Journal of Bone and Mineral Research (JBMR) 40th Anniversary Celebration: The Beginning and First Decade

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Introduction

By Rajesh V. Thakker.

"If I have seen further it is by standing on the shoulders of giants". (5 February 1675)
Sir Isaac Newton, FRS (1643 – 1727)

Publication of the *Journal of Bone and Mineral Research* (*JBMR*) was launched 40 years ago in February 1986 as a result of the determined and courageous efforts of leaders of the American Society for Bone and Mineral Research (ASBMR). These leaders (Figure 1), who were giants in our field, had the vision and foresight to establish a society-led journal that would capture the rapid acceleration in research on bone biology and skeletal disease that had begun in the late 1970s. The ensuing four decades saw major developments in molecular biology, genetics, genomics, proteomics, metabolomics, structural biology, drug design, experimental medicine, statistical methodology and clinical trials, and we, as researchers and investigators in these disciplines, have been able to stand on the shoulders of our ASBMR giants and publish high quality papers in *JBMR*, and establish *JBMR* as the leading journal in musculoskeletal biology and medicine. To celebrate this momentous 40th year of *JBMR* and the outstanding scientific, translational and clinical advances in musculoskeletal system and mineral metabolism that have been published in *JBMR*, we (editors-in chief [EiCs]) and first chair of the publications committee (Figure 2) have selected over 40 seminal *JBMR* articles and provided commentaries that encapsulate the excitement and importance of the reported discoveries. These commentaries and reflections will be published as a series of 7 articles between January -July 2026.

This opening article reports on the beginning and first decade under the stewardship of Larry Raisz (1925-2010) who was the founding EiC from 1986 to1995 (Figure 1). The article provides a narrative of the founding of *JBMR* with reflections on the beginning, the first 10 Years of *JBMR* with a tribute to Larry Raisz together with reflections on the early development, commentaries on the top ten publications selected by the editorial panel (Figure 2), and how the first decade set the stage for the future. The following 6 articles (February-July 2026) will similarly provide reflections and commentaries on the advances that occurred under the stewardships of each of the six other *JBMR* EiCs - Marc Drezner (1995-2003), John Eisman (2003-2007), Thomas Clemens (2008-2012), Juliet Compston (2013-2017), Roberto Civitelli (2018-2022) and Rajesh Thakker (EiC 2023-present) (Figure 2).

We hope you will find these articles to be enjoyable, educational and inspiring; we certainly have!

Founding of *JBMR*: Reflections - back to the beginning

By John P. Bilezikian

In 1983, the fledging ASBMR had survived a short 4-year test of time, with the help of Larry Raisz's mother who made us a $4,000 loan! It was then that the bold, exuberantly enthusiastic group including Lou Avioli, Norman Bell, Bill Peck, Larry Raisz, Larry Riggs, and Paula Stern (Figure 1) ventured further on the edge with another wild proposal: it was time to start a journal. Remembering those days, like today, I recall their collective roar: YES! That a journal could be formed soon after its Society was founded and succeed beyond anyone's wildest expectations is a testament to the vibrancy and growth of our field. The *JBMR*'s legacy of continually publishing the results of new knowledge continues unabated today and, I confidently predict, for at least the next 40 years!

The First 10 Years

By Roberto Civitelli

JBMR has reached "middle age"; the January 2026 issue marks its 40th year of publication. Over the years since its inception, *JBMR* has been and continues to be a flagship journal for dissemination of knowledge in the areas of bone and mineral disorders, skeletal biology, and related disciplines. In February 1986, when the first issue of *JBMR* was published, Larry Raisz, the first and founding EiC (Figure 1), described the genesis of the journal as "the culmination of many years of planning that started shortly after the founding of the American Society of Bone and Mineral Research"[(1)]. Today, the stature, reputation and quality of *JBMR* are taken for granted. Only a few current ASBMR members will be aware of the difficulties and risks accompanying the birth of *JBMR*. The journal was launched when ASBMR was still in its infancy – or perhaps adolescence – and had limited resources. In the mid-1980s, launching a new journal was risky for the fledgling Society, but our founders' long-term vision, entrepreneurship, tenacity, and love for the field turned what some had seen as a gamble into a resounding success and a key element for the rapid and healthy growth of the organization.

