VOLUME 6, ISSUE 14 | MAY 4, 2010

Orthopedics This Week

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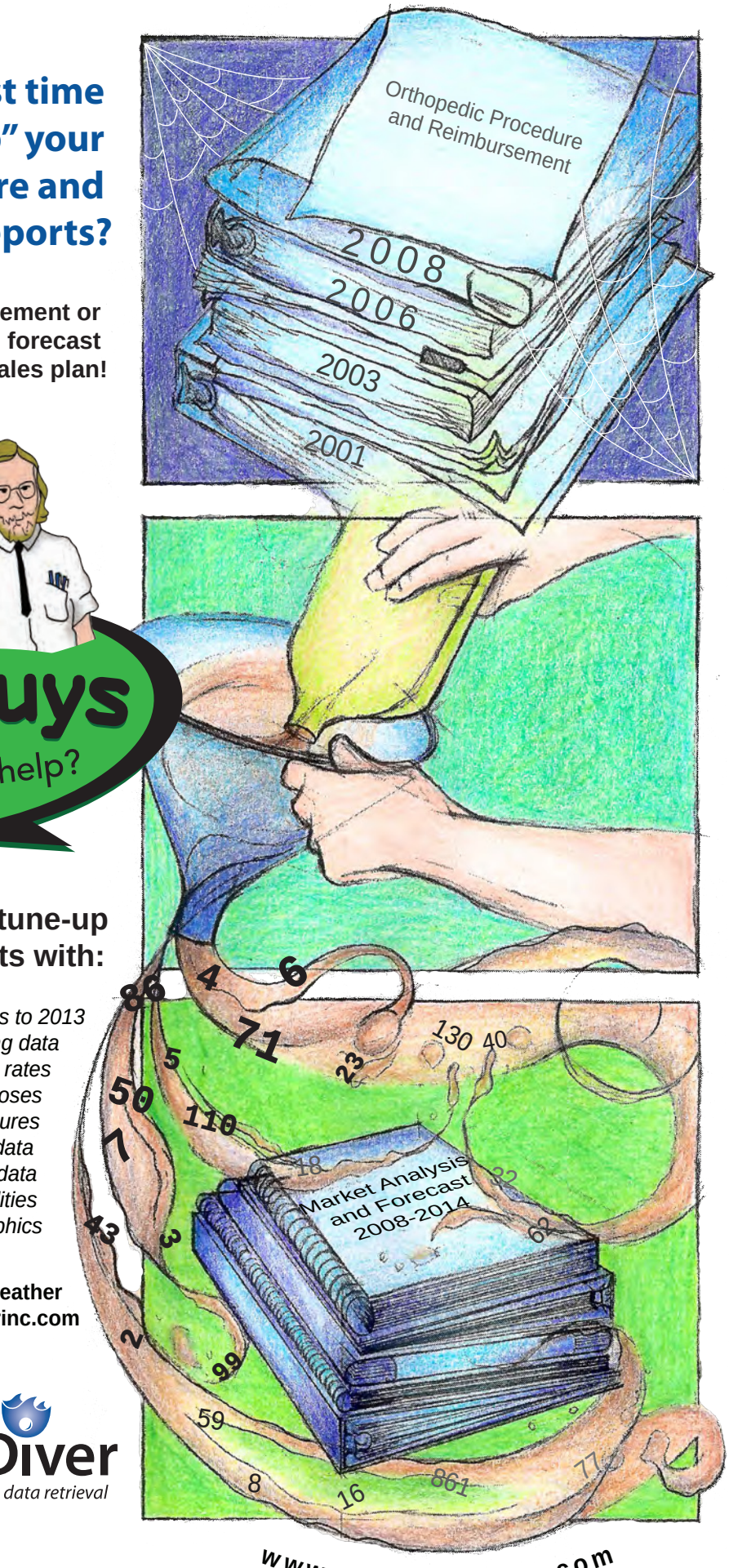

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Orthopedics This Week

VOLUME 6, ISSUE 14 | MAY 4, 2010

Orthopedic Power Rankings

Robin Young's Entirely Subjective Ordering of Public Orthopedic Companies

This Week: CONMED, Exactech, Stryker, Orthofix, and Integra comfortably exceeded Wall Street's sales and earnings forecasts in the first quarter. The average orthopedic stock is trading at 14x earnings (vs. the S&P at 22x) and the market capitalization for the industry is DOWN 1.2% in the last 30 days. Blue light special.

Rank	Last Week	Company	TTM Op Margin	30-Day Price Change	Comment
1	1	Orthofix	11.00%	(5.86%)	OFIX beat all estimates, paid more debt ahead of schedule and piled up cash. Still THE least expensive equity in ortho.
2	2	Integra LifeSciences	15.37	2.92	IART beat Wall Street's earnings estimates soundly. Posted 56% jump in earning in Q1. Wow.
3	3	Stryker	24.71	(0.12)	Double-digit sales (+12%) and even better earnings growth. Hospital equip sales +15%!
4	5	Medtronic	31.37	(2.59)	CareFusion is in the medical commodities business. They are challenging MDT's Kyphoplasty? Baloney.
5	4	Symmetry	11.48	16.3	Ten other companies are cheaper than SMA. That's amazing for a wholesaler like this.
6	9	Exactech	12.61	2.1	EXAC crushed the numbers in Q1. Wall Street expected a down quarter but EXAC delivered 33% earnings growth.
7	10	CONMED	7.73	(8.36)	Hospital spending is back and CONMED reported an unexpectedly strong 15% sales growth and 67% earnings pop!
8	6	Johnson & Johnson	27.1	(0.92)	Ummm…raised the dividend again. The new yield is 3.40%—which is better than most banks.
9	7	Alphatec	(0.44)	5.03	Selling products in roughly 60 countries, posting $250 million in annual sales, ATEC is in a new league.
10	8	Orthovita	(0.07)	(6.54)	Wall Street was expecting $25 million in Q1 sales. Actual was $24 million.

Orthopedics This Week

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Robin Young's Orthopedic Universe

Top Performers Last 30 Days

	Company	Symbol	Price	Mkt Cap	30-Day Chg
1	Symmetry Medical	SMA	$11.56	$414	16.3%
2	Wright Medical	WMGI	$18.78	$728	5.7%
3	Smith & Nephew	SNN	$51.90	$9,160	5.2%
4	Alphatec Holdings	ATEC	$6.68	$362	5.0%
5	ArthroCare	ARTC	$30.93	$833	3.7%
6	Zimmer Holdings	ZMH	$60.91	$12,360	3.2%
7	Integra LifeSciences	IART	$45.43	$1,300	2.9%
8	Capstone Therapeutics	CAPS	$0.93	$38	2.2%
9	Osteotech	OSTE	$4.25	$77	2.2%
10	Exactech	EXAC	$20.46	$263	2.1%

Worst Performers Last 30 Days

	Company	Symbol	Price	Mkt Cap	30-Day Chg
1	Regen Biologics	RGBO.PK	$0.20	$2	-55.6%
2	RTI Biologics Inc	RTIX	$3.83	$208	-13.7%
3	Synthes	SYST.VX	$113.23	13,438	-8.8%
4	CONMED	CNMD	$22.24	$649	-8.4%
5	NuVasive	NUVA	$41.60	$1,620	-7.3%
6	TiGenix	TIG.BR	$3.34	$103	-7.2%
7	Orthovita	VITA	$4.00	$306	-6.5%
8	CryoLife	CRY	$6.11	$174	-6.3%
9	Orthofix	OFIX	$34.19	$599	-5.9%
10	Kensey Nash	KNSY	$22.65	$229	-5.0%

Lowest Price / Earnings Ratio (TTM)

	Company	Symbol	Price	Mkt Cap	P/E
1	Kensey Nash	KNSY	$22.65	$229	12.30
2	Medtronic	MDT	$43.69	$48,130	13.48
3	Johnson & Johnson	JNJ	$64.30	$176,950	13.78
4	*Average*			*$11,652*	*14.19*
5	Zimmer Holdings	ZMH	$60.91	$12,360	14.68

Highest Price / Earnings Ratio (TTM)

	Company	Symbol	Price	Mkt Cap	P/E
1	Smith & Nephew	SNN	$51.90	$9,160	79.19
2	RTI Biologics Inc	RTIX	$3.83	$208	63.68
3	NuVasive	NUVA	$41.60	$1,620	37.62
4	ArthroCare	ARTC	$30.93	$833	28.59
5	Integra LifeSciences	IART	$45.43	$1,300	21.60

Lowest P/E to Growth Ratio (Earnings Estimates)

	Company	Symbol	Price	Mkt Cap	PEG
1	CryoLife	CRY	$6.11	$174	0.68
2	NuVasive	NUVA	$41.60	$1,620	0.90
3	Smith & Nephew	SNN	$51.90	$9,160	1.12
4	Integra LifeSciences	IART	$45.43	$1,300	1.16
5	Orthofix	OFIX	$34.19	$599	1.26

Highest P/E to Growth Ratio (Earnings Estimates)

	Company	Symbol	Price	Mkt Cap	PEG
1	Orthovita	VITA	$4.00	$306	13.87
2	CONMED	CNMD	$22.24	$649	8.97
3	Alphatec Holdings	ATEC	$6.68	$362	3.46
4	Symmetry Medical	SMA	$11.56	$414	2.05
5	Johnson & Johnson	JNJ	$64.30	$176,950	1.89

Lowest Price to Sales Ratio (TTM)

	Company	Symbol	Price	Mkt Cap	PSR
1	Osteotech	OSTE	$4.25	$77	0.79
2	CONMED	CNMD	$22.24	$649	0.93
3	Orthofix	OFIX	$34.19	$599	1.12
4	Symmetry Medical	SMA	$11.56	$414	1.13
5	RTI Biologics Inc	RTIX	$3.83	$208	1.27

Highest Price to Sales Ratio (TTM)

	Company	Symbol	Price	Mkt Cap	PSR
1	TiGenix	TIG.BR	$3.34	$103	99.76
2	Mako Surgical	MAKO	$14.03	$472	13.79
3	NuVasive	NUVA	$41.60	$1,620	4.05
4	Synthes	SYST.VX	$113.23	$13,438	3.96
5	Orthovita	VITA	$4.00	$306	3.30

Orthopedics This Week

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Regenexx: Recipe for Controversy?

