low curves are common in idiopathic steatorrhœa though by no means the rule, and may occur in about 40% of normals. The latest method is the xylose excretion test. This is usually abnormal in idiopathic steatorrhœa, as xylose is absorbed in the jejunum.

Every patient with macrocytic anæmia should be investigated properly. It is not enough merely to replace the deficiency of vitamin B_{12} or folic acid. Those with idiopathic steatorrhœa, often misdiagnosed in the past as suffering from pernicious anæmia, are more likely to obtain good health by the gluten-free diet than by hæmatinics. Antibiotics may be necessary to treat the megaloblastic anæmia and its neurological complications arising from the stagnant loop syndrome, or the surgeon may cure both by corrective surgery.

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The Clinical Neurology of Macrocytic Anæmia

Anæmia is macrocytic when the average volume of the red cells exceeds 94 cu. μ and when the mean concentration of their hæmoglobin is above 30% (Wintrobe 1961). Iron deficiency may mask these features of macrocytic anæmia (Mollin & Hines 1964) which may be either megaloblastic or normoblastic. The marrow becomes megaloblastic as the level of folate available to the maturing red cells falls below a critical level (Herbert 1962). If the basic cause is a shortage of vitamin B_{12}, the anæmia may be accompanied by the neuropathy of vitamin B_{12} deficiency; but if it is due to deficiency of folic acid itself (or on rare occasions of ascorbic acid) as part of a general state of malnutrition or malabsorption, then the various kinds of nutritional neuropathy are more likely to appear.

The biochemical lesion of megaloblastosis, due to shortage or blockade of folate, is a failure to form nucleoprotein from its precursors in the cytoplasm. In other areas with a rapid turnover of cells, nuclear maturation is at fault (Mallarmé 1948). In patients with addisonian anæmia, cells with abnormally large nuclei have been found in the stomach (Rubin & Massey 1953, Graham & Rheault 1954); in the mouth (Boen 1957, Farrant 1958); in the vagina (van Niekerk 1962); and very occasionally elsewhere (Boddington & Spriggs 1959). Identical findings have been reported in patients with other forms of megaloblastic anæmia (Gardner 1956, Boddington 1959). Hence the common clinical sign of glossitis.

Macrocytosis with a normoblastic marrow usually indicates hurried erythropoiesis in response to overmuch hæmolysis, with an outpouring of immature reticulocytes into the peripheral circulation. Under these circumstances neurological syndromes are related to the underlying pathological state.

Examples of such syndromes are the encephalopathy, and rare myelopathy, of cirrhosis and portal vein thrombosis; Wernicke's encephalopathy, Korsakoff's syndrome, and the neuropathy of alcoholism so often associated with chronic liver disease; myxœdema; the neuromyopathies of malignant disease; uræmia; intracranial hæmorrhage of blood dyscrasias; the retinal and cerebral infarcts of hæmoglobinopathy.

The two groups overlap. Either type of marrow, for instance, may be seen in cases of chronic liver disease or of myxœdema. Macronormoblasts are a sign of falling stocks of folate, or of a block to

its physiological activity, before frank megaloblastosis appears. This can be a dangerous moment for the nervous system. Should there be a sudden influx of folate, available vitamin B_{12} will be mobilized to the marrow with disaster for depleted neurones (Victor & Lear 1956). This may occur if folic acid is given to a patient with non-addisonian megaloblastic anæmia in whom the stores of vitamin B_{12} are also low – as in pregnancy. It is catastrophic for the patient with true addisonian anæmia (Wilkinson 1949).

Vitamin B_{12} Deficiency

The causes of vitamin B_{12} deficiency are an inadequate diet, insufficiency of intrinsic factor, and malabsorption from the ileum. In rare cases it may be due to metabolic deviation or to the blocking action of anti-vitamins.

Anæmia, neuropathy, glossitis may result from deficiency and present clinically in any combination. Addison himself described the 'flabbiness of the solids' of anæmic patients (Addison 1855). The cases of true addisonian anæmia contrast with the malnutrition of most of the others with vitamin B_{12} deficiency. Not every patient with anæmia and with neurological signs has vitamin B_{12} neuropathy. The coincidence of certain other disorders is familiar to all clinicans. Diabetes mellitus and addisonian anæmia commonly occur together (Wilkinson 1949, Arapakis *et al.* 1963). Sometimes the cause of a sensory neuropathy in a diabetic can be determined only by finding an abnormally low concentration of vitamin B_{12} in the serum (< 100 μμg/ml).

Myxœdema, presenting as dementia (Asher 1949), ataxia (Jellinek & Kelly 1960), or peripheral neuropathy (Crevasse & Logue 1959), or with the characteristic ankle-jerk first hinted at by Ord in 1884, is particularly associated with addisonian anæmia, a significant number of hypothyroid patients having both conditions (Tudhope & Wilson 1960). Hypogammaglobulinæmia may be another facet of this relation (Lee *et al.* 1964).

