will give a better idea of the degree of humoral stimulation of erythropoiesis than measuring the plasma erythropoietin level.

When we want to compare from one laboratory to another the amount of erythropoietin found in the urine in different diseases, the method of concentration must be taken into consideration. The simple way of concentration by freeze-drying after dialysis must be regarded as less destructive than precipitation or boiling. With these last methods a loss of erythropoietin may be suspected during the different procedures, although the end-product may be a more concentrated and pure one. However, so long as the only means of assaying the erythropoietin is by its biological activity and not by chemical quantitation, the easy way of concentration by dialysis and freeze-drying is most suitable for the purpose of quantitating urinary erythropoietin excretion.

As the amount of erythropoietin excreted under physiological conditions is as high as is shown in Table II, the discrimination between persons with different levels of erythropoietin excretion would be easier if the concentrates were divided in smaller doses than used in the present study—that is, injected into a greater number of mice—because the maximum response to erythropoietin is obtained with about 6–8 units per mouse (DeGowin *et al.*, 1962). The contrary would be the case in persons with lowered erythropoietin excretion.

When measuring the amount of erythropoietin excreted in the urine the sensitivity of the assay method should be shown by a calibration curve using "standard erythropoietin." In this way the 24-hour erythropoietin excretion could be given in "standard units."

The demonstration of erythropoietin in normal amniotic fluid must be taken to be in favour of the hypothesis that erythropoiesis is regulated through erythropoietin antenatally as well. It is also likely that erythropoietin in the amniotic fluid is derived from the urine, since previous investigations have shown that in anaemic fetuses erythropoietin may be excreted in the urine (Finne, 1964).

Summary

Urine from normal healthy male persons has been concentrated by means of dialysis and freeze-drying. The yield has been dissolved in saline and injected into polycythaemic mice. The concentrated urine stimulates erythropoiesis in the recipient mice and it is suggested that the effect may be due to erythropoietin. This strongly supports the hypothesis that erythropoietin is of physiological importance, not only in emergency situations but also under normal conditions as well. It is suggested that studying the 24-hour urinary excretion of erythropoietin may be a better way of estimating the erythropoietin production than assaying the plasma erythropoietin level.

A concentrate of normal amniotic fluid also showed erythropoiesis-stimulating activity. This favours the concept that erythropoiesis is regulated through erythropoietin antenatally as well as after birth.

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Medical Memoranda

Serum Hepatitis Presenting as Sudden Loss of Consciousness

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While the occurrence of hepatitis following blood transfusion may be expected in 1% (Sherlock, 1963) to 3% (Allen and Sayman, 1962) of all recipients, and a proportion of these may develop hepatic failure, the presentation as sudden unconsciousness is uncommon enough to warrant recording.

CASE HISTORY

A gravida-2 aged 27 had a caesarean section on 16 December 1962 for concealed accidental haemorrhage, during the course of which she was transfused with 1 litre of compatible blood. She made an uneventful recovery apart from a urinary infection with *Escherichia coli* treated with nitrofurantoin.

Fourteen weeks later, at the end of March 1963, she began to feel unwell with anorexia and constipation, and on 29 March was

noticed to be jaundiced. She was afebrile, and well enough to conduct her normal household duties.

On the evening of 31 March, while nursing her baby and feeling better than on the previous two days, she suddenly fell forward from her chair, dropping the child, and lay unconscious with her arms held rigid. She was admitted to the North Staffordshire Royal Infirmary one and a half hours later, when she was slightly restless but still unconscious, with no response to painful stimuli. Her temperature was 98.4° F. (36.9° C.), she was slightly icteric, and while her breath smelled of acetone no fetor hepaticus was detected. The spleen was impalpable and the liver appeared normal in size. She had no neck-stiffness, but both plantar responses were extensor. There were no other physical abnormalities, the blood-pressure being 130/70.

The following investigations were carried out. Spinal fluid: Pressure 40 mm. of spinal fluid; clear fluid containing 4 red cells and 3 white cells per c.mm.; protein 40 mg./100 ml.; W.R. negative. Serum bilirubin 4.3 mg./100 ml. Serum glutamic oxalo-acetic transaminase (S.G.O.T.) 235 units/100 ml. Alkaline phosphatase 26.7 King-Armstrong units/100 ml. Serum urea 22 mg./100 ml. Serum albumin 5.7 g./100 ml. Serum globulin 2.2 g./100 ml. Haemoglobin 114% (16.8 g./100 ml.). White-cell count 7,100/c.mm. Blood sugar 100 mg./100 ml. Prothrombin index 83% (method: Quick's one-stage). Urine contained bilirubin and increased urobilin. An electroencephalogram (E.E.G.) 36 hours

after admission showed variation of activity related to the patient's degree of unconsciousness. In general, there was marked slowing associated with some triphasic activity, and the appearances were in keeping with the presence of hepatic coma.

