ROUND TABLE DISCUSSION

SHALDON (London): An additional monitor can be fixed on the venous bubble trap. A device under development which is based on the weight of the bubble trap will, I think, prove the most suitable. However I think you can over-monitor the system. As long as you are monitoring the pressure upstream of the pump and this controls the pump, I do not see how you can get an air embolus—but I could be wrong!

MEYEROVIC (Paris): We had experience of 26 fistulas. Clotting sometimes occurred early—in the first few hours or days. We had two successes in declotting by inserting a small catheter into the vein and flushing it with a constant infusion of streptokinase.

I have a question about infection of fistulas. We had a patient who received a heavily contaminated unit of blood and developed sepsis which was cured; six months later the blood flow in the fistula suddenly increased, without fever or any other sign of sepsis. We removed the fistula because of heart failure and found bacterial contamination inside the fistula, the equivalent of an Osler's endocarditis. Has any panel member any experience of infection without direct introduction and with a sudden increase in blood flow as the only manifestation?

CONTE (Toulouse): Chez un de nos malades décédé d'une septicémie à pyocyanique la fistule artério-veineuse donnait une culture pure et abondante de pyocyanique.

The CHAIRMAN: Time is up. I thank all the panellists and I think it is fair to summarise by saying that we are all agreed that the fistula is a notable advance in dialysis technique.

DISTURBANCES OF CALCIUM METABOLISM IN TRANSPLANTED PATIENTS AND PATIENTS ON MAINTENANCE HAEMODIALYSIS

Chairman: Dr. A. R. HARRISON, London

The CHAIRMAN: This is a very large, fascinating and mysterious subject which we cannot possibly deal with completely. We are going to discuss two topics: the influence of regular dialysis on calcium and bone metabolism and the problems created by the development of autonomous (or tertiary) hyperparathyroidism in patients who have undergone successful renal homotransplantation.

To turn to the first of these topics, Dr. Curtis has already described findings indicating that regular dialysis can have a beneficial effect on these metabolic disturbances, but some members of this panel may have evidence which points in a different direction. I shall start by asking Dr. Kaye and then Dr. Schorr to discuss their experiences of these problems.

KAYE (Montreal): For the purpose of this presentation we reviewed the clinical, radiological and histological data from 28 patients on our programme. X-rays were available from all, and there were 24 bone biopsies in 20 patients. I shall confine my remarks to hyperparathyroidism.

None of these patients had symptomatic bone disease; none had fractures; none had bone pain. The majority of patients have histological evidence of osteitis fibrosa by the time they start dialysis. This agrees with the findings of Berson and Yalow who showed that the plasma
level of parathyroid hormone was always elevated in chronic renal disease when the BUN was over 50 mg/100 ml. There is a definite tendency for osteitis fibrosa to progress during the course of chronic dialysis treatment. This progression appears to be unrelated to levels of calcium, phosphorus or anything else we have been able to measure in the serum. Measurement of plasma parathyroid hormone levels in 20 of our patients by radioimmunoassay, by Dr. John Potts at Bethesda and his collaborators, has shown elevated levels in every one of these patients. The lowest level was at least 12 times normal. The degree of elevation bears little or no relationship to the severity of the bone disease.

![Graph showing levels of Alk. P/ase, Calcium, and Phosphorus over time from 1965 to 1968.]

Fig. 1. Patient J. N. Course on dialysis over 4.5 years. B = bone biopsy.

Figure 1 shows the clinical course of a patient who has been on dialysis since December, 1965—4.5 years; he is entirely asymptomatic and works a full day. His serum calcium is usually within the normal range. His plasma phosphorus fell when the frequency of dialysis was increased. His serum alkaline phosphatase began to rise in 1966 and it has been elevated ever since. He has had two bone biopsies. Figure 2 shows his X-rays—1963 on the left, 1966 in the middle and 1967 on the right; he has developed progressive eating away of his bone

![Image of three phalanges showing bone resorption.]

Fig. 2. Middle phalanx: 1963 on the left; 1966 in the middle; and 1967 on the right. The development of subperiosteal resorption is seen on the left-hand side and disappearance of cortical bone at the right superior margin of the phalanx.
in this interval. Figure 3 illustrates the first bone biopsy which shows widened osteoid seams and some evidence of osteitis fibrosa. The second biopsy, 18 months later (Fig. 4), shows much more marked osteitis fibrosa. The osteomalacia is no longer apparent. He has more fibrous tissue, more 'scalloping' of trabeculae.

