Dr. Paul Lange, a urologic surgeon, was one of the researchers behind the development of the PSA assay for prostate cancer. Lange served as Chairman of the Department of Urology at the University of Washington for 20 years. In 2007, he stepped down from that position to become director of the Prostate Cancer Research Institute, a collaboration between the University of Washington Academic Medical Center and the Fred Hutchinson Cancer Research Center.

PROSTATE FORUM: How did you come to specialize in prostate cancer?

DR. PAUL LANGE: I trained at the National Institute of Health, Duke University, and the University of Minnesota. I stayed at University of Minnesota until I became Vice Chair of the Urology Department. I then came to the University of Washington as Chairman of Urology and remained Chair for about 20 years.

During that time, my long-term research associate Dr. Robert Vessella and I set up a prostate cancer research
laboratory. Together, we worked on the implementation of the PSA assay for prostate cancer and the AFP assay for testicular cancer. Through the development of animal models and the acquisition of various patient materials, including our rapid autopsy program, we eventually attracted a variety of researchers from the University of Washington and the Fred Hutchinson Cancer Research Center. We now have a large prostate cancer research team called the Institute for Prostate Cancer Research (IPCR): 40 full-time, advanced degree researcher clinicians work with us. We are among the top 5 recipients of federal funding for prostate cancer research. I stepped down as Chair at the University of Washington five years ago to spend more time heading the Institute of Prostate Cancer Research. I'm now gradually beginning to pass on that responsibility to other people whose careers I helped nurture in one way or another.

About 15 years ago, I had a radical prostatectomy by one of my colleagues who I helped train. As my wife humorously comments, unfortunately it didn't change me. I am, for all practical purposes, cured.

What was your role in the development of the PSA assay?

Initially, I was very skeptical about the PSA assay. It had been around for a while. The Roswell Park Group had already developed an assay and claimed that it was really good, but they had also previously claimed that their radio-immune assay for acid phosphatase was really good and that turned out not to be.

When Hybritech decided to develop a sensitive assay for PSA, I
was rather skeptical, but we agreed to look at it. (We had one of the larger serum banks in the world at that time.)

Over the next two years, our lab people said that the PSA was really fantastic, but I was not sympathetic. Yet when I looked at the data in great depth, I found that it was fantastic.

I had already presented to the FDA for the AFP assay, and so I went before the FDA for the PSA assay. Even though it was the first round, and therefore not something that usually got approved, the PSA test was readily approved. This was despite the fact that a great number of even academic urologists had either never heard of the sensitive PSA or were very negative about it.

Indeed, the first abstract I wrote on our results was rejected by the AUA. We then wrote a bunch of papers on various aspects of PSA and popularized it.

I was likewise skeptical about PSA screening because PSA is made by the normal prostate gland and by prostate cancer. The amount of PSA made by the cancer cells is less than the amount made by normal cells but PSA leaks more with prostate cancer. It still leaks with normal prostates and more so if the gland is infected. In general, the bigger the gland, the bigger the leak even in non-cancerous prostates.

I was therefore very negative when I, Dr. Michael Brawer (of our group) and Dr. William Catalona (then of Washington University) were funded by Hybritech to do a PSA screening study. Indeed, we were somewhat discouraged by a variety of the organized health groups in Seattle, WA at the time. Thus, I
slowed our research, but Dr. Catalona never missed a beat.

Though we both published results on early screening, Dr. Catalona carried it much farther along. Initially, our cut-off for biopsy was a PSA of 4, but we knew very early on that that was an extremely arbitrary number and probably too high. We changed the cut-off to 2.5, again knowing that there were people with PSAs below that who had cancer and that some of them had significant cancers. Indeed, later in the PCPT trial, Dr. Ian Thompson showed very convincingly that a low PSA was not a guarantee that you didn't have cancer.

Early on, I adopted a previously described metaphor for talking about prostate cancer: some cancers were turtles and some were birds. The turtles were cancers that grew very slowly and almost never killed a man. The birds were cancers that grew quickly and always eventually “escaped.” How quickly they escaped depended on their size and species. There were an awful lot of turtles in prostate cancer, as we knew from earlier autopsy studies.

