expanding dogs inhibited sodium-potassium adenosine triphosphatase. Finally, digoxin-like immunoreactive substance has been shown to have natriuretic activity. This last finding prompted us to study whether concentrations of digoxin-like immunoreactive substance would be increased in a clinical setting such as congestive heart failure, in which natriuretic activity would be expected to be high.

Subjects, methods, and results

Plasma and urine were obtained from 15 patients with congestive heart failure (New York Heart Association class III or IV at time of study) who were not receiving digitals or other drugs known to cross react with antidigoxin antibodies—for example, spironolactone. Twelve had ischaemic heart disease and three dilated cardiomyopathy. Plasma and urine samples were also obtained from 10 normal volunteers. Liver and renal function values were normal in all subjects.

Concentrations of digoxin-like immunoreactive substance were measured by a double antibody radioimmunoassay for digoxin (RIANEL, New England Nuclear, Billerica, MA, USA). The assay was slightly modified by including additional standards at the lower portion of the standard curve. The lower limit of detectability with 95% confidence limits was 0.06 nmol/l. In this assay there was no or insignificant cross reaction with hydrocortisone, deoxycorticosterone, 11-deoxycortisol, dehydroepiandrosterone, androstenedione, 17-hydroxyprogesterone, progesterone, aldosterone, or oestriol. All samples were assayed in duplicate. In view of the observation of Valdes and Graves that the bulk of digoxin-like immunoreactive substance is protein bound and can be detected only after diluting and boiling serum,1 we measured concentrations in native serum and in serum diluted to 1/4 in deionised water and boiled for 10 minutes. We also measured digoxin-like immunoreactive substance in untreated urine, and corrected for urine creatinine concentration.

In native serum of normal subjects no digoxin-like immunoreactive substance was detected. In native serum of the similar alteration with congestive heart failure digoxin-like immunoreactive substance was detected in 11 cases with a mean concentration of 0.125 (SD 0.1) nmol/l (Student's t test, p<0.001) (table). The concentration of digoxin-like immunoreactive substance in diluted and boiled native serum was 1.09 (0.15) nmol/l compared with 1.34 (0.29) nmol/l in congestive heart failure (p<0.001). Urinary concentrations of digoxin-like immunoreactive substance after correction for creatinine were significantly higher in patients with heart failure (p<0.001).

**Digoxin-like immunoreactive substance in serum and urine**

<table>
<thead>
<tr>
<th>Native serum (nmol/l)</th>
<th>Boiled serum (nmol/l)</th>
<th>Urine (nmol/l: creatinine, nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congestive heart failure:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.125 (0.10)</td>
<td>1.34 (0.29)</td>
</tr>
<tr>
<td>Range</td>
<td>(0.0-0.30)</td>
<td>(0.93-1.61)</td>
</tr>
<tr>
<td>Normal subjects:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0</td>
<td>0.23 (0.08)</td>
</tr>
<tr>
<td>Range</td>
<td>(0.0-0.15)</td>
<td>(0.09-0.36)</td>
</tr>
</tbody>
</table>

Comment

Our results show that congestive heart failure must be added to the clinical states associated with increased concentrations of digoxin-like immunoreactive substance. Using the RIANEN assay for digoxin we found detectable concentrations of digoxin-like immunoreactive substance in 11 of 15 patients. In patients receiving digoxin digoxin-like immunoreactive substance is additive in the digoxin radioimmunoassay. Hence the presence of endogenous cross reacting material would falsely increase measured values, albeit only slightly. Impaired hepatic or renal function, which is often found in conjunction with heart failure, has been shown to increase the concentration of digoxin-like immunoreactive substance. The combined effects of congestive heart failure and hepatic or renal disease on digoxin-like immunoreactive substance may lead to more pronounced overestimation of true digoxin concentrations in patients receiving this drug.

Valdes and Graves found that diluting and boiling serum increase measurable concentrations of digoxin-like immunoreactive substance. They estimated that they proceeded to falsely elevated digoxin-like immunoreactive substance and allow determination of the total amount. We have shown that total digoxin-like immunoreactive substance is increased in the serum of patients with congestive heart failure and that the amount excreted in urine is also increased. These results suggest that the raised concentrations of digoxin-like immunoreactive substance found in congestive heart failure reflect increased synthesis of this material.

