Deep-tissue factors—Provided the turgor of the deep tissues is sufficiently low, swelling of the epidermis will lead to wrinkling. Turgor is high when the sympathetic tone is low and the vessels are dilated. Thus in sympathectomised hands, which are typically warm, dry, and swollen, the tissue turgor is too great to allow the swelling of the epidermis to lead to wrinkling. Wrinkling will also fail to occur when sufficient oedema is present.

We suggest that the phenomenon of finger wrinkling may be of value in the diagnosis and assessment of patients in whom autonomic neuropathy is suspected. The test is easy to apply and, unlike the Valsalva manoeuvre or loss of sinus arrhythmia, reflects peripheral rather than cardiac sympathetic denervation.

We thank Mr D A Bailey for allowing us to study his patients. Requests for reprint should be addressed to JAH.

[1] Lewis, T, and Pickering, G W, *Clinical Science*, 1935, **2**, 149.
[2] O'Riain, S, *British Medical Journal*, 1973, **3**, 615.
[3] Moynahan, E J, *Lancet*, 1974, **2**, 907.
[4] Lewis, T, *Clinical Science*, 1942, **4**, 349.
[5] Elliott, R B, *Lancet*, 1974, **2**, 108.

(*Accepted 28 October 1976*)

University College Hospital, London WC1E 6AU
C BULL, MB, BCHIR, house physician
J A HENRY, MB, MRCP, medical registrar

Fatal oxprenolol poisoning

We describe what we believe to be the first recorded case of fatal oxprenolol overdosage.

Case report

A 57-year-old woman was brought to the casualty department on 27 February 1976. For some time she had been complaining of discomfort in her throat that she thought might be due to cancer, but had refused to see a doctor. Her husband noticed at breakfast on the day of admission that she was rather pale and staggering, and she said that she had taken his oxprenolol tablets. He knew that he had exactly 112 40-mg tablets left and he found the bottle empty. He gave her a drink with salt and she vomited several tablets, but soon afterwards became unconscious. She was then brought to the casualty department. Her husband estimated that the time between her taking the tablets and her appearance at breakfast could not have been more than 15 or 20 minutes.

She was deeply unconscious; her peripheries were cold and clammy and she had central cyanosis. Her pulse was impalpable and her blood pressure unrecordable. Heart sounds were soft with a ventricular rate of 36/min and she had bilateral basal crepitations. She was flaccid and reflexes were absent. Her electrocardiograph showed a regular ventricular rate of 36/min with a right bundle-branch block pattern. P waves could not definitely be identified.

External cardiac massage and assisted respiration were carried out. There was no response in pulse rate to intravenous atropine and to isoprenoline. A transvenous pacing catheter was passed through the right median cubital vein and positioned in several areas inside the right venticle, but the ryhthm could not be captured. The patient died in asystole about one hour after her arrival in hospital.

Post-mortem examination showed no gross structural abnormality in any of the systems, particularly the heart, which was normal with no evidence of ischaemic heart disease. Several samples of tissue were sent for forensic examination and the concentrations of oxprenolol in the stomach, blood, brain, and liver were estimated at 1·05 g, 37·7 μmol/l (1 mg/100 ml), 267 μmol/l (7·09 mg/100 ml), and 866 μmol/l (23 mg/100 ml), respectively. The cause of death was established as poisoning from overdosage of oxprenolol hydrochloride.

Comment

Determined and prompt attempts both with drugs and electrical pacing were made to stimulate the myocardium and reverse the effects of oxprenolol, but, as in other cases of severe poisoning with cardiosuppressants, they were unsuccessful in either increasing the ventricular rate or the cardiac output. In normal therapeutic doses the antiarrhythmic effect of beta-blocking agents is accepted as being due to antisympathetic Class II effect (Vaughan Williams Classification).[1] Higher concentrations of these agents, however, which are powerful anaesthetics, also have a Class I action.[2]

The effects of beta-adrenergic drugs on cardiac contractibility are complex and include withdrawal of sympathetic support, which may be at least partially reversed by sympathomimetic agents. Naylor and Chang[3] have shown that propranolol and to a lesser extent oxprenolol and practolol reduce the capacity of the sarcoplasmic reticulum to accumulate Ca^{2+} for subsequent release, and also that a drug interaction with the cell membrane depletes the membrane-based store of Ca^{2+}. These stores are normally released and made available for the reactions associated with the excitation-contraction coupling,[4] thus affecting the rising phase of the action potential, part of which is maintained by an inward current of Ca^{2+}.[5]

This mechanism probably contributes to the dose-dependant negative inotropic effects of many of these drugs, and may explain the failure of pharmacological and electrical stimulation in this particular case. The rapid loss of consciousness in this patient was notable and was probably due to the high concentrations of the drug in the central nervous system. The degree of penetration of beta-adrenergic blocking agents through the blood-brain barrier varies with different compounds and depends on the different lipid solubilities of the drugs—for example, practolol appears in the brain in very low concentrations.

