Can Renal Bone Disease be Prevented?
Chairman: S SHALDON, London, UK

Panellists: E Ritz
A Fournier
M Kaye
D N S Kerr
W J Johnson
S G Massry
H H Malluche

S SHALDON: The title of this panel is 'Can Renal Bone Disease be Prevented?'
Some of you have a piece of paper entitled 'Can Uraemic Bone Disease be
Prevented?' – the answer to this is obviously no, as prevention must occur
before uraemia.

E RITZ (Heidelberg): I have been confronted with the most delicate task of
summarising our current state of ignorance concerning renal bone disease
and of building on this rather shaky base firm guidelines for the clinical
management of metabolic bone disease before and during maintenance haemo-
dialysis.

While dialysis bone disease still combines a high degree of prognostic
uncertainty with scientific obscurity, some major pathogenic mechanisms
have been recognised in recent years. So many able investigators in this
field have later been put on the rather unpalatable diet of eating their own
words. Therefore, short of appropriate prospective studies, I hesitate to
suggest that today renal bone disease can entirely be prevented; still it seems
safe to predict that future patients will fare a lot better than our present ones
when some sins of the past are avoided.

RATIONALE FOR PREVENTIVE THERAPY

The rationale for preventive therapy should be to substitute for the failing
kidneys' role in calcium metabolism. Failing renal function causes two
major abnormalities: parathyroid overactivity on the one hand and defective metabolism of vitamin D on the other hand. Both abnormalities must be corrected by appropriate therapy.

Secondary hyperparathyroidism is an attempt of the organism to homeostatically keep serum calcium and serum phosphate levels in the normal range. Any deviation of serum calcium and serum phosphate levels from the norm must be strictly avoided to prevent compensatory hyperparathyroidism.

PHOSPHATE RETENTION

Incapacitating nutritional hyperparathyroidism in horses and swine (bran disease, 'Schnüffelkrankheit') has been known to veterinarians for decades. This complication is seen in animals on a low calcium diet, when excessive dietary

Figure 1. Dental radiographs of a control horse (a) and an experimental horse on a high phosphorous diet (b) (autopsy specimen). Note evidence of secondary hyperparathyroidism in the horse with the dietary P-load (erosion of lamina dura and osteoclastic destruction of alveolar bone). [Courtesy of Professor Lennart Krook, Cornell-University, Ithaca, NY]
intake of phosphate exceeds the capacity of the normal kidneys to handle the phosphate load (Figures 1a, b).

Similarly, even in very early renal failure parathyroid overactivity is induced when an imbalance between a normal dietary phosphate load and diminished renal excretory capacity is caused by progressive destruction of nephrons. Slatopolsky was able to show that the development of hyperparathyroidism can be prevented when phosphate intake is reduced in proportion to the reduction of the glomerular filtration rate.

DEFECTIVE VITAMIN D METABOLISM

On the basis of clinical observations, it has been suspected for many years that faulty handling of vitamin D occurs in renal insufficiency. Meanwhile it has been firmly established that the biologically active metabolite of vitamin D, 1,25 dihydroxycholecalciferol (1,25 DHCC) is synthesised in renal tissue from a precursor substance 25-hydroxycholecalciferol (25-HCC) which is formed in the liver (Figure 2). It seems logical to ascribe osteomalacia in

![Diagram of vitamin D metabolism]

Figure 2. Scheme of vitamin D metabolism

renal failure to the absence of this biologically active vitamin D metabolite. Still, it remains puzzling that clinically, osteomalacia is no more severe in anephric patients than in patients with kidneys in situ.

It is very fortunate from a therapeutic point of view, that high doses of vitamin D are effective in the treatment of renal bone disease, although the active metabolite 1,25 DHCC is presumably not formed in uraemic patients.
The paradoxical efficacy of vitamin D may be due to a pharmacological action of high serum levels of the precursor 25-HCC which is formed in the liver. On the other hand, certain stereo-isomers of vitamin D (trans-vitamin D-derivatives) do not require hydroxylation by renal tissue in order to be effective. Therefore, circumvention of the hydroxylation step in the kidneys by trace amounts of trans-isomers in commercial vitamin D preparations might be an alternative explanation.

The spectacular effect of dihydrotachysterol shown by M Kaye may similarly be due to its biological efficacy without prior hydroxylation in the kidney.

PREVENTIVE THERAPY BEFORE HAEMODIALYSIS

Virtually all patients who start dialysis treatment have significant bone disease when studied by appropriate methods. This points to the necessity of preventing bone disease by appropriate treatment in early stages of renal failure. Therapy of established bone disease is bound to be less effective. In renal bone disease the premorbid skeleton is continuously destroyed by osteoclastic resorption and partially replaced by mechanically inferior fibrous bone or undermineralised bone. Even if this process is completely stopped by appropriate therapy, the cumulative past transformation is slow to be repaired because bone turnover is relatively slow. Therefore, in spite of normalised osteoclastic resorption we may still wind up with mechanically inferior bone.

Parathyroid stimulation by lowered ionised serum calcium levels must be avoided (1) by reducing dietary intake and intestinal absorption of phosphate; (2) by administering calcium carbonate and/or (3) by giving vitamin D or analogous sterols.

Avoidance of Phosphate Retention

Dietary intake of phosphate can to a certain extent be reduced by avoiding milk (which contains 910mg phosphate per litre) and milk products. Beyond that it is virtually impossible to devise a low phosphate diet with adequate calorie and protein content. Therefore in addition, intestinal absorption of phosphate must be lowered by oral aluminium hydroxide. There is clear evidence that aluminium is reabsorbed from the gut and accumulates in bone. Yet, avoiding aluminium hydroxide in this situation for fear of its questionable toxicity reminds one of the captain who hesitates to throw a life belt to the passenger who went overboard for fear that he might hit the drowning passenger's head. Lowering serum phosphate, in addition to its beneficial effect on parathyroid stimulation, substantially reduces the risk of soft tissue calcification (with the notable exception of vascular calcification).

Vitamin D Therapy

Undoubtedly azotaemic bone disease with predominant osteomalacic features
responds dramatically to vitamin D, whereas in the presence of pure parathyroid hormone (PTH) induced renal osteitis fibrosa its therapeutic effect is less spectacular. Yet, Verberckmoes has obtained most impressive therapeutic results with vitamin D in histologically pure PTH induced renal osteitis fibrosa without any recognisable osteomalacic lesions. Clearly vitamin D does a lot more to bone than just mineralise unmineralised lamellar osteoid, the hallmark of osteomalacia. A profound effect of vitamin D on bone metabolism must also be suspected from our own histological investigations on the effect of vitamin D in renal osteitis fibrosa.

