- MICHEL, M. L., FIELD, R. J., and OGDEN, W. W. jr. (1955): Meckel's Diverticulum: An Analysis of One Hundred Cases and the Report of a Giant Diverticulum and of Four Cases Occurring Within the Same Immediate Family, *Ann. Surg.*, **141**, 819.
- NELSON, W. E. (1959): Textbook of Paediatrics, 7th edition. Philadelphia and London: W. B. Saunders.
- PECK, D. A., LYNN, H. B., and DUSHANE, J. W. (1963): Intussusception in Children, *Surg. Gynec. Obstet.*, **116**, 398.
- PERRIN, W. S., and LINDSAY, E. C. (1921): Intussusception: A Monograph Based on 400 Cases, *Brit. J. Surg.*, **9**, 46.
- PONKA, J. L. (1956): Intussusception Due to Invaginated Meckel's Diverticulum; Presentation of Two Cases and Analysis of 52 Cases Collected from Literature, *Amer. J. Surg.*, **92**, 545.
- POTTER, C. W., SHEDDON, W. I. H., and ZACHARY, R. B. (1963): A Comparative Study of the Incidence of Adenovirus Antibodies in Children with Intussusception with that in a Control Group, *J. Pediatr.*, **63**, 420.
- ROESSEL, C. W. (1962): Perforation of Meckel's Diverticulum by Foreign Body: Case Report and Review of the Literature, *Ann. Surg.*, **156**, 972.
- ROSS, J. G., POTTER, C. W., and ZACHARY, R. B. (1962): Adenovirus Infection in Association with Intussusception in Infancy, *Lancet*, **ii**, 221.
- RUTTEN, A., and OUDEJANS, E. (1961): Abdominal Manifestations of Adenovirus Infection in Infants, *Lancet*, **ii**, 597.
- SAVAGE, P. T. (1960): An Unusual Case of Meckel's Diverticulum, *Proc. roy. Soc. Med.*, **53**, 228.
- SODERLUND, S. (1956): Meckel's Diverticulum in Children. A Report of 115 Cases, *Acta. chir. Scand.*, **110**, 261.
- SODERLUND, S. (1959): Meckel's Diverticulum: A Clinical and Histological Study, *Acta. chir. Scand., Suppl.*, **248**.
- STEYN, J., and KYLE, J. (1961): Epidemiology of Acute Intussusception, *Brit. med. J.*, **i**, 1730.
- STRANG, R. (1959): Intussusception in Infancy and Childhood: A Review of 400 Cases, *Brit. J. Surg.*, **46**, 484.
- TADDEO, M. C., and JONES, M. M. (1955): Intussusception Due to Invaginated Meckel's Diverticulum after Previous Appendectomy, *Amer. J. Surg.*, **89**, 696.
- WALSH, A. (1950): Knot in Meckel's Diverticulum Causing Acute Intestinal Obstruction, *Brit. J. Surg.*, **37**, 475.
- WATTS, G. T. (1954): Occult Intussusception, *Postgrad. med. J.*, **30**, 655.
- WEINSTEIN, E. C., CAIN, J. C., and REMINE, W. H. (1962): Meckel's Diverticulum: 55 Years of Clinical and Surgical Experience, *J. Amer. med. Ass.*, **182**, 251.
- WEINSTEIN, E. C., DOCKERTY, M. B., and WAUGH, J. M. (1963): Neoplasms of Meckel's Diverticulum, *Int. Abstr. Surg.*, **116**, 103.

ACUTE PROMYELOCYTIC LEUKAEMIA

JANE M. FULLERTON, M.B., D.P.H., F.C.Path.
Consultant Pathologist, St. Olave's Hospital, S.E.16.

P. BARKHAN, M.D., Ph.D., M.C.Path.
Consultant Haematologist, Guy's Hospital, S.E.1.

JUST over 50 cases of acute promyelocytic leukaemia (APL) have been reported since Croizot and Favre-Gilly's first case in 1949. A review was published in the English literature by the French workers Bernard, Lasneret and Chone (1963), and cases have been reported from the U.S.A. by Didisheim, Trombold, Vandervoort and Mibashan (1964), and by Rosenthal (1963), but no case is reported as having occurred in Great Britain.

