WHLE

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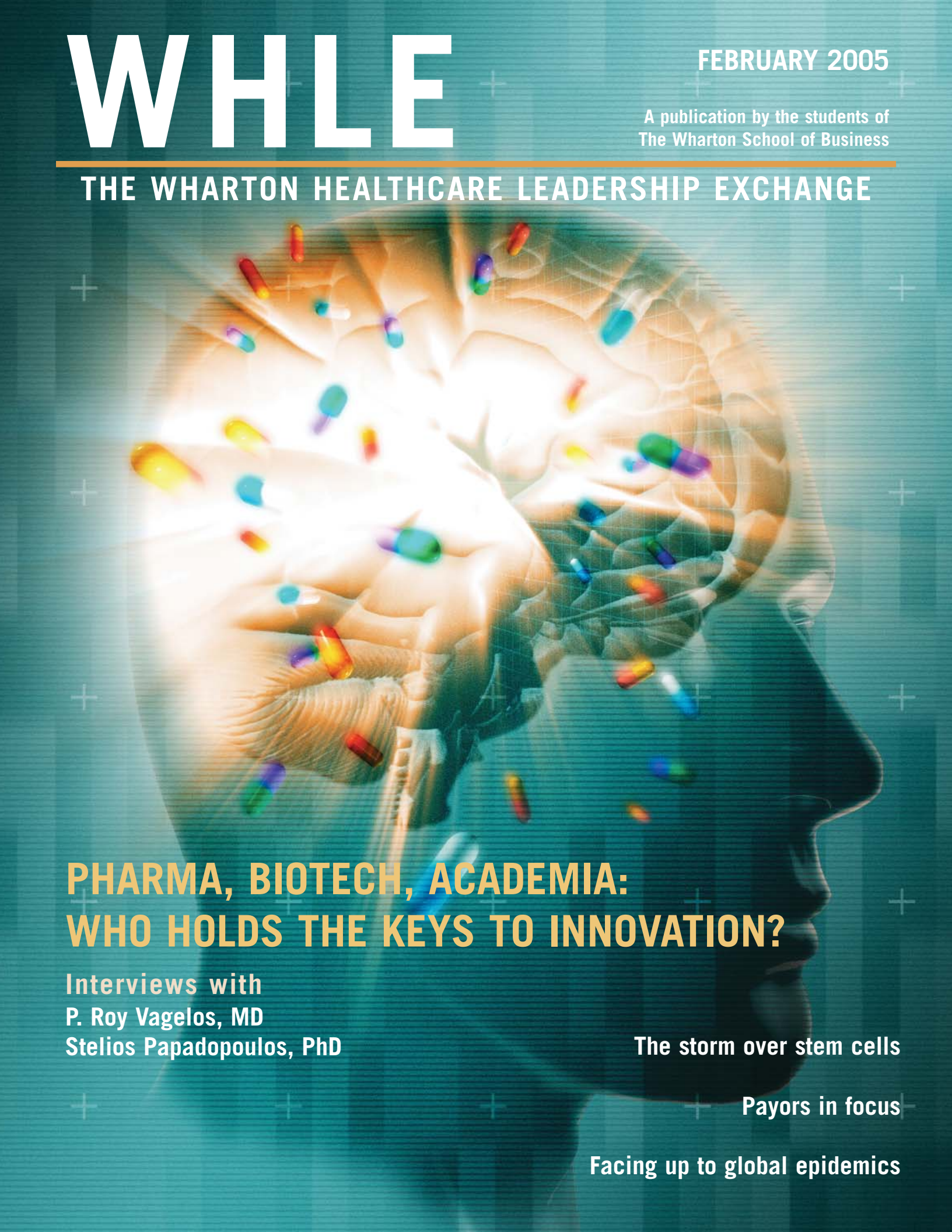
A publication by the students of
The Wharton School of Business

THE WHARTON HEALTHCARE LEADERSHIP EXCHANGE



PHARMA, BIOTECH, ACADEMIA: WHO HOLDS THE KEYS TO INNOVATION?

Interviews with
P. Roy Vagelos, MD
Stelios Papadopoulos, PhD

The storm over stem cells

Payors in focus

Facing up to global epidemics

Reflections on Leadership

The Wharton Health Care Business Conference is celebrating its 10th year of gathering the top minds from across the healthcare spectrum in Philadelphia to debate the industry's issues of the day. Participants range from leaders in drug, device, payor, and provider organizations, to bankers, consultants, academics, and venture capitalists. The student presence, both in organization and attendance, also creates a unique opportunity for generations of leaders to connect, share experiences, and learn from one another. The assembled conversations, panels, and speeches at the conference are deliberately broad in scope, combining and contrasting different opinions and backgrounds from every sector of the industry, to help participants make connections and discover insights they might not find in a narrower setting.

For the 10th Anniversary, we wanted to go farther, and sought to establish a mechanism that could extend the intellectual exchange of the event's participants beyond the boundaries of the conference itself. That instinct was the genesis of this journal, the Wharton Healthcare Leadership Exchange.

The goal of this publication, as the title suggests, is to create a forum, in print, for the exchange of ideas on the most challenging and topical issues in the healthcare industry today, and to share that exchange with both attendees of the conference as well as others who could not attend the event. To guide the conversation, we have chosen in this issue to focus on current, challenging topics across four diverse sectors in the healthcare landscape: Drug Development, Bioethics, Payors, and Global Health. For each of these areas, we invited two or three of the most experienced and relevant leaders in the field to reflect on the topic and to share their complementary perspectives. The intent is to triangulate these topics, to illuminate them from multiple angles. We have also included two conversations focused on Wharton, one with an MBA graduate and one with a member of the faculty, to highlight the school's important role in the industry.

As the healthcare industry grows more complex and increasingly interdependent, the importance of evaluating an issue from a multiplicity of perspectives increases as well. Ideas from other industry sectors, competing organizations, and different generations of leaders must be sought out and considered to thoughtfully address the contemporary challenges facing the healthcare industry. We hope that the conversations and ideas expressed in this journal contribute to that effort.

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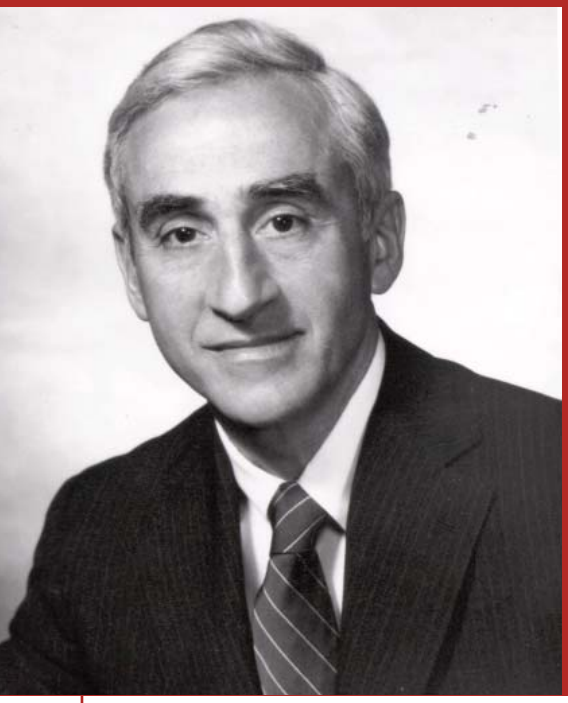
TABLE OF CONTENTS

Pharma, Biotech, Academia:
Who holds the keys to innovation?

The historical paradigm of industrial drug innovation is dramatically changing. For pharmaceutical companies, a crisis in R&D productivity and the challenges of unprecedented scale have complicated the prospects for innovation. The biotechnology universe now contains profitable, self-sufficient firms in addition to licensors and research partners. Even the academic community has radically evolved from passive research to a new focus on commercialization. Dr. P. Roy Vagelos, the former CEO of Merck & Co., Inc., describes the challenges facing the pharmaceutical industry today and the emerging symbiotic relationship between biotech and academia. Dr. Stelios Papadopoulos, Vice Chairman of SG Cowen, looks back on the evolution of the biotech industry and its interactions with both pharmaceutical companies and the academic community.

BIG CHANGES IN BIG PHARMA



P. Roy Vagelos, MD, spent 19 years leading Merck to the top of the pharmaceutical industry, including nine years as CEO. Under his leadership the company was repeatedly selected as the "Most Admired Company in America" by Fortune Magazine. Since retiring in 1994, he served for five years as Chairman of the Board of Trustees of the University of Pennsylvania and currently serves as the Chairman of the Board of Regeneron Pharmaceuticals, Inc. and Theravance, Inc.

Here, he reflects on a crisis of leadership in the industry he helped define, in which the massive scale of the industry's revenues and profitability, combined with its challenges in sustaining growth, led to decisions that have recently cast a shadow on the ethical standing of the industry. He also considers the shifting roles of universities, small companies, and pharmaceutical giants, and discusses the likely sources of scientific innovation in the coming era. His insight? You just have to follow the talent, and it is the small companies, not the big ones, that are attracting and retaining the brightest minds in science today.

WHLE: What has changed in the pharmaceutical industry compared to when you were involved?

PRV: First of all, the industry was much smaller when I started, which was in 1975. Each of the top companies was much smaller and could be impacted by a single major discovery, for instance Squibb with the ACE inhibitors. This had been a sleepy company that had done nothing important. Suddenly they had this one discovery and the leadership went around the world preaching about how you grow a pharmaceutical company. And yet there was nothing behind it. Worse, their major product, which was unique in the field, was overtaken by enalapril at Merck which had medical advantages. This is often the case with second-generation drugs. In time, Squibb was acquired by Bristol Myers.

So that is an example of a company coming up with an innovation, growing rapidly, and then disappearing. That has happened repeatedly. SmithKline came up with the first H2 receptor blocker, cimetidine, for peptic ulcers. That company too grew like blazes for a while and then was overtaken and acquired. In every instance, unless you have something new coming along, you're not going to make it. In those days, one drug could make an enormous difference; it could make a leader in the industry for a short time, a couple of years. But people didn't understand how rapidly your innovations can become just part of a class.

The industry has been transformed by numerous mergers in the past 25 years. There are fewer, larger companies as a result.

WHLE: Obviously, the industry has learned to stabilize that pattern by combining many products across many classes in a portfolio. What challenges are they facing today?

PRV: Size. Huge size. Scale like that helps those companies stabilize their revenue streams, but it also modulates sudden growth spurts as well. The chances of having a blockbuster that will cause you to grow 25% a year for five years is gone in the larger companies. You've got $30 billion or $40 billion in sales, and you need at least one blockbuster launch a year for that kind of growth, and it's just not in the cards for anybody. So size is a challenge.

