Penn Medicine

PENN ORTHOPAEDICS

EXCELLENCE *IN MOTION* 2016

INNOVATORS IN ORTHOPAEDIC CARE

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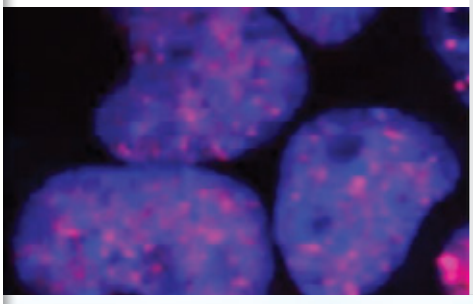

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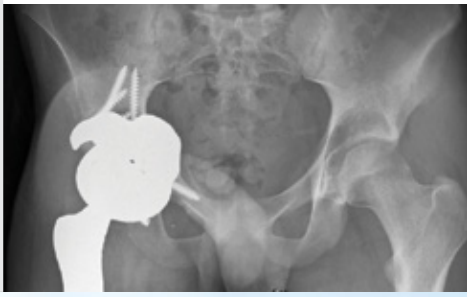


LETTER FROM **THE CHAIR**

Source: Sabina Louise Pierce

To my Colleagues,

I'm pleased to present to you the 2015 edition of **Excellence in Motion**, the newsletter of Penn Orthopaedics. The past year witnessed the culmination of a number of significant endeavors at Penn Orthopaedics, including a historic first—the world's first bilateral hand vascularized composite allotransplantation in eight-year-old Zion Harvey. You'll find Zion's story here in a personal interview, the first I've offered since he entered the rehabilitation phase of his journey. Frances Jensen, MD, FACP, Chair of Penn Neurology offers her insight, as well, into brain plasticity, a fascinating aspect of Zion's care, and the leaders of his rehabilitation team at CHOP provide a glimpse of his current status and future potential.

In 2015, Penn Orthopaedics carried forward a vision that both exemplifies its long history as the first academic department of orthopaedic surgery in the country, and a future that embraces and expands upon its missions of care, research and education. Today, we are ranked number three in NIH research funding. Our educational programs, which include a robust residency and increasing fellowship positions in multiple divisions, are nationally recognized, currently ranking 14th out of 89 programs.

Penn Orthopaedics continues to act as a catalyst for advanced clinical care across the spectrum of orthopaedic medicine and surgery, increasingly engaging the frontiers of known science and exceeding the common expectations of our field. We now manage care as disease teams, rather than practitioners, and within centers capable of diagnosis, testing, treatment and rehabilitation beneath one roof. Moreover, our faculty routinely explores areas of research that elaborate and expand upon the boundaries of orthopaedic medicine.

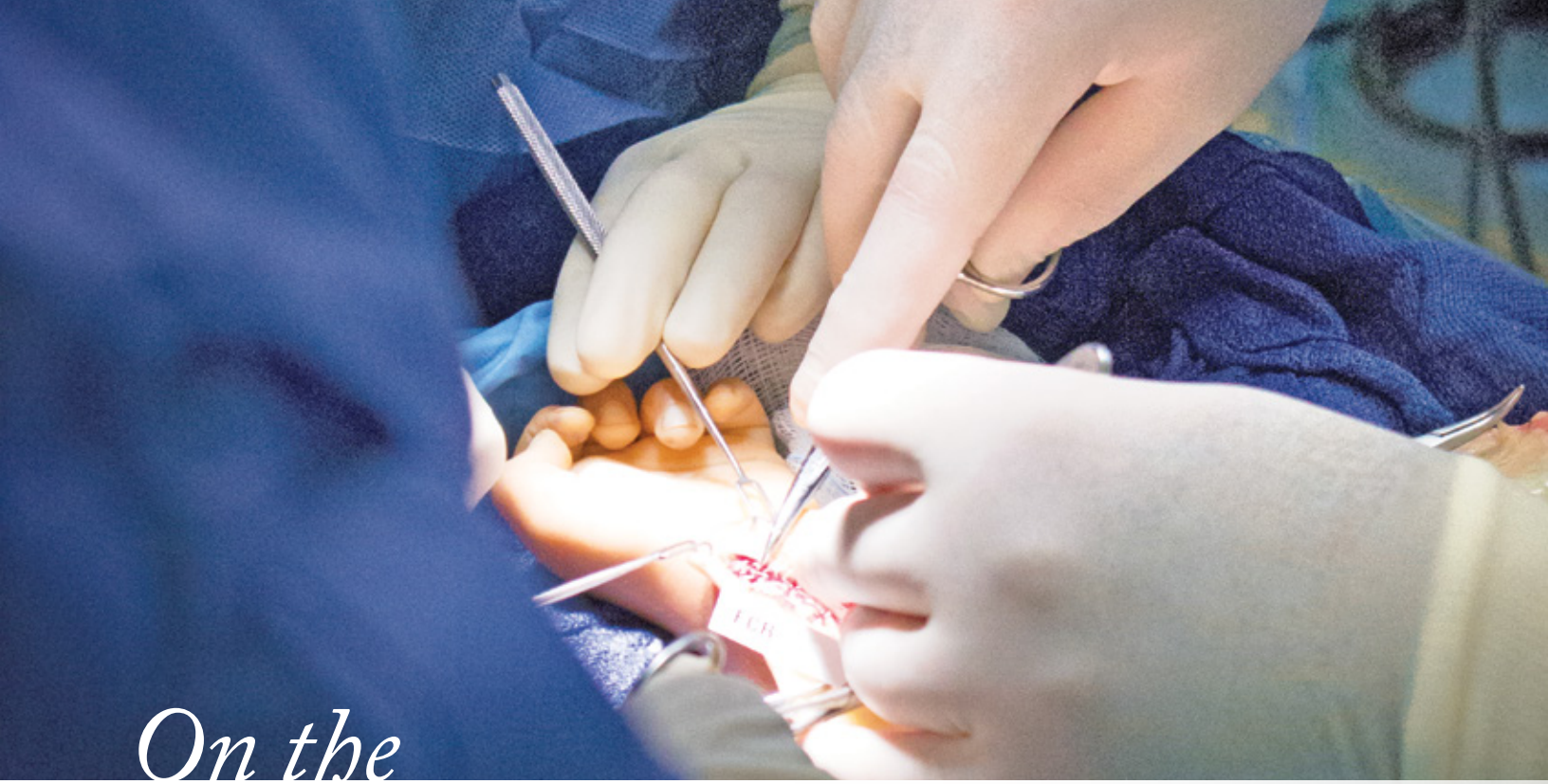
Thus this issue includes reports upon investigators at the McKay Orthopaedic Research Laboratory involved in finding a safe anabolic agent for preventing the bone degeneration that can be caused by radiation treatment for cancer and surgeons performing microbiological research to examine the correlation between acne and revision shoulder surgery and its clinical concerns.

I hope you find this issue informative and enlightening and look forward in the year ahead to building stronger, lasting relationships with our referring physicians and peers in the orthopaedic community nationwide.

L. Scott Levin, MD, FACS

Chair, Department of Orthopaedic Surgery
Paul B. Magnuson Professor of Bone and Joint Surgery
Professor of Surgery, Division of Plastic Surgery
Medical Director, Penn Musculoskeletal Center

In the near future, our 2015 Data Supplement Issue will provide a synopsis of additional advances in orthopaedic and musculoskeletal research and clinical practice now taking place, as well as highlights for all of the specialties that make up Penn Orthopaedics.



