

TPS Meeting 2011, Bastrop, TX

Dr. Heavner's Presentation

Inaugural Lecture **(Slide 1)**

When I was asked by Dr. Driver to give this presentation, I was very, very pleased and happy. Then as the time to give this presentation approached and I kept getting from Ashley requests for my slides, I realized that I really had a tiger by the tail **(Slide 2)**—to talk about all the things that I could think about that would be worth talking to you about, the trials and tribulations and rewards of getting something from the discovery phase to the patient—I could not do it in an hour.

I thought first, why are they asking me to do this? It's not so much who I am, but what I did and the experiences in my professional life. I anchor my thoughts to the fact that I was born before lidocaine was introduced in 1945. **(Slide 3)** You can imagine the number of new things that have been introduced into medicine and developments in medicine since my birth: propofol, halothane, sevoflurane, desflurane. Even the concept of paralyzing a patient during general anesthesia, stimulators, pumps, new formulations of opioid drugs, and all the regulatory and legal issues that are involved. Fortunately, I have had lots of experiences and lots of time to experience them.

I should mention a few people who have had big impacts on not just my life, but on anesthesiology and pain medicine. Of course, I should recognize my wife who for 40 years more or less, has tolerated me. When I first became interested in research, I was still a veterinary student and my professor of pharmacology was very influential in my career path. This led me to Ronald Katz who some of you folks here may know who was doing a lot of research with neuromuscular blocking drugs at Columbia University, in New York. I was going to go there and work with him, but he decided to take a sabbatical and go to Europe. So I ended up on the west coast in Seattle with Rudy de Jong. That was really one of the defining moments in my life in pain medicine. A short time before then I went to the University of Washington, Melzack and Wall published their gate control theory. Scientists and specialists interested in pain medicine and anesthesia found that very intriguing and it laid the foundation for much research.

Dr. de Jong was studying the toxicity of local anesthetics and the effects of anesthetics and analgesics on the spinal gate. I did research in both of those areas during the 12 or so years I was in Seattle. One thing that connected me to pain medicine was the fact that John Bonica was chairman of the Department of Anesthesiology at the University of Washington. As you know, he was one of the giants in modern pain medicine. The International Association for the Study of Pain was started after I came to Seattle--I attended the first meeting. And there have been a lot of other professional firsts for me since then. I was involved in the formation of the Texas Pain Society, the rebirth of the American Society of Regional Anesthesia and Pain Medicine to name a few. I would say as a side bar that those of who have not seen the recent issue of Regional Anesthesia and Pain Medicine you might look at it because there are some interesting things that bring you up to date about how pain medicine and regional anesthesia got to where it is today. There is a good article about Danny Moore who is now 90 years old. One of the things about anesthesiologists is that some of them tend to be quite old, Torsten Gorth who administered lidocaine to a human for the first time in Sweden was over 100 years old when he died.

As I said, I felt pretty uncomfortable when I actually started thinking about what I was going to talk about. I went to my colleagues and friends and said 'What do you think I should talk about?' 'What do you want to hear about?' **(Slide 4)** First thing everyone said is be sure you talk about the patient, that's what pain practice is about, it's about the patient. The other parts—science, bench, boardroom—how do they impact on getting healthcare to the patient? Some key words that came up for discussion were: allied healthcare, the physician assistant, the nurse practitioner-- how does this work in the system; time- how do you manage time? All of us, I think with our different activities, find that at the end of the 24-hour day, we wish we had another extra hour or so. The scientist—what does this mean for a scientist? Define the scientist? Regulations- regulations are paramount in that they are being introduced every day and impact on everything we do, whether it is our breakfast—having the breakfast that we want, sure it is free of contaminants. Regulations that assure that the drugs we use are safe and that they're effective. Fraudulent abuse— that of course is quite prominent in the current popular news; Money—money is everything. I was told a long time ago that if there are

any issues, any problems, forget about ideology as a root cause, forget about interpersonal relationships, there are two keywords to keep in mind—sex and money. Try to keep sex out of it, but money predominates. I will have something to say about “following the money”. And then the present double-headed gruesome monster—evidence based medicine. Back to money. Who pays for all of this, who pays for the research and discovery, who pays for the healthcare delivery and where does the money come from? And what about the physician? What is his role on how to solve this in a way compatible with the physicians’ daily life? And when you look at equal access to healthcare for people in rural America or in remote India. And then there is the issue of personalized medicine with the genome-genomics and associated verbage. How does personalized medicine fit into all of this? And then information, how to manage it? Special interest groups have to be considered. Do good vs bad. And then the oversight never, never ending oversight. And then how you get access to various things in the path from the bedside to the patient.

