PSYCHOSES ASSOCIATED WITH PERNICIOUS ANÆMIA

WITH A REPORT OF TWO CASES

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The terminal stages of pernicious anaemia are frequently complicated by mental fatigue and enfeeblement, by drowsiness and apathy and by mild depression or delirium, symptoms which are common to the terminal stages of several other disorders, while even in earlier stages of the disease the combination of a measure of apathy and mental depression is said by Vaughan 1 to be so usual that a sudden improvement in the mental outlook is as characteristic and as important a sign in pernicious anaemia of satisfactory response to liver as is a rise in the reticulocyte count. Again, it is an obvious possibility that pernicious anaemia may coincide with any type of psychosis, developing before or after the onset of the mental disorder, and it can be expected that the onset of so severe an illness would occasionally precipitate an incipient mental breakdown.

The combination of anaemia and psychosis is more frequent than can be always accounted for by mere chance, but the etiological relationship of the anaemia to the psychosis is not easily settled.

The actual incidence of psychotic changes in pernicious anaemia is widely estimated by different observers, probably on account of the individual differences of opinion as to what constitutes a psychosis. Thus Cannon and Hayes 2 in a recent textbook of psychiatry state that 5 per cent. of patients with pernicious anaemia develop distinct mental changes, while Läufer 3 found only one case of insanity in 190 cases of this anaemia, and he quotes various authorities who have found the incidence even less than this. The differences in individual conceptions of psychotic changes become plain when the symptoms described as occurring are reviewed. Apathy is recorded by Richardson, 4 Woltmann, 5 Naegeli 6 and Piney, 7 the last-named stressing the association of this with incooperativeness. Alterations of character were noticed by Naegeli, 8 Hulett 9 and Émile-Weil and Cahen, 10 and abnormal irritability by Naegeli 6 and by Bremer. 11 Langdon 12 described an apprehensive neurosis appearing as a manifestation of pernicious anaemia; Barrett 13 and Phillips 14 believe that paranoid states are common. Depressive states, varying from simple retardation to profound melancholia, are agreed to be common by most writers, while Émile-Weil and Cahen have observed states of excitement. The remaining descriptions of psychotic manifestations...
occurring with pernicious anaemia can be considered as variations of a confusional state, akin to a toxic exhaustive psychosis, with confusion, agitation and restlessness and a tendency to delirium and unpleasant hallucinations at night. Such states are described by Läufer, Naegeli, Émile-Weil and Cahen and others. The mental symptoms observed can be summed up roughly as those of delusional states, of depressive or manic states or of toxic confusional states, if one excludes irritability, apathy, mild depression and character changes which would be inevitable in a certain proportion of sufferers from pernicious anaemia. These symptoms have been most frequently found with fully developed anemia, particularly in the terminal stages, but Mathieu states that mental symptoms may occur at any stage of the anaemia, while Piney and Phillips have described symptoms commencing after the institution of liver treatment, though most agree with Émile-Weil and Cahen that mental symptoms are rare when the blood is normal.

The pathological factors underlying the appearance of psychotic symptoms have been the subject of divergent views. An original psychopathic disposition is stressed by many; thus Naegeli thinks that an abnormal constitutional ‘make-up’ is the chief cause; Schaumann and Saltzmann think that the psychosis develops in a hereditarily tainted disposition and Phillips that symptoms occur in the predisposed; Hackfield believes that such psychoses are due to environmental traumata. Schneider divides his cases into two groups, the first where the anaemia lights up an endogenous psychosis and the second where the psychosis is symptomatic of a severe anaemia. Taterka and Goldmann correlate the mental state with the anaemia and describe a case where the mental symptoms grew worse during the initial fall of hæmoglobin following liver therapy, to improve steadily as the hæmoglobin increased. Atkin found psychogenic factors, but considered the anaemia the chief cause, whereas Warburg and Jorgensen described six cases of psychosis with megalocytosis and anacidity, but without anaemia, which improved on liver treatment; Hackfield found no parallelism between the condition of the blood and the state of the psyche.

