Familial Hypophosphatemic Rickets: Pathophysiology and Medical Management

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Chronic hypophosphatemia is one major cause of rickets and osteomalacia in growing children (see Preface of this volume). There are acquired and congenital forms. In most instances, the acquired forms can be controlled by acting on the underlying cause (insufficient phosphate intake, increased renal loss secondary to a mesenchymal tumor, or an altered renal tubular function). The inherited syndromes, which will be the only hypophosphatemic states discussed in this chapter, present a challenge however, sometimes for diagnosis and always for management.

CLASSIFICATION OF THE HERITABLE FORMS

X-Linked Hypophosphatemic Rickets (XLH)

The most frequent form was recognized by Albright et al. (1) more than half a century ago. The authors coined the term vitamin D-resistant rickets (VDRR) as the patient they described presented with changes in mineral metabolism that could only be overcome by very large daily doses of vitamin D. In 1940, Christensen (2) noted the familial occurrence of the disease; and in 1958, using hypophosphatemia as the primary discriminant, Winters et al. proposed an X-linked dominant mode of inheritance (3) extensively confirmed thereafter. Recently, using large pedigrees like the one depicted in Figure 1, the mutant gene has been mapped to the short arm of the X chromosome (4). Definite linkage of the HYP locus to two DNA markers known to map to chromosomal band Xp22 has been established (5). A concentrated search for closer genetic markers is under way and should eventually allow for the isolation and cloning of the modified DNA sequence at the basis of XLH. An homologous mutation has been discovered in the mouse (6) providing an invaluable tool to study the disease at the biochemical and molecular levels (see chapter by B. Ecarot and F. H. Glorieux).
FAMILIAL HYPOPHOSPHATEMIC RICKETS

I

II

III

IV

V

Short stature, bowed legs, hypophosphatemia

FIG. 1. Pedigree of an XLH family, demonstrating sex-linked dominant inheritance of the trait over five generations. The disease is present at each generation and there is no father to son transmission. Note in Row III, the female subject who had two affected children with two different mates. (This family was referred to us by Dr. L. O. Johnson, Shriners Hospital, Twin Cities, Minnesota).

Sporadic Forms

About one-third of the VDRR patients present with a negative family history, but cannot otherwise be differentiated from the XLH form. In our cohort, we have observed in two instances, such sporadic female subjects to give birth to affected babies. This implies that sporadic cases carry, in fact, new XLH mutations, and also indicates that mutation rate for the trait is fairly high.

Autosomal Transmission

There have been rare instances of autosomal recessive (7) and dominant (8) inheritance. Clinical expression in these cases has been variable, although quite similar to the XLH phenotype. The genetic heterogeneity that likely reflects those differences will only be understood when the mutations present in those discrete groups of patients will have been mapped to different loci in the genome.

Hereditary Hypophosphatemic Rickets with Hypercalciuria (HHRH)

After isolated reports of a small number of children presenting with hypophosphatemic rickets and hypercalciuria (9,10), a detailed study of a single large pedigree established HHRH as an entity, separate from XLH and transmitted as an autosomal recessive trait (11). Interestingly several asymptomatic individuals in that pedigree were labeled as "idiopathic hypercalciuria" (12). The HHRH phenotype is similar to the XLH one with important differences. Muscle weakness has been reported in some cases, and on x-rays, rickets is associated with osteopenia (which is never found in XLH). Biochemically, postprandial hypercalciuria is associated with very...
high circulating levels of 1,25(OH)₂D (calcitriol). There is no hyperparathyroidism, and bone changes at the trabecular level are not those of overt osteomalacia. They, in fact, resemble hyperparathyroidic bone disease, with increased turnover, decreased bone volume, and no mineralization defect. It is possible that these changes are the reflection of calcitriol induced acceleration of bone turnover (13). Medical treatment is exclusively made of phosphate supplementation without the need for calcitriol addition. Because of the rarity of HHRH and the critical differences with XLH, such cases are excluded from the remainder of this discussion.