The historical context and events that led to the founding of *JBMR* are beautifully encapsulated in a 2005 Editorial by Larry Riggs[(2)], who served as ASBMR 7th President (1984-1985), and oversaw the momentous decision of establishing *JBMR*. In those years, the main preoccupation of the ASBMR leadership was survival of the Society, which had just enough resources to pay for the annual meeting; launching a new journal seemed to many members financially too risky. In the early 1980s, most of the drugs used today for osteoporosis did not exist, and forecasts for revenues from subscriptions and commercial advertisement were pessimistic. Despite these reservations, the ASBMR leadership had a clear vision of the future and of the growth potential of the field, propelled by

the same enthusiasm and excitement that had fueled the founding of ASBMR just a few years earlier.

The ASBMR Council tasked a working group (Figure 1) composed of Larry Raisz, Paula Stern, the immediate Past President, Norman Bell, the Secretary-Treasurer, and Larry Riggs, the President, to develop plans for creating a new journal that the Society would own and manage. The task force negotiated with Mary Ann Liebert, a small New York publisher, to produce the new journal, and unanimously recommended Larry Raisz as the first EiC. We can only imagine the "vigorous discussions"[2] that ensued at that auspicious 1985 Council meeting, where the proposal for a new journal was put to a vote. Lower risk and less financially burdensome alternatives were discussed, such as sponsoring an existing journal owned by a publisher or joining with other societies to co-sponsor one, but they were felt not to be adequate for the mission and needs of the Society. At the end, the proposal of founding a new journal carried the day, because – in Larry Riggs's words – "the Council had the vision and courage to … proceed despite the obvious risks"(2). And, as they say, the rest is history.

Indeed, and what a history! A call for papers was hastily issued in July 1985, and enough manuscripts were submitted for the first issue to be published in early 1986. Larry Raisz ran the journal for nine and a half years from his office at UConn, leveraging his own staff and the help of Barbara Kream and Joseph Lorenzo as deputy editors (Figure 1). For the first 5 years, *JBMR* published 6 issues a year. By 1991, the journal became monthly, underscoring a rapid growth of interest by researchers wishing to publish their work in *JBMR*. By the end of Larry Raisz's term as EiC, the circulation had risen from 1300 to 4000, exceeding the forecasts at journal foundation by a factor of 2, with a nearly fourfold increase in the number of published pages.

After almost 10 years at the helm, Larry Raisz stepped down in June 1995. The Publications Committee, chaired by John Bilezikian since its inception, endorsing the recommendation by a search committee headed by Mark Haussler, proposed Marc Drezner as Larry's successor (3). Drezner started his term in July 1995, and concurrently, production of *JBMR* transferred to Blackwell Science, Inc, a larger publisher with more international reach and experience, that further enabled Drezner to strengthen the leading position of *JBMR* and transition it to a fully electronic format for manuscript management.

Tribute to Larry Raisz, MD Founding Editor of the *JBMR* 1986-1995
By John P. Bilezikian

What do you say about a man who personified what we have all ever aspired to be in the pursuit of a career in biomedical research? That he was inspired and inspirational? He surely was; that he was smarter than most? He surely was; that he had an insatiable desire to learn and to

teach? Yes, he did. It was as the founding editor of the JBMR that Larry showed what he was really like, up close and personal. I knew because I was privileged to serve as the first Chair of the ASMBR Publications Committee for the decade that Larry served as EiC of the *JBMR*. Larry did it all. He really did! Remember the days when manuscripts were submitted by regular mail? They arrived in Larry's office that way, not by FedEx and certainly not by electronic submissions. They came slowly at first, not only because mail was slow, but also because the journal was new and upcoming; both an attraction and a deficit to gaining attention. But Larry doggedly plugged the journal, encouraging us to submit our papers. How did he know what was hot and what was not? That was easy. Larry went to all the bone meetings and submerged himself with an ability to delve deeply into whatever and however an abstract was being presented. His eyes and ears were so keen in discerning the very best of what was presented at meetings. And, of course, he never missed an abstract or an opportunity to jump to the microphone and be the first to ask the very best question! He could then come up to us, if we were so lucky, and encourage, if not cajole, us to consider *JBMR* for the forthcoming paper. Larry was the one-man *JBMR* show. Of course, there was an editorial board and there was peer review. But Larry read the submissions before they were sent out for review. He assiduously read all reviewers' comments before deciding yea, nay, or maybe. And this next point is also startling; Larry reread every paper after publication! Within hours of the latest issue's arrival, Larry would invariably call me after this re-read, first asking me what I thought of the latest issue. Before I had a chance to respond- usually to some effect that I had just only yesterday received my copy- he would launch into his own rereview of each paper and, remarkably, comment even on the lay out of the paper. He would tell me: "that table was too crowded…that figure took up too much of the page….that figure could have been a table….that table could have been a figure…..the discussion was too wordy….what a great paper…." and on and on. Will there ever be another editor like our founding editor? With enormous respect for the legends who have followed Larry, my answer is a resounding, "no!" Larry was one of a kind. He was there at the beginning and launched our journal to almost immediate pre-eminence. What an achievement as we look back over these past 4 decades and remember as vividly as yesterday how it happened and how Larry took us along for the greatest publishing journey in the field of metabolic bone diseases. It was a trip for the ages and for our history.

