Comment

This single case is worth reporting because of the early age of onset of anaesthesia and trophic change; also the very early age of onset of deafness, which led to certification as a mental defective. The cases so far described occurred at a later age, usually between 20 and 30 years.

There is little doubt that the anatomical localization of the lesion in this case is in the posterior root ganglion and the ganglia of the eighth cranial nerve; but the pathogenesis is not clearly defined. The group of cases may well include several syndromes of differing aetiology with differing clinical courses. This child may eventually prove to have a progressive degenerative lesion, possibly secondary to an inborn error of enzyme metabolism, but the rate of progression would appear to be very slow; in fact, there is very little to suggest deterioration so far. Alternatively, this might be due to a fault in the development of the posterior root ganglion.

Summary

A case of sensory radicular neuropathy is described in a boy of 8 years, who has been so deaf from early infancy that he had never acquired speech. He had impaired pain sense at the age of 15 months. There is no family history of the condition. He presented with painless ulceration of the toes, symmetrical loss of deep reflexes, the axon reflex, and impaired sensation to pain and temperature over the periphery of the limbs: proprioception, touch, vasomotor responses, and sweating remaining intact. Histological examination of the peripheral sensory nerve showed demyelination.

This case is compared with cases previously reported and the mechanism of symptomatology briefly discussed.

I am greatly indebted to Dr. P. Sandifer for permission to publish this case, and I thank Dr. D. S. Hallpike for his report on the otological findings, Dr. W. Blackwood for his biopsy report, and Dr. J. Simpson for the electrical studies.

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Statistics recently issued by the Armed Forces Medical Library, Washington, the world's largest medical library, demonstrate the immense output of literature concerning medicine and related subjects. During the year ended June, 1955, the library acquired 14,000 books, 77,000 parts of journals, and 1,182 new journal titles; it lent 168,000 volumes, answered 10,310 reference questions, and compiled 405 bibliographies of some length. In response to 101,000 orders it filmed 1,640,000 pages, and it published in the *Current List of Medical Literature* 102,645 items from 1,560 journals regularly indexed. During the year an average of 216 persons were employed by the library and the running costs were \$1.2 million.

HAEMOGLOBIN E IN BURMESE

TWO CASES OF HAEMOGLOBIN E DISEASE

BY

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Besides normal adult haemoglobin (haemoglobin A) a number of genetically determined variants are known (S, C, D, E, G, H, and I), and there is evidence, more complete in some cases than in others, that seven of these forms (not H) are the products of allelic genes, heterozygotes having varying quantities of the two kinds of haemoglobin concerned. The distribution of these genes is governed by various factors: mutation rates, genetic drift, and natural selection. A balance may be reached between the selection rates for two or more genes especially if the heterozygotes are more viable than the homozygotes, when a state of balanced polymorphism will be reached. However, the most obvious factor in the present distribution is an anthropological one.

Haemoglobin S (sickle-cell haemoglobin) is found in African Negroes between the Sahara Desert and the River Zambesi and in their known descendants elsewhere, and also in some peoples of the Mediterranean area and in some Vedoids of India and Arabia. Haemoglobin C has so far been found in West Africa and in places where it may have been introduced by West African slaves. Haemoglobin E was first reported in one child whose father was of part Indian origin (Itano *et al.*, 1954; Sturgeon *et al.*, 1955), and it was simultaneously discovered in the Siamese (Chernoff *et al.*, 1954a). It has since been observed in Veddas (Graft *et al.*, 1954) from Ceylon and in Indonesia (Lie-Inju Luan Eng, 1955). We would like to report that we had recently the opportunity of examining a group of Burmese in this country. Among 80 young adults—78 of whom were unrelated—12 with haemoglobin E were discovered. Ten had both haemoglobin A and haemoglobin E and two were homozygotes.

Haemoglobin E Disease

To describe a person as homozygous for a gene responsible for an abnormal haemoglobin is not strictly permissible unless the diagnosis by electrophoresis has been confirmed by a family study. The thalassaemia gene causes suppression of haemoglobin A formation. In microcytic disease, a condition in which AS heterozygotes also carry the thalassaemia gene, formation of A can be suppressed to such an extent that laboratory diagnosis may not be able to distinguish between the resultant phenotype and that of S homozygotes, although the genotype will be AS in one and SS in the other. Thus two individuals were recently seen in the Gold Coast (Edington and Lehmann, 1955) who, on the basis of laboratory examinations, were at first assumed to be homozygous for S, but a subsequent family study revealed that they were in fact AS heterozygotes who were carrying a thalassaemia or thalassaemia-like gene. Allison (1955) has

proposed a nomenclature which differentiates between the genotype and the haemoglobin mixtures actually found in the phenotype.

