IV). The differences were found to be slight, but the following were statistically significant: α_2 -globulin in the gastrectomy group is lower than in the other groups ($P<0.01$), and α_2 -globulin is lower in both gastrectomy and ulcer groups than in the control group ($P<0.01$).

TABLE IV.—*Electrophoresis of Plasma Proteins—Mean Values (g./100 ml.)*

Group	Globulins			
	α_1	α_2	β	γ
Gastrectomy ..	0.23	0.39	0.56	0.96
Ulcer ..	0.25	0.50	0.60	0.90
Control ..	0.29	0.54	0.63	0.84

Discussion

Improvement in post-gastrectomy symptoms is common in the early months (Muir, 1949), and these results show that late improvement is also possible in mild cases, though less likely when symptoms are severe. Late deterioration as described by Wells and MacPhee (1954) was found in one patient.

The majority, however, show little change over the five-year period, and the weight of each patient has been remarkably stable, though weight normally tends to increase with advancing years. Johnston *et al.* (1958) showed that gastrectomy patients gained weight with intensive dietary supervision, but the increase was small and not necessarily maintained when the diet returned to normal. In our patients whose symptoms improved there was no corresponding rise in weight.

While none of our cases showed levels comparable with the low serum albumin described by Forshaw (1958), the significant difference between the total protein and globulin mean values of the three groups is interesting. This may indicate a poorer absorption of protein or merely reflect a lower intake by gastrectomy patients; the intermediate position of the ulcer cases may bear a relation to altered diet. The significant, or probably significant, difference in the group comparison tends to confirm the view. An attempt to relate this to weight was unsuccessful. The significance of the alteration in α_2 -globulin fraction is not apparent.

In another investigation (Walker *et al.*, 1958) it was found that the serum lipoproteins of gastrectomy patients did not differ to any significant extent from those of ulcer and other patients.

Summary

Studies of 40 patients 10 years after Polya gastrectomy showed relatively little change in post-gastrectomy symptoms, weight, or work records between 1952 and 1957, though late symptomatic improvement occurred in four cases and late deterioration occurred in one. Improvement in symptoms was not associated with a gain in weight or haemoglobin.

Measurements of total plasma protein, albumin, and globulin, and electrophoresis of plasma proteins indicate that total protein and α_2 -globulin may be lower after Polya gastrectomy, but no gross deviations from normal were found.

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NON-ADDISONIAN MEGALOBlastic ANAEMIA, COMPLICATED BY SUBACUTE COMBINED DEGENERATION OF THE CORD

BY

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Subacute combined degeneration of the cord (S.C.D.) is classically associated with Addisonian pernicious anaemia and is attributed to malabsorption of vitamin B₁₂, due to lack of intrinsic factor consequent on gastric atrophy. S.C.D. may, however, occur in any type of non-Addisonian megaloblastic anaemia due to vitamin-B₁₂ deficiency. One such type is associated with structural intestinal changes such as fistulae or anastomoses, with diversion of vitamin B₁₂ by bacteria in stagnant areas of bowel, and another with malabsorption of vitamin B₁₂ due to short-circuit operations or small-bowel infiltration by tuberculosis or tumour. Richmond and Davidson (1958) found only five cases of each type in the literature, and described one further case of each type of their own.

The case presented here had certain features common to both types, since there was a megaloblastic anaemia, normal gastric acidity, S.C.D., operative and radiological evidence of intestinal anastomosis and fistula formation, biochemical evidence of a malabsorption syndrome with steatorrhoea, and impaired absorption of ⁵⁷Co-labelled vitamin B₁₂.

Of additional interest was the time relationship of the neurological signs to isoniazid therapy.

