presented with megaloblastic anaemia, histamine fast achlorhydria, gastric atrophy, and low serum B₁₂ levels. On treatment with vitamin B₁₂ the marrow became normoblastic, but there was no peripheral reticulocytosis; and she died two months later from aplastic anaemia. These authors suggested that underlying aplasia had prevented the anticipated response to vitamin B₁₂.

So far as we are aware aplastic anaemia has not been reported as a complication of true pernicious anaemia *per se*.

Wright (1963) has pointed out that it is doubtful if phenylbutazone has specific anti-rheumatic properties, and that its main effect is analgesic. Moreover, he claims that no adequate clinical trials have been carried out to compare the analgesic properties of phenylbutazone and aspirin.

It is apparent that whenever phenylbutazone is employed, the patient should be kept under very close clinical and haematological review.

Summary

A case of aplastic anaemia occurring in an elderly woman who had taken 10g. of phenylbutazone over a period of 11 months is reported. The patient was known to have had pernicious anaemia for ten years. The haematological complications of phenylbutazone are briefly reviewed. It is important that any patient receiving phenylbutazone be kept under close haematological review, and the drug be stopped at once should suspicion of selective or general marrow depression arise.

So far as we are aware, however, even such

early detection and immediate suspension of the drug may not alter the prognosis in any given case.

We should like to thank Dr. T. Manners for the haematological reports and necropsy details.

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ACUTE MYELOBLASTIC LEUKAEMIA PRESENTING WITH ERYTHEMA NODOSUM

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ERYTHEMA nodosum associated with leukemia is rare although a few cases have been described. The common cutaneous manifestations are petechial haemorrhages, purpuric spots, prurigo-like papules resembling dermatitis herpetiformis, exfoliative dermatitis, and occasionally erythema multiforme. The association of erythema nodosum has been reported with acute monocytic leukemia, (Bluefarb, 1960; Lynch, 1936), with chronic

lymphatic leukemia (Gate and Cuilleret, 1937); with aleukemic leukemia (Kourilsky, Beauvy and Anglade, 1937); and chronic granulocytic leukemia (Piacentini, 1956; Wintrobe and Mitchell, 1940). Recently a case of erythema nodosum as an initial manifestation of acute stem cell leukemia was published (Pinski and Stansifer, 1964), but there is no published report as yet of its association with acute myeloblastic leukemia. The following case report describes a patient who presented with erythema nodosum and was found to have acute myeloblastic leukemia.

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Case Report

The patient, a female housekeeper of 58 was admitted to Raigmore Hospital on May 25th complaining of flitting joint pains and painful red nodules on the legs of seven days duration. She said she had felt ill and had developed a sore throat which had been followed by flitting joint pains and finally by red nodules on her legs. She became febrile later with temperatures reaching 102-104 °F. There was no history of recent infection, allergy, or drug ingestion to account for the erythema nodosum. There was no record whatsoever that she had had phenylbutazone (leukaemia after this drug has been reported recently by Chalmers and McCarthy, 1964).

She gave a past history of having attended the Orthopaedic Clinic in December 1956 for pain in the right elbow, which was diagnosed as tennis elbow, and was treated with intraarticular hydrocortisone. In November 1957 she attended the Medical Clinic with a non-toxic adenoma of the thyroid, but no treatment was given. In November 1960 she was seen again at the clinic, when she had pain and swelling of the proximal interphalangeal joints and the metacarpophalangeal joints.

Investigations: Hb. 66%, ESR 25 mm., WBC 3250/cu. mm., X-ray of the hands revealed early degenerative changes, and she was diagnosed clinically as rheumatoid arthritis although the test for rheumatoid factor was negative.

Progress: She was put on iron therapy and aspirin, and her haemoglobin improved to 75%, and ESR fell to 17 mm. with considerable gain in weight. On her next visit the ESR was 14 mm., Hb. 83%, and WBC only 3000/cu. mm. She was seen again in 1962 when she had some pain in the joints of the hands. She responded well to a course of short wave diathermy, and her blood examination showed a Hb of 78%, WBC 4350 cells/cu. mm., ESR 12 mm., and a negative R.A. Latex test. She was not seen again and remained well till she developed joint pains in May 1964 and was admitted to Raigmore Hospital.

On Admission: The patient did not look very ill on admission despite the high temperature and the joint pains. The positive physical findings were the congested throat and the painful erythematous tender nodules measuring 1-4.5 cm. in diameter over the lower extremities, and the extensor surfaces of the forearms. Her temperature on admission was 100 °F and later became intermittent with the temperature rising up to 104 °F. A provisional diagnosis of acute rheumatic fever was made, but in view of the involvement of the small joints of the hand and proteinuria the collagen group of disorders or sarcoidosis were considered more probable. A haematological examination however revealed to our surprise, a white cell count of 259,300/cu. mm. of which 95% were myeloblasts with 1-4 nucleoli per cell. 70-90% of the myeloblasts contained peroxidase-positive granules on peroxidase staining. Hb 8 g./100 ml. (54%), MCHC 31%, ESR was 100 mm. The blood urea was 37 mg./100 ml., normal plasma proteins and electrophoretic pattern, ASO titre less than 12 units, and the throat swab was negative on two occasions. Sternal marrow puncture was carried out which showed the complete replacement of marrow by sheets of blasts cells and confirmed the diagnosis of acute myeloblastic leukaemia.

