NEUROPATHY AND MALNUTRITION

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For more than half a century it has been realized that defective nutrition may be responsible for disorders of the nervous system. Some of the earliest observations were made by Japanese workers. Later contributions, coming largely from those parts of the world where populations are normally subject to a deficient diet, built up a somewhat hazy clinical picture of various nutritional nervous diseases. The discovery of the vitamins and in particular that of thiamin, which was lost in the polishing of rice, seemed to put the whole field on a rational basis. Experimental work on animals was largely concerned in the withholding of a moiety of food for a variable period of time and observing the effects. Needless to say, observers were often at variance with one another and the results were too eagerly applied to man. Often uncontrolled clinical therapeutic trials supported the seemingly simple vitamin deficiency hypothesis and effective therapy appeared to be at hand. However, there were always voices of criticism which are rapidly silenced if a true advance is made. Thiamin still remains the antineuritic vitamin in spite of the fact that its deprivation, if accompanied by that of carbohydrate, does not produce neuritis, and that its therapeutic use in most cases of polyneuritis is valueless. Walshe (1941) has vigorously indicated the fallacies of the thiamin deficiency hypothesis, however it is effective in beri-beri and Wernicke's encephalopathy when early cases are treated.

The recent war provided an unprecedented opportunity for observation of the effects of nutritional deficiency. Men of many races were subjected to years of defective nutrition and abnormal environmental conditions as prisoners of war. We would expect that the most highly differentiated cells of the organism would suffer most and so, in fact, we find that the nervous system shows the severest and commonest lesions. A mass of medical literature has followed. This is largely a compendium of facts concerning clinical conditions, statistics of incidence and time relations, with relatively less information concerning biochemical and pathological changes. We now have a clearer conception of the clinical syndromes occurring under these conditions but little positive

progress has been made in the elucidation of their aetiology.

There is no evidence to suggest that these neuropathies were infective or toxic in origin for they occur in widely separated parts of the world where defective diet was the only common factor. They are essentially of a degenerative or katabolic nature arising under conditions of deprivation. Numerous difficulties beset the investigator, for whilst prisoners of war provided so much clinical material there were numerous variable factors, e.g., the degree of deficiency, the altered balance of substances in the diet, the presence of concurrent illness especially of gastro-intestinal disease possibly leading to defective absorption and defective biosynthesis. Concerning the altered balance of the diet the deficiency is a selective reduction of proteins, fats and vitamins. The significant change is not only the absolute reduction but in the now disturbed relationship between the various food factors. For example, it is in relation to carbohydrate intake that deficiency of vitamin B must be considered.

It is difficult to assess the importance of gastro-intestinal infections and consequent defective absorption, such conditions were extremely common in the Far East. However it is probable that gastro-intestinal diseases precipitated an acute deficiency upon a pre-existing chronic one. The influence of an abnormal environment upon the psyche was perhaps not as great as might be anticipated. However failures of adaptation were manifest in various ways and were sometimes predisposing factors in the onset of the more tangible maladies.

The present state of knowledge of nutritional neuropathies does not justify a classification based on specific causes, a clinical one would seem to be of more value pending the elucidation of their aetiology. They may be divided into affections of the central nervous system and peripheral nervous system. The first group comprises Wernicke's encephalopathy, reticulobulbar neuritis, ataxic and spastic paraplegias, the second contains peripheral neuritis and various sensory disturbances. In all of these conditions almost any combination is possible, especially after prolonged

operation of the causative factors. Captivity amblyopia for example was seen both with peripheral neuritis and spastic paraplegia.

Mental illness occurred with little greater frequency than in a similar population under normal conditions, that this was so indicates man's well-known capacity for adaptation to a grossly abnormal environment. When one considers Claude Bernards 'fixite du milieu' being a condition of normal mental functioning it is perhaps surprising that the severe degrees of dysfunction were a rarity.

Wernicke's Encephalopathy

In this condition there is a vascular disorder of the mid-brain constantly affecting the corpora mammillaria and frequently the periventricular grey matter. It has been known for many years as an occasional event in the course of cachetic disease especially in association with carcinoma of the stomach, alcohol and hyperemesis gravidarum. The so-called breast milk intoxication of infants in Japan is a similar condition.

Numerous cases occurred amongst prisoners in the Far East. De Wardener and Lennox (1947) review 52 cases, the largest series yet recorded, they prefer to call the condition cerebral beri-beri. Dysentery and diarrhoea were the main precipitating cause. The first symptom is anorexia, vomiting and nystagmus follow within a short period and a progressive mental deterioration develops. Emotional changes, amnesias, disorientation and a clouding of consciousness are the chief features of the mental picture. Diplopia and nystagmus are the most constant features of the eye lesions. Most cases show added signs of neuritic beri-beri, whilst a few show some combination of other central nervous signs involving cranial nerves, the pyramidal tracts or posterior columns. Severe vomiting produces a vicious circle leading to further deprivation and heralds fatality.

