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Lymphoreticular dysfunction in idiopathic steatorrhoea

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EDITORIAL SYNOPSIS Lymphoreticular function has been studied by measurement of the size of the spleen, by lymph node histology, red cell survival studies, and by antibody formation. Evidence of lymphoreticular atrophy was found in four out of 25 patients with idiopathic steatorrhoea but was not found among 29 patients with coeliac disease.

The manifestations of idiopathic steatorrhoea that bring the patient to seek medical attention are usually diarrhoea or some deficiency state such as anaemia or osteomalacia. Rarer manifestations or complications of the disease include intestinal reticulosis (Gough, Read, and Naish, 1962), hypogammaglobulinaemia (Huizenga, Wollaeger, Green, and McKenzie, 1961), and splenic atrophy (Engel, 1939). All three of these latter conditions indicate injury or alteration to the lymphoreticular system, and because of this the following study was undertaken to investigate lymphoreticular function in patients with idiopathic steatorrhoea and coeliac disease.

PATIENTS AND METHODS

PATIENTS Twenty-five patients with idiopathic steatorrhoea were studied. In all of these the diagnosis was confirmed by duodenal or jejunal biopsy. Twenty-nine patients with coeliac disease were studied. Sixteen of these had the characteristic histological features of the condition. In the other 13 the diagnosis was indicated by the presence of steatorrhoea, abnormal intestinal radiology, and a favourable response to a gluten-free diet. The term 'coeliac disease' is used to describe those in whom the diagnosis was made before the age of 15 years. Many, of course were older than this when the present study was carried out. The term 'idiopathic steatorrhoea' is reserved for those who were diagnosed after this age. This arbitrary distinction is made to separate the coeliac group, all of whom presented to a paediatric department. Case histories of patients 1, 2, and 3 are given as an appendix. The 50 patients in the post-splenectomy group had their operations at least one year before they were studied. The reasons for splenectomy were trauma, either external or because the spleen was damaged during partial or total gastrectomy, idiopathic thrombocytopenic purpura, hereditary spherocytosis, lienorenal anastomosis in patients with portal hypertension, and myelosclerosis. Twenty-five in-patients with peptic ulcer served as controls.

METHODS Blood film stained by the May-Grundwald-Giesma method were examined for Howell-Jolly bodies. At least 10,000 red blood cells were examined in each instance. Depending on the results of these counts the patients with idiopathic steatorrhoea were divided into groups A, B, and C as shown in Table I. Serum vitamin B_{12} levels were measured by microbiological assay using *Lactobacillus leichmanii* (Matthews, 1962) (normal range 140-900 μg/ml.) Serum folate levels were measured by microbiological assay with *Lactobacillus casei* ATCC 7469 (Waters and Mollin, 1961) (normal range 5·9-21 mμg/ml.)

Urinary Figlu Patients were given an oral loading dose of 15 g. of histidine and urinary Figlu was detected by conventional voltage electrophoresis on cellulose acetate strips (Kohn, Mollin, and Rosenbach, 1961). This method is not strictly quantitative but a rough grading of the 'Figlu spot' was made as +, ++, +++, where the +++ spot was equivalent to a urinary Figlu concentration of more than 500 $\mu\mu$g/ml.

Lateral inguinal lymph glands were obtained under local anaesthesia from six patients with idiopathic steatorrhoea and from six patients of the same age whose inguinal area was accessible during operations for varicose veins or inguinal hernia. These excised glands were immediately fixed in Zenker's formal saline and stained by the Dominici stain (Dominici, 1902).

Red cells from the patients were sensitized with anti-D serum, titre 1/64 (Fraser *et al.*, 1965). The cells were then labelled with ^{51}Cr and 2·5 ml. of the reconstituted blood was injected intravenously. Venous blood from the opposite forearm was taken at 10 minutes and the radioactivity of subsequent samples was expressed as a percentage of this value. The labelled cells was arbitrarily considered to have disappeared when the radioactivity in the blood was 10% or less of the 10-minute sample.

Spleen size Spleen size was studied in 21 of the patients with idiopathic steatorrhoea and in 24 of the

coeliac patients by abdominal radiographs. In addition five of the patients with idiopathic steatorrhoea had abdominal radiographs carried out after induction of a pneumoperitoneum. The spleen was seen at operation in two and at necropsy in another two of the patients with idiopathic steatorrhoea. Some patients were studied by more than one of these methods.

Surface counting over the splenic area was carried out using an Ekco scintillation counter (N559C), crystal size $1\frac{3}{4} \times 1$ in., and an Ekco scaler (529) in two patients with small spleens, one patient after a splenectomy, and in two controls.

Antibody formation Serum antibodies were estimated following injections of T.A.B. antigen (Table II), for which T.A.B. vaccine (Burroughs-Wellcome) containing *S. typhi* 10^{10}, *S. paratyphi* A 5×10^9, and *S. paratyphi* B 5×10^9 per ml. was used.

RESULTS

The details of the Howell-Jolly body counts and Rh damaged red cell survival times are given in Table I.

TABLE I

HOWELL-JOLLY BODY COUNTS AND RED CELL SURVIVAL TIMES

Type of Patient	*Howell-Jolly Bodies per 10,000 Red Blood Cells ± 1 S.D.*	*Damaged Red Cell Survival Time (hr.)*
Controls	0	1[1]
No. of patients	(25)	(6)
Post-splenectomy	30 ± 45	3 and 4
No. of patients	(50)	(2)
Range	1 ... 310	
Idiopathic steatorrhoea		
Group A	0	1[1]
No. of patients	(20)	(6)
Group B	1	3
No. of patients	(2)	(patient 4)
Group C		
No. 1.	390 ± 51	48[2]
Range	210 ... 630	
No. 2.	400 ± 32	72[2]
Range	190 ... 680	
No. 3.	430 ± 48	6
Range	290 ... 710	
Coeliac disease	0	—
No. of patients	(29)	

[1]Longest survival in group.
[2]50% of ^{51}Cr Rh- damaged R.B.C.s present at this time.

