

# PSYCHIATRIC ILLNESS AND PERNICIOUS ANAEMIA: A CLINICAL RE-EVALUATION

By

**M. D. EILENBERG, M.B., M.R.C.P., D.P.M.**

*Senior Registrar*

*Bethlem Royal and Maudsley Hospitals*

## INTRODUCTION

ADDISON (1855) in his classical description wrote of the patient's mind "as occasionally wandering" during the final stages of pernicious anaemia. The relative frequency with which different psychiatric syndromes present differs from that recorded by previous writers and is probably due to earlier psychiatric consultation in the present group, though mode of referral may also play a part. Bowman (1935) found organic confusion in 48 per cent., a death rate of 35 per cent. and a red blood cell count of below 4·0 million in 65 per cent. of his 23 cases. Herman, Most and Joliffe (1937) found organic confusion in 35 per cent. compared with the present writer's 5 per cent., a death rate of 22·5 per cent. compared with 10 per cent. and a red blood cell count of under 3·0 million in 75 per cent. of his 40 cases, compared with 25 per cent. of the present group.

The present author, having recently had experience of several patients suffering with both psychiatric illness and pernicious anaemia, obtained access to the records of 20 patients admitted to the Bethlem Royal and Maudsley Hospitals with this combined diagnosis and re-evaluated the clinical records in an attempt to define more precisely the relationship. The 20 patients had been admitted during the years 1948–1959 and represent 0·1 per cent. of the total number of psychiatric patients aged 35 years or over seen during this period.

The literature reveals that the association of pernicious anaemia and psychiatric illness is too often interpreted as implying a major causal relationship. With the acceptance of multiple causation in the production of psychiatric reactions, only a detailed analysis of case material can allow judgments to be made regarding the relative importance of pernicious anaemia, compared with other factors in the aetiology of psychiatric illness. The aetiological importance of pernicious anaemia in the psychiatric illnesses presented in this paper can be accepted if there are not other equally or more satisfactory factors contributory to the mental state or if the mental state is specific. The latter does not appear to be the case though paranoid symptoms are regarded as being present in a high proportion of patients and 65 per cent. of the present series had paranoid symptoms. The natural history of the psychiatric disorder, the environmental changes resulting from hospital admission and the physical conditions associated with old age are some of the factors requiring assessment in order to evaluate the psychiatric state and course, before assuming the aetiological importance of vitamin B<sub>12</sub> deficiency in the psychiatric illness.

At our present state of knowledge, the author considers it wiser to establish strict criteria before accepting the aetiological importance of pernicious anaemia in psychiatric illness and they should ideally be (1) no past history of

psychiatric illness; (2) no evidence of disturbed pre-morbid personality; (3) absence of psychologically or socially disturbing events preceding the illness; (4) unequivocal presence of a mental illness; (5) associated and proven pernicious anaemia; (6) resolution of a mental illness with vitamin B<sub>12</sub> treatment; (7) relapse when vitamin B<sub>12</sub> is withheld; (8) neuropathological evidence of vitamin B<sub>12</sub> deficiency.

The case reports presented as an appendix are briefly analysed in an attempt to approach the theoretical viewpoint outlined in the preceding paragraph.

#### CLINICAL DATA

Pernicious anaemia was diagnosed on the basis of clinical history and examination, coupled with full blood count, histamine-fast achlorhydria and/or megaloblastic bone marrow in 17 patients. In 3 patients only a blood count and film was done. Table I, below, summarizes the data on psychiatric diagnosis, age, neurological state and blood count.

