa and submucosa. Protein studies in

TABLE I.—*Immunoglobulin Levels (mg/100 ml) Family I*

	Age	IgG	IgA	IgM
Father	50	2000	430	115
Mother	47	1900	240	92
Brother	27	2000	320	65
Brother	16	2000	150	73
Sister	6	2400	145	55
Children	9	1900	175	110
	8	2200	145	73
	6	2000	170	77
	5	2400	145	85
	4	1900	105	38
Normal controls (232)	<12	1420 ±356	209 ±89	68 ±27

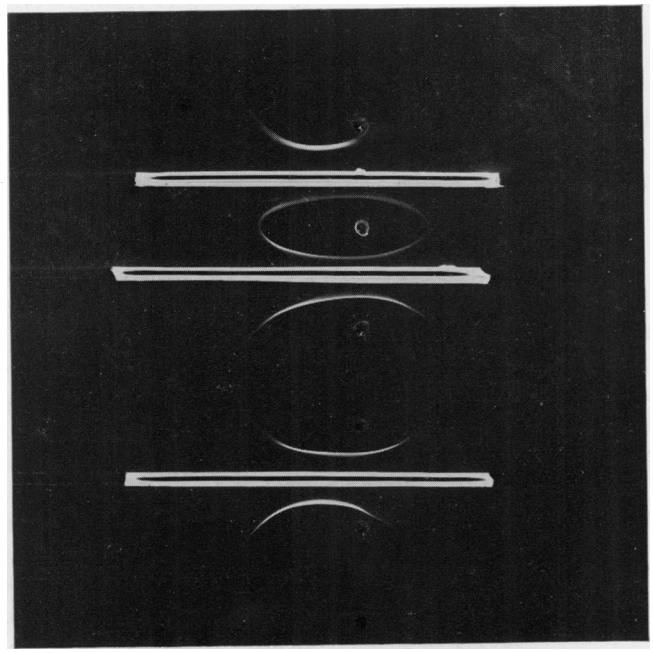

FIG. 1.—Immunoelectrophoresis of serum of patient No. 1.

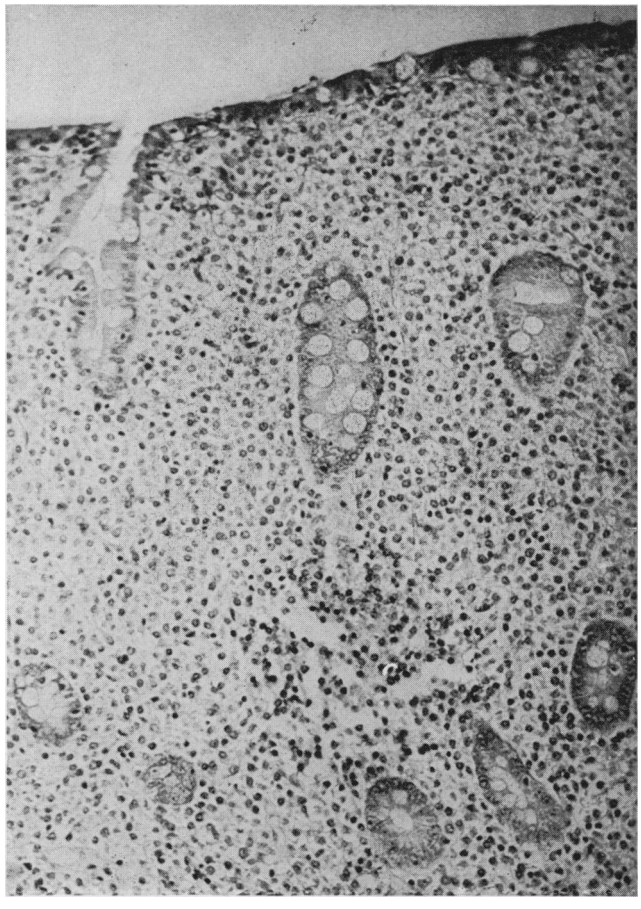

FIG. 2.—Intestinal biopsy, patient No. 2. H. & E. × 250.

3 generations of this family were non-contributory, except for an increase in IgG levels in all family members (Table I).

The patient was given tetracycline 1 g/day and later intermittent Alkeran (melphalan) and steroid therapy. This produced marked clinical improvement. However, the amount of α heavy chain which diminished at the commencement of treatment is now rising and the IgG level is diminishing. Repeat x-ray study of the gastrointestinal tract has shown no change compared with the original films. At no stage has a palpable mass been detected.