Undoubtedly vitamin D is a dangerous drug, toxic doses causing erosive release of bone mineral. Yet, it is unquestionably an effective drug. I doubt whether William Withering would have ever written his treatise on the foxglove had he been deterred by the well known side effects of digitalis. Obviously, serum calcium and particularly serum phosphate must be carefully monitored under vitamin D therapy. Further, the toxicity of vitamin D should be reduced by rigorous control of serum phosphate and possibly — in advanced osteitis fibrosa — by prior subtotal parathyroidectomy. Vitamin D should not be given unless serum phosphate levels are brought into the normal range by aluminium hydroxide before vitamin D therapy.

As outlined above, the rationale of preventive therapy should be to substitute for the failing kidneys' role in vitamin D metabolism. Consequently the administration of vitamin D to every renal patient seems theoretically perfectly logical. Still, one hesitates to indiscriminately recommend its routine use, especially in non-dialysed patients, in view of the potential hazard of deterioration of renal function in vitamin D toxicity. Therefore, until the necessity of prophylactic continuous vitamin D therapy for the prevention of renal bone disease has been clearly demonstrated in prospective studies, the common sense approach for the time being would be to restrict its use to symptomatic patients.

PREVENTIVE THERAPY UNDER MAINTENANCE HAEMODIALYSIS

In addition to the problem encountered in renal insufficiency, some new problems arise once uraemic patients are treated by maintenance haemodialysis.

Restriction of Phosphates

Obviously dietary restriction of phosphate and administration of aluminium hydroxide must be continued on maintenance haemodialysis. Yet, because of the additional phosphate losses into the dialysate, over zealous lowering of serum phosphate now carries the very definite risk of phosphate depletion with its attendant phosphate-depletion osteomalacia.

Dialysate Calcium Levels

A most important contribution to the management of bone disease under
haemodialysis has been the finding of the Mayo Clinic group that serum PTH levels can be lowered using dialysate calcium concentrations of 4 mEq/l. (We were unable to demonstrate a similar effect for elevated dialysate magnesium levels.)

Whereas the inhibitory effect of hypercalcaemia on the polypeptide synthesis of parathyroid hormone and the secretory granule release is beyond question, clear evidence is still lacking that hypercalcaemia causes complete anatomical involution once the glands have become hyperplastic, so to speak achieving 'medical parathyroidectomy'. This scepticism is nourished by Popovtzer's finding of significant parathyroid hyperplasia even 5 years after successful renal homotransplantation in spite of continuously normal ionised serum calcium levels. From a practical point of view one should therefore not be too dogmatic and not hesitate to remove excessively hyperplastic parathyroid glands, particularly since the surgical risk in experienced hands is negligible. Subtotal parathyroidectomy should certainly be considered when persistent hypercalcaemia or hyperphosphataemia, refractory to aluminium hydroxide administration, render the administration of vitamin D hazardous.

Calcium Balance under Maintenance Haemodialysis

There are conflicting reports on the skeletal and whole body calcium content of dialysis patients. Both our microradiographic studies and Dr Sieberth's (Cologne) analytical data suggest a diminished mineral content of bone matrix in dialysed patients. Diminished mineral content of bone matrix might even be encountered in the presence of normal whole body calcium, if total bone matrix mass is increased. This finding would indicate the necessity of forcing the patients into positive calcium balance, be it by raising dialysate calcium levels, by oral administration of calcium or by vitamin D therapy. In contrast to oral administration of calcium, raising dialysate calcium would have the advantage of being a self limiting process, calcium transfer ceasing when a certain serum calcium level is achieved.

Calcium has to cross cell membrane barriers before it enters bone matrix. It would therefore seem questionable whether it helps to simply 'dump' calcium into an organism (as advocated by some groups) without stimulating at the same time cellular calcium pumps in bone with vitamin D.

Water Contaminants

Some evidence, unfortunately only of an indirect nature, has been brought forward to implicate unspecified water contaminants (other than fluoride) as a cause of 'rotten bone' in several dialysis centres. This, however, has not been a major problem on the Continent.

In conclusion, although it would seem premature to state that renal bone disease can entirely be prevented, we can certainly do a lot to prevent it from becoming a threat to the success of maintenance haemodialysis.
A Fournier (Amiens): Before speaking on my main topic — the use of phosphate binders — I should like to emphasise one point: the fact that the increased incidence of renal bone disease with dialysis is not due to the prolongation of life 'per se', but to the inadequacy of dialysis.

Table I. Possible Aetiologic Factors of Bone Disease during Long-Term Haemodialysis

<table>
<thead>
<tr>
<th>Aetiologic Factor</th>
<th>With bone disease</th>
<th>Without bone disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary calcium, mean ± SD (mg/day)</td>
<td>311 ± 107</td>
<td>369 ± 150</td>
</tr>
<tr>
<td>Vitamin D (IU/day)</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>Phosphate-binding agents</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>1/10</td>
<td>3/18</td>
</tr>
<tr>
<td>Bilateral nephrectomy</td>
<td>3/10</td>
<td>6/18</td>
</tr>
<tr>
<td>Duration of dialysis, mean ± SD (months)</td>
<td>18.6 ± 5.0</td>
<td>21.0 ± 5.0</td>
</tr>
<tr>
<td>Total heparin, mean and range (U x 10^5)</td>
<td>30.12 (14-57)</td>
<td>33.99 (6.5-106)</td>
</tr>
<tr>
<td>Predialysis serum creatinine, mean ± SD (mg/100ml)</td>
<td>11.9 ± 2.0</td>
<td>12 ± 2.0</td>
</tr>
<tr>
<td>Predialysis arterial pH, mean ± SD</td>
<td>7.38 ± 0.03</td>
<td>7.37 ± 0.03</td>
</tr>
<tr>
<td>Predialysis standard HCO₃⁻, mean ± SD (mEq/l)</td>
<td>21.0 ± 2.2</td>
<td>20.4 ± 1.6</td>
</tr>
<tr>
<td>Using deionised water</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regardless of dialysate calcium</td>
<td>2/10</td>
<td>12/18*</td>
</tr>
<tr>
<td>Low dialysate calcium only</td>
<td>2/9</td>
<td>1/7</td>
</tr>
<tr>
<td>Dialysate Mn, mean and range (ng/ml)</td>
<td>13.6 (5-19)</td>
<td>11.06 (6-24)</td>
</tr>
<tr>
<td>Dialysate Fe, mean and range (ng/ml)</td>
<td>62.4 (28-117)</td>
<td>52.6 (27-232)</td>
</tr>
<tr>
<td>Dialysate Mg, mean ± SD (mg/100ml)</td>
<td>1.9 ± 1</td>
<td>1.9 ± 1</td>
</tr>
<tr>
<td>Dialysate Ca Range (mg/100ml)</td>
<td>4.9-5.6</td>
<td>5.1-7.4**</td>
</tr>
<tr>
<td>≤5.6mg/100ml</td>
<td>9/10</td>
<td>7/18**</td>
</tr>
<tr>
<td>Dialysate F, range (µmoles/litre)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>5-53</td>
<td>0.5-62+</td>
</tr>
<tr>
<td>Low dialysate Ca only</td>
<td>5-52</td>
<td>1-63</td>
</tr>
<tr>
<td>Dialysate F, &gt;6µmoles/litre</td>
<td>4/7</td>
<td>2/11</td>
</tr>
<tr>
<td>All patients</td>
<td>3/6</td>
<td>2/5</td>
</tr>
<tr>
<td>Low dialysate Ca only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum F, range (µmoles/litre)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>1-36</td>
<td>0-10.2</td>
</tr>
<tr>
<td>Low dialysate Ca only</td>
<td>1-10.5</td>
<td>0-10.2</td>
</tr>
</tbody>
</table>