If you put this together, it looks like a jigsaw puzzle, at least to me. **(Slides 5)** My presentation may look a little bit like a jigsaw puzzle as I try to touch on each of these, but I hope that at the end, at least on one hand, it all makes sense to you or on the other hand, it indicates to you or lets you understand your patient can have avant garde healthcare, but that you have to be a little bit patient in some areas to be sure that what is available to the patient is going to work and is safe for them.

Certainly when you live long enough, you realize that the more you know the more you know do not know. **(Slide 6)** I know a lot more questions than I do answers, in fact I think I’ve become a little bit more Socratic in my teaching and in my interaction with people; that is, instead of answering a question with an answer, answering a question with a question, which allows one to discover the answer.

The issue of doing good, **(Slide 7)** I think that that’s one of the most vexing things we deal with in a lab and in healthcare because what appears to be good doesn’t necessarily end up being good—but then it becomes good. I’ll give you two examples. One of them, many of you have heard about—the Chinese person who lived in a remote village. His prize stallion disappeared. The village people shook their heads and said this is bad. The stallion returned with a band of horses. The villagers said this is good.

Then the man's son tried to ride one of the horses and broke his leg. The villagers said this is bad. Next, a warlord came to take all the young men to war, but he would not take the son because his leg was broken. The villagers said this is good.

Here is a good/bad example from the perspective of pain medicine. Just last week, one of my colleagues said he had a patient for whom he felt one specific treatment was indicated but payment was not authorized for the treatment. Months were spent appealing for approval. Fortunately, the patient got better during that time. So think about what's good and what's bad, the outcome of course was a good outcome—the patient got better.

For the rest of the presentation, some numbers might help give you some perspective. Unless you've not been in contact with the real world in the last week, you know that there are now 7 billion people in the world. There are 195 official countries. **(Slide 8)** The US population, is 300 million people. And just to scale down, in Texas, there are about 25 million people. According to an Institute of Medicine recent report, more than 1/3 of people in the United States have chronic pain. **(Slide 9)** Taking this on a worldwide perspective, this represents about 2.6 billion people in the world that live with chronic pain. **(Slide 10)** So personalized medicine **(Slide 11)** for all of these would provide full time employment for healthcare people, whether in the supply providing the devices, instruments, drugs or have responsibility for providing personnel and care. But think about this—if most of these people require urine drug screening, it's a good business to be in. What if these people all would benefit from having genetic analysis, genetic profiling to know specifically what their drug enzyme metabolizing capability is, so that you could choose the correct drug, the correct dose and the correct dosing interval. It's daunting to think about doing that for every patient—it's just not possible. So, we're faced with a huge demand and there are two things about this huge demand; one is need for new and more effective treatments. The second one is a real commercial drive to meet the demand. **(Slide 12)** Driving demand is not only that in healthcare there is a need for new things in the pipeline—we know that existing treatments frequently are not effective particularly for neuropathic pain and the pain of terminal cancer. We know that one of the real problems in escalating the dose to get a desired effect is that side effects become limiting. And I don't think that there is any drug

that you use, any therapy that you use, that the side effects are not a major concern and can prevent providing appropriate care.

We know that the population is living longer. We wake up with our aches and pains, whether it be arthritic pain, neuropathic pain, cancer pain. I read recently that Billy Graham, the American evangelist who is 93 years old now, has severe macular degeneration and has a hard time seeing. He has just written a book about aging I think. In the book he wrote that he spent his whole life preparing to die, but he did not prepare to grow old. **(Slide 13)**

So we have this demand—we need new drugs, new therapies, better approaches. Therefore, we need to tell the scientists to get up in the morning and make new discoveries, the regulatory agents need to get the discoveries through the system, industry has to get these therapies to the marketplace i.e. we have to focus on getting things from the bench to the bedside.

