Metastatic Calcification and Dialysis

Soft tissue calcification (metastatic calcification) associated with advanced renal failure and high calcium × phosphate product has important practical consequences for the modern treatment of terminal renal failure. Conservative management of renal failure should therefore aim at early detection and prevention of this complication.

Soft tissue calcification may show first in the cornea,1 and deposits of apatite at the corneal limbus and on the conjunctiva, best seen with a slit-lamp but also visible with an ophthalmoscope, are a useful clinical sign of chronic renal failure.2 The eyes appear red from an inflammatory reaction in the conjunctivae.3 Arterial calcification, the commonest of the forms of metastatic calcification that are detectable radiologically, has more serious implications because of difficulties with the vascular surgery essential for regular dialysis and transplantation.4

Hyperphosphataemia is always found at some time in patients with metastatic calcification.5 An increase in the calcium × phosphate product above 75 (when both are measured in mg/100 ml) should be treated as a medical emergency and the blood phosphate concentration lowered by giving aluminium hydroxide.6 Vitamin D is especially likely to cause widespread arterial calcification.7 It has recently been shown that absorption of bone minerals can be achieved, even in uraemia, without large doses of vitamin D by giving dietary supplements of calcium carbonate and calcium phosphate.8 Haemodialysis usually gets rid of tumourous masses of soft tissue calcification,9 but other types of soft tissue calcification—such as periarticular, cutaneous, and visceral calcification—which are rare before dialysis may worsen.9-12 Arthralgia,11 pruritus,8 or even death10,12 may result.

Early workers10,13 followed the thinking of Albright's group14 that plasma calcium was the most important factor in the production of soft tissue calcification. Scribner's group15 originally advocated a reduction of dialysate calcium concentration in order to lower plasma levels.16 It is now realized that this stimulates parathyroid secretion, and, therefore, in patients who have no renal function, raises the plasma phosphate.17 There should therefore be enough calcium in the dialysate18 and in the diet19 to facilitate involution of hyperparathyroidism if this is amenable to physiological control.16

A recent report from Israel20 draws attention to a special risk of metastatic calcification during the early weeks of dialysis. There are several reasons why this may occur. Correction of acidosis makes calcium salts less soluble.21 A lower plasma concentration of calcium in complex form (in uraemia 45% of the total plasma calcium may be in this form18) is accompanied by an increase in the ionized fraction, and dialysable inhibitors of calcification,19 some of which are now identified as pyrophosphates,20 are removed. Furthermore, the effect of uraemia on connective tissue to produce a calcifiable matrix may still persist.3 Dialysis may also make the skeleton more responsive to parathyroid hormone.8

The prevention of hyperphosphataemia during the early weeks of dialysis is therefore important, since phosphate is poorly dialysed.3 Careful biochemical monitoring is needed, especially in peritoneal dialysis, and aluminium hydroxide may have to be given. The need to continue phosphate depletion should be reviewed monthly owing to the risk of causing osteomalacia from phosphate deficiency.6,15,21 In due course plasma phosphate concentrations reflect the remineralization of the skeleton, in which there may be large masses of osteoid capable of acting as "avid" bone.22 Though dialysis routines are fairly uniform the results are not, and they must be considered in the context of the incidence of osteodystrophia in the area. There are notable geographical variations in this which are probably due to differences in the content of fluoride or trace metal in the water. Lower plasma phosphate concentrations have been observed in patients with healing bone disease.16,18 than in those with osteodystrophia23 with a better understanding of its pathophysiology a reduction in the incidence of metastatic calcification in uraemia should be possible. There remains in the di-phosphonates an untried weapon for use in those cases in which prevention fails.23 They have recently been used successfully in cases of myositis ossificans24 and of calcinosis universalis.25

5 Parfitt, A. M., Archives of Internal Medicine, 1969, 124, 544.
Bladder Cancer and Smoking

Sixteen years ago A. M. Lilienfeld and colleagues showed by a case-control (retrospective) epidemiological investigation an association between cigarette smoking and bladder cancer. Their observation has since been confirmed by similar studies, and there can be no doubt about its validity. Nevertheless, doubts have been expressed about its interpretation in terms of causality on the grounds that the association is weak (the relative risk of smokers compared with non-smokers is just about double), that it seems to be absent in women, and that the mechanism is obscure.

Though weak, the association is consistent and is stronger among heavy than among light smokers. The most recent case-control study, from the Harvard School of Public Health, shows that the association also exists for women and that the relative risk is of about the same magnitude as for men. Men cigarette smokers had a relative risk of bladder cancer of 1.89 compared with non-smokers, and about 39% of the cases were related to smoking ("attributable risk"). Among women cigarette smokers the comparable relative risk was 2.00 and the comparable attributable risk 29%. None of the greater risk associated with smoking could be explained by an indirect association with type of occupation. The report also pointed out that in successive cohorts increasing rates of incidence of bladder cancer in American women are matched by an increase in cigarette smoking.

R. Hoover and P. Cole, also from the Harvard School of Public Health, have now examined in some detail trends in smoking habits and bladder cancer for successive cohorts of men and women in the United States, Denmark, and England and Wales. Their findings greatly strengthen the case for the prosecution. They show that the cohort patterns of rising rates of incidence of bladder cancer observed are in line with the corresponding patterns of rising cigarette consumption. The association is consistent for both sexes, for the three nationalities, and for urban and rural groups. In the authors’ own words, “this makes it unlikely that the findings result from an association of both smokers and bladder cancer with a third variable.” They also point out that cohort-specific rates of incidence of bladder cancer are now levelling off or even beginning to decline, and they tentatively suggest that this may be due to a concurrent levelling off of the percent of cigarette smokers and the decline of the percent of heavy smokers in recent cohorts. Another piece of the jigsaw that fits into place is the demonstration by A. J. Lea of a highly significant correlation between death rates from lung cancer and cancer of the bladder for 20 countries. The only obvious aetiological factor common to both these cancers is cigarette smoking.

How smoking gives rise to this type of cancer remains obscure. As long ago as 1955 L. R. Holsti and P. Ermolaev claimed to have produced papilloma of the bladder in mice by painting the buccal mucosa with tobacco-smoke condensates. Their findings have not been confirmed. Certain normal metabolites of tryptophan have been shown to induce cancer of the bladder in mice. In one small study these metabolites were found in greater amounts in the urine of cigarette smokers than of non-smokers, and the amounts decreased when the smokers stopped smoking and increased when the non-smokers began to smoke. And there the matter at present rests.

Cigarette smoking is one of the most lethal of the common environmental hazards. To the high risk it carries of cancer of the lung, coronary disease, and chronic bronchitis must now almost certainly be added a lower risk of cancer of the bladder.