HOWELL-JOLLY BODIES These were present in the red blood cells of five out of 25 patients with idiopathic steatorrhoea. In three of these patients (cases 1, 2, 3) the Howell-Jolly bodies were present in large numbers and persisted unchanged in number when treatment with folic acid, vitamin B_{12}, and iron was given. On this treatment the marrow became normoblastic and the haemoglobin rose considerably. A period of treatment ranging from one to three years has not reduced the number of Howell-Jolly bodies present. In two (cases 4, 5) small numbers of Howell-Jolly bodies were present and disappeared when the above treatment was given.

Howell-Jolly bodies were not detected in blood films from 29 patients with coeliac disease.

Blood films from 50 patients who had had a splenectomy contained numbers of Howell-Jolly bodies ranging from 0·0001% to 3·1%. In Table I patients are grouped according to these counts.

RHESUS-INJURED RED CELL SURVIVAL The survival time in the three patients with idiopathic steatorrhoea without Howell-Jolly bodies was normal, and in the four patients with idiopathic steatorrhoea and Howell-Jolly bodies it was prolonged. Patients 1, 2, and 3 had a longer survival time than the two patients who had their spleens removed.

Surface counting over the splenic area in three controls detected a 25% increase in counts per minute when the counting rate at two hours was compared with the counting rate five minutes after the injection of the ^{59}Cr tagged Rhesus-damaged red cells. Similar counting in patients 2 and 3 and in one of the patients after splenectomy showed no rise.

INGUINAL LYMPH GLANDS Histological sections of inguinal lymph glands from patients 2, 3, and 4 were examined by Professor J. M. Yoffey and compared with the sections of inguinal lymph glands from controls of identical ages. Preliminary examination indicated that compared with the controls they showed a marked reduction in the amount of lymphoid tissue present, a greater degree of fibrosis, and many more of the lymphocytes were pyknotic. Histological examination of inguinal lymph glands from three patients with idiopathic steatorrhoea from group A showed minor abnormalities. The histological appearance of all these lymph glands will be reported in greater detail elsewhere.

RESPONSE TO T.A.B. VACCINE The response to the H antigen is shown in Table II.

TABLE II

EFFECT OF T.A.B. VACCINE ON H ANTIBODY TITRE

Time after T.A.B. (mth.)	*Patient 1* 0	1	2	3	4	*Patient 2* 0	1	2	3	4
Dose of T.A.B. (ml.)	½	1				½	1		1	
Antibody titre										
S. typhi.	1/320	1/80	1/320			0[1]	1/40	1/40	1/80	
S. paratyphi A	1/40	1/80	1/40			0	0	0	0	
S. paratyphi B	1/20	1/640	1/20			0	1/20	1/40	0	
Non-specific Salmonella	1/320	1/320	1/320			0	0	1/20	0	

[1]0 = negative at titre of 1/20

The initial titre of O antibodies in patients 1 and 2 for *S. typhi*, S. para A and B was less than 1/20, and no change occurred during the period of four months.

Patient 1 had a temperature of 101°F. following each injection of vaccine. Patient 2 had a local erythematous reaction and her temperature rose to 99·6° following each injection.

SPLEEN SIZE IN PATIENTS WITH IDIOPATHIC STEATORRHOEA In 14 of the 19 in group A who had had abdominal radiographs the lower border of the spleen could be seen, and was within the limits of normality as given by Brogdon and Crow (1959). In five the spleen was not seen on these radiographs. Two of these five patients had a normal sized spleen at necropsy. In the other three patients the splenic area was obscured by gas or barium in the large bowel or stomach. A normal sized spleen was confirmed in three of the 14 by means of radiographs after a pneumoperitoneum.

Both patients in group B had normal sized spleens and in one (case 4) this was confirmed by inducing a pneumoperitoneum.

Two of the patients in group C had minute spleens at laparotomy. The surgeon (Mr. R. E. Horton) considered that they were less than one quarter of their normal size. In patient no. 3 the spleen was not visualized by abdominal radiographs after inducing a pneumoperitoneum, nor after air insufflation of the colon and stomach. It was considered to be less than a quarter of the normal size.

TABLE III

HAEMATOLOGICAL DATA IN PATIENTS WITH IDIOPATHIC STEATORRHOEA

Group	*Serum Folate (mμg./ml.)*	*Figlu*	*Serum B_{12} (μg/ml.)*	*Marrow*
A	1·6	+	600	M
	1·1	nd.	250	nd.+
	1·8	nd.	65	M
	3·1	++	122	M
	15·4	++	250	N
	7·3	+++	300	N
	nd.	++	205	M
	1	+++	130	M
	2	nd.	295	N
B	2·7	+++	95	M
	3·1	+++	340	N+
C	0·8	+++	850	M+
	0·8	++	500	M
	1·6	++	55	M

M = Megaloblastic
N = Normoblastic
nd. = Not done

SIZE OF SPLEEN IN PATIENTS WITH COELIAC DISEASE Radiographs of the abdomen were available in 24 of these patients and in 18 the spleen could be seen and was normal in size.

