when the menarche will occur in an individual. This would be of great value to parents and others concerned with education in health and sex.

We are indebted to the educational and medical authorities in Dorset, Essex, Oxford, and Oxfordshire for their help in obtaining the necessary data for the first part of this study. It is a pleasure to thank Mr. P. H. Leslie for his advice. We also wish to thank the medical officers of the boarding-schools in Sussex and Yorkshire for their readiness to make available to us the medical records of those who had left school, and for their interest in the study.

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FATAL CASE OF ACUTE PORPHYRIA IN A NEGRO

BY

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Acute porphyria has been reviewed in several papers since 1945. Abbott and Evans (1946) found that nearly 300 cases had been described since Günther's first case in 1911. Pyrrole metabolism is reviewed by Dobriner and Rhoads (1940) and by Welcker (1945). The following are the main clinical points.

Porphyria is a disorder of metabolism of the respiratory pigments (haemoglobin, myoglobin, cytochrome oxydase, etc.). "Acute" porphyria is almost certainly a chronic disorder, with acute episodes superimposed (Gray, Rimington, and Thomson, 1948). Barbiturates, sulphonamides, "trional," arsenicals, phosphorus, or lead may precipitate an attack (Dobriner and Rhoads, 1940), but there is no hard-and-fast distinction between the toxic and idiopathic varieties (Discombe and D'Silva, 1945).

Roth (1945) states that psychic episodes may occasionally precipitate an acute attack, and that the siblings of these patients are often hysterical or psychotic. Porphyrins are excreted in abnormal quantities during attacks and often between attacks; the usual finding is uroporphyrin III or coproporphyrin III, but Gray (1950) says, "It has never been possible to correlate the varied clinical features with any definite pattern of porphyrin excretion." He had a case in which the colourless porphobilinogen was predominant. Characteristically the urine is a red or brown colour and darkens further on standing. Hare and Wilmore (1948) quote Waldenström's epithet "la petite simulatrice" and his remark that hysteria is often suspected. Davies (1949) finds that barbiturates are given to the majority of these patients.

The acute form is commoner in women—3:1 (Abbott and Evans, 1946). The age of onset is 20 to 45 (Davies, 1949). Symptoms may be mainly abdominal, or mainly nervous, or combined abdominal and nervous as in the classic type. There may be a prodromal period of lassitude and mental disorder, and the onset is with colicky abdominal pain, nausea, vomiting, constipation, leucocytosis, tachycardia, and a rise in blood pressure; while hypotension is common in the later stages. Sometimes the pain is in the form of dysmenorrhoea. Attacks of jaundice are not infrequent and may obscure the significance of dark urine, and it is worth noting that an apparently positive Ehrlich aldehyde test is given by porphobilinogen in the urine (see below).

In nearly half the cases neurological symptoms occur, which may include confusion, delirium, convulsions, or amaurosis. Characteristically there is a polyneuritis, which may fluctuate in severity, affecting the limbs, especially the proximal segments, with or without cranial nerve and sphincter involvement. Pain and paraesthesias are common, but objective sensation is usually relatively spared. With neurological involvement the mortality is about 75% (Berg, 1945; Petrie, 1948). Subsequent attacks may occur in those who survive (Gray, Rimington, and Thomson, 1948).

Case Report

The patient, a male native of Lagos, Nigeria, aged 30, had been in London for six months preparing for examinations in accountancy. He was admitted on April 13, 1950, with the history of inconstant shortness of breath for some years, related sometimes to physical and sometimes to emotional strain. He was a hard worker, conscientious, and ambitious, but lacked self-confidence. He had worn spectacles for some weeks. Seven weeks before admission he again complained of dyspnoea, and doubted his ability to pass his examinations. After a week he complained of central abdominal pain with nausea, vomiting, and constipation, and was admitted to another hospital from which he went home against advice after three weeks.

A week later a reassuring talk relieved his symptoms, but next day he had anorexia, paraesthesias, and pains in the limbs, followed by hallucinations, insomnia, and irregular behaviour. This sequence of events strongly suggested hysteria, and he was given 3 gr. (0.2 g.) of butobarbitone at night. After this he became clear mentally, but noticed a gradual onset of weakness in all limbs. He became incontinent of urine, and was admitted to this hospital. Specific inquiry later revealed that he had had red urine on occasions for some years and for most of the last six weeks. His parents, two sisters, and three brothers had always been well, and had never mentioned similar discoloration. No siblings had died. He knew of no white ancestry.

