Pernicious Anemia in Asiatic Indians

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PERNICIOUS ANEMIA (PA) is essentially a disease of the temperate climate, affecting chiefly the white races. Friedlander reviewed the racial incidence of the disease and showed that it is rare in Negroes and comparatively rare in the dark-skinned white races such as Italians and Greeks. It is rather uncommon in Jews and is very rare in Orientals. Only a few cases have been described by Taylor and Chitkara in Asiatic Indians and by Schwartz and Rappolt in Chinese.

On the other hand, nutritional macrocytic anemia (NMA), which is almost indistinguishable hematologically from PA is frequently seen in Asiatic Indians. NMA is said to be produced by the deficiency of an "extrinsic" dietary factor, as yet unidentified. In contrast with PA, the "intrinsic factor" appears to be secreted in normal fashion by the gastric mucosa. The crucial point of difference between the two conditions thus lies in the presence or absence of the "intrinsic factor" which can only be detected by a complicated biologic test. There are, however, other important points which help in the differentiation of the two conditions and these are: (1) age incidence, (2) state of gastric acidity, (3) associated neurologic manifestations, (4) response to therapy.

1. Age incidence: PA is usually seen after the age of 40; but NMA may be found at any age, the majority of the cases being seen during the first three decades of life.

2. State of gastric acidity: Absolute achlorhydria is the rule in PA during all phases. In NMA gastric acidity is variable: some cases may show absolute achlorhydria, some hypochlorhydria and others isochlorhydria; a few may even show hyperchlorhydria.

3. Neurologic manifestations: Neurologic disturbances including subacute combined degeneration of the cord, are characteristic of PA. In NMA however, subacute combined degeneration of the cord has never been seen.

4. Response to therapy: (a) High protein diet. Some cases of NMA improve with a high protein diet alone. Such a diet has little or no effect in PA. (b) Marmite (an autolyzed yeast product). Some cases of NMA respond well to marmite, but this material is not usually effective in PA. (c) Liver extract. Both PA and NMA respond well to crude liver preparations, but refined liver extract though highly effective in PA is not equally so in NMA. (d) Folic Acid. Uncomplicated cases of NMA always show an optimum response to folic acid. In PA folic acid produces only hematologic improvement with little or no effect on the neurologic disturbance. As shown by Spies and Stone and by Wilkinson neurologic complications may appear for the first time during folic acid therapy. (e) Maintenance therapy. In NMA, unlike PA, maintenance therapy is not usually necessary.
Ordinarily, it is not possible to establish the diagnosis of PA by demonstrating the lack of "intrinsic factor" in the gastric mucosa of a suspected case of PA. For practical purposes, however, any megaloblastic anemia with absolute achlorhydria and subacute combined degeneration of the cord, which despite a well balanced diet and in the absence of any added complication always relapses on withdrawal of therapy, may confidently be labeled as a case of PA. The 3 cases described below, all of them in Asiatic Indians, fulfill the above criteria, and we have no hesitation in labeling them as cases of PA.

REPORT OF CASES

Case #1, S. R. A 63 year old Hindu priest was admitted to the Carnsichael Hospital for tropical diseases on January 13, 1949 with the following complaints: (1) tingling and numbness below the level of umbilicus for five months, (2) hesitancy of micturition for two months, (3) unsteady gait and inability to walk without support for one month.

Three years ago the patient developed anemia and was successfully treated with liver extract. (Details of investigations were not available.) After discharge from the hospital the patient relapsed twice and was successfully treated with liver extract on each occasion. Though well nourished, the patient looked pale and his face was slightly puffy. Motor power of the inferior extremities was slightly impaired. There was bilateral exaggeration of both ankle and knee jerks with extensor plantar responses on both sides. Cremasteric reflex and superficial abdominal reflexes were absent. There was definite hyperaesthesia below the level of umbilicus, with a zone of marked hyperaesthesia a little above the umbilicus. Vibration sense was diminished over both the malleoli and over the shin bones. Both the finger to nose and the heel to knee tests were defective with eyes closed. Romberg's sign was present. Muscle power and reflexes were normal in the superior extremities. All the cranial nerves were intact. Gait showed spastic ataxia. No other abnormality was found on physical examination. The laboratory data were as follows: Hemoglobin, 12.18 Gm.; red cells 3,120,000; reticulocytes 0.6 per cent; M.C.V. 118.5; M.C.H. 38.7; M.C.H.C. 32.7. Total plasma bilirubin was 0.6 mg. per cent. The Wassermann and Kahn reactions of blood were negative. A few cysts of Entamoeba histolytica were found in stool. Urine examination revealed no significant abnormality. Sternal marrow was cellular and megaloblastic. Fractional gastric analysis showed absolute achlorhydria.