Fig. 3. Bone biopsy, February, 1966, showing osteoid seams and some osteitis fibrosa.

Fig. 4. Second bone biopsy, 18 months later shows more active osteitis fibrosa with scalloping of the bone margin.
His plasma parathyroid hormone level was 4.4 mg/ml which is about as low as any of the group and yet he has quite severe bone disease.

It seems to us that the following observations can be made:
1. Most patients have bone disease by the time dialysis is started.
2. Prolongation of life by dialysis allows the bone disease to progress.
3. The levels of serum calcium, phosphorus, magnesium, urea, etc. do not correlate well with bone disease (note that I am talking only about osteitis fibrosa, not osteomalacia or metastatic calcification).
4. All patients have hyperparathyroidism, but the factors responsible for the initiation and perpetuation of this remain poorly defined.
5. There is evidence of end organ resistance to endogenous parathyroid hormone.

**Fig. 5.** Hypothesis of the changes taking place in renal osteodystrophy as it affects parathyroid hormone activity.

Figure 5 displays our schematic concept of what is taking place. With the progression of renal failure there is the development of resistance to vitamin D and parathyroid hormone. Our own contribution to the concept is the suggestion that there is resistance to endogenous and, as we have shown many years ago, exogenous parathyroid hormone. The cause of this resistance at the cell level we do not know. It is possible that it is due to an inhibitor, or an opponent, and this is why we have put in calcitonin excess as a possibility. There is no evidence for or against this at the present time. Inhibition of bone resorption causes hypocalcaemia and osteosclerosis, which we believe is the most common lesion in renal failure. This leads to further secretion of parathyroid hormone which has a variable effect dependent upon the degree of resistance. The fact that some patients will have marked evidence of hyperparathyroidism is not due to their putting out large quantities of hormone, because all such patients are putting out large quantities of hormone. Rather it is due to lower endogenous resistance, whatever may be the cause of that.
The **Chairman**: Just for the record, Dr. Kaye, what system are you using?

**Kaye (Montreal)**: It is a Kiil system, single pass, 37°C, minimum of two 14 hour dialyses a week, but for the last 2 years all new patients have been on dialysis three times a week, minimum 10 hours each time. Bath water calcium is 6 mg/100 ml.

The **Chairman**: In fact much the same system as Dr. Curtis is using, but your results are not quite so good. However, I gather that none of your patients developed symptomatic bone disease. Dr. Schorr, what has been your experience?

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### TABLE I

*Dialysis system during incubation period of bone disease at Newcastle*

| Dialyser:                  | *Chronacoil. 12 hours twice a week*  
| Blood pump:                | *Kiil. 12, occasionally 14, hours twice a week*  
| Bath water calcium:        | Used most of the time on both systems  
| Heparin dose:              | 1964-5 — 7 mg %; 1966-8 — 6 mg %  
| Long term anticoagulants:  | 25,000-35,000 units per dialysis  
| Diet:                      | Nicoumalone (Sinthrome) used in patients with poor shunt history. About 1 in 3 taking it at any one time  
| Vitamin supplements:       | 40 g protein prescribed. Actual intake very variable. No calcium supplements  

* Most patients have experienced both systems but bone disease has occurred in individuals treated almost exclusively with either. About two-thirds of all dialyses are with Kiil.

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**Schorr (Newcastle)**: We have the same system but different answers. I should like to describe what we regard as Newcastle bone disease. Our dialysis procedures are summarised in Table 1; I shall merely comment on the fact that the calcium is added to softened water. Forty-six patients are included in this review from July, 1964 to the present. Table II shows the percentage and number of patients at each dialysis year with symptomatic bone disease. Table III lists the symptoms, starting at the bottom and going up, and this is also the way they present chronologically; they usually start with pain in the feet and ankles and later have

---

### TABLE II

*Incidence of symptomatic bone disease*

<table>
<thead>
<tr>
<th>Years on RDT</th>
<th>Patients at risk</th>
<th>Number affected</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4</td>
<td>10</td>
<td>9</td>
<td>90</td>
</tr>
<tr>
<td>2-3</td>
<td>11</td>
<td>8</td>
<td>73</td>
</tr>
<tr>
<td>1-2</td>
<td>13</td>
<td>8</td>
<td>61</td>
</tr>
<tr>
<td>½-1</td>
<td>7</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>0-½</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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TABLE III