On the WORLD'S FIRST PEDIATRIC HAND TRANSPLANT

An Interview with L. Scott Levin, MD, FACS

One day in late November 2008, 22-month-old Zion Harvey was taken to the emergency room of a Baltimore hospital by his parents. Zion had been to the hospital the previous day, and released with a diagnosis of viral gastroenteritis. By the end of this day, however, he would be diagnosed with gram-positive sepsis, severe hemodynamic instability, poor perfusion, respiratory failure and anuria. Transferred to the hospital's PICU, his condition deteriorated. Over the following days, he developed bilateral necrosis of the hands and feet and kidney failure secondary to sepsis. Two months later, Zion's hands and feet were surgically removed. Soon afterward, his kidneys failed, and he began dialysis. At age four, his mother would donate a kidney to him, initiating life-long immunosuppression therapy.

Despite all of this, Zion remained a normal, precocious child, qualities that impressed L. Scott Levin, MD, FACS, Chair of Orthopaedic Surgery and Professor of Surgery (Plastic Surgery) at Penn Medicine, when the two met almost two years ago. Dr. Levin had been considering pediatric vascularized composite allotransplantation (VCA) for some time, and in Zion, he felt he'd found a perfect candidate.

Zion was not only resilient and determined, but he had a few unique advantages that might have complicated recovery in another child. First, he had already passed the hurdle of immunosuppression, with its period of adjustment and accommodation. Second, his forearms had been preserved, meaning that the donor hands could be attached to native muscles, nerves and tendons, with vast implications for future recovery of function.

The rest, as they say, is history. Zion's successful surgery, an 11-hour procedure involving a team of 40 surgeons, anesthetists and support personnel, took place in July 2015. Several months later, we joined Dr. Levin in his office at the Penn Musculoskeletal Center to talk about Zion, his surgery, its planning and what lies ahead for the field of pediatric hand transplantation.

Dr Levin, first and foremost—how is Zion today?

Zion is progressing well. He's able to move his hands and fingers, and at this point he's picking up small objects and we've started to see some sensory perception occur in his hands. He's being monitored closely, of course, for signs of rejection or infection, and we're watching his kidney function. So far, he's functioning at expectation and very much engaged in his rehabilitative therapy.

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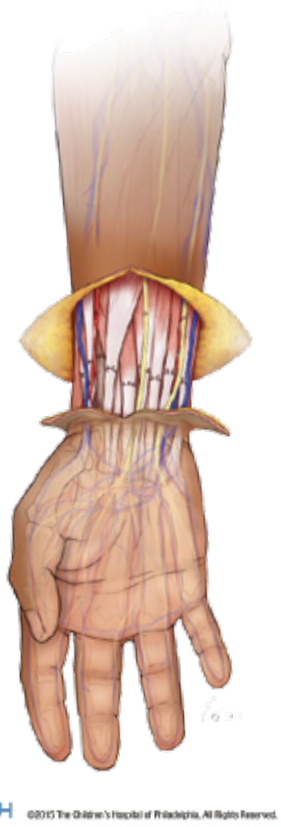

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(A) Pre-surgery medical illustration showing fully connected anatomy. (B) Surgeons performing transplant. (C) Zion before surgery. (D/E) Zion meeting with physical therapists after surgery.

How was Zion's VCA different from that of an adult?

There are physiological differences, first. The vasculature, nerves and musculoskeletal structures of children are much smaller and much more fragile than those of adults. Children respond to anesthesia differently, their intraoperative hemodynamics, fluid needs and body temperature are much more prone to fluctuation. The growth centers in children's bones are still developing, which can affect bone union and other late complications. Each of these elements presents intraoperative considerations that don't apply to adults, for the most part. Finally, and perhaps most importantly, the margin of error during surgery is much smaller for children.

How did you prepare for these differences, given that no one had ever performed this type of surgery before?

There's a book written by Gene Kranz, the NASA flight director for Apollo 13, called *Failure is not an Option*, and we took the title as our maxim. There was just no way we were going to fail. We had an established hand surgery transplantation protocol from our previous double-hand surgery (performed on an adult in 2011), so we knew how to set-up the operating rooms, and how the teams would coordinate. In addition, we had access to excellent orthopaedic, vascular, plastic and reconstructive surgeons, including Abraham Shaked, MD, PhD and Matthew Levine, MD, PhD, who have a combined 25+ years of experience performing solid organ transplants

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in children, and Benjamin Chang, MD at CHOP, who has performed microsurgical replantation surgeries for traumatic amputations in children. We also had an exceptional seasoned team of anesthesiologists, nurses and other specialists to fill specific critical roles on the team. In the end, we had more than 40 people.

Part of my role was to ensure that the team functioned as an orchestra of surgeons, nurses and anesthesiologists. So, for 18 months, we went through the procedure in mock drills, training sessions and cadaver trials—honing every step and technical execution.

There's an order, of course—first the donor hands are prepared. Then the radius and ulna are attached at each arm with hardware. Microvascular surgery is performed to connect the arteries and veins, and once blood flow is established, the muscles and tendons are reattached, and finally the nerves. Our objective throughout was to parse out the points at which something could go wrong and eliminate them—to reorganize the structure repair and optimize the efficiency of every step.

Other than your leadership, what was your role during the surgery?

Because of my training in orthopaedic surgery, plastic and reconstructive surgery and microsurgery, there was no part of the procedure I didn't take part in.

RECOVERY:
ZION HARVEY TODAY

At approximately four months post-transplant, Zion Harvey has begun to regain sensation in his wrists and the heal of his hand, according to outpatient occupational specialist Michelle Hsia, MS, OTR/L and Deborah Humpl, OTR/L at The Children's Hospital of Philadelphia (CHOP)

"He's beginning to have both deep and sensory nerve responses," Humpl says. "He's able to do some gripping with dynamic splints and he's pinching objects without a splint on."

Since his surgery, Zion has spent an average of six hours a day in an intensive program of rehabilitation therapy. For the first 8 weeks of his recovery, he was at CHOP. Thereafter, his rehabilitation has taken place near his home in Baltimore.

Early on, Zion's therapy consisted of splinting and motivational exercises to encourage the use of his fingers, as well as biofeedback and guided motor imagery techniques. An important element of his early therapy involved encouraging lateralization of his wrists and hands while gently discouraging adduction, a behavior acquired when his residual limbs served as hands to grasp and manipulate objects.

Zion's therapies also include electrical stimulation, biofeedback, range of motion, and activities of daily living that involve functionally oriented tasks. He returns to CHOP for follow-up on a monthly basis with the entire team, including Dr. Levin and members of the Department of Neurology.

As suggested by Frances Jensen, MD, the plasticity of Zion's brain has also become a focus of his rehabilitation. Hsia and Humpl note that neurologists at CHOP and at Penn are developing programs to help correlate Zion's brain mapping with his rehabilitation processes.

On the whole, it's clear that Zion is gradually returning to the life of a normal child. "When you see him holding his dad's hand and walking down a hall, you'd never know he'd had a hand transplant," Hsia says.

What We Can Learn from Zion's Brain

Monitoring Brain Synaptic Development Following Double-Hand Transplantation

According to **Frances Jenson, MD, FACP**, Chair of the Department of Neurology at Penn Medicine, monitoring of Zion Harvey's neurological development in the months and years after his transplant may have the potential to alter the approach to patients seeking hand transplantation and the rehabilitation of patients following the procedure—and may even benefit patients with traumatic brain injury.

"When we consider how the brain adapts over time, what we're looking at is nature vs. nurture," Dr. Jensen says. "We know that our brains are amazingly adaptable—particularly during the critical period of plasticity early in life when children have the molecular machinery to shape their somatosensory system on the basis of experience."

But what happens to a child who loses their hands, a primary source of sensory input to the brain, and thus the experience they provide for synaptic development—and more intriguingly, what happens when that source is restored? Dr. Jensen, Dr. Levin and their colleagues realized that Zion's case presented an unprecedented opportunity to watch a child's brain as it adapts to the re-introduction of somatosensory input.

"The areas of the brain that control his forearms had essentially taken over the portion normally occupied by the hands," Dr. Jensen says. "This makes a lot of sense because he was using his forearms as hands."