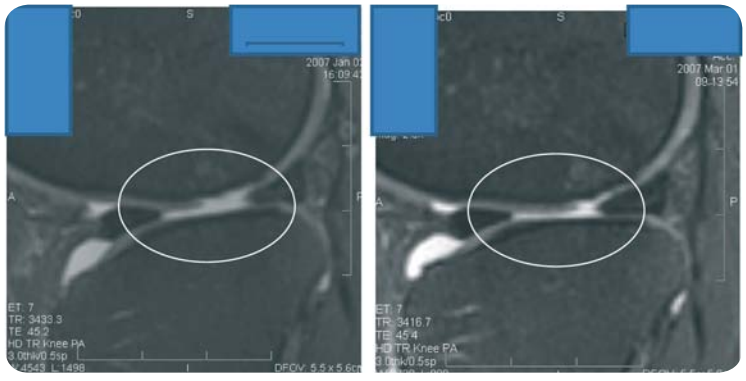
By Jacqueline Rupp

With stem cell therapies changing and morphing at an increasing rate, FDA appears more than ever open to interpretation. Clinics that offer up novel and sometimes controversial stem cell treatments may be on a collision course in fact with the agency. Some worry about the efficacy of such treatments and protecting the patient from slickly marketed innovations that lack results. Others are concerned with clinics being able to dodge regulation and review. At the same time physician-led clinics see stem cell advancements as holding a promise to patients, once removed from pharmaceutical companies and long, drawn-out trials.

Lab-Cultured Stem Cell Therapy in Colorado

Drs. Chris Centeno and John Schultz operate the only U.S.-based clinic/lab (that we are aware of) that offers lab-cultured mesenchymal stem cell (MSC) therapies to patients suffering from joint pain. Because of that, the team is raising both eyebrows and hope for orthopedic patients. The pair incorporated their clinic as Regenerative Sciences Inc. (RSI) some years back and are based in Broomfield, Colorado. Their specific technique, which is branded Regenexx, uses patient-derived (autologous) mesenchymal stem cells to treat various orthopedic indications including maladies of the hands, hips, knees, shoulders, back (non-spinal cord injury), ankles, and even bone fractures.

"We have seen the best results with partial tendon and ligament tears which are non-retracted," explains Dr. Christopher Centeno, "such as partial rotator cuff and partial ankle ligament tears. We have also seen good one-year follow-up data on knees with moderate OA [osteoarthritis] (knee replacement candidates) and will be publishing on a dataset of about 200 patients soon."



Before and after knee MRIs courtesy of the Centeno/Shultz Clinic

The Regenexx procedure is comparatively straightforward. It begins with the extraction of a sample of the patient's bone marrow, from which stem cells are isolated, cultured and then combined with the patient's own blood and re-injected into the treatment area.

Since the start of this year, Centeno's clinic has treated 333 patients with a total of 754 Regenexx injections. While other clinics may employ, for example, allograft forms of bone material which contain MSCs, the RSI clinic is the only one that cultures the patient's own MSCs into an expanded number, up to 10 million, of MSCs before injecting them back into the patient.

As for his background, Dr. Centeno is board certified in physical medicine, rehabilitation medicine, and pain management through the American Board of Anesthesia. He is the founding member of the International Cellular Medicine Society and the Spinal Injury Foundation and completed a residency at the Baylor College of Medicine and training at the Texas Medical Center and the Institute for Rehabilitation Research.

Okay, but Is It Safe and Does It Work?

Dr. Centeno has published a number of papers in peer review journals including, recently, a paper titled "Safety and complications reporting on the re-implantation of culture-expanded mesenchymal stem cells using autologous platelet lysate technique" in *Current Stem Cell Research & Therapy,* March 2010.

Lab Tech/Wikimedia Commons

The study looked at patients who were treated at Centeno's clinic for a variety of orthopedic conditions using his Regenexx culture-expanded, autologous, bone marrow-derived MSCs. As described in his paper, the cells were cultured in monolayer culture flasks using an autologous platelet lysate technique and then re-injected into the subject's peripheral joints or intervertebral discs. Follow-up MRIs over the course of two years failed to demonstrate any tumor formation at the re-implant sites. That is, incidentally, consistent with other research which has found no evidence of malignant cellular change due to and after implantation of expanded MSCs.

Another paper, a review, was published in *Medical Hypotheses,* in September 2008 titled "Regeneration of meniscus cartilage in a knee treated with percutaneously implanted autologous mesenchymal stem cells". The paper, which was authored by Dr. Centeno, presents his experience using his techniques with autologous MSC therapy and, no surprise, reports that it was a "successful harvest, expansion, and transplant of autologous mesenchymal stem cells into an adult human knee that resulted in an increase in meniscal cartilage volume."

RSI charges between $7,000-$8,500 for the treatment—depending on indication. This price includes the marrow and blood draw, lab expansion of the cells, pre-injection, re-injection of cells, and post injection(s). The procedure is not covered by insurance, something Centeno hopes will change soon. "There are about 11,000 published articles on autologous mesenchymal stem, so yes, with that type of publishing activity (several thousand papers a year), it's likely to be a foregone conclusion that at some point, in my opinion, this type of stem cell therapy will get insurance approval."

"The Regenexx procedure is needle based, so it's less invasive than traditional surgery," says Centeno. "There is also opportunity to provide MSCs with traditional or minimally invasive orthopedic surgery techniques. MSCs have been shown to aid in cartilage, meniscus, ligament, tendon, and bone healing. In addition, they also seem to improve osteointegration of grafts. For example, we have worked with local surgeons to inject cells after knee micro fracture procedures."

The FDA Conundrum

Walter Gardner, Chief of the Consumer Affairs Branch at the Center for Biologics Evaluation and Research at FDA says "Currently there are no autologous stem cell therapies licensed for use in the United States. Stem cells are regulated by Center for Biologics Evaluation and Research (CBER) as human cells, tissues and cellular and tissue-based products (HCT/Ps). Under the authority of Section 361 of the Public Health Service (PHS) Act, FDA established regulations for all HCT/Ps to prevent the transmission of communicable disease." Under these well established and carefully monitored rules, tissues based products must be used only for homologous purposes and during processing be "minimally manipulated". Culturing is not minimal manipulation according to the FDA.

There are a fair number of stem cell based products working their way through the FDA clinical study process in order to demonstrate to a

Table 1. Cartilage Volume Analysis in mm3 from the case report: Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells, platelet lysate and dexamethasone

Image	Area of Measurement	Volume (N=3)	STDEV	SE	% Change from Pre-Injection
	Cartilage Surface	2227	115.82	66.95	
Pre-Injection	Meniscus	1533	13	7.51	
	Defect	20.7	1.53	0.88	
	Cartilage Surface	2216	150.7	87.11	-0.49
6 Months	Meniscus	1545	35.1	20.29	0.78
	Defect	14.7	1.15	0.67	-28.99

Source: RSI

statistically significant degree that they are safe and efficacious. Most of these products are based on cultured stem cells. But not all. Some are based on autologous products and others are based on systems that allow physicians to harvest the patient's own stem cells.

It would appear that RSI's approach is either in a gray area or fits into one corner of the regulations where, so long as the cultured MSCs are used in the clinic and for its own patients and not sold to other clinics, they are inside the bounds of the law.

Then there is the fact that these are autologous materials. Autologous stem cell therapies use a patient's own bone marrow, blood, adipose tissues or even tooth enamel to collect MSCs. According to Dr. Centeno, using autologous source material brings the risk of disease transmission to virtually zero.

Said Dr. Centeno, "We began this procedure in 2005 as part of a bigger two-year research study that went through IRB approval [Institutional Review Board]. We asked regulatory counsel if we needed FDA approval and received the opinion that we didn't require that approval since there was no intent to make this a product, just simply use this procedure as part of our medical practice in Colorado."

He cites the example of a surgeon in his garage formulating a new surgical instrument, which he then sterilizes and uses in surgery the next day. Since the FDA only regulates drugs and devices sold in interstate commerce, Centeno says that surgeon is under no obligation to seek FDA approval for his custom surgical instrument. "However, if that surgeon started taking orders from other surgeons around the country for that device and began shipping devices 'interstate', he would then require FDA approval on the device." He says the same holds true for stem cells. FDA approval he adds, would only be needed if donor stem cells were shipped in a vial "interstate."