This form of leukaemia is characterised by a preponderance of promyelocytes, fibrinogenopaenia and a haemorrhagic, often rapidly fatal course.

This paper reports the first case of APL recorded in England.

Case Report

A 49-year-old white male storekeeper, born in England, was perfectly fit and well with no previous illnesses until three weeks prior to admission to St. Olave's Hospital on 29th September 1965.

On 11th September, he first noticed haematuria with slight loin pain, the pain being relieved by simple analgesics. He then noticed "bruises" inside his mouth, on his legs and feet and he was sent to hospital for investigation. He was admitted on 29th September.

On examination there were multiple ecchymoses. Gross haematuria was present. There was no hepatosplenomegaly or lymphadenopathy; the initial ESR was normal. The haematuria continued throughout the whole period in hospital.

The haematological and coagulation findings on admission are laid out in Tables 1 and 2. The white cell morphology is demonstrated in Figs. 1 and 2. A diagnosis of APL was made. Therapy with 6-mercaptopurine, 2.5 mg/kg/diem, with prednisolone 40 mg./diem was started on 4th October. This was supported by blood transfusions, but no remission was noted and he eventually died on 10th November, forty-two days after admission.

Necropsy. Body is that of a well built male subject showing ecchymoses on legs, arms and trunk. Brain: subarachnoid ecchymosis, but no intra-cerebral haemorrhage. Lungs: ecchymosis on pleural surfaces and the general picture was that of pulmonary oedema. The heart weighed 490 g; no obvious pathology was present. Liver weighed 2370 g, but appeared normal on cut surface. Spleen: firm in consistency, weighed 450 g. Gastro-intestinal tract showed petechial haemorrhages on the small intestine. Pancreas appeared normal, as did the adrenal glands, bladder and prostate. Lymph nodes were enlarged in the mesentery of the small intestine and in the right groin. The kidneys together weighed 445 g. and there were areas of haemorrhage in the pelvis.

TABLE 1

HAEMATOLOGICAL FINDINGS

Marrow puncture 30th September 1964.

Polymorphonuclear cells 1.25%. Lymphocytes 14.0%.
Promyelocytes 76.0%. Basophilic myelocytes 2.25%.

Blood picture 29th September 1964.

Hb 11.7 g./100 ml. WBC 3,500. Polymorphs 22%;
Eosinos, 1%; basos, 1%; lymphs 56%; monos 1%;
promyelocytes 14%.

Nucleated red cells 1%; ESR 7 mm/hr (Wintrobe).
Platelets 60,000/cu. mm.

Bleeding time $5\frac{1}{2}$ minutes (Duke's method). Clotting
time $5\frac{1}{2}$ minutes (Lee and White). W.R. and Kahn —
negative.

Total proteins 6 g./100 ml. Electrophoresis — reduced
alpha-2 globulin.

Blood urea 33 mg./100 ml.

TABLE 2

COAGULATION FINDINGS

1. White blood clots. These were small and jelly like in consistency and abnormally friable. There was a moderate degree of lysis on incubation of the clots at 37°C for 24 hours. Clot retraction was moderately reduced.
2. Prothrombin time on citrated plasma was 16-17 seconds (normal 11-13 seconds). Poor quality fibrin clots formed. The addition of 10% Al(OH)₃ adsorbed normal plasma did not shorten the time significantly.
3. Kaolin-Cephalin time (partial thromboplastin time with Kaolin) 50 seconds (normal 35-50 seconds), poor fibrin clots formed.
4. Fibrinogen titre (Sharp and others 1958), 1:16 (normal range 1:32-1:129). Again poor quality clots were noted.

Microscopy showed gross leukaemic infiltration of mesenteric lymph nodes and bone marrow. Spleen showed leukaemic infiltration and areas of extra medullary haematopoiesis. (Figs. 3 and 4). Liver congested, slight leukaemic infiltration of portal tracts, but main feature is that of extra-medullary haematopoiesis. Kidneys, pancreas, thyroid, adrenal glands and prostate show no relevant histological features. The lungs showed multiple haemorrhages, but no evidence of leukaemic infiltration.