The muscular disorders of hyperthyroidism, and myasthenia gravis, have to be considered since patients with addisonian anæmia have a more than ordinary chance of becoming thyrotoxic (McNicol 1961). In these cases also there is an overlap of autoimmune phenomena (Doniach *et al.* 1963).

Rheumatoid arthritics are apt to develop addisonian anæmia, and are also liable to a folate-deficient megaloblastic anæmia as a result of poverty and enfeeblement (Gough *et al.* 1964). The neurological syndromes of rheumatoid arthritis are confusing by their number. Apart from the familiar muscular atrophy which results from arthropathy and disuse, compression of peripheral nerves (most commonly median, ulnar and lateral popliteal) from displacement, overgrowth of pannus, or pressure of splints may lead to localized atrophy the cause of which can easily be overlooked. True rheumatoid neuropathy (Hart *et al.* 1957) has to be distinguished from the myopathy of steroid therapy (Perkoff *et al.* 1959), prednisone (Harman 1959), fludrocortisone (Maclean & Schurr 1959), dexamethasone (Golding & Begg 1960) and particularly triamcinalone (Dubois 1958, Kendall & Hart 1959) having been incriminated; as well as from the neuropathy of gold, phenylbutazone (Kelly 1954, Arden 1954), and the retinopathy (Hobbs *et al.* 1959) and neuromyopathy of chloroquine (Whisnant *et al.* 1963). Tetraplegia very occasionally results from rheumatoid spondylitis with atlanto-axial subluxation (Rogers 1961).

Another cause of neuromyopathy in a patient with addisonian anæmia is carcinoma of the stomach to which anæmic patients and their relatives are prone (Videbaek & Mosbech 1954).

Multiple Deficiency Syndromes

Multiple deficiencies may result from malabsorption and from starvation. Certain drugs, such as anticonvulsants, may cause anæmia from folate block and at the same time be directly toxic to the nervous system. Essential factors may be lost to the fœtus or to a tumour (van Dommelen *et al.* 1964), or by a failure of the usual mechanisms for retaining and transporting them (Horrigan & Heinle 1952, Herbert 1959).

Whereas a sensory syndrome is common in the early stages of vitamin B_{12} neuropathy, deficiency of thiamine and of other members of the vitamin B complex (nicotinamide, pyridoxine, pantothenate) may declare itself with dramatic mental symptoms. Wernicke's encephalopathy is an example of this. Megaloblastic madness (Smith 1960), first reported by Langdon in 1905, and optic neuropathy (Cohen 1936, Turner 1940) have to be remembered as occasional presenting signs of vitamin B_{12} deficiency.

The nutritional neuropathies of malabsorption are uncommon in this country and, with the exception of those cases due to vitamin B_{12} deficiency and some cases of alcoholic neuropathy, often not severe. With better management and longer survival of patients at risk of malabsorption, the delayed manifestation of vitamin B_{12} deficiency due to this cause (Richmond & Davidson 1958) is likely to be seen from time to time, as many years may have to pass before the reserves of vitamin B_{12} dry up (Weir & Gatenby 1963). The risk of deficiency will be greater in the patient with a slight defect of absorption since

those with a severe lesion will have had replacement therapy (Anderson 1965).

European experience in peace and war contrasts with that of tropical countries where a rich complex of nutritional neuropathies is seen. Spinal ataxia and cranial nerve palsies, especially amblyopia, deafness, and laryngeal palsy, are only less common than peripheral neuropathy, dementia and psychotic states due to multiple vitamin B deficiencies (Cruickshank 1952, Spillane 1947). The place of spastic paraplegia is more difficult to assess. Although it used to be included among the nutritional neuropathies, reports from Jamaica (Montgomery *et al.* 1964) and from South Africa (Cosnett 1964) suggest that this syndrome may have a different ætiology.

A constellation of neurological symptoms may result from an associated deficiency of minerals and glucose in patients whose anæmia is part of a malabsorption syndrome.

Apart from the well-known signs of tetany and papillœdema, a lack of calcium may ultimately cause spinal compression or a posterior fossa syndrome as a consequence of basilar impression (Robinson 1959). It can be the explanation of a waddling gait (Milkman 1930). Retention of urine and paralytic ileus (Randall *et al.* 1949) may be presenting signs of hypokalæmia. The importance of sodium chloride deficiency (Marriott 1947) should not be overlooked in the welter of new techniques, muscle cramps, hypotension and syncope being symptoms of salt lack.

The mucosal atrophy of sideropenic anæmia may lead to a secondary deficiency of the B group of vitamins (Cox *et al.* 1959), or there may be a more subtle relationship between the two (Jacobs & Kilpatrick 1964). Iron deficiency has been suggested as a cause of benign intracranial hypertension (Capriles 1963). The syndromes of magnesium deficiency are being recognized more often (Goldman *et al.* 1962) and are frequently present in chronic malabsorption (Booth *et al.* 1963), although their clinical importance is not always clear (Randall *et al.* 1959).