Both homozygotes for E (EE) and the thalassaemia-AE heterozygotes so far reported show no haemoglobin A, the first because the gene for A is absent, the second because the formation of A is suppressed. However, from all available information (see particularly Chernoff, 1955) it seems that the homozygous state shows only little foetal haemoglobin (haemoglobin F), but that in thalassaemia-AE heterozygotes the percentage of F varies from 20 to 40. (F is normally not found beyond the age of 4 months, but in some congenital anaemias it may persist beyond that age. The production of F is genetically independent from that of A and its variants.) The thalassaemia-AE heterozygotes usually suffer from a severe anaemia—thalassaemia-haemoglobin E disease. Homozygotes for E have been said to suffer from haemoglobin E disease—in analogy with sickle-cell disease (SS) and haemoglobin C disease (CC), but in view of the findings which we are presenting below it is questionable whether the word "disease" is fully applicable.

The only reports on haemoglobin E disease have been published from Siam, where five individuals had been seen. Splenomegaly was found in three, and hepatomegaly in two. All complained of tiredness, easy fatigability, and joint pains, and two showed icterus. Haematological studies revealed normal erythrocyte and low haemoglobin levels, no increase in reticulocytes, and a high incidence of target cells. Foetal haemoglobin was found in all cases, and varied from 2 to 6% (Chernoff *et al.*, 1954b).

Case 1

The first young Burman (L.K.) whose blood was discovered to show homozygous haemoglobin E was found to be a fit individual. He belonged to the aboriginal Burmese community of the Mon, which is known for its aversion to contracting marriage with other Burmese groups. He was seconded to Britain for training in aircraft engineering. His father died at the age of 54 years of a lung disease, and his mother, aged 65, was alive and well. He was the youngest of six children, all living. He was 26 years old, his height 152 cm., and his weight 49 kg. Apart from an attack of malaria in 1943 for which he was sent to hospital, his only contact with doctors was when he was treated for snake-bite in August, 1953. There was no history of anaemia, haematuria, or joint pain.

On physical examination nothing abnormal was discovered; the spleen and liver were not enlarged. The blood pressure was 90/60 mm. Hg and the electrocardiogram (Leads I, II, III, R, L, F, V₁, V₃, V₅, and V₆) was reported as normal by Dr. R. I. Duff, of the Cardiological Department St. Bartholomew's Hospital. Dr. W. D. Nichol, of the Radiological Department, St. Bartholomew's Hospital, found the heart not enlarged, the lungs clear, and no bony changes in the skull, pelvis, and humerus. Biochemical examination of the serum showed a raised bilirubin. The raised globulin, a thymol turbidity of 4 units, and a pseudocholinesterase level of 49 units (normal 55 and above) suggested some deficiency of liver function. The only abnormal constituent of the urine found was urobilinogen in increased quantity.

Biochemical Examination of Serum.—Urea, 30 mg. per 100 ml.; van den Bergh reaction: direct test, weakly positive; total serum bilirubin, 1.2 mg. per 100 ml.; serum alkaline phosphatase, 12 K.-A. units; total serum protein, 7.9 g. per 100 ml. (albumin 4.8 g., globulin 3.1 g.); pseudocholinesterase, 49 units; thymol turbidity test, 4 units; zinc sulphate turbidity, 11 units.

Urine.—A clear pale-yellow specimen of neutral reaction had a specific gravity of 1016. The centrifuged deposit showed nothing abnormal. The specimen contained no protein or reducing substance, and no acetone or aceto-acetic acid. Fouchet's test for bilirubin was negative. Ehrlich's test for urobilinogen was positive, and Schlesinger's test for urobilin was positive.

Haematological Examination.—The blood of L.K. was examined on three different occasions, on all of which a considerable polycythaemia was noted. The following values were obtained on heparinized blood in conjunction with the measurement of the plasma (and blood) volume: Haemoglobin, 13.6 g. per 100 ml.; foetal haemoglobin, 2.1%; packed cell volume, 44%; red cells, 7,470,000 per c.mm.; saline fragility, greatly reduced (see Fig. 1); target cells 5.3%; reticulocytes, 0.6%; M.C.V., 59 cubic μ ; M.C.H.C., 31%; M.C.H., 18.2 γ ; M.C.D., 7.3 μ (Fig. 2); mean thickness 1.4 μ . The red cells showed slight anisocytosis, some appeared hypochromic (Fig. 3). No polychromasia or nucleated cells were seen; in wet preparation the cells appeared "flattened." Platelets, 250,000 per c.mm.; prothrombin time (oxalated plasma), 13 seconds; white cells, 7,400 per c.mm. (neutrophil segmented cells 55%, eosinophils 3%, lymphocytes 39%, monocytes 3%); plasma volume (Evans blue technique, Crooke and Morris, 1942), 2,680 ml.; 17.6 ml./cm. height; 54.7 mg./kg. weight; 17.9 ml./square cm. surface. Blood volume (8% correction for plasma "trapped" by centrifuged red cells), 4,575 ml.; circulating haemoglobin, 622 g.

