The toxic effects of carbimazole can usually be readily recognized and controlled, and after serious toxic effects drug therapy can be continued where necessary with perchlorate. It is probably better to reserve perchlorate for this role on account of its potentially less smooth antithyroid control.

We thank Miss J. Allen, pharmacist to Hammersmith Hospital, for assistance with the abstraction of data. Our thanks are also due to various colleagues for their kind co-operation and permission to include their case records in the analysis: Drs. C. A. Birch, J. A. Campbell, E. Frankel, R. Greene, G. W. Hadley, R. Sleigh Johnson, R. Arden Jones, A. R. Kelsall, K. A. Latter, S. Locket, B. B. Morgan, W. A. Oliver, A. W. Spence, and J. Wolstencroft, and Mr. V. H. Riddell. One of us (C. D. B.) was in receipt of a grant from the Medical Research Council for part of this work.

REFERENCES

- 1 Albert, A. (1952). *Ann. Rev. Physiol.*, **14**, 481.
- 2 Aspenström, G. (1953). *Acta med. scand.*, **147**, 63.
- 3 Astwood, E. B. (1943). *J. Amer. med. Ass.*, **122**, 78.
- 4 — (1944). *J. clin. Endocr.*, **4**, 229.
- 5 — and Vanderlaan, W. P. (1946). *Ann. intern. Med.*, **25**, 813.
- 6 Barfred, A. (1947). *Amer. J. med. Sci.*, **214**, 349.
- 7 Bartels, E. C. (1952). *Ann. intern. Med.*, **37**, 1123.
- 8 — (1953). *J. clin. Endocr.*, **13**, 1305.
- 9 — and Blizard, E. C. (1945). *Lahey Clin. Bull.*, **4**, 150.
- 10 — and Sjogren, R. W. (1951). *J. clin. Endocr.*, **11**, 1057.
- 11 Beardwood, J. T., jun., and Levinson, D. C. (1944). *Clinics*, **3**, 672.
- 12 Beierwaltes, W. H. (1950). *J. Lab. clin. Med.*, **36**, 861.
- 13 Bowen, B. D., and Lenzner, A. R. (1951). *New Engl. J. Med.*, **245**, 629.
- 14 Chevalley, J., McGavick, T. H., Kenigsberg, S., and Pearson, S. (1954). *J. clin. Endocr.*, **14**, 948.
- 15 Crile, G., jun., and Fischman, E. P. (1951). *Ann. Surg.*, **134**, 18.
- 16 Davidson, L. A. G. (1953). *British Medical Journal*, **2**, 1300.
- 17 Doniach, D. (1953). *Lancet*, **1**, 873.
- 18 Dunlop, D. M., and Rolland, C. F. (1950). *Proc. roy. Soc. Med.*, **43**, 937.
- 19 Eaton, J. C. (1945). *Lancet*, **1**, 171.
- 20 Fischmann, E. J., and Fischman, A. (1948). *N.Z. med. J.*, **47**, 537.
- 21 Fraser, R., and Wilkinson, M. (1953). *British Medical Journal*, **1**, 481.
- 22 — Hanno, M. G. W., and Pitney, W. R. (1955). *Brit. J. Pharmacol.*, **10**, 1.
- 23 Fraser, T. R., Garrod, O., Hanno, M. G. W., and Jadresic, A. (1954). *J. clin. Endocr.*, **14**, 1230.
- 24 Gabrilove, J. L., and Kert, M. J. (1944). *J. Amer. med. Ass.*, **124**, 504.
- 25 Godley, A. F., and Stanbury, J. B. (1954). *J. clin. Endocr.*, **14**, 70.
- 26 Grauer, R. C., De Walt, H., and Elkin, C. W. W. (1948). *Amer. J. med. Sci.*, **215**, 63.
- 27 Greenberg, S. U., and Bruger, M. (1950). *Ibid.*, **220**, 373.
- 28 Grollman, A., and Gryte, C. F. (1944). *J. clin. Endocr.*, **4**, 444.
- 29 Himsworth, H. (1944). *British Medical Journal*, **1**, 852.