Reflections on Early Developmental History of the *JBMR*
By Marc K. Drezner

Larry's stewardship of the newly established Journal was marked by his enthusiasm, intellect, and energy, which propelled the success of the Journal's launch. Moreover, his efforts led to outstanding sustained growth for the Journal and positive change throughout a very successful first decade.

The amazing outcome of Larry's efforts was creating a remarkable scientifically sound journal before its time. Indeed, published papers in the *JBMR* during the latter years of his tenure provided a glimpse of emerging bone science[4]. As a result, the Journal quickly ascended its reputation in the hierarchal order perceived by scientists, when choosing where to submit a manuscript[4]. In accord, the number of monthly issues increased from 6 to 12 during Larry's tenure.

Not surprisingly, Larry was justifiably revered and his team, like him, was unfailingly generous with expertise and advice. We who followed Larry recognized that he had been so successful that a broad playing field awaited the end of his tenure. Thus, in some ways, the *JBMR* will always be Larry's journal and all of us who have followed him are challenged and proud to carry his legacy.

The publications that have appeared in the *JBMR* are testimony to its success over the past 40 years. Although the bone field was still relatively young in 1986, 1550 articles were published during Larry's 10-year stewardship of the journal and ten of these have been selected, as described below.

Top Ten Picks from the First Decade

1. **Parfitt AM, Drezner MK, Glorieux FH, Kanis JA, Malluche H, Meunier PJ, Ott SM , Recker RR. Bone histomorphometry: standardisation of nomenclature, symbols and units. *J Bone Miner Res 1987;2:595-610*. [5] https://doi.org/10.1002/jbmr.5650020617**
By Juliet Compston

Bone histomorphometry has a pivotal role in bone research, providing unique information about bone remodelling and structure. Fundamental to its evolution was the pioneering work of Harold Frost in 1965 demonstrating the sequential process of remodelling in adult human bone, and the earlier discovery by Milch et al in 1957 that tetracycline uptake by bone could be used to measure dynamic indices of bone remodelling. The progress of bone histomorphometry as a research tool was, however, hampered by often obscure and nonintuitive terminology and symbols, making it inaccessible to many bone scientists. Michael Parfitt summarises this aptly in the opening sentence of his paper, describing the terminology previously used as "arcane" and generally "unintelligible to those outside the field."

Recognising the need for a standardised and comprehensible terminology, the ASBMR Histomorphometry Nomenclature Committee was convened and produced its first report in 1987. Using consistent, self-explanatory, descriptive and unambiguous language the report provides a comprehensive lexicon of terms used in bone histomorphometry, lists the measurements that can be made and describes how structural and kinetic

indices can be derived. It is a true work of scholarship, in that in addition to providing accessible terminology it educates the reader in the physiological and pathophysiological significance of the measurements themselves.

The new nomenclature has been universally adopted since publication of the report, which has one of the highest citation rates (5020) of any article published in JBMR. In addition to its continuing use in basic and clinical research studies, it enables comparison of histomorphometric data across studies and provides an invaluable teaching resource for bone researchers. These key contributions have been sustained for over three decades since its publication and will continue for many years to come.

2. Black DM, Cummings SR, Genant HK, Nevitt MC, Palermo L, Browner W. Axial and Appendicular Bone Density Predict Fractures in Older Women *J Bone Miner Res 1992;7:633-8.* [6]

DOI: 10.1002/jbmr.5650070607

By Marc K Drezner.