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Haemoglobin.—The foetal haemoglobin percentage was determined on three different occasions (Singer *et al.*, 1951). It was 2.5, 2.1, and 2.1% respectively. On paper electrophoresis in barbitone buffer pH 8.6 the haemoglobin was found to migrate as a single spot. Both the hanging-strip method and horizontal electrophoresis on paper enclosed in silicone-coated glass plates were used. The haemoglobin was found to migrate faster than haemoglobin C and more slowly than haemoglobin S. This haemoglobin, as well as the ten samples of AE obtained from the ten Burmese mentioned above, was compared with other AE samples from Siam obtained by the courtesy of Miss Virginia Minnich (Fig. 4). Sturgeon *et al.* (1955) have emphasized that the identification of haemoglobin E by electrophoresis should include tests at alkaline and at acid pH. At the former, E migrates very much like C and is found between C and S; at

FIG. 1.—Saline fragility of red cells of the two Burmese homozygous for haemoglobin E. The resistance to hypotonic NaCl solutions is increased, and is at no concentration within the normal range. $\times$ — $\times$, L.K.; o — o , K.L.

FIG. 2.—Price-Jones curve of red cells of Burman homozygous for haemoglobin E.

FIG. 3.—Stained peripheral blood smear of Burman (L.K.) homozygous for haemoglobin E ($\times 850$). The diameter of the cells is nearly normal. Area with numerous target cells.

The diameter of the cells is nearly normal. Area with numerous target cells.

FIG. 4.—Comparison of the haemoglobin of L.K. (EE) with that of individuals homozygous for A, G, S, and C. Foetal haemoglobin was present in the samples of S, C, and E (5.9%, 3.8%, and 2.5%). The cells were frozen after washing and packing. They were then lysed with water and the stroma was removed after shaking with toluene and centrifuging. The haemoglobin solutions were examined by filter-paper electrophoresis at pH 8.6. The technique followed was that of Smith and Conley (1953). After drying, the haemoglobin spots were stained with "light green" dye (Dangerfield and Smith, 1955). The line of origin is shown. (Slightly enlarged, $\times 1.125$.)

the latter it resembles S in its speed of migration. We therefore examined our haemoglobin samples not only at pH 8.6 but also at pH 6.5, 6.8, and 7. (Filter-paper electrophoresis between glass plates; phosphate buffer M/10, M/15, and M/20; 200 v., 4 m-amp.; 12 to 16 hours at room temperature.) There was good resolution of the AC mixtures, but that of AS and AE samples was not as satisfactory as that demonstrated by Itano *et al.* (1954) and Sturgeon *et al.* (1955) by open boundary electrophoresis. However, there could be no doubt that at acid pH the AE mixtures were either indistinguishable from AS mixtures or migrated between AS mixtures and A samples, being quite different from AC mixtures. E by itself was found either in the same position as S or between A and S.

Case 2

The second young Burman (K.L.) to show homozygous haemoglobin E was also fit. He was a captain in the Burmese army, and was seen on a brief visit to London. He was leading an active life and was a keen sportsman. His father had died from diphtheria at the age of 51; his mother, aged 52, was alive but suffered from high blood pressure. One elder brother, aged 33, was well; one younger brother had died at the age of 3—the cause of death was unknown. K.L. was 30 years old, his height 169 cm., and his weight 54 kg. The only past illness had been an attack of malaria in 1952 which had been cured within 10 days. There was no history of anaemia, haematuria, or joint pain.

Physical examination revealed no abnormality; the spleen and liver were not enlarged. The blood pressure was 116/91 mm. Hg; and the electrocardiogram (Dr. R. I. Duff) and the x-ray examination of the chest, the long bones, and the skull (Dr. B. Green) disclosed nothing abnormal. Like the first homozygote for E, the second showed a high serum globulin and a slightly raised thymol turbidity, but the pseudocholinesterase was within normal limits, suggesting that there was no deficiency of liver function. The urine gave a positive reaction for urobilinogen, and there was a trace of protein. There was no opportunity to test for orthostatic albuminuria.

