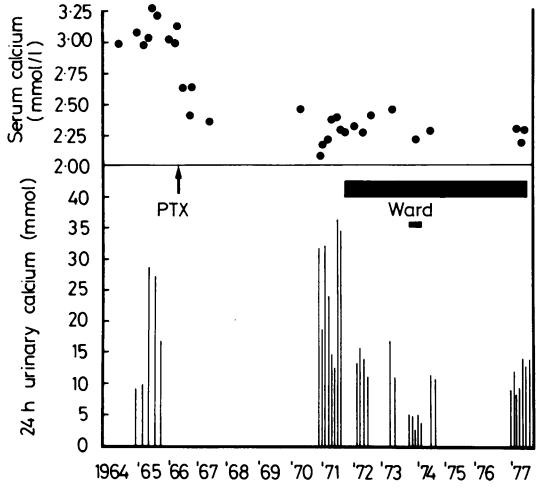

Correction of hypercalcaemia by removal of parathyroid adenoma in 1966 with persistence of hypercalciuria. Note normal calcium excretion during inpatient treatment in 1974. Shaded line represents dietary calcium restriction and sodium cellulose phosphate treatment. Serum albumin concentration ranged from 37-44 g/l.

Conversion: SI to traditional units—Calcium: 1 mmol ≈ 40 mg.

when at home. After parathyroidectomy he passed 12 calculi, ureterolithotomy was performed twice, and serial *x*-ray films showed the development of several new calculi in both kidneys. Recurrent gouty arthropathy began in 1961 but ceased after parathyroidectomy. Throughout, serum uric acid concentration ranged from 0·38 to 0·48 mmol/l (6·4-8·1 mg/100 ml) (upper limit of normal 0·42 mmol/l (7·1 mg/100 ml)) and urinary uric acid from 7·6 to 8·6 mmol/24 h (1·3-1·5 g/24 h) (upper limit of normal 6·0 mmol/24 h (1·0 g/24)). Significant bacteriuria was noted occasionally. Despite this, four analysed calculi contained no uric acid, magnesium, or ammonium, being composed only of calcium oxalate, phosphate, and carbonate. Serum alkaline phosphatase concentration and a radiological skeletal survey were normal. There was no evidence of sarcoidosis, medullary sponge kidney, thyroid disease, myelomatosis, or vitamin D abuse.

METHODS AND RESULTS

Urine calcium was measured with a Perkin-Elmer 30 Atomic Absorption Spectrophotometer.

Parathyroid function—Serum total calcium concentration was measured by a method employing cresolphthalein complexone. Serum ionised calcium concentration (measured by Orion SS 20 calcium electrode) was 1·04 mmol/l (4·2 mg/100 ml) (normal range 0·95-1·12 mmol/l (3·8-4·5 mg/100 ml)). Serum immunoreactive parathyroid hormone (iPTH) concentrations (method of Addison *et al*[2]) were 0·8 and 1·0 μg/l (normal range <1·0 μg/l). Ionised calcium and iPTH concentrations were measured during 1977 on serum taken without venous stasis and with the patient fasting. Urinary cyclic AMP (measured by competitive protein binding, Amersham) to creatinine (μmols:g) ratio was 0·245 after an overnight fast and 0·117 after an oral calcium load (see below). Both ratios are normal.[3] Serum 25-hydroxycholecalciferol concentration (method of Preece *et al*[4]) was 8·0 μg/l (normal range 3·5 to 30·0 μg/l).

Renal function—Creatinine clearances were 167 and 143 ml/min. ^{51}Cr-labelled EDTA clearance was 98 ml/min. Tubular function: abnormal glycosuria, proteinuria, and aminoaciduria were absent; plasma potassium, phosphate, and bicarbonate concentrations were normal. Minimum urine pH after oral ammonium chloride (100 mg/kg body weight) was 5·2. Maximum urine osmolality was 871 mosmol/kg.

Effect of calcium restriction and loading—We followed the protocol of C Y Pak *et al.*[3] Calcium to creatinine (mg:mg) ratio was measured on a two-hour urine sample after an overnight fast and on a four-hour urine sample after giving 1 g calcium by mouth. The ratio was 0·097 fasting and 0·200 after calcium loading—that is, calcium excretion was normal on fasting and above normal after calcium ingestion.[3]

Comment

Persisting hypercalciuria in our patient results from excessive gastrointestinal calcium absorption. Normal serum and ionised calcium and PTH concentrations and normal cyclic AMP excretion exclude hyperparathyroidism. Hypercalciuria is abolished by calcium restriction and this would not be expected if either excessive resorption of calcium from bone[5] or a primary renal calcium leak[3] was present. Fasting urinary cyclic AMP excretion is well below all values reported in "renal" hypercalciuria.[3] There is no evidence of kidney damage resulting from previous hypercalcaemia.