* for difference between groups, P < 0.02
** for difference between groups, P < 0.05
† for difference between groups, P = 0.05
Table I shows the possible aetiological factors of long term haemodialysis in two groups of patients — one with bone disease and one without (Fournier et al, 1971). The duration of dialysis was longer in the group without bone disease, and therefore it can be said from this data that the length of time on dialysis is not a parameter involved in the appearance of renal bone disease. With regard to the other parameters, the only one of significance is the dialysate concentration of calcium.

![Figure 3. Dialysate calcium, mean values, mg/100ml](image)

Figure 3 shows that all the patients with bone disease were dialysed with a calcium of less than 6.0mg/100ml with the exception of one patient who had toxic levels of fluoride in the serum. In Figure 4 it can be seen that dialysate calcium is not the only important aetiological factor in the appearance of bone disease, but that phosphate control may also be of importance since the level of phosphate between dialyses has a definite effect on the level of PTH. The variation of PTH is such that when the patients were first dialysed against a calcium of 6.5mg/100ml the decrease of phosphate from above 6.0mg/100ml to less than 6.0mg/100ml was accompanied by decrease in serum PTH. This fact was also true when patients were dialysed on a low dialysate calcium. Therefore it would appear to be advisable to use phosphate binders to decrease the PTH in these patients.

It has been shown in bone tissue culture, that decreasing the phosphate concentration in the culture medium increased the bone resorption induced by PTH. Clearly not a beneficial effect. With the aid of Bourdier we performed two successive bone biopsies in each of 13 patients who were on chronic haemodialysis. Five of these patients were controls, and eight patients had been given phosphate binders which had decreased their mean predialysis
blood phosphate from about 8.3 to 6.0 mg/100 ml. When we compared these two groups with regard to their bone parameters, we found that the only significant difference was the degree of bone resorption surface, and we reported this fact last year. We looked more carefully at the data we had collected and found that there was another factor which could explain the results. What we had omitted was the fact that out of the total of 13 patients 9 had been nephrectomised — the rest had not. Table II shows that the 13

Table II. The Effect of Aluminium Hydroxide and Bilateral Nephrectomy on Resorption Surface

<table>
<thead>
<tr>
<th>Bilateral Nephrectomy</th>
<th>No Nephrectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>With aluminium hydroxide n = 6</td>
<td>No aluminium hydroxide n = 3</td>
</tr>
<tr>
<td>Resorption surface (RS₂% - RS₁%)</td>
<td>-10.6</td>
</tr>
</tbody>
</table>

patients can be divided into four groups. Those patients who did not have a bilateral nephrectomy did not show an increase in bone resorption surface.
However, in 6 of the 9 patients who had been nephrectomised and were taking aluminium hydroxide to decrease their plasma phosphate, there was significant increase in bone resorption surface. Figure 5 shows that the effect of aluminium hydroxide is related to the decrease of plasma phosphate. The almost horizontal curve is the regression line for the 4 patients who had not been bilaterally nephrectomised: this is not significant. With regard to the 9 nephrectomised patients, it can be seen that there is a negative correlation between resorption surface and the change in plasma phosphate. These facts give rise to two problems: the first a theoretical one. There is no firm explanation, but recent findings, by Rasmussen and De Luca, confirm that the conversion of 25-hydroxycholecalciferol into 1,25 DHCC is favoured not only by PTH but also by decreasing plasma phosphate.*

In those patients who retain their kidneys, a decrease in plasma phosphate will increase the production of 1,25 DHCC which will improve calcium absorption by the gut, increase the calcium in the blood and induce a better degree of suppression of PTH. This would counterbalance the increased resorption induced by phosphate depletion per se. When there are no kidneys,

*Ed. Note. De Luca actually claimed that renal tubular intracellular calcium was the relevant parameter
a decrease in plasma phosphate will not induce an increase in 1, 25 DHCC; only the effect of phosphate depletion, namely increased resorption, will be present. The support for these theoretical explanations is that we observed an increase in plasma calcium only in patients with two kidneys, suggesting that the increase in calcium was due to better gut absorption (Figures 6, 7).

The second problem is the practical one. There is no problem in suppressing the parathyroid glands in patients with their own kidneys, but a higher dialysate calcium should be used after nephrectomy. The patients in our group were dialysed with a calcium concentration of 6.3mg/100ml and not of 7.0 or 8.0mg/100ml.

S G MASSRY (USA): Secondary hyperplasia of the parathyroid gland is one of the major derangements which underlie renal osteodystrophy in patients with renal failure. The prevention or treatment of this abnormality will play a major role in the control of renal osteodystrophy. It is now accepted that the main factor leading to secondary hyperplasia in these patients is hypocalcaemia, but the mechanisms which lead to the fall in serum calcium are not fully understood. The elucidation of these mechanisms will help to design a more rational approach to the prevention of secondary hyperparathyroidism.
Slatopolsky and his collaborators clearly demonstrated the importance of phosphate retention and provided evidence in animals indicating that the reduction in dietary phosphate in proportion to the degree of renal failure can prevent secondary hyperparathyroidism. However, other clinical data suggests that phosphate retention cannot be the only factor responsible for hypocalcaemia. We have recently reported in detail studies demonstrating skeletal resistance to the action of parathyroid hormone in patients with early and advanced renal failure, and in patients who are treated with haemodialysis. This resistance may be another factor in the development of hypocalcaemia.

In our studies we chose patients suffering from acute renal failure since the fact that they are normal, become uraemic and then become normal again is a natural experiment. In a recent study of serum calcium in 10 patients with acute renal failure every patient was hypocalcaemia — often severely so — and this hypocalcaemia was noted very early in the course of the renal failure, during the oliguric phase. The majority remained hypocalcaemic during the diuretic phase, serum calcium returning to normal during recovery.

Hyperphosphataemia also occurred during the oliguric phase, but there were some patients who had a normal serum phosphorus during this phase. One patient even became hypophosphataemic.

During the oliguric phase, hypocalcaemia was consistently present, despite hyperphosphataemia or a normal plasma phosphate. In the diuretic phase, hypocalcaemia occurred whether the patient had normal serum phosphate, hypophosphataemia or hyperphosphataemia. These data suggest that the hypocalcaemia cannot be explained solely on the basis of the hyperphosphataemia.