On examination he was markedly wasted and dehydrated. He was febrile, 99.6° F. (37.55° C.). There was bilateral conjunctivitis with mucopurulent exudate. His tongue was furred, his mouth was dry, and his breath foul. The buccal mucosa and teeth were normal. The abdomen was lax and retracted, and slightly tender in the right iliac fossa, with a nodule of faeces in the left iliac fossa. The liver and spleen were not palpable. The heart and lungs were normal, the pulse was 130, and the blood pressure 115/75. Although correctly orientated and otherwise rational, he thought that there was "somebody under the bed lifting it up and down." Visual fields were full by confrontation. There was slight weakness of the left fifth cranial nerve, his voice was very weak, and his speech a little slurred and difficult to understand. His neck was normal but the trunk muscles were weak. There was a flaccid tetraplegia, almost complete at the hips, shoulders, knees, and elbows, with very little power at the distal joints and with a coarse irregular tremor when movements were attempted. All tendon-jerks were present, the knee-jerks being very feeble. The plantar responses were normal. Sensation to pin-prick was slightly impaired over the forearms and hands; light touch, position sense, and vibration sense were normal. There was a burn from a hot-water bottle on the right calf; elsewhere the skin was normal. Tenderness was increased in the calves. He was incontinent of urine. The white cells numbered 6,000 (polymorphs 62%, lymphocytes 30%, monocytes 8%).

On the first day after admission his blood pressure was 140/100. Examination of the urine revealed: acid, a trace of protein, no Benedict reduction, no casts, cells, organisms, bile salts, or bile pigments. A blood count showed: red cells, 4,850,000; Hb, 97%; white cells, 21,000 (polymorphs 88%, lymphocytes 12%). On the second day the urine was seen to be brownish red and was then found to contain porphyrins. By this time his voice had sunk to a whisper. The weakness of the fifth cranial nerve had increased; both knee-jerks and

the left ankle-jerk were absent. His blood pressure was 120/80. On the fourth day the facial muscles were mildly affected. The sclerotics were a yellowish brown colour, but the serum bilirubin was 0.4 mg. per 100 ml.; the direct van den Bergh was negative.

On the sixth day he was generally weaker and there were paradoxical respiratory movements. Coarse rales appeared in the chest, and breathing became slow and irregular before he died. During the six days his pulse rate varied from 118 to 150, average 130. There was continued pyrexia, higher in the last 36 hours, average 100° F. (37.8° C.). On the day before death a blood count showed: red cells, 4,130,000; Hb, 84%; white cells, 13,800 (polymorphs 79%, eosinophils 20%, monocytes 1%). On the last day the blood urea was 156 mg. per 100 ml.; blood sugar 129 mg. per 100 ml.; Wassermann reaction and Kahn test negative; serum alkaline phosphatase 6 K.-A. units; direct van den Bergh positive; serum bilirubin 0.8 mg. per 100 ml. Total serum protein was 6.56 g.%—albumin 3.02 g., globulin 3.54 g.

Post-mortem Examination

This was carried out 20 hours after death by Dr. N. Orchard, to whom I am indebted for the following report.

"Lungs: marked congestion and oedema. Stomach: mucous gastritis and numerous petechiae in the mucosa. Spleen: deeply congested with very prominent follicles. Liver: firm, slate-blue in colour, with numerous small greyish-yellow areas. Kidneys: traces of foetal lobulation; capsule stripped easily; deeply congested, but a slate-blue colour evident. Brain and cord: oedematous.

"The following organs were of slate-grey or bluish colour: visceral and parietal pleura and peritoneum, myocardium, psoas and rectus abdominis muscles, liver, kidney, most of the jejunum, the caecum, and the proximal half of the ascending colon. The following were of an unusual yellow-orange colour: pancreas, cerebellum, omentum, peritoneal fat, and the sternal, vertebral, and iliac marrow. The following fluoresced with a pink or red colour in ultra-violet (Wood's) light: liver, kidneys, omentum, psoas and rectus abdominis muscles, myocardium, pericardium, aorta, costal cartilage, and sternal marrow.

"Histological abnormalities were as follows:—Right optic nerve: marked round-cell infiltration, the myelin sheaths being intact. Anterior horn cells: marked chromatolysis at all levels of the cord. Cerebellar Purkinje cells: severe degeneration. Liver: polygonal cells loaded with greyish, granular pigment. Kidneys: congested. Lungs: oedematous, congested, with early bronchopneumonia."