Second, the cause of the productivity in the Merck laboratories, from the late 70s into the 90s, was that

Merck could recruit almost anybody they wanted. That was based on our research productivity and also on some of the moves that Merck had made. For instance, Merck developed a drug, ivermectin, for river blindness, a developing world disease, without any hope of profiting from it. That was not missed by young starry-eyed people going into science thinking they might do something important for mankind. Here was a company that was willing in 1987 to contribute a product of their research to benefit poor people. They could hardly believe it. Of course, Merck was growing rapidly at that time on the basis of many products sold in the developed world. But the combination of rapid growth as well as our ethical position helped us recruit terrific leaders into every area of the company, in research, manufacturing, marketing, sales, finance, etc. We had top people in every area, and people clamoring to come to Merck. It was easy to run the company.

"Merck was the Harvard of the industry by far; no one was even close."

WHLE: So clearly the scientific and ethical profile of the company, which is legendary, was crucial to building the talent base to innovate consistently. What other actions contributed to that reputation?

PRV: For instance, we developed the technology to make Hepatitis B vaccine. That pretty much saved the vaccine industry in the United States because it was the first vaccine to be priced above the range of other classical vaccines, which were in the $10-20 range. There was a study done at Merck that concluded that we ought to get out of the vaccine business. Yet here was a vaccine program that had developed mumps, measles, and rubella vaccines, and we were already working on a Hepatitis B vaccine. So when I was presented with this recommendation, the CEO asked me what I thought we ought to do. I said the last thing we want to do is leave the vaccine business because, ultimately, prevention is the best approach to disease control. And besides, we had a product coming that I thought would be terrific; that was the Hepatitis B vaccine. So we stuck with it, and that pretty well saved the vaccine industry because that vaccine set a new pricing paradigm with a price of $100.

Furthermore, the year we came out with the vaccine was 1981, and that was the year AIDS was identified. The vaccine that we had been working on for 10-15 years was not going to be usable because it was made from blood and people feared the vaccine might be contaminated by the agent that caused AIDS. We had already started developing another approach to make that vaccine by putting the gene that codes for the antigen into yeast, and that became the technology that produced the first recombinant vaccine in the world. The vaccine became very important in the US.

Then we learned of the prevalence of Hepatitis B in China, where it was one of the top causes of disease and death. Unlike the small, high-risk groups exposed to the virus in the US, in China it was very prevalent and was transmitted at birth from mother to infant. We discovered that we could immunize newborns and completely eliminate the disease. But the Chinese could not pay anything close to a reasonable price. So we ultimately sold them the technology for $7 million dollars.

WHLE: You sold the entire technology platform for the first recombinant vaccine?

PRV: Yes, and it cost us more than they paid just to transfer the technology. They spent a year in our plant learning to make the vaccine. They then built two plants in China that had enough capacity to immunize all the newborns, 20 million children a year, and Merck did not make a penny of profit for that. But it was the right thing to do. And that was also the kind of publicity that allowed us to recruit anyone we wanted into the company. Merck was the Harvard of the industry by far; no one was even close.

WHLE: There are obviously parallels with your actions on Hepatitis B in China and the crisis of AIDS in Africa. Is the industry missing an opportunity to take the same kind of ethical stance there?

PRV: Definitely. The industry had an opportunity to take advantage of magnificent science. AIDS was noted in 1981 as a disease with an unknown cause. The virus was soon identified at NIH and the Pasteur Institute. The industry did much of the basic research in molecular biology and biochemistry to identify a number of enzymes that became targets for drug discovery. Enzyme inhibitors were designed that became drugs which ultimately were able to control, not cure, the disease. The first ones were not very good, but

each subsequent generation was better. The disease went from causing death in 100% of the patients to a chronic infection controlled by a combination of medicines. Patients could return to work and live quite normal lives. Industry carried out a miracle. Companies rightfully made money in the developed world.

However, there is a very high incidence of AIDS in Africa, parts of Latin America and Asia where people were unable to afford the drugs. What did the industry do? Instead of using their accomplishments, which were magnificent, to go and negotiate with our government and others and say, "Look, if you go in with us and set up the clinics, we'll supply the drugs," there was nothing like that. They just stonewalled and said we can't reduce our prices. "What will it do to our prices around the world?" They had every possible excuse.

"[The pharmaceutical industry] is no longer a growth industry... The big and exciting growth will take place in small companies."

They were pushed finally by two things. One was the availability of generic versions of the drugs coming out of India, which pays no attention to patents. The other factor was the anger that was building in the American public. In the end the industry capitulated to public opinion. One by one the major companies arranged excellent programs in different regions to make their drugs available to poor people. But by then they had lost the opportunity to use the great products they had invented to improve their reputations. Instead, the reputation of the pharmaceutical industry went from the top of all industries to close to the bottom.

WHLE: Let's talk about another big ethical stance you took in the industry, and that was pricing.

PRV: There are two areas of pricing. One is how you price a new product. You have to determine the value that the medicine delivers. Do you save lives? Do you keep people out of hospitals and at work? Is there money saved when you take these drugs or is it an expense to improve lifestyle? We considered those things very seriously. And we always asked, "Will people be able to afford it?" That was the crucial question, and I was always very sensitive about it. We felt that pricing had to make sense, that I could explain to a neighbor what we were charging, because they could understand the benefit they were getting from it. Merck products always delivered value.

Many drugs are still fairly priced based on value. But there have been some striking examples of very high prices among some cancer drugs where there is little relationship to value delivered.

Of course, drug prices are higher in the US than in almost all other countries. That is because drug prices are controlled by government agencies in all other countries, and they force manufacturers to accept lower prices. This price disparity is causing Americans to complain about our higher prices and to try to obtain their drugs outside the US, such as from Canada

The second issue in pricing is deciding what to do annually. The industry, during the late 70s and early 80s, was prevented from raising their prices by the government for a number of years. Inflation was really hurting them, and so when the government took the lid off, companies started increasing their prices, and Merck did also. After I became CEO I watched it for a couple of years, but it started to bother me. One year, our loss to inflation had been made up, and so I said, "Well, from now on we will increase prices in line with the rise in the CPI." This was a bombshell in the industry. The other companies all grumbled initially, but one after another they all followed us because we had the biggest market share and we went public with our pricing policy.

WHLE: That's fallen by the wayside.

PRV: Yes, obviously, last year I think prescription drug prices rose at about 2.5 times the inflation rate across the industry, which I find totally unacceptable. And so what's going to come of it? There is going to be increasing anger in people who will complain of high prices and ask for government controls. This would be a terrible outcome. Government control of prices will reduce R&D investment and ultimately reduce new product flow.

A new element will affect the marketing of drugs in the future. Drugs will be studied while they are in development to determine what portion of a population is likely to have a therapeutic response (in many drugs that is 60-70%; in some it might be 25%). Genetic studies will also identify patients likely to have side effects. Such information will affect pricing and marketing of products.

WHLE: Will that be the end of the blockbuster model?

PRV: No, but billion dollar products will not come so easily. For each product there will be a smaller number of patients, but they will respond better, and they will be happy to pay the price.

WHLE: So what is the outlook for the pharmaceutical industry going forward?

PRV: I am very optimistic about the future of the industry, but it is no longer a growth industry, at least for the largest companies. It is a mature industry, but that is not a bad thing. This is seen in the stock prices of Pfizer, GlaxoSmithKline, Novartis and Merck which have not grown appreciably over the last four years. The revenues of Pfizer, GlaxoSmithKline and Novartis have grown, but this was accomplished through mergers. The annual growth rates in revenues and profits have slowed considerably. So this is a different industry. I think it's still a great industry that will make great contributions, but I think it's a mature industry. The big and exciting growth will take place in small companies.

A lot of the scientific talent is going to smaller companies. They know what goes on in the big companies. You're swallowed up in a research organization and you work on somebody else's projects. There is some small amount of freedom for people in addition to their major assignments, but there's also huge bureaucracy. The ability to attract and retain the best people in science has disappeared, or is disappearing in the large companies.

WHLE: So where are they going now?

PRV: They're going to small companies. There has been dramatic change in people at universities. When I went into industry, I was thought to be something of a renegade, someone who was abandoning pure research, and I was going to prostitute myself by working on applied research (now called translational research). Now, though, many professors are willing to think applied. I don't think there are many university professors, deans, provosts or presidents who aren't suggesting that their people be alert to the possibility of patenting and commercializing their inventions.

Professors have learned that they can jump onto this gravy train. They have great ideas and they become founders of startup companies. They don't have to leave the university. They retain their primary job, but they are involved in some companies. And they man these companies with the best post-docs and graduate students from their laboratories. These young scientists drift right from the university laboratory into the small companies. The professor who had all these good ideas is going to be on the scientific advisory board, and the university loves it because they'll have equity in the company and receive royalties.

WHLE: So this link between academia and the start-up community is a relatively new phenomenon?

PRV: In the old days, these young people would have either remained in the university or gone to a large company. In my era many of the best ones would have come to Merck if they had interest in applied research. Almost every small company has collared a few truly outstanding people that have come out of universities; few of these go into the large pharmaceutical companies.

And what can these scientists get at a startup? They have more freedom of expression. They have a lot of close interaction among the various scientific disciplines, because they are not in a big specialized team. It's just three chemists working with two biologists or a few molecular biologists. It's much more exciting and much more interactive. And they also get a larger piece of equity, with economic incentives far bigger than they can get in a large company.

WHLE: And is that more important than stability?

PRV: The best people don't have to worry about stability; if their company is acquired or goes down the tubes, they just dust themselves off and go to the next company. The others are better off in a big company anyway. But for the people who matter, the true intellectual capital that you want to build your company around, there's not much risk.

Actually the risk is on the other side. My concern as chairman of two small companies is always how can we be sure we're not going to lose the best people. Every time we discuss compensation for the year, we think about the key people that we must retain, and we try to put enough golden handcuffs on them so that they remain because these people pick up experience very fast and are very mobile.

WHLE: Particularly given the geographic proximity in some of these innovative communities like San Francisco or Boston, it's almost a game of musical chairs. You don't need to go far to find another opportunity.

PRV: That's right, even many of our recruits in development roles, clinical folks, regulatory people, they just come from down the street. South San Francisco, for instance, was built around Genentech, and

the area is like a beehive of small companies that have sprung up.

WHLE: So if innovation is people-driven, then these entrepreneurial communities that are attracting the best talent are going to be driving it in the future?