A further possibility was that the parathyroid gland may have failed to function. However, the levels of parathyroid hormone were elevated in these patients during the oliguric and diuretic phases, returning to normal during recovery. The elevation of PTH may not have been appropriate to the degree of hypocalcaemia. A correlation between the levels of parathyroid hormone and serum calcium showed that there was an inverse correlation between these two parameters, and the data were consistent with expected normal physiological relationships. The data therefore indicated that neither hyperphosphataemia nor complete or partial failure of the parathyroid gland could account for the hypocalcaemia. The question of resistance to parathyroid hormone therefore remained to be investigated. In 11 normal patients in whom parathyroid extract was infused, there was a rise in serum calcium — the mean increase being about 1.5mg/100ml. The same patients, given the same parathyroid hormone extract during the oliguric or diuretic phase, had no change in serum calcium. The lack of response was not due to low concentrations of parathyroid hormone in the blood: there was a 30 to 40 times increase above normal. On recovery of renal function, the response to
parathyroid hormone was normal.

The cause of resistance to parathyroid hormone remains unknown, but it is possible that the acutely diseased kidney may not convert vitamin D to its active metabolite 1,25 DHCC. This point is being studied now and two patients who have received one week's treatment with 1,25 DHCC were not resistant to parathyroid hormone.

Further, during these experiments by raising the serum calcium, a fall in serum parathyroid hormone was caused.

M KAYE (Montreal): We believe that bone disease due to renal failure is largely preventable. Phosphate has already been discussed and I will not refer to it further, nor will I discuss the avoidance of fluoride intoxication.

Intestinal calcium transport is both active (when mediated by 1,25 DHCC) and passive. We believe that the active transport is depressed in renal failure, whereas the passive transport is relatively unaffected and is purely concentration dependent. We found that as dietary calcium intake increases above about 7g/day, all the patients studied passed into positive calcium balance, with the exception of one. These patients were all on dialysis and were presumably not forming 1,25 DHCC at all. What effect does this oral calcium have? It has an important effect in the intestine in decreasing phosphate absorption with the decreased plasma phosphate leading, in turn, to an increase in ionised calcium. At the same time an increase in calcium absorption presumably leads to a fall in PTH levels, and to increased mineralisation. Therefore, we consider that the amount of oral calcium is fundamental in the conservative management of prevention of bone disease.

In those patients who have reached dialysis, as Fournier and the group from the Mayo Clinic have shown, the level of the dialysate calcium is of vital importance too. In my opinion by concentrating on these fairly simple rules, dialysis bone disease can be prevented.

Nothing that I have said is new, but I think that the application of these principles has not been universal.

W J JOHNSON (USA): I am inclined to agree with Dr Ritz's statement that current techniques of therapy cannot prevent renal bone disease entirely. On the other hand, much can be done to prevent development of rapidly progressive secondary hyperparathyroidism and symptomatic osteitis fibrosa. Relatively simples measures, instituted as early as possible, will maintain serum calcium and phosphate values within the normal range during the entire period of decompensated renal failure and maintenance dialysis.

During the past ten years I have participated in the treatment of over 200 patients undergoing haemodialysis. Of this group, 170 subsequently have undergone renal transplantation, and 120 of these patients have func-
tioning renal grafts. During this period, 5 patients have undergone parathyroidectomy for secondary hyperparathyroidism, an overall incidence of only 2.5%.

From these 200 patients, I have selected 57 who were not exposed to dialysate containing fluoride and who were maintained by haemodialysis for a minimum of six months. Reasonably complete studies were available on all of these patients.

Table III. Haemodialysis, > 6 months (fluoride-free dialysate)

<table>
<thead>
<tr>
<th></th>
<th>Without bone disease*</th>
<th>With bone disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td>Number of patients</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Dialysis, months</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td>Dialysate calcium, mg/100ml</td>
<td>5.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Serum calcium, mg/100ml</td>
<td>9.5</td>
<td>8.6</td>
</tr>
<tr>
<td>Serum phosphate, mg/100ml</td>
<td>7.4</td>
<td>6.6</td>
</tr>
<tr>
<td>(Calcium) x (Phosphate)</td>
<td>70</td>
<td>57</td>
</tr>
</tbody>
</table>

* at onset of treatment

Table III shows these patients divided into four groups depending on the calcium concentration of the dialysate and on whether or not radiographically apparent bone disease was present when they entered the programme. Groups 1, 2, and 3 did not have subperiosteal bone resorption when they began dialysis therapy. They were treated with dialysate calcium concentrations of 5.3, 6.1 and 7.4 mg/100ml. Group 4 included patients with obvious, and in some cases severe, osteitis fibrosa at the beginning of dialysis. These patients were treated with dialysate calcium concentrations of 7.2 mg/100ml. Serum phosphate was not controlled in the first two groups; in groups 3 and 4, aluminium hydroxide and aluminium carbonate were given orally in order to maintain serum phosphate values within the normal range.

I would like to call your attention to the mean serum calcium and phosphate values during the last 3 months of therapy. The serum calcium value is normal in group 1, below normal in group 2, and normal in groups 3 and 4. We believe that, with a low dialysate calcium concentration, predialysis serum calcium tends to increase progressively because of increasingly severe bone resorption. You will note also that the calcium-phosphate solubility product is substantially higher in group 1 than in the other groups, tending to favour metastatic calcification. In groups 3 and 4, the treatment restored both serum calcium and serum phosphate levels to nearly normal values.
Table IV. Haemodialysis, > 6 months (fluoride-free dialysate)

<table>
<thead>
<tr>
<th>Changes during treatment</th>
<th>Without bone disease*</th>
<th>With bone disease Group 4 (D. Ca = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (D. Ca = 5)</td>
<td>Group 2 (D. Ca = 6)</td>
</tr>
<tr>
<td>Rise in serum alkaline phosphatase</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Fall in serum parathyroid hormone</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bone or joint pain</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>Soft tissue calcification</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Band keratopathy</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>Subperiosteal bone resorption</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Improved subperiosteal bone resorption</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fractures</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Parathyroidectomy</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

* at onset of treatment
D. Ca = dialysate calcium mg/100ml

After treatment for 19 to 27 months (Table IV), the following results were obtained. In patients treated with dialysate calcium concentration of 5mg/100ml and no oral phosphate binders, symptomatic bone disease developed rapidly and there was a high incidence of soft tissue calcification; one patient required parathyroidectomy after renal transplantation. One-third of the patients developed spontaneous rib fractures.

In group 2, only one patient developed symptomatic bone disease. This patient subsequently required subtotal parathyroidectomy after renal transplantation. The incidence of metastatic calcification was lowest in this group.