- 30 — Joll, C. A., Evans, H., Melton, G., and Simpson, S. L. (1944). *Proc. roy. Soc. Med.*, **37**, 693.
- 31 Irwin, G. W., Van Vactor, H. D., and Norris, M. S. (1952). *J. Amer. med. Ass.*, **149**, 1637.
- 32 Isbister, J., and Rundle, F. F. (1954). *Med. J. Aust.*, **1**, 78.
- 33 Iversen, K. (1951). *J. clin. Endocr.*, **11**, 298.
- 34 Kendrick, R. L., Balls, K., and Rose, E. (1952). *A.M.A. Arch. intern. Med.*, **89**, 368.
- 35 Kirkeby, K., and Römcke, O. (1955). *Lancet*, **1**, 374.
- 36 Lawson, A., and Barry, G. (1951). *Ibid.*, **2**, 621.
- 37 — Rimmington, C., and Searle, C. E. (1951). *Ibid.*, **2**, 619.
- 38 Lederer, J. (1949). *Ann. Endocr. (Paris)*, **10**, 44.
- 39 Lesses, M. F., and Gargill, S. L. (1945). *New Engl. J. Med.*, **233**, 803.
- 40 Lou, H., and Wulff, F. (1949). *Acta med. scand.*, **133**, 149.
- 41 Lozinski, E., and Siminovich, J. (1944). *Canad. med. Ass. J.*, **51**, 422.
- 42 McCullagh, E. P., Hibbs, R. E., and Schneider, R. W. (1947). *Amer. J. med. Sci.*, **214**, 545.
- 43 — and Sirridge, W. T. (1948). *J. clin. Endocr.*, **8**, 1051.
- 44 McGavack, T. H. (1952). *Med. Clin. N. Amer.*, **36**, 603.
- 45 — Gerl, A. J., Morton, J. H., Vogel, M., and Schwimmer, D. (1945). *J. clin. Endocr.*, **5**, 259.
- 46 — — Vogel, M., and Schutzer, S. (1947). *Amer. J. Med.*, **2**, 144.
- 47 MacGregor, A. G., and Miller, H. (1953). *Lancet*, **1**, 881.
- 48 MacKenzie, C. G., and MacKenzie, J. B. (1943). *Endocrinology*, **32**, 185.
- 49 MacKenzie, J. B., MacKenzie, C. G., and McCollum, E. V. (1941). *Science*, **94**, 518.
- 50 Maddox, K. (1949). *Med. J. Aust.*, **2**, 113.
- 51 Magnusson, P., and Sørensen, G. (1946). *Acta med. scand.*, **125**, 263.
- 52 Manson, D. I. (1953). *Edinb. med. J.*, **60**, 321.
- 53 Martin, E. M. (1944). *Canad. med. Ass. J.*, **51**, 39.
- 54 Meulengracht, E., and Kjerulf-Jensen, K. (1948). *J. clin. Endocr.*, **8**, 1060.
- 55 Moore, F. D. (1946). *J. Amer. med. Ass.*, **130**, 315.
- 56 Morgans, M. E., and Trotter, W. R. (1954). *Lancet*, **1**, 749.
- 57 Nussey, A. M. (1944). *British Medical Journal*, **2**, 745.
- 58 Palmer, M. V. (1945). *Ann. intern. Med.*, **22**, 335.
- 59 Paschkis, K. E., Cantarow, A., Rakoff, A. E., Walking, A. A., and Tourish, W. J. (1944). *J. clin. Endocr.*, **4**, 179.
- 60 Pitt-Rivers, R. (1950). *Physiol. Rev.*, **30**, 194.
- 61 Plamondon, C. A., Wiswell, J. G., and Asper, S. P., jun. (1952). *Laval méd.*, **17**, 1208.
- 62 Poate, H. (1953). *Lancet*, **1**, 879.
- 63 — (1950). *Med. J. Aust.*, **1**, 139.
- 64 Rawson, R. W., Evans, R. D., Means, J. H., Peacock, W. C., Lerman, J., and Cortell, R. E. (1944). *J. clin. Endocr.*, **4**, 1.
- 65 Reveno, W. S. (1945). *J. Amer. med. Ass.*, **128**, 419.
- 66 — (1947). *Ibid.*, **133**, 1190.
- 67 Rinkoff, S., and Spring, M. (1948). *N.Y. St. J. Med.*, **48**, 1025.
- 68 Roche, J., and Michel, R. (1955). *Physiol. Rev.*, **35**, 583.

