collagen fibrils are destroyed at an early stage, leaving behind a material rich in polysaccharide which may be in the nature of a glycoprotein.

These two lesions should be thought of as typical tissue responses resulting from some interference with the normal mechanisms of connective-tissue maintenance, but these mechanisms may, of course, be interfered with in many ways, so that many different causative factors are likely to be involved in the production of these lesions.

(Figs. 1a, 1b, and 2a appeared in *Nature*, 1951, 168, 493, and are reproduced by permission.)

[The second Lecture, with a list of references, will be published in our next issue.]

MEGALOBlastic ANAEMIA IN YOUNG ADULTS

AETIOLOGICAL IMPORTANCE OF OCCULT IDIOPATHIC STEATORRHOEA

BY

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The addition of folic acid and vitamin B₁₂ to the list of preparations available for the treatment of megaloblastic anaemia has placed a new importance on the accurate differentiation of the megaloblastic anaemia of idiopathic steatorrhoea from Addisonian pernicious anaemia. Fortunately, this is not likely to be difficult when the features are classical, and, in particular, the presence of free HCl in the gastric juice will be decisive in excluding Addisonian pernicious anaemia. It is now well recognized, however, that anaemia and other deficiencies may develop as a result of steatorrhoea in the absence of a history of intestinal symptoms. For this reason the diagnosis may easily be missed unless specifically thought of and looked for (Tuck and Whittaker, 1950).

Addisonian pernicious anaemia is rare under the age of 30; only 2.8% of the 1,600 patients collected by Wilkinson (1949) were in this age group. The occurrence of megaloblastic anaemia, unassociated with pregnancy, before the age of 30 is therefore an indication for very careful assessment before the diagnosis of Addisonian pernicious anaemia is made.

The present investigation serves to stress the difficulty that may exist in distinguishing the megaloblastic anaemia of idiopathic steatorrhoea from Addisonian pernicious anaemia. The initial observation was that a patient in whom Addisonian pernicious anaemia had been diagnosed ten years before, at the age of 26, had a macrocytic anaemia refractory to parenteral liver. The early age of onset of the anaemia and its ultimate complete refractoriness suggested an error in diagnosis, and investigation revealed that the patient was suffering from idiopathic steatorrhoea, although bowel symptoms had never been troublesome. It was decided, therefore, to re-examine, if possible, all cases of Addisonian pernicious anaemia diagnosed before the age of 30 in one medical unit during the 13-year period 1937-49. There were eight such cases out of a total of 131 with that diagnosis. Four were regular attenders at a haematological clinic; one had died in another hospital with severe refractory macrocytic anaemia two years after discharge; the remaining three were easily traced. The

seven surviving patients were thoroughly reinvestigated during 1950 irrespective of their condition at that time.

Investigation

The patients investigated fall into two distinct groups: those proved to be suffering from idiopathic steatorrhoea and those in whom the diagnosis of Addisonian pernicious anaemia was confirmed; for ease of description, the former will henceforward be considered as Group A and the latter as Group B.

The investigation of each patient included a complete clinical and haematological examination, fractional gastric analysis, oral glucose-tolerance test using 50 g. of glucose, estimation of the prothrombin index and the serum calcium, phosphorus, and alkaline phosphatase, and radiological examination of the small intestine.

In addition, with a diet containing 70 g. of fat a day, the stools were collected over four-day periods, which were marked off from one another; each period was ended by a bowel wash-out. Three collection periods were used in two patients and two in the remaining five. The stools obtained during each period were dried in bulk and the fat content was estimated by the Soxhlet extraction method.

On completion of the investigation all anaemic patients were treated intensively for a few weeks with a potent intra-muscular liver extract; blood examinations were then repeated.

Idiopathic Steatorrhoea Misdiagnosed as Addisonian Pernicious Anaemia.—As a result of the investigation the diagnosis of Addisonian anaemia was confirmed in three patients, but four were proved to be suffering from idiopathic steatorrhoea. The latter patients are described below and the points of difference from Addisonian pernicious anaemia are discussed. It will be shown that the distinction is not merely of academic interest, for in three cases the change of diagnosis was followed by a more effective therapeutic regime.