In view of the suggested physiological role of digoxin-like immunoreactive substance our results raise the intriguing possibility that concentrations of the substance are increased in patients with congestive heart failure as an adaptive phenomenon, analogous to similar alterations noted in concentrations of atrial natriuretic peptide in congestive heart failure.

Hypophosphataemia: a feature of malaria?

Many patients with malaria admitted to this hospital have unexplained low serum phosphate concentrations. I report on 17 such patients; in one the phosphate concentration seemed to be related to treatment.

Patients and findings

**Case 1—** A 36 year old Welshman was admitted after returning from Kenya with a history of fever and headache. On examination his fever was confirmed and he was unwell but alert. A blood film showed a 10% parasitaemia with Plasmodium falciparum. His condition initially improved with oral quinine and the parasite count fell, but his blood film remained positive until day 5. On day 5 his condition deteriorated and he developed headache and drowsiness. He was given quinine 3 g in saline intravenously, as is recommended for patients with this degree of parasitaemia,1 and sulfadoxine 3 g and pyrimethamine 150 mg (Fansidar) orally over days 3-5. Capillary glucose concentrations were estimated every three hours and ranged between 4.5 and 6.5 mmol/l. On day 5 he was alert and free from headache, and his condition then improved steadily.

Of 28 patients with malaria admitted between January 1984 and December 1986...
Plasma atrial natriuretic peptide in essential hypertension: effects of changes in dietary sodium

Plasma concentrations of atrial natriuretic peptides are raised in a substantial proportion of patients with essential hypertension, but the increase in these concentrations is related to changes in sodium intake and blood pressure, not is known. We have therefore studied the effect of changes in dietary sodium intake on plasma atrial peptide and on blood pressure in patients with untreated essential hypertension.

Patients, methods, and results

Twelve patients (seven men, five women; two black, 10 white) aged 39-68 years with uncomplicated essential hypertension and not receiving treatment were studied as outpatients. Plasma atrial peptide concentration, renin activity, and aldosterone and electrolyte concentrations, blood pressure, and 24-hour urinary sodium excretion (mean of two estimations) were measured with the patients having normal sodium intake, on the fifth day of a low sodium diet (10 mmol/day), and on the fifth day of a high sodium diet (350 mmol/day), the sequence of low and high sodium intakes being allocated at random.

Mean plasma atrial peptide concentrations when patients were receiving normal sodium intake were 23.5 (2.3) ng/l on the fifth day of the high sodium intake, but there was no overall significant change in values between the normal and fifth day of the low sodium intake (figure). Mean blood pressure was reduced from 119 (3) mmHg during normal sodium intake to 110 (3) mmHg on the fifth day of the low sodium intake, but there was no difference in blood pressure between the period of normal sodium intake and the fifth day of the high sodium intake (figure). Plasma renin activity and aldosterone concentration increased with the reduction in sodium intake and were suppressed on the fifth day of the high sodium intake; throughout the study there were no significant changes in plasma sodium or potassium concentration or urinary potassium or creatinine excretion and volume (results not shown).

Comment

Acute severe hypophosphataemia (less than 32 mmol/l) in the absence of total body phosphate depletion results in cellular anoxia through depletion of intracellular adenine triphosphate and may cause respiratory failure, encephalopathy, cardiac depression, and hypocalcaemia (by impaired red cell deformability). Hypophosphataemia is associated with fever, persistent vomiting, and diarrhoea but has not been reported with malaria. Giving carbohydrate or insulin may cause profound hypophosphataemia because of the intracellular shift of phosphate essential for glycolysis, glycogenolysis, and other anaerobic processes. Intraosseous calcium releases endogenous insulin (which might account for the fall in serum phosphate concentration in case 1), but hypoglycaemia may occur before quinine is given. Furthermore, White et al reported hypoglycaemia in African children with malaria without hyperinsulinaemia and suggested that impaired gluconeogenesis and glycogenolysis were responsible.

It is therefore not surprising that hypophosphataemia occurs in malaria—especially if quinine is administered—and it could aggravate the pathophysiological effects of the parasite. If these results are confirmed then serum phosphate concentration should be measured in all patients with malaria, especially those receiving intravenous quinine or carbohydrate, and hypophosphataemia should be rapidly corrected.