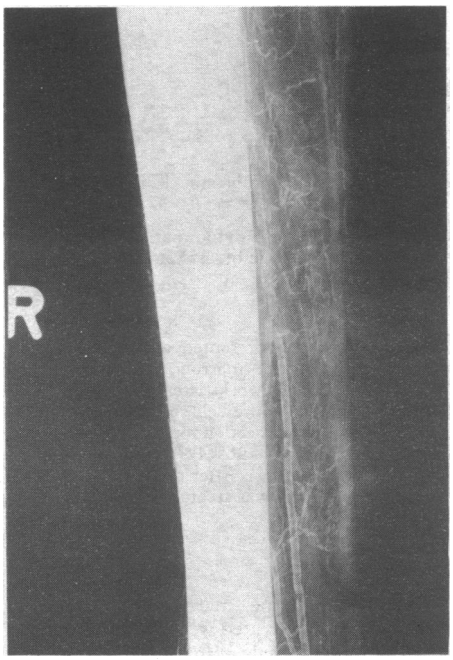
1975. A month later when maintenance haemodialysis was started, one of these areas on the posterior aspect of the right lower leg rapidly increased in size and developed into a necrotising ulcer which became so painful that the patient was incapacitated and had to be treated with morphine. Moreover, 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.

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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 (±SEM) was 0·73±0·01 mmol/l and for the 35 subjects with a distolic pressure >105 mm Hg 0·75±0·01 mmol/l. The difference for both values compared to the mean value of 0·89±0·005 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

Discussion

Varying phosphate concentrations in hyperparathyroidism could perhaps be part of the explanation as to why the level of the raised blood pressure in this disease is not related to the degree of hypercalcaemia.[1] The finding of a correlation between serum phosphate and blood pressure is also in accordance with reported associations between blood pressure and idiopathic calcium stone formation,[3] a condition in which low serum phosphate is common. The serum concentration of inorganic phosphate could possibly be important in the regulation of peripheral resistance,[4] but we should like to suggest the following events as being a more likely explanation of our findings. A rise of blood pressure causes an increased excretion of ions (exaggerated natriuresis),[5] similar to that obtained during saline diuresis. The loss of calcium stimulates the secretion of parathyroid hormone with a return of the serum calcium concentrations to normal, whereas serum phosphate will only tend to be further reset inversely to the blood pressure.

[1] Christensson, T, thesis, Stockholm, 1975.
[2] Hedstrand, H, *Uppsala Journal of Medical Science*, 1975, suppl 19.
[3] Ljunghall, S, and Hedstrand, H, *British Medical Journal*, 1975, **4**, 580.
[4] Hilton, S M, *Circulation Research*, 1971, **28**, suppl 1, 70.
[5] Kiil, F, *Scandinavian Journal of Clinical and Laboratory Investigation*, 1975, **35**, 289.

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Combination chemotherapy for thrombocytopenia with bone marrow metastases from breast cancer

Many chemotherapeutic regimens induce remission in metastatic breast cancer. All are myelotoxic and are not usually used in patients with inadequate bone marrow function. We describe successful cytotoxic treatment with vincristine, doxorubicin, and prednisolone (VDP) of four consecutive cases of thrombocytopenia with bone marrow metastases from breast cancer.

