It would therefore seem that, apart from psychological factors, intolerance is related to the size of the dose. The idea that large doses of iron are required stems partly from the suggestion of Brock and Hunter (1937) that, owing to the avidity of storage depots for iron, the plasma level must be raised above the physiological level before the bone marrow can be stimulated. No doubt this idea arose in part from the difficulty in treating patients with absorption defects, such as steatorrhoea, who are resistant to oral iron therapy. The present findings indicate that cases of iron deficiency should be treated with relatively small doses of oral iron and those who do not respond should be further investigated.

Some authors recommend that iron therapy should be continued for some time after correction of the anaemia in order to replace iron stores (Jasiński, 1949, 1950; Dunlop *et al.*, 1958). This idea is based on the views of Finch *et al.* (1950) that, after anaemia has been corrected and the erythropoietic activity has returned to normal, the absorption of iron returns to a basal level despite the depletion of the iron stores. In the present cases iron was discontinued after five weeks, or less if the haemoglobin reached 13.5 g./100 ml., and in no instance did relapse occur. At follow-up the fasting serum iron level was invariably within normal limits. All patients with symptoms were completely cured by iron therapy and were aware of a sense of well-being.

The findings in the present investigation uphold the view of Minot and Heath (1932) that the reticulocyte response is proportional to the severity of the anaemia and is correlated more closely with the initial haemoglobin level than with the initial red-cell count.

Summary and Conclusions

The results of treatment in young men suffering from uncomplicated iron-deficiency anaemia are described. All responded to oral iron, and no difference between treatment with ferrous sulphate and ferrous gluconate was found. In primary iron-deficiency anaemia an excellent clinical and haematological response can be obtained by giving doses of 600 mg. of ferrous sulphate or 1,500 mg. of ferrous gluconate daily. With this dosage no patient complained of symptoms of intolerance. At follow-up 3 to 12 months after treatment all symptoms were completely cured and no case had relapsed. Therefore, iron therapy after the blood picture has been restored to normal is unnecessary.

It is suggested that cases of iron deficiency anaemia should be treated with small doses of oral iron. Those who do not respond require further investigation.

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MEGALOBlastic ANAEMIA INDUCED BY PHENYLBUTAZONE

BY

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The production of megaloblastic anaemia by anti-convulsant drugs has been recorded in at least 40 cases, and has recently been reviewed (Stokes and Fortune, 1958). In the case described below, megaloblastic anaemia appeared to follow the administration of phenylbutazone and responded to oral folic acid. Many other toxic effects of phenylbutazone on the bone marrow have been described, notably agranulocytosis, but no case of megaloblastic anaemia has previously been reported to our knowledge.

Case History

A housewife aged 36, who had lived in South Australia since birth, was admitted to the Royal Adelaide Hospital in June, 1956. She had suffered from joint pains for some years, and had been taking phenylbutazone ("butazolidin") 400 mg. daily for the last five months. During the month before admission she had lost weight and complained of nausea, attacks of palpitation, and giddiness on bending forward. Her menses had been irregular for three years and she had had amenorrhoea for the last four months. There was no history of pernicious anaemia in relatives, and the only other drugs she had taken were thyroid extract and dexamphetamine sulphate, both prescribed for moderate obesity. During this time she continued to eat a varied and adequate diet.

The patient was pale and her tongue smooth, but otherwise she appeared to be well nourished. Her sternum was tender and the spleen tip was palpable, but there was no lymph-node enlargement. Tendon reflexes were present in the legs but sluggish. The ankle-joints were swollen, red, and tender.

The blood picture was: red-cell count, 1,100,000 per c.mm.; haemoglobin, 4 g. per 100 ml.; M.C.V., 100 cubic microns; M.C.H., 36 μ g.; M.C.H.C., 36%; platelets "plentiful"; reticulocytes, 3.4%; leucocytes, 6,800 per c.mm. (myelocytes 1%, metamyelocytes 2%, polymorphs 65%, lymphocytes 26%, monocytes 6%). Red cells showed marked anisocytosis and some poikilocytosis. Polymorphs showed a mild degree of hypersegmentation. There were six nucleated red blood cells per 100 leucocytes, and about half showed megaloblastic characteristics. The bone marrow was hyperplastic with many fully formed megaloblasts as well as intermediate types. An augmented histamine test meal with radiological control on two occasions revealed no free hydrochloric acid.

Liver-function tests showed nothing abnormal; the icteric index was 7, the serum colloidal gold 0, the cephalin-

cholesterol test negative, the zinc-sulphate test 12 units, and the serum alkaline phosphatase 10 King-Armstrong units. A glucose-tolerance curve was normal. In a fat-balance study, 270 g. of fat was ingested in three days and 6.1 g. excreted in the faeces over this period. A barium-meal examination revealed no abnormality in the oesophagus, stomach, duodenum, or small bowel.

A Schilling test on July 23 (0.6 μ g. of ^{57}Co -labelled vitamin B_{12} and 50 μ g. of intrinsic factor) resulted in 16.2% of the test dose being excreted (normal). This was repeated on August 10 without giving intrinsic factor, and 19% of the test dose was excreted.