The question now is do we just stop screening altogether, or do we try to refine the early diagnosis of prostate cancer in a way in which we do not treat (or maybe some day even do not detect) the slow growing ones (i.e. the turtles), but do detect early and treat the fast-growing ones (i.e. the birds).

I think that for now we ought to diagnose as much prostate cancer as we can after informing the patient of the risk-benefit ratios, provided they have at least a 15+-year life expectancy. Then, we ought to uniformly as possible treat the turtles with active surveillance. Of course, we should continue
to treat the more serious cancers aggressively, working ever harder on decreasing morbidity.

Men are diagnosed with prostate cancer after a high PSA and positive DRE leads to a biopsy. What does a rising PSA mean post-treatment?

Recurrence! I was one of the first to point that out that when the PSA goes up after treatment that means you've got disease somewhere. The PSA assay is a fantastic marker once the prostate gland has been destroyed. Now that we've got the PSA micro-assay, certainly anything above 0.1ng/ml can mean the cancer has recurred. With a PSA below 0.1, the issue becomes problematic, because there are certainly men with 0.04 and 0.05 PSAs that don't rise further.

There are people whose PSAs gradually rise after surgery, but the PSA velocity—that is how fast the PSA rises—is such that they are never going to have any trouble with their cancer. They're turtles—slow-growing cancers.

Exactly when you decide to simply monitor a man with a PSA rising after surgery versus when you decide to treat him is more controversial. If a man's PSA rises to 0.2, but his velocity is extremely low, should you treat? I don't think so.

There are an awful lot of men whose PSAs rise very slowly to very low levels that don't need any treatment. The question becomes where is that PSA coming from? Is it coming from low-grade cancer that will never kill or hurt a man, or from residual normal prostate tissue that is growing back, or something else?
I think anybody with a PSA above 0.4, unless their velocities are extremely flat, ought to be considered abnormal and should be considered for treatment.

For the newly diagnosed patients reading this, can you please define lymph node involvement or lymph node disease.

In all solid cancers, the cancer spreads systemically. In prostate cancer, it spreads mostly to bone. In breast cancer, it spreads mainly to bone, but also to liver and to lung. In colon cancer, it mostly spreads to liver initially and then everywhere. All cancers have their pathways to “distant” metastasis.

In most solid cancers, it also spreads—either before it heads to other sites or at the same time—to the regional lymph nodes.

Lymph nodes are structures that carry the lymph from the organ (say the prostate or the colon) to the central part of the body where it empties into the bloodstream. Cancers accumulate in these lymph nodes. In many cancers, taking out the lymph nodes is traditionally part of regional and local treatment.

In prostate cancer, we used to just take out the prostate with a perineal prostatectomy; that is, removing the prostate through an incision just below the scrotum. Few urologists then thought about removing the lymph nodes draining the prostate; maybe because it was considered too hard of an operation.

It soon became obvious that the lymph nodes needed to be
taken out, and since most of the operations were done perineally, most urologists removed them through an abdominal incision as a separate procedure before the perineal prostatectomy.

Later, they started removing them laparoscopically to avoid a big abdominal incision. At the time, removing both the lymph nodes and the prostate through an abdominal incision (i.e. a radical retropubic prostatectomy) was considered by many urologists to be too dangerous.

However, thanks to the innovations of a variety of surgeons, most prominently Dr. Patrick Walsh of Johns Hopkins University, the retropubic operation became safer and much more popular so that one could remove the lymph nodes at the same time through the same incision as the prostate gland.

However, we were rather naive in that we were taking out the lymph nodes along the external iliac vessels, which are the blood vessels that supply the leg, and the lymph nodes just below those vessels, but we weren't taking out the lymph nodes closer to the prostate gland, which were more likely to contain cancer.

Many European surgeons then started removing more lymph nodes and removing nodes closer to the prostate. That was called the “extended pelvic lymphadenectomy.” Now we know that if a lymphadenectomy is to be done, it should always be the extended type.

We also came to agree that this type of lymphadenectomy
should be done on high risk or high-intermediate risk prostate cancer and not on low risk or low-intermediate risk disease, because the chances that the lymph nodes contain cancer in these latter groups is very small. Whether or not the extended lymphadenectomy can or should be done by a robotic retropubic approach is still being debated, though I believe it can be done in experienced hands.