Case Report

In 1940 the patient had a gastro-jejunostomy performed at the Glasgow Royal Infirmary for a chronic duodenal ulcer. He was readmitted in 1943 with symptoms due to chronic indurated prepyloric and stomal ulcers. At operation the site of the gastro-jejunal anastomosis was firmly adherent to the transverse colon. The previous anastomosis was left untouched and a new gastro-jejunostomy was performed. Three years later he was again admitted because of further ulcer symptoms, and vagotomy was done, with considerable relief of symptoms.

In 1950 he was first admitted to Stobhill General Hospital with a six-months history of diarrhoea, and a barium-meal examination showed a gastro-colic fistula. Ileo-sigmoidostomy was performed and the patient discharged to out-patient supervision.

He remained well until 1951, when he was readmitted to Stobhill Hospital with a recurrence of diarrhoea. Haemoglobin was 14 g./100 ml., and a blood film normal.

The fat content of the stools was greatly increased (53.4% of the dried specimen): 54.7% was split and 45.3% was unsplit. This was attributed partly to intestinal hypermotility and partly to malabsorption consequent on his gastro-jejunostomy. A gastric test meal showed a high acid curve despite his previous vagotomy, and a barium-meal examination revealed a well-functioning gastro-jejunostomy. He was discharged, having two well-formed stools per 24 hours.

For the next five years he was seen periodically as an out-patient, during which time he remained at work and free from ulcer symptoms. He continued to have recurrent periods of diarrhoea, during which he passed up to six poorly formed stools per 24 hours; from these no organisms were isolated. During this period steatorrhoea continued.

On June 15, 1955, he was readmitted to Stobhill Hospital because he was passing five or six frothy, greasy stools per 24 hours, the first time these two characteristics had been noted. Stool frequency dropped to two per 24 hours without specific therapy, and he was discharged, only to be again admitted on July 28 with a complaint of night sweats and a clinical finding of dullness at the right base. On admission he was afebrile, the E.S.R. was 3 mm./1 hour, and a chest x-ray film showed only pleural thickening at the right base; he was discharged.

For the next 18 months he had no ulcer symptoms, continued to pass two soft stools per 24 hours, and remained at work.

On January 15, 1957, he was readmitted to Stobhill Hospital with a recurrence of night sweats and also left-sided pleuritic chest pain. He was febrile, his E.S.R. was 47 mm./1 hour, and a chest x-ray film showed right basal pleural thickening with a small left basal pleural effusion. Blood examination was normal. An axillary lymph node biopsy showed active caseating tuberculosis. Faecal fat excretion remained high, averaging over 12 g. of stearic acid per 24 hours on five successive days (normal >6 g. per 24 hours). His tuberculosis was treated with 1 g. of streptomycin and 300 mg. of isoniazid daily, and he was discharged to a chest clinic where antituberculous therapy was continued until April, 1958.

In May, 1958, he was admitted to our care at Stobhill Hospital because of paraesthesiae of the upper and lower limbs, associated with slight difficulty in walking since January, 1958. The provisional diagnosis was that of peripheral neuritis due to isoniazid toxicity.

He was found to have the signs of peripheral neuritis with muscle-wasting, impaired muscle power, and grossly diminished tendon jerks in all limbs, diminished sensation to pin-prick, and hyperaesthesia to deep pressure in the lower limbs, and normal touch sensation. There were no signs of posterior or lateral column involvement, since vibration and postural sense was normal, there was no muscle spasticity, and both plantar responses were flexor. Haemoglobin was 14.6 g./100 ml. with a normal blood film. Barium-meal examination showed a well-functioning gastro-jejunostomy with a gastro-colic fistula, and the mean daily excretion of stearic acid over a period of six days was 20 g.

He had also a pellagra-like dermatitis involving the hands, face, and lower limbs, which disappeared rapidly on treatment with folic acid, 40 mg. by mouth daily, and vitamin-B complex parenterally. There was no change in the neurological picture, and he was discharged to continue folic acid and oral vitamin-B therapy.