- 69 Rose, E., and McConnell, J. (1944). *Amer. J. med. Sci.*, **208**, 561.
- 70 Rosenbaum, H., and Reveno, W. S. (1953). *J. Amer. med. Ass.*, **152**, 27.
- 71 Soffer, L. J., Kert, M., and Gabrilove, L. (1944). *J. clin. Invest.*, **23**, 940.
- 72 Starr, P., Petit, D. W., Meister, L., and Surratt, R. L. (1949). *J. clin. Endocr.*, **9**, 330.
- 73 Surratt, R. L., Petit, D. W., and Starr, P. (1952). *Ibid.*, **12**, 719.
- 74 Stone, H. H., Petit, D. W., and Starr, P. (1952). *Ibid.*, **12**, 841.
- 75 Vanderlaan, J. E., and Vanderlaan, W. P. (1947). *Endocrinology*, **40**, 403.
- 76 Van Winkle, W., jun., Hardy, S. M., Hazel, G. R., Hines, D. C., Newcomer, H. S., Sharp, E. A., and Sisk, W. N. (1946). *J. Amer. med. Ass.*, **130**, 343.
- 77 Verel, D. (1949). *British Medical Journal*, **1**, 892.
- 78 Watson, E. M., and Wilcox, L. D. (1944). *Canad. med. Ass. J.*, **51**, 29.
- 79 — (1945). *J. clin. Endocr.*, **5**, 273.
- 80 Williams, R. H., Clute, H. M., Anglem, T. J., and Kenney, F. R. (1946). *Ibid.*, **6**, 23.
- 81 Wilson, A., and Goodwin, J. (1947). *Lancet*, **1**, 669.
- 82 Wing, E. S., jun., and Asper, S. P., jun. (1952). *Bull. Johns Hopk. Hosp.*, **90**, 201.
- 83 Wynngaarden, J. B., Stanbury, J. B., and Du Toit, C. H. (1951). *J. clin. Endocr.*, **11**, 1259.

FATAL MARROW APLASIA AFTER TREATMENT WITH CARBIMAZOLE

BY

CRAIG D. BURRELL, M.B., Ch.B.

From the Department of Medicine, Postgraduate Medical
School of London, W.12

The incidence of severe toxic reactions—that is, serious depression of haemopoietic tissue—after carbimazole is low; in the series of 1,046 cases reported by Burrell *et al.* (1956) only one case of agranulocytosis (non-fatal) occurred. Among many cases treated since this survey the following fatal case of marrow aplasia was encountered; this is the seventh published case of serious marrow depression following carbimazole (two fatal) (Table I).

TABLE I.—Severe Haematological Reactions to Carbimazole

Author	Type of Reaction	Days on Carbimazole	Daily Dosage
Greene and Morgan (1956)	Pure red-cell anaemia	1	30 mg.
Bartels (1953)	Agranulocytosis	24	40 "
Batty Shaw (1955)	"	30	30 mg. for first 16 days, thereafter 15 mg.
Fraser <i>et al.</i> (1954)*	"	30	60 mg.
Harrison (1954) ..	"	39	15 mg. for first 9 days, thereafter 30 mg.
Richardson <i>et al.</i> (1954)	Bone marrow aplasia (fatal)	54	30 mg.
Present case ..	" "	165	30 "

* Also reported in Burrell *et al.* (1956).

