of their developmental origin. Forbus has shown that the minute defects in the muscular coats of arteries which are frequently found at vessel junctions may be regarded as potential aneurysms. Whether such a defect develops into an actual aneurysmal saccular protrusion or not depends on the extent of the defect and conditions of blood pressure to which it is subjected. Whether such an aneurysm ruptures or not depends similarly on the blood pressure to which its wall is subjected and to the resistance of that wall. Probably the size of the original defect has an influence on the thickness and resistance of the wall of the saccular protrusion.

Although we are unable to find any preceding record of a congenital aneurysm situated within the brain substance, and although these lesions are doubtless much more often associated with the larger arteries at the base of the brain or in its principal fissures, our record demonstrates that such a lesion may occur. For the reasons mentioned above the incidence may be more frequent than the absence of recorded cases would suggest. A congenital intracerebral aneurysm is, moreover, a possible cause of apoplexy to be reckoned with even in the case of a young child.

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DEATH FROM QUININE POISONING

BY

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(WITH SPECIAL PLATE)

Since fatal blackwater fever is rare in Great Britain the following description of a case in which death occurred from a complaint almost indistinguishable from the most severe form of blackwater fever may be interesting. This patient had neither suffered from malaria nor left England.

Quinine is used in all parts of the world, and for many reasons. Its minor toxic effects, as in cinchonism, are well known; the occurrence of urticarial rashes after small doses—a true allergic response—is not uncommon, but if the drug is used in moderate doses fatal results are rare, except in the case of malarial patients who develop blackwater fever. Fairley (1937; Fairley and Bromfield, 1934, 1937) has brought forward evidence which demonstrates that blackwater fever can occur in patients who have received no anti-malarial treatment for many months.

History of Case

The patient, a married woman aged 34, had always lived in or near London, and had never left England. She had never suffered from malaria or any illness resembling malaria. She had had four previous pregnancies—two had miscarried and

two had gone to term. A week before admission a specialist confirmed her fear that she had again become pregnant. The day before admission she bought a box of pills, and swallowed sixteen of them some time after noon, leaving one in the box. Analysis later demonstrated that the remaining pill, weighing 0.67 gramme, contained 0.38 gramme of quinine sulphate: it seems probable, therefore, that she took a total of 6.08 grammes of quinine sulphate, or 5.04 grammes (76 grains) of the pure alkaloid. On the same evening she was taken ill with headache, vomiting, pyrexia, and increased pulse rate: there was abdominal pain and vaginal bleeding. Her husband found her in this condition and sent for her physician, who at once had her removed to hospital. His note stated: "Called at 11.15 p.m. Temperature 102°, pulse 132. Headache, vomiting; scarlet rash all over body, abdominal pain, vaginal haemorrhage, all said to have been present for many hours. No history of contact with scarlet fever, and no signs of scarlet fever."

CLINICAL FINDINGS

On admission at 2 a.m. her temperature was 102.6°, pulse 140, respirations 40. She was restless and clearly in pain, and there was a suggestion of a urine-like smell about her. The whole body was covered with a uniform copper-coloured rash. It did not fade on pressure. The conjunctivae showed an icteric tinge. The mucous membranes were a good colour and the tongue was quite clear and moist. No sign of activity was detected in the breasts. The abdomen was full and was tender all over, particularly in the lower half. Here the fundus of the uterus was palpable. In the vagina inspissated and curiously altered blood was found. This was offensive. The cervix was patulous, and the uterus was enlarged to the size of a ten-weeks gestation and was tender. No other tumour was palpable. There was slight oedema of the legs. Two ounces of urine was withdrawn by means of a catheter. This urine was black.

INVESTIGATIONS

There were signs of pregnancy complicated by abortion, but whether the miscarriage had just occurred or was about to occur was not clear. Tenderness and rigidity were noted in the abdomen, suggesting peritonitis. Finally there was the remarkable colour. In artificial light its hue was not easily decided, and it was thought by one to be icteric, by another to be that caused by prontosil soluble, by a third to be that of a *Clostridium welchii* septicaemia. The possibility of some drug idiosyncrasy remained.