COMPARISON OF PATIENTS WITH AND WITHOUT IDIOPATHIC STEATORRHOEA The duration of symptoms before a diagnosis was reached was similar in both groups. The presenting symptoms were similar. The patients with splenic atrophy were all more than 34 years old but clearly atrophy was not an invariable accompaniment of increasing age, as four of the patients without atrophy were 60 years or older. Apart from patient no. 2 and the cases with intestinal reticulosis in group A, all patients in both groups responded well to treatment.

The severity of the malabsorption, as assessed by the degree of steatorrhoea, the xylose absorption, and glucose tolerance tests, was similar in both groups. There was no difference in the extent of the deficiency states present as indicated by the initial haemoglobin, serum albumin, serum α_1, α_2, β and gamma globulin, prothrombin time or electrolytes, including calcium and phosphorus. The results of marrow examination and the serum B_{12} and folate levels are shown in Table III.

Patients 1-4 had subtotal villous atrophy. Patient 5 had partial villous atrophy, the others subtotal.

DISCUSSION

Howell Jolly bodies are nuclear remnants in the red cells and are found chiefly in association with splenectomy and splenic atrophy.

The mechanism of their production and the exact role played by the spleen in their formation is poorly understood (Crosby, 1963). The role of the spleen may be to inhibit their production in the bone marrow, or to remove them rapidly from the red cells in the circulation. Either theory or combination of them explains their increased number in the blood after splenectomy and in patients with splenic atrophy. At what stage of splenic atrophy Howell-Jolly bodies appear in the blood is not clear, but Hirschfeld and Dünner (1933) record their presence in a patient whose spleen weighed 60 g. at necropsy.

The occurrence in patients 1, 2, and 3 with splenic atrophy of a greater number of Howell-Jolly bodies than in the patients following splenectomy (Table I) must represent dysfunction greater than can be accounted for by total lack of splenic function. As the spleen is part of the lymphoreticular system, atrophy of the spleen without atrophy of the other parts of the lymphoreticular system would seem illogical. Compensatory hypertrophy of the lymphoreticular system after splenectomy may explain

the lymph node enlargement after this operation recorded by Torriola (1959) and the gradual fall in the number of Howell-Jolly bodies that usually occurs as the time interval after splenectomy increases.

A further indication of lymphoreticular malfunction greater than can be explained by splenectomy alone was afforded by the red cell survival studies. The rate of removal of the damaged cells from patients 1, 2, and 3 was considerably slower than can be explained by absence of splenic function as seen from the results in the patients after splenectomy. Histological confirmation of an abnormality of the lymphoreticular system outside the spleen is shown by the presence of abnormal lymph glands (patients 2, 3, 4).

Impaired function of the antibody-forming part of the lymphoreticular system is suggested by the minimal alteration in H antibodies following T.A.B., but no firm conclusion can be drawn from this study in view of the limited number of observations and lack of controls. A further study to evaluate immunogenic activity in idiopathic steatorrhoea is in progress. According to Topley and Wilson (1964), 5% of people immunized with T.A.B. might have titres similar to those in patients 1 and 2.

It is probable that the study of Rhesus-damaged red cell survival is the most sensitive method for the detection of lymphoreticular atrophy. In patient 4 Howell-Jolly bodies were not present after the megaloblastic anaemia was treated, and the size of the spleen was normal, yet the survival time was abnormally prolonged. Inguinal lymph node biopsy was abnormal in this patient also but this method of investigation could not be readily applied to all patients. Although there was no difference in the number of Howell-Jolly bodies present in the three patients with the very small spleen, it is interesting that the red cell survival time paralleled the severity of the manifestations of idiopathic steatorrhoea. Thus, it was slowest in patient 2 who never responded well to treatment and remained oedematous and a chronic invalid until she died, and most rapid in patient 3 who is now a fit, fully employed man. The study of patient 4 suggests that lymphoreticular atrophy may occur before there is a detectable reduction in the spleen size.

Table IV summarizes the 28 cases of splenic atrophy associated with a reasonably certain diagnosis of idiopathic steatorrhoea that we have been able to find in the literature. We suspect that splenic atrophy is not as rare as the figures suggest. Engel in 1939 found that 12 of 27 cases of idiopathic steatorrhoea that came to necropsy had spleens

TABLE IV

SPLENIC ATROPHY IN PATIENTS WITH IDIOPATHIC STEATORRHOEA

Author	*Sex and Age*	*Weight of Spleen (g.)*	*Weight of Liver (g.)*	*Type of Anaemia*
Blumgart (1923)	M 42	70	1,050	Dimorphic
Blumgart (1923)	F 44	30	560	—
Blumgart (1923)	M 30	80	Normal	—
Engel (1939)	F 42	12	—	Hyperchromic
Nordenson (1936)	58	60	—	—
Boverie (1942)	F 68	—	—	Megaloblastic
Waldenström (1947)	F 50	Marked atrophy	—	Megaloblastic
Waldenström (9147)	F 41	(Not seen on radiograph)	—	Hyperchromic
Strandell (1947)	F	60	—	Hyperchromic
Johansson (1947)	—	—	—	Megaloblastic
Niewig and Arends (1953)	M 58	10	—	Megaloblastic
Niewig and Arends (1953)	F 47	14	—	Macrocytic
Niewig and Arends (1953)	F 57	15	—	Macrocytic
Hirschfeld and Dünner (1933)	M 63	60	Atrophy	—
Hirschfeld and Dünner (1933)	F 45	8·6	Atrophy	—
Dameshek (1955)	—	Atrophy	—	—
Blegden (1936)	M 36	22	1,360	Hyperchromic
Bennett, Hunter and Vaughan (1932)	M 56	Atrophy	Atrophy	—
Rosenthal (1937)	F 38	60	Enlarged	—
Rosenthal (1937)	M 41	80	Enlarged	—
Lucksch and Sachs (1937)	F 24	40	1,400	Hyperchromic
Salvesen (1948)	M 53	Unusually small	—	Megaloblastic
Crodier, Morenas, and Croizat (1936)	F 29	de petit volume	1,500	—
Starr and Gardner (1930)	M	Atrophy	—	—
Ferreira (1938)	F 29	66	897	—
Schilling (1924)	F 32	40	—	—
Crome and Mollison (1964)	—	—	—	—
Hansen (1936)	F 52	5·5 × 4 × 2	—	—
Present series I	M 47	¼ of normal	Normal	Megaloblastic
Present series II	F 51	¼ of normal	Normal	Megaloblastic
Present series III	M 48	¼ of normal	Normal	Megaloblastic

