particularly difficult cases in whom standard treatment had failed. In three of them mexiletine alone controlled the arrhythmia, but only at the cost of intolerable adverse effects. Combined treatment with mexiletine and propranolol, which have different actions and different adverse effects, enables arrhythmia to be suppressed through co-operative antiarrhythmic action. Since adverse effects have been a major limitation to widespread use of mexiletine^{3,4} combined therapy with propranolol may broaden its usefulness as an antiarrhythmic drug by two means—by decreasing its adverse effects and by more effective arrhythmia suppression through co-operative drug action.

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Minimal-change glomerulonephritis associated with circulating anticoagulant to factor XII

Circulating anticoagulants to factor XII have been described in two patients. In one the anticoagulant was associated with discoid lupus erythematosus¹ and in the other with systemic lupus erythematosus.² In both there was also anticoagulant activity to factor XI. Furthermore, the nephrotic syndrome may occasionally be associated with a selective leak of factors IX,³ XI, and XII.^{4,5} We report a case of a circulating anticoagulant to factor XII associated with the nephrotic syndrome secondary to minimal-change glomerulonephritis.

Case report

A 16-year-old boy presented with puffiness of the face and eyes and swelling of the legs. He had a history of childhood asthma and eczema but nothing suggestive of a bleeding disorder. On examination he had oedema of the face and legs and bilateral pleural effusion. His haemoglobin concentration was 16.6 g/dl with normal blood indices. Blood urea and electrolyte concentrations were normal. Serum protein and serum albumin concentrations were low at 34 g/l and 15 g/l respectively. Results of antinuclear and other autoantibody tests were negative. DNA binding activity was less than 20 U/ml serum and C3 and C4 concentrations were normal. Urine microscopy showed red cells and granular casts. Urinary protein excretion was 30 g/24 h and was very selective (differential protein clearance 0.04). The prothrombin time was normal but the kaolin cephalin clotting time (KCCT) was prolonged at 93 s as opposed to a control of 52 s. Factor XII activity was reduced at 12%. Factor XI, IX, X, VIII, VII, V, II, and I concentrations were well within the normal range. The KCCT was corrected to within normal limits with an equal mixture of patient's and pooled normal plasmas, but the results on incubation were characteristic of a progressive inhibitor to factor XII (table). A biopsy specimen of renal tissue obtained under cover of corticosteroid therapy showed no abnormality on light microscopy and tests for immunofluorescence were negative.

The patient's nephrotic syndrome remitted with corticosteroid treatment. His circulating anticoagulant disappeared after 14 days of treatment and his

factor XII concentrations reverted to normal (80%). He relapsed on two occasions when the dose of corticosteroids was being reduced. The circulating anticoagulant activity returned with each relapse but rapidly disappeared when the corticosteroid dose was increased.

Clotting studies in patient with circulating anticoagulant to factor XII

Incubation time (s)	Control pooled normal plasma		Equal volumes of patient and control plasma		Patient's plasma	
	KCCT (s)	Factor XII (%)	KCCT (s)	Factor XII (%)	KCCT (s)	Factor XII (%)
0	53	120	58	115	93	12
30	59	—	70	60	140	—
60	60	115	80	23	172	3

KCCT = Kaolin cephalin clotting time.

Comment

This patient had typical minimal-change glomerulonephritis. The clotting studies indicated the presence of an inactivator of factor XII, whose activity increased on incubation. The nephrotic syndrome may occasionally be associated with a selective leak of coagulation factors, and acquired deficiencies of factors XI and XII have been described.^{4,5} The patient's urine was not assayed for factor XII but the repeated haematological investigations during relapse of the nephrotic syndrome strongly favoured the presence of an inactivator rather than a selective urine leak. So far as we know the association of a circulating anticoagulant and minimal-change glomerulonephritis has not been noted. The close association of the presence of circulating anticoagulant with the activity of the patient's nephrotic syndrome seems more than fortuitous. There was no clinical evidence of a bleeding diathesis to accompany the factor XII deficiency.

This case shows the importance of checking for bleeding and clotting abnormalities when performing a renal biopsy, a procedure which already has an inherent risk of haemorrhage.

We thank Dr Adrian Morley for reporting on the renal histology.

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Persistence of defective hypothalamic control of prolactin secretion in some obese women after weight reduction

In animals the hypothalamus is of fundamental importance in regulating food intake and disorder of its function, which may be congenital or acquired, results in obesity.¹ We have previously reported^{2,3} evidence for a disorder of hypothalamic function in some massively obese women. We found two distinct patterns of prolactin response

during insulin-induced hypoglycaemia—no response was seen in some obese patients who had been obese from early childhood and had a strong family history of obesity; whereas in other obese patients, most of whom had become obese in later life, a normal prolactin response was seen. Intravenous thyrotrophin-releasing hormone (TRH), which acts directly on the pituitary, resulted in a normal prolactin response in both groups of patients. We questioned whether the absent prolactin response to insulin-hypoglycaemia indicated a basic, possible genetic, disorder of hypothalamic function. We now report our findings in 12 previously obese patients who lost a substantial amount of weight one year after treatment for their obesity by jejunoileal bypass surgery.

