blind, the observers not knowing the treatment of the patient at the time of filming.

The results are summarised in the table. The single patient with Huntington's chorea who was not assessed on film deteriorated both in terms of behaviour and involuntary movements so that the treatment had to be discontinued. Of the remaining patients, although three showed some subjective improvement in wellbeing, any changes in observed involuntary movements were at best marginal and in no case did examination of the films show any improvement either in involuntary movements or gait which could be ascribed to the treatment.

Discussion

Attempts to modify brain GABA concentration have not always given consistent results. Thus Barbeau found that neither GABA itself, taken by mouth, nor a combination of isoniazid and vitamin B6, nor the GABA analogue Lioresal (β-p-chlorophenyl-γ-aminobutyric acid) modified the chorea of Huntington's disease.[2] On the other hand, Fisher *et al* noted an improvement in three out of seven patients treated with GABA in higher dosage.[3] Our finding that sodium valproate does not appear to benefit patients with choreiform movements is consistent with that of Shoulson *et al*, who found no improvement when sodium valproate was given either alone or in combination with GABA, although a probenecid-loading test showed there was an increase in the central turnover of both dopamine and 5-hydroxytryptamine.[4] Patel *et al* comment that the failure of sodium valproate to inhibit amphetamine-induced stereotyped behaviour raises some doubt about the physiological role of GABA in the striatum and in the pathogenesis of chorea.[5]

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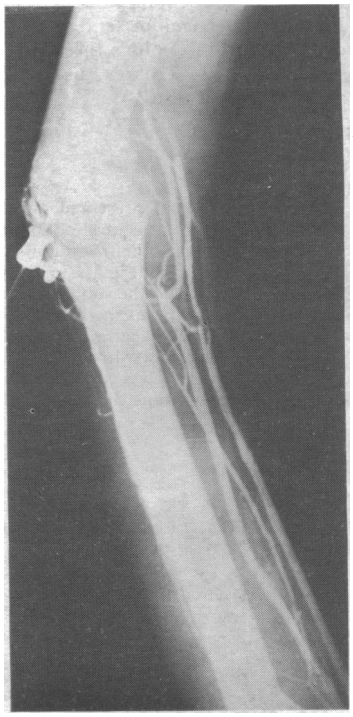
Mandril-grown graft for vascular access in Christmas disease

Widespread peripheral venous thrombosis resulting from intravenous infusions of factor IX concentrate in the treatment of Christmas disease necessitated an alternative form of vascular access. A mandril-grown graft was used after a suitable vein was found by perosseous (olecranon) venography of the arm. This vascular access has been the sole route for parenteral treatment for a severely affected patient. We report the indications, technique, and management of the case.

Case report

The patient was a 25-year-old man who had severe Christmas disease with a factor IX level of less than 1%. In 1974 home treatment with self-administered factor IX concentrate was started, venous access being via the antecubital veins. A few months later he developed severe recurrent haematuria that over the next year necessitated several prolonged periods in hospital and daily infusions of large doses of factor IX concentrate (Edinburgh DE FIX) for weeks at a time. As a result of this he developed thrombosis of all accessible veins, including the long saphenous, until eventually access could only be obtained occasionally through the smallest peripheral veins in his hands and feet.

The use of a silicone mandril[1] was proposed if a suitable deep vein could be shown for run-off, but intravenous phlebography of the arm was not possible as no suitable vein was patent. A perosseous olecranon venogram of the left upper arm, under general anaesthetic with factor IX cover, showed a patent left basilic vein (see figure). A Sparks mandril was implanted in a subcutaneous tunnel in the anterior aspect of the left forearm in a loop with the proximal end overlying the brachial artery and the distal end overlying the basilic vein. Three months later with factor IX concentrate replacement the ends of the prosthesis were anastomosed to the brachial artery and the basilic vein. To prevent thrombosis of the prosthesis, heparin 5000 units peroperatively and 5000 units six-hourly was given by constant intravenous infusion for 24 hours by a cut down into the right basilic vein. A small haematoma that developed at the venous anastomosis was treated conservatively.



Perosseous left olecranon venogram showing thrombotic occlusion of antecubital veins but a patent basilic vein.