There is also a debate over whether or not we're just increasing the accuracy of staging, or if we're actually curing more people by removing more lymph nodes. I think the data now shows that in some cases we actually cure more men. Of course, in all of them we have a much better idea of how serious the cancer is once the lymph nodes are removed and can thus manage the patient better.

What do surgical approaches to lymph node disease offer that radiation doesn't?

That is a very interesting question, because early on radiotherapists initially insisted that surgeons remove patient's pelvic lymph nodes before they would radiate. In those early days, we did a lot of lymphadenectomies on patients who were going to get radiated, because if the lymph nodes were positive, the radiotherapist would say, "Well, we don't need to radiate because the horse is out of the barn."

As surgeons began to do lymphadenectomies at the same time as radical prostatectomies, and continued removing the
prostate even if these lymph nodes were positive, the radiotherapists stopped sending patients to surgeons. They would just radiate the local gland and not worry about the lymph nodes. Or, they would give extended radiotherapy, radiating the pelvis and surrounding areas even though studies didn’t clearly show that the practice increased survival.

I believe that ignoring the pelvic lymph nodes is why a great deal of the data shows that if the patients have significantly advanced apparently local disease, that radiotherapy isn't as effective as surgery. If this is true (and there are some radiotherapists who agree), it is not because taking out the lymph nodes cures a lot of men. Personally, I believe it cures only a minority, but in all the men it allows for better early management after initial treatment. For example, the PSA becomes meaningful within 3-4 months after surgery, whereas after radiation it takes a lot more time (often years) for the PSA to be indicative of persistent disease.

But just because the PSA starts going up after surgery and biochemical recurrence occurs, that doesn't necessarily mean you've got bad disease, especially if the lymph nodes were negative and the cancer in the removed prostate was not worrisome. Sometimes biochemical recurrences occur late. Often the PSA rises very slowly. You don't need to treat every biochemical recurrence. Even when the PSA hits 0.4, there is a great deal of variation in how fast a cancer grows.

Indeed, the Johns Hopkins data (among others), showed that if you don't do anything when the PSA starts coming back that the average time before a patient may get bone metastasis is
about 10 years.

Of course, everyone wants to know where the cancer is in all men whose PSA starts rising after surgery. For example, is it just in the lymph nodes that were not removed in the pelvis or higher in the abdomen, in the bone, or in both? It used to be that in 99% of patients who had a biochemical recurrence, we didn't know where the cancer was until very late when the PSA had risen to high levels. However, we did have some clues. For example, we learned that when a patient had so-called salvage radiotherapy (radiation to the area where the prostate was because the man's PSA was detectable and rising after surgery), the PSA went down in almost everyone, but it only stayed down in 40-60%. This can only mean that: 1) there was disease in the pelvis, but the radiation didn't kill it all and/or; 2) the disease was somewhere outside the pelvic radiation field in the pelvic lymph nodes or beyond and/or in the bone.

Now, with the recent advent of better imaging approaches (particularly PET/CT imaging) we are gaining some insight into this quandary. For example, we now have Carbon-11 Choline PET/CT imaging. This technique has been widely available in Europe for some years, but only recently became available in the United States. What has been determined is that this technique can detect prostate cancer in areas (especially lymph nodes) long before it is evident by other imaging techniques.

Let's talk a little bit about the Carbon-11 Choline because some of our readers may not be familiar with the scan.

In the Carbon-11 PET/CT scan, they use the Carbon-11 Choline
isotope, which localizes to prostate cancer tissue very well. However, the half-life of this isotope is very short and so one needs very specialized equipment. As I mentioned, the Carbon-11 Choline PET/CT scan has been widely available in Europe for years. In this country, only the Mayo Clinic has it so far, at least as far as I know, and so that is where we have been sending our patients to get this study done. Obviously, all the major US prostate cancer centers are working hard to implement this approach or other possibly more effective PET approaches.

So then C-11 Choline PET/CT is used as a way to determine where the prostate cancer has spread?

