VITAMIN B DEFICIENCY AND THE PSYCHOSES: CLINICAL ASPECTS.*

By S. W. HARDWICK, M.D.Lond., M.R.C.P., D.P.M.,
Deputy Medical Superintendent, West Park Hospital, Epsom.

IN 1943 I published a paper on pellagra, in which I described in summary form twelve clinical cases from amongst patients with a psychosis of long standing at West Park Hospital. I also referred briefly to two other cases seen at the observation unit at St. Pancras Hospital, one of whom died shortly after admission, the other being subsequently discharged recovered from West Park. Since then I have encountered from time to time further cases, both amongst the West Park patients and those of recent admission to the observation unit. The diagnosis in each instance was clinical, being based on the well-known symptomatology of symmetrical dermatitis, glossitis (and often stomatitis), malnutrition and, as a rule, diarrhoea. The frequent association of malnutrition with mental disease led one to suspect that milder vitamin-deficient states, i.e. intermediate between frank pellagra and healthy nutrition, existed. I think that our clinical observations, together with subsequent research along biochemical lines, go to support this. If one adds to the foregoing the major and minor B1 deficiency states, one is forced to the conclusion that one is not dealing with academic rarities, but with a practical problem of interest to psychiatrist, physician and dietician. Moreover, recent research has yielded us powerful therapeutic weapons, such as nicotinic acid, aneurin and riboflavine, which, with certain reservations, have a specific curative effect in the corresponding deficiency conditions.

It is not my purpose to enter into the biochemical problems involved in deficiency states, but I must here mention that important and fruitful investigations have been carried out in the last few years by Prof. P. Ellinger of the Lister Institute and Mr. R. Benesch, late Maudsley Research Fellow, who utilized some of our West Park cases. The biochemical diagnosis of nicotinamide deficiency has proved a difficult task, but the nicotinamide methochloride elimination test recently described by these authors may well have surmounted a formidable obstacle, and eventually lead to earlier and more exact diagnosis.

Firstly, I shall relate briefly the histories of two recent cases of pellagra. The first patient, a female, aged 67, was admitted to West Park Hospital in July, 1945, in an agitated, remorseful and depressed condition. Her weight was 6 st. 3 lb. (normal weight 8 st.). Over her forehead and outer parts of the cheeks and over the back of the forearms and shoulders there was scaly, desquamating skin. Tongue was smooth, but not atrophic. No diarrhoea. The average 24-hourly urinary nicotinamide methochloride estimated by Prof.

* Read at the Quarterly Meeting of the Royal Medico-Psychological Association held on February 14, 1946, at 11, Chandos Street, W. 1.

Ellinger was of the low value of 1·31 mgm. She was treated with a liberal diet and large doses of nicotinamide. The pellagrous rash took about three weeks to disappear, whilst the patient remained severely depressed for a further 3–4 weeks before she began to improve. She had completely recovered from her depression by October, was thereupon discharged, and has since maintained good health and regained her usual weight. This patient had had three depressive breakdowns in the past, each clearly following a precipitating factor, the present appearing to have been initiated by the death of her sister. During the six months prior to admission to hospital she had neglected herself, given her meat rations away, and forgotten to get her meals; and she admitted retrospectively, "I lived mostly on bread, margarine and potatoes."

My second case is a Jewess, aged 62, who was seen by Dr. Caldwell at Bethnal Green Hospital in consultation. She was admitted there in 1945 for investigation, as she was convinced she had a cancer. The history showed that she had been obsessed with this idea and depressed in consequence for nine months. During the last 3–4 months she had lost much weight, as she had subsisted mainly on bread and butter and cups of tea. She had suffered from occasional diarrhoea. Her psychiatric state was one of wailing melancholia, coupled with some degree of confusion. Physically she presented an acute glossitis, had a pellagrous rash over the exposed parts of her skin, and weighed 7 st. 1 lb. (normal weight 10 st.). She was treated with large doses of nicotinamide and vitamin B1 and needed patient feeding. In two months she was free of pellagrous signs, and her agitation was much less pronounced. E.C.T. was not given as she suffered from severe essential hypertension (B.P. 240/145). She is still in hospital, disgruntled and mildly depressed, but she works hard, and no longer expresses any delusional ideas.