Well this idea is not a new one. There are references to what's called Pasteur's Quadrant i.e. Pasteur's development of vaccines as an example of going from the bench to the bedside to solve an immediate need. **(Slide 14)** It is easy say but not easy to do—take something from the bench to the bedside. Dr. Zeinali who was head of the NIH until just recently came to NIH and targeted lots of money on mandates to focus on translational research, as going from the bench to the bedside is called. After he left NIH he said, 'you know guys, it's not as easy as you think.' That hasn't stopped NIH from now developing an Institute of Translational Medicine, so we are pumping a lot of federal dollars into translational research. **(Slide 15)**

The patient. **(Slide 16)** I was sitting in the boardroom yesterday listening to the stories and the issues about patients. These discussions can go on for hours.

I am projecting a quote from Oliver Wendell Holmes. **(Slide 17)** Oliver Wendell Holmes, a distinguished scientist and scholar, contributed a lot to medicine. In the quote he points out how vulnerable people generally are in terms of their health. They'll believe anything. Listen to what the patients tell you. They're desperate and it's not because they necessarily believe something, but they want to believe it. What is unfortunate about the society that we've always lived in is that because the people are vulnerable, there are unscrupulous people who take advantage of their vulnerability. One of the

reasons why we have the FDA is to protect people from fraudulent opportunities. I spent three years working for the FDA and saw some of the reasons why the FDA first came forth. One of the stories highlighting the need is about a guy from the Department of Agriculture concerned about food safety. He had a group of people, called it the death squad, have breakfast together. After eating food purchased locally, all of the participants became sick. And so the Food and Drug Administration was developed as an agency to assure that all the things we eat daily are safe. As Oliver Wendell Holmes noted, people are willing to be scorched, blistered and they'll pay you to do it.

There's the money issue again. **(Slide 18)** So let's talk just briefly about money. This slide which quotes Louis Pasteur may appear to be a little bit out of context but I'll put it in context for you. **(Slide 19)** Basically, he sort of proves the idea of translational medicine. He said science is science and we don't really know what piece of information is going to turn into the next big thing that helps human health. It's like my colleague at the University of Washington Seattle used to say about a newborn baby. If you had to take one of the 51 babies born every minute in India and just keep one of them based on judging which one of those will turn into the next world leader, how would you do that? It is the same thing with ideas—you encourage and nurture all ideas. But this costs money.

Who pays for research and development? **(Slide 20)** This slide tells the story. You can see the changing trend over time. The bar chart shows that at first the federal government provided most of the funding. Then there is industry and then other sources of money to fund research. Where is the biggest growth spurt in funding support? It's in industry. What's industry equate to? We hope first it equates to philanthropy and doing good. But when you are in the boardroom it's about money. Which project is going to be pursued? Which project is going to make shareholders happiest? Which one is going to keep jobs? 'He who pays the piper, calls the tune.' And this raises caution for all of us who think seriously about unbiased decision-making and information at the bedside.

Who do we answer to? **(Slide 21)** 'The pressures and temptations of closer connections with commerce have introduced policy issues that are testing the fabric of these institutions.'

Now go right to the academic setting. I get email blasts every morning that tell, for example, about discovery that was made in Stanford University. Competitively, the TTUHSC coordinator wants to have announcements about great scientific advancements made at Tech each day. Who is it that wants this information—the state legislature for one. Legislators say “We want there to be a research and scholarly activity at our institution,” and we want to show people we are making progress. Think about if you have a journal; who pays for that journal? Do the society members pay for that journal. For the most part it is advertisements. Why do companies advertise in journals—because they think there will be articles in that journal that helps the company. When you read the scientific literature, look at who sponsored the studies—there’s a lot of industry-sponsored research. Look at the Journal of the American Medical Association to see who sponsors’ studies published in it. Then think about what has to be done to keep bias out of those studies. Probably $\frac{3}{4}$ of you here are taking a statin, beta-blocker or hormone replacement. There are industrial sponsored studies that will certainly convince you and convince your cardiologist that if you are not taking these drugs you are probably not going to live as long as you otherwise would. In journal editorial boardrooms how to balance the need to pay for things vs the need to keep biased and unbalanced information from getting published must be evaluated.