PRV: That's right. At Merck, I had great pride in the fact that we could collect the best intellectual capital that was available at the time at Merck. Now many are going to small companies, and not only are they joining from universities, but they're leaving large companies, too.

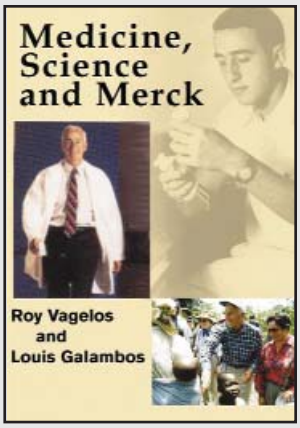
WHLE: Given the importance of universities in fueling innovation, what do you think of NIH funding? Is it still sufficiently open-ended to allow people free rein to innovate?

PRV: The NIH has a new funding initiative called the NIH Roadmap that is trying to push people in the direction of applied research. This was based on the observation by some in Congress that NIH funding doubled in a period of 5 years, and some questioned what had come out of that. Clearly, universities don't make drugs or vaccines, they do pure basic research. But the new knowledge that they generate is needed to take the big steps in drug discovery. Now Congress has slowed down the growth of the NIH and has taken a piece of NIH funding and designated it for funding applied research and even drug development at the universities. My major concern is the erosion of the budget supporting pure basic research.

Also, the universities are doing some things with that translational funding that I don't think they should be doing. They want to get into high throughput screening, making libraries of compounds, and things like that. These are industrial types of work that should not be done by students and faculty, in my opinion; I think it's a waste of talent. They're even building GMP (Good Manufacturing Practice) manufacturing facilities to produce intermediate-sized batches of chemicals. GMP facilities are very hard to run well, unless you keep them busy all the time and you have experienced professionals running them. It's just not part of the mission of universities. I think that's a mistake as well.

Besides, as I've mentioned, the faculty have no difficulty doing translational research in their laboratories on the side, anyway. I worry that some of the universities themselves are going to be transformed into industrial labs. What the universities should be doing is coming up with new knowledge, not new products, and setting the platform on which applied research is done in the industry by both small and big companies. That's the most efficient way for important new innovations to be generated and commercialized. ■

A Life of Leadership



Growing up in the 1930s as the son of Greek immigrants, P. Roy Vagelos, MD, received his first exposure to science and the pharmaceutical industry when he overheard the conversations of local Merck researchers while working at his father's luncheonette in Rahway, New Jersey. **Medicine, Science, and Merck**, the new autobiography of Dr. Vagelos written by himself and Louis Galambos, traces his dramatic progression from those humble beginnings to leadership and fame in the academic and industrial spheres. The book presents a vivid portrait of the lifelong development of an inquisitive mind guided by strong moral and ethical instincts.

The book is also fascinating in the extent to which the narrative of the autobiography reads like a narrative of the American century itself. Dr. Vagelos grew up in the Depression, and benefited from the diligence and care of immigrant parents. He went on to participate in the astounding mid-century revolution in the life sciences. His work in enzymology provided some of key foundations for more targeted and rational drug development. He helped industrialize those innovations at Merck, fueling the rapid growth of a suddenly booming industry. At the height of his leadership as CEO in the 1980s, Merck was the flagship company of a world-class American pharmaceutical industry.

This book is highly recommended for anyone seeking to better understand the historical emergence of the pharmaceutical industry; it also provides an inspiring glimpse into the roots, personality, and guiding principles of a celebrated scientific and industrial leader. All proceeds from sales of the book will go to scholarship support at the University of Pennsylvania and Columbia University. **Medicine, Science, and Merck** is published by Cambridge University Press.

A BRIEF HISTORY OF BIOTECH

Stelios Papadopoulos, PhD, is Vice Chairman of SG Cowen and one of the leading financiers in the biotechnology and pharmaceutical industries. Prior to joining SG Cowen, he served as Chairman of PaineWebber Development Corporation and worked as a biotechnology analyst at Drexel Burnham Lambert and Donaldson, Lufkin, & Jenrette. Before Wall Street, Dr. Papadopoulos was on the faculty of the Department of Cell Biology at NYU Medical Center. He is also an entrepreneur, having co-founded Exilixis, Inc. (of which he is still Chairman of the Board), Cellzome, Inc., and Anadys, Inc.

In an industry famous for rapid boom-bust cycles built on inflated expectations and impatient investors, Dr. Papadopoulos provides some much needed perspective on the big picture of the industry's evolution. What has changed in the 30 years since Genentech first opened its doors? Just about everything, from the coming-of-age of the premier firms to the explosion of small companies that have sprung up in their shadows. Aggregate public returns from the gold mine of biotech may disappoint, yet Dr. Papadopoulos isn't worried. Biotech, he says, remains a form of prospecting for scientific treasure. Most efforts fail; those that succeed change the world.

WHLE: The biotechnology industry is not even thirty years old, and many of the original pioneers are still leading the way. What is the impact of having such a young industry?

SP: By almost any definition, I would bet that three-quarters of the people in the industry today have been added during the last decade. That's a very young experience base. And since nobody has shown how things have evolved in this business in a studied way, the lessons of history are only limited to one's personal experience. That's a little scary. So if you've been around longer like I have, you see people making the same mistakes because they don't even know what questions to ask. If they'd asked, someone could have said, "Here's how it was done in 1985, here's why this drug failed, let's show how things are different now." We don't have that discussion going on today.

WHLE: Is the addition of all that human capital indicative of some sort of lifecycle inflection in the industry? Where do you see the biotech industry in terms of its lifecycle?

SP: In my mind I have not seen a lot of dramatic inflection points over the years, but rather incremental improvements, enhancements, and expansions. The exceptions are a few seminal events I would point to in the evolution of the industry. The first two involve Genentech. One is the founding of the company in 1976. The next important point was the IPO of Genentech in October 1980. That event showed how you could now grow the industry faster, bigger, and with more money, because it pointed to a new source of capital.

WHLE: Did the industry not anticipate that being an option?

SP: No. That was completely unanticipated. If you look back into the 1970s, there was a group of venture capitalists who thought they could put money into the technology. To some extent, biotech in the very beginning was nothing but a clever manufacturing technology for insulin and other proteins. There was complete naiveté about what it would take to make those kinds of drugs, because these VCs had no experience in drug development. They followed their intuition but had no clue on how much time or money was required. If Genentech had not gone public way too soon, the VCs would have run out of money and not much would have happened. Genentech had a number of alliances, but it was not selling any products. It was not reasonable for commercially immature companies to go public.

WHLE: So that assumption was overturned?

SP: Genentech showed to the world that you can go public based on exciting opportunity. If you consider that the stock market is focused on guessing future performance, then, if you can convince yourself of the company's prospects, you have accomplished your goal. And if you go back in history, there were other unproven opportunities, such as railroads or oil exploration, where people invested on the hope that new technology or ideas could make a big difference.

WHLE: Did Genen-tech's IPO pave the way for later turning points in the industry as well?

SP: Yes. The third turning point was the IPO market in 1991-1992. It was a 15-month window where all of a sudden the scale was changed. Many more companies went public, much more money was raised, and many more technologies were introduced. The fourth and most recent inflection point was in late 1999 and 2000 with the biotech and genomics boom when you had many more IPOs and much more money per IPO. Those IPO windows were important because only by focusing on them could one fully understand the extent of the industry's evolution since the previous inflection point.

"Biotech is a place where you take exceptional risk... But the occasional huge breakthroughs couldn't have come about in any other way."

WHLE: In the 80s it was the pharmaceutical industry that was really taking off and generating big returns. Now you've seen a shift whereby the pharmaceutical industry has become much more mature. Do you see biotech filling in the role of the growth industry now?

SP: I would be less focused on separating biotech from pharmaceuticals; they are really one and the same industry. The fundamental difference is just one of size. It's pretty clear that once biotech companies get big, they have the same obstacles and the same challenges that big pharmaceutical companies have. Is Amgen a biotech company? Well, Amgen was born as a biotech, but it is behaving as a smart pharmaceutical company today. Genentech is very much the same. On the other hand, I don't think there are many legacy pharmaceutical companies that are confronting their challenges very effectively. I guess the hardening of the arteries over decades is very hard to reverse.

Also, I do not subscribe at all to the notion that the biotech industry will be the discovery engine to feed the idle pharmaceutical enterprises. It's just not going to happen.

WHLE: Yet that's a pretty common assumption these days.

SP: It's nonsensical. It's not as if it does not happen. There will always be an opportunity where somebody has money and no products and somebody else has products and no money, and they make a deal. But it is very hard to give significant returns to investors without taking products all the way to commercialization. There have been no instances of biotech companies that have generated sustainable and significant returns without commercializing products.

Of course, most will not achieve independent commercial success for a number of reasons, mostly due to technology shortcomings or a failure of management. And sometimes it will be because of a discrepancy between the value of the company's stream of cashflows to investors and its value to a strategic acquirer, such that they are bought in advance of commercial success. But some will manage to go all the way and generate exceptional returns.

In fact, in aggregate, biotech may not be a good investment, because there's a lot of inefficiency and many failures. Biotech is a place where you take exceptional risk, where you try new ideas. But the occasional huge breakthroughs couldn't have come about in any other way. On occasion, some successes will be absorbed by pharmaceutical companies, which badly need them because they themselves are not configured to take extraordinary risks. But once in a while, one of these companies, because of timing, wisdom, insight, and discovery, will be able to stitch together an organization that is commercially viable and becomes the next Amgen, the next Gilead, the next MedImmune. That's what it takes.

In the early 90s, to make the case for investing in biotech, we used to ask, “What would you rather own, the entire biotech group, or Merck?” Because the total market cap of all of biotech at the time was less than Merck. And now Amgen alone is larger than Merck. So it was a good bet.

WHLE: Pharmaceutical companies own much of the commercialization real estate in terms of primary care doctors, and very few biotech companies are working on primary care-style drugs. Is there enough room in the periphery to support a model where biotechs aspire to commercialize their products themselves?

SP: It's true that you don't have a single biotech company that is about to launch an anti-hypertensive into the primary care market. That's going to be a tough proposition. On the other hand, I'm not so sure that the commercial opportunity is exclusively the area of the primary care market anyway. You still have an enormous amount of room in the cancer area. You can go to a variety of specialty medical areas where you need just a few hundred sales reps to penetrate those markets. And still, if you had a brand new Alzheimer's drug that really worked, you could still mount a charge on the GP market aggressively. So I would not assume that the GP market is out of reach for biotech.