These two cases illustrate the production of pellagra by grossly inadequate dietaries over comparatively long periods. One has to bear in mind, however, the recent emphasis on intestinal bacterial synthesis of vitamins, including nicotinamide (*vide* Ellinger, Benesch and Kay), and I suggest that there is possibly an interference with the normal synthesis in certain psychoses. Thus, depressive states may be accompanied by "functional" disorder in the gastro-intestinal tract, exhibiting itself in constipation and unpleasant subjective disturbances, which the patient often misinterprets as a blockage, etc. A further question arises, viz. how much of the psychiatric symptomatology is attributable to the pellagra; or, to what degree does the latter aggravate the mental signs? In the present state of our knowledge I am inclined to the view that these questions cannot be faithfully answered. However, Spies and his co-workers in America found varying degrees of mental disorder and disfunction in their series of pellagrins, and described amelioration with nicotinic acid. In the two cases I have described, specific therapy relieved the deficiency syndrome, removing an important factor in the total illness, and this may thereby—speaking figuratively—have broken a vicious circle.

I shall next relate briefly the case-history of a pellagrin, a patient at West Park with a long-standing mental illness. A. M. J—, now aged 55, was first admitted to hospital in 1923. She is an interesting schizophrenic, who has had numerous recurrent phases of stupor. Her case was included in the series of

periodic catatonic patients which Dr. A. Stokes and I described a few years back. The weight record of this patient shows marked fluctuations: in 1923, 7 st. 3 lb; in December, 1933, 10 st. On readmission in December, 1939, 8 st. 4 lb., falling notably during a stuporose phase in October, 1941, to less than 6 st.; April, 1942, 9 st. In August, 1942, she contracted Flexner's dysentery during an epidemic at the hospital and was treated with sulphaguanidine. In October she had relapsed into a resistive stupor and looked ill. During early 1943 she had relaxed stools from time to time, and in September she developed a typical pellagrous eruption over the back of the forearms, hands and neck. This responded dramatically to nicotinamide. In April, 1944, during another stupor phase she had a bout of loose stools, and shortly afterwards developed an acute dermatitis over the lower half of the face. A little later marked glossitis was noted. Weight 6 st. 2 lb. Subcutaneous nicotinamide relieved the glossitis and dermatitis. This patient was also amongst those investigated from the chemical side, the average 24-hourly urinary nicotinamide methochloride excretion being only 1.45 mgm. during the relapse of pellagra in 1944. The record of this patient contains no suggestion of overt pellagra before she contracted dysentery, despite previous malnutrition associated with the stupor phases. It seems likely that the disturbance caused by dysenteric infection (and possibly by sulphaguanidine medication) might have interfered with the normal production of nicotinamide, etc., by the bacterial flora, and that when the intake by mouth was reduced, a pellagrous state was precipitated. Ellinger, Benesch and others have referred to the probable relationship between dysentery and the sterilizing sulphonamides and pellagra. There is one other point of importance: the reduction of bacterially produced nicotinamide may persist for a considerable period—perhaps indefinitely. At any rate, the clinical history and the chemical findings of the case I have quoted suggest this.

Apart from the support from the biochemical side of nicotinamide deficiency in our midst, there is a further important angle of approach, viz. the pathological. I think it is not generally realized that pellagra is associated with a fairly characteristic histological picture, and I am indebted here to Dr. A. Meyer of the London County Council Central Pathological Laboratory for the following short summary: "Various changes have been reported in the C.N.S. of patients dying from pellagra. Of these, retrograde degeneration of large nerve cells is the most important from the diagnostic point of view. Other pathological changes are hyaline degeneration of capillaries and fatty degeneration. Sclerosis of the lateral and/or posterior tracts of the spinal cord is frequent but not obligatory. It is more in the nature of a Wallerian degeneration than of the patchy honeycombed appearance of subacute combined degeneration. Affection of the peripheral nerves is inconstant."