(Slide 22) The cost to society—we know the governments are concerned about the costs. Some costs are shown on this slide. Any of you that are in the medical industry know the figures just keep getting bigger. Note there are 500 companies just for products for pain management. Again to a side bar, Ed Charlton—some of you may remember his name, was in Seattle when I was there. He used to lament that one of the reasons why the British government wouldn’t fund some healthcare needs is because why get people fit for work when there weren’t jobs? For the government it was good to have some balance between the people who cannot work because of disability vs those who cannot work because there were no jobs.

Decisions aren’t unilateral—make one decision and you get one outcome—instead it’s like playing a chess game—you move one piece and it affects the whole board. This applies to most decisions we make from discovery to patient application. **(Slide 23)** I talked about translational research, the bad guy in the process is usually considered to

be the FDA, Obama passed an executive order that the FDA has got to do something about drug shortages. We've got to have the FDA stimulate industry. Will the FDA be able to stimulate industry? Why do companies quit making drugs? What can the FDA do and is supposed to do? Certainly, none of us likes to be regulated. **(Slide 24)** This cartoon is obviously a play on Moses coming down the mountain with the 10 commandments. People immediately complained about regulation. We continue to complain about regulations. Is that really where the issue is? One of the mandates the FDA first had was to be sure that drugs were safe. Drugs didn't have to be effective to be approved. The 1962 Kefauver—Harris amendment to the Federal Food and Drug Administration and Cosmetic Act said that drugs not only have to be safe but they had to be effective. This was done, in part, due to the thalidomide disaster. Some of you have heard about this in medical school. Thalidomide was marketed in Europe for treating nausea associated with pregnancy and as a sedative. Unfortunately, very unfortunately, the drug caused a large number of babies to be born without legs and arms, without appendages. However, during that time, the FDA was constantly under the gun—why haven't you approved this drug, it's available everywhere in the world except the US.

It takes time to determine the efficacy of treatments for chronic pain. **(Slide 25)** Outcome studies of chronic pain management really require a 6 months follow-up. That sounds fine, but you cannot start a prospective study and 6 months later have data ready to submit to the FDA. When I counsel students about what it takes to do a clinical trial I draw a PERT chart, which shows, from day 1 until the project is finished, all that has to be done and estimated time from start to completion. The chart shows the critical events that have to take place and how long it is going to take to do each. It's going to take much longer than 6 months to do a 6-month follow-up study.

Even the simplest study can be very complicated. You look at your patient population. Say we will look at a treatment for CRPS. Everyday I see 10 CRPS patients, so we are going to do a study on 100 CRPS patients; 10 a day, 10 days we're going to be done. Then you look at the inclusion/exclusion criteria. Maybe only 1 patient will qualify for inclusion in 10 days. It's not simple.

Here are some of the real problems (slide) in getting drugs from the bench to the bedside. **(Slide 26)** Some of the most promising drugs fail in the early phases—a drug is not as effective as thought it should be or the side effects far exceed an acceptable therapeutic ratio. If you look at the number of drugs that go through this filtering system, more than half of them won't end up getting into your pharmacy.

Diversion. **(Slide 27)** My goodness. We spent a long time on this at the board meeting yesterday. You know it's sort of like talking about prohibition and the good and bad of prohibition. Did prohibition work? It certainly made a lot of money for Joe Kennedy.