CLINICAL EXPRESSION

The classic triad is made of: (i) hypophosphatemia, (ii) progressive lower limb deformities, and (iii) stunted growth rate. Although low serum phosphate (P) is evident early after birth, it is only at time of weight bearing that progressive leg deformities (more often in varum than in valgum) and departure from normal growth rate become sufficiently obvious to have the family seek medical opinion. These abnormalities are the expression of severe rickets. It is striking that, with the exception of these symptoms, affected children are not sick. Because serum calcium levels remain normal, they never present with tetany or convulsion. They are normally active and never experience proximal myopathy. Tooth eruption is often delayed, but, when present, teeth show with a normal enamel, in opposition with the enamel hypoplasia evident in children suffering from primarily hypocalcemic types of rickets (14). This easily recognized symptom, allowing bedside differential diagnosis between hypocalcemic and hypophosphatemic rickets is often overlooked. One tooth abnormality in XLH (formation of interglobular dentin) is, however, the cause of frequent apical abscesses and early decay of permanent teeth. On x-rays, the classic signs of rickets are present. Widened metaphyses, and blurred and irregular zones of provisional calcification are evidence for defective mineralization of the epiphyseal cartilage. On histologic sections of trabecular bone, osteomalacia is characterized by excessive accumulation of unmineralized osteoid tissue and very little resorption activity. Thus there is no osteopenia, in sharp contrast with what is seen in hypocalcemic (with secondary hyperparathyroidism) osteomalacia where a very high rate of osteoclastic resorption results in severe loss of bone mass (15).

In keeping with a sex-linked dominant mode of inheritance the XLH mutation is fully expressed in the hemizygous males while it is variably so in heterozygous females. Isolated hypophosphatemia without clinical bone disease may be found in some heterozygotes, the so-called carriers for the trait (3), thus low serum P is considered as the marker for the mutation. The carrier group provides evidence that hypophosphatemia and renal P waste cannot solely explain the bone changes.

RENAL DEFECT

In its original report Albright (1) proposed, on the basis of impaired clinical responsiveness to vitamin D, that there was decreased intestinal calcium absorption
and secondary hyperparathyroidism. The latter, through its well known inhibitory effect on tubular P reabsorption, was thus at the origin of the P waste and ensuing hypophosphatemia. The development, in 1970, of a radioimmunoassay for human parathyroid hormone (PTH) in serum (16) provided unambiguous evidence of normal serum immunoreactive PTH levels in patients with untreated XLH (17). Only in those patients who had received large daily amounts of phosphate supplements were serum PTH concentrations increased. This "iatrogenic" hyperparathyroidism was the consequence of the hypocalcemic effect of phosphate loading. The wide range of PTH levels measured in the treated patients, demonstrated that renal P waste was not influenced by variations of up to 10-fold in PTH secretion.

The alternate hypothesis is based on a primary disturbance of renal tubular P transport (18). We investigated a series of male and female patients, with a protocol of rapid intravenous P infusion aiming at saturation of the P transport mechanisms (19). Under those conditions, we observed that in male hemizygotes, P reabsorption was already maximum at endogenous concentration of serum P. Increasing the load resulted in negative reabsorption or net secretion of P into the tubular lumen, the first demonstration of such a phenomenon in humans. It could only be elicited under infusion conditions because the XLH mutation apparently resulted in the dysfunction of one major component of P transport. In female heterozygotes, the maximum capacity of the renal tubules for reabsorbing P was variable and intermediate between values seen in the males and those obtained in control subjects. The remaining transport component present in hemizygotes was found to be non-responsive to PTH infusion. It was also established that calcium infusion was able to enhance net P reabsorption by that same system, and this without significant changes in serum PTH levels (20). Thus the XLH mutation appeared to neutralize that component of P transport which in the normal kidney, is sensitive to the hormone. Since the defect is less severe in heterozygotes than in hemizygotes, it suggests a gene-dose effect on one component of the renal P transport system.