Dr. Meyer and I have up to date collected 18 cases, chiefly from mental hospitals, of histologically verified pellagra. Ten of these were from West Park. A definite clinical diagnosis was only made in 9 out of the total of 18. Five of the 10 West Park cases only were diagnosed on clinical grounds as pellagra, although in 4 others this was suspected. Further discussion based on these findings is beyond the scope of this paper, but I think they do

shed light on some of the hitherto inexplicable illnesses encountered in psychiatric practice. Moreover, I am of the opinion that further analysis of our data will support the contention of some authorities that a pellagrin may show no acute pellagrous manifestations, i.e. the condition may be pellagra *sine* pellagra. One is familiar with the occasional problem of a young schizophrenic patient who comes to the autopsy table in a wasted state, with little or no subcutaneous fat, and with shrivelled, atrophic hypoplastic organs. He, or she may be "signed up" as "C.V.D.," or perhaps "exhaustion from excitement in dementia praecox." I submit that the cause of death in these patients is much more likely to be vitamin deficiency—perhaps some fall into the category of "malignant malnutrition," recently described.

The next cases I have to describe I saw in consultation with Dr. Eli Davis at St. Andrew's Hospital early in 1944. The first patient, a female, aged 58, gave a history of bronchitis two months previously and influenza three weeks before admission. She had lost weight during the past year and particularly during the last month. She felt too weak bodily to carry on with her job, and admitted that although when well she enjoyed food of all kinds, except green vegetables, she had eaten little recently. Physically she was pale, looked older than her age and had signs of bronchitis. The tongue had a raw, beefsteak-like appearance, whilst the lips were redder than usual, although there was no subjective complaint. She was mildly depressed, apprehensive, lacking in confidence, hypochondriacal, with a tendency to fixation on her bowels (was constipated). She had been upset by a recent recrudescence in enemy air activity. She was evacuated to Claybury E.M.S. hospital, where she was treated with nicotinic acid and iron, and was discharged therefrom to her home a few weeks later, apparently well.

The second patient was an elderly woman, aged 77, who had lost her husband three months previously. It was somewhat difficult to obtain a satisfactory history, but the impression I had was that she had been depressed during this period, and had neglected herself, particularly with regard to her food—making do with bread and butter, cups of tea and odd scraps. The physical signs indicating vitamin deficiency were interesting as, apart from rawness over the anterior half of the tongue, due to denudation of papillae, she presented an angular stomatitis (deep linear fissures at both angles of the mouth with a greyish sloughing base). Moreover there was bilateral circumcorneal injection, and with the aid of a hand lens Dr. Davis and I thought we saw one or two vessels actually running on to the corneal margin in the left eye. From the psychiatric point of view there were indications of mild senile dementia coupled with some confusion. On one occasion she had said her food was being poisoned. The patient was treated with large doses of nicotinic acid and riboflavin, and departed from hospital improved on 10.v.44. A barium meal taken before she left hospital excluded carcinoma of the stomach, which had been suspected on her admission.

Commenting on these two cases, the mental picture in the first is similar to that described in pellagrins by Spies and his co-workers. In the second case one might conjecture that a confusional syndrome was probably averted by prompt specific therapy. Neither case could be regarded as suffering from

pellagra. Probably the first was the subject of a nicotinic acid deficiency, whilst the other showed combined lack of nicotinic acid and riboflavine.

Thus far I have painted too rosy a picture of vitamin deficiency states in that I have selected examples where there was not only response to specific therapy measurable in physical signs, but also improvement in the mental state. My impression—from the very considerable material we have collected —is that there is a larger group of cases with evidence of nicotinamide deficiency showing varying responses to therapy. A few cases appear to show little or no response, i.e. as regards the physical and mental picture; others show amelioration in the physical signs, together with either no change in the mental state, or at most, a clearing up of a confusional syndrome with the unmasking of some underlying psychosis and/or gross organic physical disease.