weighing not more than 80 g. Three instances occurred in our series of 25. The pathological features of the atrophied spleen are fibrosis and a marked reduction in pulp tissue (Blumgart, 1923; Engel, 1939; Blegden, 1936; Lucksch and Sachs, 1937). Information on lymphoid tissue is available only for mesenteric lymph nodes. In cases of idiopathic steatorrhoea these were often enlarged, and non-specific histological features such as sinus catarrh and oedema were present (Blumgart, 1923; Lucksch and Sachs, 1937; Rosenthal 1937). Information on the peripheral lymph nodes is not available and nowhere is it suggested that the lymphoreticular system outside the spleen is affected. The finding in some of the reported cases with splenic atrophy of greater numbers of Howell-Jolly bodies than occur after splenectomy (Boveri, 1942; Waldenström, 1947), and Crome and Mollison's (1964) finding in one patient with idiopathic steatorrhoea and atrophy of a heat-damaged red cell survival time greater than that occurring in patients after splenectomy suggests that lymphoreticular atrophy was present in some of the reported patients, although not commented on.

Splenic atrophy appears to be unusual under the age of 30 years, and two reports only are available in which the presence of small spleens at necropsy on children with coeliac disease was noted (Meyer, 1932; Macrea and Morris, 1931).

Other small intestinal diseases associated with splenic atrophy are tropical sprue (Engel, 1939), lymphoma with obstruction of lactials (Crosby 1963), Whipple's disease (Niewig and Arends, 1953), and ileitis (Ramsay, 1850). Hyperthyroidism (Schur, 1908), hypopituitarism (Sheehan and and Summers, 1949), and alcoholism (Paulesco, 1898) have also been incriminated. Sickle cell anaemia is commonly associated with atrophy consequent on multiple infarction (Harris, Brewster, Ham, and Castle, 1956) and a similar mechanism is postulated to cause the atrophy of haemorrhagic thrombocythaemia (Crosby, 1963). Old age may be associated with arteriosclerotic atrophy although this is not usually associated with haematological abnormalities. There is little doubt that the spleen becomes lighter with increasing years. From the figures of d'Hellman, quoted and agreed to by Houcke, Merlen, and Houcke, (1962), the average spleen weight at 31 years is 146 g. but decreases to 116 g. by the age of 61.

CAUSE OF LYMPHORETICULAR ATROPHY IN IDIOPATHIC STEATORRHOEA Possible causes are folic acid deficiency; deficiency of other vitamins; malnutrition; lymphoreticular damage by the same mechanism that injures the intestinal mucosa; lymphocyte loss through the intestinal mucosa leading to exhaustion of the lymphoreticular tissue; overactivity of the immunological mechanisms leading to exhaustion atrophy of the lymphoreticular system; and injury by a toxic substance absorbed through the damaged mucosa.

Folic acid deficiency is suggested as the cause of the splenic atrophy associated with idiopathic steatorrhoea (Niewig and Arends, 1953). This view is based on the occurrence of a megaloblastic anaemia responsive to foilc acid therapy in many of the patients with atrophy, and the experimental observation that folic acid deficiency produces splenic atrophy in animals (Asenjo, 1948). The mechanism of the folic-acid-induced splenic atrophy is probably a slowing of the turnover rate of nucleo-protein synthesis, the splenic rate of which is exceeded only by bone marrow and intestine, and multiple splenic infarction which occurs in 70% of the animals (Asenjo, 1948).

The haematological response of megaloblastic anaemia to large doses of folic acid does not prove the presence of folic acid deficiency (Spies, Vilter, Koch and Caldwell, 1945; Moore, Bierbaum, Welch, and Wright 1945), although there is not much doubt that such deficiency was present in the reported cases. In our cases of lymphoreticular atrophy folic acid deficiency was present (Table III) as evidenced by low levels of serum folate, high Figlu excretion, and megaloblastic erythropoiesis. If folic acid deficiency is the cause of the lymphoreticular atrophy, the lowest values might be expected in those cases with lymphoreticular atrophy. When Table III is examined it is clear that the two lowest values in the group of our patients with idiopathic steatorrhoea occurred in those patients with atrophy. Of the patients with atrophy these very low values occurred in patients 1 and 2 who had the slowest red cell removal times.