Suggestions that the abnormality would be secondary to the presence of an humoral hypophosphatemic factor have not, as yet, received conclusive experimental support.

VITAMIN D METABOLISM

In contrast with what is observed in vitamin D deficiency, or pseudo-deficiency (see chapter by S. Balsan), hypocalcemia is not part of the XLH biochemical profile. This indicates adequate activity of the vitamin D-dependent intestinal calcium absorption and consequently that a primary abnormality in vitamin D availability and/or activation is not part of the XLH pathogenesis.

Because of the close link between the phosphate repletion status and the control of the synthesis of 1,25(OH)2D (21), its metabolism has been extensively studied in XLH patients. When purified 1,25(OH)2D became available we examined its effect
on the XLH phenotype (22). Although intravenous infusion of 1,25(OH)₂D caused a rapid and transient increase in tubular P reabsorption, very similar to what had previously been observed with calcium infusion, longer-term daily administration of the metabolite did not improve hypophosphatemia nor promote healing of rickets. Thus it was unlikely that a specific deficiency in the metabolite was at the origin of the abnormal phenotype. This was later confirmed by measurement of serum 1,25(OH)₂D levels (23). Untreated XLH subjects have 1,25(OH)₂D levels slightly higher than those of age-matched control subjects (Fig. 2). Because of the large overlap between the two groups, the difference may not have major physiologic significance. It would go, with the well established stimulating effect of P depletion. The increase is, however, of a lesser magnitude than the one observed in P-depleted healthy individuals (24). Despite the fact that calcitriol synthesis is more loosely regulated in normal children than in adults (25), defective stimulation of 1,25(OH)₂D synthesis has been suggested in XLH (26). It may be a direct consequence of the XLH mutation or, more likely, the inadequate perception of the appropriate signal by an otherwise normal enzyme system, as the result of altered intracellular P fluxes brought about by the primary transport defect (Fig. 10). Whatever the cause, this relative decrease in 1,25(OH)₂D synthesis is not severe enough to cause decreased intestinal calcium absorption and its obligate corollary, secondary hyperparathyroidism (17).

![Correlation between circulating 1,25(OH)₂D levels and serum phosphate (Pi) concentrations. The gray areas are delineated by the mean ± SD for each variable in the three groups of subjects considered: XLH (VDRR) before treatment (□), XLH treated with vitamin D and P (■), and age-matched controls (○). The difference in 1,25(OH)₂D levels between the controls and the two patient groups is significant at the p < 0.05 level; the difference between the XLH treated and untreated groups is significant at p < 0.001 (Student's t test for independent variates).](image-url)
MEDICAL TREATMENT

The classic approach to XLH treatment, proposed by Albright (1), was based on large (>50,000 IU/d) amounts of vitamin D. Although it improved rickets, the effective dose was usually close to the toxic range. With long term administration, the risks of hypercalcemia and renal damage were high. Phosphate salts had been advocated previously (27) as an adjunct to vitamin D treatment, in order to reduce the risk of hypervitaminosis. Most of the time dwarfism was not corrected by vitamin D treatment alone. Since renal P waste is one major expression of the XLH phenotype, emphasis has been placed in the last 20 years, on a treatment regimen based on frequent phosphate supplementation. Based on the demonstration that P alone could induce mineralization of rachitic cartilage (28), we derived a treatment regimen which provided 1-4 g of elemental phosphorus per day, administered in five divided doses, with no more than a 6-hour interval all around the clock (29). To offset the hypocalcemic effect of P supplementation that may cause severe hyperparathyroidism, large (20,000–75,000 IU/d) amounts of vitamin D were added to the regimen. This combined treatment would heal the rickets and promote growth, with frequent catch-up growth, i.e., passage from a lower to a higher percentile line on the growth chart. If treatment is started before the age of 6 years a spontaneous correction of lower limb deformities may also be obtained (Fig. 3). The dose of P needed to obtain such positive results, caused almost inevitably a secondary hyperparathyroidism difficult to control. Indeed, in three instances, we were forced to undertake subtotal parathyroidectomy to correct autonomous hyperparathyroidism. Furthermore serum alkaline phosphatase levels seldom returned to normal despite radiologic healing of rickets. This was an indication that the mineralization defect may not have been fully corrected. Indeed, by histomorphometric analysis of trabecular bone, we observed that P alone or combined with vitamin D did not correct the osteomalacic component of XLH, despite normalization of growth plate mineralization (30). This observation established that mineralization of the epiphyseal cartilage and of the trabecular surfaces did not respond in a similar fashion to manipulation of their environment (see Preface, page v). The data allowed a clear distinction between the two calcifying structures and also suggested that in XLH subjects, a specific defect might be present at the endosteal level that could play a major role in the pathophysiology of the condition.