Case Report

Between 1943 and 1951 this patient had several periods of antithyroid drug treatment with which she never persisted carefully, and often lapsed (three months on thiouracil in 1943, two months on methylthiouracil in 1946, and twenty-one months on methylthiouracil in 1949–51). During the last period (1950) she developed dermatitis, treated with antihistamines, but had no other sign of toxic reactions.

At Hammersmith Hospital out-patient department, on August 8, 1955, this married woman of 47 started carbimazole in preparation for thyroidectomy for a clinically obvious recurrence of thyrotoxicosis. She had lost over a stone (6.4 kg.) in weight, and her thyroid was avid for radioiodine (48-hour urine excretion 14.8%, "T" = 55). The initial drug dosage was carbimazole, 30 mg. a day, sodium L-thyroxine, 0.1 mg. a day, and phenobarbitone, 30 mg. twice a day. Owing to an unfortunate oversight this was continued beyond her two and a half months' visit, when she was judged euthyroid and ready for operation.

Shortly after her out-patient attendance on January 7, 1956 (five months after starting carbimazole), she first noticed a few spots on her chest, but unfortunately did not bother to report them; on January 18 a definite rash appeared on her arms and legs, and bruises developed at the right elbow, wrist, and ankle, and on both thighs. She then stopped drug therapy, but she still did not report until her routine out-patient appointment on January 21, when she was admitted at once. On admission her temperature was 99° F. (37.2° C.), and she had marked pallor of the skin and mucous membranes. A purpuric rash was present, mainly around the suprasternal notch, the nipples, the dorsal aspect of both elbows, and on both hands. Haematomata were present, as mentioned earlier, and below the right lower eyelid, while petechiae were present in the mouth and right conjunctiva. The fundi were clear. The Hess test was strongly positive with grossly prolonged bleeding and clotting times. There were no other abnormal clinical findings. Table II shows the blood picture on admission and thereafter. Sternal puncture on January 24 showed an aplastic marrow.

TABLE II.—Haematological Findings

Date	Hb	P.C.V.	White Blood Cells			Platelets (per c.mm.)
			Total (per c.mm.)	Differential		
				Polys	Lymphs	
21.1.56	54%	25%	1,500	7%	93%	2,000
23.1.56	67%					
24.1.56	65%	28%	1,700	2%	98%	1,500
26.1.56	59%	25%	3,700		100%	1,400

Chlortetracycline was started with a loading dose of 1 g. followed by 500 mg. every six hours, together with prednisolone, 15 mg. six-hourly. One pint (570 ml.) of blood was transfused on January 22, by which time she was febrile—102° F. (38.9° C.)—and had a sore throat. By the 25th there was some minor clinical improvement, but during that evening further petechiae developed. In the early hours of the 26th a left hemiplegia developed and she died a few hours later.

Post-mortem examination revealed large haemorrhages into the skin, and petechiae on both pleural surfaces, pericardium, and peritoneum were noted. There were free haemorrhages into the lungs and submucosal haemorrhages into the alimentary canal. The immediate cause of death was a massive haemorrhage into the right cerebral hemisphere. Histological examination of ileum, sternum, femur, and vertebral body showed "virtually complete aplasia involving almost all marrow cells with replacement by a few foci of lymphocytes."

Comment

This case illustrates the importance of the patient's early reporting of any toxic reactions, though we cannot know in this case whether this would have resulted in a happier outcome. It also demonstrates the seriousness of the risk of haemorrhage in marrow aplasia. No other reported serious toxic reaction to carbimazole has occurred more than two months after the beginning of therapy.