Vitamin B_{12} 100 μ g. was given intramuscularly on June 8, followed by 50 μ g. on alternate days until June 19. There was no immediate response, but on the last day of this period the reticulocyte count had risen to 4.8% (Fig. 1).

FIG. 1.—Showing immediate response to therapy.

Folic acid 20 mg. daily was then given by mouth, and the reticulocyte count rose to 15.5% and then fell. The haemoglobin level and red-cell count rose steadily and the M.C.V. decreased. There was marked clinical improvement, and the patient was discharged from hospital and folic acid was discontinued on August 24. During the period following her discharge from hospital she had intermittent severe menorrhagia, which further complicated the peripheral blood picture.

On December 7 phenylbutazone was recommenced at a lower dosage, 200 mg. daily (Fig. 2). While taking phenylbutazone she complained of marked fatigue and a return of muscle cramps in the legs. Macrocytosis again became apparent. This became less when folic acid was

FIG. 2.—The clinical course and the effect of phenylbutazone.

given also, beginning on March 19, 1957. The serum vitamin B_{12} concentration on April 5, estimated by the microbiological assay method, using *Euglena gracilis*, was total vitamin B_{12} 575 m μ g. per ml. and "free" vitamin B_{12} 20 m μ g., which were within the normal range. Both folic acid and phenylbutazone were finally discontinued in August, 1957.

Since then the patient has been well, and examination of her blood on September 25, 1958, showed: red-cell count, 5,150,000; haemoglobin, 14.9 g. per 100 ml.; M.C.V., 87 cubic microns; M.C.H., 30 μ g; M.C.H.C., 33.5%; platelets, "plentiful"; reticulocytes, 1%; leucocytes, 9,900 per c.mm. A further test meal on October 15 showed that the histamine-fast achlorhydria persisted.

Discussion

This case of megaloblastic anaemia in a young woman had a number of unusual features. Although there was achlorhydria, the normal Schilling test for vitamin B_{12} absorption makes Addisonian pernicious anaemia unlikely, a point further supported by the failure of the blood picture to respond promptly to injections of vitamin B_{12} . A serum vitamin B_{12} assay was not done before treatment, but this figure was normal some eight months after the short course of vitamin B_{12} . Pregnancy, steatorrhoea, and hepatic disease were all excluded.

Folic acid was given, as there had been little improvement in the blood picture after 12 days, but unfortunately too soon after vitamin B_{12} was discontinued, thus somewhat obscuring the significance of further blood changes. However, there was a prompt and considerable rise in the reticulocytes and the red-cell count during the next seven days. There had previously been an adequate dietary intake of folic acid, but the response to its oral administration made impaired intestinal absorption unlikely, so the possibility arose of some interference with the metabolism of this substance.

At that time (1956) a metabolic "block" had been suggested as the cause of megaloblastic anaemia occurring in epileptic patients taking barbiturates, notably phenytoin and primidone (Badenoch, 1954; Hawkins and Meynell, 1954, 1958). Most of these cases responded to folic-acid therapy. More recently Chanarin *et al.* (1958) have studied folic acid utilization by measuring the rate of disappearance of this substance from the plasma in a case of megaloblastic anaemia caused by primidone. They showed that the rate of clearance of intravenously injected folic acid and its oral absorption were normal, and concluded that the anaemia was due to interference with the "tissue metabolism" of folic acid. Girdwood and Lenman (1956) pointed out the broad similarity between the chemical structure of folic acid and the anti-epileptic drugs. The structure of phenylbutazone (3,5-dioxo-1, 2-diphenyl-4-*n*-butyl-pyrazolidine) also has analogies with folic acid and with the barbiturates. In our patient it seemed that phenylbutazone may have produced the same phenomenon, and an attempt was made to demonstrate this effect of the drug by therapeutic trial.

The propensity of phenylbutazone for producing "hypersensitivity" reactions was widely described in the few years following its introduction to clinical medicine. Effects were seen particularly in the leucocytes and liver (Steinberg *et al.*, 1953; Engleman *et al.*, 1954), and fatal cases of generalized visceral involvement were found (O'Brien and Storey, 1954; MacCarthy and Jackson, 1955; Hodge and Lawrence, 1957). In view of this, the drug was reintroduced at a lower dosage, 200 mg. daily. During this period the patient felt worse, and macrocytosis again became apparent but lessened when folic acid was given coincidentally with the phenylbutazone.

Unlike most cases previously described as having drug-induced megaloblastic anaemia, our patient had a histamine-fast achlorhydria (no gastric biopsy was available), and this has persisted. The blood picture, however, has remained normal for 14 months, and no further specific therapy has been given since the course of folic acid. This is good evidence that some factor other than achlorhydria alone produced the previous disturbance, and we feel this was phenylbutazone. Prolonged remission after one course of folic acid has been a feature of previous cases; and of 35 cases of

megaloblastic anaemia reported as due to anti-epileptic drugs 26 have been in females, most of them, like our patient, in the menstrual age group.