In addition to the degree of folic acid its duration might be expected to bear on the development of splenic atrophy. Severe megaloblastic anaemia due to folic acid deficiency is rare in the coeliac child although folic acid deficiency may be demonstrable by special tests (Dormandy, Waters, and Mollin, 1963). In the adult patient (who may for all we know have had an abnormal mucosa since the first exposure to gluten in infancy) severe folic acid deficiency is common. This might explain the very rare description of splenic atrophy in the child suffering from coeliac disease (Meyer, 1932; Macrae and Morris, 1931) who has a short-lived mild degree of folic acid deficiency compared with the more common occurrence of atrophy in the adult with a severer degree of folic acid deficiency, possibly of long duration. In tropical sprue also, where the folic

acid deficiency may be of shorter duration, the incidence of atrophy is less (Engel, 1939).

Experimental atrophy in animals appears to be cured by folic acid supplements (Asenjo, 1948). There is no evidence of this occurring in patients with idiopathic steatorrhoea. Our patients have now been treated with folic acid for periods of one to three years without a reduction in the number of Howell-Jolly bodies which might be expected if regeneration occurred. There is no information on the effect of a gluten-free diet on splenic atrophy in idiopathic steatorrhoea.

There is little evidence to support the other causes of atrophy listed above. Vitamin B_{12} deficiency occurs in idiopathic steatorrhoea (Glass, 1963). Extreme degrees of splenic atrophy were not observed in the patients who died in the concentration camps of World War II (de Jongh, 1948). Lymphoreticular atrophy has been produced in animals by thoracic duct drainage (McGregor and Gowans, 1963) and exudation of lymphocytes through a damaged mucosa might have a similar effect. However, lymphocytes were not present in samples of intestinal juice in two of our patients with idiopathic steatorrhoea. The increased levels of circulating gluten antibodies in patients with idiopathic steatorrhoea (Taylor Truelove, Thomson, and Wright 1961) may indicate overactivity of the antibody-forming mechanism. It is possible that prolonged overactivity might produce eventual atrophy of the lymphoreticular system. Undue passage of peptides into the blood from the gastrointestinal tract in idiopathic steatorrhoea has been shown to occur (Weijers and Van de Kamer, 1960; Alvey, Anderson, and Freeman, 1957; Frazer, 1960), and such passage of other substances might damage the lymphoreticular system.

Is atrophy of the lymphoreticular system of clinical significance in patients with idiopathic steatorrhoea? Until more patients with this condition are examined the answer to this question must be speculative. Defective phagocytic and antibody-forming mechanisms might predispose to infection and it may be relevant that patient 2 developed multiple lung abscesses without pyrexia or leucocytosis. Terminal infections are common in the recorded cases of splenic atrophy and Van Hees (1937) comments on the high incidence of tuberculosis in these patients.

Of greater theoretical interest in the part immunological insufficiency due to atrophy of the lymphoreticular system may play in the development of intestinal reticulosis in patients with idiopathic steatorrhoea. The association of intestinal reticulosis with idiopathic steatorrhoea was first noticed by Gough *et al.* (1962), and since then Austad *et al.* (1966) have collected 24 patients with steatorrhoea and reticulosis. Spleen size was known in 23 of these, and in four the spleen weighed less than 30 g. and in two further patients it was smaller than normal. One of the patients we report had Hodgkin's disease of the intestine (Austad *et al.* 1966). Whether the incidence of intestinal reticulosis is greater in those patients with splenic atrophy remains to be seen but a possible role of atrophy of the lymphoreticular system in the development of reticulosis is suggested by Burnet's (1964) theory for the high incidence of malignancy in infancy and old age. He suggests that it may be related to immunological insufficiency in these age groups. Similar insufficiency in idiopathic steatorrhoea might be at least partly responsible for the development of intestinal reticulosis in idiopathic steatorrhoea.

SUMMARY

Evidence of lymphoreticular atrophy was present in four of 25 patients with idiopathic steatorrhoea but was not found in 29 patients with coeliac disease. Three of these patients had extremely small spleens; the spleen of the fourth patient was normal in size. The clinical and biochemical features of the patients with and without atrophy of the lymphoreticular system did not differ. The possible aetiology and significance of this finding are discussed.

APPENDIX

CASE 1 A 34-year-old man was first seen in 1950. He had a three months' history of diarrhoea suggestive of steatorrhoea, malaise and tiredness, with some ankle swelling. Examination showed a pale, thin man with some ankle oedema and a blood pressure of 105/60 mm. Hg. His haemoglobin was 9·3 g. (63%); R.B.C.s 2·5/c.mm., C.I. 1·3, W.B.C.s 4,500/c.mm. The film showed marked macrocytosis and some iron-deficient cells were present. The daily fat excretion over a three-day period was 18 g. on a diet containing 50 g. fat each day. Barium follow-through examination showed changes consistent with steatorrhoea. Free acid was present in the gastric juice. No parasites or ova were present in the stools.

On liver injections, a low-fat diet, and oral iron he rapidly improved and his haemoglobin returned to normal. His progress was followed in the Out-patient Department, and in October 1952 his haemoglobin was 104%. Howell-Jolly bodies were still present in the blood. His weight had increased from 58 kg. to 70 kg. He continued to have weekly liver injections until April 1953 when monthly vitamin B_{12} injections and oral folic acid were substituted. His haemoglobin was 106% at this time. He stopped taking folic acid in 1957 but the vitamin B_{12} injections were continued until January 1963. In November 1963 diarrhoea returned and was accompanied by severe colicky lower abdominal pain. When he was examined six weeks later his weight had fallen to 62 kg. He looked ill and pale and his temper-

ature was 103°F. Slight papillary atrophy of the tip of the tongue was present. His blood pressure was 110/80 mm. Hg. No abnormality of the heart, respiratory system, or central nervous system was detected. In the left lower quadrant of the abdomen a tangerine-sized mass was present and appeared to be attached to the anterior abdominal wall. Rectal examination was normal. His fever declined over a period of days but recurred to give a Pel-Ebstein pattern.