The theory that toxins are generated by the disturbed metabolism consequent on the anemia is upheld by Schaumann and Saltzmann, and by Landelüdecke, who quotes a case with no cure of the psychosis on improvement in the anaemia, a fact which he explains by assuming that prolonged toxic action had destroyed neurones. Hackfield negatives the toxin theory, since so few patients with pernicious anaemia develop mental disorders and since neurological symptoms so seldom recover. It seems clear, as Hackfield states, that pernicious anaemia does not cause a psychosis in the way that syphilis causes general paralysis. The consensus of opinion favours the view of an original psychic weakness which may be augmented by environmental difficulties, giving way under the physical strain imposed by pernicious anaemia. The part played by anaemia or toxæmia or both is probably greatest in the toxic-exhaustive type of psychosis. The diminution of hæmoglobin
in the blood is probably not so important in this respect as the measure of toxæmia, although Barcroft has shown that anoxæmia can produce confusion, lethargy and irritability. The nature of the toxins concerned cannot be known until it is settled whether pernicious anaemia and the spinal cord changes are due solely to the absence of the intrinsic factor of Castle, or whether toxins are subsequently absorbed or generated.

Important as predisposition undoubtedly is, it is clear from the evidence available that the successful treatment of the anaemia usually leads to a complete cure of the psychosis, but neurological signs, as in pernicious anaemia without psychosis, are slow to improve, if they improve at all. Hackfield insists that liver treatment does not help the psychosis and that it must be separately treated, but, as a rule, with the anaæmia cured, the mildest form of persuasion and encouragement is sufficient to enable the patient to overcome his own psychological difficulties. Hackfield warns against the risk of suicide in depressed cases, and recommends insulin and glucose therapy for malnutrition and thyroid extract if the basal metabolic rate is low, but these are side-issues in treatment, to be considered in individual cases.

**PERSONAL CASES**

The first of the following two cases presents several features of interest and is one of the chief reasons for this communication.

**Case I.—E. C., female, age 33.**

Of her parents, the mother died young and left the father with six daughters, the patient being the youngest. One by one the other daughters married and finally she was left alone with her ageing father. He was a blacksmith, but age was sapping his strength and the patient had to do a great deal of her heaviest work for him, duties which came easily to her, for she was a very strong, active and adventurous girl, an excellent hockey player and swimmer, with a weakness for gambling. Life with her father was not a happy one and she hoped to escape by marriage as her sisters had done, but this prospect became increasingly less certain as the years passed. At 30 she was a disillusioned woman, resenting the comparative freedom of her sisters, tired of the drudgery imposed by house duties and the additional work in her father’s failing business, and finding the greatest difficulty in suppressing the anger and distaste she frequently felt for her father, now a querulous old man approaching 80. Thereafter she became progressively more lazy and slovenly and indulged her craving for gambling with every penny she could obtain, never, however, complaining to her sisters or showing the antipathy she felt towards her father. Following the development of extreme inertia with marked depression and delusions of unworthiness, she was certified and admitted to hospital on April 10, 1932.

*On admission* she was depressed, apathetic, retarded and mildly confused, with ideas of unworthiness and delusions of danger concerning her father. She heard hallucinatory voices telling her he was being burnt, but she was otherwise rational.

*Physically* she was fat, pale with a slight icteric tinge and with an extreme degree of erythema ab igne on her legs. The blood pressure was 98/70, pulse rate 72, the pupils dilated and sluggish in their reactions, the tonsils enlarged and septic, but nothing else of note was discovered. She complained of weakness, dyspepsia and
FEELINGS OF NUMBNESS IN THE SKIN. The urine was clear and sterile; a urea concentration test gave 3-7 per cent. and 4 per cent. of urea, and the blood urea was 31 mg. per cent.

Tests for syphilis were negative in the blood and fluid. Ephedrine gr. 1/4, three times a day, was prescribed.