Centeno says that upon receiving an "untitled letter" from the FDA questioning parts of their practice, the clinic responded and in the summer of 2009, "They visited our Colorado site," explains Centeno "and declared that since we were culturing cells, we were manufacturing a biologic drug. We again asked for them to support their position that they had regulatory authority with some logical argument, again they declined to comment." At that point the doctors filed a lawsuit but a ruling came down stating that "we couldn't file against them until they did something. We filed a notice of appeal and asked to have a court enforced mediation started," says Centeno.

For their part, Drs. Centeno and Schultz now sit on the Board of Directors of the International Cellular Medicine Society and have established a three-point process which takes a note from the IVF (in vitro fertilization) community to create safety guidelines for physicians interested in offering this therapy. "The fertility specialists have formed professional organizations that have established professional guidelines, lab guidelines with third party audits, and a re-implantation registry. We've done the same. We have worked with physicians and scientists to establish professional guidelines for safe autologous stem cell use, lab guidelines with a third party auditor (Reglera), and a third party non-profit re-implantation registry. There are now about 250 physicians and scientists that have joined this organization."

Orthopedics This Week

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The Soldier in the Pink Dress

By Robin Young

Her name is Crystal. The dress was certainly pink and it showed plenty of Crystal's shoulder, back and front. Crystal was standing among a small group of award winners for the American Academy of Orthopaedic Surgeons (AAOS) banquet this past week in Washington. D.C. Amidst the blue, gray, and black suits and evening gowns, Crystal was a colorful exotic flower.

SPC Crystal Davis/Courtesy of AAOS.org

She also had large tattoos on both shoulders, back and, yes, over the swell of her bosom.

It was hard not to notice Crystal. Lauren Pearson, AAOS's Manager of Media Relations told me that Crystal was the subject of a documentary that was a MORE award winner for 2009. She's an amputee.

All of the MORE award winners sit in the front row of a large room and then walk up to a podium when called. John J. Callaghan, M.D., President of AAOS this year, did the honors. The film, *Fighting for Life,* was the last MORE award winner to be called. Terry Sanders (co-producer and two-time Academy Award winning film maker), Tammy Alvarez (executive producer), Sgt Abdul Madjid, USMC, one of the subjects of the film and SPC Crystal Davis, U.S. Army, the other subject of the film, came to the podium.

The film documents today's military surgeons as they go through training and then deployment. It also follows two casualties of our wars in Iraq and Afghanistan as they are treated by these military surgeons and nurses. In the film we meet Crystal Davis as she is being medivaced. Her surgeon is telling her that he had to amputate her left leg and her right leg was iffy. She's negotiating hard to keep the right leg.

SPC Crystal Davis is an Army truck driver. Every other truck passed over that particular stretch of gravel in Iraq in 2008 but when Crystal's truck went over, the hidden IED detonated.

Like all great art, this film captures the powerful emotional journey that Crystal, her family, and her caregivers went through. There were very few dry eyes in the audience this past Wednesday night. Even Crystal's. When the time came for the filmmaker and producer to come to podium, Crystal came too. She also said a few words.

Paraphrasing her, she said: "I want to thank the filmmakers for helping me through my recovery. I wanted to do my best in front of the camera so having them there motivated me. I said to myself, if I can work hard in front of the camera, I can work hard behind the camera too. So I did." Crystal also thanked her father and other family members and then she ended with a joke. "So, thank you to the doctors and the filmmakers for helping me to get a leg up."

The standing ovation lasted about 10 minutes.

The intersection of art, war, and orthopedics can be unexpectedly affecting. In addition to this particular film—which is available from the American Film Foundation (contact: krisbubna@hotmail.com) and we strongly, highly, urgently suggest that your hospital or community group or church rent a copy of this film and show it—there is an exhibition and book of such art that is also available.

Sandy Gordon, AAOS's Public Relations Director, organized both the MORE Award and the exhibit of war time art ***as created by surgeons and nurses!*** To learn more about the AAOS Wounded in Action art exhibit, please visit the Web site: http://www.woundedinactionart.org/ or contact Sandy Gordon, AAOS Public Relations Director, at 847 384-4030 or gordon@aaos.org.

Here are five (of 103) works that are part of this great, great exhibition.

Home from the War by Joseph A. Pearson (36 x 25 in. Oil on Canvas)

Pearson, whose mother lost both legs to diabetes, was inspired to paint this image after seeing a young veteran, an amputee, in a coffee shop. It shows a double amputee strapping on an artificial leg. "I was moved by the sacrifice he'd made for America," he says. Joseph A. Pearson, a New Orleans, Louisiana-based artist, served as an illustrator in the U.S. Army from 1976 to 1979. He started drawing at age 5, inspired by the illustrations he saw in a Sears, Roebuck & Co. catalog. At the time, he was fascinated by "the magic of making a figure out of lines and shade." His artwork now includes portraits, murals, and human figures, but drawing figures remains his passion. "My strength as an artist lies in my passion for the familiar faces, figures, and scenes of the loving, but ordinary facets of life: the human condition. My goal is to translate this condition into a universal point of view. My impetus begins with the human spirit and the desire to witness the love that spirit brings into the world," Pearson says.

Wounded Warrior by Richard McCarthy M.D. (20 x 30 x .5 in. Acrylic on Canvas)

Dr. McCarthy's eldest son, Bryan, who spent eight months piloting an F-18 Super Hornet in Afghanistan, inspired him to paint this picture. "His audacious confidence in the ability of the Navy to bring him back home safely caused me to reflect and paint this image of determination and frailty," he says. It shows a veteran, who lost his left arm to an explosive device, in front of an American flag. As a medical student, Dr. Richard E. McCarthy visited his sister, a Navy nurse, as she cared for returning Vietnam veterans at the now-defunct Philadelphia Naval Hospital. This early exposure to wounded soldiers made a lasting impression on him. "I was struck with the stark reality of missing parts in these young warriors trying to piece their lives together," says Dr. McCarthy, who was 21 at the time. More recently, the graduation of his youngest son, Andrew, from the United States Naval Academy in Annapolis, Maryland, renewed his respect and admiration for the men and women of the uniformed services.

Naval Officer/Amputee 1973
by Peter Langan, M.D.
(24 x 48 in. Oil on Canvas)

Dr. Langan starting painting after a knee injury. This canvas shows a lieutenant commander, who has lost a leg, walking on crutches in his dress blues uniform. Dr. Peter Langan, a Mineola, New York-based orthopedic surgeon, served in the U.S. Navy with the 2nd Marine Division from 1971 to 1973, an experience that is still fresh in his mind more than 30 years later. He is well aware of the personal and professional sacrifices made by soldiers. When treating injured troops, "I try to reciprocate," he says. Dr. Langan believes that research plays a big role in orthopedic advancements, such as the development of rods and plates to stabilize fractures. But the most fundamental change has been the speed with which the wounded obtain care. "The military has done a great job in getting the hospital to the injured," he says.

Patience by John Ton
(44 x 20 in. Mixed Media: Spent Ammunition Cases)

This image, made of spent ammunition cases, depicts the "chronic patience required by a physically disabled person," Ton says. It is his hope that those who view it will reflect on this patience, and gain some patience for themselves. "Regardless of where people stand politically on the gun issue, I want them to first see the beauty of the textures and patinas of the material I have chosen," he says. As a self-taught artist, John Ton has created his own mixed media technique, by using spent ammunition casings to produce art. "There is a mountain I often hike on near Reno, where I live, that is littered with shotgun shell cases. My first thoughts were that this unsightly litter might somehow be recycled; it then occurred to me that perhaps some form of art might be made from them. They have an apparently infinite variety of colors, and the casings that have weathered in the sun for a while can fade to a very interesting light blue, lavender, and even white sometimes," Ton says. He now collects bullet shells from public and "unsanctioned" ranges in Nevada and California and uses them to make "ammosaics," with images reflecting the realities of accident victims, including those he meets as a volunteer at the V.A. Sierra Nevada Health Care System in Reno, Nevada.

Concern by COL Colin Miller, MD (8 x 11 in. Photograph)

Dr. Miller's first photo, from Afghanistan, captures the trauma on a young girl's face as her wrist injury is examined and her father looks on. When casualties increased at Ibn Sina Hospital in Baghdad, Col. Colin K. Miller, M.D., had little time for his passion—photography. Orthopedic surgeons at Baghdad E.R., as it is popularly known, had to work around the clock to operate on injured soldiers, snatching catnaps when they could. Instead, Dr. Miller resorted to taking photos in his "downtime"—out of an open Blackhawk helicopter window en route to Baghdad International Airport or while waiting in a bunker for a siren to stop.

His images immortalize intense moments from his experiences in combat medicine—experiences that have made him a better surgeon, leader, and person. "I can't imagine a better job than caring for wounded soldiers," he says.

Again, don't hesitate to contact AAOS for a copy of this powerful exhibit's book and do find a way to show the movie, *Fighting for Life* in your hospital, church or other organization.

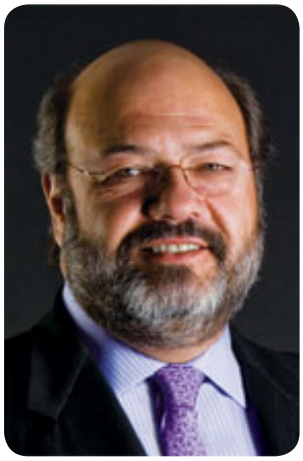
NuVasive Sues Orthofix Over Stem Cells

By Walter Eisner

RRY Publications LLC

During NuVasive's quarterly conference call with analysts on April 20, company Chairman and CEO Alexis Lukianov dropped, if not a bombshell, at least a stink bomb.

