influences. These observations therefore call for an establishment of a suitable approach; hence the creation of a therapeutic social unit in the form of a village community which offers familial care of the mentally ill.

Reactive depressions are rare, and endogenous depressions are rarely seen in hospitals or native treatment centres, in contrast to mania. Cultural factors seem not only to play a prominent part in the clinical manifestation of depressions but give an apparent preponderance of excitement whether in association with schizophrenic and manic depressive illnesses or with some ill-defined clinical condition.

From the point of view of research, what is more urgently needed is further work towards the establishment of a more complete study of the complex psychological reactions of the African and more refined analysis of the cultural institutions, of the critical analysis of the clinical data obtained, of the psychological implications of the changes in his cerebral structure and function, of the technical procedures involved in making these observations, and the statistical examination of the evidence so acquired, with the object of facilitating the task of comparison and, ultimately, of causal explanation.

I acknowledge with thanks the advice and guidance willingly given by Professor Aubrey Lewis, Dr. E. Stengel, and Dr. D. L. Davies, and for their encouragement and considerable interest in my work in Nigeria. I also thank Dr. T. H. L. Montgomery, Director of Medical Services, Western Nigeria, for permission to use the clinical material of the Aro Hospital, Abeokuta, and for his encouragement and interest. Dr. J. C. Carothers visited Nigeria during the preparation of this article, and I thank him for many helpful suggestions and, more particularly, for offering to write an introduction to it The staff of this hospital, especially the Occupational Therapy Centre, have co-operated fully in spite of our present difficulties.

REFERENCES

Ackerknecht, E. H (1943). *Bull. Hist. Med.*, **14**, 30.
Aubin, H. (1939). *Ann. méd. Psychol.*, **97**, 1.
Carothers, J. C. (1947). *J. ment. Sci.*, **93**, 548.
—— (1951). Ibid., **97**, 12.
—— (1953). *The African Mind in Health and Disease.* World Health Organization Monograph No. 17. Geneva.
Cooper, J. M. (1933). *Prim. Man*, **6**, 20.
—— (1934). *J. abnorm. soc. Psychol.*, **29**, 10.
Coriat, I. H. (1915-16). Ibid., **10**, 201.
Demerath, N. J. (1942). *Amer. J. Psychiat.*, **98**, 703.
Green, E. M. (1917). *Amer. J. Insan.*, **73**, 619.
Hallowell, A. I. (1938). *J. soc. Psychol.*, **9**, 25.
Henderson, D. K. (1920). *J. ment. Sci.*, **66**, 274.
Kempf, E. J. (1931). *Med. J. Rec.*, **133**, 22.
Klineberg, O. (1940). *Social Psychology, N.Y.*, p. 510.
Lambo, T. A. (1955). *J. ment. Sci.*, **101**, 239.
Laubscher, B. J. F. (1937). *Sex, Custom, and Psychopathology.* London.
Lewis, J. H. (1942). *The Biology of the Negro.* Chicago.
Mair, H. (1953). In *Survey of African Marriage and Family Life*, edited by A. Phillips. Oxford Univ. Press, London.
Musgrave, W. E. (1921). *Arch. Neurol. Psychiat.*, **5**, 398.
Oesterreicher, W. (1951). *Folia psychiat. (Amst.)*, **54**, 431.
O'Malley, M. (1914). *Amer. J. Insan.*, **71**, 309.
Opler, M. E. (1936). *Amer. J. Psychiat.*, **92**, 1371.
Phillips, A. (1953). *Survey of African Marriage and Family Life.* Oxford Univ. Press, London.
Seligman, C. G. (1929). *Brit. J. med. Physiol.*, **9**, 187.
Tooth, G. (1950). Studies in Mental Illness in the Gold Coast. H.M.S.O. Colonial Res. Publ. No. 6, London.
Yap, P. M. (1951). *J. ment. Sci.*, **97**, 313.