Patients, methods, and results

The patients (see table), who had normal thyroid function, were studied in hospital on a weight-maintaining diet containing at least 180 grams of carbohydrate. Informed consent was obtained for the investigation. The intravenous insulin tolerance and TRH test procedures and details of the hormone assays were as before.³

Prolactin, growth hormone, and cortisol responses to insulin-induced hypoglycaemia in six lean control subjects, 20 obese subjects (data from Kopelman et al³), and 12 obese subjects† after weight reduction, obese subjects being grouped according to prolactin response. Total integrated response equals sum of percentage increments over basal values (=100) at 30-minute intervals up to two hours. Negative response indicates overall fall in values. % IBW = % ideal body weight (assessed by Metropolitan Life Insurance Tables). Significance of difference between groups determined by Wilcoxon non-parametric test*

Mean weight		Total integrated response (mean ± SD)		
% IBW	Weight loss (kg)	Prolactin	Growth hormone	Cortisol
100	—	860 (±200)	7590 (±3000)	280 (±130)
227*	—	82 (±30)	1719 (±464)	51 (±32)
220*	—	1256 (±568)	3279 (±558)	137 (±41)
130†	43	160 (±10)	3400 (±1400)	135 (±95)
141†	39	1420 (±580)	6200 (±2200)	140 (±80)

Statistical significance			
Preoperative*			
Responders v controls	NS	NS	NS
Non-responders v controls	p<0.01	p<0.05	p<0.1
Non-responders v responders	p<0.01	p<0.05	p<0.1
Post-operative†			
Responders v controls	NS	NS	NS
Non-responders v controls	p<0.01	NS	NS
Non-responders v responders	p<0.01	NS	NS

*Preoperative: obese non-responders (n=11); obese responders (n=9).
†Postoperative: obese non-responders (n=6); obese responders (n=6).
NS = not significant.

Two distinct patterns of prolactin response to insulin-induced hypoglycaemia remained despite similar individual weight loss. There was no prolactin release in six patients, all of whom had become obese in early childhood. In contrast, growth hormone and cortisol response, which were impaired when these patients were obese,³ were not significantly different from lean controls after weight loss. In the other six patients a normal prolactin, normal growth hormone, and a normal cortisol response to insulin-induced hypoglycaemia was seen after weight loss. The prolactin response in three of this group had previously been much impaired and they had been obese from an early age. The prolactin response to intravenous TRH stimulation was normal in all 12 patients after weight loss.

Comment

A basic disorder of hypothalamic function in some women is suggested by the persistence of an absent prolactin response to insulin-induced hypoglycaemia with normal release of prolactin after intravenous TRH stimulation despite the near attainment of ideal body weight by such patients. This hypothalamic disorder is unlikely to be weight related since other women regain a normal prolactin response after similar weight loss. By contrast, the growth hormone and cortisol responses to hypoglycaemia, which are impaired in some patients when obese, became normal in all the patients after weight loss. Although a direct extrapolation from rodent obesity to human obesity is unwarranted it is of interest that the genetically obese *ob/ob* mouse has a basic disorder of hypothalamic function and abnormal prolactin secretion.⁴

The role of prolactin in man is unclear, and the impaired prolactin release in some massively obese women may be a secondary reflection of disordered hypothalamic neurosecretion rather than a cause

of excess obesity. In other species, however, prolactin appears to be one of the factors controlling fat deposition.⁵ We conclude that the defect in the prolactin response to insulin-induced hypoglycaemia in some obese patients persisting after substantial weight loss supports the hypothesis of a basic, possible genetic, disorder of hypothalamic function. What role, if any, prolactin has in the control of fat deposition in man remains to be seen.

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ONE HUNDRED YEARS AGO At the Royal Hospital for Diseases of the Chest, I have been induced to use the natural mineral water of Flitwick, a village about two miles from Ampthill, in Bedfordshire. This water, according to the analysis of Professor W White, contains in each gallon:

	Grains per Gal.
Oxide and Carbonate of Iron	144.00
Sulphate of Magnesia and Soda	59.20
Carbonate of Lime	11.54
Muriate of Magnesia (chloride)	15.16
Silica	3.40
Carbonate of Magnesia	5.42
„ Soda	0.22
Ulmic, Malic, and other acid constituents of vegetable matters	13.32

One of the most marked cases in which benefit accrued from its use was that of a railway signalman, excessively anaemic after protracted haemoptysis, and with whom all the usual ferruginous preparations disagreed. I have also notes of six other hospital patients; two debilitated after acute rheumatism, where the perchloride of iron caused headache and constipation; and four chlorotic females, on whom this potent chalybeate acted beneficially when the usual iron medicines were not well borne. I hope this note may lead my professional brethren to give this water a trial. G GODDARD ROGERS. (*British Medical Journal*, 1880.)

Correction

Comparison of serum 25-OH vitamin D concentrations in rheumatoid arthritis and osteoarthritis

An error occurred in this paper by Dr H A Bird and others (14 June, p 1416). The units for 25-OHD concentrations throughout the paper should have read "nmol/l (ng/ml)," not "mmol/l (mg/ml)."