The urine was almost black, and its centrifuged deposit showed nothing but masses of amorphous yellow deposit and a slightly excessive number of white blood cells; a Gram film revealed no micro-organisms. When daylight arrived it became clear that the colour was not that of jaundice or of prontosil soluble, but a vivid, rather coppery, mahogany brown, resembling that occurring in *Cl. welchii* septicaemia; the probability of this infection being the cause of the colour was, however, slight, since none had been found in the urine, nor was the patient ill enough. The urine was found to contain methaemoglobin in very high concentration, all four bands of which became visible when a 1 cm. layer of urine diluted to 1 in 20 was examined with the pocket spectroscop.

A specimen of blood was next examined. Aerobic and anaerobic cultures were taken, and these proved sterile; the blood, allowed to clot and then centrifuged, set free serum so dark that the surface separating clot and serum was indistinguishable in daylight. Spectroscopic examination of the serum showed a band in the red at 630 m μ ; the blood urea was 128 mg. per 100 c.cm.; the direct van den Bergh reaction was positive in fifteen seconds, and the total bilirubin was 78 units, or 39 mg. per 100 c.cm. The serum phosphatase was 14.4 units by the method of King and Armstrong (normal 4 to 14 units).

Further investigations were made at intervals to confirm the diagnosis and prognosis, with the following results: Second day after admission: red cells, 3.2 millions; leucocytes, 26,800. Third day: red cells, 1.85 millions; leucocytes, 29,800. Fifth day: band in red still present in serum but very weak; blood urea, 325 mg. per 100 c.cm.; alkali

reserve, 51 c.cm. CO₂ per 100 c.cm. plasma. Seventh day: blood urea, 540 mg. During this period the mahogany-brown colour was slowly replaced by a typical severe icterus, which in turn faded, until at the time of death, the ninth day after admission, the patient was only slightly jaundiced.

DIAGNOSIS

The differential diagnosis appeared to lie between acute yellow atrophy, *Cl. welchii* septicaemia, Marchiafava-Micheli's paroxysmal haemoglobinuria, and some fulminating haemolytic anaemia of doubtful aetiology, possibly related to the large dose of quinine taken.

Acute yellow atrophy was easily dismissed. First, the colour was far from that of simple icterus. Secondly, the blood urea was markedly raised. Such a result is unusual in acute yellow atrophy, since urea formation is confined to the liver; one patient with this disease has been found to have a blood urea too low to measure (Rabinowitch, 1929). Thirdly, the plasma phosphatase was normal. Since phosphatase is excreted exclusively by the liver, extensive destruction of liver cells would result in retention of the enzyme in the body.

The raised figure for bilirubin in the serum suggested an increased blood destruction, so the nature of the pigment giving the band in the red at 630 m μ was investigated. The band, unlike that of methaemoglobin, was not affected by ammonia or by ammonium sulphide, but disappeared on addition of sodium hydrosulphite. These properties are those of pseudo-methaemoglobin or methalbumin, a pigment first discovered by Fairley and Bromfield (1934, 1937) and shown by them to occur in the plasma of patients suffering from black-water fever, and by Janet Vaughan, Harrison, and others to occur in the plasma of patients who have received incompatible transfusions. It is believed to be formed whenever there is severe intravascular haemolysis, and to be a combination of haematin with plasma albumin.

The possibility of a *Cl. welchii* septicaemia was excluded by the absence of the organisms from the urine and by the sterility of aerobic and anaerobic blood cultures; while a Marchiafava-Micheli haemoglobinuria was excluded by examination of the urine for inorganic iron, which is always present in this condition and absent in most others (Bodley Scott, Robb-Smith, and Scowen, 1938). No iron could be detected when using the same method as these workers. Finally, a diagnosis of "acute intravascular haemolysis with consequent occlusion of the renal tubules with haematic casts" was made, the aetiology of the condition remaining doubtful.

PROGRESS AND TREATMENT

During her stay in hospital the woman slowly but surely progressed to death. An ounce or two of urine could occasionally be obtained—23 oz. in ten days. Her tongue became dry, then brown and crusty. The temperature and pulse fell slowly on the ninth day, being 99° and 108 respectively, with respirations 20. She became more and more drowsy and developed a hiccup on the day before her death.

