SUBACUTE COMBINED DEGENERATION DEVELOPING DURING LIVER THERAPY

BY

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"Initial treatment of the disease is easy, it is over maintenance treatment that the patient comes to grief." Witts made this statement in 1934, when liver and liver extracts were the only forms of therapy available for the treatment of pernicious anaemia.

Parenteral liver therapy is still in common use, and we report here the unfortunate consequences of the use of two such preparations, which were later found to contain only trivial quantities of vitamin B₁₂.

Case 1

A man aged 66 was seen by us 16 years after his pernicious anaemia had been diagnosed. During this period he had received the same brand of liver extract, 2 ml. intramuscularly every fortnight. For the two years prior to our examination he had experienced ataxia and paraesthesiae of the legs; there was a brief history of glossitis.

He was not obviously anaemic, but had signs of subacute combined degeneration—namely, increase of patellar reflexes, absence of ankle reflexes, left extensor plantar response, calf tenderness, and absence of vibration sense in the left leg. He had a mild macrocytic anaemia; Hb, 10.3 g./100 ml.; R.B.C., 3,000,000/c.mm.; P.C.V., 33%; M.C.V., 110 cubic microns; and sternal marrow biopsy showed megaloblastic erythropoiesis. Acid was not detected in the gastric juice after histamine stimulation (Kay, 1953). The serum vitamin-B₁₂ level was subnormal (25 µg./ml.)—method of Ross (1952) and Hutner *et al.* (1956). Absorption of ⁵⁷Co B₁₂ was subnormal by the urinary excretion test (Schilling, 1953), but was raised to normal by the addition of intrinsic factor.

Treatment with parenteral vitamin B₁₂ restored the peripheral blood levels to normal and abolished the glossitis and paraesthesiae. The objective neurological signs were unchanged after six months' intensive treatment.

A sample of the liver extract was obtained from the patient's doctor, and was found to contain 0.09 µg. of vitamin B₁₂/ml., measured by microbiological assay.

Case 2

A man aged 59 was admitted to hospital with a marked anaemia. Pernicious anaemia had been diagnosed 10 years before admission, and he had received the same brand of liver extract, 2 ml. intramuscularly each month, until a month before admission, when the injections were given weekly. He was pale and icteric, the spleen and liver were palpable, both plantar responses were extensor, and the patellar and ankle reflexes were diminished. Peripheral blood examination showed a macrocytic anaemia: Hb, 4.1 g./100 ml.; R.B.C., 1,390,000/c.mm.; and sternal marrow biopsy showed megaloblastic erythropoiesis. Acid was absent from the gastric juice. The serum vitamin-B₁₂ level was subnormal (45 µg./ml.). Absorption of ⁵⁷Co B₁₂ was subnormal by the urinary excretion test.

The patient died suddenly and unexpectedly in acute left ventricular failure shortly after treatment was begun. At post-mortem examination the stomach was atrophic, the liver enlarged and fatty, red marrow extended along the

length of a femur, and the lungs were oedematous; no anatomical cause for the cardiac failure was found. The liver extract with which the patient had been treated was found to contain 1.5 µg. of vitamin B₁₂/ml., measured by microbiological assay.

Discussion

Addisonian pernicious anaemia and subacute combined degeneration are manifestations of vitamin-B₁₂ deficiency resulting from absence of intrinsic factor. The standard treatment is by parenteral vitamin-B₁₂ therapy, but parenteral liver extracts still enjoy some popularity, their use being largely a matter of tradition. The haemopoietic effects of liver extracts are believed to be due entirely to their vitamin-B₁₂ content.