He told analysts towards the end of the call that NuVasive has begun legal action against Orthofix for allegedly infringing the '239 patent behind NuVasive's Osteocel Plus biologic product. NuVasive purchased the licensng rights to that patent from Osiris for $85 million in 2008.



Alex Lukianov

Orthofix: Suit Wholly Without Merit

Orthofix's CEO, Alan Milinazzo was unaware of the action, not yet having been served with papers and issued this statement the following day.

"At best, we find both the NuVasive announcement and the forum for the announcement questionable. We prefer to compete in the marketplace so that we can continue to bring next generation technologies to the market for the benefit of patients and surgeons who treat them. It is Orthofix's policy to respect the intellectual property rights of others, and we are prepared to vigorously defend ourselves against any allegations to the contrary."

During his own conference call with Wall Street analysts on April 28, Milinazzo told analysts that the suit was "wholly without merit."

He told analysts that prior to developing its own product, Trinity Evolution, the company did its due diligence and found a, "novel next-generation" product and did not infringe on the intellectual property licensed by NuVasive.

Alan Milinazzo

Biologic IP in orthopedics is a big deal and this lawsuit encapsulates business, scientific and legal issues that have yet to be decided in courts and markets. With a stroke of the pen, Alexis Lukianov and NuVasive have sent these issues to a federal court. The world of orthopedics may be about

to learn a lot about the legal nature of stem cell patents for use in promoting bone growth.

NuVasive/Osiris v Orthofix/MTF

In a nutshell NuVasive is saying that Osiris spent lots of time and money to learn that allogeneic mesenchymal stem cells (MSCs) can be harvested from a donor, dead or alive, and given to a patient without fear of rejection to promote bone growth.

Until this important breakthrough of the '239 patent, it was widely believed that allogeneic cells posed a risk of being a foreign cell surface protein that would trigger an adverse immune response in the patient receiving the cells. NuVasive says the inventors of the patent, "put those fears to rest."

Osiris began exploring ways to develop therapies and products related to MSCs in the mid 90s and filed for a patent.

Allogeneic Mesenchymal Stem Cells

The patent (No. 6,355,239), "Uses for Non-Autologous Mesenchymal Stem Cells," was issued on March 12, 2002, to the inventors, Scott Bruder, Kevin McIntosh, M.D., Daniel Marshak, M.D. and Joseph Mosca, M.D. and assigned to Osiris.

According to NuVasive, the '239 Patent, "claims, inter alia, methods for treating a human subject with allogeneic MSCs to promote connective tissue (e.g., cartilage or bone) growth."

The suit claims the patent inventors, "surprisingly discovered that allogeneic MSCs do not provoke an adverse immunological response by the patient. The inventors' teaching that allogeneic MSCs can be used in this fashion marked a significant advancement in the art."

Launching Commercial Product

Osiris launched Osteocel in 2005 as the first commercial product in the U.S. that contained adult allogeneic MSCs for use as a transplant.

In 2006, Osiris went public with a valuation of $300 million, the second-largest public stem cell company in the U.S.

In March 2006, Blackstone Medical made a deal with Osiris to distribute, non-exclusively, Osteocel for use in promoting bone growth. Blackstone was acquired by Orthofix in September 2006.

In 2008, Osiris decided to divest itself of Osteocel and took bids from potential buyers. NuVasive won the bidding and Orthofix's license to sell Osteocel, which they had been selling under the brand name Trinity, expired on July 1, 2009.

NuVasive Outbids Orthofix

After Osiris accepted NuVasive's offer in May 2008, Orthofix filed suit to stop the sale, but withdrew its complaint before the sale was completed. *Orthofix never bid on Osteocell but filed the suit to ensure the contractual rights they had to the sale of the product would be honored by NuVasive.*

NuVasive then began selling the product under their brand name, Osteocel Plus.

Orthofix Partners With MTF

To stay in the game and continue to offer a biologic product to surgeons, Orthofix partnered with MTF (Musculoskeletal Transplant Foundation) in early 2007 as part of a plan to either enhance the donor pool or explore partnerships for other allografts. Orthofix now sells that product under the trade name, Trinity Evolution.

Jefferies analyst Raj Denhoy says both products, NuVasive's Osteocel Plus and Orthofix's Trinity Evolution, compete with other bone void fills, harvesting bone from the iliac crest and even

bone morphogenic products (BMP's), such as Medtronic's InFuse and are obtained from the bone marrow of donors. An FDA medical device approval is not required because the products are considered donated tissue. Therefore, says Denhoy, efficacy has not been proven and hard data is hard to come by.

Denhoy notes there are currently studies underway regarding the products' effectiveness in promoting fusion, but none comparing the products to each other or competitive products.

Denhoy estimates that NuVasive will have sales of Osteocel Plus of $50 million in 2010, while Orthofix will reach sales of $38 million for the year. The combined sales are up 45% from sales in 2009.

Legal Journey

This lawsuit is a long, long way from seeing a jury. Patent attorneys we talked to tell us it could be up to five years before this actually goes to a trial, unless the parties settle out of court.

First, Orthofix will respond to the complaint and will likely ask for a dismissal on a number of grounds. Then the parties will undergo a long process of discovery and prepare for a Markman hearing.

A Markman hearing is a pretrial hearing in a U.S. District Court during which a judge examines evidence from all parties on the appropriate meanings of relevant key words used in a patent claim, when patent infringement is

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alleged by a plaintiff. It is also known as a "Claim Construction Hearing."

At that point, the precise infringement claims made by NuVasive will be identified. NuVasive's initial complaint alleges Orthofix directly infringes on the method claimed in one or more claims of the patent.

If a settlement is not reached at this point, there will be more motions and finally a trial.

Biological IP

In the end this case may be less about NuVasive and Orthofix and more about the nature of biological intellectual property. We're familiar with a recent federal court decision that reportedly says one can't patent nature. Discovering natural laws is different from describing methods to harness those laws for some purpose.

The United States District Court for the Southern District of New York addressed this issue a couple of months ago. On Monday, March 29, United States District Court Judge Robert W. Sweet invalidated seven patents related to the BRCA1 and BRCA2 genes, the mutations of which are associated with both breast and ovarian cancers.

Lawyers for the ACLU argued that genes are a product of nature and thus should not be subject to patenting, and that the patents would hinder scientific progress in the area of genetic technology. Judge Sweet agreed, stating that the patents were improperly granted because the patent holder did not invent or create the BRCA1 and BRCA2 genes. Myriad Genetics, the patent holder, plans to appeal.

We don't know yet if this case will address the issues of discovering what exists in nature or if the case rests on methods used to get stem cells from point A to point B.

Either way, the field of orthopedics may be about to learn a lot about the right to own stem cell technologies for promoting bone growth.

Crescent City Comeback: Orthopedics in New Orleans

By Elizabeth Hofheinz, M.P.H., M.Ed.

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In June 2006, Elizabeth Hofheinz, Senior Writer for Orthopedics This Week, and a native New Orleanian, traveled home to interview four orthopedists and a physical medicine specialist. The city and its orthopedic community were in dire straits. Programs were struggling to retain their residents, orthopedists were getting "emergency" calls from their contractors during surgery, surgeons were telling people to leave the state because their particular problem couldn't be handled, hospitals were closed with no openings in sight, the uninsured population exploded, and all of this happened with a level one trauma center that had been flooded and destroyed.

It is May 2010, and the landscape has improved dramatically. Following are the impressions of several physicians, some of whom were interviewed in 2006.

Training to be an orthopedic surgeon is rigorous, no doubt. Fortunately, the path is well established, and there are veteran orthopedists to guide you. When Katrina struck New Orleans nearly five years ago, orthopedists in the city had no guidelines. There was no book to consult on rebuilding a practice or a residency program in a city with half its population gone, the remaining half in varying degrees of psychological distress, offices and homes destroyed, governmental confusion, and loved ones dispersed around the country. They had to figure things out for themselves…and figure things out they did.

Dr. Ollie Edmunds, President of the Louisiana Orthopaedic Association, states, "**While a number of orthopedic surgeons have left the state, we have also attracted new orthopedists from around the country. Although the population of the city remains less than before the storm, the number of patients per orthopedist has returned to its pre-Katrina level. Our residents are now doing significantly more surgical cases per resident than they were before Katrina.**"

Dr. Edmunds, Professor of Orthopaedic Surgery and Chief of Hand and Upper Extremity at Tulane University Medical School, adds, "New Orleans still has that cultural uniqueness and charm that makes living here very special."

Attracting New Residents and Surgeons

Dr. Jacques Whitecloud, a specialist in Physical Medicine and Rehabilitation at Tulane was thrilled to see the doors open to a trauma solution. "Although there was a temporary trauma center after Hurricane Katrina closed Charity Hospital, the new trauma center at LSU Interim Public Hospital was officially renamed 'The Spirit of Charity Trauma Center' and is the only Level 1 Trauma Center (as designated by the American College of Surgeons) in south Louisiana."

Dr. Whitecloud says, "We have at least three orthopedic residents per year now at Tulane. With a five year program, that means we have fifteen residents at various levels of training. Prior to Katrina we had six residents a year—it was a great loss to suddenly have no residents to cover the emergency rooms in the middle of night. The Accreditation Council for Graduate Medical Education (ACGME) required us to show that our residents had plenty of cases during their training. Tulane is now fully accredited by the Residency Review Committee (RRC) of the ACGME and has more faculty than before Katrina."