Biochemical Findings

The urine when freshly passed was a red-brown colour and darkened considerably on standing. The Watson and Schwartz modification of the Ehrlich aldehyde test was positive (see below). A quantity of urine was collected over a period of some days and sent for biochemical examination. I am greatly indebted to Dr. L. Ellis for his report, as follows.

"The urine was a deep port-wine colour and did not obviously darken further on standing. Using a direct-vision spectroscope, the urine showed two absorption bands in the green closely resembling the bands of oxyhaemoglobin and a band at the junction of the green and the blue. About 15 ml. of urine was acidified with a few drops of glacial acetic acid and shaken thoroughly with about 10 ml. of tertiary amyl alcohol. After centrifuging, the upper alcohol layer showed the same absorption bands and gave a brilliant pink fluorescence under the ultra-violet lamp. It would seem that the porphyrins were excreted as metallo-porphyrins (see Chandler, Harrison, and Rimington, 1939).

"For further differentiation a specimen of urine was acidified with a few drops of glacial acetic acid, and extracted with several quantities of ether until the ether layer showed no further spectroscopic evidence of the presence of porphyrins. This indicated that all coproporphyrin had been extracted. The urine layer was then extracted with amyl alcohol and the alcohol

layer separated. This layer now contained the uroporphyrin. The ethereal extract was evaporated down to the same volume as the amyl-alcohol extract and the two extracts were compared under the ultra-violet lamp and spectroscopically. It seemed obvious that, while there appeared to be quite a fair amount of coproporphyrin, uroporphyrin was present in some excess."

Discussion

The diagnosis of acute porphyria seems to be substantiated on the sum of the findings recorded. The clinical course of the illness was in accord with the usual (albeit variable) symptomatology, and there were two further points which are not included in the introduction. Hare and Wilmore (1948) were "impressed by the degree of cachexia and debilitation" in one of their cases. Davies (1949) noted a yellow-brown tint in the sclerotics not due to bilirubinaemia.

Roth (1945) mentions the temporary or protracted attacks of amaurosis which may occur, and in his cases neither ophthalmoscopic nor post-mortem microscopical abnormalities were detected to account for the symptom. My patient made no specific complaint about his vision, and no history was obtained whether he had had intermittent amaurosis, but it may possibly be significant that he had recently worn spectacles. Equally problematical is the significance of the other early symptom—namely, the shortness of breath accompanying emotional strain.

Degeneration, pigmentation, and fluorescence of organs have been recorded. To summarize Roth (1945), the commonest central-nervous-system changes are parenchymatous degeneration in the peripheral nerves, the anterior horn cells (and to a lesser extent the posterior horn cells), the cerebellar Purkinje cells, the cerebral cortex, and the sympathetic ganglia. The changes are more marked in the peripheral nerves and lower segments of the central nervous system.

Abrahams, Gavey, and MacLagan (1947) found a striking bluish black discoloration of both rectus abdominis muscles, parts of the psoas muscle, and peritoneum, with red fluorescence under ultra-violet light in the costal cartilage, sternal marrow, rectus muscle, small intestine, and elsewhere. Prunty (1946) found ultra-violet fluorescence (microscopically) in the liver, renal tubules, costal cartilage, and parts of the central nervous system. In his case, however, the pigment granules in the liver parenchyma were of two kinds—large golden-yellow granules and small red-orange granules. It is usually agreed that acute porphyria is commoner in those of Scandinavian descent (Discombe, 1948), and there is evidence that it may be transmitted as a Mendelian dominant. If this is so, the occurrence of a case in a West African negro makes it possible that it may occur in the American negro, but, judging by the literature of both countries, it is rare. A brief survey revealed only one other case, that of Schneck (1946) in the United States, and he could find no other cases. It may be said, however, that his case, although suggestive, was not proved, for at no stage were porphyrins detected in the urine or elsewhere.

Finally, it is worth repeating a point stressed by many authors, that the diagnosis should be considered and the urine examined in any patient with obscure mental, nervous, and/or abdominal symptoms. The simplest test is that of Watson and Schwartz (1941) for porphobilinogen. Mix equal parts of urine and Ehrlich's aldehyde reagent, add a few millilitres of chloroform, and shake. Urobilinogen gives a red colour soluble in the chloroform layer, but porphobilinogen gives a red colour which remains in the aqueous layer.

Summary

A case of classical acute porphyria occurring in a West African negro is described. Post-mortem and biochemical findings are included. The literature is briefly quoted.

