In the current issue of *JASN*, Goodman *et al.* (1) describe their latest results from calcimimetic treatment. The ongoing investigations into the safety and use of these agents give promise of better management of the calcium/phosphate/bone metabolism problems that continue to trouble nephrologists and their patients.

This story actually begins with the discovery and cloning of the calcium receptor nearly 10 yr ago by Brown *et al.* (2). Such a receptor was suspected on the basis of the sequence of intracellular events that occurred during feedback inhibition of parathyroid hormone (PTH) by calcium. Initially this information provided insights into several obscure disorders, including the rare but frequently described familial hypocalciuric hypercalcemia (FHH) and the even rarer familial hyperparathyroidism, in which the receptor is respectively downregulated and upregulated (3,4). This widely distributed receptor is most importantly found in the parathyroid and renal tubule. When downregulated, the receptor requires a higher calcium to suppress PTH. At the renal tubular level (where the receptor functions to adjust calcium excretion appropriately in relation to the serum calcium level) the downregulated receptor reduces renal calcium excretion despite hypercalcemia. With upregulation of the receptor, the exactly opposite events take place and such patients have hypocalcemia and hypercalcuria. The clarification of these two bizarre syndromes provided information about how the receptor functioned, physiologically.

The next stage in this saga was the recognition of the potential for manipulating this receptor in disease states. Nemeth *et al.* (5) particularly began to explore this potential, first with calcimimetic agents (so called because they mimic the effects of calcium on the receptor to suppress PTH) and later with calcilytic agents that decrease the receptor response to calcium and raise PTH levels. Although a use for the calcilytic agents was not immediately apparent, there was clearly a role for the calcimimetics in various hyperparathyroid states. Initial reports in primary (6) and secondary (7) hyperparathyroidism documented the remarkably rapid response of the parathyroid cells to this approach. Subsequent studies have demonstrated that this response can be sustained for prolonged periods, and the study by Goodman, *et al.* delineates in greater detail the broader picture of the response. Not only is PTH suppressed, but calcium and phosphate also decline, probably largely in response to the lower PTH. This is what one would expect on the basis of the pathophysiology. Indeed, it appears to simulate (albeit in slow motion) the “hungry bone syndrome,” which occurs after parathyroidectomy. Unlike with surgery, however, this medically induced hungry bone syndrome can probably be modulated or reversed. In light of the current controversy about vascular calcification (8), which relates to phosphate, calcium, probably PTH, and possibly vitamin D, such an agent is a godsend. Current conventional therapy, using calcium containing phosphate binders and potent vitamin D metabolites is problematic at best in this respect. Thus, most of us who follow this work see an important and useful role for calcimimetics ultimately in the control of hyperparathyroidism.

For “calciophiles,” however, this may well be small potatoes. The ability to manipulate the calcium receptor is likely to provide a much bigger reward. This potential relates to recent observations about the interaction of PTH and bone. In the clinical nephrology world, most practitioners are aware of the problem of oversuppression of PTH and the resultant adynamic bone lesion (9). We, therefore, attempt to maintain PTH in a range that will not lead to excessive or deficient bone formation, both of which have important clinical implications. Increasing evidence suggests that low bone formation (adynamic bone disease) is associated with bone loss and hip fracture (10,11). Although we have shown that low bone formation can be corrected by permitting the PTH to rise, concerns have been expressed about letting this genie out of the bottle and increasing the chances of uncontrolled hyperparathyroidism (12).

Although these are real concerns, newer information about PTH physiology leads to other approaches than merely suppressing PTH. It has been discovered that the bone receptors for PTH respond better to a cycling level than a stable level (13,14). PTH release is characterized by a sudden burst of hormone release interspersed in the diurnal variation; both the hormone bursts and diurnal variation may be blunted in ESRD patients and in osteoporosis. It has recently been demonstrated that intermittent bolus doses of PTH markedly increase bone formation and bone mass while dramatically reducing fracture rate (15) in osteoporotic subjects. It is likely that this effect is at least partially due to the re-induction of PTH cycling.

The calcimimetic and calcilytic agents may allow us to select the PTH we want and control it much more tightly than with current measures. In addition, these agents may be used to restore more normal PTH cycling. Whether this will be beneficial remains to be seen, but animal studies are certainly promising. In one animal study, an adynamic model of renal osteodystrophy was markedly improved with intermittent cal-

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cimimetic therapy, which resulted in an increase in PTH cycling and increased bone formation and bone mass within a few months (16). Our own preliminary data reveal similar findings (using cimimetics) in four human volunteers with adynamic bone whose bone formation increased dramatically after a few months of treatment (unpublished observation). In another study using an osteoporotic rat model, a calcilytic agent was employed to stimulate PTH (17). In this latter study, bone formation and bone mass also improved.

In summary, the apparently obscure discovery of the calcium receptor in a basic science laboratory has expanded our understanding of calcium and bone physiology in a variety of unexpected ways. This new knowledge has already impacted understanding of calcium and bone physiology in a variety of disease states but will also expand our weapons in clinical medicine and will not only improve our understanding of several disease states but will also expand our weapons in the battle against disorders involving many millions of patients. The article by Goodman et al. is the next small but necessary step in this saga that will lead who knows where? The long-term implications of these exciting discoveries remain to be fully recognized, but it is an interesting story as it continues to unfold.

References

See related article, “The Calcimimetic Agent AMG 073 Lowers Plasma Parathyroid Hormone Levels in Hemodialysis Patients with Secondary Hyperparathyroidism,” on pages 1017–1024

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