The report of proceedings of the Scottish Society of the History of Medicine for the session 1955–6 is of wider interest than its title suggests. It includes a summary of important medico-historical publications and events during the year. It also contains the full text of the papers read before the society during the session—namely, "Some Peeblesshire Doctors, with Special Reference to Mungo Park," by the Rev. Dr. A. M. Gillespie; "John Goodsir," by Dr. H. W. Y. Taylor; and "The Maladies of Mary Queen of Scots and her Husbands," by Dr. M. H. Armstrong, who suggests that Mary was a hysterical psychopath. From January next the proceedings of the Society will be recorded in the new British quarterly *Medical History.*

CEREBRAL MANIFESTATIONS OF VITAMIN-B_{12} DEFICIENCY*

BY

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The changes in the nervous system now known to be due to vitamin-B_{12} deficiency occur in the spinal cord, peripheral nerves, and brain. By long usage the name of subacute combined degeneration has been applied to these nervous lesions, but, as suggested by Jewesbury (1954), it would now be more satisfactory to use the comprehensive term "vitamin-B_{12} deficiency" with the appropriate qualification of "megaloblastic anaemia" and/or "myelopathy," "neuropathy," or "encephalopathy."

The brain lesions which form part of the neurological syndrome of vitamin-B_{12} deficiency appear first to have been described by Preobrajensky in 1902. Thomas Addison, in his orginal classical description of pernicious anaemia, said "the mind occasionally wanders," but the cerebral symptoms are still much less familiar than those due to the spinal and peripheral nerve lesions, although they are not of infrequent occurrence. My object is to emphasize once again the importance of their early recognition and prompt treatment. The end-result of untreated cerebral lesions may be a severe dementia even more crippling than the paraplegia produced by the spinal lesions, and it may be completely irreversible when treatment is delayed by failure in diagnosis.

McAlpine (1929) said, "Mental changes occur not uncommonly in pernicious anaemia. They range from states of depression accompanied by loss of mental energy to definite psychoses. They, like the nervous symptoms, may precede the characteristic changes in the blood by many months. More frequent examination of the gastric contents and of the blood, especially for the presence of megalocytosis, is called for in primary neuroses and psychoses occurring after the age of 35, in view of the favourable results that may follow adequate treatment instituted at an early stage." This statement still holds true and needs no modification. It must be emphasized that the cerebral symptoms, like those due to lesions in the spinal cord, may precede the appearance of anaemia for long periods, sometimes for years, and that they may occur in the presence of a completely normal blood picture and bone marrow and even in the absence of spinal lesions. Greenfield and O'Flynn (1933) found that 14% of 45 patients with subacute combined degeneration of the spinal cord had normal peripheral blood counts, but there appear to be no similar statistics concerning the cerebral symptoms in relation to the blood picture, although Woltman (1924) states that 4% of 1,498 cases of pernicious anaemia had an "outspoken psychosis," while "35.2% showed lesser mental changes manifest even on casual observation."

Present Series

In a series of 25 cases of vitamin-B_{12}-deficiency syndrome with involvement of the nervous system seen in the past few years I have encountered 14 cases with well-marked

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cerebral symptoms. Signs of spinal or peripheral nerve involvement were present in all 14 cases, but in some these were very slight and detected only on careful examination. The ages of the patients ranged from 32 to 72 years; eight were 60 or older. The haemoglobin levels ranged from 32% to 105%, and in five cases were 70% or more. In one case the blood count and bone marrow were completely normal, but in all the others there was some degree of megaloblastic reaction in the marrow. A complete histamine-fast achlorhydria was present in every case.

The cerebral symptoms may be classified as mental and ophthalmological. The mental symptoms are extremely variable and include mild disorders of mood, mental slowness, memory defect which may be gross, confusion, severe agitation and depression, delusions and paranoid behaviour, visual and auditory hallucinations, urinary and faecal incontinence in the absence of overt spinal lesions, dysphasia, violent maniacal behaviour, and epilepsy. None of these symptoms is pathognomonic, and in the absence of anaemia or of spinal signs the diagnosis of vitamin-B_{12} deficiency may never be considered until the psychosis is far too advanced to respond to treatment.