Oxycontin—you can get on low cost airplane carrier in New York, go to Florida, get a script for about 100 oxycontin, fly back to New York and sell them for about \$80 each—this is one of the bad sides of the healthcare system—drugs that do a lot of good can also do a lot of bad if they are diverted. The tragedies associated with these drugs, some of them due to diversion, some of them due to the desperate nature of patients, include people dying. The overall trend of death for opioids is increasing. **(Slide 28)**

Lawyers—the lawsuits. It's the good, the bad and the ugly. When my colleague, Dr. Racz, talks about lawyers and doctors being sued he says no doctor wakes up in the morning and goes to work with the idea he or she is going to kill a patient. And you need to keep that in mind, first and foremost when you're asked to be an expert witness, when you're asked to testify against a physician. On this slide you can see lawsuit data that was published in the ASA newsletter and elsewhere. **(Slide 29)** It shows that there is an increase in lawsuits related to interventional pain medicine. Certainly the numbers that are related to just medical management of patients is quite high. The reasons show why these accidents and lawsuits occur are from the ASA closed claim project which I think most of you are familiar with. Physicians do bad things, the patients and doctors do bad things together; physicians don't cooperate, patients don't cooperate. **(Slide 30)**

There are a large number of issues—sometimes you are called into a courtroom or asked to express an opinion and you have to realize that when most of these accidents occur there is not a single cause, there usually are multiple factors.

Here are some of the patient factors that are associated with this misuse and addiction. **(Slide 31)** I'm as bad as others, I was prescribed a statin. My wife said "I get a regular supply in the mail, you can use mine." Well think about this in terms of prescription

monitoring. I get a call from CVS pharmacy saying, “we’ve noticed that you haven’t filled your prescription for a couple weeks, please call us or see your doctor to explain why you’re not taking your medications regularly.” So you see that one problem leads to another problem. Attempts to provide solutions sometimes add complications to matters. A recent article in the Wall Street Journal quoted data showing that most people over 50 years of age in US are taking 3-4 medications. Most of them are not following that prescription. They don’t take the drug as directed, they take more, they take less, they decide to quit taking it and then they don’t get better. The patient is a real factor and has to “buy into their own healthcare.”

I was on an airplane with a young lady recently and she was very much into the health issues. Her mother had low back pain. This is the sort of sad story we hear and is why we try to avoid recommending back surgery. Her mother had L5/S1 disk protrusion and she’d gone to a small community hospital where a discectomy was performed. Well guess what, it didn’t work- she still had pain. So the surgeon said ‘Aha, sometimes what we have to do is put hardware in these patients to fuse their vertebrae. So they put hardware in. Guess what, she had more pain not less. So this time, the third time she is going to the hospital so the surgeon can remove the hardware.

The daughter talked about various strategies, diet and things she had read about to correct health problems she had related to eating too much white sugar. According to her this allows fungus to grow on her body. It’s good that people buy into their healthcare, but look around you at how many people have a body mass index is over the 30 who want hip replacements and knee replacements, they wonder why they have joint pain. The patients have to play a role in their own healthcare.

So, what’s happening as a result of all that I have mentioned? **(Slide 32)** There is a search for new drugs, improved delivery of existing drugs. Pumps, stimulators—trials of oral and nasal formulations especially for breakthrough pain. And of course the cat and mouse game of how to provide drugs to patients who need them yet keep people who don’t need them from stealing them and using them. There are different strategies to prevent abuse. And we talked about identifying new targets. We’re entering into what some people refer to as the age of machines. **(Slide 33)** We are seeing all varieties of stimulators—neuromodulations, brain implants, not only for pain, but for depression, for

Alzheimer's disease, etc... spinal cord stimulators and drug infusion systems. So we certainly are seeing an increase in the use of machines in chronic pain treatment. There are radiofrequency machines. You can have almost any frequency, any power intensity you want to do something with a machine to try to help the patient with pain.

Special interest groups. **(Slide 34)** I have to talk about these for just a moment. What we are reading about everyday in the newspaper is occupy Wall Street. It ties into disparity. Why should some people be so rich and some be so poor. And is it justified. However, if you live in a capitalistic society that is incentive driven, you want to keep those incentives there. But the people who fuel the economy also need to have incentives—they need to be nurtured. It's back to the do good point. Is it bad for people to make a lot of money, if they are creative, take risks and succeed? But if they succeed and then fail and lose a huge amount of money because they fail, then I have a problem if the failure is rewarded with huge compensation. I am not making a political statement, I am just saying that for everything we do there is a good/bad.