Case 1

A woman now aged 36 was diagnosed in June, 1940, as suffering from Addisonian pernicious anaemia on the evidence of a megaloblastic anaemia combined with histamine-fast achlorhydria. There were no bowel symptoms. Parenteral liver therapy produced a very poor reticulocyte response and a slow rise in red blood cells. No abnormality of the stools was noted. Between 1940 and 1947 the red-cell count was found to be above 4 million per c.mm. on only one occasion despite intensive liver therapy. She never really felt well, but did not suffer from diarrhoea.

During the next two years her health was good, but towards the end of 1949 she again relapsed and was re-admitted to hospital in January, 1950. There was still no complaint of diarrhoea or any other alimentary upset. Her face and neck and the dorsal surfaces of her hands were diffusely pigmented and presented an exaggerated effect of sunburn. The fingers and the toes were clubbed. Haematological examination revealed a moderately severe megaloblastic

TABLE I.—*Fat Content of the Faeces on a Diet Containing 70 g. of Fat a Day*

Group	Case No. in Text	Faecal Fat Output during 4-day Periods (g.)		
		1	2	3
A	1	58.8	70.0	—
	2	34.0	22.5	33.0
	3	35.0	31.8	—
	4	39.2	54.0	—
B	—	11.8	5.6	—
	—	11.2	14.0	19.0
	—	14.1	8.4	—
Control	—	8.1	14.4	—
	—	12.3	16.5	14.3
	—	15.3	—	—
	—	5.1	10.2	—
	—	6.3	—	—

blastic anaemia with 1,900,000 red cells per c.mm., and the existence of histamine-fast achlorhydria was confirmed. An oral glucose-tolerance test gave a flat curve, with a maximum rise of 21 mg. above the fasting level of 79 mg. per 100 ml. The stools collected during both four-day test periods, although normal in appearance, contained an abnormally high quantity of fat (Table I). Radiography of the small bowel showed no evidence of a "deficiency pattern." The serum calcium was 10 mg. per 100 ml., inorganic phosphorus 3.4 mg. per 100 ml., and alkaline phosphatase 7 King-Armstrong units per 100 ml. The prothrombin index was 98%.

The anaemia was refractory to parenteral liver, and after two weeks' treatment the marrow was still megaloblastic. Folic acid then brought considerable improvement, but a complete haematological remission was not obtained until oral proteolysed liver was used. In December, 1950, when the red-cell count was over 5 millions per c.mm., she felt better than at any time since her illness started. During 1950 her weight increased by 12 lb. (5.4 kg.).

Case 2

A man now aged 39 was admitted to hospital in May, 1940, complaining of increasing weakness. He was found to have a macrocytic anaemia with megaloblastic erythropoiesis and a histamine-fast achlorhydria. There was no bowel upset. Treatment with parenteral liver resulted in a slow clinical and haematological improvement. During the next four years he received liver injections irregularly and his health was never good. In March, 1944, he had a severe attack of diarrhoea which lasted for one week, and he was re-admitted in July. Apart from large areas of brownish pigmentation on the forehead, cheeks, and extensor surfaces of the hands, the findings were essentially the same as in 1940. Intensive parenteral liver again produced a slow rise in red cells. From 1944 until 1950 he had persistent macrocytic anaemia, the severity of which varied independently of treatment. During this time he felt moderately well, but had occasional attacks of diarrhoea, when the stools were very fluid.