The ocular disturbance usually consists of dimness of vision due to optic atrophy. Retinal haemorrhages have been described, but these are associated only with severe degrees of anaemia. Optic atrophy was first described as an initial symptom of nervous involvement by Cohen (1936), and again by Aldren Turner (1940). It is by no means dependent on the degree of anaemia, and vitamin-B_{12} deficiency should be considered as a possible cause of all obscure cases of optic atrophy. Benham (1951) has described the changes in the visual fields found in this type of optic atrophy and states that the defects consist of scotomata of centrocaecal type with varying degrees of peripheral contraction. He found optic atrophy in 5 out of a series of 112 cases of subacute combined degeneration. It is extremely rare for other types of ocular lesion to occur, but Turner (1940) mentions a case described by Guillain *et al.* (1938) in which bilateral primary optic atrophy was accompanied by external ophthalmoplegia and weakness of muscles supplied by the fifth cranial nerve. Anaemia did not occur until two years later.

The distribution of the symptoms in my 14 cases is shown in Table I.

TABLE I.—*Distribution of Symptoms*

Pronounced slowing of mental processes	14
Confusion and memory defect	14
Depression of varying degree	7
Delusions	5
Hallucinations, visual or auditory	3
Optic atrophy	3
Epilepsy	2
Dysphasia	2
Extreme agitation	1
Violent maniacal behaviour	1

In four cases the psychological symptoms had first appeared two, three, seven, and eight years before the onset of anaemia or other neurological signs, and in two cases courses of electric convulsion therapy had been given. It could of course be argued that the mental symptoms were due to causes other than vitamin-B_{12} deficiency. In all but two cases, however, the mental symptoms disappeared or were greatly improved after intensive treatment, and these two patients had been severely demented inmates of a mental hospital for several months before treatment was begun, their dementia having progressed slowly during periods of seven and eight years. There is evidence that the mental changes are specifically related to a disturbance of cerebral metabolism which is corrected by adequate treatment with vitamin B_{12}.

Scheinberg (1951) has estimated the cerebral blood flow and oxygen consumption by the nitrous oxide method of Kety and Schmidt in 16 patients with pernicious anaemia, and he states that the mental symptoms in these patients were related to a decrease in cerebral metabolism which was a result of the deficiency state and not of the anaemia. Scheinberg also found electroencephalographic abnormalities which improved after treatment. Other electroencephalographic studies showing gross abnormalities in pernicious anaemia have been published by Samson *et al.* (1952) and Walton *et al.* (1954). Walton and his colleagues found abnormalities consisting of diffuse slow-wave activity not only in cases of subacute combined degeneration but also in patients with no sign of neurological involvement. Furthermore, there was no correlation of the abnormalities with the haemoglobin levels or with age. The tracings tended to improve seven to ten days after treatment with vitamin B_{12}. Further evidence of a change in cerebral metabolism has been found by Earl *et al.* (1953), who estimated the blood pyruvate levels in patients with subacute combined degeneration at the time of giving 100 g. of glucose and 90 minutes after. They found that the pyruvate levels were higher in these patients than in normal controls, but when the estimations were repeated after two weeks' treatment normal values were obtained.

The salient clinical features of my 14 cases are given in Table II.

Diagnosis

The great difficulty in establishing the diagnosis of vitamin-B_{12} deficiency with involvement of the nervous system is the lack of correlation between the haematological and neurological manifestations. There is also a similar lack of correlation between the spinal and cerebral symptoms of the syndrome. Early diagnosis is essential if treatment is to be effective, for the reversibility of neurological symptoms is largely dependent on their duration. In these 14 cases the diagnosis was established by the presence of signs of spinal involvement or peripheral neuropathy, evidence of Addisonian anaemia in the blood count or bone marrow, and the presence of a histamine-fast achlorhydria in the gastric juice, which was a feature of every case. Of the simpler diagnostic features, achlorhydria is perhaps the most constant and reliable finding, but the deficiency may occur rarely in intestinal disorders such as steatorrhoea, when free hydrochloric acid may be present in the gastric juice. In one case the blood and bone marrow were normal, but the achlorhydria and a satisfactory response to treatment provided confirmation of the diagnosis, which was largely speculative. It is necessary for other diagnostic methods to be applied in these difficult cases with normal blood counts and bone marrow, and perhaps indefinite neurological signs. The following methods have recently been introduced.

