Summary

Two infants suffering from protracted diarrhoea and treated with chloramphenicol by mouth developed bleeding episodes. There was hypoprothrombinaemia which was corrected by vitamin K.

Addendum

Since this paper was submitted, Goldman and Amadio (1969) have reviewed 12 cases from the literature and added 3 new ones. 60 infants aged 1 to 18 months with diarrhoea were treated with skimmed milk diet and succinylsulphathiazole. Hypoprothrombinaemia occurred in those infants who had not received supplemental vitamin K.

REFERENCES

- Burgio, G. R., and Vaccaro, R. (1966). Porpora nodulare del lattante. *Gazzetta Sanitaria*, **37**, 275.
 Goldman, H. I., and Amadio, P. (1969). Vitamin K deficiency after the newborn period. *Pediatrics*, **44**, 745.
 — and Deposito, F. (1966). Hypoprothrombinemic bleeding in young infants. *American Journal of Diseases of Children*, **111**, 430.
 Rapoport, S., and Dodd, K. (1946). Hypoprothrombinemia in infants with diarrhea. *American Journal of Diseases of Children*, **71**, 611.

N. MATSANIOTIS, J. MESSARITAKIS, and C. VLACHOU
St. Sophie's Children's Hospital, Paediatric Clinic of Athens University, Athens, Greece.

Serum Levels of Fibrin/Fibrinogen Degradation Products in the Haemolytic-Uraemic Syndrome

The phenomenon of intravascular coagulation is becoming increasingly recognized as having an important part, primarily or secondarily, in the pathogenesis of a wide variety of disease states. Abildgaard (1969) has recently reviewed such conditions, and of the instances he gave, the haemolytic-uraemic syndrome of Gasser appears to provide a classic example of intravascular coagulation, as suggested by Piel and Phibbs (1966).

One of the most useful methods of detecting the existence of even low-grade intravascular coagulation is the quantitative estimation of degradation products of fibrin/fibrinogen (FDP) which may also be used as an index of progress and response to treatment. Normal values of serum FDP are already known both for children (Uttley, Allan, and Cash, 1969) and for adults (Das *et al.*, 1967), as measured by the tanned red cell haemagglutination inhibition immunoassay. We have been able to study serum FDP from an early stage in the presentation of a case of the

haemolytic-uraemic syndrome and subsequently to follow progress during treatment with heparin.

Case Report

A child aged 21 months presented after the sudden onset of pallor in association with irritability and listlessness. For 2 weeks previously he had had mild diarrhoea. Shortly before his admission his mother had noticed transient jaundice, easy bruising, and a haemorrhagic rash. After a normal birth, this child had continued to develop satisfactorily and suffered no significant illnesses. There was no history of hereditary disease nor of renal disease in his family.

Examination confirmed the pallor and petechial rash with a positive Hess test. Jaundice was no longer detectable but several large bruises persisted. His blood pressure was 130/90 mm. Hg. No further clinical abnormalities were noted.

Laboratory results. Renal involvement was confirmed by the finding of protein + + +, red blood cells, and casts in the urine, the 24-hour volume of which was only 300 ml. on the first day. Blood urea nitrogen was 51 mg./100 ml. and serum K 4.1 mEq/l. Initial creatinine clearance gave a value of 17.7 ml./min. (62.0 ml./min. per 1.73 sq. m.). Urine culture was negative throughout. Hb was 6.4 g./100 ml., PCV 20%, WBC 7200, reticulocytes 10%, ESR 25 mm./hr., and platelets 81,000/cu. mm. The film showed the marked fragmentation of red blood cells and the burr cell formation typical of this syndrome.

While clotting and bleeding times were normal and the thrombin clotting time 13.5 sec. (control 12.0), serum FDP was 512 µg./ml. (normal 10.9 ± 4.7) (Uttley *et al.*, 1969). Plasma fibrinogen was normal. Factor VIII activity was 160%. Plasma haemoglobin was 48.5 mg./100 ml., and haptoglobins were absent. Urinary haemosiderin was present as was urobilinogen.

Treatment and progress. Heparin therapy was initiated with a dose of 500 I.U., and continued with the constant intravenous infusion of 1500 I.U. daily. A transfusion of 250 ml. whole blood was given on the second day. Pertinent data are shown in Fig. Over-all clotting status was monitored by daily thrombin clotting times, with and without protamine titration but never became abnormal.

Dietary salt intake was initially restricted until diuresis occurred on the eighth day. Heparin therapy was continued until all the clinical and laboratory findings had returned to normal. The most persistent abnormality was fragmentation of the red cells on the blood film.