Gydel (1957) and Newman and Sumner (1957) suggested that many cases had an inadequate diet. Stokes and Fortune (1958), in a review of drug-induced megaloblastic anaemia, noted that a "co-factor" was often present as well as the ingested drug. Such factors were menorrhagia, mild or latent steatorrhoea, and dietary deficiency, and the authors suggested that these explained the relatively uncommon incidence of blood changes despite the large number of patients taking anti-epileptic drugs. This has been further supported by a case described by Calvert *et al.* (1958) in a woman aged 39 with severe menorrhagia.

The persistent achlorhydria in our patient may well represent the co-factor potentiating in some way a metabolic effect of phenylbutazone, and this would explain why no similar case has been recorded, despite the wide use of this drug.

Summary

A case of megaloblastic anaemia in a woman aged 36 is described. The anaemia occurred after she took phenylbutazone and responded to oral folic acid. A further course of phenylbutazone caused a recurrence of the macrocytosis. Intestinal malabsorption and hepatic disease were excluded.

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A new medical centre at Elswick Works, serving the employees of Vickers-Armstrongs' various units in Newcastle upon Tyne, was opened on August 21 by Lady DUNPHIE, wife of the chairman of the company. The centre is fully equipped with x-ray room, an operating theatre, and a physiotherapy department giving a comprehensive industrial medical service. The medical officer in charge is Dr. D. McLEAN. The firm's medical services have come a long way since 1913, when they consisted only of first-aid boxes in the workshops. During the first world war "dressing stations" were opened in several shops, all manned by members of the works ambulance corps. Great progress was also made during the second world war, during which a first-aid post, a civil defence post, and an ambulance room were opened, and the first full-time medical officer was appointed with a staff of five State-registered nurses and 18 St. John nurses and nursing auxiliaries. Later two part-time doctors were also employed. The period from 1946-9 laid the foundation of the firm's industrial medical service as operated to-day: two first-aid posts were altered to house a surgery, an x-ray room, operating theatre, and physiotherapy department. In 1955 the planning of the new medical centre started, and in 1959 the new centre was completed.

Medical Memoranda

Phaeochromocytoma within the Renal Capsule

Phaeochromocytomata may arise within the adrenals or in the chromaffin tissue elsewhere, such as the abdominal paraganglia and organ of Zuckerkandl at the bifurcation of the aorta (Boyd, 1950). Such extra-adrenal tumours are known as paragangliomata. Rarely the adrenal glands themselves are ectopic. The gland was found to lie within the renal capsule in 8 out of 5,000 consecutive necropsies (O'Crowley and Martland, 1943), a condition known as adrenal-renal heterotopia. The occurrence, therefore, of a phaeochromocytoma arising in such an adrenal must be extremely rare. Such a case is reported here.

CASE REPORT

A single woman aged 57 first attended the out-patient department of the Manchester Royal Infirmary in 1952. She had been referred from the Royal Eye Hospital, where she had attended because of failing vision. Her other complaints were headaches and palpitations of 20 years' duration and a little shortness of breath on exertion. There was no family history of hypertension.

On examination the only abnormal findings were a blood pressure of 255/135 and fundi that showed arteriovenous nipping and many small white fluffy exudates. No papilloedema or haemorrhages were present and the urine was normal. The heart size was normal. A diagnosis of severe essential hypertension was made. The patient was advised to go into hospital for investigation, but she declined on two occasions as she was looking after her mother, who was ill with bronchitis. She was not seen again until April, 1957. She had kept reasonably well since 1952, and was sent up on account of an attack of vomiting following a few days' vague dyspepsia. There had been a little blood-streaking of the vomit, and her liver had been noted by her own doctor to be enlarged two fingerbreadths below the costal margin, and it was tender. There had been no jaundice. After a few days in bed she had felt better. She was seen in the out-patient department on April 5, 1957.

On examination she looked fit. Her B.P. was 180/120. The heart size was normal, but a short systolic murmur could be heard at the apex; the fundi showed a little arteriovenous nipping but no exudates, haemorrhages, or papilloedema. The liver edge was just palpable and not tender. Otherwise the findings were negative. The urine was free from albumin and sugar.

Blood.—Haemoglobin, 84%; serum albumin 3.8%, serum globulin 3.2%; bilirubin, 0.3 mg./100 ml.; thymol turbidity, 0.8 unit; serum alkaline phosphatase, 16 units/100 ml. Chest x-ray and barium-meal examinations were negative.

She was admitted for full investigation under Dr. William Brockbank on July 11. Further investigations showed normal bleeding-time, clotting-time, and prothrombin time, and a blood urea of 36 mg./100 ml. The blood pressure on admission was 230/130. After a few days in bed and treatment with reserpine, 0.25 mg. t.d.s., it had fallen to 160/90.

A needle biopsy of the liver was done on July 19. Immediately after withdrawal of the needle from the liver the patient complained of headache and feeling cold. Her pulse rate was 60 a minute and blood pressure 290/160. There was no sweating. The attack was over in a few