Symptoms of bone disease in patients on RDT

1. Pain in feet, around ankles and up Achilles tendon. First after exercise, later on standing
2. Pain in knees and groins on standing
3. Pain around the shoulders and in other bony sites
4. Acute episodes of pain associated with pathological fractures of:
   - ribs
   - femoral necks
   - spine
   - fibula
   - metatarsals
   - scaphoid
5. Development of kyphosis and loss of height
6. Proximal muscle weakness

involvement of the knee, groin, ultimately ribs and sometimes spine. Figure 6 shows the pelvic radiograph of one of three patients with bilateral femoral neck fractures; the change looks unimpressive but believe me, it is very real. We have four other patients with severe bending of the femoral necks who look as if they have fractures imminent.

Fig. 6. Crack fracture of femoral neck with varus deformity developing gradually without obvious trauma in patient dialysed for 18 months.

We have ten patients with recurrent rib fractures and three with spinal fractures. Bone healing is very prolonged with formation of a lot of abnormal looking callus. Table IV shows the incidence of radiological changes in our patients; it is evident that early on they have changes in the hands but the disease progresses with later involvement of the pelvis and chest. In the last column, a score of severity has been worked out and it is obvious that
ROUND TABLE DISCUSSION

TABLE IV
Percentage of patients showing radiological changes in bones

<table>
<thead>
<tr>
<th>Years on RDT</th>
<th>Patients at risk</th>
<th>Percentage with changes in:</th>
<th>Score of severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–4</td>
<td>10</td>
<td>hands - 100</td>
<td>feet - 100</td>
</tr>
<tr>
<td>2–3</td>
<td>11</td>
<td>hands - 100</td>
<td>feet - 82</td>
</tr>
<tr>
<td>1–2</td>
<td>13</td>
<td>hands - 100</td>
<td>feet - 92</td>
</tr>
<tr>
<td>3–1</td>
<td>7</td>
<td>hands - 100</td>
<td>feet - 86</td>
</tr>
<tr>
<td>0–½</td>
<td>5</td>
<td>hands - 80</td>
<td>feet - 60</td>
</tr>
</tbody>
</table>

it gets steadily worse over a period of time. Figure 7a shows a couple of fingers from one of our patients just prior to starting dialysis. Figure 7b shows the typical hand changes that have developed in 24 months of treatment; these include periarticular osteoporosis and striking alterations in the shaft of the phalanx; cortical bone is thinned and the trabecular pattern replaced by a coarser mesh with some small defects reminiscent of bone cysts.

Fig. 7. Phalangeal radiographs before and 24 months after starting RDT.

The biochemistry of our patients was unremarkable. The serum calcium averaged 9.4 mg/100 ml pre-dialysis for the group, with only two patients above 10.0 mg/100 ml; neither of these had symptomatic bone disease at the time. They are both early in their dialysis experience. Serum alkaline phosphatase levels are elevated in only 7 of these patients and do not correlate with bone disease.
DISTURBANCES OF CALCIUM METABOLISM IN TRANSPLANTED PATIENTS

Fig. 8. Iliac crest biopsy, decalcified, stained H and E, from patient in third year of dialysis.

Figure 8 shows one of the 25 bone biopsies we have performed on 20 patients. It is marked by increased osteoclastic activity with scalloping, diminished osteoblastic activity and only very modest osteitis fibrosa. The end result is shown in Figure 9 where the amount of total bone is about normal, the amount of undecalcified osteoid greatly increased and the total calcified bone therefore considerably decreased. Because of the marked scalloping, the structural integrity of the remaining calcified bone is further diminished.

The last slide shows one of 6 sets of parathyroids obtained at autopsy from our patients. The weights of the four glands varied between 280 and 495 mg. None of them had adenomatous change. The blood parathormone level in all our current patients has been measured by Dr. O’Riordan. They all have elevated levels, and it does not yet appear that there is any clear correlation between blood parathormone level and clinical bone disease.