In following patients under combined P and vitamin D treatment, it was also realized that serum 1,25(OH)_{2}D levels slightly decreased during therapy (23 and Fig. 2). In view of the persistent osteomalacia, an attempt was made at raising calcitriol levels in the supraphysiologic range by substituting 1,25(OH)_{2}D for vitamin D, at a dose of 30–70 ng/kg/d. Several improvements were rapidly noted (31). First, intestinal P absorption was enhanced allowing a decrease in the daily P supplementation. Second, the control of P-induced hyperparathyroidism was improved. Indeed since 1977, when the change to calcitriol was initiated, we have not seen a case of autonomous hyperparathyroidism. This observation was corroborated by examination of iliac crest biopsies showing that the indices of bone resorption, that had been triggered
by P supplements (with or without vitamin D) decreased significantly with the addition of 1,25(OH)_{2}D. At the same time, both static (extent of the calcification front, thickness of the osteoid seams) and dynamic (mineral apposition rate, mineralization lag time) parameters of bone formation were greatly improved albeit not always fully corrected (Table 1). Similar observations were made in the cortical bone from the same patients (32). Whether this positive effect on bone formation is secondary to increased availability of phosphate or represents a direct effect of 1,25(OH)_{2}D on the mineralization process is not clear. The response, however, required to maintain supraphysiologic levels of 1,25(OH)_{2}D. Such a beneficial effect of the P plus calcitriol therapy in XLH has been amply documented thereafter (33–37).

The comparison of growth patterns under various treatment regimens indicates that normalization of the growth rate is primarily the result of P supplementation. The change from vitamin D to calcitriol had no significant effect (Fig. 4). It is noteworthy that treatment did not accelerate the bone maturation rate, even when catch-up growth occurred (Fig. 5). The overall growth period was therefore not shortened and adolescent growth spurt was of normal magnitude and duration. As indicated earlier, if treatment is initiated early, lower limb deformities will improve, sometimes correcting completely without orthopedic intervention. If deformities are severe enough to provoke permanent joint damage or significant crippling corrective os-

FIG. 3. XLH patient. Left: Before any treatment; age 5 years and 10 mos; height: 102 cm; intercondyle distance: 5 cm. Right: Treated with phosphate 2.5 g/d and calcitriol 1 μg/d; age 7 years and 8 mos; height: 114 cm; straight legs.
TABLE 1. Biochemical and histologic profiles, in an XLH (VDRR) boy before and after two years of combined P and calcitriol therapy

