venography is used in the leg to assess the extent of deep vein thrombosis, we believe this to be the first report of perosseous venography of the arm in such circumstances and the first use of an arteriovenous connection in a patient with a major clotting defect.

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Urology Department, Glasgow Royal Infirmary, Glasgow G4 0SF
ANTHONY J YATES, MB, FRCSED, senior registrar

University Medical Department, Glasgow Royal Infirmary, Glasgow G4 0SF
ANN HARVIE, MB, CHB, senior house officer
GORDON LOWE, MB, MRCP, registrar
CHARLES D FORBES, MD, FRCPGLAS, senior lecturer
COLIN R M PRENTICE, MD, MRCP, senior lecturer

Department of Surgery, Western Infirmary, Glasgow G4 0SF
DAVID N H HAMILTON, PHD, FRCSGLAS, consultant

A black thyroid and minocycline treatment

A black thyroid has not been reported in man but has been found in monkeys, dogs, and rats during trials with the tetracycline, minocycline.[1] We found a uniformly black thyroid in a man given minocycline for a year.

Case report

A 69-year-old man with respiratory difficulties due to bronchiectasis and emphysema was admitted to the Austin Hospital, Heidelberg. He had clubbed fingers and toes and pigmentation of the alae nasi. A left pneumothorax with mediastinal shift was treated, but 18 days later he again became breathless, and despite reinsertion of an intercostal catheter he died. In hospital he got ampicillin but no tetracyclines. Minocycline 100 mg twice daily had been taken for nearly a year up to four months before admission.

At necropsy major findings were bullous emphysema, a left apical pneumothorax, subcutaneous emphysema, bronchiectasis, and focal pneumonia. The alae nasi were blue-black, the costal cartilages dark, the parietal bones yellow-brown, and the thyroid (10 g) uniformly black.

Haematoxylin-and-eosin sections of thyroid showed slight interstitial fibrosis, pigment aggregates in colloid, and pigment granules within most follicular cells. In heavily pigmented areas some nuclei were pyknotic. The pigment was iron-free, non-fluorescent, and associated with lipofuscin. It failed to stain with certain cationic dyes but otherwise resembled melanin.

Some formalin-fixed thyroid was washed, post-fixed in glutaraldehyde and osmium, and processed for electron microscopy. Thick, Paragon-stained sections (fig 1a) more clearly defined the pigment in the epithelium and aggregates within colloid. Both black and green pigments were seen—the black usually as discrete droplets or less commonly within green droplets. The green droplets were numerous and present singly or clumped. Nuclear changes were more obvious and could not be due to autolysis.

Thin sections stained with uranyl acetate and lead citrate (fig 1b) showed many electron-dense, rimmed bodies in the cytoplasm of many follicular cells. The rims varied in thickness, and the density of their matrix was less granular than colloid. These rimmed bodies lay free in the cytoplasm, within membrane-bound, colloid droplets or in multivesicular aggregates identical to lipofuscin. The density and frequency of the rimmed bodies differed from age-matched control thyroids.

Discussion

We have not found a previous report of a uniformly black thyroid in man. Macroscopically dark brown pigmentation of the thyroid has been reported in mucoviscidosis.[2] This lipofuscin pigmentation was attributed to chronic vitamin E deficiency with auto-oxidation of lipids. In ceroid storage disease[3] the pigment was seen histologically but not macroscopically.

Benitz *et al*[1] reported black discolouration of thyroids in monkeys, dogs, and rats but not mice after administration of minocycline. The pigment was unusual for tetracycline because it was non-fluorescent, and electron microscopy showed pigment forming within intrafollicular colloid. Minocycline, by interfering with iodide peroxidase is degraded to a black, insoluble, non-fluorescent pigment.[1] The pigment persisted in rats given 75 mg/kg/day for 38 days and then kept for one year on a normal diet. Minocycline also discoloured femora and skulls.