Dr. Ollie Edmunds


Dr. Jacques Whitecloud


Dr. Paul Gladden

Dr. Whitecloud: "In the wake of Katrina, there was only one person doing pelvic reconstructions for all of greater New Orleans. Now we have three. We still face the reality that the surgeon will often be willing to come here, but the family is hesitant."

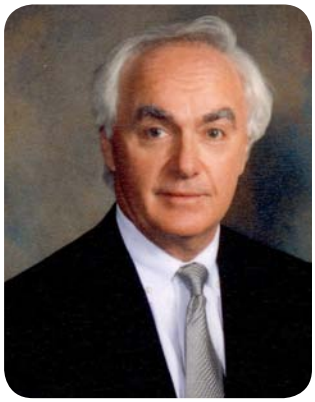
One intrepid surgeon willing to join the orthopedic rebuilding efforts is **Dr. Paul Gladden**, a Tulane traumatologist who came from Jacksonville, Florida. "In deciding to come here after the storm, I factored in a new wife (who is growing to love the city), and issues such as crime and weather. I decided that natural disasters are part of most intriguing major cities, and that crime is an issue in every major city. The benefits of the culture and environment of NOLA significantly outweigh the risks."

Traveling around the U.S., Dr. Gladden meets those who almost seem to think that rescue efforts are still underway. **"I am surprised to learn how naïve people outside of New Orleans are about the city's status. People think it is still underwater and won't make it back. The citizens of this city have done a terrific job of rebuilding, and I am glad I am here to help. The city's infrastructure is stable but could use some improvements; in particular, flood management and street repair need a boost. To my colleagues around the country I say, 'don't count us out as strong supporters and contributors to the field.'"**

Dr. John Davis, a spine specialist at Tulane, came to New Orleans from Cleveland three months before Katrina. "I was going to embark on a spinal cord injury project at Charity


Dr. John Davis


Dr. Fredric Warren


Dr. Andrew King

Hospital, but the facility didn't survive the storm and many projects were delayed. So we ended up covering the majority of orthopedic trauma call for Tulane—without residents."

Describing the path back for the residency program, Dr. Davis says, **"As part of the approval process, the RRC has requested a copy of our hurricane plans. One obstacle to getting residency slots was that we didn't have enough facilities. Not only are there more hospitals open now, but we have a presence at a hospital on the North shore of Lake Pontchartrain so our residents could continue training there in the event of yet another hurricane."**

Ideas on Further Development

Dr. Frederic Warren, Chair of Orthopaedics at Ochsner Health System, says that at times there is additional pressure on its surgeons. "Ochsner has rebuilt to a full contingent of 13 orthopedists covering all subspecialties. But the workload has changed because in addition to elective surgeries, we have had an increase in trauma. While there is now a level one trauma center, at times they get overwhelmed and have to distribute the work. In many cases it is not distributed equally because of the shortage of orthopedists at some hospitals."

The next time he has the gavel at a local orthopedics meeting, Dr. Warren has a message: "Let's join forces." He explains, "We have three training programs in metro New Orleans…we should combine our efforts. While turf issues would likely arise, together we could build one of the best training programs in the country."

Dr. Andrew King, Professor and Chairman of Orthopaedics at LSU Health Sciences Center, thinks philosophically: **"There is no bad event that doesn't have some good outcome. Everyone had to examine things in a new light, something that we don't often get to do in life. The most challenging issue has been recruitment because there is the lingering perception that New Orleans is unsafe. Anyone who comes here will definitely have an ample supply of interesting patients. Aside from the city having a certain zest and fascinating history that is celebrated by the local populace, New Orleans has always been a center of medical education."**
Dr. King: "The days of teaching people through a charity hospital are gone from the city. You must teach medical professionals in integrated hospitals of academic excellence. The idea of having a hospital that is for the indigent while the rest of the population goes elsewhere shouldn't be resurrected."

Dr. King adds that LSU will be bringing several new people on board. "We have had a lot of interest in our program and hope to hire four or five new faculty members by the end of the year. Most will be young surgeons just out of fellowship, something exciting for residents because they're closer to them in age."

Few orthopedists have the opportunity to participate in re-creating a city's orthopedic infrastructure. Those who are doing so in New Orleans are finding an unparalleled experience that provides rich growth… and seasoning.

company

OTW Wins Fourth MORE Award

Orthopedics This Week has won a prestigious American Academy of Orthopaedic Surgeons MORE Award for reporting excellence for the fourth year in a row.

Feature writer Biloine Young won in the online journalism category for her June 2, 2009, feature, *"War, Orthopedics and Great Leaps Forward."* Young shared the award for the category along with Forbes.com and ABCNews.com.

Young's article chronicled an *OTW* interview with leading orthopedic military historians at the 2008 meeting of the Society of Military Orthopaedic Surgeons (SOMOS).

The surgeon historians including retired Colonel Allan Bucknell, M.D., Professor of Orthopaedic Surgery, University of Colorado; retired Colonel John Feagin, M.D., Associate Professor Emeritus, Duke University and Colonel John Kragh, Jr., M.D., Brooke Army Medical Center. The surgeons described how surgical practices change under the stress of war and how the experiences of dealing with new kinds of trauma bring about new learning, new techniques, new insights, and new leaps forward for orthopedics.

A well-known historian, Young has published 14 books on subjects ranging from the pre-Columbian Native American city of Cahokia on the Mississippi to her most recent book about Louis Warren Hill, the son of Empire Builder, James J. Hill.

Young said it was a privilege to tell the story of war surgeons and how their experiences benefit trauma wards back home.

Robin Young, publisher of *OTW* told AAOS member at the awards ceremony on April 28:

"We are a small firm with four writers. Orthopedics is what we cover, but it is more than that.

"The act of describing the profound lessons that emerge from the tragedy of war, this meditation on our collective destiny of aging, the enigmatic process of innovation and the emotional power of the journey that patients and physicians, together, are on has affected us deeply. No matter how much is said or written or expressed in whatever art form you consider, treating the diseases and trauma of the musculoskeletal system conveys upon all of its surgeons, nurses, administrators and support people a majesty and mystery that continues to astonish, challenge and reward us at *Orthopedics This Week*—every, single day.

"For us, the MORE Award memorializes our joy and passion for what we do and we thank you so much for it."

Previous *OTW* winners of the MORE Award are Elizabeth Hofheinz, who

Biloine Young, Historian and 2009 MORE Award Winner

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won the award in 2006 and 2007, and Walter Eisner, winner in 2008.

The MORE (Media Orthopaedic Reporting Excellence) Awards were designed to, "honor members of the media who offer truthful and insightful musculoskeletal information within their stories," explained Academy President John J. Callaghan, M.D. "These remarkable journalists present accurate information to the public about orthopaedics, helping to educate our patients and the community."

Other 2009 MORE Award winners, included: *Newsweek*, the *Philadelphia Inquirer*, the *TODAY Show*, *NBC Network News* and *Consumer Reports on Health*.

—*WE (April 30, 2010)*

Zimmer 1Q10: Stabilizing

The surgeon base is stabilizing and business is growing again.

Those are words Zimmer CEO Dave Dvorak has undoubtedly been dying to say to Wall Street analysts ever since the company reformed its surgeon consulting relationships and as it recovers from the temporary suspension of sales of the Durom Hip in 2008. The company has been giving up market share to competitors ever since.

During a quarterly conference call on April 22, Dvorak told analysts that the company's reported sales rose 7.1% to

RRY Publications LLC

$1.06 billion for the first quarter of 2010. However, noting a slight down tick in the company's reconstructive business from 2009's fourth quarter, Wells Fargo senior analyst Mike Matson wrote investors that the industry's "rising reconstructive tide isn't yet floating Zimmer's boat." The company's reported reconstructive sales rose 7.2% over the first quarter of 2009.

Product categories reported the following:

Zimmer 1Q10	Sales ($ in millions)	% Change
Net Sales (Reported)	$1,060	up 7.1%
Reconstructive		up 7.2%
Hips		up 5.3%
Knees		up 7.5%
Spine		down 7.1%
Extremities		up 16.0%

Source: Zimmer Holdings

Knees, Hips and Spine

Answering questions about the company's below market rate sales growth, Dvorak told analysts he was optimistic about the end of 2010 as he anticipates new hip and knee products to ramp up.

In knees, Dvorak expects its Patient Specific Instruments and new posterior referencing instruments for its NexGen knee to be growth drivers that bring knee sales back to market rates.

In hips, the company hopes to exceed market growth rates with the introduction of its Continuum modular cup system and its MMC metal-on-metal cup system.

Spine and the reimbursement challenges of the Dynasys dynamic stabilization system continue to drag down spine sales. Dvorak said the company will invest in the business to attain a "full portfolio" of products and improve execution of sales efforts. Dvorak noted growth in several spine products such as the Pathfinder MIS platform and the Sequoia pedicle screw system. With the integration of the Abbott spine business largely complete, the company will now focus on new product development.

company

"We remain committed to the product [spine] category," said Dvorak.

War Chest

Another indication that the surgeon base was stabilizing, company CFO Jim Crines reported that operating cash flow for the quarter amounted to $260 million, up 41% from a $185 million in the first quarter of 2009. In the prior year quarter, Crines said the company resolved outstanding payments to health care professionals and institutions resulting in substantial cash outflows.