1. *Estimation of Serum Vitamin B_{12}.*—The method described by Mollin and Ross (1953), using the specific effect of vitamin B_{12} on the growth of the alga *Euglena gracilis*, promises to be of great value. It was not used in any of the 14 cases in this series, but in a patient seen recently in a mental hospital with dementia and an ataxic paraplegia, and a normal blood picture and bone marrow, serum levels of 90 and 100 $\mu\mu$g. of vitamin B_{12} per ml. were found by Dr. G. I. M. Ross before treatment, and the response to large doses of the vitamin is so far highly satisfactory. This biological method of assay is likely to be the most useful accessory method of diagnosis, and its value and application are discussed by Victor and Lear (1956).

2. *Gastric biopsy* is said to be of value in cases in which the blood and bone marrow are normal. This is performed through a specially designed gastroscope, and, according to Doig *et al.* (1950), the appearance of the gastric mucosa, although not absolutely specific, will differentiate subacute combined degeneration from other forms of neuropathy associated with achlorhydria, such as alcoholic peripheral neuritis.

3. *Electroencephalography*, as mentioned above, may be of some assistance in establishing the diagnosis, although the abnormalities found are not specific. It was done in only one case (No. 3) in this series, and slight but definite abnormalities were found before treatment, although the diagnosis was not in doubt.

TABLE II.—*Clinical Data in 14 Cases of Vitamin-B_{12} Deficiency With Cerebral Symptoms*

Case No.	Age	Sex	R.B.C. × 10^6	Hb %	Colour Index	Achlorhydria	Spinal Symptoms and Signs	Cerebral Symptoms and Signs	Results of Treatment
1	51	M	5·2	105	0·9	+	Spastic paraplegia and posterior column changes of 4 years' duration	Slowing of cerebration and poor memory. Epilepsy, ? unrelated, for 20 years	Mentality normal. Considerable recovery in paraplegia
2	42	M	3·81	90	1·2	+	Gross ataxia and loss of posterior column sensation. Areflexia and paraesthesia in limbs	Severe depression, treated by E.C.T. 3 years before onset of spinal symptoms	Completely free of spinal symptoms and depression. Areflexia remains
3	34	M	2·91	73	1·26	+	Sensory loss and weakness in arms and legs for 18 months. Ataxia. Grey hair	Loss of memory, depression, and slow cerebration and speech	Mentally normal. Slight ataxia remains. Hair darker in colour
4	68	F	3·45	70	1·0	+	Paraesthesiae in hands and feet. Slight motor weakness in legs	Poor memory and slowing of cerebration	Good recovery from all symptoms
5	72	M	2·94	70	1·2	+	Minimal sensory loss in feet. Increased reflexes in arms and legs	Gross confusion and memory loss. Visual and auditory hallucinations	Complete recovery in 10 days. Onset during treatment of anaemia
6	62	F	3·1	68	1·09	+	Spastic paraplegia. Sensory loss, but impossible to estimate	Extremely dull and slow mentality	Moderate improvement in paraplegia. Mentality remains poor
7	55	F	2·3	61	1·32	+	Severe ataxia and paraplegia. Areflexia and peripheral sensory loss. Incontinence of urine	Delusions and disorientation. Noisy and restless. Gradual mental deterioration during 8 years	No improvement in mental state or paraplegia. Blood picture returned to normal. Death from pulmonary embolus. P.M.
8	48	M	2·02	49	1·21	+	Gross posterior column defect. Minimal pyramidal signs	Optic atrophy and concentric diminution of fields. Deterioration of personality. Occasional violence and hallucinations. Epilepsy	Optic atrophy remains, but otherwise complete recovery
9	60	F	2·27	48	1·06	+	Moderate paraplegia with posterior column loss	Bizarre somatic hallucinations. Disorientation and slow cerebration. Treated by E.C.T. 2 years before onset of anaemia	Mentally normal. Considerable recovery in paraplegia
10	60	F	1·4	46	1·5	+	Severe paraplegia, wasting and incontinence	Severe dementia of slow onset during 7 years before anaemia appeared. Frequent epilepsy. Optic atrophy	No improvement. Death from pneumonia. No P.M.
11	63	F	2·75	56	1·01	+	Spastic paraplegia with severe ataxia	Drowsy and semi-stuporous. Disorientation. Bilateral deafness	Mentally normal. Walks without assistance. Deafness unaltered
12	68	M	2·07	43	1·07	+	Ataxia, paraplegia, gross peripheral sensory loss. Unable to stand or walk	Severe memory loss and confusion. Optic atrophy and concentric contraction of fields	Good recovery from sensory loss. Some residual paraplegia. Memory and cerebration good. Vision remains poor
13	32	F	1·43	32	1·14	+	Extreme ataxia and moderate paraplegia	Severe agitation and depression. Tearful and frightened	Mental state much improved. Moderate paraplegia remains
14	64	M	1·4	32	1·45	+	Spastic paraplegia. Gross ataxia. Retention of urine	Severe confusion and memory defect. Lit pipe with £1 notes. Speech unintelligible	Complete recovery from mental symptoms and considerable recovery in paraplegia. Return of normal sphincter control