Ten of our patients have received vitamin D in doses of 50,000 to 100,000 units daily for periods up to 9 months. All we have done is to raise the serum calcium and in some cases produce conjunctivitis without changing the symptoms, the radiological picture or the histology in serial bone biopsies.

The Chairman: Thank you, Dr. Schorr. Before this panel discussion started, Dr. Curtis reported that regular dialysis can have a beneficial effect on bone disease; Dr. Kaye then showed that osteitis fibrosa may progress during treatment, and Dr. Schorr has now left us in no doubt that patients on RDT can develop a progressive and severe bone disease. I shall now ask the other members of the panel for their ideas as to why there should be these marked differences in results. Professor Shackman, what is your experience at Hampstead? I think you have found evidence of bone disease in a fair proportion of your patients.

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FIG. 9. Iliac crest biopsy, undecalcified, from patient in third year of dialysis.

SHACKMAN (London): Mr. Chairman, what worries me is what criteria we ought to use if we are going to make a diagnosis of renal osteodystrophy in patients treated by long term dialysis or renal transplantation. The simplest way to make the diagnosis is by radiology and accepted biochemical evidence is reasonable enough. However, when quoting serum calcium levels we must not forget that even in the hands of experts using flame photometry, calcium levels can be misleading and may be affected by the total serum protein and the degree of acidaemia. There can also be striking individual variations in alkaline phosphatase values.

We therefore decided to make the diagnosis by bone biopsy. The biopsies are cut undecalcified and require special technique and expert interpretation. In Figure 10 you can see, in the inset, the osteoclastic resorption which I interpret to represent parathyroid overactivity. In the widened osteoid there is a darker line indicating a zone of calcification.

The biopsy is repeated 6 months later after a period of regular haemodialysis or after kidney transplantation. In Table V, I have summarised our findings in a consecutive series of 15 cases.

The Chairman: Have you had any morbidity from your bone biopsies in patients on regular dialysis?

SHACKMAN (London): No. They are done the day after haemodialysis (Kil system, 14 hours twice a week). The biopsy is taken from the iliac crest under local anaesthesia; it is very easy to do and takes only a couple of minutes. It is done with a domestic drill and a trephine of 4 mm internal diameter. There has been no morbidity and I have no anxiety about advising my patients to let me do this.
## TABLE V

Biochemistry and bone biopsies in 15 patients with chronic renal failure treated by haemodialysis, kidney transplantation, and subtotal parathyroidectomy

<table>
<thead>
<tr>
<th>Total observation (months)</th>
<th>X-ray evidence</th>
<th>Alkaline phosphatase (K.U.)</th>
<th>Plasma calcium (mEq/l)</th>
<th>Calcium × phosphate (mg%)</th>
<th>Osteoclastic activity</th>
<th>Osteoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>?</td>
<td></td>
<td>8</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>±</td>
<td></td>
<td>8</td>
<td>10</td>
<td></td>
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<tr>
<td>3</td>
<td>16</td>
<td>±</td>
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<tr>
<td>6</td>
<td>11</td>
<td>+</td>
<td></td>
<td>33</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>30</td>
<td>+</td>
<td></td>
<td>18</td>
<td>57</td>
<td>15</td>
</tr>
</tbody>
</table>

Six cases with bone biopsies before and six months after kidney transplantation (cases 4, 8, 9, 11, 12, 14). One case with bone biopsies before and six months after subtotal parathyroidectomy and before but not yet after kidney transplantation (case 7). Three cases with bone biopsies before but not yet after kidney transplantation (cases 2, 10, 15). One case with bone biopsy before kidney transplantation which failed within six weeks (case 3). Four cases with bone biopsy only before kidney transplantation (cases 1, 3, 6, 13). Cases 8 and 9 were transplanted from live donors and were treated by haemodialysis for only 2 months.

It can be seen that there is marked osteoclastic activity despite normal X-ray appearances, normal values for alkaline phosphatase and plasma calcium, and relatively low calcium × phosphate products. Successful kidney transplantation is followed by regression of bone changes but the plasma calcium still remains elevated in cases 4 and 8 and the alkaline phosphatase in cases 8, 11 and 12.
The Chairman: Dr. van Amstel, you also, I believe, feel that bone biopsies may be helpful in assessing your patients?