Discussion

The patient reported in this paper showed the two distinctive features which have been described in acute promyelocytic leukaemia (APL) viz:—predominance of promyelocytes in blood and bone marrow and fibrinogenopenia. The disease is otherwise clinically indistinguishable from the more common forms of acute leukaemia. Fibrinogen deficiency was not found in the other more common forms of leukaemia (Didisheim and others 1964, Rosenthal 1963). Although Factor V has been observed in most of the reported cases of APL it is a less specific feature than is fibrinogen deficiency since it has been found in cases of acute myeloblastic, myelomonoblastic and chronic myelocytic leukaemia (Didisheim and others 1964).

Determination of the fibrinogen level by the titre method of Sharp, Howie, Biggs and Metheum (1958), gives values in most normal patients of 1:64 or higher; the titre of 1:16 found in our patient is therefore significantly low and indicates a fibrinogen level of about 25 per cent of normal. Since the abnormally lengthened prothrombin time was not significantly shortened by the addition of adsorbed plasma which is a source of Factor V it may be assumed that a significant deficiency of Factor V was not present. The low fibrinogen level in itself would be sufficient to account for the increase of both the prothrombin time and the increased kaolin-cephalin time; fibrinogenopenia probably also accounted for the poor clot formation in these tests and for the fragile whole blood clot.

The cause of fibrinogen deficiency in APL is obscure. It does not appear to be due primarily to increased fibrinolytic activity and the deficiency is

FIG. 1—Peripheral blood film showing predominance of characteristic promyelocytic cells. (Leishmann stain $\times 325$).

FIG. 2—High power picture of promyelocytes (Leishmann stain $\times 806$).

probably a true one and not due to a qualitative alteration in the fibrinogen. There may be increased vascular utilisation of fibrinogen as a result of increased intravascular coagulation and the observa-

FIG. 3—Spleen (H & E $\times 82$). Dark areas are those of extramedullary haematopoiesis.

tion of Didisheim and others (1964), that infused fibrinogen disappeared rapidly in one of their patients is consistent with this explanation, but they note that heparin administration did not decrease the rate of fibrinogen disappearance.

While most of the reported cases of APL including that reported here have run a relatively rapid fulminating course, it is clear that the immediate prognosis is not entirely hopeless in every case. Didisheim and others (1964), report two patients who had a complete remission on 6-mercaptopurine, one surviving 8 months and the other 14 months. High dosage methotrexate therapy (Huguley, Vogler and Lea, 1965), or combination therapy consisting of the simultaneous use of vincristine, amethopterin, 6MP and prednisolone (Thompson, Hall and Moloney, 1965), may offer the possibility of more effective treatment.

Summary

The first reported case of acute promyelocytic leukaemia occurring in Great Britain is described.

FIG. 4—Spleen (H & E $\times 325$) showing cellular detail.

Our thanks are due to Dr. A. G. C. Cox, Consultant Physician at St. Olave's Hospital, for permission and encouragement in reporting this case.

REFERENCES

- BERNARD, J., and LASNERET, J., CHONE, J. (1963): A Cytological and Histological Study of Acute Promyelocytic Leukaemia, *J. clin. Path.*, **16**, 319.
- CROIZOT, P., and FAVRE-GILLY, J. (1949): Les Aspects du Syndrome Hemorragique des Leucemies, *Sang.*, **20**, 417.
- DIDISHEIM, P., TROMBOLD, J. S., VANDERVOORT, R. L. E., and MIBASHAN, R. S. (1964): Acute Promyelocytic Leukaemia with Fibrinogen and Factor V Deficiencies, *Blood*, **23**, 717.
- HUGULEY, Jr., C. M., VOGLER, W., and LEA, J. W. (1965): Acute Leukaemia Treated with Divided Doses of Methotrexate, *Arch. intern. Med.*, **115**, 23.
- ROSENTHAL, R. L. (1963): Acute Promyelocytic Leukaemia Associated with Hypofibrinogenaemia, *Blood*, **21**, 495.
- SHARP, A. A., HOWIE, B., BIGGS, R., and METHEUM, D. P. (1958): Defibrination Syndrome in Pregnancy. Value of Various Diagnostic Tests, *Lancet*, *ii*, 1309.
- THOMPSON, I., HALL, T. C., and MOLONEY, W. C. (1965): Combination Therapy of Adult Acute Myelogenous Leukaemia, *New Engl. J. Med.*, **23**, 1302.