Clinical course (Fig. 1). With institution of liver therapy, the patient showed steady and progressive improvement, both clinical and hematologic. Within one month tingling and numbness had almost disappeared and hesitancy of micturition definitely diminished. At the time of discharge from the hospital on April 8, the patient had only slight spasticity of the lower limbs with slightly atactic gait. The patient was last seen on May 9 when the blood count was: hemoglobin 16.24 Gm.; red cells 5,120,000; M.C.V. 95.7; M.C.H. 31.6; M.C.H.C. 33.0.

Case #2, Mrs. K. G.* A 54 year old Hindu widow was admitted to the hospital on October 28, 1948 with the following complaints: (1) soreness of mouth and tongue, off and on for two years, (2) tingling and numbness of hands and feet for one year. Past history and family history were noncontributory.

On physical examination the patient appeared well nourished but looked pale with a puffy face. Both the legs and feet were edematous and pitted on pressure. Tongue presented a smooth shiny appearance, devoid of all papillae. Heart was slightly dilated with a weak first sound in the mitral area; there was a systolic murmur in the mitral and pulmonic areas. Neurologic examination revealed slight loss of power in the flexors of forearms and fingers with diminished tone and power in both the lower limbs. There was bilateral diminution of ankle jerks. Plantar responses were extensor on both sides.

Our thanks are due to Dr. C. Saha, visiting physician and neurologist, Medical College, Calcutta for corroborating our diagnosis of subacute combined degeneration of the cord in Case 2.
Other reflexes were normal. Sense of position was impaired in the lower limbs and the heel to knee test was defective. Romberg's sign was well marked. There was no impairment of sensation of pain, touch and temperature.

The laboratory data were as follows: hemoglobin 5.8 Gm.; red cells, 1.41 M.; reticulocytes 1.0 per cent; M.C.V. 149, M.C.H. 41.1, M.C.H.C., 22.8. Total plasma bilirubin was 0.7 mg. per cent. The Wassermann and Kahn reactions of blood were negative. Total plasma protein was 6.26 Gm.; albumin/globulin ratio was 3.86/2.4. Examination of urine and stool revealed no significant abnormality. Sternal marrow was cellular and megaloblastic. Fractional gastric analysis showed absolute achlorhydria. Cerebrospinal fluid showed pressure 60 mm. of water; sugar 0.07 per cent; chloride 1.0 per cent; cell count 3. per cu. mm.; Wassermann reaction negative.

Clinical Course (Fig. 2). During the first twenty-two days the hematologic improvement was excellent but thereafter the response was sluggish. Clinical improvement was proportional to the haematologic improvement. Neurologic symptoms improved definitely after
six weeks of liver therapy; tingling and numbness disappeared and the patient felt stronger in her legs. After eight weeks, the patient could stand and take short walks without any support. But she was still markedly ataxic with eyes closed and the heel to knee test was grossly defective. At the time of her discharge from the hospital on March 23, 1949 the blood count was: hemoglobin 12.76 Gm.; red cells 4,240,000; reticulocyte 0.4 per cent; M.C.V. 91.9; M.C.H. 29.9; M.C.H.C. 32.5.

A thorough neurologic examination at that time showed only slight improvement with reference to reflexes, vibration sense and joint sense. Romberg's sign was, however, less marked than before and the motor power of lower limbs had definitely improved.

Case 3, Mrs. J. A 45 year old Hindu widow, maid servant by occupation, was admitted to the hospital on March 15, 1946 with complaints of extreme weakness, breathlessness and palpitation on slight exertion.