His condition began to deteriorate again in the early months of 1950. Clinical examination, in June, 1950, revealed a thin man of normal stature; the skin pigmentation was as previously described. His fingers were slightly clubbed and there was some papillary atrophy of the tongue. The red blood cell count was 3,120,000 per c.mm. and the mean corpuscular volume $113 \mu^3$; erythropoiesis was of an intermediate erythroblastic type (Innes, 1948). The gastric juice again contained no free HCl after histamine. Radiological examination showed clumping and segmentation of barium in the small intestine with some delay in passage. A glucose-tolerance test gave a somewhat flattened curve, the maximum rise being 30 mg. above a fasting level of 93 mg. per 100 ml. The serum calcium was 9.4 mg. per 100 ml., inorganic phosphorus 3.4 mg. per 100 ml., and alkaline phosphatase 6 King-Armstrong units per 100 ml. The prothrombin index was 91%. The fat content of the faeces passed during two of the three four-day collection periods used was abnormally high. In the other period the fat was at the probable upper limit of normal (Table I). Parenteral liver extract did not affect the anaemia, but folic acid caused great improvement both in the blood count and in the nutritional state. On November 11, 1950, the red-cell count was 4,730,000 per c.mm., but slight macrocytosis persisted (mean corpuscular volume $102 \mu^3$).

Case 3

A man now aged 32 was admitted to hospital on May 20, 1947. Five years previously, when a prisoner of war, he had a severe attack of untreated "dysentery." Afterwards he suffered from progressive weakness, and in 1943 was discharged from the Army on psychiatric grounds. Between 1944 and 1947 the weakness gradually increased and his weight slowly fell. He had noticed, since 1939, that the

skin of his face and neck was abnormally dark; in the spring of 1947 this colour became much more intense, and within a few weeks it spread over the rest of his body. At the same time the weakness became profound and his weight fell by about 14 lb. (6.4 kg.) in two months. Apart from the attack of "dysentery" he had never suffered from diarrhoea.

Examination revealed a well-developed young man with evidence of recent loss of weight. There was mild glossitis with papillary atrophy; a diffuse brownish pigmentation covered his face, neck, forearms, and hands; it was also present in large patches on the front of the chest, abdomen, and thighs. There was no clubbing of the fingers or toes. A test meal showed histamine-fast achlorhydria. Blood examination revealed a macrocytic anaemia, and erythropoiesis was megaloblastic. The stools were normal in appearance. Addisonian pernicious anaemia was diagnosed, and after three injections of a crude liver extract the reticulocytes reached a peak of 16%. The red-cell count rose satisfactorily and after discharge on June 15 he continued to make good progress.

When seen in August, 1950, he had no complaint. There was no physical abnormality apart from the pigmentation, which was unchanged. The blood count was satisfactory (red blood cells 4,740,000 per c.mm.), but there was still macrocytosis (mean corpuscular volume $103 \mu^3$). Free HCl was found in the gastric juice even without histamine stimulation. Radiography of the small intestine revealed an unusually coarse pattern in most of the jejunum, with clumping of the barium. The serum calcium was 10.4 mg. per 100 ml., inorganic phosphorus 3.6 mg. per 100 ml., and alkaline phosphatase 8 King-Armstrong units per 100 ml. The prothrombin index was 101%. The amount of fat in the faeces passed during both four-day test periods was above normal (Table I). Although the diagnosis was changed to idiopathic steatorrhoea the same treatment was continued.

Case 4

A woman now aged 34 was admitted to hospital on August 6, 1945. In 1943 she had an attack of "dysentery" which was accompanied by painful ulcers in the mouth. Afterwards she suffered from increasing tiredness, but there was no recurrence of diarrhoea.

Examination revealed severe megaloblastic anaemia and a histamine-fast achlorhydria. Her tongue was atrophic. A refined parenteral liver extract produced a low reticulocyte response. Her symptoms improved slightly and she left hospital against advice on September 8, when the red-cell count was only 840,000 per c.mm. above the admission level. While in the wards she had no diarrhoea.