The value of bone densitometry, particularly dual-energy X-ray absorptiometry (DXA), in the diagnosis and management of osteoporosis has been established through decades of research and clinical practice. Indeed, by 1990 several prospective studies had established an inverse relationship between bone mass in the appendicular skeleton and the risk of subsequent fractures of the hip and most other types of fractures in women. However, at that time there had been no prospective studies of the predictive value of densitometry of the proximal femur, in comparison to measurements at other sites, or the predictive value of bone mass measured by DXA. Therefore, to determine prospectively if older women with lower bone mineral density (BMD) would have a higher incidence of fractures, Black et al ., in the paper noted above, began to expand their database by recruiting at four sites in the United States and thereby creating a prospective study cohort of 9,704 women at least 65 years of age. Their studies revealed that reduced BMD of the proximal femur and spine is strongly associated with an increased risk of all non-spine and of wrist fractures in elderly women. Notably, the magnitude of the association between BMD and all fractures or wrist fractures was similar regardless of the site or method of measurement. This suggested that measurements of bone mass at the proximal femur, spine, and appendicular sites have similar predictive value for the overall risk of non-spine fracture in postmenopausal women.

While these studies are incomplete in several ways, they paved the way for future studies detailing the relationship between a measurement site to a fracture site (in men and ethnic minorities, as well as many other groups) and contributed to the major role DXA now has in fracture risk assessment in clinical practice. Not surprisingly, therefore, the data reported in this study were cited in 485 subsequently published

investigations between 1992 and 2025. Moreover, the papers citing the work were in turn highly cited, thereby establishing that the paper by Black et al. was wide-reaching and impactful in the bone sciences.

3. **Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ III. Incidence of clinically diagnosed vertebral fractures: A population-based study in Rochester, Minnesota, 1985-1989. *J Bone Miner Res 1992;7:221-7.*** [7] ***https://doi.org/10.1002/jbmr.5650070214***
*By Roberto Civitelli***.**

The consequences of fractures on people's health have been known since antiquity, but it was the pioneering work of Fuller Albright in the 1940s that led to recognizing that many vertebral and hip fractures occur after minimal trauma, and this is what we now call fragility or osteoporotic fractures. In the following decades the focus was put on hip fractures, because of the enormous social and financial consequences for public health. In this context, vertebral fractures had taken a back seat, even though it was known that they may be more frequent than hip fractures. Until the late 1980s, very few epidemiological studies existed on the prevalence of vertebral fractures in women and men across the lifespan, and they were largely inconsistent. Cyrus Cooper and coworkers at the Mayo Clinic collected data in local populations over 5 years and found that the number of vertebral fractures after minimal trauma increases earlier than hip fractures in women, corresponding to the years after menopause. They also showed that both vertebral and hip fractures increase steeply with age and equally in both sexes, although the upward inflection occurs about 10 years later in men than in women. These findings established that the age-adjusted vertebral fracture rate in women is approximately two-fold greater than in men and debunked a commonly held belief that men are not at risk of low trauma fractures. Other epidemiologic studies have later confirmed these findings in larger populations and established a correlation between bone density and fragility fractures. However, this article remains the foundational evidence for the public health consequences of osteoporosis and provided a strong basis and rationale for developing pharmacological agents to decrease the rate of fracture in populations at risk.

4. **Genant HK, Wu CY, Van Kuijk C, Nevitt MC. Vertebral Fracture Assessment Using a Semiquantitative Technique. J Bone Miner Res 1993;8:1137-1148.** [8]
https://doi.org/10.1002/jbmr.5650080915
By John P. Bilezikian

The detection of a vertebral fracture by conventional X-rays, when accompanied by a clinical event, like back pain, can be obvious. The detection of a vertebral fracture when there is no history of a recent event or recollection of a past event may be challenging. The decision to obtain an X-ray of the vertebral spine may be triggered by loss of height that is greater than the normal age-related decline. It may be advised in

the context of someone who has developed a kyphosis, scoliosis, or both. The hypothesis underlying this classic paper is that vertebral fractures occur in those who may not present with a suggestive history, and that they can be identified, and measured semi-quantitatively, by conventional X-ray imaging.

In this classic paper by Genant et al., the detection of vertebral fracture by visual inspection of the X-ray was defined in semi-quantitative terms, even among populations who had not sustained an identifiable clinical event. A set of 57 X-rays obtained from the Study of Osteoporosis Fractures was evaluated by two independent observers, one experienced and one inexperienced. The vertebral bodies, T8-L4, were graded visually on the basis of percentage reductions in anterior, middle and/or posterior heights: grade 1 (20-25%) grade 2 (25-40%); grade 3 (> 40%). There was excellent intra- and inter-observer agreement. This population was 'enriched' in terms of risk for prevalent or incident fractures. For both the experienced and inexperienced observer, the reproducible identification of vertebral fractures was excellent.

This publication was a breakthrough in demonstrating our ability to identify the presence of osteoporotic fractures among those who did not necessarily have a documented clinical event. It also helped to grade the extent of the fracture by simple visual inspection. Furthermore, this report by Genant et al. enabled studies of populations who were at risk for vertebral fractures using simple X-ray technology.

