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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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.

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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/ml⁵) 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 Controls (n = 29)	209 159.0 (98.7-224.3)	105 114 (93-130)	15.6 11.2 (6.4-16.0)	0.80 0.89 (0.34-2.10)	0.50 0.53 (0.19-1.17)	<0.5 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.

activated PTT fell from 115 seconds to 100 seconds. Initially factor IX activity did not rise after infusion, owing to binding of factor VIII in the factor-IX deficient substrate by the inhibitor.¹ After eight days' treatment the inhibitor level had fallen to less than one unit/ml; a rise in factor IX activity from 130 to 200% after infusion was then seen. Factor VIII activity remained stable at 3%. No evidence of intravascular coagulation was observed; his platelet count ($400-500 \times 10^9/l$), fibrinogen ($3.8-5.7 g/l$), and fibrinogen/fibrin degradation products ($5-10 \mu g/ml$) remained stable.

Twenty-one days after operation, after Proplex infusion (45 units/kg), the haematoma was removed and the wound resutured. Infusion was repeated next day (15 units/kg) then none was given for two days. The wound started to bleed again, whereupon four units of red cells were transfused, and Proplex (23 units/kg) given daily. Again, wound bleeding rapidly stopped; no further transfusion was required. Proplex (23 units/kg reducing to 15 units/kg daily) was continued for four weeks, until wound healing was complete.

Effect of varying dilutions of three factor IX preparations on partial thromboplastin time (PTT) of normal citrated plasma

Preparation	Proplex (Hyland)	Prothromplex (Immuno)	Factor IX (Edinburgh Protein Fractionation Centre)	Control
Factor IX assay (U/ml)	21.1	17.8	22.1	0.88
PTT (seconds)				133
" dilution 1/20	145	142	120	
" dilution 1/40	106	123	123	
" dilution 1/100	81	129	116	
" dilution 1/200	82	121	100	
" dilution 1/400	84	126	123	

Transient hepatitis developed 43 days after operation; all tests for hepatitis B antigen (haemagglutination, immunoelectrophoresis, radioimmunoassay, electron microscopy) remained negative, but the immunoelectrophoresis test for its antibody had become positive. The patient was discharged home eight weeks after operation and has remained well, with an undetectable inhibitor level.

In an in vitro study (see table) dilutions of Proplex were incubated with normal citrated plasma for one minute before determination of the PTT. Shortening at high dilutions was observed, suggesting the presence of activated coagulation factors. Two other factor IX concentrates showed less procoagulant activity. No preparation affected the kaolin-activated PTT in this way.

Discussion

Experience with prothrombin complex concentrates and other factor VIII bypassing fractions in treating bleeding due to factor VIII inhibitors is limited but encouraging. Nevertheless, the effects on bleeding and on coagulation tests are inconstant and not always related.¹⁻⁴ In our patient severe external bleeding was seen to cease immediately after treatment, recur after stopping treatment, and again cease on restarting treatment. This therapeutic effect was paralleled by shortening of the PTT in vivo and in vitro, possibly due to bypassing of the factor VIII stage of the coagulation cascade by activated factors (IXa, Xa). Intravascular coagulation due to activated factors has been reported with such concentrates in man and experimental animals but no evidence of this was seen in our patient. Further experience is required to establish their place and dosage.

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Chronic lymphocytic leukaemia uncovered by successful treatment of acute myeloid leukaemia

Case report

A 59-year-old man presented in March 1971 with a 10-day history of purpura, recurrent haemoptysis, and weight loss. Examination showed lymphadenopathy in the right axilla only, minimal hepatomegaly, and no splenomegaly. Haemoglobin was 12.9 g/dl, and white cell count $52 \times 10^9/l$ ($52\,000/mm^3$)—blast cells $47 \times 10^9/l$, small lymphocytes $3 \times 10^9/l$, polymorphs $1 \times 10^9/l$, and monocytes $1 \times 10^9/l$. Platelet count was $430 \times 10^9/l$. The bone marrow was hypercellular, with 85% blast cells and 15% small lymphocytes. The blood and marrow blasts were large, with a moderate nuclear:cytoplasmic ratio and two or three nucleoli, and about half contained Auer bodies in the cytoplasm. Acute myeloid leukaemia (AML) was diagnosed.

A five-day course of once-daily cytarabine intravenously and thioguanine by mouth was followed by two 100-mg doses of daunorubicin intravenously and a further five daily injections of cytarabine. Two weeks after the start of treatment his white cell count was $20 \times 10^9/l$, with blast cells $10 \times 10^9/l$ and small lymphocytes $8.8 \times 10^9/l$ (see figure). He rapidly went into good remission, although 35% of all nucleated marrow cells were small lymphocytes.

White cell counts during induction and maintenance treatment.

From 1972 to late 1975 he remained in good remission with a normal haemoglobin and platelet count. The white cell count stabilised initially at $7 \times 10^9/l$, with small lymphocytes $4 \times 10^9/l$ and polymorphs $3 \times 10^9/l$, but gradually rose. On examination in March 1974 he had a cellular marrow; myelopoiesis looked normal, with blast cells $2.9 \times 10^9/l$; erythropoiesis was active; and normal numbers of megakaryocytes were present. Half of all the nucleated cells, however, were small lymphocytes.

Between December 1975 and April 1976 the white cells increased from $25 \times 10^9/l$ (small lymphocytes $17 \times 10^9/l$, polymorphs $7 \times 10^9/l$) to $32 \times 10^9/l$ (lymphocytes $26 \times 10^9/l$, polymorphs $6 \times 10^9/l$). Membrane marker analysis showed that only 2% of the lymphocytes were T cells (E rosettes) ($0.5 \times 10^9/l$), while most mononuclear cells reacted to an anti-B cell serum and carried surface immunoglobulin (surface Ig).¹ The density of surface-Ig staining on most B cells (about 95%) was low. The surface-Ig phenotype of these cells was $\mu + \gamma - \alpha - / \kappa - \lambda +$. The same mononuclear B-cell population was seen in the bone marrow, which also contained a few T lymphocytes (10%). Thus membrane marker analysis confirmed the diagnosis of overt typical chronic lymphocytic leukaemia (CLL).

Discussion

This patient had an appreciable lymphocytic infiltration of the bone marrow when the AML was diagnosed. It therefore seems likely that he presented with AML and a concomitant lymphoproliferative disorder. Acute leukaemia sometimes occurs with CLL, and CLL may rarely terminate in a blastic phase.² It is, however, unlikely that our case would fall into this category because in the few cases in which the blastic cells were analysed in detail they constituted the transformed population of the original CLL alone, expressing the same B-cell surface phenotype.³ Occasionally, alkylating agents such as