It used to be fashionable for biotech companies to claim that they were going to become fully-integrated pharmaceutical companies, and then of course very few made it. Then they wanted to appear realistic and said they were going to do nothing but alliances. And the answer is neither of these two extremes. The only viable way is to carry forward your projects as far as you can, with whatever funding or resources are available, choosing always the most efficient path from a risk-reward and dilution point of view. And you are not even going to contemplate alliances or vertical integration; all you have to do at the outset is assemble good people and do good science. There's no need then to worry about anything else. When you have something to put through the clinic, at some appropriate time in advance of that you can assemble the right clinical team, or forge an alliance for that. You expand slowly and gradually, and it's usually through a combination of proprietary work and alliance work, and at some point, if everything works out, you launch a product on your own. It sounds simple-minded; it is rather subtle in execution but conceptually straightforward.

WHLE: Like MedImmune, which operated in that hybrid phase for 10 years, through multiple products, then launched Synagis and really took off.

SP: Sure. You don't have to worry about climbing Mt. Everest from the base. All you have to worry about is climbing to the next base camp and from there to the next one. It's not that complicated.

WHLE: How is the academic community and its relationship with the biotech industry evolving?

SP: The biggest thing that has changed in the last 30 years is the increase in the number of scientists of the highest academic caliber who are also commercially sensitive. In the 70s, it was considered almost dishonest for an academic scientist to be affiliated with commerce. Nowadays it's almost an expectation. Scientists are finding that there is real intellectual stimulation in connecting with rigorous people on the commercial side, because rigor is not a monopoly of the academic community. Now, you have role models, very accomplished academics who have embraced commerce and have founded companies. Now, every professor is his own vigilante for commercial opportunities. They are now able to ask, “What drug can come out of this interesting research?” And that's a lot more efficient than some third-rate VC scouring the universities or the publications.

WHLE: Does this imply that technologies are going to be coming to the VCs in a more mature state, closer to commercialization?

SP: In some ways, things are actually coming up earlier because the inventors are sensitized, so they see far in advance what can come out of their own work. And that's not always good. For instance, in the 80s, we started companies based on biological observations upon which we could make molecules that could become drugs. Then, in the late 90s, we started to create companies prior to those biological observations based on genomics considerations. That added anywhere from one to five years to the necessary evolution of the company, and several times the amount of risk. As a result, the VCs have become really gun-shy about technology platforms, and they've gone overboard in the other direction with specialty pharma, companies that are essentially trying to develop discrete numbers of compounds in a certain disease area, but on occasion without a common mechanism of action or therapeutic category.

Still, there is always room for a big idea. For instance, take RNAi. Alnylam, the leading company in that group, went public in 2004 with immature technology by today's stock market criteria, but it had a big idea with big names behind it.

WHLE: What differences do you see between America and Europe in supporting innovation and biotech as an industry?

SP: I actually do not think Europe has a realistic

chance against the US. The reason is not the quality of academic science. Europe simply does not have sufficient density of academic scientists with commercial expertise, experienced entrepreneurs who understand how to bootstrap operations and grow companies, and local capital markets for post-venture financing. You certainly have a bunch of great scientists, and you can always find the occasional great CEO and grow a company to take public on the US market. But you cannot hope that all of a sudden there will be a major market in Germany or some other country that is going to embrace those little companies.

Also, there are not enough role models. There's not even a single real success story for a biotech company in Europe. You could have called Celltech such a company, but even Celltech grew to its size through acquisitions, and then was acquired by UCB. The expected glorious biotech company par excellence, British Biotech, became an embarrassment. Serono is the self-proclaimed largest biotech company in Europe, but other than clever marketing and arbitrary self-designation there's no justification for it. Serono has been around forever. Their claim to the title is based on the fact that a large part of their sales comes from recombinant proteins. This is true, but J&J and Roche can make similar claims, yet they do not call themselves biotech companies.

"[Genentech] is the deserved successor to the Merck of the 70s and 80s in terms of bringing breakthrough new medicines to the market."

The places where biotech has flourished in the US are very much driven by a crossroads of good universities, VCs, and one or two lightning rod companies that became very successful, such that a lot of their people can then go off and start other companies. The original hub was built around Genentech's decision to go to South San Francisco in 1976. People were worried about recombinant DNA, and South San Francisco was nothing but decrepit industrial facilities, and so nobody minded. South San Francisco is now unrecognizable. It's the most exciting biotech hub anywhere, and it's all because of Genentech. And the Cambridge area is really the intersection of MIT, Harvard, Biogen, Genetics Institute, Genzyme, and all the other companies. Even if a few of the new companies in Europe were very successful, it will be at least 10 years before the environment starts to look even a little bit like what it does in the US.

WHLE: Is there a collaboration opportunity in China and India, where companies could do development work to take their $5M in Series A funding through Phase II? Is that something that's going to happen?

SP: I'm not so sure. First of all, biotech is not labor intensive, it's intellectually intensive. In software, you can subcontract for 1000 lines of code, or in the apparel business you can pay a nickel for a thousand stitches and be fairly certain of what you want and what you will receive. Not so in biotech. You actually need observation, thought, and reaction, to achieve greatness. You also need strict adherence to the protocols, so the risk is just too high. This isn't a question of manufacturing cars or jeans. For drugs, you can't have sloppy work lead to inexpensive drugs. You have to meet a threshold of performance that isn't just adequate, it needs to be very good, because you don't price them based on performance.

WHLE: With the apparent intensification of activity and interest in the sector based on its rapid growth, where do you see biotech going in the next 10 years?

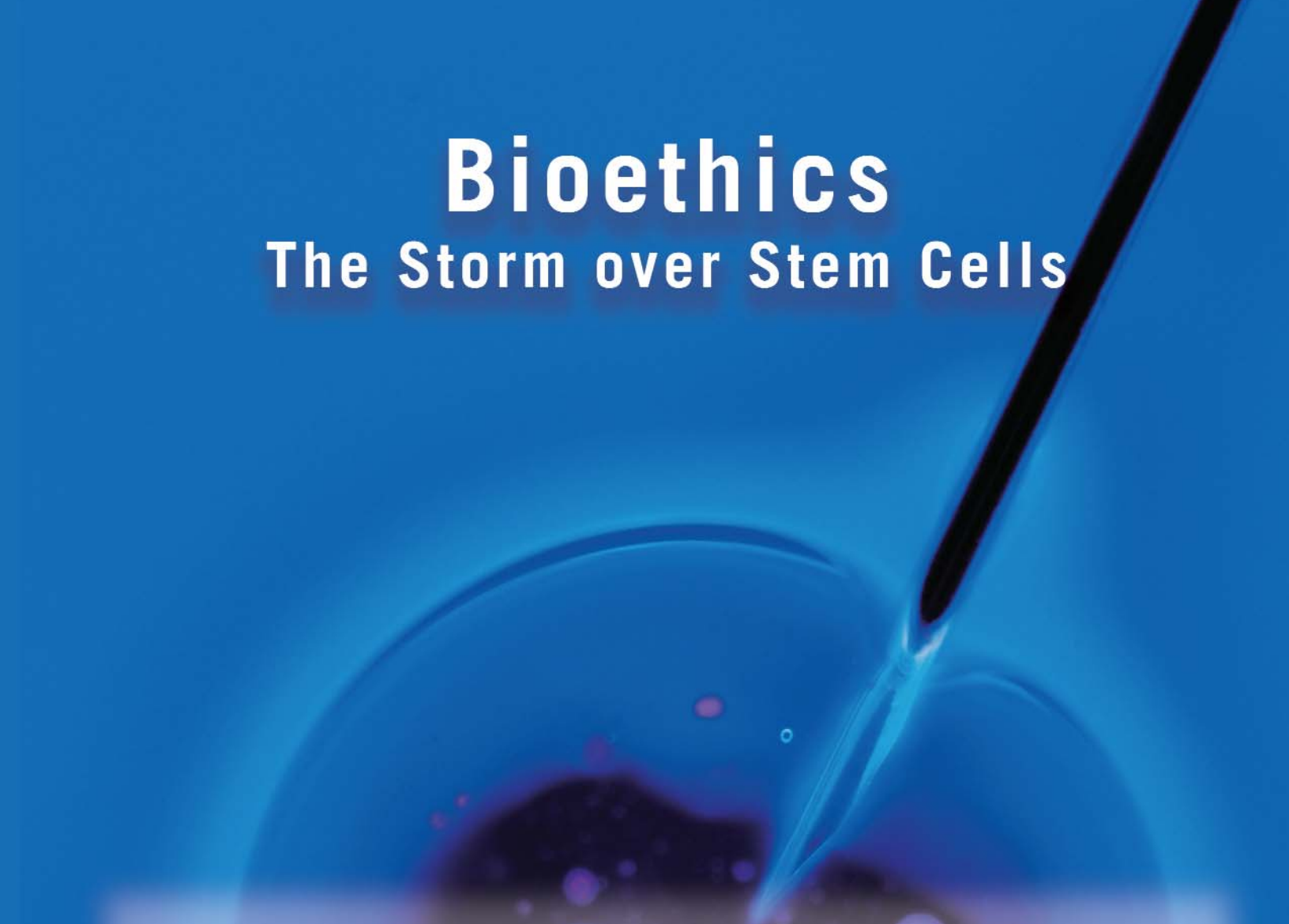
SP: I see continued domination by the US. I see continuing boom/bust cycles with the stock market between excitement and disappointment. The ideas being tried will be even more varied; whether earlier or later will depend on whichever concept is fashionable at the time. I believe there will be ever more biotech companies that graduate to become fully integrated sustainable enterprises. And the last generation of companies like Amgen and Genentech and MedImmune will become even more evolved, sophisticated pharmaceutical companies. The hope is that they retain some of the entrepreneurial, exciting ways of risktaking.

Genentech has done it extraordinarily well. If you ask, "Who is the deserved successor to the Merck of the 70s and 80s in terms of bringing breakthrough new medicines to market," it's Genentech. It's not Pfizer, it's not Glaxo, it's not Amgen. In terms of actual molecules and important discoveries, it's Genentech.

Finally, the industry will continue to be perplexing, because even though history repeats itself, it does so with subtle twists every time. ■

Bioethics

The Storm over Stem Cells



The stem cell research debate is characterized by inflammatory claims by both sides. Opponents of stem cell research insist that the use of embryos in research is a slope too slippery to negotiate and believe that the destruction of an embryo is ethically equivalent to the death of an adult human. Proponents of stem cell research argue that these new tools hold the cure to currently intractable diseases like Alzheimer's and Parkinson's. In the US, the result of this debate is a patchwork of legal restrictions and a murky ethical environment. We spoke with three leaders in the field of stem cell research: **Dr. Charles Jennings** of the Harvard Stem Cell Institute, **Dr. Alan Colman** of ES Cell International, and **Dr. Arthur Caplan** of the Center for Biomedical Ethics at the University of Pennsylvania in an effort to frame the debate and offer visions for the future of stem cell research.

