

official statements (or of *The Rising Tide*) were shown to the college for comment, despite a happy tradition of consultation on such matters; no doubt agreement could be reached, for on essential purposes there is no dispute. Why not let the new awards go simply to good schemes for improving the services?—they could be called, say, “development awards,” and could go to places that have nothing, to leading centres to enable them to do still better, and to all points in between. Tested repute rather than formal designation may safely continue to identify what is worth demonstrating.

The pattern of small steps forward across the country will be varied. If we are to make strides to keep our feet dry this £6 million will need to be followed by much more.

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## Disequilibrium hypercalcaemia

The management of a patient with severe hypercalcaemia is largely determined by the stability of the condition. Many patients, particularly those with mild hyperparathyroidism, have a raised serum calcium concentration which is stable over a long period,<sup>1</sup> so detailed investigation may precede treatment.<sup>2</sup> The stability of the hypercalcaemia reflects a balance between the destruction and the formation of bone (equilibrium hypercalcaemia)<sup>1-3</sup>; but when this balance is disturbed the resultant hypercalcaemia (disequilibrium hypercalcaemia) is unstable and may present as a hypercalcaemic crisis.<sup>4</sup>

In disequilibrium hypercalcaemia net bone destruction leads to an increased calcium load which must be excreted if homeostasis is to be preserved. Unfortunately even in the presence of normal renal function some of this calcium will be reabsorbed<sup>5</sup> and accumulates in the extracellular fluid with resultant hypercalcaemia. As the serum calcium concentration rises the function of the distal tubule becomes progressively impaired and its ability to conserve salt and water is lost.<sup>6-7</sup> The main defence against the threat of volume depletion is to increase sodium reabsorption by the proximal tubule of the kidney, but since the transport of calcium is closely linked with sodium<sup>8</sup> the ability to excrete the excess calcium load is restricted. The problem is compounded by contraction of the extracellular fluid volume, which reduces the glomerular filtration rate and thus the filtered calcium load. The combination of all these renal changes may result in an unstable serum calcium concentration which tends to rise and may reach values that threaten life.

Malignant disease is the commonest cause of hypercalcaemia in a hospital population,<sup>9</sup> but hyperparathyroidism with osteitis fibrosa and renal impairment may also lead to disequilibrium hypercalcaemia.<sup>1</sup> The main cause of hypercalcaemia in vitamin D intoxication and sarcoidosis is an increase in calcium absorption,<sup>10</sup> but both conditions can lead to resorption of bone,<sup>10-11</sup> calcification of soft tissue, and nephrocalcinosis, and may lead to renal impairment and disequilibrium hypercalcaemia. This is particularly true in hypoparathyroidism treated with vitamin D, where hypercalcaemia may be precipitated by an increase in calcium intake, treatment with thiazide diuretics,<sup>12</sup> or impaired renal function. Less common causes include immobilisation in any condition associated with increased bone turnover, including Paget's disease, thyrotoxicosis, hyperparathyroidism, or the action of thiazides in mild hyperparathyroidism.<sup>13</sup>

The cause of disequilibrium hypercalcaemia is usually apparent from the history, physical examination, or simple investigations. In one study three-quarters of the patients with malignant hypercalcaemia had obvious metastases at presentation.<sup>14</sup> A hypercalcaemic crisis needs prompt treatment, which should not be delayed by any detailed investigations: few, if any, biochemical measurements reliably distinguish between the various causes of hypercalcaemia. The serum phosphate concentration has little discriminating value,<sup>9-15</sup> and though estimation of the parathyroid hormone activity may be helpful it is not invariably so<sup>16</sup>—certainly treatment should not be delayed by waiting for the result.