5. **Slemenda CW , Christian JC, Williams CJ, Norton JA, Johnston CC Jr . Genetic determinants of bone mass in adult women: a re-evaluation of the twin model and the potential importance of gene interaction on heritability estimates. J Bone Miner Res1991;6:561-7.** ***(9)***
DOI: 10.1002/jbmr.5650060606
By John A Eisman.

In the late 1980's , it was recognised that axial bone density was largely affected by genetic factors. This was established through twin studies, in which the co-variance between homozygous (rMZ) twin pairs was considerably greater than between heterozygous (rDZ) twin pairs. Thus, studies of various measures of bone in the axial and peripheral skeleton had reported that broad-sense heritability (H^2), which is calculated as 2(rMZ-rDZ) and is a measure of the proportion of total phenotypic variation in a population that is due to all genetic factors including additive effects, dominance and epistasis, was 70-80%.

Slemenda and colleagues re-examined these conclusions and, in particular, two critical underlying assumptions in the twin model viz; that environmental factors are similar between MZ and DZ twins and that there are no quantitative gene-gene interactions.

Firstly, in their twins they examined a number of environmental factors known or thought to affect bone. These included height and weight, calcium intake, caffeine intake as well as alcohol, smoking and usual exercise in the previous year. They found that these factors were more similar in MZ than DZ twins but considered the differences not to be sufficient to have driven the higher intra-class covariance, i.e., rMZ greater than rDZ. Secondly, they examined the narrow-sense heritability (h^2), which estimates the proportion of variance due to additive genetic effects only. Since identical twins share identical genes, h^2 in rDZ should not be greater than rMZ. However, this prediction was violated at several bone sites in their data and in that of earlier studies. Even correction for the various similarities in environmental factors did not correct for these violations. This led them to consider non-additive gene interactions, i.e., "quantitative gene interactions within or among chromosomal loci …the most likely candidate." They gave a simple example of genetic variance being due to variants in two interacting genes. MZ twins would always share the same variants whereas DZ twins would only share the same two variants 25% of the time. Therefore, H^2 would contain 150% of variance due to two interacting genes compared to 100% of non-interacting genes. They further concluded that family studies have great potential to unravel these genetic mechanisms.

If this is the case, and there seem not to be any contradictory data, then the importance of this study has probably not been fully recognised as studies seeking genetic factors in the bone field rapidly expanded with the availability of genome-wide association studies (GWAS). It is interesting that even with very large scale GWAS, only genes with small effect size have been identified. As genetic tools become more powerful, re-thinking the potential of family-based studies as proposed by Slemenda and colleagues may be the way of back to the future.

6. **Heaney RP. The bone remodelling transient: implications for the interpretation of clinical studies of bone mass change. J Bone Miner Res1994;9:1515-23.** ***(10)***
https://doi.org/10.1002/jbmr.5650091003
By Juliet Compston.

Measurement of BMD is widely used to assess fracture risk and to monitor the effects of disease and its treatment. DXA, introduced in the 1980s, has transformed clinical practice and is used in clinical trials as part of the assessment of interventions for bone disease. However, the interpretation of changes in BMD in response to disease or its treatment is more complex than might at first appear and has to take into account the influence of both transient and steady state changes in bone remodelling. The bone remodelling transient, which was the focus of this paper, results from changes in remodelling rate and is a temporary alteration in the balance between bone resorption and formation, lasting for only one remodelling cycle.

In this paper the impact of the bone remodelling transient on changes in BMD measured by DXA was explored using computer simulation, informed by data from bone histomorphometry and calcium tracer kinetics. Heaney demonstrated how the magnitude of the bone remodelling transient varied according to baseline bone mass, remodelling rate and remodelling period. He showed that even large increases in BMD following antiresorptive therapy could result from filling of the remodelling space without any long-term improvement in the overall balance between resorption and formation. For example, when a high remodelling rate was combined with low bone mass, the transient bone gain with treatment could exceed 30%. In the untreated perimenopause, apparent bone loss of between 5 and 8% could be explained by increased remodelling space.

These and other examples in Heaney's paper illustrated how changes in BMD in untreated and treated disease could easily be misinterpreted if the transient effect of changes in remodelling rate was not considered. Increased BMD in response to antiresorptive therapy predominantly resulted from filling in of the remodelling space created by high bone turnover, improved bone strength by stabilising trabecular structure and reduced the risk of trabecular penetration. The creative, data-driven approach used by Heaney provided novel insights into how changes in remodelling rate affect BMD and challenged prevailing beliefs about the mechanisms underlying changes in BMD in response to antiresorptive therapy.