4. *Muscle biopsy*, preferably from the lower legs, is at present being studied as a diagnostic method by my colleague Dr. A. L. Woolf. He has found definite changes in the terminal fibrils of peripheral nerves stained vitally with methylene blue in cases of subacute combined degeneration with only minor neurological signs. These changes consist of "ballooning" of the myelin sheath very similar to that which is seen in sections of the spinal cord and brain, excessive branching of the terminal fibrils, and defective formation of the subneural apparatus. If these changes are eventually shown to be specific this may be a diagnostic procedure much easier of application than the complicated ones mentioned above.

The occasional difficulties in diagnosis are well illustrated by the following case histories.

Case 1

A man aged 51 was admitted to the Midland Centre for Neurosurgery on August 24, 1955, for investigation of weakness of the legs which had increased during the previous four years. The increase in weakness had been rapid during the past few weeks, and in addition slowness of speech and cerebration and poor memory had appeared. He had had infrequent epilepsy for the past 20 years, and for the past eight years had had pain in the mid-dorsal region since being struck a heavy blow by the end of a wire rope which broke during his work.

On examination the cranial nerves were normal. His speech and responses to questions were very slow and his memory was defective. There was no motor or sensory abnormality in the arms. The legs showed a mild spastic paraplegia with increased tendon jerks and extensor plantar responses. There was impairment of sensation to pinprick and light touch, and also to temperature up to the fourth dorsal level. Joint and position sense were grossly impaired in the feet and vibration sense was lost up to the pelvic brim. Romberg's sign was pronounced and his gait was very unsteady.

Radiography of the spine showed collapse of the vertebral bodies of D 4 and D 7 with pronounced wedging, but lumbar puncture revealed no spinal block and the C.S.F. was normal apart from a slight change in the middle zone of the colloidal gold curve. Myelography revealed no filling defect at any level of the vertebral column, in spite of the collapsed vertebral bodies. The blood picture was completely normal, the haemoglobin being 105%, and the bone marrow was also normal. The Wassermann reaction was negative. A histamine-fast achlorhydria was present.

A tentative diagnosis of vitamin-B_{12} deficiency with both spinal and cerebral changes was made, and after an initial dose of 100 μg. of cyanocobalamin ("cytamen") there was a rapid improvement in cerebration, followed later by a marked improvement in the ataxia and weakness of the legs. Some spasticity was still present after nine months, but the patient had returned to work and could walk for long distances and stand for long periods. Although it is improbable that his epilepsy is related to the deficiency, it is interesting that he has had no further fits during the nine months since leaving hospital. The mental changes in this patient were much more noticeable in retrospect after treatment.

Case 8

A man aged 48 was admitted to the Midland Centre for Neurosurgery on December 9, 1954. A gradual deterioration of personality had been noticed by his family during the previous 12 months. He had become irritable and complained of occipital headaches. Occasional vomiting occurred and sometimes the headaches were accompanied by a transient diplopia. Dimness of vision had slowly appeared. Three months before admission he had noticed soreness of the feet and calves and his gait had become unsteady. One month before admission he had had occasional incontinence of faeces and urine, and peculiar trance-like "absences" in which his arms moved in an incoordinate way. Three weeks before admission to the centre he was admitted to another hospital because of his disordered behaviour. He poured large amounts of salt, pepper, vinegar, and sugar on all his food, of whatever kind, and poured tea on the floor instead of into a cup. He was seen to have several epileptic attacks, and after these he became violent and maniacal for long periods and was given intramuscular paraldehyde, which later caused a large abscess in the left buttock. It was stated that a blood count done one month previously had shown no abnormality, the haemoglobin being 100%, but full details were not given.