Early treatment with large doses of parenteral thiamin offers the greatest chance of recovery. Symptoms begin to disappear within 48 hours in the reverse order of their appearance, but minor mental changes may persist for a few months. Some cases retain a Korsakoff, like psychosis. During treatment peripheral neuritis may become more evident and increase in carbohydrate in the diet may precipitate a relapse.

Thiamin deficiency is considered to play the major part in the causation of this encephalopathy by many authors. The evidence is as follows:—

1. It occurs under conditions of thamin deprivation.
2. In the Far East it occurred when classical

beri-beri was at its peak incidence (Burgess, 1946 and others).

3. Individual cases are often associated with signs of neuritic beri-beri.
4. There is a rise in fasting blood pyruvate (Wortis, *et al.*, 1942).
5. The dramatic effectiveness of therapy with vitamin B₁₂.

The above does no more than indicate that if thiamine deficiency plays some part, it is probably only operative in the presence of a high carbohydrate diet. It does not occur in uncomplicated starvation, in anorexia nervosa for example, and seems to be an essentially acute phenomenon depending on a sudden deprivation occurring in the course of a longer standing one.

Various states of stupor and coma have been attributed to deprivation of other essential substances. Encephalopathy has occurred in association with pellagra and acute complete nicotinic acid deficiency has been considered the cause. Sydenstricker *et al.* (1939) treated cases successfully with nicotinic acid and Jolliffe, Bowman, Rosenblum and Fein (1940) reporting 150 so-called cases of nicotinic acid deficiency encephalopathy found the lowest mortality in those treated with nicotinic acid.

Nutritional Retrobulbar Neuritis

As there is no proof of a neuritis many authors prefer the term 'captive amblyopia.' Before the recent war many cases of retrobulbar neuritis were believed to be due to nutritional disturbance were reported. Fifty years ago the Japanese described cases of amblyopia occurring in association with beriberi. In 1911 Stannus recognized its occasional association with pellagra. Since that time others have found similar visual disturbances with a syndrome considered to be due to hyporiboflavinosis occurring in the tropics. It has also been found in hyperemesis gravidarum (Ballantyne, 1941) and with pernicious anaemia (Cohen 1936).

In World War II retrobulbar neuritis was frequent occurrence in prisoners of war. There was a general tendency for it to appear later than beri-beri, usually after four months and commonly in one year. In some cases it was the only sign of disease, in others there was an association with any one of the other nutritional neuropathies. The onset may be sudden or more frequently an insidious deterioration in visual acuity. Complete amaurosis is, however, rare and the condition appears to be self limiting. Photophobia and unusual sensations in the eyes are common early symptoms in the more acute cases. On examination visual acuity is rarely below 6/60, and concentric contraction of the visual fields is common.

Central scotomata are frequently present but more difficult to demonstrate. The ophthalmoscopic findings are variable and bear little relation to the degree of lost function. Temporal pallor is extremely common. Deepening of the optic cup, macular degeneration and obliterative arterial changes have been observed. It must be emphasized that some cases showing the grossest deterioration of function may show little deviation from the normal variation in the fundus appearances.

Treatment is directed to an all-round increase in the diet particularly of first-class animal protein and vitamins of the B group. Response is not dramatic and improvement does not seem to be enhanced by the use of riboflavine which has been considered to be the responsible deficient factor. The condition tends to recover but may remain subnormal for an indefinite period. Twenty Indian soldiers, who were known to have neuropathy during captivity, were examined by the author one year after their release. Seventeen of these had some loss of visual acuity, nine showed definite temporal pallor, eight showed some contraction of their fields. Defective night vision was the commonest complaint among them, most observers of European prisoners consider this to be rare.

The following evidence suggests that hyporiboflavinosis may play some part in the aetiology :—

1. Its association with other conditions thought to be due to lack of riboflavine, namely stomatitis, glossitis, scrotum dermatitis and keratitis.
2. Its appearance with these conditions when the diet riboflavine levels were low.
3. Tendency for a diminished incidence when riboflavine levels were higher.
4. An increase in the limbus vessels in 96 per cent. (Ridley), although this finding has not been confirmed by some other workers.

The facts that response to riboflavine therapy is not dramatic and that deterioration sometimes occurs when the diet is increased are against the hypo-riboflavine hypothesis. The aetiology remains obscure for the present. It may be that individual susceptibility is the determining factor.

Paraplegias

Many cases of degeneration of the long tracts of the spinal cord were encountered amongst prisoners. The cases fall mainly into two groups, those with signs of pyramidal tract degeneration and those with signs of posterior column disease. A few cases showed signs of both lesions and many were associated with retrobulbar neuritis.