For treatment she received 4.5 litres of fluid intravenously, of which 700 c.cm. were 4.2 and 5 per cent. sodium sulphate and 400 c.cm. 6 per cent. sodium bicarbonate. The rest was 5 per cent. glucose saline. She took also 7½ litres of fluid orally. All other treatment was symptomatic.

NECROPSY FINDINGS (48 HOURS AFTER DEATH)

The patient died on the tenth day. The following is a summary of the pathologist's findings: "The brain contains the stained cerebrospinal fluid. The heart is slightly dilated and there is thickening of the mitral valve. The trachea contains foul fluid. There are oedema of the lungs and collapse of the left lower lobe. The intestinal tract is normal. In the liver is fatty change. The spleen shows terminal congestion. The kidneys probably contain excess iron. Their papillae are somewhat swollen. The bladder contains thick turbid fluid. There is acute cystitis. The vagina has superficial incrustations at the vault. The uterus is slightly enlarged, is

empty, and contains stained mucus. There is thick fluid in the tubes and a corpus luteum in the right ovary."

Histology.—Sections of the kidney show some post-mortem degeneration. The glomeruli are for the most part unaffected (Plate, Fig. 1). There is some engorgement of the peritubular capillaries. Almost all the tubules are choked by a granular, amorphous yellow deposit (Fig. 2), which in sections stained by Lepehne's technique proves to be some complex haemoglobin derivative—the haematin found after excretion of haemoglobin by an acid urine (Baker and Dodds, 1925). Sections stained for inorganic iron show practically no haemosiderin granules. There is no microscopical evidence of nephritis. The liver shows some post-mortem degeneration, but is otherwise normal. There is no excess of inorganic iron.

Discussion

An almost exactly similar case is recorded by Terplan and Javert (1936). This they claim to be the first recorded in their literature, and they mention seven others collected from abroad, all occurring in the first three months of pregnancy. Their patient was given 6 grammes (93 grains) of quinine, and died six days after admission. The full time interval is not given. All the patients were in the early stages of pregnancy and all died with a gross obstructive renal lesion.

Chopra, Sen, and Bhattacharya (1935) point out that haemoglobinuria is common in the Tropics after quinine therapy; but they are unable to say if it is caused by the quinine, is due to an inherent susceptibility of the corpuscles, or if the disease for which quinine is administered is responsible. They were able to demonstrate increased fragility of corpuscles in a malarious patient who developed haemoglobinuria on two of three occasions when he was given quinine.

H. M. Raven (1937) records the death of a patient aged 50 who took 240 grains of quinine. She died very soon afterwards, and "the necropsy revealed no signs of organic disease." It seems highly probable that this patient suffered from an idiosyncrasy to quinine similar to that of the patient of Terplan and Javert, and it is possible that more cases of this will be observed in the future, in view of the continued belief in the efficacy of quinine as an abortifacient. It is most improbable that any form of treatment will be efficacious, owing to the delay in admission to hospital. If the patient is seen soon after the onset of symptoms massive alkalization might be effective, using intravenous sodium bicarbonate (6 per cent.) in quantities of 500 to 600 c.cm., thus obtaining an alkaline urine; but in most cases the renal tubules will be blocked before this can be done.

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According to the Department of Public Health more than 9,000 natives died from malaria in the Transvaal during the year ended March 31, 1939. The heavy rains at the end of 1938 and the beginning of 1939 made conditions favourable to malarial mosquitos. The chief difference between this epidemic and that of 1937 was not one of severity but of extent, the 1939 epidemic reaching over a far greater area and going as far south as Pretoria.

YI-CHENG CHAO, STORER HUMPHREYS, AND WILDER PENFIELD: A NEW METHOD OF PREVENTING ADHESIONS
(For Legends, see Text)

FIG. 1

FIG. 2

FIG. 3

C. K. VARTAN AND G. DISCOMBE: DEATH FROM QUININE POISONING

FIG. 1.—Section through cortex of kidney. The glomeruli are seen to be for the most part unaffected.

FIG. 2.—Section through tubular portion of kidney. The collecting tubules are seen to be choked by a granular amorphous deposit.