I have not sufficient time to deal with this problem, but will quote another case, in brief, as an illustration:

Patient L. N—, a female, aged 50, had been always delicate and nervous, reserved, unsociable. She was said to have been ill since 1919 with neurasthenia, arthritis, etc. An uncle and brother had both attempted suicide. Just before admission to the observation ward she had been up all night screaming, saying she could not sit, stand or walk. She accused her husband of ill-treating her, e.g. said he had broken her arm. She said her back was broken. Her husband reported that she had never eaten meat or green vegetables because of a long-standing dysphagia—living mainly on potatoes, bread, margarine and jam. She had taken very little nourishment for three weeks and had become very thin. She had been depressed, absent-minded and confused. At the observation ward significant physical findings were a dry ichthyotic skin, a smooth tongue, angular stomatitis and flat nails. Subjective dysphagia present. Her mental picture was one of agitation, restlessness and confusion, with superadded paranoid features. She was treated vigorously, with a full diet and nicotinic acid. The angular stomatitis cleared in 2–3 weeks, but glossitis was still present six weeks later. Considerable amelioration was noted in the psychiatric syndrome, particularly as regards the confusion. She died, however, two months after admission to the mental hospital, and at autopsy was found to have a carcinoma of the pancreas with metastases.

Most of the cases I have observed and diagnosed as nicotinic acid deficiency states present similar features, and have similar diagnostic criteria to those previously described by Sydenstricker and his colleagues. I have only rarely encountered cases resembling those described by Joliffe (viz. an encephalopathic syndrome consisting of stupor or clouded consciousness, together with cogwheel rigidities of the extremities and grasping and sucking reflexes). While Joliffe's clinical data are highly suggestive, I think further work along clinico-biochemical lines is indicated. I have, however, observed occasionally a dramatic response to nicotinamide therapy in patients with few or none of the usual physical signs. Recently I saw a young married woman, aged 18, who had a history of influenza three weeks prior to admission to hospital. The initial illness was associated with high fever, headache and drowsiness so that an encephalitis was suspected. She got up after a few days in bed, but neglected her young baby. Her expression became vapid, her voice changed; she made

silly mistakes and weird statements, e.g. that the sirens were less frequent now. She had taken food indifferently. In hospital she was in a euphoric, carefree, hypomanic-like state, but was also poorly oriented and confused. There were no gross physical signs beyond notching of the lateral border of the tongue and obvious generalized wasting (2 st.). She received nicotinamide subcutaneously, and improved dramatically in her mental state within a few days.

Unfortunately, mainly owing to war conditions, it was found impossible to carry out laboratory investigations into vitamin B1 deficiency states. Nevertheless, I have met with a number of cases, both at observation wards and in general hospitals, where the diagnosis of nutritional deficiency chiefly associated with vitamin B1 lack was justified on clinical grounds. The majority of these cases were alcoholics, but the accompanying psychosis was not always of a confusional pattern. In the non-alcoholic cases gross gastro-intestinal disorder was the rule. I shall confine myself to brief reports on three examples only, the first two of which are almost certainly examples of the Wernicke syndrome. There has been a rejuvenated interest in this syndrome recently following Alexander's work, where comparable lesions were found in pigeons fed on thiamine-free diets. Campbell and his co-workers have contributed notable papers on the subject, and Dr. Meyer's recent paper stimulates further interest, since he describes therein lesions in the anterior hypothalamus, which were probably associated with manic-like symptoms.