She was not seen again until September, 1950. Her health had remained fairly good in the interim, although she was constantly underweight; diarrhoea was not experienced. Liver injections were given regularly each month. She looked well and there was no clubbing of the fingers or pigmentation of the skin. There was a moderate macrocytic anaemia (red cells 3,550,000 per c.mm.) and the sternal marrow contained many intermediate erythroblasts. The presence of a histamine-fast achlorhydria was confirmed. A glucose-tolerance test gave a very flat curve, with a maximum rise of 17 mg. above the fasting level of 84 mg. per 100 ml. Radiography of the small bowel revealed a well-marked "deficiency-pattern." The serum calcium was 9.8 mg. per 100 ml., inorganic phosphorus 3.2 mg. per 100 ml., and alkaline phosphatase 7 King-Armstrong units per 100 ml. The prothrombin index was 95%. The stools were rather bulky, but otherwise showed no macroscopic abnormality. The high fat content of the faeces collected during both four-day test periods proved the existence of steatorrhoea (Table I). The anaemia did not respond to parenteral liver, but folic acid proved very active. In February, 1951, the patient was 10 lb. (4.5 kg.) heavier than in September, 1950, and felt extremely well. The red-cell count was then 4,860,000 per c.mm. and the mean corpuscular volume $86 \mu^3$.

Differential Diagnosis

In Addisonian pernicious anaemia and idiopathic steatorrhoea accompanied by megaloblastic anaemia certain clinical and haematological features are encountered which are common to both disorders. A consideration of the various forms in which each condition may exist reveals that the clinical picture of one merges gradually into the other. This is illustrated by the four cases described above, for they presented no outstanding clinical evidence of the sprue syndrome, other than a "liver-factor" deficiency anaemia, and the resemblance to Addisonian pernicious anaemia was therefore very close. In particular, the relative absence of symptoms of intestinal upset and the achlorhydria which was demonstrated initially in all cases were important factors in long obscuring the correct diagnosis.

Intestinal Symptoms.—Gee (1888) recognized that diarrhoea was by no means a necessary accompaniment of the "coeliac affection," and this contention has since been supported by many authors; it is, however, still not realized widely enough. Steatorrhoea without obvious evidence of intestinal dysfunction has recently been described as occult (Anderson, 1950a). Analysis of the present cases illustrates how apparently innocuous, and therefore misleading, the bowel symptoms may be. Case 1 had no diarrhoea, and Case 2 only occasional attacks, in a period of ten years; Cases 3 and 4 were similar in that the only manifestation of intestinal dysfunction was an attack of so-called "dysentery" which immediately preceded the other symptoms. No macroscopic abnormality of the faeces was noted at any time while the patients were in hospital, and even on direct questioning none could recall that their stools had ever been bulky, pale, frothy, or offensive. Two of the patients with confirmed Addisonian pernicious anaemia complained initially of more diarrhoea than any of those with idiopathic steatorrhoea. In this series, therefore, the incidence of diarrhoea was of no value as a clinical pointer to the diagnosis of idiopathic steatorrhoea.

Gastric Analysis.—All the patients in Group B and all but one in Group A (Case 3) had persistent histamine-fast achlorhydria. Case 3 was exceptional in that, although achlorhydria was demonstrated initially, free HCl was present, even without histamine stimulation, three years later. It is certain that the patients in Group A were wrongly diagnosed as suffering from Addisonian pernicious anaemia largely because they happened to have achlorhydria. If free HCl had been present in the gastric juice such a diagnosis would not have been entertained. Although numerous cases of Addisonian pernicious anaemia without achlorhydria have been reported (Askey, 1944), few fulfil the necessary diagnostic criteria, and, indeed, some may have been examples of occult steatorrhoea. It is fortunate that free HCl is more often present than absent in idiopathic steatorrhoea. A study of the literature reveals that 60–80% of cases show free HCl in the gastric juice after histamine injection.

In contradistinction to the above features, which, with the exception of the return of free HCl in the gastric juice of Case 3, were valueless in respect of differential diagnosis, various other findings—clinical, haematological, radiological, and biochemical—served to separate the two groups of patients. Recognition of steatorrhoea depended finally on fat-balance studies.

Skin Pigmentation.—Three of the patients in Group A (Cases 1, 2, and 3) had marked brownish pigmentation of the skin, the sites of election being the face, neck, and dorsal surfaces of the hands and wrists. Many different types of skin lesion have been described in the sprue syndrome, but brownish pigmentation, irregularly distributed, is one of the commonest; the relevant literature has been reviewed by Kaufman and Smith (1943). Brownish pigmentation of a diffuse or blotchy type also occurs occasionally in Addisonian pernicious anaemia, and Brown (1946) noted this feature in 3 out of 78 cases. Its value in differential diagnosis is therefore limited, but its incidence is probably relatively greater in the sprue syndrome than in Addisonian

pernicious anaemia. None of the three confirmed cases of Addisonian pernicious anaemia exhibited abnormal pigmentation.