The nerves in Zion's hands and forearms will regenerate at the rate of about 1mm per day. During this time, and for the foreseeable future, Zion will be monitored to track how his brain adapts. The team hypothesizes that, over time, his hands will retake the territory previously lost to his forearms. A part of the practical value of these observations, Dr. Jensen explains, is that the information it provides will offer insight into the efficacy of specific types of physical therapy.

"What we hope to see in observing Zion is the correlation between physical therapy and development of the hand portion of the brain," she says. "Extrapolating from this evidence may help us determine which types of therapy are best suited to rehabilitation in all patients, independent of age, with hand amputation."

In the future, it may also be possible from information gleaned from Zion's brain development to tell whether someone is a good choice for hand transplantation—and how to optimize the brains of potential transplant recipients that might not otherwise be candidates for surgery.

There are, in addition, other potential advantages. "The work that we're doing around VCA allografts like Zion's might also be applicable to artificial prosthetics", Dr Jensen says. "It's a fascinating prospect, but the brain should re-wire to a prosthetic, and learn to interact with it in much the way it does a transplanted hand." Studying Zion's reaction to various forms of rehabilitation treatment could also provide valuable insight for advancing the treatment of patients who have sustained traumatic brain injury.

None of this would be possible, Dr. Jensen stresses, without the type of collaboration possible only at institutions like Penn. "This is the kind of thing we can do at Penn much more easily because we're basically pulling in two institutions, Children's Hospital of Philadelphia and Penn, as well as their respective neurology, psychology, physical therapy, and orthopaedic departments, as well as the engineering school at the University of Pennsylvania. We have this very collaborative group—and this kind of integration is really what we do best."

What clinical advances beyond that gained by having performed the first pediatric VCA have emerged as a result of Zion's surgery?

One of the areas that we're exploring now has to do with neuroplasticity. Zion hasn't had hands since he was two years old. This means that we don't really know what's happened to the neural pathways and synapses in his brain that would have developed since then to accommodate movement, sensation, dexterity and responses to the environment. We know from people who've had traumatic brain injury and stroke that the brain rewires itself to adjust to injury. So we've been monitoring Zion's brain to determine how, when and where this development takes place. Among other things, this may help us in the protocols for treatment of patients with brain injuries, and we've submitted a grant to the Department of Defense to support this effort.

Another area of research arising from surgeries like Zion's has to do with improving the risk/benefit ratio for lifelong immunosuppression in children. To achieve this goal, we've initiated a research program at Penn, funded by the Department of Defense and the Wyss Foundation, to discover safer and less toxic immunosuppression regimens.

(A) Zion undergoing physical therapy after surgery. (B) Seated (L to R) at a press conference: Dr. Levin, Zion and his mother, and Dr. Chang.

What's next for Zion? What are the expectations for him in 5 or 10 years?

Our belief is that Zion's hands will grow normally. I can say this with some confidence because we've been doing finger, hand, and arm replants in children with traumatic amputation for some time and have every reason to believe that the growth centers in the bones transplanted to Zion will respond in the same way as in these replantations. It's natural for transplant patients to undergo some degree of rejection, which is very treatable if caught early. So Zion will be monitored here and at home for redness, swelling and other signs of rejection. Finally, we have every anticipation that Zion will gain normal sensation and function in his hands as they reinnervate from his central nervous system. The reason for doing this surgery was to restore him to the kind of life that other children enjoy, to let him feel like a normal child and do all the things that children do. If all goes well, and we have every expectation that it will, we'll then be able to offer this surgery to other children who've either lost their hands to traumatic amputation or illness or who were born without hands.

I should add a note of caution here, because since Zion's surgery, we've been contacted by more than 250 families seeking our help. Someday I hope to help 1,000 kids like Zion. But the process of developing a pediatric hand transplantation program is a careful and deliberative one, and there are circumstances—particularly the availability of donor hands—that we cannot control. We're at the very beginning, and it's going to take time. ■

ZION'S TRANSPLANT TEAM *(in alphabetical order)*

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N. Scott Adzick, MD, MMM, FACS, FAAP
Sandra Amaral, MD, MHS
H. Jorge Baluarte, MD
Scott P. Bartlett, MD
David J. Bozentka, MD
Emily Braham, MSW, LSW
Robert B. Carrigan, MD
Benjamin Chang, MD
Caitlin Clarke
David Cohen, MD
Kathy Dunleavy, RN
Jeffery Feldman, MD
Kelly Ferry, MOT, OTR/L
Sara L. Fisher, MS, CCLS
Michele Friday, RN
Wayne W. Hancock, MD, PhD, FRCPA
Richard D. Hasz
Liz Henry
Michelle Hsia, MS, OTR/L
Deborah Humpl, OTR/L
Sonja Joiner-Jones, RN
Suhail K. Kanchwala, MD
Jason Kim, MD, MSCE
Stephen J. Kovach, III, MD
Scott H. Kozin, MD
Roberta Kramer, RN
Melissa Lanning, NP
Krisha Le Palma, PharmD
Debra Lefkowitz, PsyD
L. Scott Levin, MD, FACS
Todd Levy, MS, OTR/L, CBIST
Ines C. Lin, MD
Justin L. Lockman, MD
Sonya Lopez, RN, MSN, CRNP, CCTC
Leanne Magee, PhD
Maureen Mallon, RN
Christine McAndrew, PA-C
John McCloskey, MD
Michelle Nardone, DPT, PT
Kim M. Olthoff, MD
Jo Ann Palmer, CRNP, MSN, CCTC
Elisha Rampolla, RD, CSP, LDN
Laura Ramspacker, RN
Mohamed A. Rehman, MD
Abraham Shaked, MD, PhD
Sagine Simon MSN, RN, CPN, NEA-BC
David R. Steinberg, MD
Megan Synder
Stephanie Thibaudeau, MD
Teresa Weckesser, RN
Janet Weinstein
Anisa Yalom, MD
Dan A. Zlotolow, MD

Preventing Radiation-induced Bone Damage:

PTH1-34 and Enhancing DNA Repair through Canonical Wnt Pathway

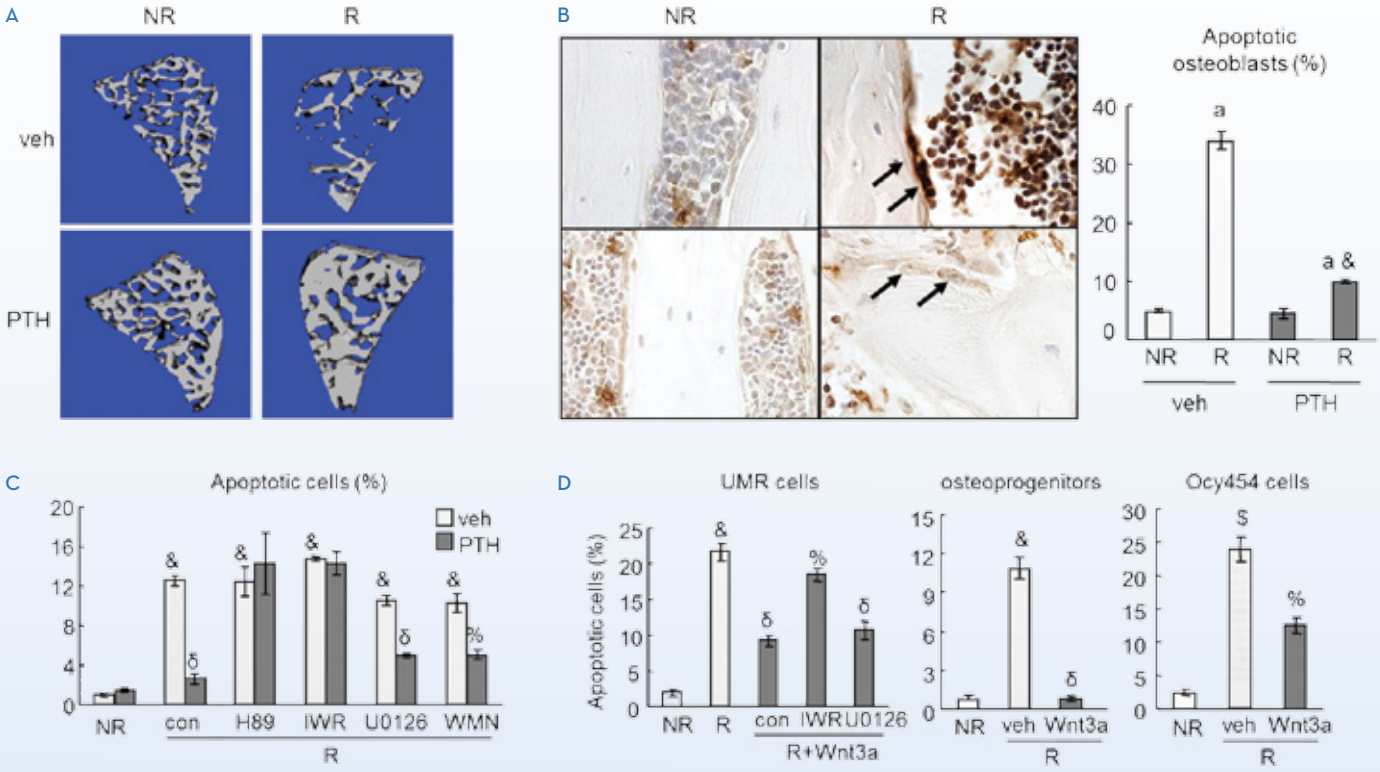
In a series of studies, researchers at Penn Medicine demonstrated that PTH1-34, the FDA-approved treatment for osteoporosis, provides a protective effect for irradiated bone. Because PTH1-34 is contraindicated in cancer and for patients with prior radiation therapy, a subsequent study (reviewed herein) was performed to elucidate the mechanism for this effect so that this knowledge may be applied to future studies to determine use in the clinical setting.