7. Slemenda CW, Miller JZ, Hui SL, Reister TK, Johnston CC Jr. Role of Physical Activity in the Development of Skeletal Mass in Children. J Bone Miner Res 1991;6:1227-33. *(11))*
DOI: 10.1002/jbmr.5650061113
By Peter R. Ebeling.

Physical activity is a key preventative measure used to maintain bone health. We know that high intensity progressive resistance training can increase BMD and that multiple types of exercise reduce the risk of falls. In addition, as much as 25-40% of adult bone mass is acquired during puberty and the pre- and early pubertal periods exhibit the greatest response to mechanical load. This is important because peak bone mass (PBM) determines half of the variance in BMD at age 65 years and a 10% increase in PBM could delay development of osteoporosis by thirteen years. Therefore, regular physical activity during growth and adolescence may increase PBM, possibly reducing the number of fractures in adulthood.

In this regard, the seminal paper by Slemenda from the group led by Conrad Johnston was the first to show that moderate increases in physical activity among children were associated with important increases in skeletal mass at several critical sites, including the hip. This study enrolled 118 children (59 twin-pairs) aged 5.3-14 years, who were participating in a

prospective study of calcium supplementation and bone mass. Physical activity was measured at baseline and 6 months using a questionnaire administered to the children and their mothers, while all other measures were baseline. The two physical activity assessments showed good within-person agreement for total and individual activities. Most physical activities were consistently positively associated with BMD in the radius, spine, and hip. A summary measure (total hours of weight-bearing activity) was also significantly related to BMD in the radius and hip, independently of age or sex. Self-reported sports and play activities were also associated with BMD, but neither time spent watching television nor, interestingly, hours of physical education classes, were associated with BMD. Non-weight bearing exercise (biking and swimming) did not show positive associations with BMD; in fact, some showed negative univariate associations.

This was the first paper to demonstrate the influence of physical activity to meaningfully increase BMD in children. Those children with activity levels 1 SD (standard deviation) above the mean (i.e. 2.7 hr/day) had about 0.06 g/cm^2 greater BMD than children with average activity levels (1.6 hr/day). This implies more active children may emerge from adolescence with 5-10% greater PBM, which could yield an important decrease in the future incidence of osteoporotic fractures.

8. **Danks JA, Ebeling PR, Hayman J, Chou ST, Moseley JM, Dunlop J, Kemp BE, Martin TJ. Parathyroid Hormone-Related Protein: Immunohistochemical Localization in Cancers and in Normal Skin. J Bone Miner Res1989;4:273-8.** *(12)*
DOI: 10.1002/jbmr.5650040221
By Rajesh V. Thakker.

Hypercalcemia as a complication of malignancy had been recognised since the 1920s, and in 1941 Fuller Albright described a patient in whom hypercalcemia and hypophosphatemia resolved after irradiation of a single bone metastasis from a renal carcinoma. Alright suggested that the tumour was secreting parathyroid hormone (PTH) or a parathyroid hormone-like protein, and studies over subsequent years confirmed that a systemically acting factor was responsible for the hypercalcemia, and the term humoral hypercalcemia of malignancy (HHM) was coined. During the 1980s the search for this humoral factor, which increased nephrogenous cyclic AMP but was not recognised by PTH immunoassays, intensified and culminated in 1987 with the group led by T Jack Martin identifying a 141-amino acid protein that had 8 of its first 13 residues identical to PTH, hence the term parathyroid hormone-related protein (PTHrP).

Danks et al (1989) then pursued immunohistochemistry studies that cemented the role of PTHrP as the causative factor for HHM, and also paved the way for its new roles as an important paracrine factor for cell differentiation and as a tumour marker. In this study, Danks and

colleagues raised polyclonal antibodies against PTHrP(1-16) and PTHrP(1-34) in New Zealand White rabbits. The polyclonal antiserum against PTHrP-(1-16) did not cross-react with PTH-(1-34) in radioimmunoassays and at high concentrations neutralised the biological activity of PTHrP *in vitro* and *in vivo*. An immunoperoxidase method was developed to detect PTHrP in histological specimens and the localisation of PTHrP in the spinous keratinocyte layer of normal skin accorded with this cell type being one of the differentiating features of squamous cell carcinoma. PTHrP was also detected in all 34 samples of squamous cell cancers, irrespective of location, but was absent in 20 of 21 adenocarcinomata, the exception being a breast cancer, thereby supporting the specificity of the immunohistochemical method. Moreover, PTHrP was detected in samples of renal cortical carcinoma and melanoma, which like breast cancer can be associated with HHM. Intriguingly, PTHrP staining was found in small cell carcinomata of the lung which are rarely associated with HHM, and this indicated that PTHrP is either not secreted, or not secreted in adequate quantities to cause hypercalcaemia.