The rapidity of onset of severe symptoms in our patient was alarming. The estimated time between ingestion and the onset of symptoms was only 15 to 20 minutes, and the intrinsic stimulating effect of oxprenolol did not appear to offer any protective mechanism.

[1] Vaughan Williams, E M, in *Symposium of Cardiac Arrhythmias*, ed E Sandøe, *et al*, p 449. Soderstalje, Sweden, A B Astra, 1970.
[2] Coltart, D J, and Shand, D G, *British Medical Journal*, 1970, **3**, 731.
[3] Naylor, W G, and Chang, A, in *International Symposium: New Perspectives in Beta Blockage*, ed D M Burley, *et al*, p 56. Horsham, Ciba Laboratories, 1973.
[4] Naylor, W G, and Merrilees, N C R, in *Calcium and the Heart*, ed P Harris and L Opie. New York, Academic Press, 1971.
[5] Beeler, G W, and Reuter, H, *Journal of Physiology*, 1970, **207**, 211.

(*Accepted 4 November 1976*)

Royal Halifax Infirmary, Free School Lane, Halifax
A KHAN, MB, BS, medical registrar
J M MUSCAT-BARON, MD, MRCP, consultant physician

Successful treatment of ischaemic ulceration of the skin in azotaemic hyperparathyroidism with parathyroidectomy

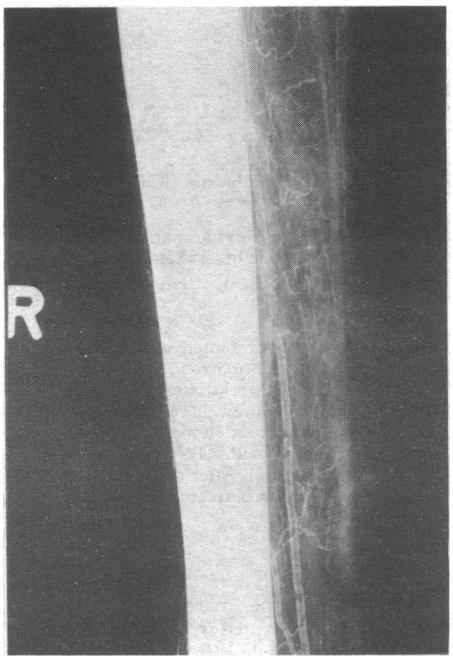
Ischaemic ulceration of the skin in azotaemic hyperparathyroidism has rarely been described.[1-4] We report two cases of this unusual condition.

Case reports

Case 1—A 63-year-old man on haemodialysis for hypertensive nephrosclerosis noticed reddening and itching of the skin of his lower legs in February 1973. Within a few days small, painful ulcers developed that enlarged progressively, reaching a size of approximately 8 × 10 cm in November 1973. Due to the pain the patient became incapacitated, and generalised itching appeared. Serum calcium ranged from 2·7-2·9 mmol/l (10·8-11·8 mg/100 ml) and phosphorus from 1·6-2·6 mmol/l (5·0-8·2 mg/100 ml); serum alkaline phosphatase was 14-19 KA units (normal $\leqslant$ KA units). The calcium content of the skin was 640 mg/kg dry weight (normal $<$400 mg/kg). Several local therapeutic trials and intravenous antibiotics failed to improve the ulceration. Subtotal parathyroidectomy was performed in November 1973. Histological examination showed generalised nodular adenomatous hyperplasia. Three weeks after surgery pain and itching had disappeared and the ulcers were healing within four months.

Case 2—A 52-year-old man with polycystic kidney disease noticed tender, hardened, dark red patches on the lower parts of both legs in November

1975. A month later when maintenance haemodialysis was started, one of these areas on the posterior aspect of the right lower leg rapidly increased in size and developed into a necrotising ulcer which became so painful that the patient was incapacitated and had to be treated with morphine. Moreover, generalised itching appeared. Using mammographic techniques we saw an impressive network of calcified small soft-tissue vessels in both legs with preponderance on the right side (figure). Biopsy showed necrosis, abundant calcium deposits in the subcutaneous fat, and considerable medial calcification and intimal proliferation in small arteries. Serum calcium was 2·6 mmol/l (10·2 mg/100 ml), phosphorus between 1·0 and 1·6 mmol/l (3·1-5·0 mg/100 ml), alkaline phosphatase 50 IU (normal range ⩽42 IU). Serum parathyroid hormone was considerably raised at 1650 ng/ml (normal ⩽40 ng/ml). On 19 February 1976 three parathyroid glands were removed that showed nodular, adenomatous hyperplasia. Postoperatively serum calcium dropped to 2·2 mmol/l (9·0 mg/100 ml), alkaline phosphatase to 28 IU, and serum parathyroid hormone to 210 and 182 ng/ml on March 3 and May 18 1976, respectively. Two days after operation the itching had disappeared and the patient was without pain. The ulcers had healed completely within three weeks.



Mammographic picture of right lower leg in case 2 showing extensive network of calcified small soft tissue vessels.