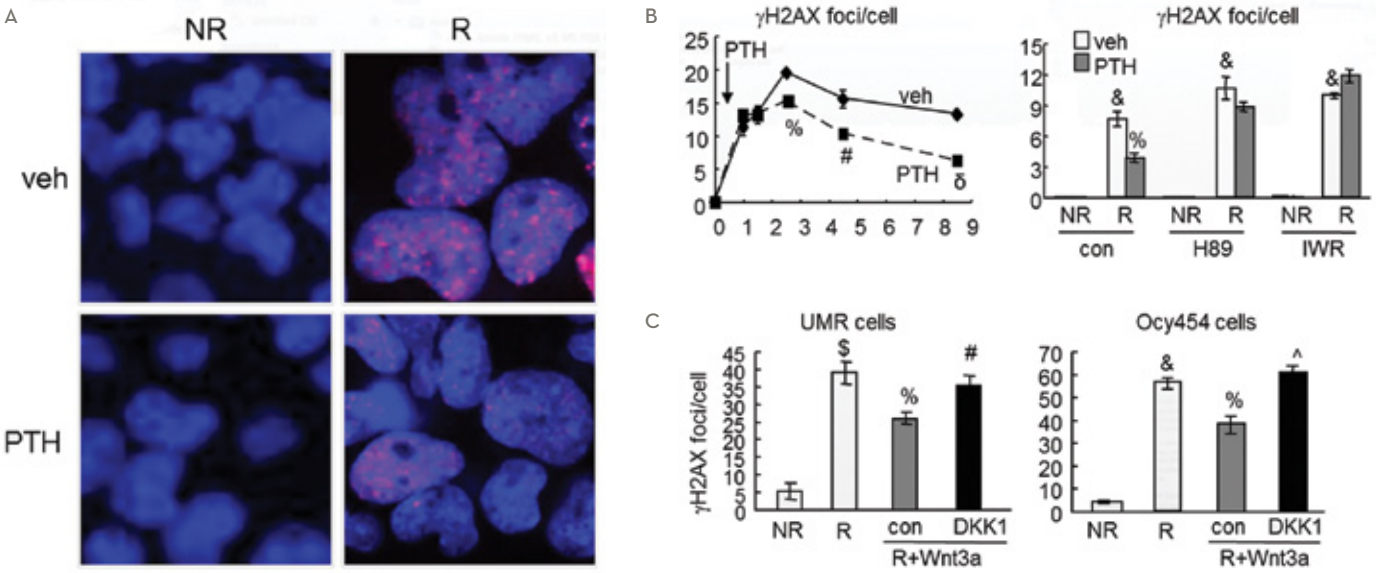
Bone damage is a common and irreversible late effect of radiation therapy for patients with solid tumor malignancies. Radiation-induced bone damage presents in a number of ways, including osteopenia, osteoradionecrosis and increased susceptibility for bone fracture. These adverse events can have a substantial effect on patient morbidity and mortality, particularly for elderly patients, who comprise a large proportion of patients receiving radiation therapy.

Bone is a dynamic structure, constantly maintaining and repairing itself through the balance of osteoclasts that break down bone cells and osteoblasts which rebuild them. The mechanisms of radiation-induced bone loss remain unknown, but bone histomorphometry and serum chemistry analyses suggest the culprit is the loss of functional osteoblasts and increased osteoclast activity. Radiation strongly affects osteoblasts and their precursors, osteoprogenitors, altering their differentiation and proliferation and increasing their sensitivity to apoptosis. Radiation therapy also induces lesions in the DNA of cells. Among these lesions, DNA double strand breaks (DSBs) are the most deleterious. While the cells attempt to repair the damaged DNA, most cells ultimately undergo apoptosis. The result is unusually high bone cell death coupled with the absence of osteoprogenitors to form new cells, leading to structural deterioration of the bone.

No treatment currently exists for radiation-induced bone damage. Osteoporotic bone loss, by contrast, has had an FDA-approved therapy since 2002, when recombinant human parathyroid hormone (PTH1-34) was introduced. Most other therapies for osteoporosis work by preventing the loss of bone. By contrast, PTH stimulates bone formation. An endocrine regulator of calcium and phosphorus homeostasis, PTH builds bone through a potent anabolic action on osteoblasts and osteocytes, where the PTH receptor is highly expressed and delays apoptotic signals—permitting more time for cell repair.

PTH protects radiation induced bone loss (A) and preserves functional osteoblasts (B), by regulating the Wnt pathway (C).
(D) Wnt3a directly regulates the survival of osteolineage cells.





(A/B) γ-H2AX assay demonstrates that PTH accelerates DNA repair in osteoblasts after radiation in a Wnt- β-catenin-dependent manner. (C) Wnt3a decreases γ-H2AX foci number in radiated osteoblastic (UMR) and osteocytic (Ocy454) cells via activating the canonical β-catenin pathway.

The bones of patients receiving PTH injections have a net gain in volume, as well as increases in connectivity and plate-like microarchitecture. This anabolic effect of PTH is largely the result of activation of protein kinase A (PKA), a well-defined signal transduction pathway in osteoblasts.

Despite a contraindication in patients with cancer and for patients with prior radiation therapy, the agent's capacity to rebuild bone led the orthopaedic research team at Penn Medicine to initiate a series of investigations to explore the mechanism of action of PTH1-34 in the hope that this information could be applied elsewhere to develop a safe, efficacious agent with similar capabilities.

The investigating team included Penn Orthopaedics, Penn Physical Medicine and Rehabilitation and the McKay Orthopaedic Research Laboratory (among other institutions) and the series of studies they have produced has achieved several promising results. Among these was the demonstration in a preclinical radiotherapy model that daily injection of PTH1-34 alleviates radiation-induced osteopenia by improving osteoblast survival, [Bone 55 (2013) 449–457] and the following study, which describes the anabolic mechanisms by which PTH1-34 blocks osteoblastic apoptosis to attenuate radiation-induced damage on bone.