THE PROMISE OF STEM CELLS

Charles Jennings, PhD, is the Executive Director of the Harvard Stem Cell Institute. Prior to joining the Harvard Stem Cell Institute, Dr. Jennings worked as an editor for Nature. He was the founding editor of Nature Neuroscience, and from 2000-2004 he was the executive editor responsible for all biomedical Nature Research titles (Nature Genetics, Nature Structural and Molecular Biology, Nature Medicine, Nature Biotechnology, Nature Neuroscience, Nature Cell Biology, and Nature Immunology). Dr. Jennings received his PhD from University College London (UCL) and completed post-doctoral work at Harvard University and the Massachusetts Institute of Technology.

Here, Dr. Jennings discusses the medical promise of stem cells and the rationale for founding the Harvard Stem Cell Institute. Dr. Jennings touches on the key facets of the debate raging around stem cells: science, regulation, and ethics. He anticipates that as stem cells begin to deliver medically relevant results on a broad scale, the current impediments to progress in stem cell research will begin to fall by the wayside.

WHLE: Can you describe the origin and mission of the Harvard Stem Cell Institute?

CJ: The institute came about as an initiative driven by Doug Melton and David Scadden at Harvard, two professors engaged in stem cell research. They realized that there was tremendous potential at Harvard to create an institution focused on stem cells that combined expertise in various disciplines across the University ranging from basic science to clinical practice to government and law. In addition, stem cells had been in the news recently and generated tremendous public support. They felt these two factors would make a compelling case for Harvard to do something extraordinary given stem cell research's potential to transform medicine in the decades to come. Doug and David took that vision to the Harvard leadership who made the institute a priority for university fundraising. The formal announcement was made in April of 2004. The overall mission of the institute is to support any aspect of stem cell research that has the ability to improve human health.

WHLE: What is the promise of stem cells? What medical benefits could this research provide?

CJ: The debate surrounding stem cells today has become quite heated, and I think the responsible position is to say we do not know how quickly this work will come to fruition. However, stem cell therapy is already saving thousands of lives a year in the case of bone marrow transplants. Skin grafts are really a form of stem cell therapy.

It is increasingly clear that even cancer is a disease of stem cells. The reason that cancer is so difficult to eradicate is because the therapies that have been developed to decrease tumor mass may not necessarily always eliminate the cancer stem cells. They may be a small portion of the whole, but if they are not killed the cancer is able to relapse following treatment. An understanding of stem cell biology in the context of cancer is likely to have some real payoffs in the not-too-distant future.

The use of stem cells for transplantation in diabetes and Parkinson's disease has an excellent scientific basis and although we cannot make the claim of benefit today, we have good reason to believe stem cells will show benefit in treating these diseases in the future. Stem cells may also affect the treatment of type I diabetes in the future. Whether these benefits arise five years or ten years from now, it is difficult to say.

One area where I think the promise of stem cell transplantation is less clear is in the area of Alzheimer's disease. I say that because Alzheimer's involves widespread and non-specific degeneration of large areas of the brain. It will be very challenging to replace all of those damaged neurons with new ones and to recreate a functioning brain.

I think that stem cell researchers should take some responsibility for the popular notion that stem cells can and will be able to treat this disease. In the heat of the debate, when someone makes exaggerated claims, scientists are not always as quick to correct those claims as they should be.

I would emphasize, however that embryonic stem cells may be useful not only for transplantation therapy but also as a research tool. In the case of Alzheimer's disease, for instance, there is a good prospect that embryonic stem cells will yield insights into the disease mechanism even if they are not useful for transplantation therapy.

"No one even foresaw embryonic stem cells as an issue ten years ago."

WHLE: Is the institute designed to circumvent restrictive federal legislation in order to realize this promise?

CJ: We are not in existence just for that reason. In order to fulfill our objectives, however, we have decided to seek private funding so as to avoid some of the restrictions. We would welcome a change in policy by the administration, and, over time, I am sure that change in policy will happen. We would certainly apply for NIH funding under those circumstances. I think given the nature of stem cell research, there would still be a strong case for seeking private funding even if NIH funding was available because private investment can really boost the development efforts in a way that NIH funding cannot always do.

I should point out that we are not just confined to embryonic stem cell research. We are also very interested in adult stem cells and you often see a debate on whether adult or embryonic stem cells are better. It often becomes very ideological, and it should not be an either-or decision.

WHLE: How would you compare the regulatory issues and legislation surrounding cloning within the United States and other countries?

CJ: Reproductive cloning is completely legal in the United States apart from a few states such as California and New Jersey, yet it has been appropriately outlawed in Britain. What we have in the United States is a ridiculous patchwork of regulations. For example, we have reactionary limitations about what can be done with federal money, but we have a complete regulatory vacuum in terms of what can be done with private money. Moreover, we have wide variations from state to state and some states have outlawed various forms of stem cell research. So what you ultimately have is an abjuration of responsibility at the federal government which has left a gap in regulation and a patchwork of very different laws in different states. The British system is more stringent. It is analogous to the systems in California and New Jersey that clearly define what you can and cannot do.

WHLE: Until the federal government adopts more consistent legislation, the institute is acting outside of the bounds of what the federal government has determined to be fundable. How do you as an institution make the ethical decisions to guide what you will do?

CJ: The process overall is tightly regulated. Any process that involves human subjects must be approved by an institutional review boards (IRB). To the extent that the work involves human subjects, including human donors, those procedures must be reviewed by the IRB. In addition to that, the University has created its own additional layer of regulation in the form of a stem cell research committee that was appointed by the provost and reports to the provost. It is composed of people who are knowledgeable of what has occurred, including bioethicists, scientists, lawyers, and administrators. These people are not involved directly in the institute, but are very knowledgeable about the science and ethical issues. Any procedure that involved the derivation of human embryonic stem cells would have to be approved by that independent committee.

WHLE: What is the ethical test that you use for approval?

CJ: There is not one simple test that can be encapsulated in a few words. The committee looks at the facts and considers it carefully. There are two main arguments that opponents of embryonic stem cell research typically propose. The first argument is the notion of a slippery

slope. In other words, doing this work is the first step along the road to reproductive cloning.

Our response to that is that this argument is nonsense. It is perfectly feasible to distinguish the two and put regulatory standards in place to permit simple therapeutic cloning while prohibiting reproductive cloning. Two states, California and New Jersey, have enacted legislation that has done just that and Massachusetts and other states are considering it. Other countries including Britain have similar laws so there is plenty of specimen legislation available to protect against the slippery slope argument. The reason we do not have that legislation is that opponents of stem cell research do not want it because they would lose their most effective argument against stem cell work. The fear of reproductive cloning is frankly a way of scaring the voters, and opponents of stem cell research do not want to lose that.

The other argument, which is more substantive, is that the only way to make embryonic stem cells at the moment is to destroy an embryo. The stage at which that is done is at a simple blastocyst stage where the embryo consists of a few hundred cells and is only a few days old. This is prior to the state at which it is implanted in the womb and you cannot speak of a pregnancy having been established. It is just a ball of cells that bears no resemblance to a human being even though it is capable of developing into one with some degree of probability. It is no more a human being than an acorn is an oak tree. Without wishing to dismiss the concerns of people who share that view, I think those people who are involved in stem cell research do not believe it is equivalent to destroying human life.

WHLE: How might this ethical debate change in the future?

CJ: I do not think that it is possible to identify one simple ethical test to encompass all of these issues because the science is evolving so fast that new issues keep coming up. No one even foresaw embryonic stem cells as an issue ten years ago. Scientific advancements have brought these ethical issues to the forefront, and it will happen again in the future.

Looking into the future, my personal view is that there will always be people who will not support stem cell research. Ultimately, some people will believe life begins at conception and that a blastocyst is morally equivalent to an adult human being and cannot be destroyed under those circumstances. Some of these people will never be persuaded to the contrary on that point. But I think the clinical benefits of the science will become more and more compelling as the population continues to age. The urgency of the medical need will be more obvious. In the long term, I am optimistic that the balance of public opinion will shift. ■

A PATCHWORK OF REGULATION

Alan Colman, PhD, has been Chief Scientific Officer of ES Cell International (ESI) since April 2002. ESI is a small Singapore based company whose mission is to develop embryonic stem cell-based therapies for the treatment of diabetes and congestive heart failure. Dr. Colman obtained a PhD under John Gurdon, a pioneer of the field of nuclear transfer, at the Laboratory of Molecular Biology in Cambridge, UK. From 1987 until March 2002, he was research director of the company PPL Therapeutics in Edinburgh, UK. This company specialized in the production of transgenic livestock that produced human therapeutic proteins in their milk. PPL attracted considerable media attention because of their participation in the technique of somatic nuclear transfer. This work led to Dolly, the world's first sheep cloned from an adult somatic cell (1996), Polly and Molly, the first cloned transgenic livestock (1997), Diana and Cupid, the first livestock with targeted genetic changes (2000), Millie et al., the first cloned pigs (2000) and, finally, Austin and crew, the first homozygous, alpha gal transferase knock out pigs (2003).

Here, Dr. Colman speaks about the impetus behind his move to Singapore, increasingly a country at the hub of life science research. He also addresses the current state of stem cell regulations in the US and abroad and the implications of these limitations on stem cell research. He expects recent efforts to secure non-federal funding for basic stem cell research in California and through the Harvard Stem Cell Institute to begin to transform the field and potentially provide the proof of concept that will one day validate the promise of stem cell therapies.

WHLE: Could you please describe your background? You are perhaps best known for your work in cloning Dolly the Sheep.

AC: I did my first degree at Oxford in biochemistry and then did my PhD with John Gurdon in Cambridge who was the pioneer of somatic nuclear transfer. He developed the ability to take a nucleus from a specialized frog cell, transfer it to an embryo whose own nucleus had been destroyed, and make a normal frog. So I grew up in that sort of environment.

In the early 80s, whilst a university teacher, I got introduced into venture capital and the creation and analysis of business plans. By the mid-80s, whilst working closely with a venture capitalist in assessing investment opportunities, I told him that in my academic work I had been able to make frog eggs secrete the protein interferon. At that time, interferon was thought to be the panacea for all ills. Everyone thought that interferon would be a wonder drug. And so he suggested that we start a company with me producing human interferon from injected frog eggs. Unfortunately, even working 24 hours a day, 365 days a year, I could only have made enough interferon to cure a slightly sick mouse. So that was not quite the way to go.

