developed anorexia, nausea, and vomiting associated with considerable weight loss. Initially gastric carcinoma was diagnosed, but the results of investigations confirmed the presence of Addison's disease (see table). Despite replacement therapy, three months later he had further nausea and vomiting, and died. Necropsy showed extensive carcinoma of the pancreas destroying both adrenals.

Results of ACTH and cortisol estimations in two patients with Addison's disease due to carcinoma. Normal ranges for our laboratory given in parentheses

	Urinary free cortisol excretion (10-850 nmol/24 h)	Serum cortisol concentration (166-660 nmol/l)		Serum ACTH concentration (10-118 ng/l)	
		9am	Midnight	9am	Midnight
Case 1	Nil	168	104	260	
Case 2	22	243	193	586	155

Conversion: SI to traditional units—Urinary cortisol: 1 nmol/24 h ≈ 0·36 μg/24 h. Serum cortisol: 1 nmol/l ≈ 0·036 μg/100 ml.

Case 2—A 60-year-old man was admitted in July 1976 with a three-month history of anorexia, nausea, vomiting, and weight loss. He had no family history of autoimmune disease and smoked 5 oz of tobacco per week. There was increased pigmentation over his legs and head associated with postural hypotension. The results of investigations confirmed Addison's disease (see table). No autoimmune antibodies were present and there was no evidence of tuberculosis, his chest *x*-ray film being normal. Replacement therapy resulted in rapid symptomatic improvement and he remained well on follow-up with normal chest *x*-ray films. Six months later the same symptoms recurred despite adequate replacement therapy. On this occasion the chest *x*-ray film showed an enlarged right hilum. He died shortly afterwards and necropsy showed a primary oat-cell carcinoma of the bronchus with a large abdominal tumour mass extending across the midline destroying both adrenals and directly invading the liver. No other metastases were seen.

Discussion

Tiredness, nausea, vomiting, and weight loss are early symptoms of Addison's disease and are entirely non-specific. Not until later in the disease do postural hypotension and hyponatraemia occur, thereby facilitating the diagnosis. In both our patients the initial symptoms were identified as being due to Addison's disease and were relieved by appropriate replacement therapy. When similar symptoms occurred some months later these were shown not to be due to Addison's disease but to malignancy.

Over 90% of adrenal tissue has to be destroyed before symptoms of adrenal hypofunction develop. Bilateral adrenal metastases occur early in carcinoma and our cases show that the adrenals may be destroyed before the primary site can be identified. In the first case bilateral adrenal spread occurred nine months before pancreatic carcinoma was suspected. In the second case adrenal metastases must have been present bilaterally for at least six months before evidence of the primary tumour was found, despite repeated chest *x*-ray examinations. At necropsy the only evidence of tumour spread was a locally invasive retroperitoneal mass destroying both adrenals.

A careful search in patients presenting with Addison's disease may allow carcinoma to be diagnosed early, at a stage when the primary tumour is small and possibly amenable to surgery, radiotherapy, or chemotherapy. Furthermore, if the adrenals are the only site of tumour spread, resection of the primary tumour and bilateral adrenalectomy could be considered. Conversely, in some patients with obvious malignancy, symptoms often attributed to the non-specific effects of tumour growth may in fact be due to Addison's disease. Despite the common occurrence of tiredness, nausea, vomiting, and weight loss in patients with carcinoma, malignant destruction of the adrenals is thought to be uncommon and there are few reported cases of the results of ACTH and cortisol estimations in patients with Addison's disease due to carcinoma. If Addison's disease was diagnosed in some of these patients considerable symptomatic relief might be obtained by adequate replacement therapy.

[1] Vieweg, W V R, *et al*, *Cancer*, 1973, **31**, 1240.

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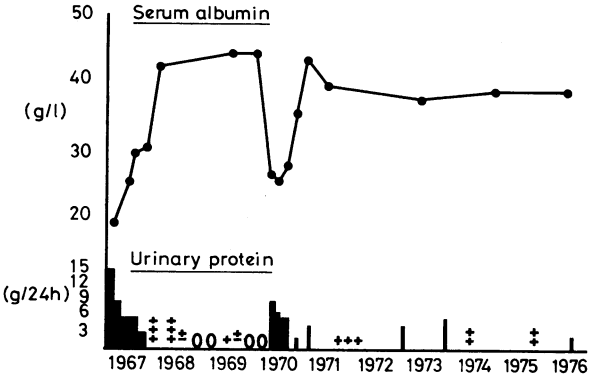
Spontaneous remissions of nephrotic syndrome in renal amyloidosis

The nephrotic syndrome caused by renal amyloidosis may remit when the disease underlying amyloid formation can be treated successfully.[1-3] Increasing knowledge about the nature of amyloid has recently led to the advocacy of new methods of treatment for the "primary" form of this condition. The value of any treatment for amyloidosis must be judged by comparison with the natural history of the disease. We describe spontaneous fluctuations in the clinical expression of renal amyloidosis that must be taken into account in the evaluating of treatment for it.