TABLE I

Case No.	Sex	Diagnosis	Age in Years	Neurological Abnormality	At Time of Psychiatric Presentation		
					Hb%	R.B.C. 10 <sup>6</sup> /cu.μ	M.C.V. 78-94 cu.μ
1	F	Dementia .. ..	73	Present	96	3.9	—
2	F	Senile paranoid state ..	76	Present	83	4.5	—
3	*F	Depression .. ..	66	Present	90	4.0	90
4	*F	Hysteria .. ..	48	Present	52	2.8	89
5	F	Dementia .. ..	70	—	109	5.2	100
6	F	Senile paranoid state ..	70	—	96	4.5	102
7	*F	Depression .. ..	79	—	63	3.5	105
8	F	Hypomania .. ..	57	—	86	4.7	—
9	F	Dementia .. ..	68	—	94	4.7	95
10	*F	Depression .. ..	64	—	54	2.7	111
11	*F	Hysteria .. ..	47	Present	88	3.6	117
12	M	Dementia .. ..	64	Present	86	4.8	91
13	*M	Dementia .. ..	84	Present	30	—	—
14	*M	Depression .. ..	42	Present	47	2.0	118
15	*M	(a) Acute confusion ..	38	Present	56	2.4	102
		(b) Schizo-affective state	42	Present			
16	*M	Depression .. ..	75	—	52	2.2	104
17	*M	Depression .. ..	64	Present	60	1.6	—
18	M	Depression .. ..	62	Present	75	3.2	125
19	M	Alcoholic hallucinosis ..	46	Present	84	4.2	105
20	M	Depression .. ..	62	Present	90	4.8	96

Asterisks denote those patients who presented psychiatrically and a diagnosis was made by the psychiatrist.

The average age at the time of psychiatric presentation was 64.7 years with a range of 38 years–84 years. The average length of psychiatric history was 12.4 months with a range of 2 weeks–7 years. From these figures, the average length of time between the diagnosis of pernicious anaemia and the onset of the psychiatric disorder was calculated as 3.0 years.

The functional psychoses diagnosed in 12 patients consisted of 8 patients with depressive illness, 1 with hypomania, 1 with a schizo-affective state and 2 with senile paranoid states. The 7 organic states consisted of 1 acute confusional state, 1 alcoholic hallucinosis and 5 dementias. The neuroses were represented by 2 patients with conversion hysteria. No attempt was made to assess personality though it seems worth recording that half of the group were described as “methodical”, “conscientious”, “hardworking”, or “responsible” in their occupation.

Table II, summarizes data on physical state, treatment and outcome.

TABLE II

Case No.	Age in Years	Diagnosis	Physical Abnormality	*Specific Treatment	Improvement 0-4 Plus
1	73	Dementia	Arteriosclerotic heart failure	E.C.T.	++
2	76	Senile paranoid state	Bilateral cataracts, osteoporosis of spine	—	0
3	66	Depression	Bilateral cataracts	—	+++
4	48	Hysteria	—	—	+
5	70	Dementia	Arteriosclerotic heart disease	—	0
6	70	Senile paranoid state	Gross arteriosclerosis	—	0
7	79	Depression	—	—	0
8	57	Hypomania	—	—	++++
9	68	Dementia	Arteriosclerosis with hypertension	E.C.T.	++
10	64	Depression	Rheumatoid arthritis, varicose ulcers of legs	E.C.T.	++++
11	47	Hysteria	Disseminated sclerosis	—	+
12	64	Dementia	Bilateral cataracts	Phenelzine	+
13	84	Dementia	—	Phenelzine	+
14	42	Depression	—	—	++++
15	38	(a) Acute confusion	—	—	++++
	42	(b) Schizo-affective state	—	—	++++
16	75	Depression	Arteriosclerosis	E.C.T.	+++
17	64	Depression	Gout	—	++++
18	62	Depression	—	—	++++
19	46	Alcoholic hallucinosis	—	—	++++
20	62	Depression	Hypertension	—	+++

\* Denotes treatment other than vitamin B<sub>12</sub> or general in-patient routine. Cases Nos. 1-11 are females, Nos. 12-20 are males.

A diagnosis of dementia was made in Cases Nos. 1, 5, 9, 12 and 13. Of this group Cases Nos. 1, 5 and 9 had evidence of gross cardiovascular disease, were over 65 years of age, had satisfactory blood counts and failed to respond to vitamin B<sub>12</sub> treatment. The neurological abnormalities sufficient to warrant a clinical diagnosis of vitamin B<sub>12</sub> neuropathy (Jewsbury, 1954) in Case No. 1 was not supported by post-mortem examination and exemplifies the difficulty in assessing the pathological significance of neurological abnormality in old age (Critchley, 1931). In Case No. 1 pernicious anaemia presented with acute confusional state 8 years prior to the dementia and in Case No. 9 a severe physical illness 6 months prior to psychiatric presentation. Thus, though pernicious anaemia may be considered contributory to the psychiatric illness, particularly in Case No. 9, the factors described above that are common to the 3 cases appear to be of greater aetiological significance. Case No. 12 had cortical atrophy, episodic loss of consciousness, normal serum B<sub>12</sub> levels, and failed to respond to vitamin B<sub>12</sub> treatment suggesting a dementia of primary origin, rather than secondary to vitamin B<sub>12</sub> deficiency. The EEG changes suggest the latter and a prolonged follow-up will be necessary to clarify the diagnosis. In Case No. 13 an old man of 84 years, there was insufficient information to reach a conclusion.

