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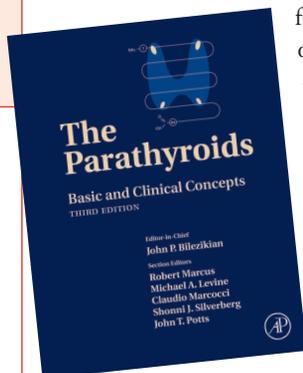
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**Primary Hyperparathyroidism: The Experts' Expert**

John P. Bilezikian, MD, Chief of the Division of Endocrinology at NewYork-Presbyterian/Columbia University Medical Center and Director of its Metabolic Bone Diseases Program, is an international authority on primary hyperparathyroidism. Since 1992, Dr. Bilezikian has co-chaired all four National Institutes of Health worldwide workshops on asymptomatic primary hyperparathyroidism, which just had its latest management guidelines published in the October 2014 issue of *The Journal of Clinical Endocrinology & Metabolism*. He has served as Editor-in-Chief



for all three editions of *The Parathyroids* – a 900-plus-page authoritative reference with 66 chapters by nearly 100 contributors from around the world. First printed in 1994, the textbook's third edition published in 2014. And he and his

colleague, Shonni J. Silverberg, MD, lead one of the longest and largest prospective studies of primary hyperparathyroidism that has ever been continuously supported by the NIH. The study, now in its 30th year, was renewed in April 2014 for another five years.

**An International Focus on Asymptomatic Primary Hyperparathyroidism**

In the early 1970s, the automated serum screening chemistry panel was introduced in the United States and, as a result, the prevalence and incidence of primary hyperparathyroidism were found to be much higher than previous estimates. “In addition, the clinical profile had shifted from a symptomatic disorder, with hypercalcemic symptoms, kidney stones, overt bone disease, or a specific neuromuscular dysfunction, toward a more asymptomatic state,” notes Dr. Bilezikian. “Asymptomatic primary hyperparathyroidism was characterized as a disorder in which there are neither signs nor symptoms typically associated with hypercalcemia or parathyroid hormone excess.

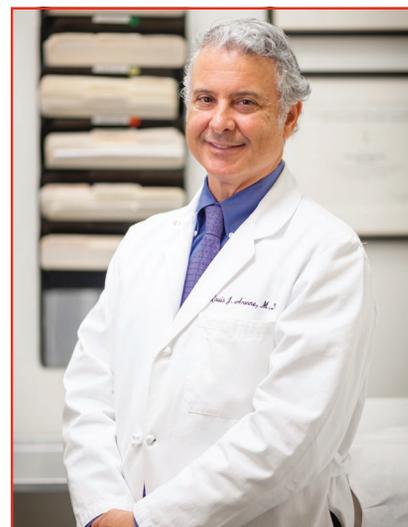
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**Insights into the Metabolic Consequences of Obesity**

In 2012 the Comprehensive Weight Control Center, directed by Louis J. Aronne, MD, FACP, came under the aegis of the Division of Endocrinology, Diabetes and Metabolism at NewYork-Presbyterian/Weill Cornell Medical Center. A leading authority in weight management and obesity, Dr. Aronne has conducted more than 60 clinical trials for the management of obesity and metabolic disease. He is the former President of the Obesity Society and Vice Chairman of the American Board of Obesity Medicine. Dr. Aronne has authored more than 70 papers and book chapters on obesity and edited the National Institutes of Health *Practical Guide to the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. He served as a consultant to the VA Weight Management/Physical Activity Executive Council in the development of the MOVE program, the nation's largest medically based weight control program.

Following, Dr. Aronne discusses the medical and other clinical consequences of obesity, as well as research, treatments, and

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Dr. Louis J. Aronne



## Primary Hyperparathyroidism: The Experts' Expert (continued from page 1)

The diagnosis is often discovered subsequent to routine chemical panels that typically include a blood calcium ordered for any number of other conditions. When the results indicate an elevated calcium level, it generally leads to a search and diagnosis of hyperparathyroidism. So what do you do about people who are asymptomatic? The challenge before us was defining clear recommendations for diagnosis and management.”