Methods

To explore the survival effect of PTH on osteoblasts and the downstream pathways following irradiation, the investigators combined *in vitro* and *ex vivo* approaches to replicate the circumstances of normal bone. Thus, a variety of osteoblast-like cells (UMR) and osteocytes (OCY454) were utilized.

The cells were then irradiated, followed by the addition of PTH1-34. In some cases, UMR cells also received Wnt3a, a stimulant of the canonical Wnt pathway to elevate β-catenin activity. PTH1-34 or Wnt3a was also added after radiation of *ex vivo* calvarial organ culture to confirm *in vitro* data. This organ culture preserves much of the skeletal structure and offers greater physiological relevance. Staining followed radiation in order to detect apoptotic cells. Cells were then fixed, made permeable, and incubated with marker antibodies, which could then be quantified to ascertain post-radiation levels of apoptosis and DNA repair. A variety of staining and immunofluorescence procedures were also performed to enhance the measurement of the effects of PTH and the activated PKA and Wnt canonical pathways on irradiated cells.

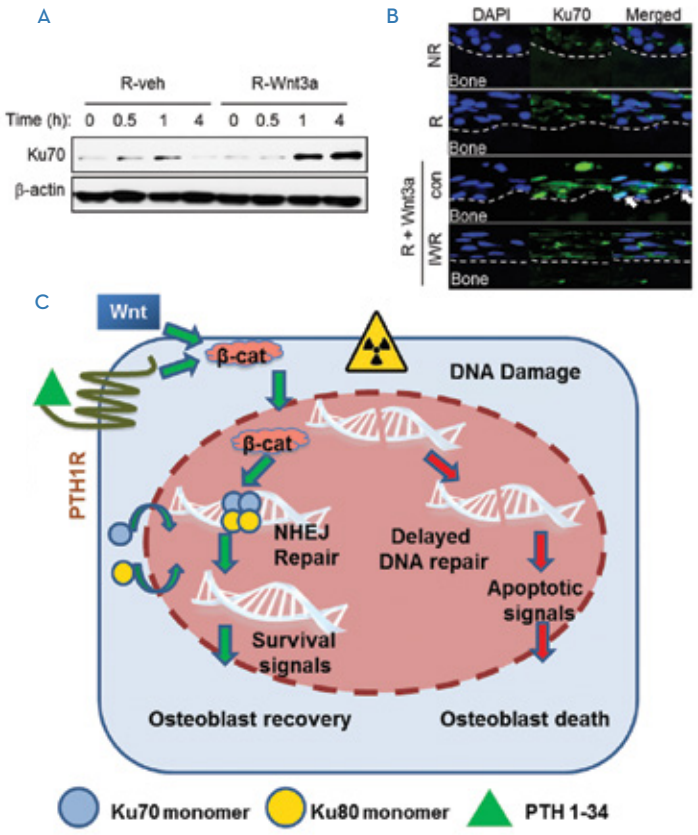
Results

PTH Alleviates Radiation-induced Apoptosis in Osteoblasts via PKA/β-catenin Pathway

Following radiation, the percentage of apoptotic osteoblasts increased from 1.0% pre- to 12.6% post-irradiation. Adding PTH1-34 post-irradiation decreased that percentage to 2.6%. The irradiation of osteoprogenitor cells resulted in an increase in apoptosis from 10% before to approximately 50% after radiation. In PTH1-34-treated samples, apoptosis was almost completely blocked.

Neither irradiation nor PTH1-34 altered the mRNA expression of β-catenin in osteoblastic cells, but did increase the amount of its protein and stimulated nuclear translocation, a requirement for β-catenin to activate Wnt target genes.

Inhibitors were introduced to substantiate pathway activity in the cell lines. In every instance, the inhibitors abrogated the study effect, demonstrating that PTH1-34 activates PKA and the canonical Wnt/β-catenin pathway to alleviate radiation-induced osteoblastic cell death.



(A) Wnt3a induces Ku7O amounts in a time dependent manner. (B) Immunohistochemistry of Ku7O in rat calvarial organ culture at 6h after radiation. Arrows point to Ku7O+ calvarial osteoblasts. (C) Schematic of possible scenarios after radiation and the role of PTH or WNT in influencing the fate of a radiated osteoblast.

PTH1-34 accelerates DNA Repair Post-irradiation

The irradiation of osteoblast-like (UMR) and calvariae (osteoblasts) cells caused a rapid increase in γ-H2AX, a sensitive marker for DSBs. The addition of PTH1-34 to UMR cells post-radiation significantly reduced the number of γ-H2AX foci/cells at 2, 4, and 8 hours. Similarly, a 16-fold increase occurred in the population of γ-H2AX foci/cells at 6 hours following the irradiation of calvariae. PTH1-34 greatly suppressed that increase. In irradiated cells, a 4.2-fold increase in DNA damage (DSBs) occurred at 8 hours. PTH1-34 treatment completely blocked that increase. The introduction of an inhibitor substantiated that PTH1-34-accelerated repair of radiation-induced DNA damage of osteoblasts is via the PKA/β-catenin pathway.

Effects of Activating the Wnt Canonical Pathway in Post-Irradiated Bone Cells

After the irradiation of UMR osteoblast cells, staining showed that Wnt3a, a canonical Wnt, strongly suppressed radiation-induced apoptosis. Similar to PTH1-34, the use of Wnt inhibitors, in this case to the canonical pathway, counteracted irradiation-induced apoptosis. The effect of decreasing apoptosis with Wnt3a was also observed in osteocytes and calvarial osteoblasts. Using γ-H2AX foci staining, Wnt3a, as with PTH1-34, reduced the γ-H2AX foci number, in this case by 33% in osteoblastic UMR cells. Inhibitors prevented Wnt3a from decreasing the number of γ-H2AX foci/cell. Thus, the Wnt canonical pathway decreases the extent of radiation-induced DNA damage and apoptosis, thereby protecting osteoprogenitors, osteoblasts, and osteocytes.

Ku70 Mediates DNA Repair and Cell Survival Effects of PTH and Wnt3a after Radiation

Ku70 is a protein that binds to the ends of DSBs to join them together during DNA repair as a component of the non-homologous end-joining (NHEJ) pathway. An increase in Ku70 levels, therefore, suggests a concomitant increase in DSB repair. The addition of Wnt3a to UMR cells brought about an eight-fold increase in Ku70 at four hours, an effect that requires the Wnt/β-catenin canonical pathway, and had a similar effect on calvarial osteoblasts. When added to UMR and calvarial cells, PTH1-34 also provoked increases in Ku70 levels. Together, these findings demonstrate the β-catenin pathway-dependent up-regulation of Ku70 could be among the mechanisms for accelerated DNA repair by PTH1–34 and Wnt3a.