One month after successful anastomosis the first infusion of factor IX concentrate (1800 units) was given. After six infusions over a two-week period flow through the prosthesis suddenly stopped and at operation clot adherent to the injection site was removed with a Fogarty catheter. Over the next six months about 40 separate infusions of factor IX concentrate were given via a No 21 "Butterfly" (Abbot) needle with the tip of the needle as near as possible to the centre of the stream. The concentrate was infused slowly in an attempt to minimise the possibility of a high local concentration and subsequent thrombosis. On withdrawal of the needle, the pressure applied to the bleeding point was sufficient to maintain haemostasis without obstructing the flow. A second mandril thrombosis has occurred and was again successfully managed. Despite intensive investigations no cause has been found for his recurrent haematuria, and there has been no response to courses of tranexamic acid or steroids.

Comment

Vascular access is often difficult in patients receiving multiple intravenous infusions or injections. Unfortunately, all available concentrates of factor IX contain variable amounts of factors II, VII, and X as contaminants. It was appreciated early that some of these factors might be partially activated, and the risk of intravascular clotting was predicted. Many authors have advised routine testing of such concentrates for procoagulant activity immediately before the infusion is given. With the advent of home treatment pretesting was not practical, and it has become apparent that such concentrates might induce thrombophlebitis in man,[2] and in animals there is evidence of disseminated intravascular coagulation.[3] In our patient, infusions of Edinburgh F IX concentrate resulted in multiple superficial venous thromboses so that venous access became impossible. The fibrinolytic inhibitor, tranexamic acid, may possibly have contributed to the problem by upsetting the equilibrium between coagulation and fibrinolysis.

A valuable adjunct in the preoperative assessment of this patient was the perosseous olecranon venogram. Although perosseous

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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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

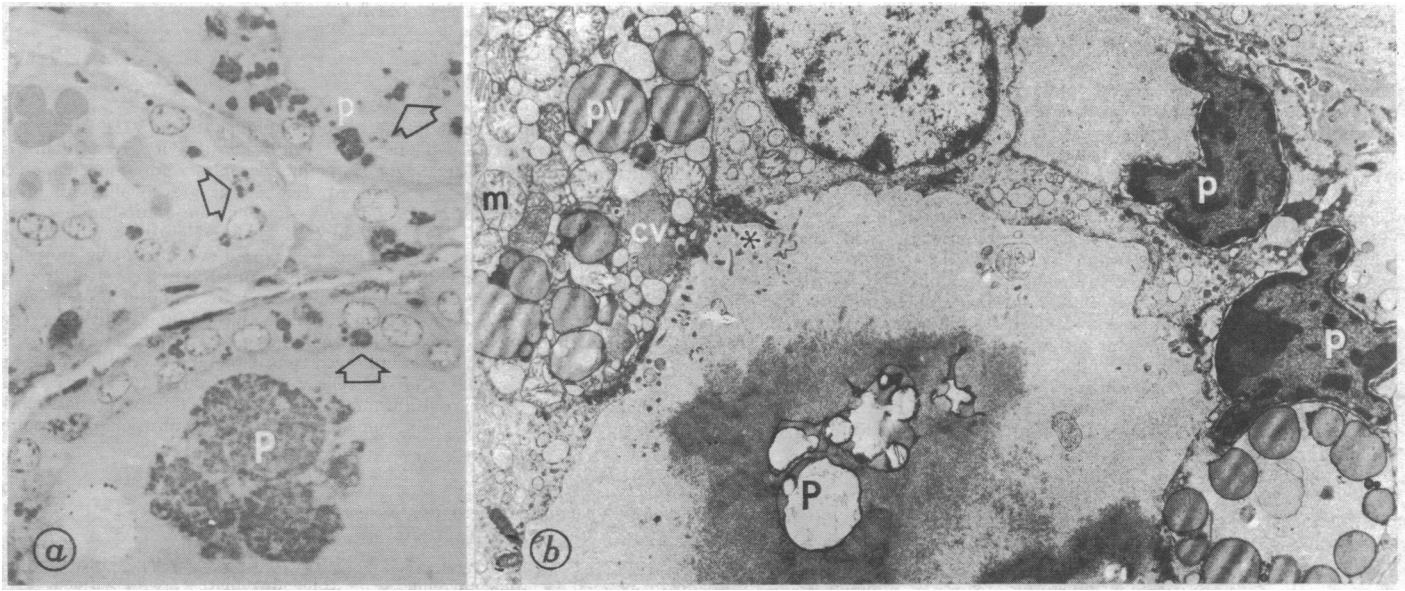

Fig a. Pigment granules are present in many epithelial cells (arrows), some of which contain pyknotic nuclei (p). Several aggregates of pigment (P) are seen in the colloid. Epon-Araldite section stained with Paragon. Original magnification: ×510. Fig b. Electron-dense material (P) associated with distorted 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.