I wish to thank Dr. Russell Fraser for advice, assistance, and permission to publish this case; also the department of pathology, Postgraduate Medical School, in particular Dr. J. H. Little, for assistance.

REFERENCES

- Bartels, E. C. (1953). *J. clin. Endocr.*, **13**, 1305.
 Burrell, C. D., Fraser, R., and Doniach, D. (1956). *British Medical Journal*, **1**, 1453.
 Fraser, T. R., Garrod, O., Hanno, M. G. W., and Jadresic, A. (1954). *J. clin. Endocr.*, **14**, 1230.
 Greene, R., and Morgan, D. C. (1956). *Ibid.*, **16**, 391.
 Harrison, A. R. (1954). *Lancet*, **1**, 396.
 Richardson, J. S., Sarkany, I., and Campbell, C. D. (1954). *British Medical Journal*, **1**, 364.
 Shaw, A. B. (1955). *Ibid.*, **2**, 246.

SIGNIFICANCE OF *H. INFLUENZAE* IN BRONCHIECTASIS OF CHILDREN

BY

E. C. ALLIBONE, M.D., Ph.D., F.R.C.P.

P. R. ALLISON, Ch.M., B.Sc., F.R.C.S.

AND

K. ZINNEMANN, M.D., M.Sc.

From the Departments of Paediatrics and of Thoracic Surgery, Leeds General Infirmary, and the Department of Bacteriology, Leeds School of Medicine

The incidence of *Haemophilus influenzae* in bronchoscopic aspirations of 100 consecutive cases of bronchiectasis in young people in the Leeds area was reported in 1943 by Allison *et al.* The investigation was based on one examination per patient; *H. influenzae* was found in 63%.

As antibacterial agents became available their activity against capsulated and non-capsulated *H. influenzae* strains was investigated with a view to using them as tools in further investigations and in the therapy of chronic conditions due to *H. influenzae* (Gordon and Zinnemann, 1945; Zinnemann, 1950, 1953; Finland and Wilcox, 1950; Love and Finland, 1954). Franklin and Garrod (1953) reported on the effectiveness of systemic chloramphenicol in reducing the amount of sputum and at the same time eliminating pus and *H. influenzae* from the sputum of bronchiectatic children. Mulder *et al.* (1952), using the full range of antibiotic drugs then available, had previously described similar findings in adults. Results with chloramphenicol equally as good clinically as those obtained by Franklin and Garrod (1953), but without adequate bacteriological examinations, had also been reported by Wynn-Williams and Moyes (1951) and Harris *et al.* (1952).

Present Investigation

In 1952, therefore, although precise evidence was lacking, it appeared probable that *H. influenzae* played a major part in maintaining chronic inflammatory processes in the bronchial tree, and that it could be suppressed by systematic use of antibacterial agents. We decided to investigate bronchiectatic children to see whether (1) findings identical with those obtained by Allison *et al.* (1943) could be repeated in younger age groups, which presumably represent an earlier stage of the disease, (2) by means of the therapeutic test to try to extend the evidence for the significance of *H. influenzae* in purulent bronchiectasis, and (3) to try to influence the condition therapeutically. Therapeutic results will be the subject of a separate clinical report.

Patients Investigated.—The group under investigation consisted of 32 children aged 4–15 years with purulent bronchiectasis, established clinically and radiologically. Before a bronchogram was taken under general anaesthesia, specimens for bacteriological investigation were collected by bronchoscopic aspiration. Apart from using general anaesthesia in place of local analgesia the technique was identical with that described by Allison *et al.* In addition, both maxillary antra were washed out with 5 ml. of physiological saline; the washings were centrifuged at 1,500 r.p.m. for 10 minutes and the deposit examined microscopically and by culture. The bacteriological technique used for culturing was that employed by Allison *et al.* In particular we should like to stress the importance of a very heavy inoculum; we used a ball of mucopus the size of a large pea (about 1–1.5 cm. diameter) which, without any washing