He was given six weekly injections of liver extract before his readmission to us on December 19 because of severe diarrhoea. Estimation of stearic acid showed continuing severe steatorrhoea, and the haemoglobin was now 8.6 g./100 ml. Sternal puncture revealed a megaloblastic marrow with normal leucopoiesis and platelet formation. A gastric test meal gave a high acid curve, and a Schilling test showed grossly subnormal urinary excretion of ⁵⁸Co-labelled vitamin B₁₂, with no increase in excretion when

the test was repeated with intrinsic factor. These findings excluded Addisonian pernicious anaemia.

The neurological signs of severe peripheral polyneuropathy were still present, but in addition there was gross ataxia, with Rombergism and impairment of postural, proprioceptive, and vibration senses in the lower limbs, indicating posterior-column involvement. There was also slight muscle spasticity of the lower limbs, suggesting lateral-column involvement, though the plantar responses were flexor.

It was thought that the diagnosis was non-Addisonian megaloblastic anaemia, with neurological manifestations of vitamin-B₁₂ deficiency, secondary to malabsorption of vitamin B₁₂ in a structurally altered intestine. Folic acid and oral vitamin B were continued, and in addition he was given vitamin B₁₂ 1,000 µg. thrice weekly by intramuscular injection. His haemoglobin rose rapidly to 12.4 g./100 ml.; four weeks later his walking had greatly improved and he was no longer grossly ataxic.

Discussion

The earliest sign of neurological involvement in this patient was a polyneuritis which began in January, 1958. The blood picture in May, 1958, was normal, at which time the polyneuritis was well established. After the introduction of folic acid in May, 1958, the onset of the peripheral blood changes of vitamin-B₁₂ deficiency was probably delayed, owing to the temporary maintenance of normoblastic erythropoiesis by this treatment. This would suggest that before folic acid therapy is instituted in malabsorption states with steatorrhoea, the possibility of deficiency of vitamin B₁₂ should be investigated. This would clarify early neurological signs in such patients, and recognition of the early stages of S.C.D. in non-Addisonian megaloblastic anaemia would be more likely. The introduction of vitamin-B₁₂ therapy would then prevent progressive neurological damage.

The progression of S.C.D. and the presence of a megaloblastic marrow following treatment with liver extract are of interest. These findings support the advice of Adams and Timbury (1959) that, because of the poor vitamin-B₁₂ content of most liver extracts, cyanocobalamin should always be used.

It is noteworthy that the onset of polyneuritis and pellagra coincided with a course of isoniazid, and it was then thought that both might be related either to a malabsorption syndrome with nicotinic acid and riboflavine deficiency or to isoniazid therapy. Polyneuritis had only rarely been reported as a complication of tuberculosis prior to isoniazid treatment (Harris, 1926; Ford, 1944). Since then several authors have reported polyneuritis in patients with tuberculosis treated with isoniazid (Katz *et al.*, 1944; Dixon *et al.*, 1956). It is believed that polyneuritis is more frequent with high and prolonged dosage schemes (Biehl and Nimitz, 1954), though these authors found that 8% of patients receiving 6–10 mg. of isoniazid per kg. body weight daily developed polyneuritis. Dixon *et al.* (1956) were of the opinion that some patients might develop neuropathy on moderate dosage of isoniazid, and noted that the condition improved spontaneously when the drug was discontinued. It is believed that our patient developed polyneuritis due to vitamin B₁₂ deficiency, occurring in an established malabsorption syndrome, and not because of isoniazid therapy or nicotinic acid and riboflavine deficiency. This is supported by the facts that the patient's daily dose of isoniazid never exceeded 6 mg. per kg. body weight,

and that even when the drug was discontinued in April, 1958, the polyneuritis progressed relentlessly until the full clinical picture of subacute combined degeneration of the cord was established by December, 1958. Moreover, this progression, despite treatment with a vitamin-B complex parenterally, suggested that malabsorption of these substances was not the primary cause of his neuropathy.