Case 2.—A 40-year old Arab male has also been under observation for the same period of time. He presented with a similar clinical picture, namely, severe malabsorption and α heavy chain disease in the serum, again of the αI Type. The initial radiographs of the intestine were less striking— only a malabsorption pattern was seen. Intestinal biopsy revealed almost complete villous atrophy with preservation of epithelium, relative sparsity of crypts and a moderate

TABLE II.—*Immunoglobulin Levels (mg/100 ml) Family II*

Children	Age	IgG	IgA	IgM
1	7	900	175	73
2	9	1400	195	37
3	10	1400	115	63
4	14	1500	290	73
5	12	1950	400	63
6	6	1200	105	77
Wife	37	1250	365	105
Normal controls (232)	<12	1430 ±356	209 ±89	68 ±27

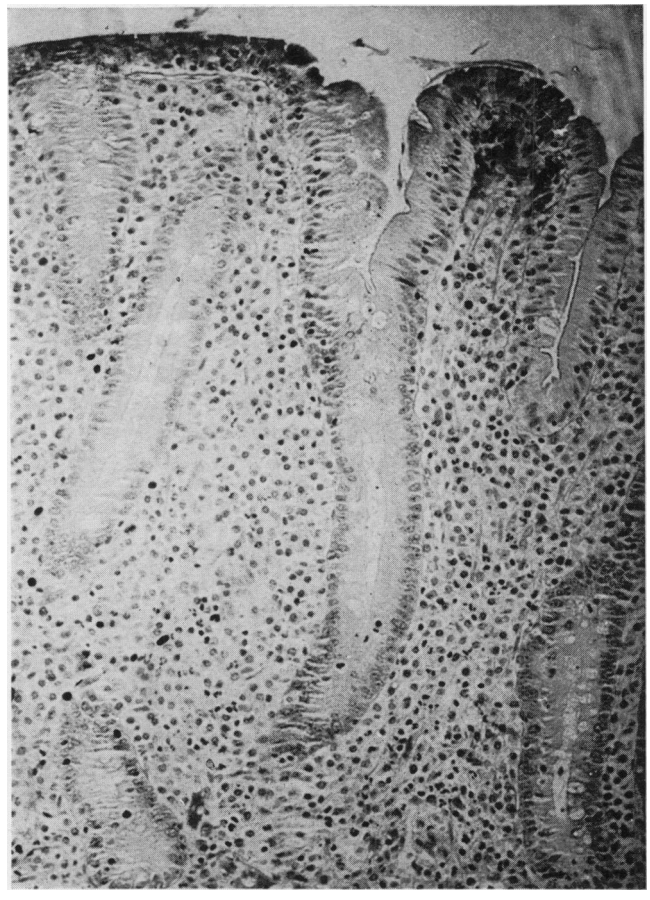

FIG. 3.—Second biopsy of patient No. 2. H. & E. × 250

heavy infiltration by uniform round cells throughout the lamina propria (Fig. 2). The diagnosis of intestinal lymphoma was made by 3 pathologists. Family studies have not revealed hypergammaglobulinaemia or dysgammaglobulinaemia (Table II). The malabsorption disappeared on tetracycline therapy and the α heavy chain diminished gradually from about 2600 mg/100 ml to about 550 mg/100 ml (Table III). X-rays of the intestine are now normal. Two intestinal biopsies on 2 occasions during this year revealed a marked improvement. The last biopsy showed only partial villous atrophy and increased plasma cell infiltration (Fig. 3, 4), which could be normal for the Arab population.

The marked improvement and possible recovery of the second patient on anti-

TABLE III.—*Immunoglobulin Levels* (*mg*/100 ml)

Date	IgG	IgA	IgM
17.10.71	730	2700	43
15.12.71	870	2225	51
14. 6.72	1450	1300	48
3. 9.72	1100	975	26
4. 4.73	1200	750	39
11. 7.73	950	550	39

biotic therapy cast doubts on the original diagnosis of a malignant condition. Complete recovery after antibiotic therapy has been reported previously (Rogé, Druet and March, 1970). Alpha heavy chain disease may therefore be regarded as an immune response of the gut to a noxious agent, or agents, followed by a clonal evolution of a functionally abnormal

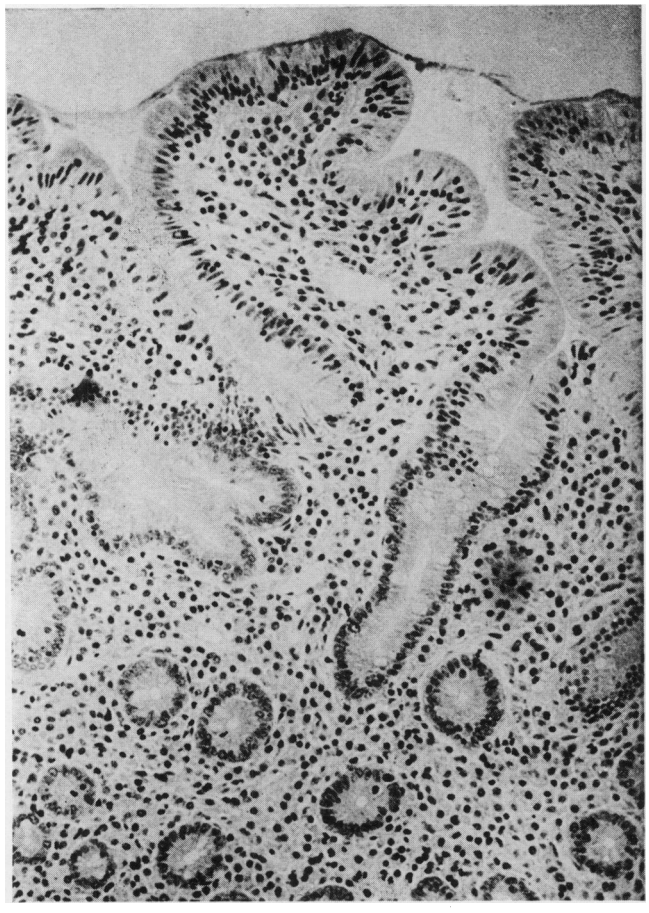

FIG. 4.—Third biopsy of patient No. 2. H. & E. × 250.

plasma cell. On the other hand, severe monotonous uniform cell infiltration with destruction of the glands is suggestive of a malignant process.