Previously, parathyroid surgery was nearly always advised for patients with the disease. Ambiguity around surgical treatment and issues related to diagnostic criteria, medical management, and monitoring led to the convening of a Consensus Development Conference on the Management of Asymptomatic Primary Hyperparathyroidism. Held in October 1990 at the National Institutes of Health, the conference was sponsored by the Office of Medical Applications of Research and the National Institute of Diabetes and Digestive and Kidney Disorders.

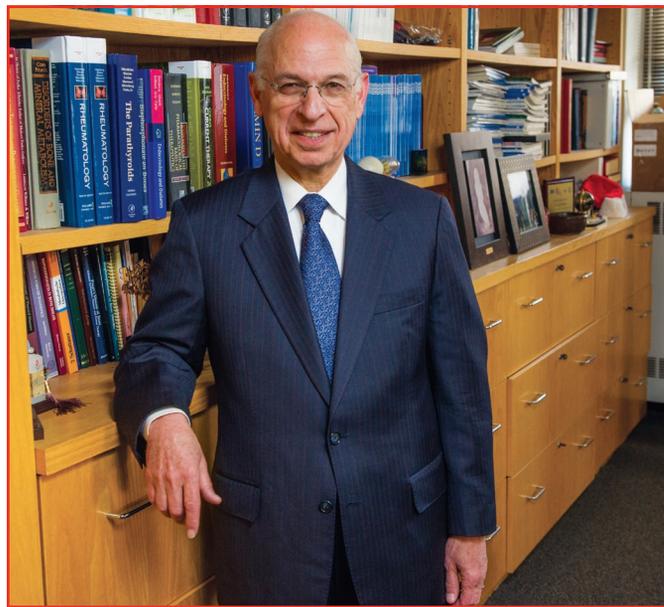
“In the decade that followed many studies shed new light on the issues considered by the Consensus Development Panel,” says Dr. Bilezikian. “In 2002, with a great deal more data on the natural history of asymptomatic primary hyperparathyroidism, better understanding of bone involvement, significant advances in surgery, the introduction of promising medical therapies, as well as indications of cardiovascular risk and other concerns, it was time to reevaluate the conclusions of the 1990 Consensus Development Panel.”

An assembly of experts in the field from around the world gathered once again at the NIH for the “Workshop on Asymptomatic Primary Hyperparathyroidism: A Perspective for the 21st Century.” The summary of the workshop was published in the December 2002 issue of *The Journal of Clinical Endocrinology & Metabolism*. A third conference was held in 2008, followed by a fourth in 2013. “These conferences have led to established guidelines and international acceptance as to how we manage patients with hyperparathyroidism,” says Dr. Bilezikian.

The most recent conference examined data accumulated in the five-year period between 2008 and 2013 to determine whether they supported changes in recommendations for surgery or nonsurgical follow-up. The summary of the workshop, published in the October 2014 issue of *The Journal of Clinical Endocrinology & Metabolism*, included the following recommendations:

- perform more extensive evaluation of the skeletal and renal systems
- include evaluation of skeletal and/or renal involvement in the guidelines for surgery
- develop more specific guidelines for monitoring those who do not meet guidelines for parathyroid surgery

The current guidelines, notes Dr. Bilezikian, are likely to lead to a recommendation for parathyroid surgery more frequently than the last set of guidelines. However, asymptomatic patients who do not meet surgical guidelines can be followed safely without surgery, at least for a period of years. Monitoring of these patients should focus on changes in the serum calcium concentration, significant reductions in bone mineral density, occurrence of a fragility fracture, or changes in renal endpoints.