On April 14 a gruel test meal revealed complete achlorhydria. Cultures of the fasting juice gave a growth of streptococcus viridans.

On April 15 the blood count was as follows: red cells 2-8 million; haemoglobin, 75 per cent.; colour index 1-84; white cells 11,200. Apart from a mild degree of poikilocytosis, no abnormal cells were observed in a stained film.

Pernicious anaemia was diagnosed, but it was decided to withhold liver for a time and watch for changes in the blood picture.

On April 18 a small inflammatory area appeared above the left knee anteriorly. The blood pressure had risen to 110/80 and the ephedrine was stopped.

On April 20 an incision was made in the inflamed area after spraying with ethyl chloride, and pus was obtained.

On April 22 an area of cellulitis was spreading upwards from the original focus. A further incision was made under gas anaesthesia and a swab taken, from which a pure growth of a hemolytic streptococcus was obtained on culture. The blood count at this stage was: red cells 2-6 million; haemoglobin 70 per cent.; colour index 1-84; white cells 10,400. The film showed poikilocytosis as before and two normoblasts were seen. Two c.c. of Armour's liver extract for intramuscular injection were given and repeated daily afterwards. Hydrogen peroxide syringing and eusol soaks were applied to the wounds.

On April 23 N.A.B. 45 gm. was given intravenously and 50 c.c. of polyvalent antistreptococcal serum subcutaneously.

The urine was now alkaline, contained albumin and indican, but no urobilin, and an excess of ammonium phosphate in the deposit. Van den Bergh reaction, positive indirect.

On April 24 the cellulitis was still spreading up the thigh, and two further incisions were made under ether anaesthesia; the original incisions were enlarged and all joined subcutaneously. All pockets were opened and packed with eusol soaks. A further 75 c.c. of antistreptococcal serum was given, the liver injections being continued daily.

On April 26 further incisions were made under ether and joined up as before, N.A.B. 45 gm. being given intravenously. It was felt that any further operative interference would be useless, and the prospect of recovery appeared most unfavourable. Improvement in the local condition was, however, maintained from then onwards, and by May 2 the infection was obviously subsiding, with a copious flow of pus from all wounds. The blood count showed: red cells 3-7 million; haemoglobin 65 per cent.; colour index 1-88; white cells 16,600. Two c.c. of liver extract were now given every other day. The urine was alkaline, contained much indican, and urobilin was present. The deposit contained an excess of ammonium phosphate. Improvement continued smoothly and a coincident improvement in the mental condition was observed.

On May 15 ordinary liver extract was given by the mouth in place of the injections, two tablespoonfuls twice a day. The red cells had risen to 3-9 million and the haemoglobin remained stationary at 65 per cent. The white count was 12,000. The patient remained apathetic and easily tired, but was quite rational and expressed no delusions.

On June 20 the counts were 4-3 million; haemoglobin 70 per cent.; white cells 10,000. Four carious teeth were extracted and two of four cultures of the roots gave a growth of streptococcus viridans, the other two being sterile. The patient was now getting up and the wounds were practically healed.

On August 1 the tonsils were dissected out under ether anaesthesia by Mr. D. MacAlister.

On August 15 the blood count was: red cells 6·1 million; haemoglobin 80 per
16

ORIGINAL PAPERS

cent.; colour index .66; white cells 4,000. The urine was clear and a sugar curve normal.

Because of the relatively mild anaemia and the absence of changes in the blood film and because of the complicating presence of streptococci, liver was now withheld and the patient put on massage, exercises, occupational therapy and tonics, such as iron and strychnine, improvement continuing for some time.

Toward the end of the year complaints of lassitude and depression became frequent, and by January of 1933 it became apparent that the same psychosis with which the patient was first admitted was again developing, the delusions of unworthiness and the fears for the safety of the father being prominent as before.