Investigations The urine was normal. Stools contained no occult blood. Haemoglobin was 73%; W.B.C.s 10,400 c.mm. (7,200 polymorphs), platelets 545,000/c.mm. The film showed macrocytosis and anisocytosis. Normoblasts 300/c.mm, E.S.R. 65 mm./hr.; 4·7% of the red cells contained Howell-Jolly bodies. The marrow showed mild megaloblastic change, most marked in the white cell series. The serum vitamin B_{12} level was 850 $\mu\mu$ g./ml.; folate level 0·8 mg./ml.; Figlu excretion + + +. The serum bilirubin was 0·3 mg. %, alkaline phosphatase 10 K.A. units, serum albumin 2·05, α_1 globulin 0·45, α_2 0·85, β 1·1, γ 1·8. Prothrombin index was 100%. A barium follow-through showed the features of steatorrhoea. A barium enema was normal. A jejunal biopsy showed a flat mosaic pattern when examined with the dissecting microscope and histologically subtotal atrophy.

The history of steatorrhoea and megaloblastic anaemia suggested very strongly the diagnosis of idiopathic steatorrhoea, and the development of pain and weight loss, associated with a Pel-Ebstein fever and abdominal mass, suggested that an intestinal reticulosis had developed.

At laparotomy (Mr. R. E. Horton) a mass, originating in the jejunum 36 in. from the duodeno-jejunal flexure, was found adherent to the anterior abdominal wall and colon. This was dissected from the anterior abdominal wall but a partial resection of the colon was necessary before the mass and affected part of the jejunum could be removed. Many mesenteric glands were enlarged. The spleen was very small, approximately a quarter or less of normal. Histology of the lesion showed it to be characteristic of Hodgkin's disease without involvement of the mesenteric glands.

A deep venous thrombosis of the left leg developed post-operatively and bilateral pulmonary infarcts occurred. Anticoagulants were given and he recovered satisfactorily. Great difficulty was experienced pre-operatively in cross-matching this patient's blood because of the presence of a cold agglutinin, and an irregular agglutinin which was probably anti-I.

Six months post-operatively his weight had risen to 68 kg. and his haemoglobin was 83% although he had not been taking his folic acid regularly.

CASE 2 A 51-year-old woman presented with one year's history of diarrhoea and vomiting, a widespread rash, and swelling of the ankles. For five weeks pain in her right thigh had prevented her from walking. Her weight had fallen 7 kg. during the year. She had had rheumatic fever at the age of 16. Her family history was not relevant.

She was small, emaciated, and pigmented. A moist eczematous rash was present at the limb flexures and covered most of her body. Movements of the right thigh were painful. The arms and legs were markedly oedematous. Her blood pressure was 110/70 mm.Hg. Basal rales were present. No abnormality was detected in the heart or central nervous system.

Investigations Her haemoglobin was 74%, W.B.C.s 4,600/c.mm. (polymorphs 2,300/c.mm.). The blood film showed marked macrocytosis of the red cells, a right nuclear shift of the polymorphs, and many Howell-Jolly bodies. The bone marrow showed megaloblastic haemopoiesis. The serum vitamin B_{12} was 500 $\mu\mu$ g./ml., serum folate level 0·8 mμg./ml., and Figlu excretion + + +. Thirty-eight grams of fat were excreted daily over a five-day period on a diet containing 100 g. of fat each day. Of 25 g. of D xylose, 3·4 g. was excreted in the urine in five hours. Total serum proteins were 3·2 g.% (albumin 1·4 g., α_1 globulin 0·2 g., α_2 globulin 0·4 g., β globulin 0·4 g., γ globulin 0·8 g.). Plasma sodium was 139 mEq/l., plasma potassium 2·5 mEq/l., plasma chloride 109 mEq/l., plasma calcium 5·7 mg/100 ml., plasma inorganic phosphate 2 mg./100 ml. The plasma urea was 11 mg./100 ml. The serum alkaline phosphatase was 26 K.A. units/100 ml.

General thinning of the bones was present and a marked double scoliosis of the spine. A pseudo-fracture of the shaft of the right femur was present just below the lesser trochanter. Marked flocculation of barium occurred in the small intestine.

Histological examination of a right iliac crest biopsy showed thickened osteoid seams indicative of osteomalacia. After several unsuccessful attempts to obtain a peroral jejunal biopsy and because the diagnosis was still uncertain, laparotomy was performed by Mr. R. E. Horton. The spleen was very small, being about the size of a horsechestnut. Biopsies from jejunum and ileum both showed subtotal villous atrophy.

The patient was put on a low-fat, high-protein diet, given folic acid, vitamin B_{12} and iron, potassium supplements, and Calciferol. The diarrhoea disappeared and the pain in her thigh improved and she was discharged from hospital.

Seventeen months later she was readmitted because of increasing oedema and general malaise. While in hospital she developed multiple lung abscesses and *Pseudomonas pyocyaneus* was cultured from her sputum. She was seriously ill for six weeks but improved when intravenous colomycin, prednisone, and a gluten-free diet were given. On discharge from hospital she was ambulant and almost free of oedema. She died at home several months later following an attack of bronchitis. A necropsy was not performed.