Biochemical Examination of Serum.—Urea, 38 mg. per 100 ml.; van den Bergh reaction: direct test, negative; total

serum bilirubin, 0.7 mg. per 100 ml.; serum alkaline phosphatase 16.5 K.-A. units; total serum protein, 8 g. per 100 ml. (albumin 4.7 g., globulin 3.3 g.); pseudocholinesterase, 84 units; thymol turbidity test, 5 units; zinc sulphate turbidity, 12 units.

Urine.—A clear golden-coloured specimen of acid reaction had a specific gravity of 1028. The centrifuged deposit showed nothing abnormal. Heat acetic acid test and sulphosalicylic acid test demonstrated a trace of protein. There was no reducing substance, acetone, or aceto-acetic acid. Fouchet's test for bilirubin was negative. Ehrlich's test for urobilinogen was positive, and Schlesinger's test for urobilin was positive.

Haematological Examination.—The blood of K.L. was examined on two occasions. The following values were obtained on oxalated blood: haemoglobin, 16.3 g. per 100 ml.; foetal haemoglobin, absent; packed cell volume, 46%; red cells, 8,440,000 per c.mm.; saline fragility, greatly reduced (see Fig. 1); target cells, 8.9%; reticulocytes, 1.5%; M.C.V., 55 cubic μ ; M.C.H.C., 35%; M.C.H., 19.3 γ ; M.C.D., 6.2 μ ; mean thickness, 1.8 μ . The red cells showed

only moderate anisocytosis and no poikilocytosis (Fig. 5). No polychromasia, punctate basophilia, or nucleated cells were seen. Platelets, 140,000 per c.mm.; prothrombin time, 15 seconds; white cells, 8,600 per c.mm. (neutrophil segmented cells 60%, eosinophils 2%, basophils 1%, lymphocytes 33%, monocytes 4%).

Haemoglobin.

There was no foetal haemoglobin when the blood was tested on two different occasions (Singer *et al.*, 1951). Paper electrophoresis at pH 8.6 showed in this, as in the first case, only one component, with the mobility of haemoglobin E. On lowering the pH of the buffer a change was again demonstrated in the comparable speed of this haemoglobin and that of haemoglobin S.

FIG. 5.—Stained peripheral blood smear of Burman K.L., homozygous for haemoglobin E ($\times 850$). Normal thickness with low diameter.

Discussion

The homozygous combination of S haemoglobin leads in the great majority of cases to a severe haemolytic anaemia—sickle-cell anaemia. Homozygous haemoglobin C disease has so far been found to be a relatively less serious disorder. So far as one can judge from the observation on two individuals, homozygous haemoglobin E disease seems to be an even less severe condition. L.K. suffers from a mild haemolytic anaemia leading to a slightly raised serum bilirubin and an increase in urinary urobilinogen, but there is no enlargement of the spleen and no bony changes were noted. The cells are somewhat hypochromic, very thin, but of nearly normal diameter. The resulting low corpuscular haemoglobin is, however, compensated by a rise in the number of cells similar to but exceeding that seen in the hypochromic anaemia of iron deficiency and thalassaemia major. The high cell count of 7,470,000 cells per c.mm. is usually seen only in polycythaemia vera or secondary polycythaemia caused by lack of oxygen. There was no increase in blood volume, and the white-cell count and the platelet count were normal. L.K. had been living at sea level in the last five years, and there was no suggestion of heart or lung disease which might cause a lack in oxygen.

In K.L. the only sign of increased haemolysis was the positive urobilinogen test in the urine. The reticulocyte count and the serum bilirubin level were still within the upper limit of normal. There was not even a slight anaemia,

as in the case of L.K., and the cells, though small, were fully saturated with haemoglobin. Whereas in L.K. the microcytosis was mostly due to an excessive thinness of the red cells, in K.L. it could be related to a smaller diameter of the cells rather than to low M.C.T. As in L.K. so in K.L., the low mean corpuscular haemoglobin was compensated by a rise in the absolute number of cells. There was no suggestion of polycythaemia vera or a polycythaemia secondary to any condition other than the microcythaemia.

Although the group of Burmese so far examined is small, it is significant that the incidence of haemoglobin E should amount to 15%, and it may be expected that the Burmese resemble the Siamese in that respect.