Cases Nos. 2 and 6 were both 70 years or over, the former had senile changes in her spine and eyes, the latter gross arteriosclerosis. Both had siblings with a history of psychiatric illness and both patients failed to respond to vitamin B<sub>12</sub> treatment. Thus senile cerebral changes in genetically predisposed individuals

seems a more satisfactory formulation of their psychiatric illness than pernicious anaemia.

Of the patients with affective disorders, Cases Nos. 3 and 20 showed slow resolution of their depressive illness with general supportive measures following hospital admission. As Case No. 20 had an 8-year history of pernicious anaemia, a spontaneous recovery of his depression seems the likeliest explanation and though less likely an explanation in Case No. 3 this cannot be excluded. Cases Nos. 10 and 16 failed to respond to vitamin B<sub>12</sub> treatment but responded to E.C.T. suggesting that the depressive illness was independent of pernicious anaemia. The depression in Case No. 17 resolved prior to the diagnosis of pernicious anaemia being made, his hospital admission resulting in separation from a demanding fiancée. Case No. 17 is thus an example of Engyesis (Davies, 1956). Case No. 18, a patient with manic depressive psychosis, stayed too short a time in hospital for adequate assessment.

Cases Nos. 4 and 11 had a long history of hysterical symptoms on a basis of personality disorder and responded little to vitamin B<sub>12</sub> treatment, whilst Case No. 19 repeated his past pattern of response to 2 weeks abstinence from alcohol.

Of the remainder, Case No. 15 presented with symptoms of an acute confusional state which responded dramatically to vitamin B<sub>12</sub> treatment whilst equal therapeutic success was seen in Cases Nos. 7, 14 and 18. Case No. 7 who had a past history of depressive illness 10 years previously appeared to react adversely to disagreements with her son but though the external situation did not change, she lost her morbid ideas and was able to deal realistically with the situation, within 10 days of commencing vitamin B<sub>12</sub> treatment. Case No. 14, who had failed to respond to orthodox treatment for his depression, responded rapidly to vitamin B<sub>12</sub> treatment once the correct diagnosis was established and he made a complete recovery. Case No. 18 showed a therapeutic response on 2 occasions to vitamin B<sub>12</sub> treatment once the diagnosis of pernicious anaemia was made, the last illness resolving within three weeks.

No relationship between psychiatric improvement and change in blood count or neurological state was found, only 1 case showing improvement of the latter with psychiatric improvement. Also no relationship was found between the severity of the psychiatric illness, e.g. degree of depression and the neurological state.

#### DISCUSSION

It is thus apparent that if an attempt is made to apply the 8 criteria proposed in the introduction of 20 patients, only 4 cases (Cases Nos. 7, 14, 15 and 18) might be considered examples of psychiatric illness secondary to pernicious anaemia, the evidence being most convincing in Case No. 14 and 15(a). In an attempt to find external validation for this view the author reviews below studies relevant to the possible underlying mechanisms for understanding this relationship and indicates which aspects support the clinical analysis above.

Following the discovery of abnormal electro-encephalograms in patients with pernicious anaemia (Romano and Engel, 1944), Samson, Swisher, Christian and Engel (1952), studied 14 patients with pernicious anaemia by serial EEGs. A delirious state was diagnosed in 13 patients, though the criteria for this diagnosis would not necessarily be generally accepted and 12 patients suffered with sub-acute combined degeneration. A qualitative frequency analysis of the

EEG carried out on 11 patients revealed that 9 showed significant EEG improvement during vitamin B<sub>12</sub> treatment, 6 having a return to a normal EEG pattern. It is of particular interest that the EEG improvement preceded any change in red blood cell count though it approximated to the time of the reticulocyte response. Walton, Kilott, Osselton and Farrall (1954) studied the EEG of 80 patients with pernicious anaemia in relapse, 50 under treatment and 10 patients with miscellaneous anaemia. Of 80 patients, 64 per cent. had abnormal EEGs which bore no relationship to age, degree of anaemia or presence of neurological involvement. Those patients showing sub-acute delirious reactions had abnormal EEG records which reverted to normal within 7–10 days following the commencement of treatment. However, despite this, there was not a close relationship between EEG abnormality and mental state.