Dr. John P. Bilezikian

### Studying Hyperparathyroidism at NYP/Columbia

In addition to his global role in furthering care of patients with primary hyperparathyroidism, Dr. Bilezikian and his faculty at NewYork-Presbyterian/Columbia have pursued and continue to develop a number of significant related research projects since receiving a major grant from the NIH in 1984. “The research supported by this grant has helped us define the natural history of this disorder, elucidate the densitometric and histomorphometric features of this disease, and has been instrumental in providing data to the NIH workshops,” says Dr. Bilezikian. “We’ve published well over a hundred papers just on the basis of this one grant alone.”

These research efforts are multiple and diverse, with a current emphasis on establishing risks for complications, including bone disease. “Bone disease in severe primary hyperparathyroidism can be accompanied by bone pain, skeletal deformities, pathological fractures, and proximal muscle weakness with hyperreflexia,” explains Dr. Bilezikian. “Bone mineral density is usually low in this disorder, but it is reversible following surgery for the hyperparathyroidism. As one of only a handful of centers in the country with access to high-resolution peripheral quantitative computed tomography, we have been able to delve into the microarchitecture of bone in a noninvasive, safe imaging approach for this disease and every other disease we study. This technology has, in fact, revolutionized our ability to do research in hyperparathyroidism, as well as in osteoporosis and other metabolic bone disorders.”

According to Dr. Bilezikian, hyperparathyroidism also has many potential target organs that it affects, and since it’s an asymptomatic disease primarily, very sophisticated methodology is required to determine whether there are concerns with regard to some of these target organs. “Among the issues that we are looking at closely are the likelihood of cardiovascular disease, as well as renal and brain manifestations in these patients,” he notes.

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## Insights into the Metabolic Consequences of Obesity (continued from page 1)

therapies conducted by the Comprehensive Weight Control Center that might alter the course of the disease before patients develop diabetes, high blood pressure, heart disease, and other health conditions.

### Why do you believe that obesity is a disease?

Recent studies show that it's hard to lose weight because of impairments in neurohormonal signaling that occur once a person has gained excess weight. In addition, resistance to maintaining weight loss is a result of persistent changes in weight regulating hormones. These hormones are produced by the fat cell, stomach, intestine, and pancreas, and should give satiety signals to the brain when working properly. Obesity has been classified as a disease state due to dysregulation of this signaling and because of the impairment in physical and emotional well-being that a patient experiences when they gain excess weight. Obesity contributes to at least 50 other medical conditions that we spend a lot of time treating. And finally, there is clear evidence that losing even a small amount of weight is good for your patients' health – even a 10 pound weight loss substantially reduces the risk of type 2 diabetes. So there is no question any longer that obesity is, in fact, a disease, and we have to be more sophisticated in our management. We're trying to treat the complications of obesity by treating the obesity itself. There is no better way to prevent diabetes.

### What is obesity medicine?

Obesity medicine is a new specialty that recognizes that obesity is a disease, and that treating obesity is the best way to prevent diabetes. We've discovered that obesity causes damage to the circuits in the brain that control weight. As a result, the signal going from your fat cells, stomach, and intestines to your brain is diminished, and so your brain tells your body to gain more weight. What we've also learned is that there are at least eight hormones that stop you from losing weight. It's not that it is someone's fault; it's not that they don't want to lose weight, but there is something physical going on.

Our Comprehensive Weight Control Center is one of the premier centers in the country treating obesity. We see this as a hub that develops new ideas and new treatments that clinicians can use to treat the most complex cases. We've done more than 60 trials of new medical and behavioral treatments, including one I developed called BMIQ.

### How does BMIQ work?

BMIQ is a comprehensive medical weight loss program that allows doctors, nurse practitioners, and dietitians from any healthcare setting to manage their patients. The program offers numerous tools, including diet plans and up-to-date education on the management of obesity for healthcare professionals. For patients, we include food trackers, a curriculum of 20 sessions to learn how to manage their weight, and other support mechanisms. What we're trying to do is give healthcare providers the tools to treat their patients' weight problems.