The first case, F. P—, a male, aged 66, was admitted to St. Mary Abbotts Hospital on 2.viii.43 complaining of "hearing voices." He was reputed to have imbibed quantities of "red biddy" in the past, and gave as his recent alcoholic consumption at least four pots of ale daily. Recently he had been living on his own and neglecting himself regarding food. He was hallucinated for sight, seeing the faces of men and women, and he expressed grandiose delusional ideas—for example said he had a £100,000 bank note in the Bank of England. At the observation ward he was disoriented, confused, hallucinated for sight and hearing, suggestible and confabulating. Physically there was an old abdominal operation scar (? perforated D.U. in past), absent knee-jerks and ankle-jerks, tender calves, and some sensory changes over the lower limbs. Dysarthria present. No tremor of tongue or hands. The pupils were fixed to light and the convergence reaction was poor, but there was no external ophthalmoplegia. Blood and C.S.F. negative. He received aneurin 200 mgm. three times daily parentally and 50 mgm. nicotinic acid four times daily. Ten days later the psychotic features appeared to have cleared completely—no evidence of hallucinosis, no gross confusion and no confabulation. He was, however, still euphoric and boastful. He stated that before his illness he had been practically starving. The pupils now appeared to give reaction to light more readily. He was transferred back to the general hospital. Before his discharge home the tendon reflexes in the lower limbs were showing signs of recovery.

The next case presents features which contrast sharply with the former. E. H—, a male, aged 52, said to be a hard-working and successful publicity agent, had drunk heavily for years (10 pints daily). He had had no previous

breakdown. Just before admission he had eaten little and irregularly, and suffered from a succession of colds. At the observation ward he was somewhat muddled, not accurately oriented in time, exhibited mild memory defects, and was lacking in spontaneous conversation. He was elated at periods and depressed at others. Physically he looked unwell, with unequal irregular pupils, which gave a sluggish light-reaction; he was unsteady on his feet. No other gross finding. A week after admission he seemed much worse in his general physical and mental states. His memory had deteriorated in that he forgot recent events; he was reported by the nurse to be continually offering to give away large sums of money. Two days later he had sunk into a drowsy semi-stuporose condition, was incontinent and needed hand-feeding. Physical examination revealed some weakness of conjugate lateral movements, but there was no nystagmus. Knee-jerks and ankle-jerks were very brisk. There was questionable weakness of the right upper limb, and questionable diminution of sensation to touch and pain over all four limbs. Grasping reflexes were positive. Treatment with large doses of aneurin (50 mgm. 4-hourly by injection) was then commenced. A fortnight later, when at West Park, he had emerged partially from his stupor into a Korsakow-like state, in which he was completely disoriented for time and place, imagining he was at his home, and apologizing to the doctor for his inability to keep an appointment that day. Grasping and sucking reflexes were present and there was probably some glossitis. Parenteral multiple vitamin therapy was instituted (aneurin, riboflavine and nicotinic acid). One month later the patient's mental state had cleared and his physical condition was rapidly improving. Soon afterwards he was discharged from hospital care, appearing normal both mentally and physically.

The last case was that of a man, aged 61, who had had a gastric ulcer for years—had perforated nine years previously. A recrudescence of symptoms occurred six months before admission to general hospital. For three months he had taken slops only, and little at that. Ten days before admission he was restless, depressed, said he had muddled things up. He was said to drink moderately—one or two pints of beer daily. In hospital a barium meal showed a chronic pre-pyloric gastric ulcer, which gastroscopy confirmed. He was transfused before operation because of anaemia due to haemorrhagic leaking, and given prophylactic thiamine. After partial gastrectomy he was placed on the usual post-gastrectomy routine—small drinks of water, gradually increasing in amount, etc. Six days after operation he developed a psychosis—became restless, and said that he was being tortured and killed. When I saw him he had signs of peripheral neuritis in all four limbs—loss of power, particularly at the wrists and ankles, reduced knee-jerks and absent ankle-jerks, and reduction to vibration and pain sensation. There were no signs of ophthalmoplegia, nystagmus, etc. Probably there was collapse of the left lower lobe. Psychiatrically, he was hallucinated for hearing, saying that he was being hounded by people—being called names, and accused of such things as speaking German. He was treated with large doses of thiamine intravenously and subcutaneously. Four days later he was reported more amenable and had been moved back to the open dormitory. He was still hallucinated and deluded—said he had heard gramophone records representing him to be Hitler singing in opera.