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>10/80</th>
<th>9/82</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum P (mg/dl)</td>
<td>&gt;3.5</td>
<td>2.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Alk. phos. (IU/l)</td>
<td>&lt;300</td>
<td>480</td>
<td>260</td>
</tr>
<tr>
<td>1,25(OH)₂D (pg/ml)</td>
<td>28-58</td>
<td>27</td>
<td>38</td>
</tr>
<tr>
<td>BV/TV (%)</td>
<td>19 ± 3</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Tb.Th (μm)</td>
<td>141 ± 20</td>
<td>—</td>
<td>187</td>
</tr>
<tr>
<td>OV/BV (%)</td>
<td>2.4 ± 0.5</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>OS/BS (%)</td>
<td>17 ± 4</td>
<td>75</td>
<td>56</td>
</tr>
<tr>
<td>O.Th (μm)</td>
<td>10 ± 2</td>
<td>28</td>
<td>13</td>
</tr>
<tr>
<td>MAR (μm/d)</td>
<td>1.0 ± 0.1</td>
<td>0.75</td>
<td>1.03</td>
</tr>
<tr>
<td>Mlt (d)</td>
<td>11 ± 2</td>
<td>38</td>
<td>12</td>
</tr>
<tr>
<td>dLS/OS (%)</td>
<td>35 ± 4</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Oc.S/BS (%)</td>
<td>1 ± 0.5</td>
<td>1.8</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* Improvement in mineralization (decreased osteoid parameters and normalized mineralization rate), with no change in resorption activity is evident. Control values were obtained from age-matched healthy subjects.

BV/TV, bone volume/tissue volume; MAR, mineral apposition rate; Tb.Th, trabecular thickness; Mlt, mineralization lagtime; OV/BV, osteoid volume; dLS/OS, dual label surface/osteoid surface; OS/BS, osteoid surface; Oc.S/BS, active resorption surface; O.Th, osteoid thickness.

Osteotomies could be made as soon as metabolic control is obtained (38). If not, correction should be postponed until after the growth period is completed.

Metabolic control of the bone lesions is indicated by a normal growth rate, normalization of serum alkaline phosphatase, and radiologic healing of rickets. At that stage, it may be necessary to decrease the dose of 1,25(OH)₂D to avoid episodes of hypercalcemia with their potential deleterious effect on renal function. Because hypercalciuria will always precede hypercalcemia close monitoring of urinary calcium excretion is the best way to titrate calcitriol needs. Phosphate requirements are best evaluated with the growth rate. (Fig. 6).

Once epiphyses are closed, one can rightly question the importance of maintaining a demanding treatment regimen. Adult patients who have stopped taking medication exhibit often clinical, and always histologic evidence of osteomalacia (39 and Table 2). Whether they should be maintained under long term calcitriol treatment with or without phosphate remains to be established.

OSTEOBLAST DEFECT

Several facts point towards bone cells, namely the osteoblast/osteocyte cell line, being a likely target for the XLH mutation. First there is the evidence that heterozygous female subjects are hypophosphatemic but present with a variable degree of bone involvement. Some, even, never experience any clinical abnormalities. Second, the demonstration that P and vitamin D supplementation will heal the mineralization defect at the epiphyseal plate (rickets) but not at the endosteal surface...
FIG. 4. Growth curves of 4 XLH female patients. Dotted lines indicate periods of treatment with phosphate and vitamin D. Solid lines indicate growth under phosphate and calcitriol therapy. Patients CO and JB exhibit catch-up growth. Patient NR stopped growing at age 14. Patient LM's compliance to the phosphate regimen became difficult to control around puberty.

(osteomalacia), suggests that a bone resistance to vitamin D is present that could only be overcome by supraphysiologic doses of calcitriol (30–31). Finally, XLH bone presents with a specific abnormality (Fig. 7) that consists of hypomineralized periossteocytic lesions (HPL), which suggest an inability of the osteocyte to maintain and/or control its mineralized microenvironment (40–42). We never observed HPL in bone specimens obtained from vitamin D deficient or dependent patients, or from patients with tumor induced osteomalacia where hypophosphatemia is often more severe than in XLH.

Since osteocytes are "haven been" osteoblasts, an evaluation of the relationship between HPL and bone mineralization in XLH was attempted (43). HPL were more frequently present in young growing osteons, than in resting osteons or interstitial bone, indicating that HPL improve with bone aging and calcification. In 31 XLH
FIG. 5. Correlation between chronologic and bone ages in 5 XLH patients (including those in Fig. 4). The diagonal line represents identity between the 2 measurements. Overall, patients' evolution followed this 1:1 line. No accelerated skeletal maturation was induced by therapy.