Instead, I raised the idea of using chicken eggs to produce human proteins and that brought us to the Roslin Institute in Scotland. In the course of negotiations to fund such chicken work there, we learnt of a technology developed by the Roslin Institute that would allow a similar sort of thing to be done with sheep. So instead of making valuable proteins in the eggs of chickens you could make valuable proteins, human proteins, in the milk of sheep.

WHLE: How did you plan to commercialize this innovation?

AC: Based on the concept above, a company was started in 1986 called, initially, Caledonian Transgenics, but it eventually became known as PPL Therapeutics. The whole remit of this company was to make huge amounts of human proteins cheaply and compete with,

and hopefully replace, some of the alternative means of making human proteins for therapeutic use. We became busy making these human protein-producing sheep with names like Tracy the Transgenic. These were the most famous sheep in the world before Dolly. Before we went to the pains of making sheep producing particular proteins, we made transgenic mice with the same gene constructs. We succeeded in making mice producing so much erythropoietin in their milk, that on scale up to sheep, we estimated that three sheep would produce the current world supply. Unfortunately, the intellectual property landscape for such work was a minefield.

Instead, we concentrated on our own clinical leads. However, we needed to improve the technology, and that is where Dolly came in. The cloning technology was pioneered next door at the Roslin Institute by Keith Campbell and Ian Wilmut. With my background in nuclear transfer, I immediately recognized that if cloning could be done in mammals, it would offer a novel way to genetically manipulate large animals and remove or alter existing genes. Dolly was the proof of principle of a technology that we predicted could be used to manipulate the genomes of large animals. Cloning using somatic nuclear transfer was the only way to do this that we could see at that time, and still remains the only way. Unlike mice, there are no embryonic stem cells (ES cells) available for large animals that could be used for the purpose.

"If embryonic stem cells can deliver the goods, stances will change."

WHLE: How did your involvement translate into your current work in stem cells?

AC: In a contemporary development to the work on Dolly, Jamie Thomson in 1998, described the generation of human embryonic stem cells which could differentiate into all sorts of human cell types. The prospect was raised of combining the two technologies to make customized (to individual patients) hES cells which could be used for cell therapy purposes without fear of immunorejection. Although, I viewed this combination as a pipedream, I nevertheless became very interested in the application of hES cells to diabetes. We started a small group within the company in about 1999, but the company got into financial troubles and could not afford the distraction. I decided to try and spin out the stem cell work. I trawled venture capital outlets in the US and the UK but there was just no money available to support this type of venture at the time. Stem cells are a very high risk area for venture capital. Serendipitously, an opportunity came up in Singapore for me to do this in a commercial context at ES Cell International and I took it.

WHLE: Can you talk in a little bit more detail about the mission of ES Cell International (ESI)?

AC: The company was started by a joint investment on the part of Australian business angels and a venture capital fund run by the Singapore government. The Economic Development Board, which is an organ of the Singapore government, has set up a fund devoted to biotech investments in Singapore and abroad. At the time I joined, the main business of ESI was selling stem cell lines. It had six of what were said to be 72 Bush-approved ES lines. The number of approved stem cell lines is now probably about 22, and that is it for the next four years in federally-supported research in the US. I joined with the intention of developing a clinical focus for ESI and, for technical reasons, the best target at that time was diabetes. So we started building up a team to develop a way to convert hES cells to pancreatic islet cells that could address the disease.

WHLE: What originally prompted your move to Singapore? Was it a means of circumventing oppressive stem cell regulations in the US and EU?

AC: The move was simply opportunistic. I wanted to do certain types of work in a commercial setting and I found that I could not easily do that in the US or UK because the private funds were not available. I had an offer from Singapore, visited it, and found the infrastructure here very good. In terms of the regulations, at the time I came people were saying, "Oh, are you going to Singapore because it has lax regulation and so forth. In terms of biomedical research you can do anything you want." Of course, that is not the case. They did not have formal legislation about stem cells when I came, but I was leaving a country that already had enacted the most liberal regulations in the world, the UK. So leaving the UK was certainly not a means of escaping repressive legislation. Singapore is adopting the UK legislation, more or less.

WHLE: Without written legislation, how do companies such as ESI assess the acceptability of their own work?

AC: Most scientists do not work in a moral vacuum and are well aware of the prevailing, if sometimes unstated, limits to their experimental activities. As a company wishing ultimately to trade in Europe and North America, we have to be conscious of the image we project. When I started in Singapore, there were no written guidelines in my area but there are now, and these guidelines will be strengthened soon by appropriate legislation. Singapore is very sensitive to any image that because it is in Asia, they flaunt rules that would exist elsewhere. So they *de facto* adopted a British position that has relatively liberal rules and everyone is keeping to those. Keep in mind that this is a country in which the money, the funding of research within the country, comes from one source. People know that if they do something that the government would not like, their funding is gone for some time. You get a very compliant scientific population here, the same as the rest of the civilian population. People anticipate the limits of where they can go based on what they see now. It self-regulates at the moment, but my understanding is that it is very effective.

WHLE: US regulations are noticeably different from those adopted in the UK and in Singapore. What are the implications of the US regulations?

AC: It is a schizophrenic situation in the US. Private companies can do what they like, there are no regulations. Companies can make new embryonic stem cell lines if they want. Even academic groups can do that. One of my colleagues, Doug Melton at the Harvard Stem Cell Institute, made 17 new lines available. The only issue is that you cannot use federal funding to work with any of these new lines. Because a lot of academics get their money through the NIH, this legislation restricts them to the existing cell lines. People feel that this is anti-scientific, anti-progress. It is quite clear that every line is different, and these lines are very idiosyncratic. Some can do some things, some can do others. Scientists want complete freedom to make new lines and they cannot do that in the US with federal dollars.

WHLE: That puts a hold on a lot of the basic research that is occurring. Is this research something that venture-funded companies could take on?

AC: This is still a young area which needs huge investment into basic research. Companies just do not have the resources to invest in enough basic research. If the academic community is impeded in its ability to work in these areas, then that is going to limit the amount of work that is going to come out of basic science. That is where the downside is for this type of legislation.

Apart from the restrictions imposed on hES research, the acrimonious debate on the morality of hES research has had other pernicious consequences. The current US position arose from a wish by President Bush to meet the demands of the conservative right. It is a tightrope act reflecting a polarization of views within different communities in the US. Irrespective of the legislation, some academics, particularly in the Midwest, do not even want to work on the existing embryonic stem cell lines because of the stigma that might be attached to them within their rather myopic local communities. I find the whole US situation perplexing: If you adopt a moral position (not a political position), it has to be consistent. If tax dollars or not tax dollars gets you out of it, that isn't moral to me.

WHLE: Are these kinds of impediments to research peculiar to the US?

AC: Clearly in the US, the degree of impediment depends on whether you are working with or without federal support. In Germany, the situation is more problematic. In Germany there is similar legislation that allows people to work on lines that were made before January 2002, but it is criminal for anyone resident in Germany to work on lines that were made after that date. They can be imprisoned and lose their job. Moreover, it looks like if a professor, quite a senior appointment in Germany, is even discussing collaboration by email with people abroad on lines that were made after that date, that is an offense under the law in Germany. So you can see that there are very many different positions throughout the world on this issue. And then Proposition 71 [funding of $3 billion for stem cell research in California over ten years] comes along and that is going to send enormous waves everywhere in many different ways.

WHLE: How do you think this debate is going to change over the next ten years?

AC: Nothing helps change moral stances like good results. If you look at the history of IVF or kidney transplantation, all of these developments were treated very negatively when they came out. IVF was condemned by the medical community, never mind anyone else. Kidney transplantation was thought to be terrible when it first came out. With the realization that these things can help people enormously, they become more acceptable. Once these strategies are successful, people's views change. If embryonic stem cells can deliver the goods, then stances will definitely change. I'm absolutely sure of that. ■

SEARCHING FOR CLARITY

Arthur L. Caplan, PhD, is currently the Emanuel and Robert Hart Professor of Bioethics, Chair of the Department of Medical Ethics and the Director of the Center for Bioethics at the University of Pennsylvania in Philadelphia. Prior to coming to Penn in 1994, Caplan taught at the University of Minnesota, the University of Pittsburgh, and Columbia University. He was the Associate Director of the Hastings Center from 1984-1987.

Dr. Caplan writes a regular column on bioethics for MSNBC.com. He is a frequent guest and commentator on National Public Radio, CNN, MSNBC, the New York Times, Washington Post, Philadelphia Inquirer and many other media outlets. He has served on a number of national and international committees including as the Chair of the Advisory Committee to the United Nations on Human Cloning, the Chair of the Advisory Committee to the Department of Health and Human Services on Blood Safety and Availability, a member of the Presidential Advisory Committee on Gulf War Illnesses, and the special advisory panel to the National Institutes of Mental Health on human experimentation on vulnerable subjects, among others.

In our conversation, Dr. Caplan outlines the complex legal and regulatory landscape surrounding stem cell research and critiques the arguments put forward by opponents of the technology.

WHLE: What is the mission of the Center for Bioethics at the University of Pennsylvania?

ALC: The Center's mission is to promote public understanding of ethical, legal, social and public policy implications of advances in the life sciences and medicine.

We pursue this mission in two ways: research and outreach. As it pertains to research, the Center surveys, analyzes and compiles information on a variety of different medical activities. Some of our ongoing projects today focus on topics that include genetic testing and engineering, human research, end-of-life care, reproductive technologies and transplantation.

The Center is also heavily involved in outreach and public service-related activities. In addition to the Center's involvement in the media, we sponsor a variety of public lectures, symposia and workshops on timely ethical issues.

WHLE: Stem cell research is an evolving field with regulatory and legal standards that differ between countries around the world. Does this concern you?

ALC: I think the variations in standards that exist today do not link up to clear-cut ethical arguments. As a result, there are some misunderstandings and confusion. For example, when people have said no cloning for research, what they are really afraid of most of the time is reproductive cloning. Cloning for research does not lead to that unless you allow a cloned embryo to be put into a woman's body. So you might as well have a regulation that prohibits that rather than stopping the creation of cloned embryos for research purposes. Some other countries have passed these laws because they think that every embryo is a person from the moment it's created, but I don't think that argument has been persuasively and effectively made. It may be the position of a significant minority of people, but I am not sure it is the majority position anywhere in the world. So, part of my problem is that these variations in regulatory standards rest on confusions, unarticulated arguments and misunderstand-

ings of how to regulate the field. This leads to problems because the variations slow down research, if companies have to deal with different regulatory environments. In some areas of the world, they risk letting certain nations like China, Singapore and Korea move ahead because they are not regulating the field very closely at all. This would be true in the United States too, meaning that we would fall behind, except for the recent California referendum on funding stem cell research. So when the variations in regulatory standards exist, scientists and financial support tend to flow to those regions that are the least regulated. This could put us at a significant disadvantage as well. So I would rather see standardized regulations around the world and I would like to see them based upon sound ethical and factual understanding instead of confusion.