Discussion

Two different types of skin ulceration occur in azotaemic hyperparathyroidism. The first consists of cutaneous or subcutaneous calcified plaques, and the second of ischaemic necrosis of the skin.[5] The rarity of the syndrome complicated diagnosis in our two patients. The clinical presentation was typical, however, namely—slowly progressive, extremely painful skin ulcers in patients with terminal renal failure. Signs of secondary hyperparathyroidism may also be present. Diagnosis may be confirmed by skin biopsy showing severe medial calcification and intimal proliferation of small subcutaneous arteries. Mammography, however, which is noninvasive, may also be a useful technique as shown in case 2. The ulcers are usually resistant to various types of treatment. Subtotal parathyroidectomy was the only treatment to induce a rapid disappearance of pain and healing of the ulcers in our patients. Moreover, considerable improvement of vascular calcifications occurred in one patient after four months. This shows that subtotal parathyroidectomy should be considered in patients with this type of incapacitating manifestation of secondary hyperparathyroidism.

The precise pathogenesis of necrotic skin lesions remains uncertain. An ischaemic process due to calcium deposition may be of importance. The concept of calciphylaxis also seems to offer a suitable pathogenetic explanation since soft-tissue calcification and necrosis may be provoked after the previous application of certain sensitising agents. Azotaemia, a diet high in phosphorus, secondary hyperparathyroidism, and vitamin D may be important sensitising factors. Their precise contribution, however, as well as the nature of the process precipitating calciphylaxis, are still not clear.

1 Richardson, J A, *et al*, *Annals of Internal Medicine*, 1969, **71**, 129.
2 Massry, S G, *et al*, *American Journal of Medicine*, 1970, **49**, 416.
3 Cooksley, W G E, and Craswell, P W, *Australian and New Zealand Journal of Medicine*, 1972, **2**, 142.
4 Winkelmann, R K, and Keating, F R, *British Journal of Dermatology*, 1970, **83**, 263.
5 Anderson, D C, Stewart, W K, and Piercy, D M, *Lancet*, 1968, **2**, 323.

(*Accepted 10 November 1976*)

Department of Medicine, Kantonsspital Aarau, Switzerland
A BLUMBERG, MD, head of nephrology department
Division of Nephrology, University of Southern California, Los Angeles, California 90033, USA
P WEIDMANN, MD, associate professor of medicine

Serum phosphate inversely related to blood pressure

A relation has long been known between hypercalcaemia, primarily that caused by hyperparathyroidism, and blood pressure, recently confirmed in a large Swedish population study.[1] Thus we considered it of interest to investigate if such an association also existed within the normal ranges for serum calcium and phosphate concentrations.

Subjects, methods, and results

Over 2000 men aged 49-50 years participated in a general health survey focused on risk factors for coronary heart disease.[2] When those with previously known diseases or regular medication, or both, had been excluded there remained 1768 apparently healthy individuals. Blood pressure was recorded in the morning after 10 minutes' rest in the recumbent position. Serum phosphate was analysed with a molybden complexing method adapted for a continuous-flow system.

No correlation was obtained between serum calcium and supine systolic or diastolic blood pressure. There was, however, a highly significant correlation between serum phosphate and both systolic and diastolic pressure ($P<0·001$). The mean values for both pressures increased with declining phosphate concentrations, and among individuals with a low serum phosphate there was a higher frequency of raised blood pressure (table). Among the 80 individuals with systolic pressure above 160 mm Hg mean phosphate ($\pm$SEM) was $0·73\pm0·01$ mmol/l and for the 35 subjects with a distolic pressure >105 mm Hg $0·75\pm0·01$ mmol/l. The difference for both values compared to the mean value of $0·89\pm0·005$ mmol/l obtained from the entire healthy population is highly significant ($P<0·001$). There was no correlation between serum calcium and phosphate and no differences were obtained for calcium between individuals with high or low serum phosphate. Also serum sodium and potassium were almost identical in the two groups and, compared with matched controls from the same health survey, individuals with a low serum phosphate did not display any other differences for coronary risk factors. In the entire population there was an inverse relation between serum phosphate and body weight ($P<0·01$) but the correlation between phosphate and blood pressure persisted also when this was regarded.

Systolic (SBP) and diastolic (DBP) blood pressure in relation to serum concentrations of inorganic phosphate in a population of apparently healthy middle-aged men

Phosphate concentration (mmol/l)	No of subjects	SBP (mm Hg)		DBP (mm Hg)	
		mean ± SEM	% >160	mean ± SEM	% >105
–0·60	135	137 ± 1	8·9	86 ± 1	2·9
0·61–0·70	224	135 ± 1	7·1	85 ± 1	3·1
0·71–0·80	410	132 ± 1	5·1	83 ± 1	2·0
0·81–0·90	418	132 ± 1	4·3	82 ± 1	2·4
0·91–1·00	322	129 ± 1	2·5	79 ± 1	0·6
1·01–1·10	162	127 ± 1	1·2	80 ± 1	1·9
1·11–	97	125 ± 1	2·1	80 ± 1	0
All	1768	131 ± 1	4·5	82 ± 1	2·0