the diagnosis. Halasz\textsuperscript{7} showed that a fifth of patients, with an initial diagnosis of acute cholecystitis, were found to have disease in the right kidney, liver, or pancreas which would not have been helped by laparotomy. Several reports of trials of early surgery, however, show that careful clinical assessment results in few diagnostic errors.\textsuperscript{8-12} During the 48 hours after admission plain radiographs, routine chemical estimations of serum, microscopy of the urine, and a full blood count may be followed by ultrasonography, which can detect specific signs (stones, thickening of the wall, or increased diameter of the gall bladder).\textsuperscript{13,14} Cholecintigraphy is a quick method of showing blockage of the cystic duct.\textsuperscript{15} This period of 48 hours is also a time of active treatment with intravenous fluids and antibiotics and careful assessment of fitness for operation.

If the diagnosis of acute cholecystitis is upheld and the patient is fit for operation "the question is whether postponement offers any advantage."\textsuperscript{16} This cannot be answered on technical grounds because some cholecystectomies are easy and some are difficult, quite irrespective of timing, although the indications are that difficulties increase after seven to 10 days and have not always abated after two to three months:\textsuperscript{16} it is essential in all cases and at all times for an experienced surgeon either to perform or to directly supervise the operation. In 90-95\%\textsuperscript{10} of early cholecystectomies an informative intra-operative cholangiogram may be obtained,\textsuperscript{10,11,17,18} and this is important because up to two-fifths of patients require exploration of the common duct.\textsuperscript{19} Residual stones are no more common after early than after delayed surgery.\textsuperscript{10,11,15,17-19} The crucial question of the respective mortality and morbidity rates is difficult to assess because surgery during a trial is likely to be especially careful.\textsuperscript{20} Nevertheless, there is no evidence of any appreciable difference: mortality rates of 0-1\%\textsuperscript{20} are reported, with no record of ductal injuries.\textsuperscript{19} The advantage of early operation to both patient and hospital is that treatment is completed in one admission,\textsuperscript{20} and for a few fortunate patients there is timely removal of a gangrenous gall bladder in spite of unremarkable physical signs. Among patients who have to wait the traditional two to three months for readmission, 10-20\%\textsuperscript{21} relapse\textsuperscript{19} and require a second emergency admission, while the total time away from home and work is always longer.\textsuperscript{21}

One of the major developments in emergency abdominal surgery over the past 20 years has been recognition of the place of definitive procedures in emergency operations for perforated peptic ulcer\textsuperscript{22} and for the obstructed or perforated colon.\textsuperscript{23} Acute cholecystitis is not usually so pressing an emergency, but the case for performing cholecystectomy on the next operating list, after two or three days of preoperative treatment and assessment, must now be considered to be established.

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\textsuperscript{22} Jordan GL, DeBakey ME, Duncan JM Jr. Surgical management of perforated peptic ulcer. \textit{Ann Surg} 1974;179:628-33.

Magnesium deficiency and diuretics

Identifying dangerous side effects produced by drugs is notoriously difficult. The difficulties are compounded when the drug in question is used in the long-term treatment of many patients. In these circumstances experience may be widely disseminated, and important but rare sequelae may be overlooked by individual doctors. Though oral diuretics are now in their third decade, new problems are emerging. Some, such as impotence (reported in the Medical Research Council trial\textsuperscript{30} of treatment of mild hypertension), are quite unexpected. Other side effects are predictable in the light of the known physiological actions of diuretics, though their clinical importance may not be clear. The influence of diuretics on magnesium metabolism and the relation between magnesium and potassium deficiency belong to this second class.

Thiazide and loop diuretics acutely induce substantial urinary losses of magnesium.\textsuperscript{2,3} Potassium-retaining diuretics probably do not have this effect\textsuperscript{1} and, indeed, may produce magnesium retention.\textsuperscript{6} The degree of magnesium depletion produced by potassium-losing diuretics is rarely severe enough to cause a classical clinical picture of magnesium deficiency with neuromuscular irritability and tetany; indeed, the condition may readily be overlooked since serum magnesium concentrations may not reflect an intracellular deficit.\textsuperscript{7} The belief that diuretics may have important effects on magnesium balance is supported by the finding of low magnesium concentrations in the skeletal muscle of patients undergoing prolonged diuretic treatment for congestive cardiac failure.\textsuperscript{8} In such cases, however, the magnesium deficiency may not directly be due to diuretics\textsuperscript{8}: secondary aldosteronism, protein-energy
malnutrition, and treatment with digoxin all tend to produce negative magnesium balance.