NaNakorn *et al.* (1956) found the incidence of haemoglobin E to be 13.6% in 1,006 Siamese, but none was seen in 213 Chinese. Lie-Inju Luan Eng (1955) found an incidence of 3.6% in 500 Indonesians. Aksoy *et al.* (1955) found it to be 3.6% in 167 Veddas from Ceylon, but observed none in Sikh (Europoid-Mediterranean) and Nepalese (Mongoloid) Indian soldiers. Similarly, Lehmann and Sukumaran (unpublished) found no haemoglobin E in a series of aboriginal communities of the Nilgiri Hills in Southern India, among whom, however, the sickle-cell trait is present with considerable frequency. No haemoglobin E was found among 166 Australian aboriginals (Horsfall and Lehmann, 1956). On the other hand, one example was discovered among 131 Eti-Turks (Aksoy *et al.*, 1955); they are a small Arabic-speaking group in Southern Turkey among whom the gene for sickle-cell haemoglobin has been found with high frequency. No haemoglobin E was found in 110 pure Turks and in what amount to some thousands of examinations of bloods from all over Africa and Europe. The one exception is a patient with thalassaemia-haemoglobin E disease found among the "Cape Coloured" in South Africa (Budtz-Olsen and Brain, personal communication). Such an observation was not unexpected in view of the Malayan admixture which, under the Dutch, had contributed to the formation of the "Cape Coloured" group (Lehmann, 1955).

It is possible that haemoglobin E will be found to play a similar part in South-East Asia to that of sickle-cell haemoglobin in Africa. If this is so it will have similar implications to those already noted for that of haemoglobin S in anthropology, pathology, and population genetics.

We hope to extend the present investigation of the Burmese and to combine it with a determination of blood-group frequencies that is being carried on by Dr. A. E. Mourant and Miss E. W. Ikin, of the Blood Group Reference Laboratory, London.

Summary

Among 80 young Burmese, 12 were found with haemoglobin E. Ten were heterozygotes for adult haemoglobin and haemoglobin E (AE). Two were haemoglobin-E homozygotes (EE). They were considered fit and led active lives. On examination evidence was found of a mildly haemolytic condition. The red cells were much smaller than normal, and the resulting low mean corpuscular haemoglobin was compensated by an increase in the number of red cells to 7,400,000 and 8,440,000 per c.mm. respectively.

The distribution of haemoglobin E in Asia is discussed.

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MASSIVE BLOOD TRANSFUSION FOR TRAUMATIC POST-PARTUM HAEMORRHAGE

BY

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This case is worthy of record because of the large amount of blood that had to be transfused, and because the patient failed to respond satisfactorily until blood had been transfused by the intra-arterial route and operation performed.

Case Report

A 7-gravida aged 31 had had five full-term deliveries and one miscarriage. The last full-term delivery in 1952, at home, had been precipitate and the baby died. The miscarriage was in 1953. During the present pregnancy she had been very well but required much persuasion to come into hospital for confinement.

Labour started spontaneously on August 19, 1954. The first stage lasted ten minutes and the second stage five minutes. A living female infant weighing 7 lb. 4 oz. (3.3 kg.), was delivered at 7.25 a.m. A slight loss of blood accompanying delivery of the baby had been noted, but no significance had been attached to it. The placenta and membranes were expelled complete at 7.33 a.m., and there was then an immediate loss of 50 oz. (1.4 litres) of blood. Ergometrine, 0.25 mg., was given intravenously, and at the same time 0.25 mg. intramuscularly. The house-surgeon passed a speculum but no tear was noted. At 7.55 a.m. the pulse rate was 108 a minute and blood pressure 90/7. Dextrose (5%) intravenous transfusion was started whilst blood was being cross-matched, and at 8.45 a.m. (pulse rate now 125) blood transfusion was begun. The patient responded to this. By 9.15 a.m., and after 3 pints (1.7 litres) of blood, the pulse rate had fallen to 112 and the blood pressure was 80/60. The uterus was well contracted and there did not appear to have been further loss.

During the morning slight blood loss was noted at intervals, and the blood was obviously clotting. The blood pressure remained at 80/60, and morphine, $\frac{1}{4}$ gr. (16 mg.), and methedrine, 10 mg., were given intravenously at 11.10 a.m.

One of us (G. G. L.) saw the patient for the first time at 12.45 p.m., when she was being transfused with her ninth pint of blood. Blood pressure was 50/nil and the pulse rate 100. The total loss had so far been estimated at 130 oz. (6½ pints, or 3.7 litres). Dr. T. R. Steen, consultant anaesthetist, anaesthetized her (atropine, 1/200 gr. (0.32 mg.) intravenously; nitrous oxide, oxygen, and ether) and G. G. L. explored the uterus manually. There were no placental fragments, no inversion, and no rupture. A left-sided cervical tear extending into the left fornix was found and sutured, and the uterus was packed. Bleeding appeared to be