Hence the questions posed by ourselves and by others are: Do all cases of intestinal lymphoma in underprivileged populations evolve as a result of α heavy chain disease, or is intestinal lymphoma a heterogeneous group as evident from the pathological findings (Rappaport *et al.*, 1972)? Could the lymphoplasmocytic response of the gut in cases of histiocytic lymphoma be secondary to the lymphoma? In a number of proven cases of intestinal lymphoma in Israel and in patients from South Africa and Iran, no α heavy chain could be detected. (Sera were shipped to us by Dr Novis and Professor Dutz.) These observations cast doubt on the hypothesis of Rappaport *et al.* (1972) and Rambaud and Matuchansky (1973) that α heavy chain disease and Mediterranean lymphoma are always evolutionary phases of one entity. On the other hand, it would appear that some patients do indeed transform from α heavy chain disease to intestinal lymphoma (Bognel *et al.*, 1972; Ramot and Many, 1972). This needs a well planned prospective study.

Environmental and genetic factors

In Israel, primary intestinal lymphoma with or without malabsorption and childhood lymphoma affect the same

TABLE IV.—*Immunoglobulin Levels* (*mg*/100 *ml*)

		IgG			IgA		
Children	No.	Mean	S.D.	*P*	Mean	S.D.	*P*
Gaza	232	1420	356		209	89	
				<0·0005			<0·0005
Europe	220	1071	221		141	95	
				<0·10			<0·0005
Armenia	62	1112	300		183	83	

ethnic groups (Hulu, Ramot and Sheehan, 1970; Aghai *et al.*, 1973). Hence the search for environmental factors seems obvious.

Chronic gastrointestinal infections and diarrhoea occur frequently in these populations. Significantly higher IgA and IgG levels are found in Arab children and adults compared with East Europeans (unpublished data) (Table IV). Unfortunately, we have no data on the gammaglobulin levels and type distribution in North African Jews.

These observations support the assumption that the Arab population is exposed to repeated infections. In a search for predisposing factors, the immunoglobulin levels were determined in 101 relatives of 10 patients who died of this disease. In most cases only brothers and cousins were tested. The results, however, were discouraging. Extensive family studies in the cases described in this report did not reveal an α heavy chain disease in any other family member. The finding of a dysgammaglobulinaemia in family I is difficult to interpret. Further family studies are necessary.

Other immunological investigations in the 2 cases presented, namely B and T lymphocytes in the blood (determined by fluorescence and rosette formation and lymphocyte transformation induced by phytohaemagglutinin), were normal. EBV titres were repeatedly negative in both patients. No studies have been performed on macrophage function.

In the search for genetic factors in the evolution of the disease, we have previously reported the presence of the intestinal isozyme of serum alkaline phosphatase in a number of patients with intestinal lymphoma (Ramot and Streifler, 1968). Recently, 6 additional cases have been studied. In 4 of them this isozyme was again detected, regardless of their country of origin (2 were from South Africa, the other 2 Israeli Arabs). This isozyme was markedly increased in some of the patients. The control group was 100 normal adult Arabs. This observation, including family and blood group studies, needs confirmation on larger clinical material.

Lymphoreticular dysfunction as a predisposing factor

Non-neoplastic malabsorptive disorders seem in many instances to have preceded the development of primary intestinal lymphoma (Gough *et al.*, 1962; Brunt *et al.*, 1969). The former proved to be coeliac disease in the Western world. There is suggestive evidence that coeliac disease may also be accompanied by lymphoreticular dysfunction and that the latter may accompany other malabsorptive disorders of the small intestine. Robb-Smith described a disease entity characterized by progressive hyperplasia of the abdominal lymph nodes and later pointed out its association with steatorrhoea on the one hand and its pathological similarity to lymphosarcoma on the other (Robb-Smith, 1964). He suggested that the hyperplasia might be secondary to an autoimmune process in the gut which terminates in malignancy. Coeliac disease has also been found on occasion to be associated with splenic atrophy (McCarthy

et al., 1966). The latter, in turn, may bear a biological significant relationship to lymphoreticular dysfunction on the one hand and to intestinal lymphoma on the other. Small spleens have been observed in a number of patients with intestinal reticulosis. Moreover, primary small intestinal lymphoma is usually not accompanied by splenomegaly, even when the abdominal lymph nodes are extensively involved. Finally, patients with childhood lymphoma, of the Burkitt type, with abdominal presentation usually have normal spleens. All the presented evidence would emphasize the importance of studying macrophage function in the afore-mentioned disorders.

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