The object of therapy is to raise and maintain the serum vitamin B₁₂ to a normal level. The serum vitamin-B₁₂ levels can be estimated only by the laborious technique of microbiological assay. Mollin and Ross (1953) showed that the individual requirement for vitamin B₁₂ varies widely from case to case, and suggested that as a general rule maintenance treatment should consist of 40 µg. of vitamin B₁₂ intramuscularly every 10 days or 160 µg. intramuscularly every 21 days. With these figures in mind we have reviewed the liver extracts commonly used in this country (see Table); it

Vitamin-B₁₂ Content, Dosage, and Cost of Liver Extracts

Manu- facturer	Prepara- tion	Stated Vitamin B ₁₂ Content	Maintenance Dose Recommended by Manufacturer	Cost of Recommended Maintenance/ Month
1	{ a b	Not stated 5 µg./ml.	1-2 ml. every 4-5 weeks 4 ml. " 3-4 "	4d.-8d. 1s. 1d.-1s. 5d.
2	{ a b c	2 " " 4 " " 20 " "	8 " " 4 " 4 " " 4 " 1-2 " " 4 "	6s. 6s. 3s. 6d.-7s.
3	{ a b	2 " " 20 " "	5 ml. every week or 2 weeks 1-2 ml. alt. days 1 ml. every 1-2 weeks	5s.-10s. 7s. 6d.-15s. 4s. 6d.-9s.
4	{ a b	Not stated 20 µg./ml.	2-4 " " week 1-2 " " 2-4 weeks	4s. 8d.-9s. 4d. 10d.-3s. 4d.
5	{ a b	Not stated " High "	2 ml. " periodically " 1-4 ml. every 4 weeks	1s. 10d.-7s. 4d. 4s. 4d.-8s. 8d.
6	{ a b	2 µg./ml. 20 " "	2-4 " " week 2 " " 2 weeks	6s. 10d. 9s.
7	{ a b	12 " " 10 " "	1 " " week 4 " " 4 weeks	1s. 8d. 2s.
8	{ a b	2 " " 10 " "	2 " " 2 weeks 4 " " week "	6s. 5s.
9	{ a b	20 " " 2 " "	1 " " 2 weeks 2 " " 4 "	1s. 6d. 1s. 4d.
10	a	2 " "	2 " " 2 "	1s. 6d.
11	a	Not stated	2 " " 4 "	1s. 4d.
Various	Vitamin B ₁₂	40 µg. 160 " "	10 days 21 " "	7d.-11d. 1s. 3d.-1s. 10d.

is obvious that with one exception (9a) the doses recommended by the manufacturer are sadly inadequate as judged by the recommendations of Mollin and Ross. It is also worthy of note that the cost of maintenance therapy with liver extracts, expensive enough when the doses recommended by the manufacturer are used, would be between 10 to nearly 80 times the cost of an equivalent amount of crystalline vitamin B₁₂ if the doses of liver extract were increased to ensure that each patient received the amount of vitamin B₁₂ recommended by Mollin and Ross.

Liver extracts and preparations of vitamin B₁₂ may deteriorate on storage if exposed to light, but deterioration of the liver extract can hardly be regarded as playing a part in these two cases, because random samples of the preparations have been found to have a similarly low vitamin-B₁₂ content. It should be mentioned that in neither case did the manufacturers state the vitamin-B₁₂ content of the extract.

However much we may decry the sale of liver extracts with such vitamin-B₁₂ content, it is the physician who must bear the responsibility for inadequate treatment of the patient. Until the physician is prepared to use the large dosage of liver extracts needed to ensure adequate intake of vitamin B₁₂ or until the manufacturers increase the vitamin-B₁₂ content of liver extracts and alter their recommendations it would seem that the only justifiable course is to use solutions of pure vitamin B₁₂ in all cases.

Summary

Two patients with pernicious anaemia who relapsed and developed subacute combined degeneration while receiving treatment with liver extracts are described. The relapses were probably due to the low vitamin-B₁₂ content of the liver extracts. Attention is drawn to the poor vitamin-B₁₂ content of most liver extracts, and the practical importance of this is emphasized.

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Medical Memoranda

A Small Outbreak of Bornholm Disease in the Gambia

Since Sylvest (1934) gave a full description of the recorded outbreaks of Bornholm disease up to 1931, there have been many reports of further outbreaks from different parts of the world. The only previous report from West Africa we could find was by Colbourne (1954), who recorded a small outbreak in the Gold Coast (Ghana) with limb pains as the predominant feature. We record here a small outbreak of the disease in a European community in the Gambia, West Africa.