The skin lesions were believed to be those of pellagra, which is found in chronic deficiency of nicotinic acid and riboflavin (Sydenstricker, 1941). It is probable that the pellagra was caused by grossly impaired absorption of nicotinic acid, and this view is supported by the rapid response of the skin lesions to a parenteral vitamin-B complex. It is possible that isoniazid therapy, by interfering further with carbohydrate metabolism, contributed to the production of pellagra, since it is known that pellagra becomes worse during isoniazid therapy.

It is worth repeating that the neurological signs were unaffected by isoniazid withdrawal, by long-continued dosage of vitamin-B complex and folic acid, or by liver extract given parenterally for six weeks. This suggests that the primary cause was, in fact, a developing vitamin-B₁₂ deficiency, which liver extract was unable to prevent, presumably because of its low vitamin-B₁₂ content.

Summary

A case of non-Addisonian megaloblastic anaemia with subacute combined degeneration of the cord, associated with severe malabsorption in a structurally altered intestine, is presented. There was a history of tuberculosis treated with isoniazid.

It is suggested that before folic acid is given in the treatment of such cases deficiency of vitamin B₁₂ should be excluded, especially in the presence of early neurological involvement.

The possible relationship of vitamin-B₁₂ deficiency and isoniazid treatment to the neurological changes is briefly outlined.

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The 1959 edition of the Association of British Chemical Manufacturers' directory, *British Chemicals and their Manufacturers*, is now available. This new edition contains over 12,000 products named systematically and in accordance with British Standard 2474:1954—*Recommended Names for Chemicals Used in Industry*. Copies are available, free of charge, to all persons or firms genuinely interested in the manufacture or purchase of chemicals, from the association, Cecil Chambers, 86, Strand, London, W.C.2.

EXPERIMENTAL STUDIES ON BYSSINOSIS

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Byssinosis is a disease occurring among cotton-mill workers (Schilling, 1956). Its main symptoms are dyspnoea and a feeling of tightness in the chest. These are usually most prominent when the workers return to the cotton-mill after absence from work for a few days, during the week-end, or a holiday. The respiratory symptoms are generally ascribed to the inhalation of the dust produced in the card-rooms of the mills. However, the way in which the dust produces the symptoms of byssinosis is not known. It has been shown that the symptoms are accompanied by a decrease of the maximal breathing capacity and an increase in airway resistance (McKerrow *et al.*, 1958). It has been suggested that histamine or some other active substance in the cotton dust is responsible for the dyspnoea of byssinosis. According to another hypothesis the symptoms are a manifestation of an allergic (antigen-antibody) reaction to the cotton dust (Haworth and Macdonald, 1937).

We have studied the effect of cotton dust on the lung ventilation in two men who had not previously been exposed to the dust in the cotton-mills. Extracts of cotton dust were inhaled in the form of an aerosol, and the changes in the lung ventilation produced by the extracts were studied with the nitrogen clearance method (Bouhuys *et al.*, 1956). This method involves continuous recording of the nitrogen concentration in expired gas during oxygen-breathing. The "lung-clearance index" (L.C.I.) (Becklake, 1952) is the amount of ventilation required to wash out the nitrogen from 1 litre of the lung volume down to 2% nitrogen in end-tidal gas. The clearance of nitrogen from the lungs is delayed, and the L.C.I. increased, in patients with asthma and in normal subjects after inhalation of histamine (Bouhuys *et al.*, 1960).

Experimental

The extracts were prepared from a sample of mixed cotton dust collected in a ventilator in a card-room. 3 g. of the dust was ground with sand in a mortar, 50 ml. of saline was added, and the sample was allowed to stand overnight at 4° C. The sample was filtered the next day and the filtrate used for the experiments. The activity of the extracts seemed to deteriorate with time, and for this reason fresh extracts were always used. The aerosol of the filtrate was produced in a nebulizer (Rooth, 1949) in the same way as histamine aerosols had been produced in a previous investigation (Bouhuys