Scheinberg (1951) basing his technique on the nitrous oxide method of Kety and Schmidt, studied the cerebral metabolism of 16 patients with pernicious anaemia. Fifteen of the group had sub-acute combined degeneration and 13 were in haematological relapse. The abnormal mental status was briefly recorded from 1 plus to 4 plus on the presence of organic mental symptoms, 15 patients being classified. EEGs were performed on 11 out of 16 patients. Scheinberg found a good correlation between severe neurological involvement, abnormal mental status and low cerebral oxygen consumption and that cerebral metabolism reverted towards normal with vitamin B<sub>12</sub> treatment though not completely so.

It is not possible at the present time to specify precisely the biochemical functions of vitamin B<sub>12</sub> either within the central nervous systems or the body generally. Nevertheless, certain reactions pertaining to the function of the former have been described. Ling and Chow (1953) demonstrated an increase to normal in blood sulphhydryl compounds (mainly the glutathione fraction) in 2 pernicious anaemia patients following vitamin B<sub>12</sub> treatment. Glutathione is probably a co-enzyme in one of the steps of glucose metabolism (Strickland, 1956) and glucose is the main source of energy for the brain. In this respect it is of interest to note that Earl, Hawary, Thompson and Webster (1953) demonstrated an abnormal pyruvate curve in 3 cases of untreated sub-acute combined degeneration, the curve returning to normal with vitamin B<sub>12</sub> treatment. The phospholipids, lecithin and kephalin found in great abundance in the white matter of brain contain modified forms of serine and the latter's conversion from glycine requires the presence of vitamin B<sub>12</sub> (Bicknell and Prescott, 1953). Nucleic acid and its nucleotide subgroups are essential constituents of nerve cell cytoplasm and nuclei, and ribose nucleic acid (R.N.A.) is found to disappear from the cytoplasm on electrical stimulation of nerves (Canterow and Schepartz, 1954). Vitamin B<sub>12</sub> is involved in nucleic acid synthesis and is required for the formation of deoxyribose nucleic acid *via* thymidine synthesis. Vitamin B<sub>12</sub> may thus be seen to play an essential part in chemical reactions relating to carbohydrate metabolism, phospholipid and nucleic acid formation, all of major importance to the central nervous system. A summary of recent research is available from the proceedings of the 4th International Congress of Biochemistry (Arnstein, 1960).

The four cases (Nos. 7, 14, 15 and 18) presented above illustrate some aspects of the above findings. Thus clinical response was marked within 3 weeks and this parallels the cerebral physiological disturbance noted in the EEG and metabolic studies presented above, in which reversion to normal occurred 7–10 days following the commencement of vitamin B<sub>12</sub> treatment. The cases also agree with the EEG studies in failing to find correlation between blood

count, neurological status and improvement. Thus Case No. 15 (first admission) showed a fall in haemoglobin level in the presence of marked psychiatric improvement following vitamin B<sub>12</sub> treatment. Though the possible biochemical disturbance underlying the physiological ones are briefly sketched insufficient detailed knowledge of the chemical reactions precludes further worthwhile discussion of this relationship.

The availability of radioactive isotopes of vitamin B<sub>12</sub> provides a useful tool for studying the relationship of pernicious anaemia and psychiatric illness. However, unless the clinician can define more clearly the syndromes he meets in practice, inconclusive results will inevitably follow the application of precise techniques to a heterogeneous sample of patients.

#### SUMMARY

Twenty patients with psychiatric illness and pernicious anaemia have been clinically re-evaluated with particular emphasis on their aetiological relationship. It is argued that only 20 per cent. of cases falling into this group show a direct relationship between their psychiatric illness and pernicious anaemia. Pertinent studies of cerebral metabolism to support the view presented in this paper are reviewed.

#### ACKNOWLEDGMENT

The author thanks Dr. Michael Shepherd, Senior Lecturer, Institute of Psychiatry, Maudsley Hospital, London, S.E.5, for his help and constructive criticism.