Clubbing of Fingers and Toes.—In 1950 both the fingers and the toes of one patient in Group A (Case 1) and only the fingers in another (Case 2) were clubbed. The patients concerned were those who had been under treatment for the longest time, but the duration of the clubbing could not be ascertained. Clubbing of digits is a well-known feature of idiopathic steatorrhoea, but it does not occur in tropical sprue or uncomplicated Addisonian anaemia. The association of macrocytic anaemia and clubbing is therefore very suggestive of idiopathic steatorrhoea, provided that other more common causes of clubbing can be excluded.

Glucose-Tolerance Test.—Oral glucose-tolerance tests, using 50 g. of glucose, were performed on all patients, except one (Case 3) in Group A. The results were strikingly different in the two groups—in Group B the curves fell within the normal range, the average maximum rise above the fasting level being 62 mg. per 100 ml., whereas in Group A the corresponding figure was 22.6 mg. per 100 ml. A low tolerance curve can be expected in about 50% of cases of idiopathic steatorrhoea (Thaysen, 1926).

Radiological Features.—Radiological examination of the small bowel was normal in all patients of Group B and in one of Group A (Case 1). The remaining Group A patients showed changes characteristic of the sprue syndrome. It is of interest that the deficiency pattern persisted in Case 3 although the anaemia was cured.

Haematological Features

At the first examination all patients of both groups had macrocytic anaemia and megaloblastic erythropoiesis characteristic of Addisonian pernicious anaemia in relapse.

The immediate effect of parenteral liver therapy is detailed in Table II. The method of Della Vida and Dyke (1942) was applied retrospectively to compare the actual rise of

TABLE II.—*The Immediate Effect of Parenteral Liver Therapy Compared with that Expected on the Basis of a Diagnosis of Addisonian Pernicious Anaemia*

Group	Case No. in Text	Red Blood Cells (mill. per c.mm.)			Reticulocytes (%)	
		Initial	Expected in 14 Days	Actual in 14 Days	Expected	Actual
A	1	2.06	3.04	2.53	18.3	8
	2	2.04	3.03	2.75	18.4	7
	3	2.33	3.19	3.10	14.2	16
	4	1.56	2.76	2.10	26.7	9
B	—	1.63	2.79	2.83	25.4	28
	—	0.95	2.41	2.29	41.5	38
	—	1.32	2.62	2.71	31.9	29

red blood cells in the first two weeks of treatment with that expected on the basis of a diagnosis of Addisonian pernicious anaemia; this was possible because weekly blood counts were available. The reticulocyte response expected, on a similar basis, was calculated from the formula of Isaacs and Friedman (1938). The initial response was suboptimal in three patients of Group A (Cases 1, 2, and 4); in the other (Case 3) the rise of reticulocytes and red blood cells was satisfactory.

Cases 1 and 2 pursued very similar courses over a period of ten years; despite intensive treatment with refined or crude liver extracts they had persistent macrocytic anaemia, which varied in severity from time to time. The blood count in Case 3 was easily maintained for three years at an almost normal level, but slight macrocytosis was always present. No haematological investigations were carried out in Case 4 until 1950, when there was a moderate degree of macrocytic anaemia. The same three patients, who responded poorly to parenteral liver in the beginning, were therefore still anaemic several years later. The use, over several weeks, of a refined liver extract in high dosage brought no haematological improvement in any of them.

Treatment had a quite different effect on the patients in Group B. All three had an adequate initial response to liver (Table II), and in 1250 two had normal blood pictures, while the other, although slightly anaemic, with a red-cell count of 3,850,000 per c.mm. and a mean corpuscular volume of $100 \mu^3$, had a normoblastic marrow. The anaemia responded rapidly to an increased dosage of refined liver extract and the macrocytosis disappeared.