The special interest group that I've had personal experiences with is the animal rights activists. I think that what these people and others who raise issues and bring them to the national attention do make us think. Are there better ways to do what we do? But what I object to in the animal rights movement is people use lies and misinformation to perpetuate or to launch an attack against someone.

Legislators might be considered a special group that needs to be educated otherwise they talk about doctors gone wild—doctors responsible for drug abuse, all the problems with the opioids. Misinformation or lack of information by the special interest groups can lead to more bad than good.

Information. **(Slide 35)** I couldn't find the specific quote, but it was about how quickly new information is coming forward. It was something like in the '70s the amount of new information doubled about every 10 years. And now we have new information double in a matter of 10 minutes. Information management, an issue for all of us with Twitter, with Facebook, with the internet. If information is available, there's a pretty good chance that your patients will know it and they are going to ask you about it, and they're going to want to know why you don't know about it. Here's one of the cartoons that many of my colleagues would say 'yeah, I see that everyday.' **(Slide 36)** It says that the dose must

be adjusted because the patient is just not as happy as the people on TV. Go to the chat sites on the computer and see what people are saying about the drug you're administering and what they think should be administered. Usually in most places now, the patient is pretty informed before they come to see you. Many of them will already have a diagnosis, they will already "know" what needs to be done, all they need for you to do is write the prescription. I am not sure what is the best way to manage information. I try to put priorities on information I need and I try to look at those information sources that meet my needs. It's not easy because information sources change almost daily. So first, there's the challenge of keeping up with the information sources that best keep up with your needs. And secondly, getting that information.

One thing we talked about yesterday at the TPS board meeting was the role of continuing medical education. Some feel that continuing medical education does not change your practice, does not change behavior. I can remember when I was taking management courses at the FDA, one frustration I had was that I would go to a good seminar and get great ideas. Then I would come back and work with colleagues who did not have that same information. I felt like I was in a big sea trying to tell other people who had not attended the training what changes should be made. It was difficult to get "buy in" because people did not understand what I was trying to do. One way to address this, I think, is to introduce team exercises that involved allied health personnel as well as physicians early in medical education. Maybe you should bring your staff to CME events like this. They need to hear what you're hearing.

There were other great topics discussed at the Board meeting yesterday. For example what happens when a regulatory person comes into your office—it's not what you have to do, it's what you AND your staff have to do. If your staff does not know what to do/does not do it, then you are extremely culpable. I think team teaching can be an important way to get the information that translates into use in your work place.

One thing that gets us from the bench to the bedside is people with wild ideas. How do you know when a wild idea is good or bad? It's a problem for journal reviewers and editors who may say 'that's a damn crazy idea and it should never appear in the literature'. So we see the medical publications, in general, are quite conservative. One needs to be cautious because if something is in the literature, then a lawyer may pull

out this paper and say ‘doctor, it says you should do this, did you do it?’ You can’t say well just because it’s in the journal doesn’t mean it’s true or that you should be doing it. We’re put into boxes where we have to make intelligent decisions about what is published. But we have to encourage people who have these “stupid, dumb ideas” because many of them turn out to be really great things. **(Slide 37)** I remember working with Dr. Racz when we were trying to develop the lysis procedure over 20 years ago and the resistance we met. The procedure is still not fully accepted but there certainly are people who think that it is very effective and many patients have benefitted very much from it. That’s an example of something that in my lifetime I’ve seen go from inception to clinical introduction.

People think I’m crazy to pursue epiduroscopy—it’ll never work. If I can learn something by looking into the epidural cavity of a patient that helps advance this specialty, it’s something worthwhile, I think. If it benefits a lot of patients then that’s great. We need to be sure we encourage creativity. Be sure that we can deal with it, in terms of the regulatory aspects and the patient expectation.

I will end my presentation with what I think we all should do **(Slide 38)**—do good, enjoy life and don’t waste time. You can steal anything from me but my time. I can replace a car, but I can’t replace my time, once it’s gone, I can’t get it back. **(Slide 39)**—So this is not the end, it’s the beginning; do good, enjoy life, don’t waste time.