The relation, if any, between this "absorptive" hypercalciuria and previous primary hyperparathyroidism is not clear. Idiopathic "absorptive" hypercalciuria is not uncommon and chance association is a serious possibility.

Given the chemical composition of the calculi and the severity of the hypercalciuria, it seems likely that hypercalciuria is the major cause of recurrent stone formation in our patient. Successful surgery for primary hyperparathyroidism does not invariably ensure correction of a stone-forming tendency. Careful postoperative follow-up is necessary.

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Scombrotoxic fish poisoning

Fish in Britain is generally a safe food; elsewhere poisonous fish are common and dangerous. The occurrence of four cases of scombroid fish poisoning within a short time suggested that the disease may be commoner than is generally recognised. Only one outbreak has been reported in Britain.[1]

Scombroid fish are the dark-meated marine fish—mackerel, tuna, bonito, and skipjack. In scombroid poisoning the flesh of the fish is toxic (ichthyosarcotoxic) and neither washing nor cooking appreciably reduces the activity of the toxic principle.[2]

Case reports

Cases 1 and 2—Mr and Mrs B bought two smoked mackerel. Mr B ate his immediately, but Mrs B decided that hers was too rich (not "off") and after one or two mouthfuls gave the rest to her husband, who finished it. Two hours later Mr B developed severe headache, nausea, and slight diarrhoea and went to bed, where he became hotter and hotter and his scalp began to itch. He felt anxious and noticed that his trunk and arms had turned bright red. Two hours after the onset the redness began to fade and all the symptoms rapidly disappeared. Mrs B suffered only transient slight nausea. Both Mr and Mrs B are healthy, have never experienced these symptoms before, and have eaten many smoked mackerel both before and after this incident.

Cases 3 and 4—Mr and Mrs C bought three fillets of smoked mackerel, which looked, smelt, and felt completely normal. Mr C ate his first and Mrs C hers 20 minutes later. The third fillet was left in the refrigerator. An hour and a quarter after he had finished Mr C began to feel unwell and became conscious of his heart beat, which felt exaggerated and fast. He felt hot and his wife told him he looked red and flushed in the face and hands. A little later he had one episode of diarrhoea. He had neither headache nor nausea. Mrs C became ill about half an hour after her husband, with a moderately severe headache; a feeling of hotness, especially in the face, which flushed bright red; and, a little later, a brief attack of diarrhoea. Both felt slightly itchy. Within three hours their symptoms began to subside and shortly thereafter they felt completely normal. The experience alarmed them sufficiently to contact the local environmental health department. Both had eaten smoked mackerel regularly for several years. Fortunately the third fish was available for examination.

No investigations were carried out on the patients. The fish was divided

into two parts—one was retained for bacteriological examination and the other dispatched frozen to the Torry Research Station at Aberdeen for chemical analysis. The total bacterial count was less than 500 organisms/g, consisting largely of coagulase-negative staphylococci. The Torry Research Station reported that the fish seemed in good condition but was very lightly cured (salt/wet weight 0·9 %, as opposed to the usual 3 % to 5 %). The result of the mouse inoculation test for *Clostridium botulinum* was negative. The histamine content of the meat was 1480 mg/l (normal < 50 mg/l).

Comment

The manifestations of scombroid fish poisoning closely resemble those of a histamine reaction and include nausea, abdominal pain, diarrhoea, flushing, headache, rashes, vomiting, palpitations, and pruritus. In severe cases burning of the mouth, dizziness, and respiratory distress have been reported.[3] The onset is rapid—a few minutes to a few hours—and recovery is usually complete four to eight hours later. One death only was reported in three series totalling 1660 cases.[2]

The toxins are formed by the action of contaminating bacteria on fish muscle, which in scombroid fish is particularly rich in histidine. Histidine is decarboxylated by bacterial enzymes to histamine at temperatures between 20 and 30°C.[4] Fish with histamine concentrations of 100 mg or more/100 g of flesh are usually toxic.[5] Nevertheless, as Aiso (cited by Halstead[2]) has shown that 450 to 500 mg of histamine taken by mouth by human volunteers evoked no response at all, the true nature of scombrotoxin remains unknown, though antihistamines have been shown to give symptomatic relief.