The two groups of patients therefore reacted differently to parenteral liver. While complete correction of the abnormal erythropoiesis was obtained in all patients in Group B, those in Group A were either refractory (Cases 1, 2, and 4) or fully responsive without alteration of the macrocytosis (Case 3).

Faecal-fat Output

Final differentiation of the two groups was achieved by fat-balance studies. The diet in all cases contained 70 g. of fat a day. Over nine four-day collection periods in the Group A patients the faecal fat varied from 70 g. to 22.5 g.; the corresponding figures for seven four-day periods in Group B were 19 g. to 5.6 g.; and for nine periods in five control patients 16.5 g. to 5.1 g. (Table I). Fourman *et al.* (1948-9) calculated that the probable upper limit of normal for the total fat output in four days, on a 70 g. fat diet, was 23 g. This figure being accepted, increased output of fat was demonstrated in the Group A patients during all the test periods except one. In Cases 2 and 3 the increase was very slight.

Fourman *et al.* (1948-9) showed that the fat content of faeces collected over four-day periods has a coefficient of variation of about 30%. Despite this, they considered that the estimation of single four-day specimens is usually adequate for the diagnosis of steatorrhoea. They contended, however, that for the detection of very slight defects in absorption a 12-day test is necessary. Israëls and Sharp (1950) agreed with this opinion; they described a patient with steatorrhoea in whom a six-day test gave a normal result (98% absorption) but a subsequent 12-day test revealed only 85% absorption. In other words, the short test period is adequate only if the result is abnormal. Case 2 bears out this point, for the fat output was within normal limits in one four-day period, although definitely increased in the other two. In the light of this work it is unfortunate that two of the patients in Group B could be submitted only to eight-day tests. All that can be claimed is that during this time there was no evidence of increased fat output, and, with the absence of other features of steatorrhoea, the diagnosis of Addisonian pernicious anaemia was considered to be proved.

The Therapeutic Importance of Accurate Diagnosis

The change of diagnosis was followed in the three anaemic patients by more effective treatment. The substitution of oral folic acid for parenteral liver was a decisive measure, resulting in great haematological improvement. In two cases folic acid alone raised the red-cell count to normal levels, but in the other (Case 1) proteolysed liver was required in addition to complete the remission. In all three cases a considerable degree of hypochromia developed as the red blood cells rose, but this responded satisfactorily to intravenous iron. With this treatment the blood picture in Cases 1 and 4 became normal and the only residual abnormality in Case 2 was slight macrocytosis. Remission of the anaemia was accompanied by marked subjective improvement and rapid increase in weight.

These findings conform to the now well-recognized view that folic acid is the treatment of choice for idiopathic steatorrhoea when the marrow is, or was originally, megaloblastic. That folic acid is not always completely successful, however, has been shown by Davidson and Girdwood (1946) and Davidson, Girdwood, and Innes (1947). They described some patients in whom the haematological response to folic acid, although excellent at first, stopped short of normal

levels, and then a further rise was obtained by giving an oral proteolysed liver preparation. Case 1 reacted in exactly this way.

Discussion

The investigation, although confined to cases of megaloblastic anaemia under the age of 30, reveals that occult idiopathic steatorrhoea is a significant clinical entity which may long remain undiagnosed unless fat-balance studies are made. Frank steatorrhoea is easily recognized, and Anderson (1950b) stated that the real importance of steatorrhoea lies in the frequency with which it is occult. In the absence of any clinical indication of intestinal dysfunction the secondary manifestations are likely to be accepted as primary disorders.

The resemblance to pernicious anaemia in the four cases described was greatly heightened by the existence of achlorhydria; if free HCl had been present initially in the gastric juice, the diagnosis in all cases, except Case 3, which responded adequately to parenteral liver, would probably have been achrestic anaemia. Indeed, it is possible that the basic abnormality in some cases of this condition is an unrecognized steatorrhoea. Wilkinson (1948) and Israëls and Sharp (1950) described a case of refractory macrocytic anaemia, originally diagnosed as achrestic anaemia, in which it was five years before the onset of fatty diarrhoea brought the true diagnosis to light.