#### REFERENCES

- ADDISON, T., *London Med. Gaz.*, 1855, **43**, 517.  
 ARNSTEIN, H. R. V., *Vitamin Metabolism* (Proc. 4th Int. Cong. of Biochemistry; Ed.: W. Umbrett and H. Molitor), 1960. London: Pergamon Press.  
 BICKNELL, F., and PRESCOTT, F., *The Vitamins in Medicine*, 1953. London: W. Heinemann.  
 BOWMAN, K. M., *Amer. J. Psych.*, 1935, **92**, 371.  
 CANTEROW, A., and SCHEPARTZ, B., *Biochemistry*, 1954. London: W. B. Saunders & Co.  
 CRITCHLEY, MACDONALD, *Lancet*, 1931, *i*, 1119.  
 DAVIES, D. L., *Brit. J. Soc. Med.*, 1956, **10**, 123.  
 EARL, C. J., EARL, M. F. S., HAWARY, E. L., THOMPSON, R. H. S., and WEBSTER, G. R., *Lancet*, 1953, *i*, 115.  
 HERMAN, M., MOST, F., and JOLIFFE, N., *Arch. Neurol. and Psych.*, 1937, **38**, 348.  
 JEWsbury, E. C. D., *Lancet*, 1954, *ii*, 307.  
 LING, C. T., and CROW, B. F., *J. Biol. Chem.*, 1953, **202**, 445.  
 ROMANO, J., and ENGEL, G. L., *Arch. Neurol. and Psych.*, 1944, **51**, 356.  
 SAMSON, D. C., SWISHER, S. N., CHRISTIAN, R. M., and ENGEL, G. L., *A.M.A. Arch. Int. Med.*, 1952, **90**, 4.  
 SCHEINBERG, P., *Blood*, 1951, **6**, 213.  
 STRICKLAND, K. P., *Guy's Hosp. Rep.*, 1956, **105**, 108.  
 WALTON, J. N., KILOH, L. G., OSSELTON, J. W., and FARRALL, J., *EEG and Clin. Neurophysiol.*, 1954, **6**, 45.

#### APPENDIX

##### BRIEF CLINICAL SUMMARY OF CASES

###### Case No. 1

Mrs. F.P., aged 73 years. Family history of 1 brother "neurasthenic" and 1 sister who died in a mental hospital. Past history of puerperal depression at the age of 25 years and certified at the age of 65 years with a diagnosis of "acute confusional state". Recovery followed treatment with "Anahaemin" after pernicious anaemia was diagnosed at a general hospital.

*Present history* (of two months duration), of fatigue, dyspnoea and wandering, incoherent talk, delusions of being poisoned, disorientation, depression and incontinence.

*Physical examination*: B.P. 170/100, enlarged left cardiac ventricle, absent ankle reflexes and Rhombgism present. A Hb. was 96 per cent., R.B.C. was 3.9 million, W.C.C. was 5,500 c.mm. and blood films showed slight macrocytosis. "Campolon" and "Cytamen" were given, followed by 3 E.C.T.s because of persistent marked depression. The depression resolved and the dementia became more marked. Re-admitted 1 year later, depressed negativistic and

disorientated. Hb. was 89 per cent. and R.B.C. was 4.0 million. Death occurred 1 year later from heart failure. Post-mortem revealed senile dementia, arteriosclerotic left ventricular failure, but no evidence of subacute combined degeneration.

*Case No. 2*

Miss M.B., aged 76 years. Diagnosed pernicious anaemia 11 years previously. Family history of 1 sister aged 40 years with affective disorder.

*Present history* of 1 month's duration, ideas of reference, delusions of being poisoned, that she can perform miracles.

*Physical examination* revealed cataract of both eyes, absent knee and ankle reflexes and senile osteoporosis of the spine. A Hb. of 83 per cent., R.B.C. of 4.5 million and W.C.C. of 9,500 c.mm. was reported. No change in her clinical state was noted on discharge after 4 months treatment with "Anahaemin".

*Case No. 3*

Mrs. G.C., aged 66 years.

*Present history* of 6 months duration of leg pains, tiredness and depression preceded by deteriorating vision and housing problems. Examination revealed bilateral cataracts, a bromide rash with mild confusion which resolved within 2 weeks revealing an underlying agitated depression; weakness and spasticity of both legs, diminished vibration sense and unequal ankle reflexes were present. Hb. was 90 per cent., R.B.C. was 4.0 million and W.C.C. was 8,600. "Camplon" was prescribed daily and the mental state slowly resolved over the next 3 months with no change in blood picture or neurological state.