Previously she had been treated in this hospital in 1941 for macrocytic anemia. At that time the marrow was megaloblastic and the gastric juice showed complete achlorhydria. Treatment with liver extract apparently cured the anemia. Subsequently she attended the outdoor anemia clinic off and on from 1942 to 1944 and was treated with liver extract. She discontinued injections of liver extract for over six months, had a bad relapse in 1945, and was admitted to Medical College Hospital, Calcutta where she was again apparently cured with liver extract. Thereafter, she had no maintenance therapy for over six months and had her present relapse. She also gave a history of bleeding piles for the past two years.

On physical examination the patient looked pale but was not emaciated. The tongue was smooth and shiny. The spleen was just palpable and the liver could be felt 4 cm. below the costal margin. The heart was slightly dilated and a systolic murmur was audible in mitral and pulmonary areas. Blood pressure was 95/60. No other abnormality was found on physical examination.

The laboratory data were as follows: hemoglobin 8.93 Gm.; red cells 1,370,000; reticulocytes 0.4 per cent; M.C.V. 167.8; M.C.H. 55.2; M.C.H.C. 38.8. The total plasma bilirubin was 1.0 mg. per cent. Total plasma protein was 4.5 Gm.; albumin/globulin ratio was 2.3/2.2. Total blood cholesterol was 100 mg. per cent. The Wassermann and Kahn reactions of blood were negative. No significant abnormality in stool and urine. Sternal marrow was hypercellular and markedly megaloblastic. Fractional gastric analysis showed absolute achlorhydria.

Clinical Course (Figs. 3 and 4). The patient was treated with folic acid; during the second course of folic acid therapy the patient began to complain of a dragging pain in her right leg with weakness in both the lower limbs. On examination slight anesthesia was found in a small area on the dorsal aspect of the middle of the right leg. Left knee jerk was absent, and the right knee jerk was diminished. Finger to nose and heel to knee tests were found to be defective with eyes closed. Gait was ataxic and Romberg's sign was present. There was, however, considerable hematologic improvement with folic acid therapy. With the appearance of neurologic complications, folic acid was discontinued and the patient was given liver extract, both proteolyzed and parenteral, which brought her blood count almost to normal levels. But the neurologic symptoms, though improved, still persisted. After her discharge from the hospital on May 22, 1946 she had maintenance therapy with parenteral liver extract until the end of July 1946. Thereafter, she again discontinued her attendance and was again admitted to the hospital with a bad relapse on May 1, 1947. In addition to usual symptoms of anemia she also complained of a constant dragging pain along the thighs. Neurologic examination showed objective signs similar to those found in April 1946. With rest and hospital diet (rice 8 oz., fish 6 oz., peas 2 oz., bread 8 oz., eggs 2, milk 1 1/2 pint, butter 1/2 oz., sugar 1 1/2 oz. Plantain 1), the blood count went down still further. Bone marrow at this stage was cellular and megaloblastic, and gastric analysis showed absolute achlorhydria. From May 13 to May 30 the patient was given 14 doses of 2 oz. of finely minced meat incubated with gastric juice containing free hydrochloric acid from normal persons with normal blood counts according to the method of Castle. This produced definite improvement of blood count as shown in figure 4. The blood count improved further with proteolyzed liver powder (P.L.E.) and the patient was
discharged on June 21, 1947 when her neurologic symptoms had nearly disappeared. Thereafter she did not return for nearly one year. She next came to the outdoor clinic on May 13, 1948 with a relapse when her blood count was: hemoglobin 6.67 Gm.; red cells 1,360,000; reticulocytes 0.6 per cent; M.C.V. 154.4; M.C.H. 49.0; M.C.H.C. 31.8. She again improved with liver extract and her blood picture reached almost normal levels.

![Graph showing hematologic response](image)

**Fig. 3.**—Hematologic response of J., Case 3, from March 16, to July 25, 1946.

**Fig. 4.**—Hematologic response of J., Case 3, from May 6, 1947 to November 8, 1948.

**Analysis of Data**

**Blood Picture**

All the 3 cases had macrocytic anemia. Case 3 has been under our observation for over nine years; her anemia always relapsed whenever she did not have
maintenance therapy. The other 2 cases have been under our observation recently, but they were also reported to have suffered from relapses which invariably responded to liver therapy.