I am indebted to Dr. A. Kahan, under whose care the patient was admitted, for permission to publish the case and for his encouragement and advice; to Dr. N. Orchard for the post-mortem report and the preliminary detection of porphyrins; to Dr. L. Ellis, biochemist to the Lambeth Group Laboratory, for his report on the urine findings; and to Dr. J. Olu-Mabayojé, who had known the patient for many years, for his help with the history.

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FOLLOW-UP OF RHESUS-NEGATIVE PRIMIGRAVIDAE DEVELOPMENT OF RHESUS IMMUNIZATION

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Rhesus immunization in the first pregnancy has been found only very exceptionally, apart from patients who had previously received a transfusion of rhesus-positive blood. Few authentic cases of rhesus immunization of the first-born child have been mentioned in the literature (Boorman, Daley, and Dodd, 1947).

It has been suggested that the immunizing stimulus is provided during labour by a small "blood transfusion" given to the mother by the foetus through the breakdown of the syncytial placental layer. During the second pregnancy small "booster doses" of foetal blood reaching the maternal circulation stimulate antibody formation further, and the "full-blown" picture of rhesus immunization develops. The assumption that the first pregnancy or labour provides the first antigenic stimulus seems to be necessary to explain the development of antibody formation during the next pregnancy, in which presumably identical conditions obtain with regard to the placental barrier as in the first pregnancy.

Stratton (1943) has shown that the rhesus factor can be discovered on the foetal red blood cells at the eleventh week of development, but it seems improbable that such an immature foetus could provide enough antigenic

material to produce antibodies in the maternal serum. Occasionally, however, antibodies are discovered in the early weeks of a second pregnancy. The following case illustrates this point.

A married woman aged 25 had her first baby on February 23, 1948. The infant, of 30 weeks' gestation and weighing 2 lb. 15 oz. (1.33 kg.), was born spontaneously. Serological investigations were performed on the mother at the ninth and twenty-seventh weeks and eight days after delivery. The result of all three investigations was Group B rhesus-negative, the serum containing no anomalous antibodies.

The patient became pregnant again in September, 1948. The first specimen of blood investigated early in January, 1949, at 16 weeks' gestation, showed definite signs of rhesus immunization by containing blocking anti-rhesus antibodies of fairly high titre (1:32). Several repeat investigations gave essentially identical results, and on May 3 a baby suffering from haemolytic disease of the newborn was born. She weighed 4 lb. 7 oz. (2 kg.). Despite a blood transfusion of rhesus-negative blood, she died of kernicterus at the age of 7 days. The diagnosis was confirmed at necropsy (Dr. Baar).

It was thought advisable to follow up a number of primigravidae after delivery, for a comparatively long period, to see whether any antibody formation followed delivery and whether the antibody could be proved to be present by routine serological methods. If the assumption is correct, that the primary immunizing dose is given during labour or afterwards, one could hope to find antibodies in sera of exceptionally good reactors without a further stimulus having been applied.

The investigation was undertaken on 62 primigravidae who were all seen antenatally and delivered at Sorrento Maternity Hospital, Birmingham. They were also followed up post-natally there. The serological investigations covered determination of the blood group, rhesus type, and investigation for antibodies in the serum. The latter was done by means of saline- and albumin-suspended cells, ten of which were rhesus-positive and two rhesus-negative. All the sera were also tested by means of the indirect Coombs test. The cord blood was also investigated. This investigation included the group and rhesus type and, from 1948 onwards, the direct Coombs test. Consecutive rhesus-negative primiparae were selected, and only those excluded who produced a rhesus-negative infant. The post-natal investigations were undertaken at various intervals. In most, the second specimen was obtained about eight days after delivery, and in no case were anomalous antibodies found. Several patients were followed up further at intervals up to two years. Two patients developed anti-rhesus antibodies. Their clinical and serological details follow.

Case 1

A woman aged 24 was delivered of a healthy, normal, full-term baby on October 20, 1947. This baby showed no icterus or other sign of haemolytic disease. His blood type was Group A rhesus-positive.

Further specimens were investigated from the mother, and approximately two years later the following results were obtained: The cells were confirmed as Group O rhesus-negative, the serum agglutinated strongly rhesus-positive albumin-suspended cells and did not agglutinate rhesus-negative cells. An indirect Coombs test with rhesus-positive cells was positive. Three weeks later a further specimen gave identical results. The serum was tested with a large battery of fully typed cells and agglutinated every sample cell which contained the D antigen. The titre of the antibody was found to be fairly low (1:2) against CDe/CDe and cDe/cDe. At the same time a specimen of blood from the patient's husband was investigated and found to be Group A rhesus-positive (most likely genotype CDe/CDe).