When first seen he was wasted and cachectic and appeared to be anaemic. He answered questions lucidly, but was very slow in his replies. There was bilateral optic atrophy, with a visual acuity of 6/18 and some concentric contraction of the fields and slight enlargement of the blind spot, but other cranial nerves were normal. Motor power was weak in the arms, but co-ordination and sensation were normal. Both legs were oedematous and a spastic paraplegia with increased reflexes, a left extensor plantar response, and a doubtful right extensor response were present. There was no definite impairment of sensation to light touch or pinprick in the legs, but gross loss of position sense and vibration sense, and Romberg's sign, were present. The oedema was obviously due to a large abscess in the left buttock. He was found to have a macrocytic anaemia with a haemoglobin of 49% and a leucocytosis of 16,500 with 85% of polymorphs, but there was no pyrexia. At this time the tentative diagnosis was spinal and cerebral metastases, probably from a carcinoma of the stomach, as on December 14 a histamine-fast achlorhydria was found.

The abscess was drained and the pus gave a pure culture of *Cl. welchii*. Following the drainage of the abscess he developed visual and auditory hallucinations and was very violent. He then became semi-stuporous. He was given blood transfusions and large doses of vitamin B_{12}, and also chlortetracycline. By December 27 he had greatly improved. There was no mental confusion or detectable sensory disturbance in the legs and the haemoglobin had risen to 80%. He was discharged from hospital on January 15, 1955, and the neurological signs, apart from the optic atrophy, which was unchanged, consisted only of a slight spastic weakness of the legs, causing very little disability. He has since remained well on a dose of 500 μg. of cyanocobalamin monthly, and there has been no further mental disturbance.

Treatment

It is certain that much larger doses of vitamin B_{12} are needed for the treatment of neurological manifestations of deficiency than for the maintenance of a normal blood count, and, indeed, neurological symptoms may appear, as in Case 5, when the haematological response to treatment seems to be satisfactory. Infection also may cause a rapid evolution of neurological symptoms, as is shown by Case 8. An effective routine dosage of vitamin B_{12} for the treatment of spinal or cerebral manifestations of deficiency is an initial dose of 1,000 μg., followed by 500 μg. twice weekly for the first month and thereafter not less than 100 μg. weekly for the next six months. If monthly injections are given it is safer to use a large dose of 1,000 μg., as much of the vitamin is lost in the urine. If infection occurs it is advisable to increase the dose considerably. Oral preparations of intrinsic factor with vitamin B_{12} are still not fully evaluated and should not be used for the treatment of neurological symptoms. Liver preparations are obsolete, and, although they served a useful purpose before pure preparations of vitamin B_{12} were available, their therapeutic efficiency was very variable and unreliable.

Histopathology of the Cerebral Lesions

Many papers have described the spinal lesions of subacute combined degeneration since the first account by Lichtheim in 1887, and in the early part of this century there were several scattered references to the cerebral lesions, but in many of them the diagnostic criteria were inadequate by modern haematological criteria. It is probable that some of the lesions described, such as perivascular haemorrhages and changes in blood vessels, were due to anoxia associated with severe anaemia which may or may not have been truly Addisonian, rather than to a deficiency of vitamin B_{12}.

Adams and Kubik (1944) appear to have been the first authors definitely to state that the cerebral lesions are essentially the same as those found in the spinal cord and consist of diffuse although uneven degeneration of the white matter, with relatively little proliferation of the fibrous glia or of specific changes in nerve cells. They state that the pathological process is unique and easily distinguished from that of other diseases involving the white matter and from that of pellagra. In pellagra, as was pointed out by Greenfield and Holmes (1939), the lacunar appearance due to gross distension of the myelin sheaths which is characteristic of subacute combined degeneration is absent and chromatolysis is present in many ganglion cells, especially the anterior horn cells and cells of the cranial motor nuclei. The Betz cells of the motor cortex in pellagra show the "central neuritis" described by Adolf Meyer, and the degeneration of corticospinal tracts which occurs is probably secondary to this and not to a demyelinating process primarily affecting white matter.

Histology of Two Fatal Cases

Dr. A. L. Woolf and I have made full histological examinations of the brains and spinal cords in two fatal cases of vitamin-B_{12} deficiency which presented clinically with severe spinal symptoms and mental disturbance.