WHLE: Given the need for a global standard, what role do you see the United Nations playing, if any?

ALC: I would like the UN to split the issues between reproductive cloning and cloning for research. I think you could get instant agreement around the world that cloning for reproduction makes no ethical sense simply because it is so dangerous, forgetting about all the other questions. Animal data shows it does not work very well. So, trying to clone a person when you have produced so many dead or deformed calves, sheep and goats makes no sense. We would not allow that to happen in the production and testing of a human drug so why we would allow such a practice for making a baby makes no sense either. That said, if you split the issues between research and reproductive cloning, you might get some agreement on research cloning because then the position of some countries would shift since they are primarily worried about reproductive cloning. Ultimately I think you should establish research cloning to be carefully reviewed and monitored and have reproductive cloning banned. Do I think that will happen? No, simply because part of the politics today revolves around keeping the issues linked together. The side that can't overcome the benefits associated with therapeutic cloning keeps the two issues linked in order to ensure they have a chance to win on banning all cloning. They have a stake in keeping things confused, if you will.

"The slippery slope argument is always something that has to be taken into account, but that is why people invented stairs and terraces."

WHLE: You emphasize the importance of "trust" among the public, legal, academic and industrial communities as stem cell research advances. Can "trust" persevere in this inconsistent regulatory environment?

ALC: No, it's not likely to persevere. If you see people worried that there are countries out there that have no regulations and they are in it just to get ahead, make money or be first, that is dangerous because the public then starts to believe that these countries are not going to do anything except to try to pursue their narrow self interests. Trust also won't exist when there is private sector sponsorship, because people are going to ask, "To whom are they accountable? If the answer is no one, why should we trust anything that they do?" The history of privately-sponsored research in recent years has been grim. There have been all kinds of reasons to be distrustful of the private sector, particularly pharmaceuticals and biotechnology: covering up adverse events, drug recalls, overpricing, etc. This recent history is bad. The private sector can't say that they've done well up until this point, so the public should trust them. No one will buy that.

WHLE: How would you characterize the funding process for stem cell research in the US? Federal funding is limited to only a few specified cell lines while private funding is exempt from restrictions. Does this concern you?

ALC: That problem exists because the government's position is a "have your cake and eat it too" strategy. That is to say, there are a number of politicians who can favor the federal restrictions while feeling that the private sector can pull the work along. These politicians can then say to some of their constituents that they oppose cloning on pro-life grounds, but tell others they are for research at the same time. That policy has fallen apart more recently because it has become clear that private money just is not going to come in at this stage and with the passage of the referendum in California, people can see that California has now made a huge investment. So what we are watching now is a scramble at the state level to find ways where they can prevent biotech companies, scientists and stem cell-related

industries from moving to California. The strategy of saying, "I am against embryo destruction as a matter of federal policy, but of course I want research to be done in my local state" did work initially. But now, California's investment has killed that option. California's investment is bigger than what could have been expected under a Kerry administration.

WHLE: Two ethical arguments continue to arise in the debate on stem cell research. The first involves the notion of a "slippery slope" whereby stem cell research is a first step along a path that leads to human reproductive cloning. The second involves the ethical considerations surrounding the blastocyst stage of an embryo and whether this qualifies as a human life. How do you react to these arguments?

ALC: The slippery slope argument is always something that has to be taken into account, but that is why people invented stairs and terraces. We know what to do with slopes. You try to graduate them so we don't fall down them. There may be a slope that leads from allowing research cloning in a dish to an entire village of cloned people, but if you don't want that outcome, you can institute stopping points, strict review policies and tough penalties to preclude slipping down the slope. Therefore, I don't find the slippery slope worry very compelling. If you took the argument seriously, you would be saying, “You can't do anything ever about anything because there are slopes that lead to unacceptable conclusions by anybody's values.” For example, you can't have gunpowder because you'll have World War II. You can't have explosives, because you will have terrorism. You can't have the automobile because it leads to highway carnage. Clearly, the slope must be taken into account, but it must not drive policy.

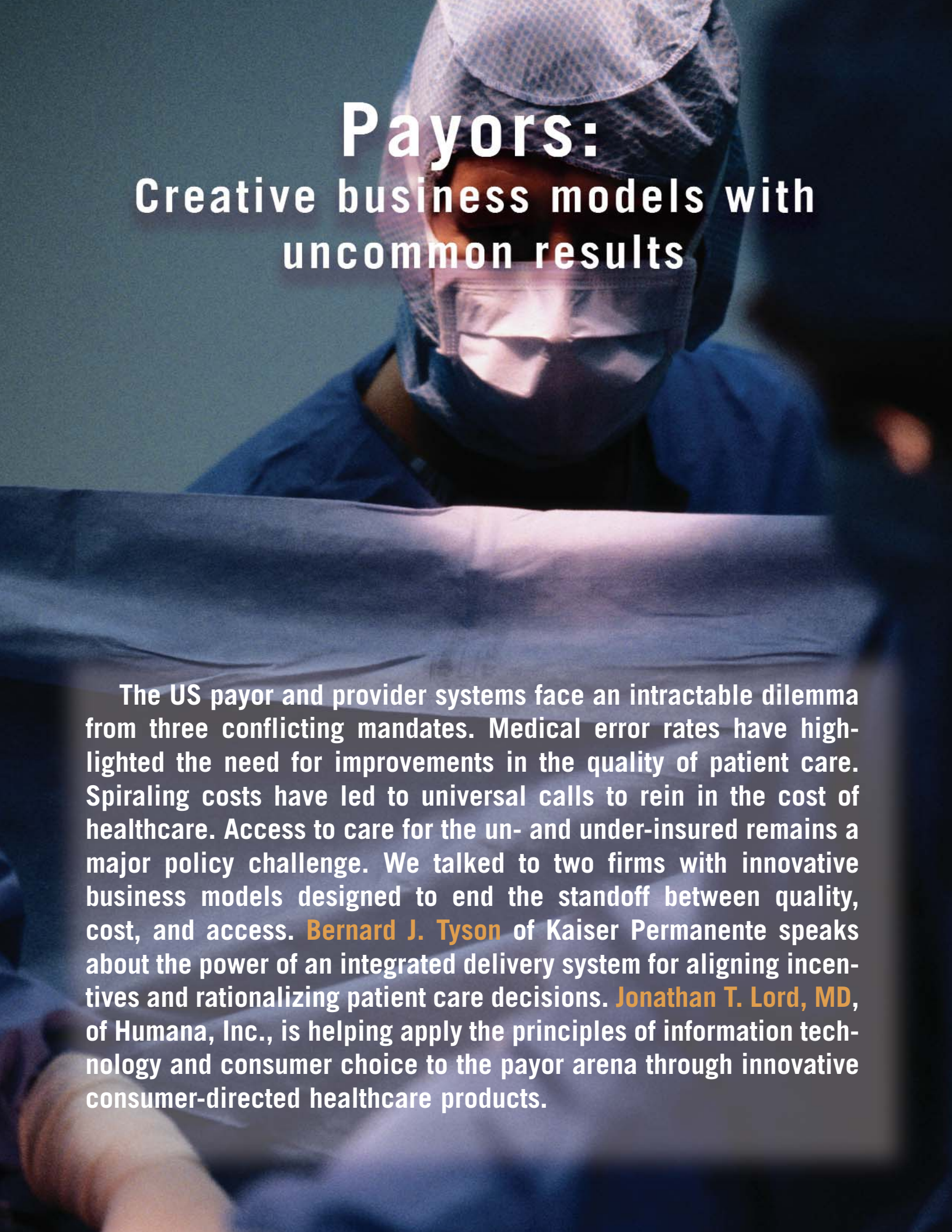
Regarding the blastocyst argument, it's confusing to label a blastocyst a human life. If you went down to Home Depot, which sells hardware, plumbing equipment and supplies, there are likely enough materials on site to construct say 18 houses. If the store burned down you could say 18 houses were destroyed, but that would be inaccurate. You would want to say that ingredients for 18 houses were destroyed. The houses themselves are not destroyed because they do not exist, but the potential to make them out of the parts has in fact been lost. So, you might say eighteen potential houses were in fact lost. This analogy is closer to what the blastocyst represents. It's a potential, possible person. Even under the best of circumstances, the science tells us that at least half of all blastocysts that are made by sexual intercourse do not make it to become babies. So, it's always been a long road for any blastocyst to become a person. It may be true that every life begins with conception, but it is not true that every conception begins a life.

WHLE: Are there any other ethical issues we have not mentioned that you think will be important in the future?

ALC: The debate over intellectual property and stem cells will be important in the future. The major question in the future, assuming stem cell research is successful, will be to determine who owns the techniques responsible for producing therapies. I think we are going to see some heated battles over intellectual property. I think that patents today on stem cells may not hold up in the future because it is not clear what the stem cells do yet. There are a few issued and more likely to come, but there will be a battle over both how well existing patents hold up and when one should issue new patents. Do you issue another one when someone has isolated a new kind of stem cell or do you wait until they can claim true patient benefit? To me, most patents today are composition patents and few target a use.

WHLE: How do you think the stem cell debate will change over the coming decade?

ALC: I think that things were getting grim for stem cell research in the US until the infusion of funds from California. Before that, it appeared as if stem cell technologies would be done by others elsewhere. I think the landscape has changed completely following California's investment. Young scientists are going to be willing to put their careers on the line to see if they can make something happen here and now it's all up to the science. The future will be determined by whether the science pans out. ■



Payors:
Creative business models with uncommon results

The US payor and provider systems face an intractable dilemma from three conflicting mandates. Medical error rates have highlighted the need for improvements in the quality of patient care. Spiraling costs have led to universal calls to rein in the cost of healthcare. Access to care for the un- and under-insured remains a major policy challenge. We talked to two firms with innovative business models designed to end the standoff between quality, cost, and access. Bernard J. Tyson of Kaiser Permanente speaks about the power of an integrated delivery system for aligning incentives and rationalizing patient care decisions. Jonathan T. Lord, MD, of Humana, Inc., is helping apply the principles of information technology and consumer choice to the payor arena through innovative consumer-directed healthcare products.

