not uncommon in human populations. Further research seems desirable on the copper contents of human dietaries, and on the intricate interrelationships between the absorption and metabolism of copper, iron, and calcium.

SUMMARY

Young rats fed on a diet of raw minced beefsteak developed signs of copper deficiency as evidenced by hypochromotrichia, slight anaemia, and a slight reduction in the rate of weight increase.

The deficiency could be prevented by the addition to the meat of copper sulphate or of impure ferrous carbonate containing copper.

Chemical analyses showed that the meat contained the expected amounts of copper. A defect in its absorption, probably due to the high phosphate content of the meat, therefore seemed probable.

In adult rats hypochromotrichia could be prevented, and in young rats partially prevented, by the addition of calcium carbonate to the diet. The calcium carbonate contained only traces of copper, and presumably acted by counteracting the high intake of phosphate.

My thanks are due to Dr. L. J. Harris for his criticism; to Dr. I. M. Sharman, Mr. B. J. Constable, Mr. S. G. Impey, and Mr. K. R. Symonds for help in various ways; and to Mrs. E. Collinson and Mr. P. E. N. Martin for looking after the animals. The copper estimations, kindly carried out by Dr. J. M. Walshe, were indispensable for the interpretation of my results.

T. MOORE, Sc.D.,

Dunn Nutritional Laboratory, University of Cambridge,
and the Medical Research Council.

REFERENCES

- Hart, E. B., Steenbock, H., Waddell, J., and Elvehjem, C. A. (1928). *J. biol. Chem.*, **77**, 797.
Hundley, J. M. (1950). *Proc. Soc. exp. Biol. (N.Y.)*, **74**, 531.
Moore, T., and Sharman, I. M. (1960). *Brit. med. J.*, **2**, 1704.
Schultze, M. O., Elvehjem, C. A., and Hart, E. B. (1934). *J. biol. Chem.*, **106**, 735.
Scott, P. P., and Scott, M. G. (1960). *Proc. Nutr. Soc.*, **19**, iv.

Medical Memoranda

Fatal Marrow Aplasia During Chlorpropamide Therapy

Although it is difficult to obtain any accurate indications of the extent to which chlorpropamide is at present prescribed, the risk of serious marrow damage arising from its administration is evidently small. Nevertheless, the possibility should be borne in mind during the initial stages of treatment.

CASE REPORT

A woman aged 63 at death had been under the care of Dr. C. S. D. Don at Manchester Royal Infirmary for diabetes mellitus since October, 1958. As simple dietary restriction proved unsuccessful, tolbutamide (0.5 g. t.d.s.) was given. The initial response was satisfactory, but from January, 1960, appreciable hyperglycaemia developed. Because of this, chlorpropamide (375 mg. daily) was substituted for tolbutamide at the beginning of June, 1961.

On July 21 a rash appeared on the chest and neck, followed four days later by a sore throat, which was unrelieved by penicillin therapy. The patient was referred to Monsall Hospital by her family doctor on July 27 as a possible case of diphtheria. On examination she was somewhat dehydrated and dyspnoeic, and was unable to speak clearly. Her neck was erythematous, swollen, and

tender, while her tonsils were enlarged and covered by thick membranous slough. Rales were audible over both lung bases, and the percussion note was impaired on the left side. Glycosuria was absent, and the blood sugar was 110 mg./100 ml. The total leucocyte count was 250/c.mm., of which only 5% were neutrophil polymorphs. Initial treatment with chemotherapy and intravenous Hartmann's solution was followed on July 28 by transfusion of 1 pint (570 ml.) of fresh blood, but she collapsed and died the same day. A blood count shortly before death gave the following results: Hb. 13.9 g./100 ml. (94%); total leucocytes 200/c.mm. (neutrophil polymorphs 1%, lymphocytes 97%, monocytes 2%); platelets 64,000/c.mm.

At necropsy there was extensive pharyngeal ulceration with oedema of surrounding structures, including the larynx, and tracheobronchitis with pulmonary congestion and oedema. The heart was flabby and dilated, and there was atheroma of the aorta and coronary arteries. Two small chronic peptic ulcers were present in the pyloric antrum. The liver was moderately fatty. The only other abnormalities were congestive splenomegaly and mild nephrosclerosis. Marrow films were unfortunately not obtained until 72 hours after death and were of poor quality. However, it was evident that cellularity was reduced and that the majority of nucleated cells were lymphocytes, plasma cells, and reticulum cells. Only small numbers of erythroblasts and myeloid cells were present, most of them fairly mature, and megakaryocytes were difficult to find.

These appearances, in conjunction with the platelet count during life, suggest that there was a general disturbance of haemopoietic activity rather than a selective suppression of granulocyte production, although the latter was the important clinical factor.

COMMENT

The initial oral hypoglycaemic agent, carbutamide, was soon discarded because of the frequency of toxic marrow damage. It was replaced by tolbutamide, which has proved to be remarkably free from side-effects, and so far as is known only one case of fatal aplastic anaemia has been reported (Jost, 1959). However, tolbutamide has only a mild and short-acting hypoglycaemic action, and its effect often diminishes with time. In the last three years chlorpropamide has been widely used, since it has a greater and more prolonged hypoglycaemic effect, and often proves successful in cases no longer responsive to tolbutamide. Like the latter, it is a sulphonylurea. A variety of toxic effects, including mental and visual disturbances, dyspnoea, skin rashes, and jaundice, have been recorded, but the incidence of these may have been related to the rather large doses given in early trials. The only previous report of fatal marrow damage appears to be that of Karlin (1960) in a man of 59 who developed agranulocytosis after three weeks of therapy (500 mg. daily). Karlin, however, draws attention to several reports of non-fatal haematological reactions, and to these may be added that of Grace (1959), who recorded thrombocytopenic purpura within five days of beginning therapy (500 mg. t.d.s.). It has been pointed out that the frequency of these reactions increases with the dose administered, and Bloom (1961) thinks that the dose should never exceed 500 mg. daily. In the case reported the amount administered was well within this limit.

LESLIE L. R. WHITE, M.D., B.Sc., D.C.H.,
Department of Pathology, Booth Hall and
Monsall Hospitals, Manchester.

REFERENCES

- Bloom, A. (1961). *Brit. J. clin. Pract.*, **15**, 41.
Grace, W. J. (1959). *New Engl. J. Med.*, **260**, 711.
Jost, F. (1959). *J. Amer. med. Ass.*, **169**, 1468.
Karlin, H. (1960). *New Engl. J. Med.*, **262**, 1076.