In group 3, most of the patients showed striking improvement in serum parathyroid hormone concentrations, and in 4 patients the values actually fell into the normal range. Alkaline phosphatase values also remained normal in almost all patients. Symptoms of bone disease and radiographically apparent subperiosteal bone resorption did not develop. Two patients, however, experienced fractures — a spontaneous asymptomatic rib fracture in one and a minor compression fracture of lumbar vertebrae in the other.

In group 4, although all the patients had obvious bone disease at the onset of dialysis, serum parathyroid hormone concentrations and the appearance of the bony lesions showed improvement in 62% of the patients, while
in the remaining patients neither aspect of the disease showed evidence of worsening. Two patients experienced minor traumatic fractures during the period of treatment. None of the 37 patients treated on the high calcium low phosphate regimen have required parathyroidectomy or treatment for fractures.

Figure 8. Improvement in subperiosteal bone resorption after haemodialysis with a dialysate calcium concentration of 7.5mg/100ml.
(With permission of the Editor Mayo Clinic Proceedings 1972 47, 110. Vosik et al)

Figure 8 shows the fingers of a patient who had severe bone resorption at the beginning of dialysis. You will note the striking improvement that was achieved after six months of dialysis with a high dialysate calcium concentration after serum phosphate values were brought under control. Similar improvement occurred in 8 other patients within three months after serum calcium and phosphate values were restored to normal.
Figure 9. Effect of dialysate calcium concentration on bone resorption

Summarised in Figure 9 are results of microradiographic studies of bone biopsies obtained before dialysis and after a period of dialysis with three dialysate calcium concentrations: 5, 6 and 7mg/100ml. The patients biopsied included those with the most severe bone disease. While bone resorption increased on the low dialysate calcium regimen, it decreased with the intermediate regimen. When the dialysate calcium concentration was increased to 7mg/100ml and serum phosphate values were lowered, bone resorption did not decrease as consistently in all patients. These results are inconclusive because of the small number of patients studied in each group. But they suggest that the microradiographic technique apparently did not demonstrate, in this group of patients with severe hyperparathyroidism, the beneficial effects that were shown in most patients with milder disease, by measurements of parathyroid hormone and serial radiographs of the skeleton.

Suppression of parathyroid hormone secretion, however, provides benefits beyond the period of dialysis therapy, as shown in Figure 10. Serum immunoreactive parathyroid hormone concentrations are shown for individual patients immediately before successful renal transplantation and at variable periods afterwards. You will note that patients showing the highest immunoreactive parathyroid hormone concentrations preoperatively were the ones
who had persistent increases in immunoreactive parathyroid hormone for as long as a year after transplantation.

In contrast, the patient whose values are shown in Figure 11 was well controlled on dialysis as indicated by serum calcium and phosphate values that, for the most part, fell in the normal range and by the striking decrease in immunoreactive parathyroid hormone concentrations. After renal transplantation, the patient actually showed mild hypocalcaemia rather than the expected hypercalcaemia; severe hypophosphataemia did not develop, and serum immunoreactive parathyroid hormone concentrations quickly returned to normal.

Our experience indicates that maintenance of normal serum calcium and phosphate values resulted in:

1. A decrease in serum immunoreactive parathyroid hormone concentrations, in some cases into the normal range during dialysis, and a more rapid return of hormone values toward normal after renal transplantation.
2. Prevention or reversal of radiographic evidence of subperiosteal bone resorption in most patients.

3. Avoidance of the need for parathyroidectomy in all but a small number of patients (2.5%).

4. Avoidance of any appreciable increase in soft tissue calcification.

We believe, therefore, that decreasing the serum phosphate level and correcting the calcium deficiency are important factors in correcting dialysis osteodystrophy.

D N S KERR (Newcastle upon Tyne): The incidence of bone disease reported from different dialysis centres varies widely (Fournier, 1971; Siddiqui & Kerr, 1971). Most of this variation is accounted for by asymptomatic hyperparathyroidism, detected on skeletal surveys and explained by inadequate control of plasma phosphate. Before we made serious efforts to control plasma phosphate, we had mild hyperparathyroidism in most of our patients on dialysis, the grade of osteitis fibrosa in individual bone biopsies correlating with the duration of dialysis. Osteitis did not progress but neither did it heal. We have since shown that aluminium hydroxide administration controls the plasma level of immunoreactive PTH and reduces the histological evidence of hyperparathyroidism in most patients (Hill et al, 1973).
Nonetheless, we have a serious bone disease problem, and the comparison with Birmingham reported to this society two years ago (Siddiqui et al, 1971) confirmed that we have it worse than most other centres. That study also showed that bone pain and pathological fractures were associated with radiological evidence of osteomalacia and osteoporosis, not of hyperparathyroidism. Osteomalacia increases with time on dialysis and only becomes a significant problem from the third year of dialysis onwards. This was also the conclusion drawn by Ritz (1972) from the collaborative study of German patients. In our centre, patients are treated conventionally with 27 to 30 hours of Kiil dialysis at a bathwater calcium level of 6mg/100ml — techniques which appear to protect the patients of Birmingham and some London centres. Dr Moorhead has told us at this conference that the Royal Free Hospital, which once seemed immune, is now seeing osteomalacia, but it remains a more slowly progressive disease than in Newcastle.*

This susceptibility of our patients which is also shared by those in Sheffield, Plymouth and South Wales, led us to speculate that some metabolic poison might be absorbed from our tap water which inhibited calcification of osteoid as Dr Ritz mentioned. We described here two years ago, one patient who made a remarkable clinical recovery and healed all her 32 indolent fractures when her dialysate fluid was made with distilled water in place of base softened water. She has since died and study of her healed fractures shows that they were filled with poorly calcified osteoid.

In the meantime, however, we had started further patients on treatment with deionised water dialysate. Five of the first six reported marked clinical improvement and another patient healed long standing fractures of her femoral necks (Posen et al, 1971). Unfortunately, the success story ends there. We have now treated 27 patients for an average of six months with deionised water dialysate and have obtained bone biopsies large enough for quantitative

Table V. Changes in bone histology after an average of 6 months' treatment with dialysis fluid made from distilled or deionised water in 27 patients. Aluminium hydroxide, calcium salts and vitamin D and its analogues were not administered. Quantitative bone histology was performed as described by Ellis and Peart (1973)

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>2p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Osteitis fibrosa Grade 0-5</strong></td>
<td>1.63</td>
<td>1.46</td>
<td>0.3&gt;2p&gt;0.2</td>
</tr>
<tr>
<td><strong>Osteomalacia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamellae</td>
<td>5.93</td>
<td>6.59</td>
<td>0.3&lt;2p&lt;0.4</td>
</tr>
<tr>
<td>% Mineralisation</td>
<td>87.9</td>
<td>85.8</td>
<td>0.3&lt;2p&lt;0.4</td>
</tr>
<tr>
<td><strong>Osteoporosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mineralised bone are (% field)</td>
<td>21.2</td>
<td>20.3</td>
<td>0.5&gt;2p&gt;0.4</td>
</tr>
</tbody>
</table>

*Today we heard that it takes 9 years for the average patient at the Royal Free Hospital to develop fractures; in Newcastle it takes 3 years.
analysis before and after treatment. Table V shows that there is no histo-
logical evidence of improvement. The grade of osteitis fibrosa fell very
slightly but osteomalacia, judged by the number of birefringent lamellae or
by the percentage of unmineralised bone, and osteoporosis, shown by the
area of mineralised bone, both got worse. None of these differences is sig-
nificant at the 5% level, but they follow trends which are also apparent in our
patients treated with softened water. Whatever may be the explanation for
the symptomatic relief and accelerated healing of fractures seen in a few
patients, it does not appear to be due to healing of the osteomalacia.