Van Amstel (Leyden): Yes, I think it is very difficult to speak about bone disease without the help of bone biopsies. We have also examined bone biopsies by tetracycline labelling and undecalcified section. In Table VI, I have summarised the observations in 7 of our patients who were more intensively studied by a semi-quantitative technique.

**TABLE VI**

*Tetracycline labelling iliac crest bone*

<table>
<thead>
<tr>
<th>Patients</th>
<th>M</th>
<th>E</th>
<th>V</th>
<th>Y</th>
<th>H</th>
<th>K</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteopenia</td>
<td>++</td>
<td>±</td>
<td>±</td>
<td>—</td>
<td>+</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Bone formation</td>
<td>++</td>
<td>++++</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Bone resorption</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>++(+)</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Mineralisation</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Months on dialysis</td>
<td>20</td>
<td>13</td>
<td>13</td>
<td>9</td>
<td>6</td>
<td>11</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Age</td>
<td>51</td>
<td>46</td>
<td>32</td>
<td>20</td>
<td>27</td>
<td>37</td>
<td>20</td>
</tr>
</tbody>
</table>

You can see that there are large differences in bone resorption between the patients but the majority have extensive bone resorption which is sometimes compensated and sometimes, as in the first patient, not compensated by bone formation. We have seen disturbances of mineralisation in only two patients and in these we saw a broad field of undermineralisation on the bone formation side, suggesting that bone had recently been formed with a lower
degree of mineralisation, in which tetracycline had already been precipitated. In 3 of the patients we saw incorporated in the bone an older part with good mineralisation and big osteocyte lacunae suggesting that there had been an earlier malacic phase which was now healing.

None of these patients had any radiological evidence of bone disease at the time of biopsy. We conclude that you can have marked bone disease without radiological abnormality and that there is a wide variation in the histological picture in the affected bones. Also, although we have no sequential biopsies, we conclude that there is a tendency for osteomalacia to heal in patients on regular dialysis.

The Chairman: With what dialysis system?

Van Amstel (Leyden): With a dialysate calcium of 6 mg/100 ml and with two 14 hour dialyses per week with the Kil.

The Chairman: Perhaps the other members of the panel will comment on the papers we have heard, including Dr. Curtis’s. Can anyone suggest why it is that the results of what is essentially the same system of treatment are so widely different in different units. Is it simply that different methods of investigation are being used to assess progress? It does not look like it really; any other suggestions?

O'Dwyer (Dublin): It is very difficult to compare results like this in different units. We had the opportunity of seeing the effect on bone disease of dialyses of different standards over a period of some years. When we started regular dialysis treatment in 1964, because of the big commitment in acute renal failure we could provide our patients with dialysis once a week only. Eventually the situation improved for the survivors and for others coming into the programme—dialyses three times a fortnight and eventually twice a week. Over the years this amounts to a pool of about 50 patients plus 27 who have been transplanted, though not all of these are relevant. We have not performed bone biopsies or measured blood parathormone levels, but we have encountered severe clinical bone disease which has forced us on five occasions to perform parathyroidectomy.

The bone disease is a mixture of osteomalacia, osteoporosis and secondary hyperparathyroidism and it has been particularly severe in those who have received inadequate dialysis—I imagine that prolonged inadequate dialysis may produce osteoporosis by affecting protein metabolism. There is some evidence of bone disease in all the patients who have had prolonged dialysis but the five who were bad enough to require parathyroidectomy had one thing in common: they had either survived from the period of inadequate dialysis or they had a slowly progressive renal disease and therefore suffered from prolonged chronic renal insufficiency before starting dialysis. They presented a similar mixed picture radiologically as other patients on the programme who had remained symptom-free. Four of the five had big parathyroid nodules and the fifth had five fairly normal looking parathyroid glands.

All of these patients improved symptomatically—they obtained relief from the bone pain or recurrent fractures that forced us into operation. Incidentally, pain in the ankles on walking was also the first symptom in our patients. All but one of these operations have been carried out fairly recently and there has so far been little improvement radiologically. In selecting patients for operation we have had no help from serum calcium, phosphorus or alkaline phosphatase levels. It was a clinical decision in a rather desperate situation. We now think that we should be doing parathyroidectomies on a lot more patients and earlier.

Méry (Paris): We had two patients who definitely improved clinically after the removal of hyperplastic parathyroid glands. These two were on regular haemodialysis.