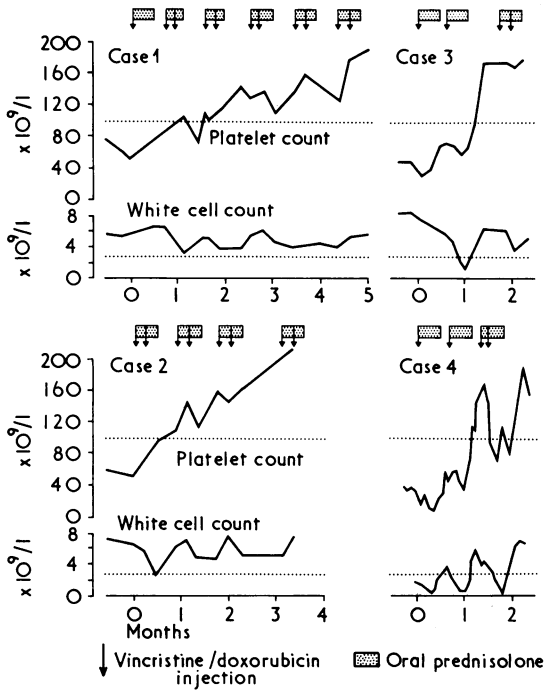
Patients and methods

Treatment was repeated every 28 days (see figure). Intravenous vincristine 1·4 mg/m^2 (maximum dose 2 mg) and doxorubicin 40 mg/m^2 (maximum dose 100 mg) were given on days 1 and 8, although some patients received a single injection initially. Oral prednisolone 20 mg daily was given on days 1-14.

Case 1—A woman aged 36 presented with metastatic breast cancer, malignant infiltration of the bone marrow, and thrombocytopenia. Oophorectomy was performed but 10 weeks later thrombocytopenia (46×10^9/l (46 000/mm^3)) and bone marrow infiltration persisted. The platelet count steadily improved with VDP (single injection for the first course), and after eight months remained normal with complete tumour remission.

Case 2—Four years after mastectomy for breast cancer a 63-year-old woman developed thrombocytopenia. The bone marrow was infiltrated by malignant cells. She responded transiently to nandrolone and prednisolone but six weeks after stopping androgen treatment the platelet count was 42×10^9/l (42 000/mm^3). It returned to normal within one month of starting VDP and remained normal eight months later with complete tumour remission.

Case 3—Two years after mastectomy for breast cancer a 55-year-old woman developed metastases with malignant infiltration of the bone marrow. She failed to respond to nandrolone and dexamethazone and three weeks after stopping androgen treatment the platelet count was 48×10^9/l (48 000 mm^3). She responded well to VDP (single injection for the first two courses/ and remained in complete remission with a normal blood count and bone marrow for 12 months. She developed septicaemia after the first course of VDP which required antibiotics.



Platelet and white cell counts in four patients on combination chemotherapy for metastatic breast cancer.

Case 4—A 35-year-old woman presented with metastatic breast cancer, malignant infiltration of the bone marrow, and thrombocytopenia. She underwent oophorectomy, but two weeks later the platelet count had fallen to 22×10^9/l (22 000/mm^3) and the white cell count to $1{\cdot}2 \times 10^9$/l (1200/mm^3). She was treated with VDP (single injection for the first two courses) and three months later her platelet count was 196×10^9/l (196 000/mm^3) and the white cell count was $7{\cdot}5 \times 10^9$/l (7500/mm^3). After the first course of chemotherapy she developed septicaemia, which was treated with antibiotics.

Comment

Thrombocytopenia and bone marrow metastases from breast cancer have been successfully treated with a combination of high-dose prednisone, ovariectomy, adrenalectomy, and 5-fluorouracil.[1] All our patients treated with VDP developed neutropenia, with septicaemia in two cases. All required blood transfusion, but not platelets or granulocytes. There were no other complications.

Transient thrombocytosis after treatment with *Vinca* alkaloids has been reported in animals and man.[2] This is unlikely to have caused the prolonged increase in platelets in our patients. Tumour cells are probably more sensitive to chemotherapy than platelet precursors, which may be suppressed by the tumour in the marrow. Thus patients with bone marrow metastases should be given the most effective antitumour treatment available. We gave combined chemotherapy with VDP because we have found it effective against metastatic breast cancer.[3] The results suggest that it may be effective in bone marrow depression with malignant bone marrow infiltration. This does not apply to non-metastatic marrow aplasia.

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[1] Sugarbaker, P H, *et al*, *Archives of Surgery*, 1973, **107**, 523.
[2] Robertson, J H, and McCarthy, G M, *Lancet*, 1969, **2**, 353.
[3] Dady, P J, *et al*, unpublished communication.

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