A laparotomy scar – the outward sign of surgical reconstruction of the alimentary tract and of the potential hazards of malabsorption – must always arouse suspicion of hypoglycæmia as the cause of epilepsy of late onset and of other obscure neurological symptoms (Moersch & Kernohan 1938).

Folic Acid and the Nervous System

A neuropathy of folate deficiency has not so far been identified. This paradox needs examination.

Whereas the concentration of vitamin B_{12} in the serum is related logarithmically to that of the spinal fluid, being about thirty times greater (Worm-Petersen 1962, Simpson 1964), the distribution of folate is very different, with serum levels often a half or a third those of the fluid (Herbert & Zalusky 1961). This arithmetical relation persists even in states of folate deficiency (Herbert 1964). Thus clinical deficiency of folic acid as measured by changes in the marrow or in the nuclear structure of epithelial cells (Gardner 1956) may seldom, if ever, be severe enough to drain the nervous system of folate.

The normal range of vitamin B_{12} and folate levels in the serum and in the spinal fluid are contrasted in Table 1 with the levels recorded in two patients with megaloblastic anæmia. One was intoxicated with phenytoin which she had been taking for eight years. The other, a 55-year-old woman with recurrent urinary infection due to a congenital abnormality of the kidneys, had a severe neuropathy which had begun towards the end of a course of treatment with nitrofurantoin totalling 12 grams. Her blood urea had been normal at the start of therapy.

Table 1

Concentration of B_{12} and folate in blood and spinal fluid in folate-dependent megaloblastic anæmia

	B_{12} μμg/ml		*Folate ng/ml*	
	Serum	*CSF*	*Serum*	*CSF*
Normal range	150–600	0–30	4–21	9–60
Case 1	152	<20	2	4
Case 2	171	<20	2	10

Case 1—Female, aged 49. Chronic epilepsy: phenytoin 300 mg/day for eight years. January 1965: Megaloblastic anæmia; nystagmus, ataxia

Case 2—Female, aged 55. Urinary infection: nitrofurantoin 400 mg/day for thirty days. November 1964: Megaloblastic anæmia; sensorimotor neuropathy

Phenytoin and nitrofurantoin are both potentially neurotoxic. Neither the cerebellar lesion of phenytoin, which may progress to necrosis of Purkinje cells (Utterback 1958), nor the neuropathy of nitrofurantoin, due to demyelination of peripheral nerves and motor and sensory roots (Collings 1960), responds to folic acid therapy.

Phenytoin toxicity depends on the rate of parahydroxylation of one of its phenol groups, an enzymatic process within the liver which is subject to genetic influence (Kutt *et al.* 1964); that of nitrofurantoin on the activity of its 5-nitrofuran group which it has in common with other known neurotoxic drugs, such as nitrofurazone (Szczukowski *et al.* 1958, Politano *et al.* 1958).

Phenytoin (Hawkins & Meynell 1958) and nitrofurantoin (Bass 1963) may cause a megaloblastic anæmia which responds promptly and completely to folic acid, in pharmacological dose by mouth, but incompletely to parenteral vitamin B_{12}. The hydantoin ring, which is common to phenytoin and nitrofurantoin, is structurally similar to the pterodyl nucleus of folate so that

these drugs may act by competitive inhibition. Either they may block the transport of folate across the cells of the jejunal mucosa, or they may inhibit its reduction to its physiologically more active form, tetrahydrofolate. This important reduction is inhibited by the synthetic antifols (Woods 1964) and also by deficiency of ascorbic acid, the latter causing the megaloblastic anæmia of scurvy (Goldberg 1963).

Although phenytoin and nitrofurantoin can thus jam the metabolism of folic acid sufficiently to cause megaloblastic anæmia and can penetrate the blood-brain and blood-CSF barriers in sufficient strength to cause permanent neural lesions, they seem unable to disturb the metabolism of folic acid within the nervous system.

There are, however, at least two reports in the literature which suggest that shortage of available folate can cause neurological symptoms under appropriate conditions.

The middle-aged woman described by Spillane (1959) was treated for alcoholic neuropathy with thiamine for five months before she developed megaloblastic anæmia and encephalopathy with a very abnormal EEG. Within a week of starting therapy with folic acid she had recovered from encephalopathy, her anæmia had improved, and the EEG had returned to normal.

Herbert's folate fast (1962) provided the second example. Living for nearly five months on a diet of thrice-boiled vegetables, thus restricting his daily intake of folate to less than 5 μg, he developed a megaloblastic marrow after 19 weeks. A little earlier, at fourteen weeks, he had found himself becoming forgetful, he had been unable to sleep and had been irritable. Both anæmia and mental symptoms cleared up within forty-eight hours of adding folic acid to his soup (Herbert 1962).

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