A consideration of Case 3 shows just how difficult the diagnosis of idiopathic steatorrhoea may be. Not only were the clinical and haematological findings compatible with pernicious anaemia, but the therapeutic response to parenteral liver was satisfactory. When, therefore, occult steatorrhoea is associated with histamine-fast achlorhydria and megaloblastic anaemia which responds promptly to parenteral liver extract, differentiation from Addisonian pernicious anaemia will be impossible on purely clinical grounds. Histamine-fast achlorhydria is, however, not very common in idiopathic steatorrhoea, and an adequate response to parenteral liver is seldom obtained. These two features are likely to be encountered in combination on only very rare occasions. This is fortunate, for it is impracticable to undertake fat-balance studies in all cases of apparently typical Addisonian pernicious anaemia on the chance of finding an isolated case of steatorrhoea.

The substitution of pernicious anaemia for the correct diagnosis did not prove an overwhelmingly serious error in any of the patients. They were not denied the benefits of dietary therapy, because in the absence of bowel symptoms and vitamin deficiencies (at the time of review there was no clinical or biochemical evidence of deficiency of the fat-soluble vitamins A, D, and K) none was necessary.

The only therapeutic weapon used until the correct diagnosis was established was parenteral liver extract. Its effectiveness varied greatly not only from patient to patient but also from time to time in the same patient. In the two who were followed closely for 10 years the red-cell count fluctuated quite independently of therapy, indicating a varying degree of refractoriness. Nevertheless a fair, if suboptimal, state of health and nutrition was maintained. Eventually the three patients who remained persistently anaemic failed completely to respond to parenteral liver during an intensive trial period. The intermediate marrow picture present in two of them suggested that liver was still producing some haemopoietic effect, but this must have been minimal and just sufficient to prevent further fall in the blood count. In the other the frankly megaloblastic marrow, which did not change during the period of intensive treatment, reflected a complete loss of the influence of liver. Folic acid then brought about improvement.

This series of events supports a hypothesis put forward by Girdwood (1950). He suggested that as the disease advances there is a progressive lack of absorption of haemopoietic agents, vitamin-B₁₂ deficiency in the early stages being succeeded by a state in which the tissues are depleted of folic acid. A period of successful liver or vitamin-B₁₂ therapy

will therefore end in complete refractoriness, at which stage only free folic acid will produce haematological benefit. Without doubt, however, other unknown factors are involved, for folic acid is not always completely successful in curing the anaemia.

Whatever the explanation, the beneficial clinical, nutritional, and haematological effect of folic acid in idiopathic steatorrhoea accompanied by megaloblastic anaemia makes accurate diagnosis a matter of great importance. It is all too easy, if anaemia is macrocytic and megaloblastic and associated with a histamine-fast achlorhydria, to diagnose Addisonian pernicious anaemia. In all such cases a careful assessment of the initial effect of parenteral liver extract or vitamin B₁₂ is necessary, and, if not classical, a fat-balance test should be the next investigation irrespective of the gross appearance of the stools or a history of intestinal dysfunction. A positive result from this somewhat laborious procedure is an indication for vitamin B₁₂ or liver to give place to folic acid.

Summary

Seven cases diagnosed as Addisonian pernicious anaemia before the age of 30, in the period 1937-49, were reinvestigated during 1950.

Alimentary symptoms were insignificant, but in three patients the initial response to parenteral liver was sub-optimal.

The diagnosis was confirmed in three patients; but four, including all three who responded poorly to liver in the beginning, were proved to be suffering from idiopathic steatorrhoea. These latter cases are described in detail, and their differentiation from Addisonian pernicious anaemia is discussed.

Various clinical, haematological, biochemical, and radiological features were suggestive of steatorrhoea; the demonstration of defective fat absorption was conclusive. No evidence of deficiency of the fat-soluble vitamins D and K was found.

The therapeutic importance of accurate diagnosis of occult steatorrhoea is stressed.