It might be argued that six months was not long enough. However, we
have shown that this is long enough to reduce the plasma level of fluoride to
normal so it should provide an opportunity to remove any other readily avail-
able solute.

Moreover, many of these patients have continued on deionised water after
the end of our six months' trial, while receiving dihydrotachysterol, phos-
phate binders, and other agents under test. They have not so far shown any
histological improvement. Indeed, the only patients in whom we have ever
seen osteomalacia heal after the start of regular dialysis, are those who
have received a successful transplant.

My answer to the question "Can dialysis bone disease be prevented?"
must remain "No".

H H MALLUCHE (Germany): I would like to make a few comments on the
value of bone biopsy for diagnosis of renal bone disease. There are two
alternatives to bone biopsy that give complementary and limited information:
one is biochemical and the other is radiological. The correlation of serum
biochemistry and tissue abnormalities is rather poor. There is a certain
relationship between the degree of hypocalcaemia and the amount of osteoid
in the skeleton; in addition, elevated levels of serum alkaline phosphatase
correlate with the number of osteoblasts, irrespective of the underlying
pathology, be it osteomalacia or osteitis fibrosa (OF). However, no signi-
ficant correlation between the degree of OF and serum calcium levels has
ever been reported.

X-rays of the skeleton may give very valuable information when inter-
preted correctly. However, whereas the X-ray appearances are primarily
determined by the state of cortical bone, bone biopsy gives information on
cancellous bone. As a consequence of its higher turnover rate, metabolic
changes in the skeleton are reflected earlier and faster in cancellous bone.
In addition in cortical bone signs of endosteal and Haversian resorption are
evidence of the cumulative past history of the skeleton, whereas the actual
state of bone histology is more truly reflected in cancellous bone. Lastly,

apart from Looser's zones, there are no radiological signs specific for
osteomalacia, whereas the degree of osteomalacia is closely reflected in iliac crest histology.

All these arguments point to the value of the information obtained by bone histology. Since clinical symptoms can only be expected when a considerable fraction of the healthy skeleton which existed before the onset of renal failure has been destroyed, the value of an early assessment of the degree of bone pathology that can be obtained by bone biopsy is quite obvious. What kind of information can we reasonably expect from bone histology?

We get information firstly on bone mass, secondly on the intensity of OF, and thirdly on the presence or absence of a mineralisation block, in other words of osteomalacia. The presence or absence of osteosclerosis or osteoporosis can be judged from the volumetric density, ie from the percentage of spongiosa volume represented by cancellous trabeculae. The effect of hyperparathyroidism upon the skeleton is reflected by the degree of renal osteodystrophy, in other words, the extent of endosteal fibrosis (Figure 12) and the intensity of osteoclastic bone resorption (Figure 13).

In order to assess adequately the degree of parathyroid hormone activity,
both changes at the endosteal surfaces of the trabeculae and the much neglected changes of osteocytes within bone trabeculae should be evaluated. Activation of osteocytes and osteoclastic resorption had been shown to correlate with serum PTH levels. Assessing the degree of OF is of paramount importance for the correct indication of vitamin D therapy or subtotal parathyroidectomy.
As far as osteomalacia is concerned (Figure 14), I would like to emphasise that the total amount of osteoid does not reflect the degree of the mineralisation block, as incorrectly assumed by others. The total amount of osteoid is determined both by the birth rate of osteoid seams, which is elevated for instance in hyperparathyroidism even without any osteomalacia, and by the life span of the individual osteoid seams, which is prolonged in osteomalacia. The point I want to make is that in order to judge the severity of osteomalacia we must have some additional information on the rate of bone mineralisation, which can be easily obtained by in vivo staining of the mineralisation front with tetracycline.

Finally, let me answer some practical questions for the nephrologists.

**How should we biopsy?** I prefer to use Burkhard's electric drill with which samples are taken from the iliac crest (Figure 15).

![Image showing a bone biopsy procedure](image)

**Figure 15.** Between the drill and the pincette one sees a 3cm long cylinder with a diameter of 0.5cm which has just been removed.

**How should bone biopsies be assessed?** It is vitally important to study undecalcified bone sections. It is useless to try to evaluate decalcified bone sections. Sections should be embedded in plastic and stained with techniques that permit differentiation of mineralised and non-mineralised bone, such as van Kossa or Masson-Goldner. This is of obvious importance for the diagnosis of osteomalacia.

**When should we perform a biopsy?** A bone biopsy is routinely performed in our unit during the phase of conservative treatment of advanced renal failure, or as soon as possible after haemodialysis is started. In my view, repeat
bone biopsies are indicated to be able to assess results of therapy or when changes in therapy are in question.

S SHALDON (London): We have heard Drs Ritz, Fournier and Massry discuss physiological disturbances, and then we heard about the practical management of dialysis patients, finally returning to diagnosis and prevention. We appeared to lose vitamin D after Dr Massry, but we found it again with Dr Malluche. This is rather important for two reasons: there is some experimental data in the rat which Dr Krempien and co-workers have not published, but to which I have had access. They have succeeded in producing an experimental form of rat bone disease with five-sixths bilateral nephrectomy and irradiation of the remaining one-sixth of the kidney. In doing this they have been able to prevent the development of this bone disease by the use of:

1. Phosphate binders alone
2. Phosphate binders in combination with low doses of vitamin D
3. Phosphate binders with dihydrotachysterol.

However, when they used high doses of vitamin D they produced demineralisation and advanced metastatic calcification. When they used 1,25 DHCC or 25-DHCC it produced the same result. The interesting point is that the vitamin they used is only commercially available, to the best of my knowledge, in Germany and is marketed by Merck under the name of Vigantol. It is reportedly vitamin D₃ – cholecalciferol – and it may explain some of the discrepancies when one uses the loose term 'Vitamin D' which is a commercial preparation and is not the pure vitamin. We have evidence that it is a highly dangerous, but also I think an extremely necessary drug.

W DRUKKER (Amsterdam): What is the best type of phosphate binder? Calcium carbonate might provoke hypercalcaemia, aluminium hydroxide is often not very well tolerated, and seems to be inconstant in its activity.