CASE 3 This 48-year-old man noticed a change in his bowel action following tetracycline given for bronchitis. His stools assumed the characteristics of steatorrhoea and over eight weeks he lost 28 lb. in weight. There was no childhood history of diarrhoea. Eighteen years previously he was put on a bland diet for two years because of a peptic ulcer. There was no family history of significance.

On physical examination he was a thin, middle-aged man weighing 51 kg. He was slighly pale but his tongue was well papillated. Slight finger clubbing was noted. His blood pressure was 110/75. Other systems were normal.

Investigations The haemoglobin was 80% and the P.C.V. 35%. The total white cell count was 7,600/c.mm., (polymorphs 4,500/c.mm., eosinophils 200, lymphocytes 2,900/c.mm.). A blood film showed macrocytosis and polychromasis. Scanty normoblasts were present and 500 of 10,000 red blood cells contained Howell-Jolly bodies. The platelets numbered 148,000/c.mm. The white cells showed a right nuclear shift. Bone marrow examination showed megaloblastic erythropoiesis. Serum folate level was 1·6 mμg./ml; serum vitamin B_{12} 55 μμg./ml.; Figlu ++; serum iron 234 μ g./100 ml. Free acid was present in the gastric juice. Of a 25 g. oral load of D-xylose 1·5 g. was excreted in the urine in five hours. The daily faecal fat excretion was 37 g. over a five-day period while he was on a diet containing 100 g. of fat. There was no rise in the blood glucose level following 50 g. of glucose orally.

Barium examination of the small intestine was consistent with steatorrhoea. Jejunal biopsy showed subtotal villous atrophy.

The plasma electrolytes, calcium, inorganic phosphate, bilirubin, and alkaline phosphatase levels were normal. The serum protein levels were albumin 2·65 g., α_1 globulin 0·35, α_2 globulin 0·5, β globulin 1·05, γ globulin 1·35.

Radiographs of the abdomen after induction of a pneumoperitoneum and tomography of the splenic area following air insufflation of colon and stomach showed no splenic shadow.

When the patient was put on a high-protein, low-fat diet and folic acid, the diarrhoea stopped, his haemoglobin rose to 100% and he gained 10 kg. in weight.

The number of Howell-Jolly bodies in the peripheral blood streams remains unaltered.

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REFERENCES

Alvey, C., Anderson, C. M., and Freeman, M. (1957). Wheat gluten and coeliac disease. *Arch. Dis. Childh.*, **32**, 434-437.

Asenjo, C. F. (1948). Pteroylglutamic acid requirement of the rat and a characteristic lesion observed in the spleen of the deficient animal. *J. Nutr.*, **36**, 601-612.

Austad, W. I., Cornes, J. S., Gough, K. R., McCarthy, C. F., and Read, A. E. (1966). Steatorrhoea and malignant lymphoma. (In preparation).

Bennett T. I., Hunter D., and Vaughan, J. M. (1932). Idiopathic steatorrhoea (Gee's disease). *Quart. J. Med.*, **25**, 603-677.

Blegden, E. (1936). To tilfelle av stenosis isthimi aortae. *Norsk Mag. Laegevidensk.*, **97**, 927-938.

Blumgart, H. L. (1923). Three fatal adult cases of malabsorption of fat. *Arch. intern. Med.*, **32**, 113-128.

Boveri, R. M. (1942). Howell Jolly bodies and splenic atrophy. *Guy's Hosp. Rep.*, **91**, 81-90.

Brogdon, B. G., and Crow, N. E. (1959). Observations on the 'normal' spleen. *Radiology*, **72**, 412-414.

Burnet, M (1964). Immunological factors in the process of carcinogenesis. *Brit. med. Bull.*, **20**, 154-158.

Cordier, V., Morenas, and Croizat, P. (1936). Etude anatomo—pathologique d'un cas de sprue. *Arch. Mal. Appar. dig.*, **26**, 361-368.

Crome, P., and Mollison, P. L. (1964). Splenic destruction of Rh-sensitized, and of heated red cells. *Brit. J. Haemat.*, **10**, 137-154.

Crosby, W. H. (1963). Hyposplenism: an inquiry into normal functions of the spleen. *Ann. Rev. Med.*, **14**, 349-370.

Dameshek, W. (1955). Hyposplenism. *J. Amer. med. Ass.*, **157**, 613.

Dominici, H. (1902). Polynucléaris macrophages. *Arch. Méd. exp.*, **14**, 1-72.

Dormandy, K. M., Waters, A. H., and Mollin, D. L. (1963). Folic-acid deficiency in coeliac disease. *Lancet*, **1**, 632-635.

Engel, A. (1939). Om sprue och mjälatrofi. *Nord. Med.*, **1**, 388-392.

Ferreira, M. (1938). Consideracoes sobre o chemado 'sprue nao tropical' a proposito duma observacao pessoal. *Lisboa méd.*, **3**, 91.

Fraser, I. D., McCarthy, C. F., and Read, A. E. (1966). Howell Jolly bodies in idiopathic steatorrhoea. *J. clin. Path.* (In press).

Frazer, A. C. (1960). Pathogenetic concepts of the malabsorption syndrome. *Gastroenterology*, **98**, 389-398.

Glass, C. B. J. (1963). Gastric intrinsic factor and its function in the metabolism of vitamin B_{12}. *Physiol. Rev.*, **43**, 529-849.

Gough, K. R., Read, A. E., and Naish, J. M. (1962). Intestinal reticulosis as a complication of idiopathic steatorrhoea. *Gut*, **3**, 223-239.