The patient reported died in respiratory failure. During the previous 18 months he had taken tetracyclines including minocycline 100 mg twice a day for a year until four months before death. In experimental studies in dogs minocycline accumulates in brain, bone, and thyroid.[4] The non-fluorescent pigmentation of this man's thyroid we attribute to specific concentration of minocycline within the

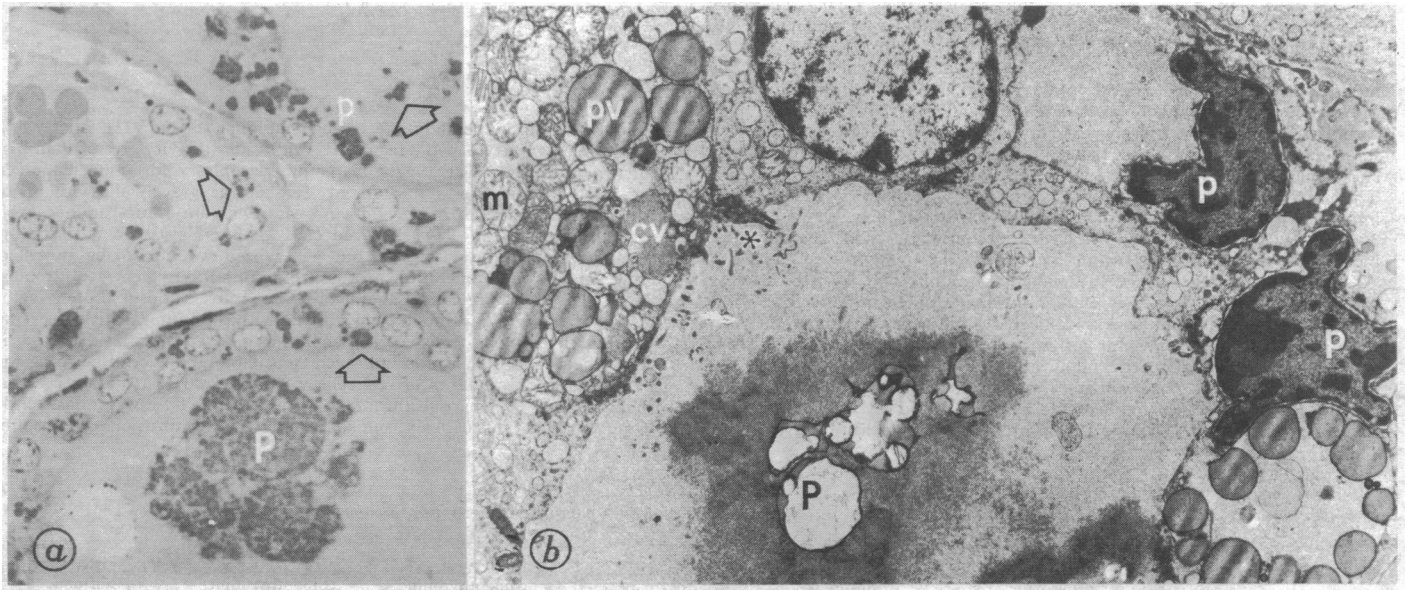

Fig a. Pigment granules are present in many epithelial cells (arrows), some of which contain pyknotic nuclei (p). Several aggregates of pigment (P) are seen in the colloid. Epon-Araldite section stained with Paragon. Original magnification: ×510. Fig b. Electron-dense material (P) associated with distorted vesicles is present in the central colloid space. Autolytic microvilli (asterisk) are present, but sparse colloid vesicles (cv) are closely associated with swollen mitochondria (m) and rimmed bodies or pigment vesicles (pv). One of the pyknotic nuclei (p) appears to be associated with vesicles of various diameters. These vesicles correspond to the pigmented granules seen by light microscopy. Original magnification: ×3410.

thyroid, and increased lipofuscin deposition. Increasing use of minocycline could produce additional examples.

Pigmentation of the thyroid need not cause functional upset. However, nuclear pyknosis indicates epithelial damage, and the studies of Benitz *et al* showed that minocycline has an antithyroid effect. Patients on long-term minocycline should have their thyroid function monitored.

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Department of Pathology, University of Melbourne, Austin Hospital, Heidelberg, Victoria 3084, Australia

H D ATTWOOD, MD, FRCPA, professor of pathology
XENIA DENNETT, BSC, PHD, senior tutor

Attempted prevention of neonatal thyrotoxicosis

Without treatment the mortality from neonatal thyrotoxicosis is 12%.[1] In the case reported here the fetus was recognised as being at risk when the mother was five months pregnant. Carbimazole was given to the mother in an effort to control the fetal thyroid.

Case history

A 29-year-old woman had a partial thyroidectomy at the age of 11 for Graves's disease. At 16 she became hypothyroid and was started on thyroxine 0·3 mg daily.