Overall Dvorak told analysts that the company will seek to keep its growth rate on track and be "active" in business development opportunities. He believes it will be a very healthy year for consolidations and the market will see "more activity," in the coming year.

With great operating cash flow and over $800 million in cash, Zimmer will not be short of money to make a deal.

—WE (April 26, 2010)

NuVasive 1Q10: Good Vibrations

NuVasive Chairman and CEO Alexis Lukianov was downright giddy as he opened the company's quarterly conference call with Wall Street analysts on April 20. Before reporting that first quarter 2010 revenues rose

Wikimedia.org

36.3%, Lukianov announced that he was going to pop a surprise spine anatomy quiz on his, quite shocked, new CFO, Michael Lambert.

Lambert, who has been with the company for only a few months and he did not come with a spine, background, nervously laughed and said, "I can't believe he's doing this to me." Gracefully, the new CFO answered a question this writer didn't even understand.

Such is the state of life at the Cheetah on the West Coast, NuVasive, at the beginning of 2010.

Exceeded Expectations

First quarter revenues were $109.1 million. Lukianov told analysts that

company

the company expected the growth rate for all of 2010 to remain in the 30–35% range. As consolidation expectations permeate the industry, the company ended the quarter with $178 million cash in the bank.

Said Lukianov, "We exceeded our expectations, achieving revenue growth of over 35%, driven by continued adoption of the XLIF technology, stronger traction from our new product launches, and aided in part by the positive reimbursement progress during the quarter. Our financial performance across earnings and operating cash flow signal a great start to what will be another outstanding year."

"Today's results mark NuVasive's 24th quarter, and sixth year, of consecutively meeting or exceeding expectations as a public company. Our keen focus on being the most creative spine technology company in the world and achieving exceptional results through speed of innovation, Absolute Responsiveness, and superior clinical outcomes will continue to drive us toward our goal of becoming the number four global spine company."

What Recession?

The change in the volume of spine procedures during the Great Recession didn't even seem to faze Lukianov as he added, "Even if the growth in spine would have hit zero, we still felt we could have hit our numbers."
BMO Capital analyst, Joanne Wuensch said, "This is reminiscent of concerns at the end of 2008 and entering 2009 regarding a slower spine market because of the economy, where the company bucked the trend as it continued to roll-out new products, train new physicians, and break into new geographies with its XLIF technology."

Orthofix Lawsuit

Chairman Lukianov made a surprise announcement during the call. He said NuVasive was suing Orthofix for alleged patent infringement related to NuVasive's biologic product, Osteocel Plus and Orthofix's Trinity Evolution. Osteocel revenues were approximately $13.5 million in the quarter according to estimates from CanaccordAdams analyst, Bill Plovanic. Plovanic expects Osteocel revenues of $59.5million and biologic sales of $74.9 million for 2010.

Continued Growth

Wells Fargo analyst, Mike Matson estimates that NuVasive currently has an 11% share in the thoracolumbar market and a 3% share in the cervical market. This suggests, "continued cervical growth along with further penetration of biologics into NuVasive's existing procedures, deeper account penetration, and continued geographic expansion are likely to drive further revenue growth," noted Matson.

Who can blame Lukianov for his good mood having won a big reimbursement victory during the quarter for the company's XLIF procedure, adding sale reps and watching the company's stock go from the mid $20 in January to the mid $40 in March.

The cheetah is living on good vibrations at the moment.


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—WE (April 29, 2010)

company

Orthofix's Stimulating 1st Quarter

Source: media1.break.com

Orthofix, following the trend of first quarter revenue reports of competitors, had a very good first quarter of 2010.

Orthofix's first quarter sales were up 8%, allowing the company to make an additional $5 million debt repayment from their Blackstone purchase ahead of schedule.

Total revenues were $138.8 million, which allowed the company to maintain its revenue guidance of $568 millio – 576 million for 2010. Wells Fargo Securities raised its 2010 and 2011 revenue estimates from $571 million to $572 million and from $611 million to $614 million, respectively.

President and CEO Alan Milinazo said,

> "Orthofix benefitted from its diverse revenue streams in the first quarter, demonstrating continued year-over-year improvement in the company's consolidated operating profitability. We were very pleased with not only the continued improvement in our Spinal Implants & Biologics Division, but also the strong performances of our Spine Stimulation and Orthopedic Divisions."

Orthofix 1Q10	Sales ($ in millions)	% Change
Net Sales (Reported)	$138.8	up 7.7%
Total Spine	$71.7	up 8.5%
Spine Stimulation	$41.9	up 12.9%
Implants & Biologics	$29.8	up 3.5%
Orthopedics	$36.2	up 22.3%
Sports Medicine	$23.6	down 2.5%
Other	$7.3	

Source: Orthofix

Milinazo reported that total first quarter sales in the company's spine sector were up 8%, to $71.7 million. Spine stimulation revenue increased 13%, to $41.9 million, driven by the continued success of the company's devices, which include the only FDA-approved stimulator for the cervical spine.

Implants and Biologics

Spinal implants and biologic revenue, driven primarily by an increase in U.S. sales of lumbar and cervical spine implant devices, was $29.8 million. This was only a 3% increase. The biologic revenue from the spinal implants division decreased compared with the prior year, which included the impact of the transition to recording a marketing fee for Trinity Evolution versus previously recording full end user sales for the company's prior stem cell-based allograft. Under the previous accounting method, the division's revenues would have shown a 9% increase.

The spine implant devices were driven mainly by the company's recent introductions of the Firebird pedicle screw system, Pillar SA interbody device, and Ascent LE POCT system. Because the company does not purchase inventory of Trinity Evolution it does not incur any associated costs of sales. As such, the gross profit margin for the new allograft is 100% of the recorded revenue, which compares favorably to the gross profit margin of approximately 50% of sales for the prior allograft.

Milinazo commented on the alleged patent infringement suit filed by NuVasive saying the company hadn't been served yet with the legal papers, but that any allegations of infringement were, "wholly without merit."

Tight Expense Management

Wells Fargo analyst Mike Matson noted the company's margin improvements but cautioned that Orthofix's tight expense management

company

may be limiting the growth of its spine business. The company has three spine product line launches this year including the Phoenix MIS system, a new line of PEEK spacers, and a deformity system. But given the need to roll out instrument sets and train surgeons, Matson expects these to have more of an impact in 2011.

With sales increasing 8% for the quarter, margins improving and revenue guidance maintaining, the company was able to raise its earnings forecast for shareholders by $0.14 per share.

—WE (April 29, 2010)

large joints

Bone Loss… a Pediatric Problem?

If you're turning 40 and just beginning to think about bone loss, you may be 40.5 years too late. According to a new study from North Carolina State University and the U.S. Army Research Institute of Environmental Medicine, very early calcium nutrition may have more impact than previously thought.

Along with his colleagues, Dr. Chad Stahl, an Associate Professor in the Department of Animal Science at North Carolina State University, has

long studied how much calcium babies need in order to optimize bone density and strength when they get older. The infant food industry fortifies most baby formulas with calcium at levels substantially above those found in breastmilk. This differential level of fortification has been based largely on older studies suggesting that breastmilk's calcium is substantially more usable than that in baby formulas.

In this study, the researchers bottle-fed 12 piglets a calcium-rich diet and another 12 piglets a calcium-deficient diet during the first 18 days of life. Blood samples were drawn frequently, and the piglets were weighed daily. At the finish, the researchers collected samples from the animals' bone marrow, livers, kidneys, and small intestines. They also tested their hind legs for bone density and strength.

large joints

They found no differences between groups in terms of blood markers of calcium status and growth. These data support the previously suggested concept that, unlike what happens in adults, calcium absorption in newborns is not dependent on vitamin D. They also documented marked differences in bone density and strength such that the calcium-deficient piglets were compromised. When they looked at the bone marrow tissue which contains all the material (known as mesenchymal stem cells) that will eventually become bone-forming cells, they discovered that many of the calcium-deficient piglets' cells appeared to have already been programmed to become fat cells instead of bone-forming osteoblast cells. Fewer osteoblasts in early life may translate to a diminished ability for bones to grow and repair themselves throughout the remainder of life.

In the news release, Dr. Stahl stated, "…It also points to a potential paradigm shift in which health professionals might want to begin thinking about osteoporosis not so much as a disease of the elderly, but instead as a pediatric disease with later onset."

To this latter point, Dr. Stahl commented to *OTW,* "I think all that is required is a change in mind set. Putting greater emphasis on the importance of early life nutrition for lifetime bone health is really all that is needed. If we view osteoporosis as a pediatric disease, we will want to monitor bone development from a much earlier age."

As for next steps, Dr. Stahl told *OTW,* "We will be quantifying the impact of early life nutritional insults on lifetime bone integrity and we will be determining the mechanism behind the nutritional programming of mesenchymal stem cells."

—EH (April 28, 2010)

Help for Chlamydia-Induced Arthritis

No history of Chlamydia? No matter…you may end up with Chlamydia-induced reactive arthritis. But there is hope from a new multicenter trial. According to this federal study, led by the University of South Florida (USF) College of Medicine, combination antibiotics effectively treat Chlamydia-induced reactive arthritis (ReA)—a major step toward management, and possibly cure, of this disease.