On admission 40 ml. of 50% glucose was injected intravenously but produced no change in her condition. Six hours later her temperature had risen to 105° F. (40.6° C.). A provisional diagnosis of fulminant hepatitis was made, and an intravenous infusion of 1 litre of 10% dextrose containing 2 g. of potassium chloride was given every six hours. Neomycin 1 g. was administered every six hours by stomach-tube, and prednisolone 20 mg. six-hourly by intramuscular injection.

Within two days she was afebrile, and during the next three days she gradually returned to full consciousness, at which point the following investigations were done: serum bilirubin 3 mg./100 ml.; S.G.O.T. 95 units/100 ml.; serum glutamic pyruvic transaminase (S.G.P.T.) 230 units/100 ml.; thymol turbidity 6 units; colloidal gold ++; prothrombin index 20%. The E.E.G. had improved, with a generalized increase in frequency.

Intravenous therapy was stopped, neomycin being continued for a further week. Prednisolone was given by mouth, the dose gradually being reduced, finally stopping two weeks after admission. At this point the patient appeared quite normal. The serum bilirubin had fallen to 1.1 mg./100 ml., though S.G.P.T. remained raised at 210 units/100 ml.

By 17 May, six weeks after admission, the serum bilirubin was 0.9 mg./100 ml. and both S.G.O.T. and S.G.P.T. were 20 units. An E.E.G. showed only occasional slow activity, with a dominant 9 to 10 cycles per second activity posteriorly.

In September, six months after the initial illness, a bromsulphthalein excretion test showed 9.4% retention after 45 minutes, but other standard biochemical tests of hepatic function were normal. The E.E.G. had also returned to normal.

DISCUSSION

The differential diagnosis in this case lies between hypoglycaemia associated with liver failure (Tomlinson, 1955), encephalitis, and a sudden onset of hepatic coma due to fulminant hepatitis and consequent liver failure.

The first is excluded by a normal blood sugar before any treatment was given. While encephalitis can exist without abnormality of the spinal fluid, the E.E.G. abnormalities—namely, the marked fluctuation in activity and the presence of paroxysmal activity of polyphasic ("triphasic") type—were felt to be more suggestive of hepatic coma with subsequent recovery. The development of her symptoms 14 weeks after blood transfusion made a diagnosis of serum hepatitis probable.

In the many published series of hepatic coma and of viral hepatitis sudden unconsciousness is rarely mentioned as a manifestation even in cases which eventually proved fatal. Several authors (Lucké, 1944; Stokes *et al.*, 1945; Sodeman, 1946; Murphy *et al.*, 1948; Walshe, 1951; Ducci and Katz, 1952) stress the constant sequence from lethargy to noisy confusion, and only terminally the onset of coma, in fulminant hepatitis. Others remark that the onset of unconsciousness may occur rapidly within hours (Davidson and Summerskill, 1956;

Havens, 1962); Adams and Foley (1953) speak of occasional abrupt disturbances of consciousness, and Stokes and Miller (1947) mention that patients might be admitted in coma or suddenly lapse into coma after admission. Fernando and Thanabalasunderam (1951), in a series of cases of infective hepatitis, mention one young woman who had been ill for some days and "became unconscious and was admitted jaundiced and comatose." However, no case seems to have been described in which the dramatically sudden onset of unconsciousness was the outstanding feature of the illness. Indeed, the mechanism of hepatic coma, as understood at present (Sherlock, 1961)—namely, cerebral intoxication by nitrogenous substances, with fluid and potassium depletion, serotonin deficiency, and disordered carbohydrate metabolism as possible subsidiary factors—makes a sudden transition from a completely normal status into deep coma unlikely.

The second notable feature is the rapid and complete recovery. Sherlock (1963) estimates that only 1% of patients becoming comatose as a result of infective hepatitis are likely to recover, though Katz *et al.* (1962) treated 23 comatose patients with corticosteroids, nine eventually recovering.

These two unusual facets suggest that the mechanism was a rapid disturbance of liver function with a profound effect on cerebral function, without gross hepatic necrosis having occurred. Perhaps the biochemical abnormalities were different from those encountered in "conventional" hepatic encephalopathy.

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