On January 5, 1933, the blood count was: red cells 3.1 million; haemoglobin 60 per cent.; colour index .97; white cells 7,000. Poikilocytosis was present in the film and occasional megaloblasts were found. It was not felt justifiable to withhold liver any longer and two tablespoonfuls of the extract were then given daily.

On February 8 the red cells numbered 4.5 million; haemoglobin 60 per cent.; colour index .67. There had been a steady improvement in the mental condition, although the haemoglobin had remained stationary.

On February 17 a fractional gastric analysis was made following the injection of 1 c.c. of 1/1000 histamine acid phosphate, with adrenalin m. 3 of a 1/1000 solution.

There was no free acid in the fasting juice, but the curve was a normal one for an ordinary test meal, being low for a histamine effect. Streptococcus viridans was grown from the fasting juice.

On February 28 a further gastric analysis following a meal of 50 c.c. of 7 per cent. alcohol was made, complete achlorhydria being found. It was then assumed that had histamine been given at the time of admission, acid would have been found.

On March 10 the red cells numbered 4.3 million; haemoglobin 70 per cent.; colour index .81; the film being clear. This was not considered satisfactory, but the patient was feeling so well that her discharge could not be delayed and she was discharged on March 11, 1933, with instructions for her to report if not satisfied with her condition.

On October 18, 1933, she was readmitted as a voluntary patient for a few days, at my request.

She had found work in a factory, and felt well except that she tired rather easily and was greatly worried by persistent tingling in the extremities, information that was volunteered without questioning. An alcohol test meal gave a normal curve, and a histamine curve proved much higher and normal for its type. In both cases there was free acid in the fasting juice. The blood count showed: 4.3 million red cells; haemoglobin 75 per cent.; colour index .87; white cells 11,600. The fasting juice was cultured and numerous colonies of a hemolytic streptococcus were found in the juice for the first time. A vaccine was made from these and sent to her doctor, who has been treating her with it. The patient was warned to increase her liver diet. In February of this year she wrote to say she was improving.

COMMENT

The return and increase of free acid in the gastric juice are noteworthy in this case. The close association of achlorhydria on the one hand and of pernicious anaemia and subacute combined degeneration on the other was first shown by Hurst and Bell,25 who also suggested the importance of hemolytic streptococci in the intestinal tract. Exceptions have occurred; Wilkinson 26 gives a fairly long list of cases to date where free acid was
PSYCHOSES ASSOCIATED WITH PERNICIOUS ANÆMIA

Present in the gastric juice, but it is sufficiently rare to call the diagnosis into question. Hurst,27 Conyngham and Joliffe 28 and Davidson 29 have reported instances of the return of acid following treatment.

Vaughan states that the therapeutic action of liver is seriously inhibited by the presence of sepsis, and this may explain the rather slow response in this case.

The mental state was a mild melancholia with some confusion. The return of symptoms in the absence of liver treatment was striking, but improvement took place before any rise in the haemoglobin content could be demonstrated.

Case II.—J. H. P., male, age 57.
The patient was a labourer and had been a cheery, bluff, garrulous man. There was a fairly strong history (obtained from his wife) of prolonged alcoholism, although the patient only confessed to an occasional glass of beer. His health had been generally good, but two years before admission he had had a total extraction of his teeth because of their foul condition.

One year before admission he began to be troubled with pins and needles in the feet and legs, and five months later complained of weakness of the legs. During the following two months he was treated for myalgia with no benefit. He then attended a hospital and blood was taken from a vein for examination, but no change was made in the treatment. His wife watched the development of failing memory, drawing speech, general lassitude and marked irritability. His appetite became poor and he lost weight, finally becoming bedridden with extreme weakness and drowsiness and complaining of intense headaches. Fourteen days before admission he was removed to a Poor Law Hospital and his case diagnosed as a Korsakoff's psychosis from alcoholism, being admitted to the Mental Hospital with this label on June 1, 1931. Mentally he represented a typical Korsakoff case with marked loss of memory for recent events, coupled with complete disorientation in time and space, confabulating freely and confidently when questioned, due allowance being made for his weakness and drowsiness.