John D. Carter, M.D., Associate Professor of Medicine in the USF Health Division of Rheumatology was the lead author of the study, a double-blind, placebo-controlled trial involving 42 patients randomly assigned to three groups—rifampin plus doxycycline, rifampin plus azithromycin, or placebo.

Patients treated with the combination antibiotics improved significantly more in measures of the swelling and

large joints

John Carter, M.D./University of South Florida

tenderness of joints and symptom assessment. In fact, the researchers report, 22% of patients receiving combination antibiotics experienced complete remission of reactive arthritis, while none in the placebo group did. Significantly more patients receiving combination antibiotics tested negative for Chlamydia bacteria in their blood or joint tissue following treatment.

Dr. Carter told *OTW,* "We have previously published pilot data suggesting that this treatment approach works, so the clinical response that we observed in the study participants who were on active therapy was not a surprise. The important difference with this new study was that all of the participants had to be polymerase chain reaction (PDR)-positive for *Chlamydiae* in their peripheral blood (peripheral blood mononuclear cells) or synovial tissue in order to be randomized to treatment. Unfortunately, there is not a diagnostic test for Chlamydia-induced ReA; PCR-positivity on the synovial tissue is probably the most accurate and specific test we currently have available. We performed follow-up PCR testing in these study subjects. Those participants randomized to combination antibiotics were not only significantly more likely to respond clinically, but they were also significantly more likely to clear their PCR infection."

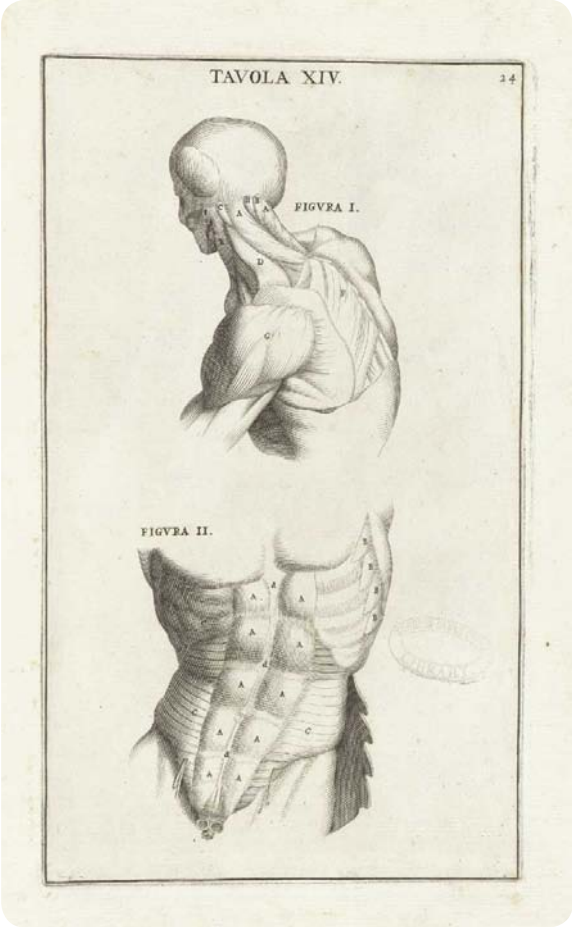
As for what Dr. Carter would like orthopedists to know about this work, he commented to *OTW,* "Epidemiological data suggest that ReA is vastly underdiagnosed (or misdiagnosed). Health care providers are often reluctant to diagnose this condition (or don't even consider it) in patients who do not display the 'classic triad' of symptoms (arthritis, conjunctivitis, and urethritis) or in those individuals who are HLA-B27 negative. Recent data demonstrate that the majority of patients with ReA do not display the classic triad of symptoms and are, in fact, HLA-B27 negative. To complicate matters further, acute *Chlamydia trachomatis* infections are often asymptomatic, but can still cause *Chlamydia*-induced ReA. Indeed, the majority of subjects in our study who were PCR-positive for *Chlamydia* had no known history of a chlamydial infection. Therefore, we need to heighten our senses to this possible diagnosis."

—EH (April 29, 2010)

Muscles, Bones Very Interconnected

You mean they *don't* talk often? But of course, says new research. A team led by Dr. Marco Brotto, the Director of the Muscle Biology Group at the Schools of Nursing and Medicine, University of Missouri-Kansas City (UMKC)

large joints



Wikimedia Commons

has found evidence that bones and muscles are more interconnected than previously thought.

Brotto's team observed that defects in genes important for muscle function also created changes in bones. The reciprocal effect happens when mutations are made that affect bone function. The researchers discovered that bones act like glands to secrete hormones that are detected by muscles. Reciprocally, muscles are releasing factors that are detected by bones affecting bone mass and strength. The group also distinguished a type of prostaglandin released from bone cells. Other findings revealed that the Wnt pathway, which is important for normal development, could be linked to wasting diseases in both muscles and bones.

Regarding the regulation of calcium metabolism, the researchers focused on a muscle specific phosphatase called MIP that may be involved in regulating calcium. Researchers removed the MIP from mice (these mice had muscle weakness, faster aging, and reductions in bone densities…they also had weakness in smooth muscle function of the contracting arteries and vessels. The female mice developed osteoporosis, but the males did not. This supports previous data that calcium regulation is different between the two sexes, which may explain why women are more likely to get osteoporosis.

Regarding fractures, the UMKC team hypothesizes that it may be caused from a breakdown in communication between muscles and bones. Perhaps the muscles put too much force on the bones at the wrong time.

As for what orthopedists should know about this work, Dr. Brotto told *OTW,* "First, I feel that there is a revolution coming. Systems biology is changing our thoughts about tissues and organs, and their roles in maintaining health or predisposing to diseases. Second, as we discover the biochemical signaling from bones to muscles and vice versa that either favors diseases or health, we will open doors to new treatments. Last, breakthroughs will require collaborations of the type we have established; these teams will be essential for the translation of bench research into effective treatments."

When asking what they were surprised to learn, Dr. Brotto commented to *OTW,* "How little we know. We can pride ourselves for discoveries, but humbleness can be very powerful as it opens our minds to new possibilities. For example, none of us expected that the biochemical effects of factors released from bones and muscles cells could affect each other so quickly and potently. We were also surprised that the crosstalk between muscles and bones is not limited to skeletal muscles, but goes beyond and involves cardiac and smooth muscles. Full characterization of these factors and learning to precisely control them will be incredible and will hopefully lead to better health for mankind."

—EH (April 30, 2010)

people

"Tiger" Joins Active Implants

Well known industry insider, Tom "Tiger" Buford is the new Vice President, Global

people

Tom "Tiger" Buford/Active Implants Corporation

Research & Development for Memphis-based Active Implants Corporation.

"Tiger is a proven leader with a 25-year record of successfully commercializing orthopedic technology and products," stated Michael R. Mainelli, President & CEO of Active Implants. "We are excited about his exceptional background, drive, and character and are delighted to have him on our team."

According to an April 26 company announcement, Buford has brought over 50 orthopedic devices to the marketplace while working for the world's leading orthopedic companies.

His career started at Smith & Nephew as a product development engineer. He progressed through a series of increasing responsibilities with Sulzer Orthopedics, Wright Medical Technologies, and most recently as Vice President Research & Development with NovaLign Orthopaedics. He was that company's third employee. He received a BS in mechanical engineering from the University of Memphis.

Buford holds two patents for knee prosthetics: System of inserts for the tibial component of a knee prosthesis—U.S. Patent # 5,047,058, and Prosthetic knee with posterior stabilized femoral component—U.S. Patent # 5,405,398.

Many readers may also be familiar with Tiger's blog at www.orthostreams.com. We note Tiger is also a master social networker with over 500 connections on his LinkedIn page.

Headquartered in Memphis, with research facilities in Netanya, Israel, Active Implants is developing cushion-bearing technology for the orthopedic industry. The company's first product, the TriboFit Hip System is a Class III approved CE mark device sold throughout Europe. The company's second product, the NUSurface Meniscus Implant is designed to treat meniscal deficiency, has also received CE mark and is in early studies in Europe.

—WE (April 27, 2010)

spine

Flexuspine: IDE for FSU

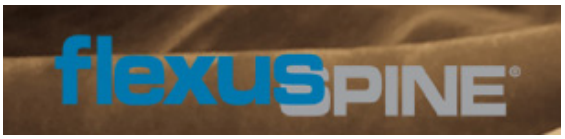
It's a celebration of precision at Pittsburgh-based Flexuspine… These lumbar luminaries have announced that the FDA has granted conditional approval to begin the initial phase of the Investigational Device Exemption (IDE) for a feasibility study of its Functional Spinal Unit (FSU). As indicated by the company, this is the first approved clinical study for a total spine arthroplasty system in the U.S.

The FSU, which contains an interbody disc component (Core) and posterior dynamic resistance component (Dampener), is designed to provide an alternative to fusion by reestablishing mobility in an affected segment of the lumbar spine.

"We are extremely proud of reaching this milestone after completing the tremendous amount of work that went into the development of the FSU device. We are moving into this next phase of our business to verify and validate the science and technology behind the product," stated Vincent Jannetty, President and CEO of Flexuspine, in the news release.

Jannetty told *OTW*:

> The ability to bring the vision of an investigational device like the FSU to



Flexuspine, Inc.

market takes perseverance. We have faith in our concept of total spine arthroplasty and have not rushed the design or evaluation process; instead we are taking the time necessary to do our best to get the job of motion preservation right.