### What do you see as the interplay between cancer, diabetes, and metabolic disease?

There is very little question that mechanisms found in obesity and diabetes stimulate the growth of tumor cells. By managing those

problems, it appears you can reduce the risk of getting cancer and the risk of recurrence of cancer. Interestingly, oncologists are most attentive to what we're doing. It looks like being obese will reduce your chances of survival, and the treatments for cancer in many cases cause women to gain weight. Would we get better outcomes if we could stop the weight gain that results from these treatments? That's why we developed BMIQ – to deliver quality weight management in just such a medical setting.

### What makes diabetes and obesity prime targets for precision medicine?

The same treatment doesn't work in everybody. One diet may seem to work better for one person; another diet works better for another. Physical activity definitely helps. Trying to change behavior definitely helps. Medication can help some people. Surgery can help some people. Virtually anybody who has a weight problem can lose weight. But there's no single cure for everyone.

### Is weight loss only about diet and exercise?

In the past, all we've done is said, "Eat less and exercise more." That's never going to work. If it were that simple, I wouldn't have a job. Whether it's new medical or surgical therapies, for obesity medicine to be more widely accepted we need to educate physicians and we need to allow them to have access to centers such as ours.

### Do weight loss drugs work?

Medicines didn't really make sense 10, 15, 20 years ago, but they do now. We know that hypothalamic POMC [pro-opiomelanocortin] neurons, which play a fundamental role in the control of energy balance, are damaged in obesity. Medications appear to amplify or mimic signals through the hypothalamus, reducing appetite and increasing energy expenditure. In the future, we think that people will take these medicines to treat obesity – and to prevent hypertension, diabetes, and high cholesterol from developing. We're also working on new, minimally invasive devices and minimally invasive surgical procedures with gastroenterologists, in addition to new medicines.

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## Primary Hyperparathyroidism: The Experts' Expert (continued from page 2)

### Hypoparathyroidism: The Other End of the Spectrum

Parathyroid hormone deficiency or hypoparathyroidism – the polar opposite of primary hyperparathyroidism – is also the subject of intense study by Dr. Bilezikian and his colleagues. “While hyperparathyroidism is a disease of excess production of parathyroid hormone and high calcium, hypoparathyroidism is a disease in which there isn’t enough parathyroid hormone and low calcium,” says Dr. Bilezikian. “This condition is much more uncommon. In fact it’s called an orphan disease because it occurs in fewer than 200,000 in the U.S. population. Nevertheless, life without parathyroid hormone can be difficult. Low calcium levels produce very disturbing clinical features, including spontaneous twitching that can be very serious and even life-threatening if it occurs in a major muscle such as the larynx.”

Another NIH grant – now 10 years out – has enabled the Division of Endocrinology at NewYork-Presbyterian/Columbia to also be at the forefront of research of this parathyroid disorder. “We have been able to define the clinical manifestations of hypoparathyroidism, particularly skeletal abnormalities, using the same CT technology described earlier,” says Dr. Bilezikian. “Hypoparathyroidism is the only classic endocrine deficiency disease for which the missing hormone, PTH, is not yet an approved treatment. Our research team has been one of the lead study groups in the development of methods for replacing parathyroid hormone in these patients.”

Results of studies led by the Division of Endocrinology at Columbia and published in the *Journal of Endocrinological Investigation* and *The Journal of Clinical Endocrinology & Metabolism*, respectively, demonstrated an association with

recombinant human PTH(1-84) therapy in hypoparathyroidism and improvement in quality of life measures for one year and continued improvement on this therapy five years out. “We found that ongoing treatment with PTH was not only associated with improvement in biochemical and skeletal indices, previously well-documented, but also in mental and physical health as documented by the RAND 36-Item Short Form (SF-36) Health Survey,” says Dr. Bilezikian.

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