Hansen, K. (1936). Die einheimische Sprue. *Zbl. inn. Med.*, **57**, 425-431.

Harris, J. W., Brewster, H. H., Ham. T. H., and Castle, W. B. (1956). Studies on the destruction of red blood cells. The biophysics and biology of sickle-cell disease. *Arch. intern. Med.*, **97**, 145-168.

Hees C. A. van (1937). Thesis 'de steatorrhoea', p. 154. Leyden.

Hirschfeld, H., and Dünner L. (1933). Zur diagnose und Pathogenese de Milzatrophic. *Z. klin. Med.*, **125**, 536-546.

Houcke, E., Merlen, J. F., and Houcke, M. (1962). Les atrophies de la rate. *Lille méd.*, **7**, 85-92.

Huizenga, K. A., Wollaeger, E. E., Green, P. A., and McKenzie, B. F. (1962). Serum globulin deficiencies in non-tropical sprue, with a report of two cases of acquired agammaglobulinemia. *Amer J. Med.*, **31**, 572-580.

Johansson, G. A. (1947). Quoted by Waldenström.

de Jongh, C. L. (1948). *Malnutrition and Starvation in the Western Netherlands* 90. General State Printing Office, The Hague.

Kohn, J., Mollin, D. L., and Rosenbach, L. M. (1961). Conventional voltage electrophoresis for formiminoglutamic-acid determination in folic acid deficiency. *J. clin. Path.*, **14**, 345-350.

Lucksch, F., and Sachs, H. W. (1937). Sektionsbefund bei einem fraglichen Fall von einheimischer Sprue. *Virchows Arch path. Anat.*, **299**, 786-792.

Macrae, O., and Morris, N. (1931). Metabolism studies in coeliac disease. *Arch. Dis. Childh.*, **6**, 75-96.

Matthews, D. M. (1962). Observations on the estimation of serum vitamin B_{12} using Lactobacillus leichmannii. *Clin. Sci.*, **22**, 101-111.

McGregor, D. D., and Gowans, J. L. (1963). The antibody response of rats depleted of lymphocytes by chronic drainage from the thoracic duct. *J. exp. Med.*, **117**, 303-320.

Meyer, A. (1932). lüber Coeliakie. *Z. klin. Med.*, **119**, 667-686.

Moore, C. V., Bierbaum, O. S., Welch A. D., and Wright, L. D. (1945). The activity of synthetic lactobacillus casei factor (folic acid) as an anti-pernicious anemia substance. 1. Observation on four patients: two with Addisonian pernicious anemia, one with nontropical sprue and one with pernicious anemia of pregnancy. *J. Lab. clin. Med.*, **30**, 1056-1069.

Niewig, H. O., and Arends A. (1953). Erythroblastic anemia: a manifestation of folic acid deficiency. *Blood*, **8**, 175-181.

Nordenson, N. G. (1936). Om mjältatrofi. *Nord. Med.*, **4**, 3342-3344.

Paulesco (1898). Sur un cas d'arrit dans le developement de la rate. *J. Méd. intern.*, **2**, 114.

Ramsay, H. A. (1850). Gastroenteritis of 12 months duration exhibiting in autopsy an entire absence of the spleen and calcurous depositions in both lungs. *Charleston Med. J. and Rev.*, **5**, 728-732.

Rosenthal, H. (1937). Darmbefunde bei der einheimischen Spru. *Virchows Arch. path. Anat.*, **298**, 706-727.

Salvesen, H. A. (1948). Symptomatic sprue. *Gastroenterologia (Basel)*, **73**, 166-172.

Schilling, V. (1924). Über die diagnose einer Milzatrophie durch den befund von Kernkugeln als Teilerscheinung pluriglandulärer Insuffizienz. *Klin. Wschr.*, **3**, 1940-1962.

Schur, H. (1908). Ueber eigenartige basophile Einschlüsse in den roten Blulkörperchen bei einem Falle von abgelaufenem Morbus Basedowii mit nachfolgender schwerer makrocytische Anämie. *Wien. med. Wschr.*, **58**, 441-512, 514-445.

Sheehan, H. L., and Summers V. K. (1949). The syndrome of hypopituitarism. *Quart. J. Med.*, **18**, 319-378.

Spies, T. D., Vilter, C. F., Koch, M. B., and Caldwell, M. H. (1945). Observations of the anti-anemic properties of synthetic folic acid. *Sth. Med. J.* (*Bgham., Ala.*), **38**, 707-709.

Starr, P., and Gardner L. (1930). Biochemical study of two patients with condition simulating sprue. *Amer J. trop. Med.*, **10**, 283-293.

Strandell (1947). Quoted by Waldenström.

Taylor, K. B., Truelove, S. C., Thomson, D. L. and Wright, R. (1961) An immunological study of coeliac disease and idiopathic steatorrhoea: serological reactions to gluten and milk proteins. *Brit. med. J.*, **2**, 1727-1731.

Topley, W. W. C., and Wilson, G. S. (1964). *Principles of Bacteriology and Immunity*, 5th ed., p. 1847. Edward Arnold, London.

Torriola, M. (1959). *La Melza Abruzzini*. Rome.

Waldenström, J. (1947). Successful treatment of liver-refractory anemia with synthetic lactobacillus casei factor. *Blood*, **2**, 426-439.

Waters, A. H., and Mollin, D. L. (1961). Studies on the folic acid activity of human serum. *J. clin. Path.*, **14**, 335-344.

Weijers H. A., and van de Kamer, J. H. (1960). Celiac disease and wheat sensitivity. *Pediatrics*, **25**, 127-134.