Laboratory tests show that during a calcium infusion there is normally a curvilinear relation between the serum calcium concentration and the calcium excretion expressed per unit of glomerular filtrate.<sup>17</sup> The relation may be less clear in severe hypercalcaemia due to changes in acid-base state, renal damage, or abnormal protein binding of calcium—for example, in myeloma—but it does provide a reasonable approximation for clinical use. The relative contributions to the genesis of hypercalcaemia of calcium load (rise in calcium excretion) and tubular reabsorption (shift to the right in the relation between calcium excretion and serum calcium) can be assessed and changes in these two variables monitored during treatment.<sup>18-19</sup>

Treatment should begin with intravenous saline to re-expand the extracellular fluid, restore the glomerular filtration rate, and reduce the stimulus to reabsorption of sodium and calcium. The average sodium deficit is around 10 mmol(mEq)/kg body weight,<sup>20</sup> but continued fluid and further electrolytes are usually required because of persisting nephrogenic diabetes insipidus.<sup>6-7</sup> Rehydration alone may reduce the hypercalcaemia by over 0.5 mmol/l (2.0 mg/100 ml),<sup>20</sup> and some patients may not need any additional treatment.

In forced saline diuresis large volumes of saline (10-20 litres for 24 hours) are given together with a loop diuretic (frusemide 100-200 mg two-hourly) to inhibit calcium reabsorption by the kidney.<sup>21-22</sup> This combination may lower the serum calcium concentration by as much as 1.0 mmol/l, but close laboratory support is essential to prevent serious imbalance in the electrolytes, and few centres have the facilities or the skill required.

The alternative is to reduce the calcium load by the use of agents which inhibit bone resorption. At present the choice is either calcitonin,<sup>23-26</sup> mithramycin,<sup>27-28</sup> or phosphates.<sup>29-30</sup> Corticosteroids act slowly and their effects are unpredictable,<sup>30-32</sup> while indomethacin has proved disappointing in the treatment of malignant hypercalcaemia.<sup>33</sup> The bisphosphonates offer considerable promise; disodium etidronate is

effective if given intravenously,<sup>34</sup> while dichloromethylene bisphosphonate<sup>34 35</sup> and aminohydroxypropylidene bisphosphonate<sup>36</sup> are effective by mouth or intravenously. Unfortunately none of these preparations is generally available at present.

The crucial principle of management is that treatment of disequilibrium hypercalcaemia takes priority over investigation. The aim must be to reduce serum calcium to a safe but not necessarily normal concentration (say, below 3 mmol/l; 12 mg/100 ml) while investigations are completed and definitive treatment planned.

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## Antiemetics and cytotoxic drugs

The chemotherapy of cancer has emerged from being a last ditch operation practised by enthusiasts to a well recognised form of treatment widely used and which is highly successful in some forms of neoplastic disease. The use of drugs for this purpose seems likely to increase. Unfortunately nearly all chemotherapeutic agents have serious and unpleasant side effects. For doctors myelosuppression is probably the most worrying, but most patients would say without hesitation that their main concern is the nausea and vomiting caused by some cytotoxic drugs. So severe and repellent may these symptoms be that patients with full knowledge of the implications may opt to stop treatment rather than continue to suffer.

Nausea and vomiting have never been very popular research topics, though they did receive some stimulus during the second world war when the authorities were looking for a drug which would minimise sea sickness in those taking part in beach landings. A vomiting centre was originally shown in the floor of the fourth ventricle in 1891,<sup>1</sup> but our present understanding of the central mechanism controlling vomiting is mostly based on a series of papers published in the 1950s.<sup>2</sup> Studies in cats identified an area on the dorsilateral aspect of the reticular formation, which when stimulated produced vomiting and which was thought to be the coordinating centre for the various activities concerned with vomiting. The same work confirmed that there was a further more superficial area in the area postrema which was stimulated by various circulating emetic agents including apomorphine, morphine, and copper sulphate, and which in turn activated the vomiting centre. This area has been termed the chemoreceptor trigger zone. Recently attention has been directed to the possibility that dopamine is a neurotransmitter in the stomach and may be concerned with vomiting.<sup>3</sup> We still do not know how closely these findings in animals correspond to the mechanisms in man, but they appear very similar, so that emetic agents and antidotes may be tested in animals.

Not all cytotoxic drugs cause vomiting. Among those with an emetic action cisplatin is in a class of its own, but others