*Case No. 4*

Mrs. L.E., aged 48 years.

*Past history* of nail biting and somnambulism as a child and sexual frigidity in adulthood. At the age of 31 years she developed hysterical paralysis of legs following her father's death.

*Present history* of 1 month's inability to walk, hysterical amnesia and depression within 8 weeks of a pan-hysterectomy. Examination revealed loss of postural sense in legs, absent ankle and knee reflexes, parasthesiae in fingers and toes, with hysterical anaesthesia of the legs. Hb. was 52 per cent., R.B.C. was 2.8 million, W.C.C. was 6,400 c.mm. and blood film was macrocytic. Massive "Cytamen" dosage was given and 5 months later she had a Hb. of 80 per cent. and R.B.C. of 4.2 million. On discharge 2 years following admission her Hb. was 95 per cent., R.B.C. was 5.0 million, her gait had greatly improved, the reflexes were still absent with absence of vibration and postural sense in legs. Psychiatrically she showed variable depression, emotional instability and occasional vomiting, but no amnesia.

*Case No. 5*

Miss R. G., aged 70 years.

*Present history* of 1 month's confusion wandering and talking to herself. On examination she misidentified people, she showed lability of mood, amnesia, disorientation, incontinence and delusions of being poisoned. Physically, the patient had slurred speech, tremor of arms, hyperaesthesiae of both feet, enlarged heart and auricular fibrillation. The E.C.G. supported a diagnosis of degenerative heart disease. Hb. was 109 per cent., R.B.C. was 5.2 million and W.C.C. was 9,000 c.mm. "Cytamen" was given with little clinical change.

*Case No. 6*

Mrs. A.L., aged 70 years. Family history of schizophrenia affecting 1 brother and 1 nephew, 1 sister had an illness "similar to the patient".

*Past history* at the age of 60 years of "cerebral arteriosclerotic dementia" which resolved in 5 months following admission to a mental hospital when pernicious anaemia was diagnosed. Liver injections were given regularly for only the past 2 years.

*Present history* of 7 years paranoid ideas, accusing people of thefts, and amnesia with exacerbation of symptoms in the past 6 months. Physical examination revealed gross arteriosclerosis. Hb. was 96 per cent., R.B.C. was 4.5 million, W.C.C. was 5,700 c.mm. and blood film was reported "suggestion of macrocytosis". "Hepostab" was given but no clinical change noted on discharge 4 months later.

*Case No. 7*

Mrs. E.W., aged 79 years. Family history of 1 cousin with "nervous trouble", 1 daughter "hysteria".

*Past history* at age of 69 years of a depressive episode following death of her grandson.

*Present history* of 2 weeks depression, insomnia and suicidal ideas following domestic friction. Hb. was 63 per cent., R.B.C. was 3.48 million and W.C.C. was 6,600 c.mm. "Cytamen" was prescribed and the morbid thoughts were rejected within 10 days of commencing treatment though her social situation preceding admission remained unchanged. On discharge Hb. was 80 per cent. and R.B.C. was 3.4 million, despite addition of ferrous sulphate and ascorbic acid tablets.

*Case No. 8*

Miss E. DeK., aged 57 years.

*Past history* of "nervous exhaustion" at age of 53 years and "melancholia" at the age of 53 years.

*Present history* of elation with unco-operative and aggressive behaviour. Hb. was 86 per cent., R.B.C. was 4.7 million. Patient had received monthly vitamin B<sub>12</sub> injections after a diagnosis of pernicious anaemia was made 5 years ago and she discharged herself from hospital within 3 days.

*Case No. 9*

Mrs. M. L., aged 68 years. Family history of 1 sister with a diagnosis of schizophrenia.

*Past history* 6 months ago of being "moribund" at home with absent vibration sense in legs and at that time her Hb. was 42 per cent., R.B.C. was 1.44 million, M.C.D. 8.7  $\mu$ ., and W.C.C. was 4,500 c.mm. Though receiving liver injections at home these were not regularly maintained.

*Present history* of 1 month's duration of depression, nihilistic delusions, guilt, restlessness and patchy amnesia with perseveration. Physically the patient showed evidence of arteriosclerosis and a B.P. of 205/115. "Hepalon" and "Cytamen" was given though the blood count was Hb. 94 per cent., R.B.C. 4.7 million and W.C.C. 5,000 c.mm. The depressive element responded to E.C.T. but the underlying dementia remained.