I wish to thank Professor Sir John McNee, in whose wards the patients were investigated and treated, for much encouragement and helpful advice in the preparation of this paper.

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RISKS OF NEEDLE BIOPSY OF THE LIVER

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Needle biopsy of the liver has now been adopted in many institutions throughout the world, but it is still regarded with misgiving by those who recall the frequent complications encountered by the pioneers of this procedure. Their doubts are not allayed by the high mortality figures mentioned in the literature, such as 1.0% by Snapper (1951), 0.93% by Kumpe (1949), 0.89% by Hoffbauer (1947), 0.60% by Webb and Werthammer (1949), 0.5% by Lichtman (1949), 0.3% by Sherlock (1949). The situation was in fact rather better than these figures suggested, for nearly three years ago there were records of 3,650 biopsies with seven deaths, a mortality rate of 0.19% (Terry, 1949b).

Mortality Rate

Over 10,000 liver biopsies have been reported in the literature since 1939, and it therefore seems an opportune moment to reassess the risks entailed. The various series are shown in Table I, which reveals that in 10,600 needle

TABLE I.—Incidence of Deaths and Significant Complications in 10,600 Needle Biopsies of the Liver

Author	No. of Biopsies	No. of Deaths	No. of Complications
Haex (1950)	1,500	0	1
Gillman (1948)	1,000	1	—
Schiff (1951)	1,000	1	2
White (1951)	761	1	1
Klatskin <i>et al.</i> (1950) ..	650	0	0
Davis (1951)	500	1	6
Sherlock (1949)	450	2	—
Hoffbauer (1949)	400	0	0
Topp <i>et al.</i> (1948)	361	0	4
Ricketts (1950)	300	0	0
Caravati <i>et al.</i> (1950) ..	300	0	1
Roholm <i>et al.</i> (1942) ..	297	2	—
Volwiler <i>et al.</i> (1947) ..	278	1	—
Meneghello <i>et al.</i> (1951) ..	253	0	0
Clay <i>et al.</i> (1949)	225	0	3
Terry (1952)	207	0	2
Friedrich <i>et al.</i> (1948-9) ..	200	0	0
Moyer <i>et al.</i> (1951)	200	1	1
Wolff <i>et al.</i> (1950)	170	0	—
Reynolds (1950)	150	0	—
Stone <i>et al.</i> (1950)	136	0	1
Awraad (1949)	130	0	—
Koch <i>et al.</i> (1948)	100	0	—
Parekh (1949)	100	0	—
Harris (1948)	90	0	—
Harkins <i>et al.</i> (1951)	75	0	0
Maxwell <i>et al.</i> (1950)	75	0	0
Rossmiller <i>et al.</i> (1950) ..	75	0	0
Herrera <i>et al.</i> (1947)	72	0	—
Webb <i>et al.</i> (1949)	70	0	1
da Silva <i>et al.</i> (1947)	70	0	—
Buck (1948)	56	1	0
McHardy <i>et al.</i> (1948)	50	0	—
Baron (1939)	48	1	—
King (1948)	48	0	—
Meredith <i>et al.</i> (1950)	44	0	0
Sanes <i>et al.</i> (1948)	44	0	1
Hoffman <i>et al.</i> (1950)	43	1	—
Brick (1948)	42	0	—
Beierwaltes <i>et al.</i> (1946) ..	30	0	—
Total	10,600	13 (0.12%)	24*

* Among 7,532 biopsies, or 0.32%.

The Royal Sanitary Institute has accepted an invitation from the Corporation of Hastings to hold the 1953 Health Congress in Hastings from Tuesday, April 28, to Friday, May 1, inclusive. Forty nations were represented at the 1952 congress, which was attended by 2,140 experts on health. Amongst them were five delegates from the Soviet Union specially charged with the mission of investigating British public health methods.

biopsies of the liver performed by modern techniques there has been a mortality rate of 0.12% and a complication rate of 0.32%. It is instructive to analyse these 13 fatalities, details of which are given in Table II.

The 11 deaths from haemorrhage all occurred in patients of hopeless prognosis; in the remaining two there is no