O'Dwyer (Dublin): Did you get any help from the biochemistry in these?
MÉRY (Paris): Not definite. They had a rather high serum calcium level but were not truly hypercalcaemic.

KAYE (Montreal): Is it not likely that if we have patients whose nutritional intake is poor, whose calcium intake may be low, whose vitamin D intake is poor, whose serum phosphorus levels are high, who are not getting the best, the most frequent dialysis, that we are going to see a lot more bone disease? And if we remove all these factors, in other words give them the best of dialysis, is it not likely that parathyroidectomy will be unnecessary?

VAN YPERSELE (Louvain): I would agree with that statement. We have dialysed 64 patients, some for only 3 months, some for almost 3 years, and we have had only one case of parathyroid disease identified by X-ray of the hands. This contrasts with the experience which has been reported here in which 100% of the patients who had been dialysed for more than 6 months had X-ray evidence of hyperparathyroidism. In our centre we use bath water with a calcium of 7 mg/100 ml; one might ask: ‘Does this not lead to metastatic calcification?’ Only 2 of our 64 patients have developed metastatic calcification. Regarding the use of soft water, is its calcium content absolutely nil?

The CHAIRMAN: Virtually nil. The calcium exchanges almost completely with sodium.

O’DwyER (Dublin): As I have told you, we have quite a lot of bone disease. The calcium content of Dublin water is virtually nil and we add 5.5 mg/100 ml of calcium. We have had no metastatic calcification except in the limbus of the cornea. Furthermore two patients who are on dialysis after cortical necrosis have developed bone disease but have not calcified their kidneys.

The CHAIRMAN: Nobody has come up with the real answer to these differences. I hate to suggest that the Newcastle patients are impoverished, poorly dialysed, put on a bad diet and dialysed with too much soft water. Dr. Schorr, I am sure you would like to add something.

SCHORR (Newcastle): I am a member of two camps, having spent the last year in Newcastle and having previously worked in Denver to which I am now returning. In Denver we used a different dialysis system—twice weekly 5 hour dialysis on twin coils which I think most would agree is not very adequate. We also strikingly had no bone disease.

Denver was also different from Newcastle and most other centres in the use of high calcium bath water. We used softened water but added calcium to between 8 and 9 mg/100 ml. Now one must ask where does the calcium go? It did not end up in tissue calcification—none that we could find. Denver has a heavy transplant emphasis so we transplanted many of these patients and did a series of calcium balances post-transplant. They did not go into negative calcium balance after transplantation.

These patients received kidneys from living related donors, well matched. With the use of ALS we were able to get by with little or no steroid dose. Only one patient out of more than 100 transplant survivors in this group ended up by needing a parathyroidectomy (Alfrey et al., 1968). So I am not sure that adequacy of dialysis is going to be the answer and I will opt for the calcium content of the dialysis fluid, or perhaps something else that we do not know how to measure.

The CHAIRMAN: I suppose the ‘something else’ could be differences in the concentrations of substances other than calcium in domestic water supplies. (In reply a question from the floor): Is everyone using acetate in the dialysis fluid? . . . Everyone is.

HORNUM (Copenhagen): Nobody has commented on the possibility of phosphorus depletion occurring through dialysis. I suppose that there are several centres using aluminium hydroxide, but nobody has said that, even with the use of aluminium hydroxide, they had thought of
adding phosphate to the dialysis solution. Phosphorus depletion might be a cause of mineral depletion.

The Chairman: We must now get on with the second part of our discussion—the emergence of autonomous hyperparathyroidism after transplantation. Dr. van Ypersele and Professor Méry have some data on this. Then I am going to ask the panel some awkward questions: 'What is its incidence; how often is it serious enough to require surgery; how often is it a transient phenomenon; can we, before transplantation, predict which patients are likely to develop tertiary hyperparathyroidism; if so, what is the optimum time for parathyroid surgery; finally, should we do a total parathyroidectomy, or leave them a bit?'

Van Ypersele (Louvain): We have been able in the last few years to follow 27 patients who had been transplanted for more than 6 months and in all these patients evidence of autonomous hyperparathyroidism has been sought by the determination of serum calcium. Hyperparathyroidism has been diagnosed only once.