*Case No. 10*

Mrs. A.S., aged 64 years.

*Past history* of 1 month's duration of delusions of her leg being cancerous, talking to herself, paranoid ideas, disorientation and restlessness.

*Physical examination* revealed old rheumatoid arthritis and varicose ulceration of both legs. Hb. was 54 per cent., R.B.C. was 2.7 million, W.C.C. was 4,000 and a blood film was macrocytic. Massive "Cytamen" dosage was given and 2 months later the Hb. was 80 per cent. but no change in her psychiatric state had occurred. Full recovery with no residual abnormality followed treatment with 11 E.C.T.s.

*Case No. 11*

Mrs. I.B., aged 47 years.

*Past history* of being an ineffectual, complaining and self-centred personality with 8 years history of disseminated sclerosis.

*Present history* of exacerbation of personal traits. Physically absent knee and ankle reflexes with extensor plantar reflexes were noted. Hb. was 88 per cent., R.B.C. was 3.6 million, W.C.C. was 10,000 c.mm. and the blood film was macrocytic. "Cytamen" was given but a very limited psychiatric improvement followed and the patient died one year later of the complications of neurological disease.

*Case No. 12*

Mr. W.G., aged 64 years.

*Past history* of partial gastrectomy at the age of 53 years and a diagnosis of pernicious anaemia was made at the age of 61 years. He was maintained on 250  $\mu$ g. I.M. "Cytamen" monthly.

*Present illness* of 1 year's history of episodic loss of consciousness without convulsions, gradual loss of memory and initiative, social irresponsibility and ethical deterioration. Psychiatric examination showed that the patient was disorientated, was confabulating, had amnesia and euphoria. Physically, early bilateral cataracts and absent ankle reflexes were found. Hb. was 86 per cent., R.B.C. was 4.8 million and W.C.C. was 5,500 c.mm. Following "Cytamen" 1,000  $\mu$ g. I.M. for 2 weeks, the Hb. rose to 110 per cent. but there was little change in his psychiatric state, though he became less aggressive following Stelazine treatment. A.E.G. showed evidence of generalized atrophy and E.E.G. revealed mild generalized non-specific abnormality which showed some improvement 5 months later.

*Case No. 13*

Mr. B., aged 84 years. The patient was found wandering, disorientated, restless, aggressive and unco-operative. No adequate information from patient or other sources was available. Physical examination revealed generalized pupura more evident on the lower limbs and absent ankle reflexes, whilst the psychiatric diagnosis was dementia. Hb. was 30 per cent., W.C.C. was 3,600 c.mm. and the macrocytic blood film was reported. Following "Cytamen" 200  $\mu$ g. I.M. on alternate days a reticulocyte response of 18.4 per cent. was noted and 2 months later, despite vitamin B complex and ascorbic acid, the Hb. was 80 per cent. With Stelazine minimal psychiatric improvement occurred.

*Case No. 14*

Mr. L.B., aged 42 years.

*Present history* of 2 years of depression, feeling a failure, diminished libido and lack of energy which persisted despite psychotherapy and E.C.T. given at different times. Following a



complaint of dyspnoea his Hb. was found to be 47 per cent., R.B.C. was 2·0 million and W.C.C. was 3,100. Paraesthesiae were experienced in his legs. One week after commencing "Cytamen" a reticulocyte response of 11·0 per cent. was noted. Two weeks later the psychiatric state was normal though the paraesthesiae remained and 7 weeks later the Hb. was 94 per cent., R.B.C. was 5·4 million and W.C.C. was 5,000 c.mm.

*Case No. 15*

Mr. J.M., an Indian, aged 38 years.

*Present history*, 2 weeks duration with periods of confusion during which he had religious visions. Mentally he was disorientated, resistive and incoherent though lucid intervals would follow. Physical examination revealed glossitis, loss of vibration sense in the legs and absent right ankle reflexes. His Hb. was 56 per cent., R.B.C. was 2·4 million; a macrocytic film was reported and EEG showed a generalized non-specific abnormality. Seven days later following "Cytamen" injections (100 µg.) a reticulocyte response of 7·0 per cent. occurred and an almost complete resolution of the mental state was noted despite a Hb. of 48 per cent. On discharge 1 month later the Hb. was 88 per cent. Four years later an acute illness characterized by ideas of reference, visual hallucinations, awareness of an evil influence and elated mood occurred. Loss of vibration sense was still noted. Hb. was 83 per cent. and R.B.C. was 4·5 million. A diagnosis of schizo-affective disorder was made which resolved in 1 month concurrently with increased "Cytamen" dosage.