These observations would be of purely theoretical interest if magnesium were not so profoundly important biochemically. Magnesium is the second most common intracellular electrolyte and plays an essential part in many metabolic processes requiring hydrolysis and transfer of phosphate groups: prominent among these is the hydrolysis of adenosine triphosphate (ATP), a central component of the cellular pumps which maintain the homoeostasis of sodium, potassium, and calcium. For instance, magnesium deficiency may raise the free intracellular calcium concentration and so increase vascular tone and reactivity. Clinical relevance has been claimed for these observations in a small Danish study which reported a negative correlation between mean blood pressure and serum magnesium. To cast the epidemiological net wider, magnesium deficiency has been incriminated in the greater number of deaths from ischaemic heart disease observed in soft-water areas.

A more direct cause for clinical concern is that magnesium is required for the activity of the sodium-potassium ATPase, which helps maintain the gradient of sodium and potassium across the cell membrane. Impairment of this pump and the resultant partial depolarisation of the cell membrane give rise to hyperirritability of excitable tissues. Further, when the capacity to pump potassium into the cells is reduced attempts to correct potassium depletion by administering potassium salts would also be inhibited since the major reservoir would be inaccessible. This would, therefore, tend to perpetuate the cardiac consequences of potassium depletion. Both these effects do occur in patients with magnesium deficiency. Severe magnesium deficiency has been reported in association with serious cardiac arrhythmias (particularly digoxin-provoked arrhythmias), and these have responded to infusion of magnesium. One recent study reported evidence for an important relation between magnesium and potassium depletion in patients treated with diuretics. Administering potassium failed to correct the intracellular potassium depletion until magnesium deficiency was corrected. Serum potassium concentrations necessarily rose as a result of administration of potassium whether intracellular potassium rose or not, so that without tissue analysis a misleading impression would have been obtained.

At present there is no convincing evidence that diuretics may induce severe intracellular potassium depletion masked by magnesium deficiency. Studies of total body potassium and exchangeable potassium in patients treated with diuretics have not always shown any important potassium depletion (though the insensitivity of the methods does not exclude minor changes), but one recent study showed a dose-dependent reduction in body potassium in patients treated with hydrochlorothiazide. In any case the clinical relevance of magnesium deficiency induced by diuretics would not be settled by such measurements: the problem will be resolved only by evidence (or lack of it) of increased cardiovascular morbidity and mortality in patients treated with diuretics who have not developed what would be conventionally accepted as hypokalaemia. There is indirect evidence in favour of such a view. The incidence of ventricular premature beats is increased in patients treated with potassium-losing diuretics, even when the reduction in serum concentrations of potassium is only of a very modest degree. The significance of such ectopic beats is uncertain, but the abnormality which causes them may possibly also cause more serious ventricular arrhythmias.

The case against the use of potassium- and magnesium-losing diuretics on these grounds is not particularly strong. Perhaps more relevant information will come from the results of the Medical Research Council trial of treatment in mild hypertension, since the consequences of treatment both with diuretics and with beta-blockers are being carefully monitored in that study. In the meantime advice on treatment must remain provisional. Clinicians should, however, be aware of the possibility of combined deficiency of potassium and magnesium in patients in whom arrhythmias seem to be associated with the use of potassium-losing diuretics despite acceptable serum potassium concentrations. Measurement of the serum magnesium concentration may help, but it will not necessarily exclude the diagnosis when the results of such measurements are normal. In the absence of tissue analysis (and here the white blood cell seems the most promising tissue) the only options are substituting a potassium-sparing diuretic or cautiously administering magnesium. Where the aim of diuretic treatment is the excretion of fluid there are usually no other choices, but where diuretics are being used to lower blood pressure a switch to a beta-blocker is another important possibility. Here perhaps the dislodging of diuretics from their pre-eminence as first-line treatment has some justification.

The possibility of increased cardiovascular morbidity from subclinical potassium and magnesium deficiency has to be coupled with anxieties about the effect of prolonged diuretic-induced glucose intolerance, while a positive factor is the increasing evidence that beta-blockers reduce the incidence of reinfarction in patients with ischaemic heart disease. Admittedly, we have to extrapolate some way from those considerations to arrive at the otherwise healthy patient with hypertension who has not previously had a myocardial infarct, but clinical medicine demands such extrapolation where decisions have to be made on incomplete evidence. What evidence we have today is raising suspicions about diuretics as first-line drugs in hypertension. The next few years should show whether such suspicions are justified.

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