Figure 11 shows the course of a lady of 44 who was admitted for the first time in November, 1964, with terminal renal failure from chronic glomerulonephritis. She was treated by peritoneal dialysis and then by regular haemodialysis for 9 months. On 9th August, 1965, she received a cadaver kidney. One year after transplant she became jaundiced and we were forced to discontinue Imuran. Since that time she has received only prednisone in a dose ranging from 50 mg per day initially, down to 15 mg per day now. Figure 11 shows the serum levels of calcium, phosphate and creatinine since March, 1967. Although hypercalcaemia occurred from time to time it was never very high—the maximum level was 11.6 mg/100 ml. Serum phosphate was low and renal function satisfactory as evidenced by a plasma creatinine concentration of 1 mg/100 ml up to August, 1967. This was confirmed by a creatinine clearance of 40 ml/minute.

From August, 1967, on she developed progressive renal failure, plasma creatinine rising to 2 mg/100 ml. We suspected that autonomous hyperparathyroidism played a role in the decline in renal function and did a renal biopsy, which showed slight nephrocalcinosis. There was no X-ray evidence of metastatic calcification or calcium deposits in the kidney. Four

Fig. 11. Changes in plasma calcium, phosphate and creatinine prior to and after parathyroidectomy in a transplanted patient suffering from tertiary hyperparathyroidism. The simultaneous rise in calcium and creatinine concentration observed at the end of the evolution illustrates the hazards of parathyroid substitutive therapy (Vit. D and calcium).
ROUND TABLE DISCUSSION

parathyroids weighing 1.3 g were removed on 10th January, 1968. There was no problem of controlling the postoperative hypocalcaemia with a constant dose of about 8,000 units vitamin D per day and a small calcium supplement. Her renal function did not improve after correction of her hypercalcaemia but at least it did not deteriorate further until a few weeks ago when she suddenly developed hypercalcaemia and her serum creatinine rose. Discontinuation of vitamin D quickly restored both serum calcium and creatinine levels to their previous values.

This case illustrates the fact that autonomous hyperparathyroidism may develop as late as 18 months after transplantation and demonstrates the dangers of substitution therapy which may be needed when all the parathyroids have been removed.

We have had a second case of hyperparathyroidism but without hypercalcaemia. This lady was dialysed for about 18 months and during her treatment developed hyperparathyroidism, as evidenced by bone X-ray. She was treated unsuccessfully with supplementary vitamin D and calcium. She received a cadaver transplant 14 months ago. We thought that she might develop hypercalcaemia after transplantation and followed her serum calcium carefully, but throughout these 14 months we have never seen a raised serum calcium. Urinary calcium

Fig. 12. Persistence of X-ray signs of hyperparathyroidism after transplantation.

a. 10 months prior to transplantation.
b. 14 months after transplantation.

Neither hypercalcaemia nor hypercalciuria have been observed in this patient.
excretion was measured repeatedly and we have never found it to exceed 200 mg/24 hours. Nevertheless, as can be seen in Figure 12, the subperiosteal erosions which were found in one of her fingers 10 months before transplantation are still present 14 months after the operation. Other evidence for persistent hyperparathyroidism was found in a slightly elevated, thermolabile, serum alkaline phosphatase and increased hydroxyproline excretion. Nevertheless we have not operated on this patient, thinking that, since she has no hypercalcaemia or hypercalciuria, she should not suffer any renal damage.

Méry (Paris): At the Necker Hospital in Paris out of 103 transplantations function of the transplanted kidney was good for at least 3 months in 75 cases. Among these 75, what appeared to us to be definite autonomous hyperparathyroidism occurred only twice. The first case was a young man of 25 with glomerulonephritis who has been on RDT for 15 months and had signs of hyperparathyroidism prior to transplantation. During the second month after transplantation his serum calcium began to rise, reaching 12 mg/100 ml and the plasma phosphorus decreased to 1.9 mg/100 ml. He then developed some bone pain and passed a stone from his transplanted kidney. Three out of four hyperplastic parathyroids were removed 7 months after transplantation and his condition improved rapidly. Now, two years after parathyroidectomy he has had no recurrence of his symptoms of hyperparathyroidism and he does not receive any corticosteroids.