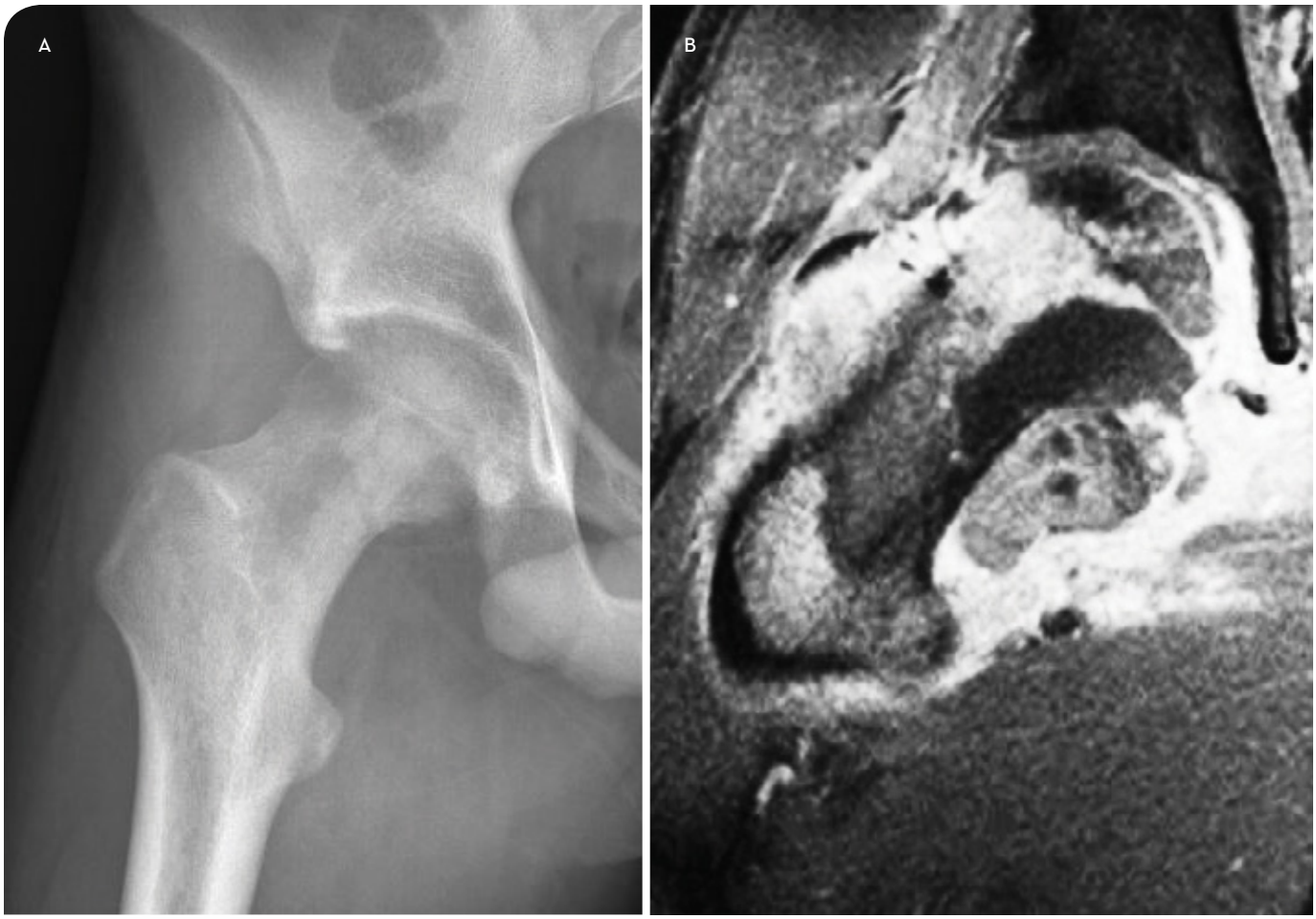
Discussion

These *in vitro* and *ex vivo* studies demonstrate that PTH rescues radiation-induced osteoblast apoptosis by accelerating the repair of DNA double-strand breaks and suppressing apoptotic signaling, and provides mechanistic explanation for the authors' previous finding that PTH1–34 alleviates the loss of local trabecular bone after radiation by preserving bone lining osteoblasts.

However—concern exists about the use of PTH in cancer patients, particularly those with an increased baseline risk for osteosarcoma and among patients who previously received radiation therapy. For this reason, the revelation that the canonical Wnt pathway has similar effects in protecting osteoblasts from radiation damage is significant. It is known that agents other than PTH1-34, including sclerostin-neutralizing antibody, can activate Wnt/β-catenin. Sclerostin is an osteocyte-specific protein that diffuses to bone surface, binds to osteoblasts, and then negatively regulates Wnt-mediated osteoblastic bone formation. Sclerostin appears not to be associated with any cancer and therefore targeting it should have less concern.

The neutralizing antibody against sclerostin is clinically proven to be a potent anabolic treatment for osteoporosis and is currently in a Phase 3 clinical trial. The authors are now testing this antibody treatment in the animal model of focal radiotherapy developed for their studies of PTH1-34. ■

Reference // 1) Chandra A, Lin T, Zhu J, Tong W, Huo Y, Jia H, Zhang Y, Liu XS, Cengel K, Xia B, Qin L. PTH1-34 blocks radiation-induced osteoblast apoptosis by enhancing DNA repair through canonical Wnt pathway. J Biol Chem. 2015 Jan 2;290(1):157-67. doi: 10.1074/jbc.M114.608158. Epub 2014 Oct 21.



(A) Radiograph of the right proximal femur showing high-grade osteosarcoma. (B) Coronal MRI of the same patient demonstrating surrounding soft tissue mass.

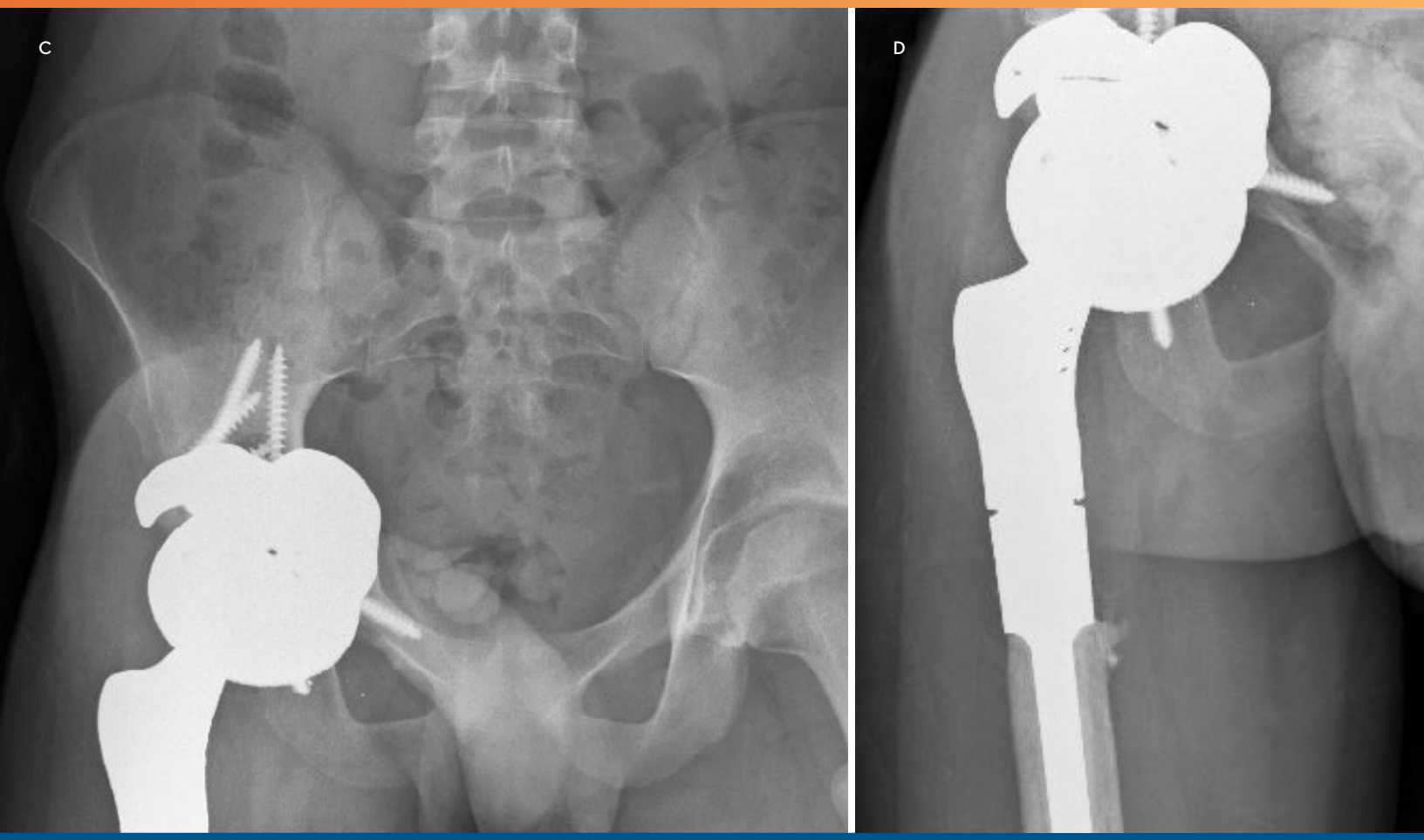
Surgical and Medical Management of Osteosarcoma

Primary bone sarcomas are rare (~1% of all adult cancers) and occur from infancy through late adulthood. The majority of patients with these tumors have pain at the bony site in addition to stiffness or swelling in an adjacent joint. Treatment varies depending on tumor type, grade, and location, as well as the age of the patient. The most common bone sarcomas include osteosarcoma, chondrosarcoma, and Ewing sarcoma.