Yes. What the Europeans have shown us is that when this scan shows tumor in the pelvic lymph nodes, almost always at surgery those lymph nodes are positive, but there are also other lymph nodes that are positive that don't “light up” with the PET scan.

Thus, what the Europeans have done extensively (and we and others in the US are doing increasingly) is to surgically remove the remaining pelvic lymph nodes (and sometimes lymph nodes above the pelvis) in men who have positive C-11 Choline PET/CT scans.

So far, what we know is that initially after such a procedure the PSA often declines, frequently to undetectable levels and sometimes remains undetectable for years. However, in most, the PSA starts rising again indicating reactivation of disease. To date, most of us believe that this approach has value in many men, because it delays the necessity of hormone therapy and,
hopefully, increases survival.

You did a study in which you detected prostate cancer in the bone marrow of men about to have surgery. Many of those men ended up doing fine despite having cancer spread already. Can you speak a bit about that?

Yes. This is an area in which our laboratory has been focusing on for decades. It is called cancer dormancy. Cancer dormancy has become a major and exciting area for cancer biologists, but creates a confusing picture for the cancer patient. Very briefly, the idea is that in many cancers, if not all, cancer cells are out there circulating long before the primary cancer is destroyed. These cancer cells just sit there. In some patients, they grow and kill. In others, they sit there and remain dormant indefinitely or for very long periods of time. We've actually known about cancer dormancy in many cancers for decades. In breast cancer, 10 years later women will develop bone metastasis even though they were reassured initially that everything was fine. It's the same thing in prostate cancer.

We have increasingly more sophisticated ways to detect these circulating cells. When we find them in the blood we call them CTCs, or circulating tumor cells. When we find them in the bone marrow we call them DTCs, or disseminated tumor cells. In prostate cancer, CTCs are generally only detectable in advanced cancers, but DTCs are a different story. In general, we have found that most men have DTCs before the prostate is removed and that a great number have them after the surgery for years. For example, in those men we think we've
cured (those whose PSA is still 0 five years after treatment), somewhere around 30-40% continue to have DTCs in their bone marrow.

Thus, many men with prostate cancer have what we think are tumor cells in their bone marrow even though in most they will never get the cancer back clinically. What we believe is that we're removing the primary cancer site (e.g. the prostate) not in an effort to stop the cancer cells from escaping the organ, because they've always been escaping, but to stop the primary cancer from developing escaping cells that can readily stick at other sites (e.g. the bone) and grow, or from developing cells that can release factors that make cells that are already out there turn from dormant to active.

This new way of looking at cancer and its spread becomes confusing, because the patient asks, "If my cells were already outside the prostate gland, why are you taking out my prostate?" The paradigm of let's get that tumor out before it escapes is still a useful concept for those who aren't used to dealing with uncertainties.

But, in fact, I think most experts now believe that cancer cells are out there circulating from very early on. Stopping the cells in the primary cancer from escaping is not as important as stopping those cells that have always been escaping from turning into cells that do bad things. Exactly what that all means is still very much up in the air, but I am all but certain that as we understand cancer dormancy better, amazing new therapies will emerge.

With newer imaging techniques many men appear to have
cancer limited to the pelvis and the lower abdomen, but because of your work we know the cancer cells have spread widely. What factors limit the extent of prostate cancer spread?

The theory is that if you remove or radiate positive lymph nodes, just like with cells in the primary cancer, you're stopping those lymph nodes from shedding cancer cells into the bone marrow. These lymph node cells may in fact be cells that are not as dormant.

The problem with radiating them is that many times you radiate the nodes that the Carbon-11 Choline PET/CT says are positive, but you don't radiate the other ones (which we now know are often positive).

Are there any downsides to removing more lymph nodes than fewer?

As far as the patient's immunity is concerned, we don't think there is any effect if we remove the lymph nodes surgically. There is no evidence to believe that.

Dr. Snuffy Myers, I believe, thinks that radiating—particularly the retroperineal lymph nodes—does affect the immune system. And, of course, there has always been this problem of radiation perhaps making the patient less able to tolerate chemotherapy—even when we just radiate the pelvis. While I think there is something to that, many radiotherapists don't believe it. I don't think we have enough studies yet. In my own personal experience, though, I do think radiation does affect the immune system somewhat.