The second patient is a young man of 22 with chronic pyelonephritis who has been on RDT for 3 months. He had evidence of hyperparathyroidism before transplantation and in the second week after transplantation his serum calcium rose, his serum phosphate fell below normal and bone pains occurred. We performed parathyroidectomy much sooner than in the first case—at the seventh week after transplantation—and 3 out of 4 hyperplastic parathyroids were removed. Improvement was much slower than in the first case. Three years have elapsed since his parathyroids were removed; he has shown no recurrence of hyperparathyroidism and he too does not receive corticoids.

We thought that two other patients were developing autonomous hyperparathyroidism after transplantation because they developed the same clinical and biochemical picture as the first two. We were prepared to remove their parathyroids but after a few months their clinical and biochemical symptoms reverted to normal. Several years have gone by with no evidence of hyperparathyroidism.

The Chairman: Some very important points have come out and one of my questions has been answered: apparently this can occasionally be a transient phenomenon. Can we tell prior to transplantation which of these patients are going to require parathyroid surgery?

Méry (Paris): I think we cannot. In 8 patients we thought, before transplantation, that we might have to perform parathyroidectomy after the transplantation. As I have said, in 2 cases we had to do it, in 2 we had transient hyperparathyroidism, and in the 4 others nothing abnormal occurred so we did not have to face the decision.

The Chairman: Professor Méry did subtotal parathyroidectomy with good results. Dr. van Ypersele did total parathyroidectomy with equally good results except that one of his patients was pushed into hypercalcaemia and declining renal function by substitution therapy. What is the consensus of opinion—total or subtotal?

Van Amstel (Leyden): We have done one subtotal parathyroidectomy in one patient (Table VII).

Schorr (Newcastle): If the disease is hyperplasia, I do not think they need operation because it is going to go away. If it is adenoma they need just that one taken out.
ROUND TABLE DISCUSSION

TABLE VII
Serum calcium and phosphate levels before and after renal transplantation and subtotal parathyroidectomy

<table>
<thead>
<tr>
<th>Time in days after transplantation</th>
<th>Serum Ca* mg/100 ml</th>
<th>Serum P mg/100 ml</th>
<th>P clearance ml/min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before transplantation</td>
<td>9.8–10.3</td>
<td>5.2–9.4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>10.0</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>10.4</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>42–76</td>
<td>11.0–11.7</td>
<td>1.2–2.0</td>
<td>40–50</td>
</tr>
<tr>
<td>180–301</td>
<td>9.8–10.5</td>
<td>2.1–2.4</td>
<td>15–20</td>
</tr>
</tbody>
</table>

* The normal upper limit in our laboratory is 10.6 mg/100 ml. From: Folia med. neerl., 1967, 10.

SHACKMAN (London): We have done four total and two subtotal, but I do not really know whether we should have done them.

O’DWYER (Dublin): I think, if you do it at all, you should do a total parathyroidectomy. The problem is whether to do it at all. A point in favour of doing it before transplantation is that if you are using cadaver grafts most of your patients will require a good deal of steroid therapy. The one patient whose parathyroids we were forced to remove after transplantation had been put on to steroids to prevent rejection and his skeleton almost disintegrated. After parathyroidectomy, although he did not live long, he was able to get up and move around after previously being bedridden, and his fractures healed. By contrast, another young girl had well marked radiological bone changes before transplantation and while on dialysis. She received a good transplant and within a few months her bones are healing; she had no bone symptoms at any time. I think it is very difficult to know. We have acted on purely clinical criteria, i.e. pain or fracture.

The CHAIRMAN: Gentlemen, the time has now come to terminate this discussion and I must make way for our President, Mr. Walsh, who will make his closing remarks.

The President’s closing remarks:

After thanking all who helped in the organisation of the conference, the President gave this final exhortation:

‘We must not become ossified or calcified as a society. We must be prepared to improve our meetings and be alert to what makes a good meeting. Have we entirely forgotten acute renal failure? Should one have less papers and more discussion? We tried to do something in that direction this year with the round tables; do you like these or not? Should one set a particular subject a year ahead, giving people one year’s warning that it will be discussed, possibly in a complete half session?

I am sure you are all full of ideas now, but unless these ideas percolate to the people whose job it is to run the next meeting, they are wasted. So I would ask you, if you have thoughts about this, convey them to some member of the Council. Council members are not there to propagate their own ideas, but to act as your representatives. They cannot represent you unless they know what you want.’

REFERENCE


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