Physically he was emaciated, with bedsores on sacrum and buttocks. The skin and mucous membranes showed a marked pallor, but the cheeks were high-coloured, and there was a slight general icterus. The tongue was red, glazed and dry. There was a cardiac haemie murmur and the pulse was rapid and weak. Coarse moist râles were present over both lungs. Muscle power was fairly good, but there was incoordination in all limbs, and the legs were spastic. Coarse muscle tremors occurred irregularly. Joint sense was diminished in the feet. The abdominal reflexes and the knee- and ankle-jerks were absent, the plantar reflexes indefinite. There was no skin anaesthesia and no deep tenderness. The pupils were normal.

Tube-feeding was instituted, and because of a mild delirium developing at night mild sedatives were ordered. On June 4 the Kahn test was negative in the blood and fluid. The blood urea was 21 mg. per cent. The urine was acid and contained albumin, acetone and indican. A confident diagnosis of alcoholic polyneuritis led to a regrettable delay, and it was not until June 7, while the case-details were being written out from a notebook, that the truth became apparent. On that day a blood count showed: 1-6 million red cells; 45 per cent. haemoglobin; colour index 1-41; white cells 6,000. A film showed marked poikilocytosis and polychromasia with frequent normoblasts and megaloblasts. The Van den Bergh reaction gave a delayed, direct positive and the urine contained urobilin. On the same afternoon 1 c.c. of Armour's liver extract for intramuscular injection was given intravenously by mistake, but without any ill
effect, and another 1 c.c. was given subcutaneously. Ordinary liver extract was commenced in doses of two tablespoonfuls three times a day. On June 14 there were 1-9 million red cells; 52 per cent. haemoglobin; colour index 1-37; white cells 5,600; on June 22, 4-1 million red cells; 60 per cent. haemoglobin; colour index -97; white cells 8,800. The progress in general health was remarkably rapid, and on July 6 the red cells numbered 4-2 million; haemoglobin 80 per cent.; colour index -95. The bedsores were healed, weight was increasing, and the patient was sitting up in bed very jovial and very garrulous.

On July 17 the count was: red cells 5-3 million; haemoglobin 80 per cent.; colour index -75; white cells 4,400. The film appeared normal. The mental improvement was definite, but lagged behind the improvement in general health, while the paralysis of the legs remained severe.

On August 8 the red cells numbered 6-3 million; haemoglobin 105 per cent.; colour index -83; white cells 9,000.

A test meal showed no free acid in the resting juice or in the first three tubes, but no further specimens were obtained owing to active resistance on the part of the patient.

He was now normal mentally and physically, except for the incoordination of the limbs. The knee- and ankle-jerks were still absent, the right plantar reflex extensor and the left flexor.

Massage and exercises effected a great improvement in his condition, and on May 20, 1932, he was discharged from hospital, walking with difficulty.

On December 13, 1933, in response to an enquiry, he wrote that he felt wonderfully well, but was rather weak from the knees down, although he could get about fairly well.

COMMENT

This was a straightforward case, but the Korsakoff syndrome was unusual. The diverse origins of such syndromes are, of course, well known; cases have been described due to intoxication from arsenic, lead, mercury, tuberculosis, diabetes, influenza, typhoid fever and erysipelas, and also occurring in encephalitis lethargica, malaria, ruptured cerebral aneurysm, and other conditions, as well as alcoholism. In this case, with no pernicious anaemia and a little more alcohol, he might well have developed a pure alcoholic Korsakoff's syndrome.

These two cases support the view that the mental changes developing in pernicious anaemia depend on the state of the psyche when the disease develops. If the disease becomes severe enough, a toxic confusional state is produced. The treatment is mainly that of the anaemia.

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PSYCHOSES ASSOCIATED WITH PERNICIOUS ANÆMIA

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