- Calcitriol
- Phosphate salts
- Assess results by:
  - Growth curve
  - Correction of deformities
  - Radiological healing
  - Serum alkaline phosphatase activity

- Monitor dosage of:
  Phosphate with:
  - Titration (Δ 1.5 mg/dl, 40-60 mins after dose)
  - Clinical results
  Calci
  - Urinary Ca (mg) / Creat (mg): < 0.3
  - 3 months (on random morning sample)
  - Serum iPTH q 6 months

FIG. 6. Basic components of the medical therapeutic scheme for hypophosphatemic patients. See text for details.
patients, the analysis of HPL frequency and its changes with treatment showed that in contrast to therapy with vitamin D and P, treatment with P and 1,25(OH)$_2$D reduced HPL frequency in all cortical areas in correlation with improvement of dynamic parameters of bone mineralization. HPL frequency also decreased progressively with the duration of the treatment, further demonstrating that the lesion resulted in part from defective cortical mineralization. However HPL frequency is unrelated to the severity of osteomalacia in untreated children and the lesions persist in more than 20% of young osteocytes despite complete correction of bone mineralization parameters (Fig. 7). These observations give substance to the early proposal that there may be an osteoblast primary metabolic defect in XLH (41).

We hypothesize that the XLH mutation may affect the osteoblast/osteocyte cell line in a way analogous to what is observed in the renal tubular cell. An unifying concept could thus be proposed to explain the clinical expression of the XLH trait (Fig. 8). The alteration in transcellular P flux will be particularly evident in the kidney where most of the solute transport is active (against the concentration gradient) and will affect vitamin D hydroxylation in an ancillary fashion. Even if the intestinal P transport is involved, it will not be of significance since most of the P flux is there along the concentration gradient (passive diffusion). The proportion of involved bone cells may make the difference between health and disease. Lyonization of the affected X chromosome in females is probably the main mechanism for variability in the expression of the mutation.

**CONCLUSION**

More than 50 years after the first description of XLH, and despite assignment of the mutation to a specific chromosomal segment, we do not yet know the protein whose synthesis is directed by the normal allele of this mutant gene. The pivotal role of the renal P transport defect in the pathophysiology of the disease has helped to delineate an efficacious, albeit demanding, treatment regimen combining phosphate salts and calcitriol. Healing of rickets and osteomalacia can be achieved to-
FIG. 7. Hypomineralized periosteocytic lesions (HPL) in cortical bone of an XLH patient. Arrowheads point to the poorly mineralized areas oriented towards the bone surface. A: Untreated patient; a thick osteoid seam (white) is present at the surface indicating active osteomalacia. B: Under P and calcitriol therapy, osteomalacia is healed, but HPL persist right under the surface. Undecalcified sections, stained with toluidine blue, viewed under polarized light, ×300.
FIG. 8. Unifying hypothesis to explain the phenotypic expression of the XLH (HPDR) mutation. The major effect is on the renal tubule which is the main controlling site of phosphate homeostasis. A possible intestinal defect will only have a minimal impact while the osteoblast defect may tilt the balance from health to disease (see text for details).

ACKNOWLEDGMENTS

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REFERENCES

DISCUSSION

Dr. Arnaud: What form of treatment should be recommended for young adults with fused epiphyses?

Dr. Glorieux: This is an important question for which we have not yet a clear answer. The treatment regimen implemented in children is very demanding, so we would rather quit than to have a haphazardly controlled administration of phosphate which may lead into problems of secondary hyperparathyroidism. At the moment we have separated our young adults in...
three groups, those who are not interested in continuing and treatment is stopped, those who are very keen to continue the complete treatment, and those who will accept some form of treatment that would exclude heavy phosphate load, and we give them calcitriol alone. In two or three years we may be able to decide on the best course of action. What is certain is that bone biopsies in untreated adults with or without symptoms have uniformly demonstrated overt osteomalacia.

