Total gastrectomy has been advocated by Zollinger and Craig (1960a and b) in the treatment of these cases, whether or not a resectable pancreatic tumour is present. This procedure was not carried out in our case, because of the patient's poor general condition, the magnitude of the surgery already undertaken, and the presence of the great dilated veins in the fundal and hiatal regions. However, a radical subtotal gastrectomy was achieved. He has remained well for two years, having now a high platelet count but no evidence of polycythæmia. The tumour being malignant, it is feared that further ulceration may occur, as metastases develop. It is proposed to estimate the night acid secretion, and to test for fæcal occult blood at intervals, in an effort to anticipate further ulceration and its complications.

Summary

A case of the Zollinger-Ellison syndrome is described. A large non-beta-cell carcinoma arising in the tail of the pancreas apparently caused a 'back pressure' effect on the spleen. The resulting splenomegaly and venous engorgement made detection of the tumour difficult. The clinical problem was further complicated by an abnormal blood picture initially suggestive of polycythæmia vera.

I wish to thank Mr. R. C. B. Ledlie for permission to publish this case, and for his help and encouragement; Dr. J. B. Harman and Mrs. E. M. Ledlie who managed the hæmatological aspects; Dr. N. F. C. Gowing for the histology studies; Dr. H. M. E. Kay for the extensive hæmatological investigations; Dr. J. J. Stevenson for the radiological investigations, and Professor R. A. Gregory, who examined the tumour for gastrin-like activity.

REFERENCES

- FITTS, W. T., ERDE, A., PESKIN, G. W., and FROST, J. W. (1960): Surgical Implications of Polycythæmia Vera, *Ann. Surg.*, **152**, 548.
- GREGORY, R. A., TRACY, H. J., FRENCH, I. M., and SIRCUS, W. (1960): Extraction of a Gastrin-like Substance from a Pancreatic Tumour in a Case of a Zollinger-Ellison Syndrome, *Lancet*, **i**, 1045.
- LOUGHRIDGE, J. J., NEILL, D. W., and WILLIS, J. (1960): Zollinger-Ellison Syndrome: Report of a Case, *Brit. J. Surg.*, **48**, 158.
- RAWSON, A. B., ENGLAND, M. T., GILLAM, G. G., FRENCH, J. M., and STAMMERS, F. A. R. (1960): Zollinger-Ellison Syndrome with Diarrhœa and Malabsorption, *Lancet*, **ii**, 131.
- ZOLLINGER, R. M., and CRAIG, T. V. (1960): Ulcerogenic Tumour of the Pancreas, *Amer. J. Surg.*, **99**, 424.
- , — (1960b): Endocrine Tumours and Peptic Ulcer, *Amer. J. Med.*, **29**, 761.
- , and ELLISON, E. H. (1955): Primary Peptic Ulcerations of the Jejunum Associated with Islet Cell Tumours of the Pancreas, *Ann. Surg.*, **142**, 709.

FOLIC ACID DEFICIENCY IN HAEMOLYTIC ANAEMIA

J. FORSHAW, M.A., M.D.(Camb.), M.R.C.P.

Consultant Physician

Hæmatology Laboratory, Sefton General Hospital, Liverpool, 15

LILIAN HARWOOD, F.I.M.L.T.

Senior Technician

FOLIC acid deficiency with a megaloblastic bone marrow picture may develop in both the acquired and hereditary types of hæmolytic anaemia (Chanarin, Dacie and Mollin, 1959). This is attributed to the demands of increased erythropoiesis, and it is particularly liable to occur when the dietary intake of folic acid is poor (MacIver and Went, 1960).

The purpose of the present paper is to describe a patient in whom an acute hæmolytic episode rapidly produced folic acid deficiency, and after spontaneous recovery of the hæmolysis the folic acid deficiency was almost completely corrected without treatment.

Case Report

A man, aged 34, was admitted to hospital in July 1962, complaining of breathlessness on exertion, lassitude and intermittent lower abdominal pain for two weeks. He had never had any previous illnesses and he had not taken any drugs. There was no family history of anaemia. His diet had consisted mainly of corned beef, sausages, fish cakes, potatoes and bread, and he ate green vegetables very rarely.

On examination he was pale and the spleen was

palpable 4 cm. below the costal margin. His weight was 9st. 2lb.

Investigations: Hb. 7.8 g./100 ml., w.b.c. 1,450/cu. mm. (polys 67%, lymphs 29%, monos 1%, eosins 2%, basophils 1%), platelets 160,000/cu. mm., reticulocytes 1%. Examination of the stained blood film showed moderate anisocytosis and poikilocytosis. Bone marrow examination showed erythroid hyperplasia, numerous megaloblasts and a decrease in the polymorphs, the differential count being: blast cells 4%, myelocytes and metamyelocytes 43%, polymorphs and band cells 8%, proerythroblasts 7%, normoblasts 11%, megaloblasts 24%. 54% of the megaloblasts were in the basophilic stage.

The serum vitamin B₁₂ level was 140 µg./ml. (normal range 140-950 µg./ml.). In the histidine loading test (Kohn, Mollin and Rosenbach, 1961) there was a large amount of FIGLU in the urine. Schumm's test was positive. The direct Coombs' test was positive to an anti-human globulin dilution of 1/64. In the gamma-globulin neutralization test (Dacie, 1951) agglutination of the red cells was not inhibited by addition of gamma-globulin to the antiglobulin serum. Twenty-four autohæmolysis was increased to 4.6%. No antibodies were demonstrated in the serum.