**Marrow Picture**

The marrow was megaloblastic in all the cases. In Case 3 marrow was always megaloblastic during the relapses.

**Gastric Acidity**

All the cases showed absolute achlorhydria. In Case 3 gastric analysis was done on four different occasions, in 1941, 1946, 1947 and 1948, always with identical results.

**Neurologic Complications**

Signs and symptoms of subacute combined degeneration of the cord were well marked in Cases 1 and 2 but less so in Case 3. In Case 3 the neurologic complications apparently developed during folic acid therapy but improved with liver therapy. With liver therapy Case 1 showed excellent improvement and with maintenance therapy there was no further recurrence of neurologic manifestation. In Case 2, however, neurologic manifestation though improved, still persisted.

**Effects of Therapy**

1. **Liver Extract.** Cases 1 and 3 showed satisfactory hematologic and neurologic improvement with crude liver extract. Ultimate neurologic response in Case 2 was, however, not proportional to the hematologic improvement which could be considered satisfactory. Refined liver extract was tried in Case 2 only without any immediate favorable effect on neurologic complication.

2. **Folic Acid.** Case 3 received folic acid during her admission in 1946. This produced considerable hematologic improvement as reported previously by Das Gupta and Chatterjea and shown in figure 3. But during the course of folic acid therapy neurologic complication appeared for the first time. Appearance of neurologic complication during folic acid therapy is typical of pernicious anemia.

3. **Minced meat incubated with gastric juice.** During a relapse in 1947, Case 3 was given minced meat previously incubated with gastric juice from isochlorhydric persons for fourteen days in the course of eighteen days. This produced a definite improvement of blood picture though prior to this experiment, with almost a similar diet there was a fall in the blood count (fig. 4). This experiment provides further evidence in favor of the diagnosis of PA.

**DISCUSSION**

In a careful examination of a very large number of Indian patients with macrocytic anemia during a period of fifteen years only 3 cases of PA were seen. During this period, however, a few cases of typical PA were seen in Europeans and Anglo-Indians. In 1940 Taylor and Chitkara reported 5 cases of PA in Indians and contended that PA was not rare in the Punjab. In the same issue of the Journal, Napier commented editorially: "The position in the Punjab
might be different but we do not think that the evidence presented in the paper justifies the statement that PA is not rare in the province. Though Chuttani\(^5\) in 1948 reported the follow up information of the 2 cases originally described by Taylor and Chitkara and supported their diagnosis, nevertheless, the contention that PA is not rare in the Punjab is still to be substantiated. Taylor and Chitkara published their paper eleven years ago and since then no further case has been reported either from Punjab or from any other part of India. The prevailing idea that PA is rare in Indians remains to be disproved.

With the advent of folic acid and vitamin B\(_{12}\) our ideas regarding the pathogenesis of PA and NMA have required some modification. Recent experiments of Berk, Castle et al.\(^6\) and Ungley\(^7\) suggest that the role of the intrinsic factor is only to facilitate the absorption of vitamin B\(_{12}\), which is now known to be identical with the extrinsic factor. Thus, PA appears to be a pure deficiency disease in which a deficiency of vitamin B\(_{12}\) is brought about through lack of the intrinsic factor as a result of irreversible pathologic changes in the gastric mucosa. In NMA on the other hand, the intrinsic factor being present in presumably optimum quantity, some amount of vitamin B\(_{12}\) is always absorbed and is available for preserving the integrity of the nervous system. This appears to be a probable explanation for the invariable absence of neurologic complications in NMA.

Complete cure of NMA with folic acid seems to indicate, as suggested editorially by Dameshek\(^8\) that this disease may be a manifestation of folic acid deficiency. The excellent hematologic response to folic acid in PA is indicative of a probable disturbance of folic acid metabolism in this condition.

In conclusion it is obvious that the respective role of folic acid and vitamin B\(_{12}\) with reference to each other and in the pathogenesis of PA and NMA is still far from clear.

**Summary**

Three cases of pernicious anemia in Asiatic Indians are reported. The prevailing idea regarding the low incidence of pernicious anemia in Indians is corroborated. The pathogenesis of pernicious anemia and nutritional macrocytic anemia is discussed briefly.

**REFERENCES**

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