She was given blood transfusion, and was put on prednisolone and 6-mercaptopurine. The erythema faded considerably two days after the treatment was started, the nodules subsiding and becoming less

FIG. 1.—Peripheral blood film—peroxidase stain—showing prominent granules in the myeloblasts.

painful, but her general condition deteriorated rapidly. Her throat became more inflamed and she developed chest infection, and despite further treatment with broad spectrum antibiotics she died on the 3rd of June, three weeks after the first sign of her illness.

Necropsy: The liver weighed 2400 g. and although there was no macroscopic abnormality, microscopic examination revealed extensive leukaemic infiltration of portal tracts and sinusoids. The bone marrow was greyish pink in colour and the histological section showed myeloblastic infiltration. The pulmonary arteries contained leukaemic cell thrombus, probably a terminal phenomenon. No other cause for erythema nodosum was discovered.

Discussion

Erythema nodosum is a hypersensitivity reaction of the skin characterised by a tender nodular erythematous eruption in the dermis and subcutaneous tissues, located most commonly over the anterior surface of the legs, occasionally over the extensor surface of the forearms, and rarely on the backs of upper arms, and about the head, face, and eyes. Recognised causes of erythema nodosum are infective diseases (bacterial, viral, spirochaetal, and fungal), drugs, and certain diseases of unknown etiology. Infective causes include tuberculosis, streptococcal infection, leprosy, whooping cough, gonorrhoea and bartonellosis, lymphogranuloma venereum, and measles. Other associated disorders are spirochaetal disease like syphilis, and fungal diseases like coccidioidomycosis, trichophytosis, and histoplasmosis. Drugs causing erythema nodosum include iodides, sulphonamides, bromides, salicylic acid, arsenic and phenacetin. It has also been described in association with sarcoidosis, and ulcerative colitis.

In the above case no known cause for erythema nodosum was discovered. It is interesting to note that when she was seen in 1960 the white cell count was only 3250/cu. mm. Unfortunately the blood film was not done when the nature of

white cells could have been studied. The white cell counts on the next two occasions were also low, being 3000 and 4350 cu./mm. respectively, the latter in June 1962, but when she was admitted this time in May 1964 the picture was that of acute myeloblastic leukemia. This was a rare presentation of acute myeloblastic leukemia, this diagnosis should be considered as a possibility whenever one is confronted with a case of erythema nodosum.

I wish to express my thanks to Drs. J. Ronald and J. Knox, under whose care the patient was admitted, for permission to publish this report: Dr. R. Saaedand, Sister Ross for all the help; Mr. I. Gordon for haematological investigations, and Mr. W. Rose for the photographs.

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ANAEMIA ASSOCIATED WITH PHENOBARBITONE

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IT HAS been established that treatment with phenobarbitone may produce a macrocytic blood picture. In 1958 Hawkins and Meynell noted macrocytosis in as many as 34 per cent of a group of epileptics receiving phenobarbitone alone. However only two well documented cases of megaloblastic anaemia due to this drug have been reported. (Chanarin, Laidlaw, Loughridge, and Mollin, 1960; Sherwin, Wait, and Cooper, 1960). The purpose of this paper is to present a third case.

Case Report

A woman aged thirty six was admitted to the Victoria Infirmary, Glasgow. She had been thought to be normal until sudden right-sided spasticity appeared at the age of four, and epilepsy at five. Since then she had taken phenobarbitone intermittently, and in the last four or five years had taken 180 mg. daily, with convulsions at about monthly intervals. She led a sheltered life and was well looked after at home. In 1950 severe burns of face and hands necessitated several plastic operations, and in 1958 she was operated on for deformities of the right arm and leg resulting from the spastic condition.

Three weeks before admission she complained of nausea, vomiting, diarrhoea and weakness. There was heavy menstrual loss with abdominal pain. Her general practitioner treated obvious anaemia, but there was no response to intramuscular iron. Pheno-

barbitone was continued in usual dosage and 100 mg. chlorpromazine given daily for a few days.

Investigations: On admission on September 16th, 1963 she was confused and febrile. There was heavy vaginal bleeding. Hb. 2.7 g./100 ml., RBC 0.69 mill./cu. mm., PCV 8 ml./100 ml., MCV 116 cu.µ, MCHC 34%, WBC 800/cu. mm., reticulocytes 1.2%, platelets 19,000/cu. mm. Films showed well-stained red cells, marked anisopoikilocytosis, and many macrocytes. Macropolycytes were present, and a few megaloblasts. Two pints of group A, rhesus positive blood were given, and serum specimens taken before and after transfusion for vitamin B₁₂ and folic acid activity estimation. Direct Coombs test was negative at a dilution of 1 in 40.

Progress: On the following day her condition allowed sternal marrow aspiration to be done before further transfusion of two pints of blood. Erythropoiesis was megaloblastic, with many extremely early forms, with fine nuclear structure, and obvious nucleoli. Few late forms were seen. Giant metamyelocytes and precursors were present, and the metamyelocytes had abnormal nuclear configuration. Mitotic figures were increased.

While serum estimations were awaited the patient was given 1000 µg. vitamin B₁₂ intramuscularly daily for four days with oral iron and her usual phenobarbitone. A chest infection was treated with intramuscular penicillin. Her condition improved, though heavy vaginal bleeding continued. On September 19th direct Coombs was positive at dilutions of 1 in 5 and 1 in 10, negative at 1 in 40. Hb. was 7.4 g./100 ml., reticulocytes 2%, WBC 1,800/cu. mm. (neutrophils 64%) megaloblasts present in blood film. On September 24th the platelet count was still extremely low at a level of 38,000 per

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