Case reports

Case 1—An Englishwoman developed bilateral pulmonary tuberculosis in 1947 when aged 18. After a left artificial pneumothorax she was treated with sodium aminosalicylate and isoniazid. In 1966 she developed gross peripheral oedema with normal jugular venous pressure and blood pressure. There was no evidence to suggest reactivation of tuberculosis. The serum albumin concentration was 19 g/l and urinary protein excretion was up to 14 g/24 h. Blood urea concentration was 13·3 mmol/l (40 mg/100 ml). A needle renal biopsy specimen showed deposition of amyloid in relation to the glomerular basement membrane and in the blood vessel walls. She was treated with diuretics, and by July 1967 the nephrotic syndrome had remitted (fig).



Case 1: spontaneous remissions of nephrotic syndrome in 1967 and 1970.

During the next 21 months the urine was protein-free when tested on four occasions and showed only a trace on four other occasions.

The nephrotic syndrome relapsed in January 1970. The following measurements were made: serum albumin 29 g/l, urinary protein excretion 6-8 g/24 h, blood urea 4 mmol/l (24 mg/100 ml), serum creatinine 106 μmol/l (1·2 mg/100 ml), creatinine clearance 40-60 ml/min. The proteinuria was poorly selective, IgG/albumin clearance ratio 0·33. A second needle biopsy showed more extensive deposition of amyloid in the glomeruli and electron microscopy showed fusion of the foot processes which was particularly distinct in the region of amyloid deposition. Diuretic therapy reduced the oedema and proteinuria decreased. The serum albumin rose eventually to 48 g/l and has remained above 36 g/l to date. Diuretics were discontinued for 18 months. The development of hypertension and deteriorating renal function led to regular haemodialysis in December 1976.

Case 2—In 1937 a 16-year-old English girl developed pulmonary tuberculosis. After a right artificial pneumothorax her sputum became free of tubercle bacilli by 1938. In 1947 she developed ulcerative colitis which ran an intermittent course until 1957, since when her bowel action has remained normal. In 1965 she developed nephrotic syndrome with a serum albumin concentration of 28 g/l and urinary protein excretion of 6 g/24 hours. The blood urea concentration was normal. She declined renal biopsy and gradually lost her oedema with diuretic therapy. In outpatients urinary protein was subsequently recorded as a trace or one plus and the serum albumin rose to 44 g/l, indicating a trivial amount of proteinuria.

In 1967 the nephrotic syndrome relapsed. A renal biopsy specimen showed florid amyloid deposition. She was discharged on diuretic treatment but failed to attend as an outpatient. She reappeared in 1972 in advanced renal failure and was found to have unilateral renal vein thrombosis. After treatment with anticoagulants and peritoneal dialysis conservation management of the renal failure was possible for 10 months before regular haemodialysis became necessary in September 1972.

Comment

Histological evidence of regression of amyloid is scanty in patients with amyloidosis who improve clinically with treatment of the under-

lying disease. In those described by Lowenstein and Gallo[1] renal deposits of amyloid persisted despite clinical remission of the nephropathy. Both our patients had spontaneous remissions of nephrotic syndrome without treatment for the underlying disease. In one the urine became protein free and in the other the proteinuria became trivial. In both the serum albumin concentration returned to normal. Yet renal biopsy specimens before and after the period of remission in case 1 showed progression of amyloid deposition. In both patients amyloidosis eventually led to chronic renal failure.

Interest grows in new treatments for amyloidosis.[4 5] Whatever the mechanisms underlying the spontaneous fluctuations in the nephropathy in these cases their course emphasises the need for care in assessing new therapies. The low incidence of this condition imposes formidable logistic problems in organising controlled trials, but without such trials new treatments will be difficult to evaluate.

[1] Lowenstein, J, and Gallo, G, *New England Journal of Medicine*, 1970, **282**, 128.
[2] Triger, D R, and Joekes, A M, *Quarterly Journal of Medicine*, 1973, **42**, 15.
[3] Omer, H, and Wahab, S M A, *British Medical Journal*, 1976, **1**, 375.
[4] Jones, N F, *Clinical Nephrology*, 1976, **6**, 459.
[5] Lyle, L R, Parker, B M, and Parker, C W, *Journal of Immunology*, 1974, **113**, 517.

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Hexapropymate self-poisoning

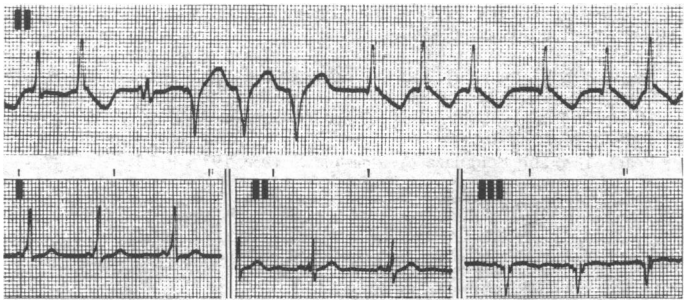
Hexapropymate, a carbamate with similar pharmacological properties to meprobamate,[1 2] is available without prescription in Belgium under the trade name Merinax. Each Merinax tablet contains 400 mg of hexapropymate. Self-poisoning is uncommon and has not been reported in Britain. We report here a case of severe poisoning.