A FOURNIER (Amiens): I use mainly aluminium hydroxide (marketed under the name Aludrox) or a product called in France ALU 3.

SHALDON: What do you recommend in terms of weight of pure aluminium hydroxide?

FOURNIER: We use 3 to 5g: in tablet form up to 15 tablets per day.

SHALDON: Dr Johnson, have you anything to say about the latest developments in phosphate binders now commercially available in the USA?
W JOHNSON (Minnesota): There are three preparations that are produced by Wyeth: one is a liquid basogel which has three times as much aluminium carbonate, measured as aluminium oxide actually, as the standard preparation that can be bought at the drug store. We tried giving this in a single dose, which is one ounce (3g) of aluminium oxide, but this was not well tolerated. Many of the patients developed nausea and some diarrhoea, from use of this preparation. We now give it in divided doses. Another preparation is again a capsule made by Wyeth. It is well tolerated and is given in a dose of 2g three times a day, generally with meals.

S SHALDON: Dr Massry, would you care to tell us about the non-commercial preparations?

S MASSRY (Los Angeles): I think that Dr David Ogden from Tucson has reported at a recent meeting that he incorporated phosphate binders in cookies. The patients liked these cookies very much and were able to tolerate them. I personally have sampled them and found them edible. This might be a way to overcome the unpleasant taste of aluminium hydroxide.

SHALDON: The latest development I think is aluminium oxide which is reported to be ten times more potent but is not yet commercially available.

M SEGAERT (Roeselaere, Belgium): To what extent is pruritus in haemodialysis patients related to hypercalcaemia per se? Is the calcium phosphate product, or skin calcification, more important in its pathogenesis?

R VERBERCKMOES (Leuven): If pruritus is due to the calcium content of the skin, how would you explain the fact that parathyroidectomy relieves pruritus immediately?

MASSRY: First of all I do not think that pruritus in haemodialysis patients, or patients with uraemia, is due to the high calcium content in the skin. This might be a factor which predisposes to it, but it is not essential. I agree with the statement that if you perform a sub-total parathyroidectomy, the pruritus disappears immediately. Calcium in the skin which we found to be high in some patients on dialysis might become low weeks or even months after sub-total parathyroidectomy, but is still high at the time when pruritus disappears. I think that the level of serum calcium is important, because if one does a sub-total parathyroidectomy, the calcium in the blood falls within a few hours or days, and the pruritus disappears. If one treats these patients with vitamin D and gets the serum calcium back to its original level, pruritus reappears. However, it is known that hypercalcaemia due to primary hyper-
parathyroidism in non-uraemic patients will not cause pruritus so that the level of serum calcium is not the only factor. It appears to us that uraemia in combination with increased calcium in the skin might predispose to pruritus when serum calcium becomes elevated. In data has has not been published by the Peter Brent Brigham Group it is claimed that the level of magnesium might also be important.

J COBURN (Los Angeles): I should like to comment about the statements made that it is clear that you have to have a nephrectomy before failure of vitamin D conversion to 1,25 DHCC occurs. At the moment this is unknown for there are no methods available to measure 1,25 DHCC effectively. The only measurements made have been in vitamin D deficient animals using isotopic tracers, so that one does not know how much is being produced. It is therefore premature to state that kidney tissue has to be absent before 1,25 DHCC is decreased. Reduced kidney mass, kidney disease or some metabolic factor in uraemia may also be involved.

C van YPERSELE (Louvain): Could the speakers comment on the possibility that altered Vitamin metabolism in liver disease plays a role in the bone disease of uraemic patients?

SHALDON: In my opinion, yes.

RITZ: It is purely speculative, but it would confirm our clinical impression. There are various explanations for it, but my clinical impression is that there is a definite correlation between the two.

SHALDON: For those of you who are not quite clear as to the implication of this, it is that if the liver is diseased the ability to produce the active metabolite of the vitamin may be impaired, and that the first stage in the production of active metabolites of vitamin D would appear to be the liver and not the kidney. Would any of the panel like to comment on this?

MASSRY: I think that there is some data in experimental animals which shows that 25-HCC is lower when uraemia is induced. However there is data in humans to suggest that 25-HCC is normal or sometimes elevated. The answer to whether there is a disturbance in the first stage conversion of vitamin D is still not settled.

B ROBINSON (Birmingham, UK): The conclusions of Dr Kaye about calcium balance conflict with our observations that bone disease during dialysis can progress in spite of positive calcium balance as measured by whole body
neutron activation. Would he care to comment? Would the panel comment on the role of magnesium in bone disease and optimum dialysate levels of magnesium?

Z VARGHESE (London): What was the plasma magnesium during the diuretic phase of Dr Massry’s acute experiments?

E MacSEARRAIGH (Eire): We hear much about the role of calcium; what about the low magnesium in ectopic calcification?

M KAYE (Montreal): Regarding the question by Dr Robinson, there is no doubt about the value of positive calcium balance. You have two other factors, phosphate and fluoride, and my remarks on calcium are only valid if the phosphate is controlled and you are not exposed to toxic levels of fluoride.

SHALDON: Would Professor Kerr and/or Dr Johnson care to comment on the magnesium levels?

D N S KERR (Newcastle upon Tyne): We do have by accident some data on magnesium in bone disease. We had two parallel groups of patients, one of which was treated by chance with a magnesium concentration of 1mg/100ml in the dialysis fluid and another group which was treated with a level of 1.9mg/100ml. This was due to two different commercial sources of our dialysate fluid, and there was very little difference in the incidence of bone disease between these two groups. There was no difference in the incidence of osteomalacia, pain or fractures. There is a slight, not quite significant difference in several parameters of hyperparathyroidism suggesting that the group with the high magnesium dialysis fluid, all of whom have hypermagnesaemia, have slightly less hyperparathyroidism. In acute experiments the use of a very high magnesium dialysis fluid as Pletka and his colleagues showed, does depress PTH levels, although nothing like as dramatically as a change in dialysis calcium.

F MARSH (London): Is there any reason to suppose that 1,25 DHCC is more effective than AT 10 in the treatment of renal osteodystrophy?

KAYE: Could I please suggest that we stop using the term AT 10? We should be talking about dihyrotachysterol either 2 or 3.

I do not know the answer to that question. I think that we will have to wait until Drs Coburn and Massry have more data available on the long term use of 1,25 DHCC. It may be too dangerous — it may be ideal.
J LEVI (israel): Would the panel tell us what concentration of ionised calcium should be used in the dialysis fluid of patients on dialysis today?

MALLUCHE: When we raised the dialysate calcium from 3.0 to 3.75mEq/l calcium concentration rose to 3.5 to 4.3mEq/l. In only one patient did we see a remission of the mineralisation block as well as a lessening of PTH effect on the skeleton. All other patients showed no decrease and in some patients there was an increase in PTH activity on iliac crest histology.