The four cases all occurred in November, 1956, in Fajara, a mainly European residential area 9 miles (14.5 km.) along the coast from Bathurst, the capital town. All the patients had been in the Gambia for at least six months.

CASE REPORTS

Case 1.—A European woman aged 30 complained of severe pain of sudden onset in the lower part of the anterior thorax on the right side. Her temperature varied between 101 and 103° F. (38.3 and 39.4° C.). She was admitted to hospital, given symptomatic treatment, and discharged after three days. During that time no localizing physical signs in the lungs, pleura, or abdomen were found. Her W.B.C. was 10,000/c.mm., with a normal differential count. Her thick blood film was negative for malarial parasites. Three days after her discharge from hospital she had a second and even more severe attack of pain affecting the left side of her chest in a comparable position to her first attack. The pain was very acute and spasmodic in character, and was

aggravated by coughing, yawning, and sneezing. She also complained of frontal headache. Her temperature in this attack varied between 103 and 104° F. (39.4 and 40° C.). On examination moderate tenderness and hyperaesthesia were found over the left lower intercostal muscles. Her symptoms subsided gradually and cleared in three days, no specific treatment having been given again. Three weeks after her illness (30 days after the onset of the first attack), when she was in good health, her blood was tested for the specific neutralizing antibodies to the five types of group B Cocksackie viruses (Dalldorf, 1952) and showed neutralizing antibodies to four of them. This being a single convalescent serum, however, no definite laboratory confirmation could be obtained.

Case 2.—The husband of the first patient, a European aged 32, three days after his wife's first attack suddenly experienced the onset of severe spasmodic pain in the region of the xiphisternum which lasted 36 hours. He was admitted to hospital, where his temperature was found to vary between 101 and 102° F. (38.3 and 38.9° C.). No localizing physical signs were found and his W.B.C. was 9,400/c.mm., with a normal differential count. No malarial parasites were found in the thick blood film. He was given analgesics and discharged after three days. Blood taken three weeks after his illness showed neutralizing antibodies to four of the five types of group B Cocksackie viruses tested. This also being a single convalescent serum, no definite laboratory confirmation of the diagnosis could be obtained.

Case 3.—A week after the occurrence of Case 2 a European man aged 40 had sudden onset of pain in the right lower intercostal muscles, described by the patient "as if I had been kicked in the ribs during a Rugger match," and accompanied by profuse sweating. On examination his temperature varied from 100 to 101° F. (37.8 to 38.3° C.). There was moderate tenderness but no hyperaesthesia over the affected area. The illness lasted three days, during which time he was not sent to hospital, remaining ambulant except for the first 24 hours. During his illness the W.B.C. was 8,900/c.mm., with a normal differential, and the thick blood film was negative for malarial parasites. Serum taken on the third day of his illness, and again 20 days later, and sent for neutralization tests in tissue culture (monkey kidney), with the five types of group B Cocksackie viruses, failed to give any evidence of recent infection with these viruses.

Case 4.—On the same day as in Case 3 a European man aged 37 experienced a sudden onset of severe pain in the right lower intercostal muscles, which he described as if a brass plate were being screwed into him. On examination his temperature varied between 101 and 103° F. (38.3 and 39.4° C.) and there was marked tenderness over the site of the pain, although no hyperaesthesia could be elicited. His W.B.C. was 10,000/c.mm., with a normal differential, and a thick blood film contained no malarial parasites. His illness lasted three days, during which time only analgesics were given. Serum taken during his convalescence (three weeks after the acute attack) and tested for neutralizing antibodies to the five types of group B Cocksackie viruses gave no evidence of recent infection with these viruses.

COMMENT

One or two interesting points about these four cases include the fact that all the attacks (five in four patients) lasted three days, all the patients were aged 30–40 years, and despite the fact that two of them had young children none of these developed an attack. All the patients had the pain in the same site—the lower intercostal muscles—whereas the cases described by Colbourne from the Gold Coast experienced the pain mainly in the limb muscles.

Although in the one case where acute and convalescent serum were available (Case 3) no serological evidence of recent infection with the group B Cocksackie