*Case No. 16*

Mr. C.H., aged 75 years. Family history of 1 brother who had a depressive illness at the age of 70 years.

*Present illness* of 4 years duration characterized by depression, irritability and inability to work which responded partly to 2 courses of E.C.T. Present admission precipitated by 2 suicidal attempts. Mentally he was depressed, retarded and hypochondriacal. Physically, evidence of thickened arteries was noted. Hb. was 52 per cent., R.B.C. was 2·2 million and W.C.C. was 9,100 c.mm. "Cytamen" and "Campalon" was given with a rise of Hb. to 86 per cent. and R.B.C. of 4·0 million after 8 weeks with no psychiatric change of note. Considerable but not complete clinical response occurred following 10 E.C.T.s. The Hb. was 94 per cent. on discharge 9 weeks later.

*Case No. 17*

Mr. G.B., aged 64 years.

*Present illness* of 9 months duration characterized by depression, loss of weight, insomnia, indecisiveness following his mother's death and associated with fiancée's insistence on marriage. Mentally, he was depressed, irritable, retarded and mildly amnesic. Physically, his liver was firm and palpable, diminished knee reflexes, absent ankle reflexes and loss of vibration sense in his legs were recorded. Hb. was 60 per cent., R.B.C. was 1·6 million, and a macrocytic film was reported. In addition X-rays confirmed a clinical diagnosis of gout. Six days after commencing "Cytamen" a reticulocyte response of 15·5 per cent. was recorded. Almost complete resolution of the psychiatric state was apparent prior to the diagnosis of pernicious anaemia and was related to separation from a demanding fiancée. He was re-admitted 9 months later for two days during which complete resolution of a transient depression with paranoid ideas occurred. The latter followed a general hospital admission for treatment of a fractured leg. Hb. was 92 per cent., R.B.C. was 4·4 million. No neurological abnormality was found.

*Case No. 18*

Mr. C., aged 62 years.

*Past history* of depression at the age of 56 years successfully treated with E.C.T. One year later depression associated with pernicious anaemia. treated with liver injections.

*Present history* of 6 months duration of depression, hypochondriasis, weeping, self-reproach and inability to work. Physically, his liver and spleen were palpable, bilaterally absent ankle reflexes were noted with absent deep sensation in the right leg. Hb. was 75 per cent., R.B.C. was 3·2 million, and a macrocytic blood film reported. Three weeks after commencing "Cytamen" marked mental improvement occurred despite lack of improvement in neurological state and sub-optimal blood count.

*Case No. 19*

Mr. R.D., aged 46 years. Family history of father and 2 brothers being "drunkards". The patient had a long history of excess alcoholic intake (15-20 pints of beer daily) with recurrent hallucinosis resolving with abstinence. A diagnosis of pernicious anaemia was made 2 years previously and the patient received injections of liver regularly.

*Present illness* of 7 weeks depression hearing voices and still drinking heavily. Physically, motor weakness was present in both legs with impairment of touch and pin-prick sensation and diminished reflexes left arm and leg were noted. No evidence of dementia was present. Hb. was 84 per cent., R.B.C. was 4·2 million and a mild degree of macrocytosis was reported.

One week later he was mentally normal and the Hb. was 85 per cent. In view of his past psychiatric history the improvement, concurrent with the giving of "Cytamen" appears coincidental.

*Case No. 20*

Mr. A.P., aged 62 years.

*Past history* of being invalided out of the army during 1914–18 war on psychiatric grounds.

*Present illness* of 1 year's duration characterized by depression, hypochondriasis, restlessness, impotence and work deterioration. On admission Hb. was 90 per cent., and R.B.C. was 4·8 million. Physically, his B.P. was 180/115 and vibration sense in legs was absent. A diagnosis of pernicious anaemia and depression was made elsewhere when the patient was 54 years, no neurological signs then being present. His psychiatric state gradually improved during the following months with recovery of potency.