**Dr. Marx:** Could you give us some additional thoughts about the "sick" osteoblasts in hypophosphatemic rickets. The high serum alkaline phosphatase in this state seems puzzling, since it is generally an indication of active osteoblastic function. Could this be clarified by evaluating serum levels of osteocalcin (bone-gla-protein)?

**Dr. Glorieux:** It is true that alkaline phosphatase levels are increased but values are never as high as those seen in vitamin D deficiency or dependency, which may easily exceed 1000 IU/l in the untreated state. So, there may be a blurred response in XLH. Studies using cultured osteoblasts, as shown by Dr. Ecarot may help in understanding these differences. As far as changes in osteocalcin levels, they seem to parallel those of alkaline phosphatase, and at this point, we have yet to evaluate what additional information they could provide.

**Dr. Mautalen:** We have assessed the cortical bone density of 12 such children (1). Before puberty, it was well below normal values, even though in the majority of them rickets was cured on films. However, bone mineral density of the spine was in all patients above normal. This agrees with what you said regarding the increased bone volume of these patients. Do you think that to measure bone mineral density of the cortical bone has a place to monitor the efficiency of therapy in these children?

**Dr. Glorieux:** My concern with single photon absorptiometry is that because of the bone changes in size and shape during growth, we never measure twice exactly the same area in the appendicular skeleton. I hope that dual x-ray densitometry, just becoming available, because of its high degree of sensitivity and discrimination, will allow to precisely assess metaphyseal areas on a longitudinal basis.

An intriguing question, along those lines, is what will happen in well controlled children with higher bone density when they become adults. Will female subjects be at an advantage when they will be at risk for post-menopausal osteoporosis?

**Dr. Pettifor:** It is also possible that if they have osteomalacia when they go into the menopause, they may actually not lose bone, because there is reduced mineralized bone surface for the osteoclast to resorb.

**Dr. Arnaud:** When we were treating a large contingent of these patients at the Mayo Clinic, we found, as the bone got better, that we were able to decrease the amount of phosphate. Presumably, when bone finally heals up, you don’t need quite as much phosphate. We found it rather important to pull back on the phosphate load in order not to aggravate the induced hyperparathyroidism.

**Dr. Glorieux:** Clearly, at initiation of therapy higher doses of phosphate and calcitriol are required. This is why we do have to monitor them on a regular basis. When bone is healed you may decrease the phosphate load, but it is very important not to change its administration timetable. I am convinced that the night dose is critical for obtaining the kind of results I described. This is not only because normophosphatemia is maintained for a good proportion of the 24-hour period, but also because growth is a very active process during the night. As far as the dose of calcitriol is concerned, calciuria is the monitoring index.

**Dr. Paunier:** Hypercalciuria may be an important and difficult problem with this type of treatment and certain children develop nephrocalcinosis (2). How do you deal with this problem? What level of urinary calcium excretion do you accept?
Dr. Glorieux: In our experience, in 20 patients treated for at least 7 years with the combined therapy, the duration of hypercalciuric episodes averaged 0.2 months per year. Nevertheless, in several of those children, we observed increased echogenicity of the renal pyramids, which is often translated into nephrocalcinosis. The term has a negative connotation and yet when we looked at renal function, by clearance methods, it was absolutely normal in all subjects (3). Others have the same experience. Nevertheless hypercalciuria has to be closely monitored. When measured on the second urine sample of the day, the calcium/creatinine ratio should be below 1.13 (mmol/mmol). This figure was derived from results obtained in about 50 normal children.

Dr. Marx: It is worth emphasizing that the nocturnal phosphate dose may be of particular importance not only because most growth seems to occur during the night but because night is the interval during which serum phosphorus attains the highest levels of the 24-hour cycle in normal.

Dr. David: I have two questions. The first one concerns the calcification of the entheses that were shown to be very frequent in young adults in a recent publication by Polisson et al. (4). In your experience are such calcifications also observed in children and adolescents? The second question refers to the pathogenesis of the tubular phosphate reabsorption defect in XLH. Several years ago you have postulated that the affection could result from the absence of a PTH dependent tubular phosphate reabsorption component. However, from more recent studies the phosphaturic effect of PTH appears to be normal or even exaggerated. Where do we stand actually on that point?