This study revealed that PTHrP staining could provide a useful diagnostic marker for squamous differentiation in tumours, and importantly heralded further investigations into the paracrine role of PTHrP in the differentiation of skin and its appendages, and other tissues.

9. Meyer RA Jr, Meyer MH, Gray RW. Parabiosis suggests a humoral factor is involved in *X*-linked hypophosphatemia in mice. J Bone Miner Res 1989;4:493-500.[13]

https://doi.org/10.1002/jbmr.5650040407

By Roberto Civitelli.

The *Hyp* mouse had been used as a model of X-linked hypophosphatemic rickets (XLH) since 1976, when it was first described by Francis Glorieux and coworkers. The mutation that caused the hypophosphatemia (loss-of-function mutation of *Phex*) was identified only about two decades later, but in the late 1980s, the mechanism of disease was not yet clear. An intrinsic defect of phosphorus handling by the kidney proximal tubule was postulated as a likely cause, but no defect in phosphorus transport had been found in tissues other than the kidney in *Hyp* mice. In this conceptually simple, yet transformative study, Ralph Meyer and colleagues from Marquette University, Milwaukee, WI, postulated the existence of a humoral factor that regulates phosphorus homeostasis, and used parabiosis to join the circulations of one *Hyp* mouse with a normal mouse. They found that the hypophosphatemic syndrome, including abnormalities of renal phosphorus handling, $1,25(OH)_2D$ regulation, and bone mineral content developed in the normal parabiont, which was then able to re-establish normal homeostasis once separated from their *Hyp* parabiont. This was the first demonstration that hypophosphatemic rickets involved a circulating factor. The authors also correctly surmised that the same or a similar humoral factor might be the cause of tumor-induced

osteomalacia, considering the close pathophysiologic and clinical abnormalities. It would take over a decade to identify fibroblast growth factor 23 (FGF23) as the phosphorus regulating hormone that is produced in excess in both XLH and tumor-induced osteomalacia. Three decades later, a therapeutic agent, an anti-FGF23 antibody that effectively corrects the metabolic abnormalities in phosphaturic conditions, has become available, transforming the lives of patients affected by these debilitating conditions and underscoring the historic relevance and long term impact of this initial discovery.

10. **Hock JM, Gera I. Effects of continuous and intermittent administration and inhibition of resorption on the anabolic response of bone to parathyroid hormone. J Bone Miner Res. 1992:65-72.** ***(14)***
DOI: 10.1002/jbmr.5650070110
By Thomas L. Clemens.

The science that shapes our contemporary understanding of how parathyroid hormone (PTH) functions both as physiological regulator of bone resorption and a potent bone anabolic pharmaceutical has a fascinating backstory, rich in discoveries by basic and clinical scientists. To frame this history, it is instructive to consider teleologic arguments from evolutionary biologists, which attribute the simultaneous emergence of parathyroid glands and endochondral skeleton in *tetrapods* as coupled adaptations that enabled mineral ion homeostasis in terrestrial vertebrates, whereby scarce calcium ions stored in bone mineral could be acutely mobilized by PTH without impacting bone mass. The chronological timeline of PTH research begins in the late 19th century with the identification of parathyroid glands as unique anatomical structures. Their precise role however, remained controversial until 1925, when James Collip definitively established PTH’s effects on blood calcium levels in dogs infused with parathyroid gland extracts. Subsequent clinical investigations in patients with parathyroid disease defined the main pathophysiological features of PTH deficiency (hypocalcemia) and hormone excess (hypercalcemia), the latter accompanied by severe bone loss and osteitis fibrosa. During this time and as early as 1929, papers from leading bone scientists including Fuller Albright reported that rats treated with PTH (gland extracts or purified peptide) did not show the expected bone loss but rather had *increased* bone mass. Because these findings were hard to reconcile with the well-established clinical picture of bone loss in patients with hyperparathyroidism they were ignored by most skeletal biologists. It was John Parsons, a British pharmacologist and frequent visitor to the Aurbach/Potts laboratory in Boston, whose persistent study of this phenomenon led him to propose that the apparently dual actions of PTH could be explained purely by pharmacokinetic principles. Thus, sustained high circulating levels of PTH, as seen in hyperparathyroidism, would result in bone loss whereas intermittent exposure following exogenous administration would produce anabolic activity. It is at this point in the

history of PTH research that the studies by Hock and Gera took center stage.