The Penn Orthopaedics Sarcoma Program is devoted to the management of patients with benign and malignant tumors of bone and soft tissues. The program's mission is to build a world-class multidisciplinary clinical team complemented by a strong foundation of basic and translational research to better diagnose and treat patients with bone and soft-tissue sarcomas.

The management of patients with osteosarcoma involves an individualized multidisciplinary approach beginning with accurate diagnosis. At Penn, musculoskeletal radiologists and pathologists, medical/pediatric oncologists, radiation oncologists and surgeons from several specialties including orthopaedics, neurosurgery, plastics surgery and general surgery review sophisticated imaging studies as well as tissue from minimally invasive, image-guided needle biopsies. MRI scans with specific tumor sequences allow orthopaedic oncologists to better plan surgical procedures by accurately determining the tumor characteristics and extent.

The objectives of osteosarcoma treatment include preservation of limb function and prevention of disease recurrence, progression or metastasis. Limb preservation techniques for malignant tumors of bone and soft tissue are a specialty of the Sarcoma Program at Penn Medicine. These procedures are personalized to the patient taking into account age, location and stage of the tumor and other adjuvant or neoadjuvant medical treatments. Patients with osteosarcoma require chemotherapy before and after surgery to remove the bone tumor.



(C) Acetabular reconstruction with a tantalum uncemented component and multiple augments. (D) Proximal femoral megaprosthesis with reconstruction of the abductor and iliopsoas tendons.

RK, an 18-year-old, began experiencing pain in his right hip in June of 2014. The pain gradually worsened, requiring increasing doses of pain medication. Imaging studies at an outside institution initially suggested a benign synovial condition called pigmented villonodular synovitis (PVNS). With the development of worsening symptoms and a limp, repeat imaging studies were ordered, and these showed a destructive bone-producing lesion in the proximal femur with a surrounding soft tissue mass (Figs. A and B on previous page).

RK was referred to the Penn Orthopaedic Oncology service and had a CT-guided needle biopsy of the right proximal femur lesion that revealed a high-grade osteosarcoma. Staging studies showed no evidence of metastasis. The patient began systemic chemotherapy and was scheduled for resection of the primary tumor in January 2015. Because his osteosarcoma was located in the proximal femur and extended into the hip joint, his surgical options included a hindquarter amputation or an extraarticular wide resection and complex hip/acetabular reconstruction.

RK opted for limb salvage, and a team of hip reconstruction and orthopaedic oncology surgeons was assembled.

A successful extraarticular resection of the right hip joint and proximal femur was performed with negative margins and 70% necrosis of the tumor as a result of chemotherapy. Reconstruction involved a proximal femoral megaprosthesis with reconstruction of the abductor and iliopsoas tendons and a complex acetabular reconstruction with a tantalum uncemented component and multiple augments (Fig. C and Fig. D above).

After surgery, RK was in a hip abduction brace for 6 weeks and protected weight bearing for three months to allow bony ingrowth into the tantalum acetabular component.

Having completed chemotherapy, RK remains cancer free, and is now walking with a cane and working to regain right leg strength in physical therapy. He will be followed closely for signs of local or systemic recurrence of osteosarcoma.

The Importance of Limb Salvage in Orthopaedic Oncology

At Penn, every effort is made to perform limb salvage in order to maintain the function of the extremity and minimize the risk of local recurrence—although amputation of the limb remains necessary for 5-10% of patients.

The need for limb salvage is especially acute in younger patients with osteosarcoma and, in this respect, RK is typical of many patients referred to Penn Medicine. When limb salvage can be achieved, it involves a combination of coordinated therapies as well as the contribution of specialists with extensive training in surgery for the disease and in the methods, approaches, and types of therapy most likely to lead to recurrence-free survival. The follow-up to surgery, including rehabilitation and monitoring, is also of critical importance.

Surgical management of osteosarcoma has benefited from advances in the technology of internal fixation, soft tissue attachments to prostheses, and biologic options to recreate living bone. When osteosarcoma occurs near a joint, the most common method of reconstruction involves metal prosthetic joints. Improvements in biomechanics, metallurgy and engineering have allowed for the development of advanced, modular prostheses that provide a more durable, long-lasting reconstruction for patients who are candidates for limb salvage surgery.

Osteosarcoma Research at Penn and the Future of Sarcoma Treatment

The vision for the Sarcoma Program is multifaceted, starting with the development of a strong foundation of basic and translational research in Sarcoma at Penn. This has been approached through the development of collaborative research programs at Penn Medicine, Penn Veterinary Medicine, and The Children's Hospital of Philadelphia (CHOP), and relationship building with other renowned sarcoma programs throughout the US. The program will work to take scientific discoveries from Penn and move them to Phase I clinical trials for patients with sarcoma, as well as use the existing sarcoma tissue bank and add new patient samples for genomic analysis to identify patient-specific therapeutic targets for treatment and improve outcomes. Currently, discoveries made at the Penn Veterinary School using a vaccine-based approach in dogs with osteosarcoma has shown excellent results and plans are underway to move this treatment into clinical trials for children with osteosarcoma.

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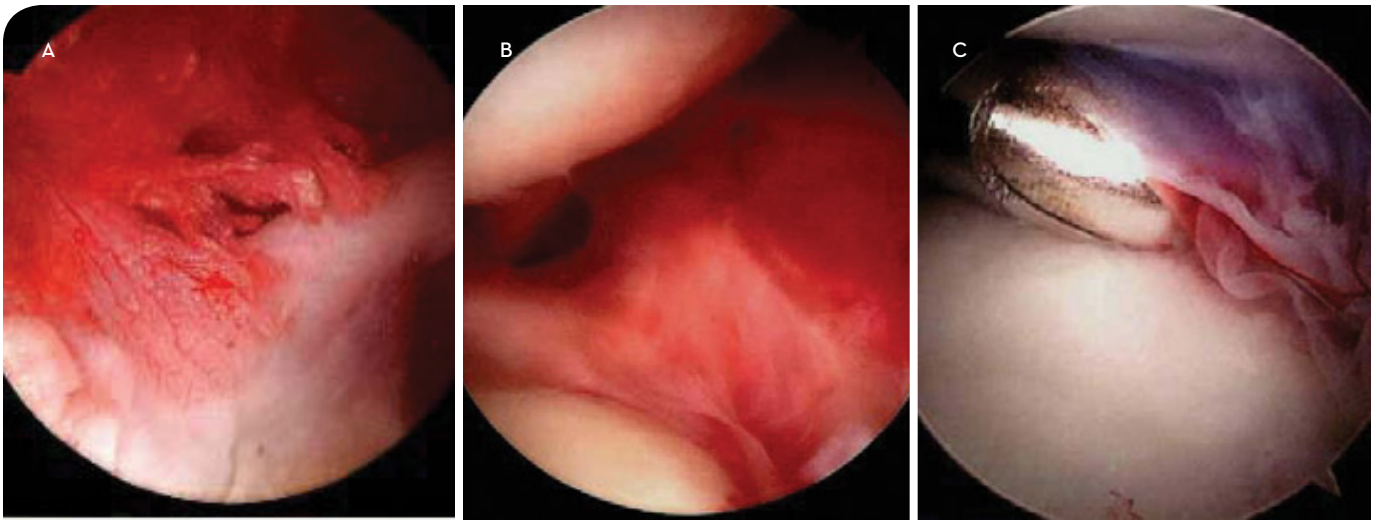
Future advances in the treatment of patients with osteosarcoma will likely come from the laboratory in the form of new drugs or biologic agents that can specifically target the tumor cells to prevent metastasis. The prospect that patients at the Sarcoma Program at Penn Medicine will have access to these therapies is greatly increased by the Program's affiliation with the Abramson Cancer Center, home to advanced genetic research and conduit for Penn patients to advanced clinical trials across the nation. ■



(A/B) Representative arthroscopic images of the inflammation and synovitis seen in patients with *P Acnes* infection. Articular cartilage is typically preserved, but the joint is characterized by hypertrophic, inflamed tissue. (C) An arthroscopic shaver is being used to remove or clean out this affected tissue.