Percutaneous renal biopsy was performed on the 23rd day, the features being essentially those of a progressive proliferative glomerulonephritis, with focal but significant glomerular hyalinization. No definite glomerular necrosis, no arteriolonecrosis and no thrombosis were seen, but the features were compatible with the clinical diagnosis. There was in addition evidence of fibrin deposition within the glomerular capillaries.

TABLE
Serum FDP Estimations by Two Methods

Day	1	2	3	4	5	6	8	10	12	14	16	18
Capillary method x	544	272	136	39.6	39.6	39.6	18.8	4.95	4.95	4.95	4.95	4.95
Microtitre y	512	256	128	48.0	48.0	48.0	26.0	16.4	16.4	16.4	16.4	16.4

Regression equation $y = 0.9571x + 10.8817$; correlation coefficient 0.9983.

Withdrawal of heparin did not result in any rebound phenomena. Extensive virological and bacteriological investigation failed to demonstrate any of the infections known to precipitate the condition. Renal function was not significantly impaired after the episode, creatinine clearance having risen to 25 ml./min. (90 ml./min. per 1.73 sq. m.).

During a follow-up, of 9 months, laboratory findings remained normal, including serum FDP. The only episode of possible relevance had been a *grand mal* attack, investigation of which revealed an epileptic focus on the EEG. There was no previous history of such attacks and no family history of epilepsy.

Methods and Results of FDP Determinations

The capillary tube method of Israels *et al.* (1968), was used for day-to-day determination of serum FDP. This variation of the tanned red cell haemagglutination inhibition immunoassay allows a fairly accurate quantitation to be available within 2 hours. Specimens were later reassayed together by the micro-titre method, as used by Das *et al.* (1967), which, while giving a more accurate determination, does not lend itself to rapidly available results. Results are shown in the Table, and confirm the reliability of the capillary method.

Comments

It has been felt for some years (Abildgaard, 1969; Piel and Phibbs, 1966) that the haemolytic-uraemic syndrome may be an example of localized or disseminated intravascular coagulation, often preceded by and triggered off by an enteric or upper respiratory tract infection. The syndrome has many similarities to the Schwartzman phenomenon, and theoretically treatment with heparin should prevent the occurrence of further intravascular coagulation by means of its antithromboplastin and antithrombin activity, while allowing the fibrinolytic enzymes to degrade fibrin already deposited. Fibrin degradation products have already been shown non-quantitatively in this syndrome by Monnens and Schretlen (1967) and quantitated at a level of 140 $\mu\text{g./ml.}$ in one of the cases of Brain *et al.* (1968), later rising to about 300 $\mu\text{g./ml.}$ The failure to show pretreatment depletion of consumable clotting factors such as factor VIII and fibrinogen has also been noted in most cases

reported before, and gives support to the possibility that the haemolytic-uraemic syndrome represents localized (renal) intravascular coagulation rather than the disseminated phenomenon (Gilchrist *et al.*, 1969).

The finding and quantitation of raised serum FDP confirms the presence of either localized or disseminated intravascular coagulation, and indicates the need for anticoagulation.

The results of heparin therapy have been reviewed by Brain *et al.* (1968). In view of the known history of the disease, it cannot be claimed that the satisfactory outcome of this particular case is directly related to the heparin given. Its interest, however, lies in the demonstration of the value of the detection and serial estimation of serum FDP as an extremely sensitive measurement of abnormality in the initial diagnosis and subsequent therapeutic management.

The Fig. shows the fall of serum FDP occurring

FIG.—Laboratory findings in a case of the haemolytic-uraemic syndrome during treatment with heparin.

after the initiation of heparin therapy. The rise in the platelet count occurred some 48–72 hours later, and thus the fall in serum FDP was the first measurable index of improvement. Heparin was continued until the blood film no longer showed signs of fragmentation.

We feel that the rapid capillary method of estimating serum FDP was of great value in the management of this case, and should prove of similar value in future cases.

Summary

Serum levels of fibrin/fibrinogen degradation products have been assayed throughout the course of a case of the haemolytic-uraemic syndrome. A rapid method of estimation was of value in monitoring progress and assessing the effect of heparin therapy.