Case report

A 28-year-old man was admitted in October 1977 having been found unconscious in a local park. His pockets contained four empty hexapropymate packets. Each packet had contained 10 400-mg tablets. No other history was available.

He was deeply unconscious with no response to maximally painful stimuli. Corneal, gag, and cough reflexes were absent. He was hypotensive (blood pressure 75/0 mm Hg), hypothermic (rectal temperature 28°C), and cyanosed. Immediate endotracheal intubation was required. An irregular pulse was noted and his electrocardiogram showed bouts of tachycardia, probably supraventricular, but with evidence of intraventricular block (see fig). He was treated with intravenous fluids, rewarming, and assisted ventilation. Gastric lavage was performed, and large amounts of vomit removed from the bronchi. His supraventricular tachycardia rapidly reverted to sinus rhythm of 100/min with a blood pressure of 100/70 mm Hg. He had signs of left lower lobe collapse, which was confirmed by chest radiographs.

Blood sugar, urea, creatinine, electrolytes, and serum amylase concentrations were normal. He was acidotic with a blood lactate of 6·9 mmol/l (62·1 mg/100 ml), arterial pH 7·053, P_{CO_2} 6·25 kPa (47 mm Hg), P_{O_2} 15·3 kPa (115 mm Hg), bicarbonate 13·8 mmol(mEq)/l. The blood and urine contained no salicylates, barbiturates, glutethimide, or paracetamol. Urine analysis, verified against known samples of hexapropymate, showed excretions of 878 mg, 197 mg, and 80 mg of hexapropymate on the first three days respectively after admission. Electrocardiograms showed sinus rhythm, apparent short P-R intervals, delta waves, and rSR pattern in chest leads V1 and V2, suggestive of a type B Wolff-Parkinson-White syndrome (see figure). Liver function tests showed mild hepatocellular damage which gradually resolved.



Top: electrocardiogram, standard lead II, showing tachycardia on admission. Bottom: electrocardiogram, standard leads I, II, and III, showing sinus rhythm and apparent short P-R interval due to delta waves.

His rectal temperature rose to 37°C over 12 hours, but he remained deeply unconscious with absent reflexes for four days. During this period erythematous and urticarial macules appeared over his legs. These may have been caused by hexapropymate or by sensitivity to ampicillin administered to combat inhalational pneumonia. Consciousness returned on the fifth day, during which he was febrile and had rigors. Blood cultures, midstream urine, and sputum were sterile. He subsequently recovered fully. He admitted to having taken 40 400-mg hexapropymate tablets, but denied taking any other drugs. He had arrived in this country two days before admission to hospital, having bought the tablets in Belgium.

Comment

Poisoning with about 16 g of hexapropymate induced deep coma in our patient and led to respiratory depression, hypothermia, inhalational pneumonia, and lactic acidosis. Prompt resuscitation and supportive measures resulted in complete recovery. The effects of hexapropymate poisoning[3] seem to be similar to those of other carbamates.[4] The tachyarrhythmia found on admission may have been induced by hypoxia or hypothermia. Only one episode of tachycardia was noted in 20 cases of hexapropymate poisoning reported to Brussels's poison centre.[5] The effects of hexapropymate in the Wolff-Parkinson-White syndrome have not been reported.

We thank Mr B Yeoman of the Regional Toxicology Centre, Dudley Road Hospital, Birmingham, for analysing the urine.

From 27 December 1977 Merinax (Hexapropymate) became available solely on prescription.

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[2] Troch, E, *Acta Anaesthesia Belgique*, 1958, **9**, 49.
[3] Noirfalise, A, *European Journal of Toxicology*, 1971, **1**, 50.
[4] Jenis, E H, *et al*, *Journal of the American Medical Association*, 1969, **207**, 361.
[5] Le Centre Anti-Poisons de Bruxelles. Information on file.

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Where are the untreated depressives?

In the course of a clinical trial of antidepressant drugs[1] it proved more difficult than expected to acquire a numerically adequate series of suitable patients referred as outpatients or admissions to the specialist psychiatric services. Abandonment of a similar trial for lack of patients has been reported already,[2] using selection criteria based on those of the MRC trial of treatments for depressive illness.[3] The criteria for inclusion in our study[1] were much less exclusive: (*a*) the referring doctor considered the quality and degree of the patient's depressive affect indicated the use of a tricyclic antidepressant drug; (*b*) the psychiatrist agreed on the treatment indications; (*c*) the patient should not have been prescribed any antidepressant in the three months before referral. We have studied possible reasons for this "shortage" of depressives.

Patients, methods, and results

Experience at Crichton Royal Hospital—Twelve general practitioners who regularly referred patients to JCL were asked to refer suitable patients for the trial. In the first year from July 1974 a total of 14 patients were so referred, of whom only seven could be included in the trial. A second appeal letter was sent out and the next year yielded a further 19 referrals for the trial, of whom nine were suitable. A third letter in June 1976 resulted in only