Dr. Glorieux: Concerning your second question, it is still open. Several theories have been proposed. First, there is our observation that parathyroid hormone infusion does not increase phosphaturia in male patients. Then there are suggestions that the kidney could also be hyperresponsive to parathyroid hormone, and more recently a circulating hypophosphatemic factor was suggested to be the culprit (5). The final answer will come from the isolation of the gene itself, and the subsequent characterization of the abnormal gene product. With regard to enthesopathies, we have not seen them, they have only been reported in adult patients, and that may be the difference.

Dr. Arnaud: What about genetic counseling in this condition? And is its incidence increasing or decreasing?

Dr. Glorieux: When counseling is sought by affected individuals, the answer is simple: offspring of female patients will have one in two chances to be affected, while all the daughters and none of the sons of affected males will carry the abnormal gene. The disease is not severe enough to consider prenatal diagnosis. Incidence is around 1 in 10,000 births and appears stable and evenly distributed in all population groups.

Dr. Pettifor: It seems strange in this disease that one develops so-called tertiary hyperparathyroidism, when in fact there was a recent study (5) that was unable to show any increase in parathyroid hormone levels in normal individuals given an acute phosphate supplement. It has been shown that 1,25(OH)$_2$D might directly act on the parathyroid glands, altering the calcium set point. In XLH, there appears to be a failure of the renal tubular cell to increase 1,25(OH)$_2$D production in situations of hypocalcemia or hyperparathyroidism. This lack of response might predispose the XLH patient to chronic mild hypocalcemia, due to phosphate supplementation, and chronic mild hyperparathyroidism, which in a normal individual would have been suppressed by the appropriate increase in 1,25(OH)$_2$D levels. Calcitriol therapy in XLH might thus have an added advantage of decreasing PTH secretion directly and thus decreasing the prevalence of tertiary hyperparathyroidism.

Dr. Glorieux: I agree entirely. Unfortunately during those early episodes of tertiary hy-
perparathyroidism seen in patients treated with phosphate and vitamin D, circulating levels of calcitriol could not be measured. What is evident, however, is that shifting from vitamin D and P to P and calcitriol has been concomitant with the disappearance of severe hyperparathyroidism, which strongly suggests that the mechanism you propose, is correct.

Dr. Bonjour: I would like to come back to the problem of hyperparathyroidism and calcium metabolism in XLH. It is interesting to compare Pi depletion in normal and mutant individuals with regard to renal handling, urinary excretion and plasma levels of calcium. Pi depletion leads to a decrease in the capacity of the renal tubule to reabsorb calcium. This change is associated with both hypercalciuria and hypercalcemia that most likely result from the mobilization of calcium from intestinal and skeletal sources due to the elevated production of 1,25(OH)2D. And, in Pi depletion PTH secretion is decreased. In sharp contrast in Hyp mice, we observed (7) that, although there is, like in Pi depletion, a decrease in the capacity of the renal tubule to reabsorb calcium, there is no apparent increased mobilization of calcium from intestinal and skeletal sources, as reflected by the absence of hypercalciuria. Therefore, in the mice, the decrease in the capacity of the renal tubule to reabsorb calcium is associated with a trend for hypocalcemia and hyperparathyroidism. Thus, it appears that in XLH there is a “renal calcium leak” that cannot be compensated by an increased input of calcium, probably because of the deficient response of 1,25(OH)2D production to Pi depletion. Furthermore, the increased PTH secretion does not allow it apparently to normalize the renal handling of calcium.

Dr. Glorieux: In our patients, PTH infusion induced a rapid decrease in calciuria. This appears different from your observations in the Hyp mice. As you pointed out, the mice are slightly hypocalcemic (with progressive hyperparathyroidism), and that is not found in their human counterparts.

REFERENCES