Three weeks later the hallucinosis had apparently gone, but the patient still exhibited paranoid traits towards other patients. There was considerable improvement in the neuropathy—the tendon reflexes could now be elicited and there was improvement in power in the hands. Residual sensory disturbances in the lower limbs were still detected. The patient departed for his home shortly after this.

I think these cases provide interesting material for comparison, but I will only draw attention to one or two points. The first patient with a confusional-hallucinatory syndrome and with features reminiscent of G.P.I. presented signs of peripheral neuritis, and of a midbrain lesion. Moreover, he appeared to respond to thiamine and nicotinic acid. The second case, who passed from a confusional state into increasing stupor, also had evidence of a progressive mesencephalic lesion. Thiamine therapy alone appeared to check and ameliorate these conditions up to a point. The addition of nicotinic acid and riboflavine later may have relieved the residual signs—in fact, the patient's state at this time approximated closely to the encephalopathic syndrome described by Joliffe. The third case, which appeared to develop gross peripheral neuritis following a gastrectomy, had no physical signs suggesting a cerebral lesion, but nevertheless developed an acute psychosis, which responded *pari passu* with his physical improvement.

It is not my intention to discuss Korsakow's psychosis and delirium tremens. Peripheral neuritis seen in various alcoholic states is generally accepted as being due to B_1 lack. It may well be that centrally placed lesions may explain the psychosis in the Korsakow syndrome, and that the variable results of B_1 therapy are related to the severity and reversibility of these lesions. I am aware that there is no unanimity of opinion concerning this subject and the role of vitamins in delirium tremens.

It is impossible to cover comprehensively even major aspects of vitamin deficiency in relation to the psychoses in the short time at our disposal. The foregoing cases described were selected deliberately to illustrate points in etiology, symptomatology, etc. Moreover, although nicotinamide and thiamine deficiencies are well recognized and exemplified in our material, one has to remember that other fractions of the B complex, like pyridoxine and pantothenic acid, may be associated with syndromes yet to be described. No mention has been made of vitamins A, C, D, etc., since, so far as we are aware, they are not directly related to disease of the C.N.S.

In conclusion the following remarks will perhaps serve the purpose of a summary to our papers and indicate some present trends of opinion :

(1) Pellagra may accompany and complicate a chronic psychosis. Various factors probably operate in its production, such as (*a*) faulty feeding—inadequate vitamin intake in the food ; (*b*) diminished utilization of bacterially synthesized vitamin—itself due to destruction of synthesized vitamin, non-production, or malabsorption, e.g. from a diseased mucous membrane ; (*c*) liver disease ; and (*d*) possibly non-utilization of available vitamins by the body cells.

(2) Severe vitamin B deficiency may cause death. Death from " exhaustion of acute mania," death in malnourished chronic psychotics, death asso-

https://doi.org/10.1192/bjp.92.387.310 Published online by Cambridge University Press

ciated with certain gastro-intestinal disorders may have its explanation on such a basis.

(3) Pellagra and nicotinamide deficiency states may accompany and complicate an acute psychosis. There is evidence that deficiency itself produces mental symptoms which are explicable on the basis of a biochemical lesion in certain parts of the C.N.S. No serious attempt has been made with our material to correlate the pattern of the psychosis with the deficiency condition. Depressive, manic and paranoid reactions have been observed—similar to the experiences of others. Varying degrees of confusion are common in our experience. Probably a proportion of cases previously diagnosed as toxic-exhaustive psychoses are due to acute or subacute vitamin deficiency.

(4) Wernicke's encephalopathy, due to vitamin B1 lack, is likely to be diagnosed more frequently when a more thorough analysis of its symptomatology and its variants has been established. The relationship between the Wernicke syndrome and organic disease of the upper gastro-intestinal tract is striking, and suggests destruction of normally available vitamin or non-absorption. In contrast I suggest that disease of the lower regions of the small gut is more likely to be complicated by nicotinamide deficiency states.

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