Cases of spastic paraplegia were rare. The onset is acute or insidious. Some appear to be self

limiting at any stage of severity, others end fatally. An improvement in the nutritional state may lead to improvement, this is probably due to the recovery of coexisting peripheral neuritis.

Ataxias without signs of pyramidal tract degeneration are far more common. The onset is mostly insidious. A loss of vibration sense in the lower limbs is an almost constant finding. The severer cases show a gross ataxia with loss of position sense and frequently added signs of a peripheral neuritis with weakness and wasting of muscles. A reversal of the state of nutrition leads to considerable functional recovery but some loss of vibration and joint sense often remains. The aetiology is obscure apart from the association with gross nutritional deficiency. The following illustrative case showed both types of cord lesion :—

Lieutenant H. was taken prisoner in Malaya in February, 1942. In October he noticed difficulty in lifting his legs and poor vision. He was admitted to hospital and his vision continued to deteriorate for two months until he was unable to read. By this time he was unable to walk. In February, 1943, he received Marmite and all symptoms began to improve. On release he was found to have slight loss of visual acuity, a moderate spastic paraplegia and signs of slight posterior column degeneration. When last seen one year after his release in India he had a typical spastic gait with exaggerated deep reflexes and extensor plantar responses. There was no sensory change except for loss of vibration sense at the ankles. He complained of poor night vision. Routine investigations were negative.

Peripheral Neuritis

Neuritic beri-beri was the most common form of nutritional neuropathy seen among prisoners during the war. In this form neuritis occurred soon after the start of captivity when thiamin intake was below the minimum daily requirement of 3 mgms. 1,000 non-fat-calories. It is interesting to note that the earliest cases occurring some four weeks after capture were in alcohol addicts. After longer periods of malnutrition peripheral neuritis appeared in combination with other neuropathies and later with famine oedema.

The clinical picture shows every degree of severity, from the mild cases with only subjective findings to those with complete loss of limb function. The onset is often heralded by pains in the feet and claudication. The lower limbs are most frequently affected. Muscle power is lost, wasting and the diminution of deep reflexes is progressive. There is a variable patchy sensory loss. This condition is associated with an affection of the heart manifest in tachycardia and enlargement. Treat-

ment is by complete rest and general improvement in the diet with additional thiamine. Here again an increase in the carbohydrate intake may cause an exacerbation of the condition. There is a relationship between the aetiology of peripheral neuritis and Wernicke's encephalopathy, probably the operative factors are qualitatively similar but different in time and intensity. In both, thiamine deficiency is significant in its relation to carbohydrate intake rather than in its direct effect upon the nervous system. A disturbance of the carbohydrate enzyme system with a rise in blood pyruvate has been demonstrated in arsenical neuritis. It is possible that this disorder of metabolism is common to the various so-called causes of peripheral neuritis.

The common syndrome of painful feet amongst prisoners of war may be due to disturbed function of the peripheral nerves but objective neurological signs are slight and variable. The condition has not, therefore, been discussed in this review.

The exact aetiology of neuropathies accompanying malnutrition remains obscure for the present. Given a state of severe deficiency the clinical syndrome resulting probably depends not only upon lack of specific substances but upon the more intangible factors of individual susceptibility, cell vulnerability and disturbed biosynthesis. It is easier to search for exogenous causes than endogenous ones.

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LAY CLINICIANS

No. 8

Often when reading a book or play one comes across an excellent description of some disease. Such accounts are always of interest to the doctor and they often show surprisingly accurate powers of observation and clinical acumen. We hope to print some of these 'case records' from time to time and for those who would like to try their hand at naming the author, this information will be given at the end of the extract.

'There had been this apparent quiet for half an hour, and Dorothea had not looked away from her own table, when she heard a loud bang of a book on the floor, and turning quickly she saw Mr. Casanbon on the library steps clinging forward as if he were in some bodily distress. She started up and bounded towards him in an instant; he was evidently in great straits for breath. Jumping on a stool she got close to his elbow and said with her whole soul melted in tender alarm:

"Can you lean on me, dear?"

'He was still for two or three minutes, which seemed endless to her, unable to speak or move, gasping for breath. When at last he descended the

three steps and fell backward in the large chair which Dorothea had drawn close to the foot of the ladder, he no longer gasped but seemed helpless and about to faint. Dorothea rang the bell violently, and presently Mr. Casanbon was helped to the couch; he did not faint, and was gradually reviving, when Sir James Chettam came in, having been met in the hall with the news that Mr. Casanbon had "had a fit in the library."

Mr. Casanbon had been overtaken by a coronary thrombosis and this account, as perhaps Dorothea's action suggests, is from a woman's pen. The book is 'Middlemarch' by George Eliot.