Propionibacterium Acnes Infection
in Shoulder Arthroscopy Patients with Postoperative Pain

Propionibacterium acnes (*P acnes*) has become a prime suspect in shoulder infections leading to revision surgery in patients having shoulder arthroplasty. Researcher and orthopaedic surgeon Russell Huffman, MD, and team performed a prospective study at Penn Medicine to examine the incidence of *P acnes* infection in patients having arthroscopic shoulder surgery.

In recent years, *Propionibacterium acnes* (*P acnes*) has been implicated as a significant cause of shoulder surgery failure. It wasn't always this way. For most of its known history (first described by Unna in 1896), *P acnes* was considered a minor contaminant rather than a primary pathogen in anatomical sites beyond the skin. A non-spore-forming, gram-positive anaerobic bacillus normally associated with common acne, *P acnes* resides in the hair follicles and sebaceous pores of the skin. Under ordinary circumstances, *P acnes* infection beyond this superficial habitat is rare. When such infections do occur, however, they lack the defining symptoms of deep tissue infection. Fever, erythema and elevated inflammatory markers, for example, are absent in most *P acnes* deep-tissue infections.

P acnes became a pathogen of interest in shoulder surgery when its pathogenicity was confirmed in an increasing number of deep tissue infections following open arthroplasty surgery. Notably, few reports emerged to shed light on the *P acnes* risk for arthroscopy, the minimally invasive (and presumably less hospitable to infection) alternative to open surgery.

Thus, Russell Huffman, MD, and co-investigators John Horneff III, MD, Jason E. Hsu, MD, Pramod B. Voleti, MD, and Judith O'Donnell, MD, initiated a prospective study at Penn Medicine to examine the incidence of *P acnes* infection in patients having arthroscopic shoulder surgery.[1]

Methods – Over a period of more than four years (January 1, 2009 until April 1, 2013), the team prospectively collected data on all revision shoulder arthroscopies performed at Penn by Dr. Huffman. More than half of these revisions (60%) were for surgeries originally performed at outside hospitals. From this population, the team isolated 68 patients who had revision procedures for pain, stiffness or weakness. Cultures were then obtained from these patients.

Because extended incubation times required for isolating *P acnes* raise concerns for false-positive findings in many studies, the author's study design incorporated a control group of 32 patients undergoing index arthroscopy. This number provided a study certainty of 90% and allowed the demonstration of a true association between positive cultures and clinical failure after shoulder arthroscopy.

Results – Of the 68 patients who underwent revision shoulder arthroscopy between January 2009 and March 2013, 16 (23.5%) were positive for *P acnes*. In the control group, only 1 patient (3.2%) had *P acnes* growth. *P acnes* should therefore be considered in cases characterized by refractory postoperative pain and stiffness.

Discussion

The results of this study show a significant association between positive *P acnes* cultures and failure after shoulder arthroscopy, and a rate of *P acnes* infection in patients undergoing revision shoulder arthroscopy higher than previously published.

It is interesting to see that even the "lower risk" shoulder arthroscopy patient is not immune to the effects of *P acnes* infection, though not as high as that in shoulder arthroplasty patients. It is equally interesting that infection symptoms can present as much as 2 years or more after surgery. Because of these findings, clinicians must be conscious of *P acnes* in patients who present with unexplained pain and stiffness after otherwise uncomplicated shoulder arthroscopy.

Diagnosing *P acnes* infection

Diagnosis requires careful attention to the patient's history and physical examination, especially for increasing pain and decreasing range of motion. A thorough infection diagnostic workup requires multiple modalities including: physical examination, imaging, blood work with a white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and shoulder aspiration culture with cell count.

A high index of suspicion for infection should exist when *either* physical examination or radiographic imaging is concerning. This is because a patient presents signs of infection during the physical examination may not have any infectious signs on radiography, and vice versa.

Physical examination – *P acnes* infections of the shoulder are difficult to assess on physical examination because of the indolent nature of the bacteria. Stiffness, limited range of motion and continued pain are the most likely symptoms to present and may appear years after the initial surgery.

Imaging – Imaging has been shown to offer little additional information to aid in making a definitive diagnosis. However, evaluation of the painful postoperative shoulder should always include plain radiographs (anterior-posterior view, scapular-Y view, and axillary view) to rule out subluxation of the humeral head, heterotopic ossification, hardware failure, joint arthrosis or other mechanical causes that contribute to joint pain and stiffness postoperatively.

Laboratory Evaluation and Culture – Prolonged incubation and proper specimen handling are necessary to minimize false-negative cultures when *P acnes* infection is suspected. Multiple surgical tissue specimens remain the gold standard when aspirates are negative and clinical concern is present. A seven-day incubation period seems to be sufficient time for *P acnes* growth if all the tasks of collection and preparation are under ideal anaerobic conditions; under aerobic conditions, however, incubation should last at least two weeks.

Preventing *P acnes* Infection

Perhaps the best way to treat a potential surgical site infection is to prevent it from happening in the first place. Strategies to decrease the chance of infection can be performed in the pre-operative and perioperative periods, and many of these strategies have become the standard of care for orthopaedic surgical care.

Preoperative Surgical-Site Preparation – Preoperative surgical-site antiseptic solutions are generally ineffective for the prevention of *P acnes* because the active bacteria reside within the hair follicles and sebaceous glands deep within the skin.

Other methods of reducing infection which go beyond just surface cleaning may be more efficacious, however.

Perioperative Preventative Procedures – Many techniques for decreasing the rate of *P acnes* infection can be implemented in the operating room at the time of surgery. These include proper hair clipping and draping of the surgical site, the use of proper ventilation flows, reduced operating theater traffic, and sterile autoclaving of surgical instruments and equipment. The use of separate knives for the skin (where infection resides) and deeper layers during surgery may also reduce the incidence of infection.

Antibiotic therapy is often not sufficient as a lone means of prevention, particularly with regard to shoulder surgery involving the use of implants, the components of which may harbor resistant strains of *P acnes*.

Post Surgical Treatment for *P acnes* Infection

Successful treatment of *P acnes* infection includes a high clinical suspicion in the post-surgical patient with continuing complaints. Typically the treatment of a deep infection in the shoulder requires a multimodal approach with antibiotics, surgical debridement, and potential revision surgery. In the setting of infected arthroplasty or fracture nonunions, a staged surgical approach may be best.

In the case of an obvious infected shoulder arthroplasty immediately after surgery, treatment options include 1- or 2-stage exchange, resection arthroplasty, irrigation and debridement, antibiotic suppression, and arthrodesis. This approach is in compliance with the standard guidelines of orthopedic care for an infected arthroplasty.

In the instance of indolent *P acnes* infection, the choice of operative treatment is not as easily discerned, as the diagnosis is often elusive. Most practicing orthopaedic surgeons, however, agree on a multimodal approach with antibiotics and surgical treatment. ■

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