To test Parson's pharmacokinetic hypothesis, Hock and Gera designed studies to directly compare the effects of continuous vs. intermittent PTH. Groups of rats received PTH 1-34 for 12 days either administered by continuous infusion or daily subcutaneous injection. Infusion at 4 µg/100 g day increased femur calcium and dry weight whereas rats infused 8 µg /100 g had no change in bone mass. Infusion at 16 µg/100 g resulted in hypercalcemia and death. By contrast, daily injection of 8 µg/100 g PTH increased bone mass with greater trabecular thickness and number. Importantly, the anabolic effects of PTH administered by either route was not diminished in animals pretreated with the antiresorptive dichloromethylene diphosphonate and thus did not require bone resorption, which was the prevailing dogma. These findings demonstrated conclusively that the anabolic and catabolic activities of PTH were separable based on their pharmacokinetic profiles achieved using different dosing modalities which, in turn, provided essential feasibility data for the development of human PTH-1-34 (Forteo®) as the first FDA approved anabolic treatment of osteoporosis. For these reasons the paper by Hock and Gera is considered seminal in the annals of bone and mineral research, and its findings continue to inspire current work aimed at defining the cellular and molecular mechanism(s) that mediate the full range of PTH action.

Setting the Stage for the Future
By Marc K. Drezner

During his tenure as EiC, Larry Raisz set the stage for a brilliant future of the *JBMR*. Moreover, he taught us all that while editing a journal is a significant challenge, it is also one of the most enjoyable jobs you can ever be assigned. He chose to step down as the EiC in 1995, when the Journal was just entering its adolescence, a time when instituting major changes was anticipated and the ASBMR Council supported risk-taking. Larry had built a sense of excitement and new discovery that had become palpable and exhilarating. As a result, submissions doubled and diversified to include sites of research activity around the world. Moreover, with this increased activity, it became evident that submitted papers began to reflect evolving advances in applied techniques of molecular biology, genetics and drug discovery. Thus, the building blocks that Larry established for the Journal set the base for movement to keeping up with the pace of innovation that was essential to being on the curve for an outstanding Journal. The further developmental changes made by the Journal included elements that were established under the leadership of EiCs to come.

Disclosures

The authors have nothing to disclose and all authors state that they have no conflict of interest.

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John Bilezikian (Conceptualization, Writing - original draft, Writing - review & editing), Roberto Civitelli (Conceptualization, Writing - original draft, Writing - review & editing) , Thomas Clemens (Conceptualization, Writing - original draft, Writing - review & editing), Juliet Compston (Conceptualization, Writing - original draft, Writing - review & editing), Marc Drezner (Conceptualization, Writing - original draft, Writing - review & editing), Peter Ebeling (Conceptualization, Writing - original draft, Writing - review & editing), John Eisman (Conceptualization, Writing - original draft, Writing - review & editing), Rajesh Thakker (Conceptualization, Project administration, Supervision, Writing - original draft, Writing - review & editing).

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Figure 1
ASBMR members who established *JBMR* and the first deputy editors in1986. Members of ASBMR working group tasked with creating *JBMR* : Larry Raisz (President 1980-1981, and EiC1986-1995) , Larry Riggs (President 1985-1986), Paula Stern (President 1984-1985) , Norman Bell (Secretary-Treasurer and President 1986-1987), Lou Avioli (First President 1979-1980) and Bill Peck (President 1983-1984). First deputy editors Barbara Kream (President 2007-2208) and Joseph Lorenzo.

Figure 2
Panel selecting and writing commentaries for the editors' top picks from *JBMR* articles, Members of the panel comprised: *JBMR* EiCs Marc Drezner (EiC 1995-2003 and President 2008-2009) , John Eisman (EiC 2003-2007), Thomas Clemens (EiC 2008-2012), Juliet Compston (EiC 2013-2017), Roberto Civitelli (EiC 2018-2022 and President 2013-2014) and Rajesh Thakker (EiC 2023-present); John Bilezikian (first chair of the publications committee 1986-1994 and President 1995-1996) ; and Peter Ebeling (First EiC of *JBMR* Plus 2017- 2021 and President 2021-2022).