The first of these two cases was No. 7 in Table II, a woman aged 55 whose mentality had gradually deteriorated during the previous eight years. At first she was mildly confused and her memory was defective, but deterioration was very slow. Early in 1955 her gait became ataxic and gross delusions and disorientation appeared. In September pernicious anaemia and subacute combined degeneration were diagnosed, but intensive treatment produced no improvement in her ataxic paraplegia or her mental condition and she was certified and admitted to a mental hospital. The blood picture had become normal, but she was grossly deluded, noisy and restless, incontinent of urine and faeces, and severely paraplegic, with loss of tendon reflexes in the legs and arms, severe ataxia and bilateral extensor plantar responses. Phlebothrombosis and oedema of the legs developed and she died of a pulmonary embolus on January 3, 1956. Necropsy revealed a large pulmonary embolus and also a severe haemorrhagic cystitis. Macroscopic examination of the brain and spinal cord revealed no gross abnormalities.

Sections of the spinal cord showed the typical "status spongiosus" of subacute combined degeneration, with pronounced changes in the posterior and lateral columns. Serial sections of the brain showed diffuse degeneration in the white matter with myelin staining, particularly in the centrum semiovale on both sides. More focal areas of degeneration were seen in the frontal lobes and the brain stem. Nissl staining showed no pronounced changes in nerve cells, but there was some microglial proliferation in the frontal lobes, and swollen pale glial cells were seen in many areas. Occasional macrophages filled with fat were seen in the degenerated areas in sections stained with Scharlach R, but these were not as numerous as in the second case.

In the second case examined histologically the brain and spinal cord and clinical details were kindly supplied by Dr. D. J. O'Sullivan, of the Royal Hospital, Wolverhampton.

A woman aged 51 had complained of inability to walk and numbness in her feet for about a year. She was admitted to hospital on December 31, 1955. During the previous two months her ankle had become swollen and her tongue sore, and considerable mental confusion and disorientation had appeared. She could give no coherent story of her complaints or their duration and had no idea of time or her surroundings. She had a severe flaccid paraplegia with areflexia in the legs, severe sensory loss, and extensor plantar responses. She was incontinent of urine and faeces. Addisonian anaemia, with a haemoglobin of 50% and a typical megaloblastic marrow, was present. She became increasingly stuporous, and in spite of large doses of vitamin B_{12} and blood transfusions she died on January 5, 1956. Necropsy showed death to be due to purulent bronchopneumonia and haemorrhagic cystitis. The cut surface of the spinal cord showed some translucency of the posterior and lateral columns, but there were no conspicuous macroscopic changes in the brain.

The neuropathological findings were similar to those in the first of these two cases. The appearance of the spinal cord was again the typical "status spongiosus." The areas of degeneration in the cerebral white matter were widely scattered, but more focal and smaller in area than in the other case. They were pronounced in the corpus callosum, but were also seen in the frontal and parietal lobes. The pale foci in sections stained for myelin showed a corresponding distribution of fat globules in macrophages in sections stained with Scharlach R. Mallory's stain showed a slight excess of fibrous glia in some degenerated areas, but this was not a prominent finding. The staining reactions of the cerebral lesions were in all respects similar to those in the spinal cord in both cases, and we are able to confirm Adams and Kubik's (1944) statement that the cerebral and cord lesions are almost exactly alike. Furthermore, the demyelinating process involves the peripheral nerve as far down as the terminal fibrils in muscle, as mentioned above. The only histological difference in these two cases is that in the first, in which the mental symptoms had been present for eight years, the cerebral lesions were more diffuse than in the second case with a much shorter duration of dementia, where the lesions were mainly foci of small size.

Summary

The brain lesions which form part of the neurological syndrome of vitamin-B_{12} deficiency, although they have been recognized for more than half a century, are still much less familiar than those which occur in the spinal cord and peripheral nerves, to which by long usage the term "subacute combined degeneration" has been applied. The end-result of unrecognized and untreated cerebral lesions may be a severe dementia, even more crippling than the paraplegia produced by the spinal lesions, but early treatment will produce complete remission.