When she was 21 she aborted a macerated female fetus at 28 weeks. She had not had any antenatal care. The fetus weighed 1868 g, and at necropsy a goitre and an enlarged left ventricle of the heart were noted. At the age of 23 she gave birth to a 36-week boy weighing 2160 g and 43 cm long. During the first day he developed exophthalmos. The second day his heart rate was 200/min and his spleen became palpable. Treatment was started with carbimazole, Lugol's solution, hydrocortisone, and digoxin but he died four days after birth. His weight at death was 1760 g. Necropsy showed slight jaundice, an enlarged (7·5 g) and slightly nodular thyroid, and increased heart weight (25 g), with dilatation of both ventricles.

The patient was first seen at this hospital in July 1973 when she was five months pregnant. She was euthyroid but had bilateral exophthalmos and diplopia. As she was likely to have another affected baby she was given carbimazole 5 mg three times a day and her dose of thyroxine was increased to 0·4 mg daily. On this regimen she felt well during the rest of her pregnancy and remained euthyroid. At 37 weeks she was delivered of a healthy girl. The infant's heart rate was 140/min just before delivery and 130/min immediately afterwards. The Apgar score was 10 at one minute. She weighed 3420 g, was 52·1 cm long, and her head circumference was 34·3 cm. Cord blood hormone levels are shown in the table.

The child was placed in the special baby care unit. The day after delivery she developed a tachycardia of 140-150/min, was noted to be feeding voraciously and sweating, and her eyes appeared prominent. Thyroid and spleen were palpable. Treatment with carbimazole 0·75 mg three times daily was initiated and continued in reducing doses for three weeks, by which time her heart rate had fallen to 120/min and her weight had risen to 3810 g.

Fourteen months after delivery the mother's blood levels of long-acting thyroid stimulator (LATS) and LATS protector were measured. No LATS was found, but the concentration of LATS protector (27 U/ml) was consistent with that associated with the development of neonatal thyrotoxicosis.[2] At 2½ years of age the child was completely normal.

Comment

This appears to be the first published report of an attempt to protect a fetal thyroid against maternal thyroid-stimulating immunoglobulins. Carbimazole crosses the placenta more readily than thyroid hormones,[3 4] and the treatment succeeded in keeping the fetus euthyroid in utero, since the fetal heart rate, birth weight, and cord blood concentrations of thyroid hormones were all normal. Clinical thyrotoxicosis became apparent one day after birth only as the transplacentally administered carbimazole lost its effect.

I thank Dr Susan Dirmikis and Dr Sheila Lewis for their help.

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Regional Endocrine Centre, North Middlesex Hospital, London N18 1QX

IAN RAMSAY, MD, MRCP, consultant physician

Successful treatment with prothrombin complex concentrate of postoperative bleeding in a haemophiliac with a factor VIII inhibitor

Prothrombin complex concentrates have been used recently in the treatment of severe bleeding in haemophilic patients with factor VIII inhibitors.[1-4] We report here a patient in whom such treatment appeared impressively successful.

Case report

A 44-year-old moderately-affected haemophiliac (factor VIII activity 3%, one-stage assay) developed a factor VIII inhibitor (activity greater than 27·5 units/ml[5]) six days after vagotomy and pyloroplasty for duodenal ulcer. Factor VIII infusions were stopped. He became gravely ill, with major wound bleeding and infection, and was treated with antibiotics, aminocaproic acid, and transfusion of washed red cells (4 units/day). A small bleeding vessel in the wound was tied, but generalised wound oozing persisted. Thirteen days after operation prothrombin complex concentrate (Proplex, Hyland Division, Travenol Laboratories) was infused (dose 30 units factor IX/kg body weight); wound oozing stopped within minutes. This dosage was repeated that day and next day, then reduced to 15 units/kg daily for six days. The patient's condition improved considerably, no active bleeding was seen, and only four units of red cells were required to maintain a stable haemoglobin. The partial thromboplastin time (PTT) was consistently shortened from 300 to 115 seconds, 15 minutes after infusion. The kaolin-

Hormone concentrations in cord blood of baby studied. Median control values (with ranges in parentheses) are given for comparison

	Total thyroxine (nmol/l)	^{131}I-triiodothyronine resin uptake (%)	Free thyroxine index	Total triiodothyronine (nmol/l)	Free triiodothyronine index	Thyroid-stimulating hormone (mU/l)
Baby	209	105	15·6	0·80	0·50	<0·5
Controls (n = 29)	159·0 (98·7-224·3)	114 (93-130)	11·2 (6·4-16·0)	0·89 (0·34-2·10)	0·53 (0·19-1·17)	6·4 (<0·5-28)

Conversion: SI to traditional units—Thyroxine: 1 nmol/l ≈ 0·08 μg/100 ml. Triiodothyronine: 1 nmol/l ≈ 0·7 ng/ml.