SHALDON: Could you please restate what the level of your dialysate calcium was for the benefit of the audience.

MALLUCHE: The levels were 3.5 to 4.3mEq/l.

SHALDON: That is, 7.0 to 8.6mg/100ml.

JOHNSON: We have data on percent bone resorption in patients on three different concentrations — 5.0, 6.0 and 7.0mg/100ml. The percent of bone resorption, determined by the microradiographic technique of Jowsey, increased on the low calcium regime and decreased on the intermediate calcium regimen. There was no substantial decrease in resorption at the high calcium dialysate level (7.0mg/100ml). The comparison of groups on dialysate calci- ums of 6.0 and 7.0mg/100ml did not show a significant difference. I therefore feel that our information is inconclusive as far as bone resorption is concerned.

SHALDON: We still do not have the answer yet: should the calcium level be tailored to the patient or should they all have a high dialysate calcium?

KERR: I do not think that it is generally known, but the centre which has re- ported the lowest incidence in England is the Fulham Hospital, where they use a level of 6.0mg/100ml.

MASSRY: There is a tendency now to use 8.0mg/100ml because it suppresses PTH levels. We have measured soft tissue calcification in patients who have dialysed for one year on 8.0mg/100ml; in all cases the skin calcium was raised by two to three times, which indicates that the long term use of this level of calcium may be very dangerous.

SHALDON: Did you control phosphates?

MASSRY: We did not, but hypercalcaemia per se can produce soft tissue
calcification even in primary hyperparathyroidism where phosphate is very low.

SHALDON: What is it deposited as?

MASSRY: I wish I knew.

F PECCHINI (Sazurra, Italy): Do you not think that we are able to evaluate bone mass by radiological measurements in long bones?

MALLUCHE: I think that there are problems of methodology and microradiography. In our experience it is difficult to judge osteoid cell activity from radiography where you do not see the cells, but only the traces of cellular activity on the mineral surface. I feel that it is better to look at the cells rather than to rely on indirect evidence of cellular activity.

RITZ: On the magnesium question. There have been claims that serum PTH levels can be lowered by raising the magnesium levels. It has been clearly shown that one is able to stop the secretory release of preformed PTH by magnesium. We were unable to find long term suppression of serum PTH levels in patients dialysed against 2.3mEq/l of magnesium, when adequate calcium concentrations were used in the dialysate at the same time. I would hesitate to advocate raising the dialysate magnesium for an effect which has not been clearly shown up to now.

P H BAGROS (Tours): What is the incidence of hypercalcaemia when one is giving calcium and vitamin D, and patients are already hyperparathyroid?

FOURNIER: In 5 out of 15 patients on dialysis for one year we were surprised to see an increasing serum calcium, and when I realised that these patients, since commencing dialysis, had been receiving 2,000 units of vitamin D and oral calcium supplement of between three and six calcium tablets per day. We stopped this, and within one month calcium level was normal.

W R CATTELL (London): Would the panel comment on the pathogenesis of proximal myopathy in the presence of normocalcaemia in patients with minimal radiological evidence of bone disease?

RITZ: We were interested to discover a few months ago an experiment in which we could study cellular calcium paths without isolating osteocytes, and we studied the sarcoplasmonic reticulum in striated muscles of uraemic rabbits. We found a significant decrease in the pumping activity. We also found a
delay in repolarisation in the proximal musculature of uraemic animals. Surprisingly, there is no response whatsoever to 1,25 DHCC and I think that one has to distinguish clearly two entities in uraemia:

1. The vitamin D dependent proximal myopathy which has been clearly described.

2. An additional, 'toxic' myopathy - occurring in the proximal musculature which is unresponsive to vitamin D.

V ANDREUCCI (Parma): Dr Shaldon, could you give us your opinion on the ideal calcium concentration in the dialysate?

SHALDON: I do not know. I am sure that Dr Massry's warning is correct, and that we should be going down, although I am not sure how low.

N POKROY (Kfar Saba, Israel): Has any member of the panel any suggestions as to why the serum calcium falls when the phosphate rises?

MASSRY: I think that there is no doubt that a rise in serum phosphate can produce a fall in serum calcium, probably based on physico-chemical equilibria between blood and the shell of the bone. I think that this is probably an important thing, but I do not think that the hypocalcaemia of renal failure can be completely explained by the phosphate.

FOURNIER: I do not think that the dialysate concentration of calcium should go below 6.0mg/100ml. I have no special comment to make on the fall in serum calcium as phosphate rises.

KAYE: I think that this is a fundamental question: I do not agree with Dr Massry. It is not a straight physico-chemical process, and there is nobody to my knowledge who has the answer.

KERR: There must be at least two mechanisms: if you infuse phosphate acutely, calcium always falls, as Dr Massry suggested. If you manipulate phosphate, calcium does not respond predictably. In some patients to whom you give too much aluminium hydroxide serum phosphate falls below 1mg/100ml: they do not get hypercalcaemia. In other patients when you drop the phosphate, the serum goes up to 12 or 13mg/100ml; when you let the phosphate rise, the calcium comes down again.

FOURNIER: One explanation of the decrease of plasma calcium when phosphate rises, according to recent work, would be that increasing phosphate
will induce a transformation of the osteoclasts into osteoblasts, thereby increasing bone formation.

KAYE: This is not a haphazard phenomenon: the problem in man is that there are so many things happening at the same time, but if you take rats with renal failure and put them on varying phosphate intakes there is a linear relationship between ionised calcium in the blood and the level of phosphate. If you remove the parathyroids, the same phenomenon is observed.

RITZ: I think that we are in the happy position that every one of the panellists is right. I think that Dr Massry is right, there is a physico-chemical equilibrium. However, as soon as you disturb a regulated system in the organism, there will be a reaction and it depends on the degree of the reaction — the reaction in this case being secondary hyperparathyroidism, whether the calcium rises, goes down, or stays within the normal range.

JOHNSON: We have observed two patients in whom we lowered the phosphate levels when they commenced haemodialysis. They then became severely hypercalcaemic — serum calcium levels rose to 14.0, 15.0 and 16.0mg/100ml and the onset of hypercalcaemia seems to occur coincidently with the rapid lowering of the serum phosphate level. Serum thyrocalcitonin levels were high. We have no explanation for the high calciums and two of the patients had to have parathyroidectomy for severe hypercalcaemia.

Another observation that has been made is the transfer rate of calcium across the dialysing membrane — and this is affected by the concentration of serum phosphate. We do not know whether this is related to the binding of calcium to the membrane or some other factor, but this could explain some of the peculiar changes seen in patients who are on dialysis, and may become hypercalcaemic on a dialysate calcium concentration of 6.0 - 7.0mg/100ml when the serum phosphate level is extremely low.

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PART IV
METABOLIC ASPECTS OF URAEMIA
Chairman: Professor Dr R K A Kluthe