We did thorough literature searches to learn all we could. Our engineers tested all components up to, or beyond, industry accepted ASTM testing standards. We have put together an excellent group of surgeon advisors providing consistent feedback of all design efforts with regular reviews of the device and implantation technique, including cadaver human factor evaluations. Everything that could be evaluated prior to human implantation was evaluated; instruments, technique, sizing, etc.

A significant milestone was the first-in-man series of surgical cases performed in South Africa, with advisor Dr. Louis Nel, Jr. These patients are closely followed, and, in the months and years ahead, will continue to provide clinical data that will be important input into future studies.

The conditional approval by the FDA to begin a U.S. feasibility study is an important milestone for Flexuspine and the FSU. This study will include a limited group of patients that will be followed under strict guidelines. The results from that patient group will be reviewed with the FDA and the outcome of that meeting will be another big milestone for Flexuspine. Cautious progress is what makes innovation in medical devices safe and successful.

—EH (April 26, 2010)

The Picture of Success: Arthur R. Bartolozzi, M.D

By Elizabeth Hofheinz, M.Ed., M.P.H.

Yeast + grapes triggers a series of chemical interactions which make one of the most storied and interesting compounds known to man—wine. Dr. Arthur Bartolozzi, an orthopedist with Booth Bartolozzi Balderston Orthopaedics in Philadelphia, *was* always good at chemistry. This seasoned surgeon and wine aficionado has crafted a career treating professional athletes, advancing research, and paying tribute to his colleagues in sports medicine.

Born in Trenton, New Jersey, Arthur Bartolozzi played baseball and routinely brought home solid report cards. "My dad worked in public health and my mom helped out in our family store. While my parents encouraged me to study, it was my paternal grandparents who pointed me in the direction of medicine."

While Arthur Bartolozzi was drawn to atoms and crystals, Caesar and Plato also held their allure. "History is fascinating, but I liked the fact that the sciences were more predictable. I took advanced science classes in high school and made a plan to apply to medical school one day."

While pursuing a major in chemistry (de rigeur for all budding physicians), Dr. Bartolozzi continued to hear the siren song of the humanities and took a tour through the world of literature and foreign language. "At Brown University, I leaned toward the humanities and I enjoyed playing baseball and rowing crew. On a whim I applied to the University of California San Diego (UCSD). I really had no intention of going to the interview but my dad encouraged me to fly out there. Sunshine, 80 degrees, and the fact that they had one of the largest research endowments in the country flipped a switch in my head."

It's always good to spend time with one's grandparents…you never know when they might teach you something useful for the OR. Dr. Bartolozzi:

> *"While I found oncology and cardiology interesting, orthopedics was just miraculous in its ability to create dramatic effects on people's lives. During those days joint replacement was coming into its own as a useful technique and I was amazed to see the transformation of people who had come in crippled and later walked out of the hospital. My grandmother had taught me to knit, which gave me a certain level of comfort when it came to manual surgical skills."*

"In 1982 I started a general internship at 'Penn,' which was followed by year of bench research looking at the mechanical properties of single osteons."

With his eyes wide open and his future before him, Dr. Bartolozzi entered the world of sports medicine. "Dr. Joe Torg was the head of sports

medicine at Penn and took care of all the university teams, in addition to the Philadelphia Eagles and Sixers. He was one of the originators of the idea of integrating the work of the doctor and the athletic trainer. My career was so enhanced by his mentorship that I started the 'Philadelphia Sports Medicine Congress' to honor doctors and athletic trainers while recognizing Dr. Torg."

"Dr. Irwin Schmidt, an orthopedist and a true gentleman, taught me the magic of respectful patient and staff interaction. He was kind to everyone and acted in a manner that engendered trust. From a surgical perspective I learned excellence from Dr. Robert Booth, whose dedication and hard work motivated me to pursue knee surgery. He taught me how to do curative procedures with successful outcomes, which made it an exciting area to pursue. Years ago a serious knee injury would be a career ending event for an athlete…now tearing up one's knee is almost a rite of passage."

Dr. Bartolozzi got his own rite of passage when he headed out west. "I went to the University of California Los Angeles (UCLA) to interview for their sports medicine fellowship. While there I went to a game at the Rose Bowl, which was enormously exciting. As if that weren't enough, UCLA had an excellent lab and a renowned fellowship director, Dr. Gerald Finerman (also from Penn). While there I met Dr. Bert Mandelbaum, who has become a great friend and mentor. His incessant energy and true love of sports medicine has made a lasting impact on me."

Armed with research expertise and surgical savvy, Dr. Bartolozzi returned to Philadelphia.

> *"I went to Pennsylvania Hospital to join Dr. Richard Rothman in practice as a specialist in sports medicine. It was important that I be near family and I was pleased to join a prestigious practice with a reputation for excellence. Under Dr. Rothman's influence and guidance, and with the advantage of a reputable program and hospital, I was able to attract a number of professional and collegiate sports programs to Pennsylvania Hospital and our practice. In 1997, when Dr. Rothman left for Jefferson, along with my partners, Drs. Booth and Balderston, we formed 3B Orthopaedics. Our triumvirate has survived and flourished."*

Like a business accelerator spins out companies, Dr. Bartolozzi has spun out sports medicine specialists—nearly 60 since the inception of the Pennsylvania Hospital training programs. "For 17 years I have been Director of the sports medicine orthopaedic fellowship program at Pennsylvania Hospital and Co-director of the primary care sports fellowship. During their time with us, each fellow does a research project and then presents their findings to the Philadelphia Orthopaedic Society for Sports Medicine. Year after year, our fellows have consistently had some of the best research projects as voted on by the sports medicine practitioners in the greater Philadelphia area. It has been exceptionally gratifying to see them build successful careers in academics and private practice. Jim Lubowitz, a former fellow, is now editor of the *Journal of Arthroscopy* and a number of our fellows have gone on to head fellowship programs of their own."

As for his own research, Dr. Bartolozzi notes,

> *"One memorable project was a review of ACL reconstruction in patients over 50 years old. When I trained, I was told that if you were over 35 years of age you were too old for ACL reconstruction. Now I consider that very young! We demonstrated that age was not the most important factor*

but rather it is the activity level—that simply being over 50 wasn't a negative."

Dr. Bartolozzi can sometimes see around corners. "I saw a trend toward minimally invasive (MI) surgery during the nineties and because of my familiarity with arthroscopic techniques and working in small spaces, I tried to extend this concept to all of the surgeries that I performed. Fascinated, I delved into creating instruments that would permit an MI approach to knee replacements. I developed a minimally invasive tensioning device that has greatly improved my ability to accurately perform knee replacement with an approach that favors more rapid recovery. I also have a great interest in fluid and hydration and we are about to publish our research identifying the actual cause of cramping in athletes."

If given his druthers—and a substantial grant—Dr. Bartolozzi has several ideas for new research pursuits. "I am very interested in injury prevention and would ideally like to accurately identify females who are at risk for ACL tears. In addition, I'm greatly interested in developing reliable interventions to better prevent these injuries. Another area I would love to be able to devote unlimited resources to is the development of scientific methods to replant and regrow human cartilage that closely resembles and functions like nascent cartilage. It is the future and in my opinion, the Holy Grail of Orthopedics."

Many patients have brought significance to his work, says Dr. Bartolozzi.

"Every day that I encounter patients who are gratified by my efforts is a meaningful day. I recall a basketball player in his last game of college who tore all the major ligaments in his knee. After three surgeries and extensive rehabilitation he went to play basketball on a professional team in Argentina and his team won the equivalent of the NBA championship. When he returned to the U.S. he came by my office, gave me a team photo, and thanked me for helping him."

"Another patient was a senior football player recruited by a big college football program. When he injured his knee the school rescinded its scholarship offer. This young man recovered, went to one of the best academic schools in the country, and set virtually every football record for the school. Most recently, a patient who had his knee replaced several years ago left a photo of himself and his son completing a marathon. He had not even been able to walk in the mall prior to his surgery. I don't make a habit of telling knee replacement patients to run marathons."

Dr. Bartolozzi has witnessed the toll that injuries take on athletes. He notes, "Players are often devastated by injuries; there is no way to measure the personal satisfaction that I have derived by interacting with athletes, their families and coaches and helping athletes return to pursue their passion."

Describing standout moments with his children, Dr. Bartolozzi says, "My kids grew up in the training rooms of the Philadelphia Flyers and the Philadelphia Eagles; when they were younger, they would arrive an hour before game time, watch dad examine injured players and then wait in the training room for more injured players to file in! As my children have grown up, I made a conscious and personal decision to be home more and travel less. This necessitated that I relinquish the team physician responsibilities for the high demand professional teams."

Dr. Bartolozzi's two sons, one a sophomore at Harvard and one a junior in high school, got to see a lot of dad, both at home and on the road. "My wife and I have always enjoyed bringing the boys skiing, fishing and travelling. In particular, we have all enjoyed visits to Italy to practice speaking Italian, to study wine and eat gelato. My interest in chemistry triggered my passion for wine. I enjoy speaking with wine makers about the science of wine and I have great fun collecting and drinking great wines with friends and family."

Dr. Arthur Bartolozzi…getting better with time.

Orthopedics This Week

VOLUME 6, ISSUE 14 | MAY 4, 2010

Orthopedics This Week | RRY Publications LLC

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