An attempt is made to clarify the clinical picture so far as cerebral symptoms are concerned and to emphasize once again that they deserve more attention in psychiatric diagnosis. The symptoms may be classified as mental and ophthalmological, the latter nearly always being due to optic atrophy. They are illustrated by reference to a series of 14 personal cases. Good recovery from varying degrees of mental derangement occurred in 11 cases after intensive treatment with vitamin B_{12}. The cerebral symptoms preceded the appearance of Addisonian anaemia or of spinal and peripheral nerve involvement by several years in some instances.

The evidence that these cerebral symptoms are specifically related to the deficiency and not to anaemia is discussed by reference to recent literature. The diagnosis is also discussed and reference is made to the used of recently developed techniques, such as the assay of vitamin B_{12} in the serum, using the alga *Euglena gracilis*, gastric biopsy, and electroencephalography. These methods may be very valuable in cases in which there is no evidence of macrocytic anaemia, megaloblastic reaction in the bone marrow, or subacute combined degeneration of the cord.

The histopathological findings in two fatal cases are briefly described. These confirm that the lesions in the brain in patients with established vitamin-B_{12} deficiency and psychotic symptoms are essentially similar to those found in the spinal cord in subacute combined degeneration, and consist of diffuse and focal areas of degeneration in the cerebral white matter, with relatively little proliferation of fibrous glia.

I am grateful to my colleagues Professor P. C. P. Cloake and Dr. E. R. Bickerstaff for allowing me to include Cases 9 and 3 in the series; to Dr. A. L. Woolf for the extensive histological examinations; and to Dr. G. I. M. Ross, of Westminster Hospital, for serum vitamin-B_{12} assays.

References

Adams, R. D., and Kubik, C. S. (1944). *New Engl. J. Med.*, **231**, 1.
Benham, G. H. H. (1951). *J. Neurol. Neurosurg. Psychiat.*, **14**, 40.
Cohen, H. (1936). *Lancet*, **2**, 1202.
Doig, R. K., Motteram, R., Robertson, E. G., and Wood, I. J. (1950). Ibid., **2**, 836.
Earl, C. J., El Hawary, M. F. S., Thompson, R. H. S., and Webster, G. R. (1953). Ibid., **1**, 115.
Greenfield, J. G., and Holmes, J. MacD. (1939). *British Medical Journal*, **1**, 815.
—— and O'Flynn, E. (1933). *Lancet*, **2**, 62.
Guillain, G., Lereboullet, J., and Auzépy, P. (1938). *Bull. Soc. méd. Hôp. Paris*, **54**, 1449.
Jewesbury, E. C. O. (1954). *Lancet*, **2**, 307.
Lichtheim, L. (1887). *Neurol. Zbl.*, **6**, 235.
McAlpine, D. (1929). *Lancet*, **2**, 643.
Mollin, D. L., and Ross, G. I. M. (1953). *British Medical Journal*, **2**, 640.
Preobrajensky, P. (1902). *Neurol. Zbl.*, **21**, 727.
Samson, D. C., Swisher, S. N., Christian, R. M., and Engel, G. L. (1952). *A.M.A. Arch. intern. Med.*, **90**, 4.
Scheinberg, P. (1951). *Blood*, **6**, 213.
Turner, J. W. A. (1940). *Brain*, **63**, 225.
Victor, M., and Lear, A. A. (1956). *Amer. J. Med.*, **20**, 896.
Walton, J. N., Kiloh, L. G., Osselton, J. W., and Farrell, J. (1954). *Electroenceph. clin. Neurophysiol.*, **6**, 45.
Woltman, H. W. (1924). *Amer. J. Psychiat.*, **3**, 435.

Speaking to the Section of General Practice of the Manchester Medical Society on November 26, Mr. D. LL. GRIFFITHS, F.R.C.S., said that 8% of the patients attending an orthopaedic out-patient clinic were complaining of pain in or down the arm. About half of these had demonstrable shoulder lesions, and another quarter were considered to be suffering from cervical spondylosis. Referring to the question of the pathology of these conditions, Mr. Griffiths stressed the importance of what were coming to be recognized as collagen diseases. Surgical treatment had limited value, and there was a danger of over-treatment by physical methods. It had to be admitted, he concluded, that we knew so little of the proximate mechanism of pain production in the arm that the approach to the individual patient had to be largely empirical.