Virus complement fixation tests were negative three weeks and six weeks after admission. L.E. cells were

not found. The serum bilirubin was 0.7 mg./100 ml., the alkaline phosphatase 16 K.A. units/100 ml. and the flocculation tests were normal. In the xylose absorption test, 5 g. xylose were excreted in the urine in five hours. A three day test of fat excretion in the stools showed an average of 2.8 g./24 hours.

Progress Nine days after admission the hæmoglobin had fallen to 7.2 g./100 ml., the white cells numbered 4,100 and the reticulocytes were 6%. The direct Coombs' and Schumm's tests were now negative, but serum haptoglobins were absent.

Eighteen days after admission, the hæmoglobin was 9.5 g./100 ml., and the reticulocytes 12%. The bone marrow contained fewer megaloblasts and a greater number of polymorphs, the differential count being: Blast cells 5%, myelocytes and metamyelocytes 18%, polymorphs and band cells 33%, proerythroblasts 6%, normoblasts 27%, megaloblasts 8%. There was still a large amount of FIGLU in the urine.

Six weeks later the hæmoglobin was 12.4 g./100 ml., and the reticulocytes 1%. Autohæmolysis was normal. FIGLU was still present in the urine, but the amount was much less than previously. The serum vitamin B₁₂ level had risen to 220 µg./ml. The spleen was not palpable, and he had gained 12 lbs in weight.

In January 1963, the hæmoglobin was 12.8 g./100 ml. The stained blood film showed a normal appearance of the red cells, but there were a large number of polymorphs with hypersegmented nuclei, 35% having 5 lobes, 13% 6 lobes and 3% 7 lobes. A slight trace of FIGLU was detected in the urine, and the serum haptoglobins were absent.

He was then given 15 mg. folic acid by mouth daily for four weeks. Following this treatment, the hæmoglobin rose to 14.8 g./100 ml., 14% of the polymorphs had 5-lobed nuclei and none had 6- or 7-lobed nuclei. There was no FIGLU in the urine. The Coombs, and Schumm's tests remained negative, but haptoglobins were still absent in the serum.

Discussion

At the time of this patient's admission to hospital

the evidence for hæmolysis was not particularly obvious, there being no reticulocytosis, polychromasia or raised serum bilirubin, and the initial diagnostic problem was that of a young man with a megaloblastic anæmia. Hæmolysis was confirmed by a positive Schumm's test, and the transiently positive direct Coombs' test suggests an autoimmune mechanism. Hasty treatment with folic acid or vitamin B₁₂ could have obscured the correct interpretation of the situation, as the delayed reticulocytosis might then have been attributed to the treatment. This case, therefore, illustrates the importance of looking for evidence of an associated hæmolytic anæmia in patients with megaloblastic erythropoiesis.

The short duration of the symptoms, and the absence of a reticulocytosis until several days after admission suggest that the hæmolysis had only developed recently, and that this rapidly produced severe folic acid deficiency. It has been shown that in normal subjects fed on diets deficient in folic acid, the stores of folic acid become sufficiently depleted to give abnormal histidine loading tests in four to six weeks (Knowles, Prankerd and Westall, 1961). It is not remarkable, therefore, that in this patient, who never ate green vegetables, deficiency of folic acid developed rapidly and that after hæmolysis ceased the folic acid deficiency was largely corrected by a normal diet. However, although the development of folic acid deficiency in hæmolytic anæmia has frequently been observed, spontaneous recovery has not been reported previously.

We wish to thank Dr. E. H. Moorhouse for his assistance and Dr. D. C. Watson for permission to publish this case.

REFERENCES

- CHANARIN, I., DACIE, J. V., and MOLLIN, D. L. (1959): Folic Acid Deficiency in Hæmolytic Anæmia, *Brit. J. Haemat.*, **5**, 245.
 DACIE, J. V. (1951): Differences in the Behaviour of Sensitized Red Cells to Agglutination by Antiglobulin Sera, *Lancet*, **ii**, 954.
 KNOWLES, J. P., PRANKERD, T. A. J., and WESTALL, R. G. (1961): Folic Acid Requirements in Man, *J. Physiol.*, **157**, 24P.
 KOHN, J., MOLLIN, D. L., and ROSENBAUGH, L. M. (1961): Conventional Voltage Electrophoresis for Formimino-glutamic-acid Determination in Folic Acid Deficiency, *J. clin. Path.*, **14**, 345.
 MACIVER, J. E., and WENT, L. N. (1960): Sick-cell Anæmia Complicated by Megaloblastic Anæmia of Infancy, *Brit. med. J.*, **i**, 775.

TWO CASES OF ACUTE IDIOPATHIC CIRCUMSCRIBED GANGRENE

P. M. J. TOMBLESON, M.B., B.S., D.A., D.Obst.R.C.O.G.

Late House Physician

Royal Sussex County Hospital, Brighton

P. IRONSIDE, M.B., B.S.

Late Registrar in Pathology

THE association of peripheral gangrene with diabetic or atherosclerotic vascular disease is well known. Other causes include the action of drugs such as ergot, direct contact by chemicals, frostbite and

burns. Polyarteritis nodosa affecting the arterial tree at any level down to the arterioles may cause gangrene, as may occlusion of the venous blood flow (venous gangrene). These characteristically