The fish referred to in our report may have contained up to 250 mg of histamine. Though few bacteria were found at examination, bacterial growth presumably occurred before and perhaps after the demonstrably inadequate curing.

Prevention is a matter of adequate refrigeration or preservation as soon after catching as possible. Though most affected fish appear normal, those showing any putrefactive changes around the gills or tasting sharp or peppery, whether cooked or uncooked, should be discarded.

We are grateful to the staff of the Department of Microbiology of the Torry Research Station, Aberdeen, for the chemical analysis of the fish.

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Abnormal cerebrovascular regulation in hypertensive patients

Hypertensive patients are known to have an increased risk of cerebrovascular accidents. The reasons for this are not fully understood, although it has been postulated that the normal control mechanisms of the cerebral vasculature may have failed. Patients with chronic hypertension show normal total and regional cerebral blood flow under resting, normocapnic conditions. Nevertheless, the response of cerebral blood flow to a change in $PaCO_2$ is frequently employed as a test of the integrity of the cerebral vasculature.

Patients, methods, and results

Newly diagnosed essential hypertensive patients were considered for inclusion in the study. Hypertension was defined as a mean diastolic pressure of >100 mm Hg for blood pressure recordings measured on three separate occasions. Patients were excluded if they were known or suspected to be suffering from any other conditions apart from hypertension, or if they were on any form of medication. Ten patients fulfilling these criteria were matched for age and sex with normal volunteers.

Cerebral blood flow was measured by the ^{133}Xenon inhalation method of Wyper *et al.*[1] Details of the procedure have been described fully elsewhere.[2] Recordings were made at normocapnia and during inhalation of 5 % CO_2.

At normocapnia there was no significant difference between cerebral blood flow or $PaCO_2$ in the two groups (table). Under hypercapnic conditions a comparable increase in $PaCO_2$ was achieved for each group. Cerebral blood flow rose satisfactorily in the normal subjects, but there was a mean fall in the patients. Individually all normal subjects showed a good response of cerebral blood flow to change in $PaCO_2$, while in only five patients did the blood flow rise and in five it actually fell in response to hypercapnia. Analysis by Fisher's exact test shows this difference to be significant ($P = 0{\cdot}016$).

Comparison of values for 10 hypertensive patients and 10 age-matched normotensive control subjects. Values are means ± SE of mean. (Mean arterial pressure calculated as diastolic pressure plus one-third pulse pressure)

	Normotensive	Hypertensive
Cerebral blood flow at normocapnia (ml/100 g/min)	45·9 ± 2·0	46·6 ± 1·6
Cerebral blood flow at hypercapnia (ml/100 g/min)	55·0 ± 3·0	46·5 ± 1·9
$PaCO_2$ at normocapnia (kPa)	5·61 ± 0·16	5·43 ± 0·09
$PaCO_2$ at hypercapnia (kPa)	6·77 ± 0·21	6·36 ± 0·13
% Reactivity	11·8 ± 1·8	−2·0 ± 3·8
Age (years)	48·3	50·0
Mean arterial blood pressure (mm Hg)	91·4 ± 3·1	134·3 ± 4·2

Conversion: SI to traditional units—$PaCO_2$: 1 kPa ≈ 7·5 mm Hg.

Cerebrovascular reactivity was calculated as a percentage using the formula: % Reactivity = [Exponential (log change in CBF/(change in $PaCO_2$) − 1] × 100. A significant difference between the two groups was found, with $P < 0{\cdot}02$ (Mann-Whitney test).

Comment

These results indicate significant impairment of cerebrovascular reactivity to CO_2 in a group of hypertensive patients. Previous studies have given conflicting results in hypertensive patients.[3–5] Nevertheless, in Tominaga's study[5] several subjects had either concomitant medical problems or were taking various medications.

Novack *et al*[3] measured cerebral blood flow by the nitrous oxide method, which reflects total cerebral blood flow, while the method we used measures mainly flow in cerebral grey matter. Iliff *et al*[4] showed an abnormal response to hypocapnia, but gave little clinical information about any concomitant disease. The results of our controlled study receive support from other work we have performed, in which a further 13 (unmatched) hypertensive patients with no known vascular problems showed similar findings.

Various anatomical changes occur in the cerebral vasculature of the hypertensive patient. The mechanisms whereby cerebral vessels respond to changes in $PaCO_2$ are controversial, but our results indicate that there may also be a functional disorder in these vessels. Possibly this might be important in the pathogenesis of strokes, and it is of interest that the same functional abnormality has been reported in diabetic patients.[2]

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