REFERENCES

- Abildgaard, C. F. (1969). Recognition and treatment of intravascular coagulation. *Journal of Pediatrics*, **74**, 163.
- Brain, M. C., Baker, L. R. I., McBride, J. A., Rubenberg, M. L., and Dacie, J. V. (1968). Treatment of patients with microangiopathic haemolytic anaemia with heparin. *British Journal of Haematology*, **15**, 603.
- Das, P. C., Allan, A. G. E., Woodfield, D. G., and Cash, J. D. (1967). Fibrin degradation products in sera of normal subjects. *British Medical Journal*, **4**, 718.
- Gilchrist, G. S., Lieverman, E., Ekert, H., Fine, R. N., and Grushkin, C. (1969). Heparin therapy in the haemolytic-uraemic syndrome. *Lancet*, **1**, 1123.
- Israels, E. D., Rayner, H., Israels, L. G., and Zipursky, A. (1968). A microhemagglutination-inhibition assay for the quantitation of fibrinogen breakdown products. *Journal of Laboratory and Clinical Medicine*, **71**, 333.
- Monnens, L., and Schretlen, E. (1967). Intravascular coagulation in an infant with the hemolytic-uremic syndrome. *Acta Paediatrica Scandinavica*, **56**, 436.
- Piel, C. F., and Phibbs, R. H. (1966). The hemolytic-uremic syndrome. *Pediatric Clinics of North America*, **13**, 295.
- Uttley, W. S., Allan, A. G. E., and Cash, J. D. (1969). Fibrin fibrinogen degradation products in sera of normal infants and children. *Archives of Disease in Childhood*, **44**, 761.

W. S. UTTLEY

Department of Child Life and Health, University of Edinburgh.

Ethylene Chlorohydrin Intoxication with Fatality

Ethylene chlorohydrin is a most noxious poison that is oxidized in the body to chloroacetic acid which then inhibits the tricarboxylic cycle enzymes.

It has been used as a solvent and to prepare ethylene glycol and ethylene oxide. The germination of seed potatoes can be hastened by its application. Industrially its toxicity is well known, but the poison is also found commonly in the home as a

photographic cement (Cinecol, Johnsons of Hendon).

Neither poisoning in childhood nor death in any age-group by drinking ethylene chlorohydrin have previously been described.

Case Report

The 23-month-old male patient drank approximately 2 ml. Cinecol at 1 p.m. and vomited immediately. He rapidly became pale, cyanosed, and showed respiratory difficulty, and was admitted to his local hospital for emergency treatment which included an infusion of 5% dextrose in normal saline following gastric lavage.

At 6 p.m. the child had a generalized convulsion and his pupils became fixed and dilated. 2 ml. paraldehyde were administered intramuscularly but he continued to twitch. Another convulsion occurred at 8 p.m., which responded to 30 mg. intramuscular phenobarbitone. His systolic blood pressure fluctuated between 50–80 mm. Hg and his pulse rate varied from 86–140/min.

At the Regional Poisons Centre at 10 p.m. he was pale, cyanosed, and his blood pressure was unrecordable. His pulse rate was 200/min. and his rectal temperature was 36 °C. The heart sounds were faint and respiration was shallow. The pupils reacted to light and he responded to stimulation.

Hydrocortisone was given intravenously in a dose of 10 mg./kg. but this did not raise his blood pressure, nor did a second prescription. Soon after this had been given the patient vomited, became apnoeic, and had a cardiac arrest.

He died less than 12 hours after drinking the chemical.

On admission here, his blood urea was 92 mg./100 ml., and his serum bicarbonate was 12.4 mEq/l. The serum electrolytes were normal and his urine was free from sugar, protein, and blood.

Necropsy. The child weighed 15.9 kg. and showed no underlying disease.

The lungs were oedematous and congested. The right lung weighed 168 g. and the left 120 g. Pulmonary haemorrhage was marked, especially posteriorly. Petechiae were present in the subepicardium, the thymus, and beneath the liver capsule. This organ weighed 600 g. The spleen weighed 55 g. and had a toxic follicular pattern. There were 23 agonal intussusceptions in the small bowel, but no other significant abnormalities were found.

Microscopically, the changes seen were non-specific. Capillary bleeding had taken place into the pulmonary alveoli. There was early necrosis of the liver parenchyma, with nuclear vacuolation, cytoplasmic swelling, and small foci of polymorph infiltration, which were also observed in the portal tracts. The changes were most obvious at the periphery of the liver lobules. Acute inflammatory cells were present in the adrenal medulla and karyorrhexis was very striking in the germinal centres of the lymph nodes and spleen. In the kidney there was tubular swelling, and the brain showed widespread neuronal enlargement with cytoplasmic