Editorial

The hormonal basis of the pathogenesis of osteoporosis remains elusive. Abnormalities have been postulated in this disease for the major calcium- and skeletal-regulating hormones: parathyroid hormone (PTH), calcitonin (CT), and vitamin D metabolites. Unfortunately, there is no general consensus that secretory differences exist between normal subjects and osteoporotic patients for this family of hormones (1). However, these conclusions about the lack of hormonal abnormalities in osteoporosis are based primarily on single serum measurements of these hormones. Single measurements do not adequately reflect the hormonal production of an endocrine gland, especially for hormones secreted in pulses.

PTH is secreted in a pulsatile manner (2). Although demonstrated decades ago, the pulsatile secretion of PTH has been recently revisited with improved measurement methods (2–4). Prank et al. (5), have expanded this concept by demonstrating that the detailed pattern of PTH secretion in patients with osteoporosis can be distinguished from normal subjects.

Prank et al. (5), found that the time series of normal serum PTH could generate two alternating patterns—one characterized by low and the other by high predictability. Osteoporotic patients had uniformly poorly predictable time series. The authors created a discriminating statistic by fitting a time series model to the pooled data from normal subjects, and showed that with this model they could distinguish data from normal versus osteoporotic patients. Although the large numbers of sequential blood samples required make such techniques rather impractical for clinical application at present, the future development of a PTH sensor that could continuously monitor serum concentration would advance this approach.

Two recent scientific events are fostering a renewed interest in time series analysis—the development of neural networks in computer algorithms and the attempted application of chaos theory to complex biological systems. Although focused on using neural networks, Prank et al. (5) showed that a traditional approach to linear time series prediction (autoregressive integrated moving average or ARIMA) could also serve as a valid discriminating statistic. In 1976 Box and Jenkins (6) wrote the modern day classic on ARIMA modeling, but the text is rather impenetrable to all but the most dedicated aficionado of the subject. In contrast, neural networks make the fitting of very complex linear or nonlinear models to time series data easy; the trap is to use such methods as "black box" tools, without gaining insight into the underlying prediction processes involved. Fortunately, the authors are very sophisticated with neural networks, and in addition are conversant with the intricacies of Box–Jenkins modeling. Indeed, they have performed parallel analyses with these two methods on their data, and produced a time series tour de force. They have introduced a statistic called average relative variance (ARV), which after analyzing the beginning of a time series, calculates just how good a prediction model is at forecasting some more of the time series. This is the essence of time series modeling—how well can you predict future results.

The data of Prank et al. (5), seemed well modeled by neural networks with only linear activation functions. Similarly, their ARIMA models are purely linear. Nevertheless, their data showed nonuniform dynamics in that the normal PTH time series alternated between periods of low and high predictability. This fact, that the dynamics of normal PTH secretion has bistable characteristics, implies that the system has a major nonlinear component. This in no way implies that the underlying dynamics are chaotic, but it suggests that the dynamics must be more interesting than the simple linear models used in the study.

Perhaps the type of complex quantification of the dynamics of PTH by Prank et al. (5), will be necessary to understand physiologic and pathologic parathyroid gland functions. The authors question whether the two-state dynamics of normal PTH secretion might be related to cycles of bone resorption and bone formation. If the anabolic effects of the hormone are mediated by its pulses (9), this could explain the observations that intermittent administration of PTH caused bone net bone formation, while continuous administration caused resorption (3). Whether the richness of the dynamics in the system will reveal to us important aspects of the physiology is uncertain, yet function and form are linked, and the prospect of unraveling mechanisms of physiology through the study of dynamics is a most appealing one.

As the authors point out, trying to reconcile the results of linear and nonlinear prediction on nonlinear systems has been anything but simple. Ideally, one would want to remove the linear component from the experimental data, and then see if the residual data had nonlinear predictability. Unfortunately, this approach is fraught with difficulties (7), and the issue of disentangling data from biological systems which are blends of linear, nonlinear, and stochastic elements remains unsolved (8).

Why be concerned with linear versus nonlinear predictability? Although prediction can serve as a discrimination tool, that which is predictable is also in principle controllable. Although the theory for control of linear systems is well developed (6), recent research has enabled the control of nonlinear chaotic systems (9), and we even have the glimmer of hope that such methods may be applicable to biological systems (10, 11). Whether such time series tools might have applicability for future methods of control of PTH secretion and bone resorption is an intriguing prospect.

While the studies of Prank et al. (5), extend the evolving concepts about the pathogenesis and treatment of osteoporosis, they also have their limitations. The studies have been performed in an understandably small number of patients who may not be entirely representative of a heterogenous disorder such as osteoporosis. Some of the normal patients had low predictability very similar to osteoporotic patients; in its present form, the time series methods of Prank et al. (5) would misclassify a not insignificant percentage of patients. In addition, because the serum pattern of PTH is but one component of the hormonal milieu of the skeleton (1), a variety of genetic and environmental factors will have to be incorporated into a rational understanding of the pathogenesis and treatment of osteoporosis. Nev-

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ertheless, we remain intrigued by the implication of time-series analysis of endocrine function.

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