THE POWER OF INTEGRATED CARE

Bernard J. Tyson is the Senior Vice President of Brand Strategy and Management at Kaiser Permanente. Prior to his current role, he served as Chief Operating Officer of Kaiser Foundation Health Plan, Inc.'s Regions Outside California (ROC), which serves 2.8 million members in 16 states and the District of Columbia. In 1998 Mr. Tyson was one of five healthcare executives nationwide to be recognized with the "International Emerging Leaders in Health Care Award", sponsored by The Health Care Forum and Korn/Ferry International. He is Chairman of the Board for the Kaiser Foundation Health Plan in the Mid-Atlantic States and is a board member for the Alliance of Community Health Plans (ACHP). He also serves on the advisory committee for the National Committee for Quality Health Care (NCQHC).

Here, Mr. Tyson discusses the unique business model of Kaiser Permanente, and its many advantages for improving quality of care, affordability of care, and physician satisfaction. He also examines the myriad challenges facing the payor/provider landscape today and in the future. Kaiser Permanente, he suggests, is well-equipped to rise to those challenges with an integrated delivery model and a focus on new technology. The problem is finding a way to help other systems and regions replicate the organization's unique success.

WHLE: How is Kaiser Permanente's business model differentiated from others in the industry?

BJT: Let's strip the giant organization down to its core in very simple terms and then we'll rebuild it to demonstrate how it works. At the simplest level, the organization has been designed to self-finance a delivery system that has been built over the last 50-plus years. We take money in and give money out to take care of a population of members who choose to stay with and be a part of Kaiser Permanente. The secret of our success has been our ability to finance a healthcare delivery system for 50-plus years.

Our quality-of-care indicators are better than, if not the best of, any of the branded names that you hear across the country. Our heart disease program in San Francisco is incredible. In fact, we've been able to demonstrate that you have a 30% better chance of surviving a heart attack with Kaiser Permanente versus any of the other health systems in Northern California.

WHLE: What were the origins of the integrated delivery model?

BJT: Here's how it happened. The medical group model that Kaiser Permanente put in place years ago was rejected by many during that time. The notion of what we were trying to do was considered to be socialized medicine and communistic. There is a rich history about how our practice was welcomed or not welcomed by the industry. In fact some doctors were even rejected from most of the medical societies during that time.

Things have changed. Our physicians tended to hunker down and work extremely hard to prove that this was a better way to practice medicine. They believed that having a group of colleagues of varying specialties, motivated to work in an integrated community, would produce better outcomes for patients and a better work environment for providers. The January 2005 issue of SF Magazine named Kaiser Permanente as one of the best places for a doctor to work. Our physicians are more satisfied working with us than in nearly any other environment.

WHLE: Why is that?

BJT: It's no secret. Our physicians spend the majority of their time practicing what they went to school for. They govern themselves more than you will find in a fragmented delivery system. What we have here is a group of doctors who have been selected to

come into this environment and contract with the health plan to provide care to a given population. They don't have to spend their time and energy dealing with the other issues that other groups deal with: insurance, billing, and office management. They spend time practicing medicine.

And there is another positive aspect to the system. In healthcare there is tremendous fragmentation. For us, the secret sauce is vertical integration. There aren't any disincentives to force us to choose one mode of therapy over another, because we have total line of sight. So if it makes sense to do more work in an outpatient setting, then we gear the funds to support that practice. The same is true to support hospitalization, home health and any other appropriate care setting. We also have pharmacy services included in our model.

"Our physicians spend the majority of time practicing what they went to school for."

So what you end up with is not only a physician who can practice his or her profession, but also an infrastructure that supports that physician, hospital, pharmacy, and colleagues, all working together to make the best medical decisions possible.

In the 1990s, the company went through financial difficulties. While we insulated our doctors from that experience, we still had to change our strategy given the reality of competing in a very competitive marketplace. As part of our new strategy, we moved to link our patients with personal physicians, and that was a major cultural change for our doctors. They need to be responsible for their patients no matter what time of day or night. And they need to have the infrastructure in place to maintain the relationship with their patients when they are out-of-pocket.

WHLE: What was the impact of that initiative on customer relationships and doctors?

BJT: The biggest benefit was with our patients. Patient satisfaction went up tremendously when patients learned that they could choose their physician and begin to form a relationship with their provider. We are very intent on clearing up the misconception in the marketplace that you can't have a personal physician when you belong to Kaiser Permanente or that when you have one, you can't see them the majority of the time.

There have been growing pains on the other side, though, as physicians get used to managing a persistent panel of members as opposed to an urgent care model. They are managing a population now instead of just managing demand. In some cases that was a challenging adjustment. But we worked through the majority of those growing pains.

WHLE: What are the elements of the Kaiser Permanente business model that are contributing to better medical outcomes?

BJT: Several things. Most important is an incredible focus on prevention and evidence-based medicine. What we've created is a learning environment. We strive to better understand how to care for individuals and populations in the most cost-effective way possible. The centerpiece is to create an environment where people are willing to learn and accept that one way might be better than another based on evidence.

Part of our strategy going forward is to leverage that model as much as we can with best practice sharing and cross-fertilization. There are inherent geographic boundaries that are a challenge. We have the best heart program in California, but we also have members in other geographic locations. It's a very labor intensive and cumbersome process to transfer that knowledge into the organization and into operations.

So the second strategy for improving outcomes is an IT system that will allow us to do real time research to better understand how medicines work within certain illnesses, groups, and populations and to rapidly spread best practices across our organization in real time. We will invest over $3 billion to create a system that is seeded with the best proven medical practices to provide a set of options that our physicians can choose from as they treat certain illnesses. The incredible turnaround for information and conclusions that we can draw from it will increase 100-fold. Right now, we have a Care Management Institute that serves as a think tank and repository for best practices. Within the CMI, physicians will find the latest on heart disease management, diabetes, depression, etc.

Once Electronic Medical Records (EMR) become the standard, that information will be readily available online. Our ability to spread proven practices throughout our group model without geographic constraints is going to improve the quality of our care and services and it will become even more affordable.

WHLE: Do you have systems in place to measure quality?

BJT: Much of this is still people-driven. Just like other health systems, we have, in many cases, old systems that don't talk to each other. We take data from the hospital system, the pharmacy system, and the utilization system and then sit down and manipulate it to produce certain outcomes. Technology allows us to integrate this information.

We feel strongly that part of what is wrong with the healthcare system is this technological immaturity. Our industry is in the 21st century but is still heavily reliant on paper records. It's time to fund infrastructure for how we share information. Can you imagine going to your bank and seeing them pull out a paper record? Or worse, having them tell you they don't even know right now how much money is in your account? It's a fundamental issue that needs to be addressed to take healthcare to the next level in this country.

David Brailer, the new National Health Information Technology Coordinator, is watching us closely as he drives the agenda from a national standpoint. He's a strong believer in the technology, but there is still a lot of fragmentation.

WHLE: Does the lack of competition within your value chain put you at a disadvantage in providing a competitive product?

BJT: My personal experience has been that the market takes care of that for us. If you asked me years ago what I considered to be our value proposition, I would have said high quality healthcare at an affordable price. If you talked to our customers they would consistently say that once they got into the office and saw the doctor, everything was great. But the pathway for getting there was cumbersome and clearly lacking in superior customer friendliness and convenience. At that time, our price point was 20-30% below our competitors, and at the end of the day it was not service that kept you at Kaiser Permanente; it was your belief that we provided high quality care at an affordable price. As a result you were willing to sacrifice somewhat on choice and you gave us a pass on some of the service issues.

Now, in most of our markets where our price points are around parity with the market, service has become much more critical in the value proposition for gaining and retaining members. There are plenty of choices in the marketplace with which we need to compete. We've made great strides in providing excellent service and choice as a result of that competitive pressure.

WHLE: What elements of Kaiser Permanente's strategy help to drive costs down?

BJT: It's all about the alignment of the incentives. Our doctors do not gain anything by filling up hospital beds with Kaiser members, but at the same time they don't lose anything by not filling them up.

In fact, it's an issue that we are struggling with right now as we've introduced high-deductible products. The physicians have prided themselves that there are no disincentives in place to making the right choice. And for the member, there are no real barriers to getting the care that the physician is offering as part of their relationship. We're concerned that with the introduction of high deductible products, members will act differently than they have in the past. At a $5 copay, they may take preventive action, but at $100, they may choose not to do it, and that could affect our prevention initiatives. We need to be able to deliver a high deductible product that will still motivate a mother with an asthmatic child to do preventative care up front, rather than have the incentives in place where she avoids paying the money up front so that the child ends up in the emergency room and all these benefits kick in.

WHLE: What are your thoughts on consumer-directed health plans?

BJT: There are a couple of missing components to really having a consumer-directed health plan. The whole notion that we have to provide incentives to motivate the consumer to make certain health purchasing decisions is problematic.

For instance, I'm in the healthcare industry and I wouldn't know how to go about selecting the best surgeon to do a gall bladder surgery. I'd still be totally reliant on the delivery system to help answer that question for me. The majority of consumers do not have the information and the knowledge to make many choices. I hope that in the future, we will get there, but as of right now, what patients know are their benefits such as deductibles and how much they'll have to contribute. What they don't have is information on the true costs and benefits of getting that gall bladder surgery or of getting certain medications, and so on.

We can make those kinds of choices in almost any other industry. I can decide between AT&T, Cingular, and Verizon and can make a pretty good choice as to where my dollar gets the most leverage for phone services. But most of us don't have enough knowledge to make certain choices in the healthcare industry.

The second issue is the way the dollar is distributed

in the healthcare industry; almost 90% of people with consumer-directed health plans will not spend up to the deductible limit to the level where the insurance will kick in. The model is very attractive to the healthy, the population that will use less than the cost-sharing limit. But you have a much smaller population that is driving 80-90% of the costs that is highly reliant on the delivery system and will use up the deductible amount in no time at all.

That said, we need to face the reality that if we don't change our practices, we will get left in the dust. Though I would argue passionately that this may not be the right answer, our purchasers and others have demanded that we give them some options, produce products where they can share the cost more with their workers, and we have responded. In addition, we do feel strongly that the consumer-directed philosophy of educating consumers and involving them in their care decisions is absolutely correct. What we are doing with our EMR system will help our customers make choices in partnership with the delivery system.

"The decision points for our members will be focused much more around care rather than insurance options."

I believe that, with the evidence the employers are pushing and where the government appears to be going, the whole notion of consumer-directed health plans is a reality. What you'll see from us, though, is that the decision points for our members will be focused much more around care rather than insurance options.

WHLE: What are the most important issues that need to be addressed over the next 10 years by Kaiser Permanente and by the rest of the payor/provider industry?

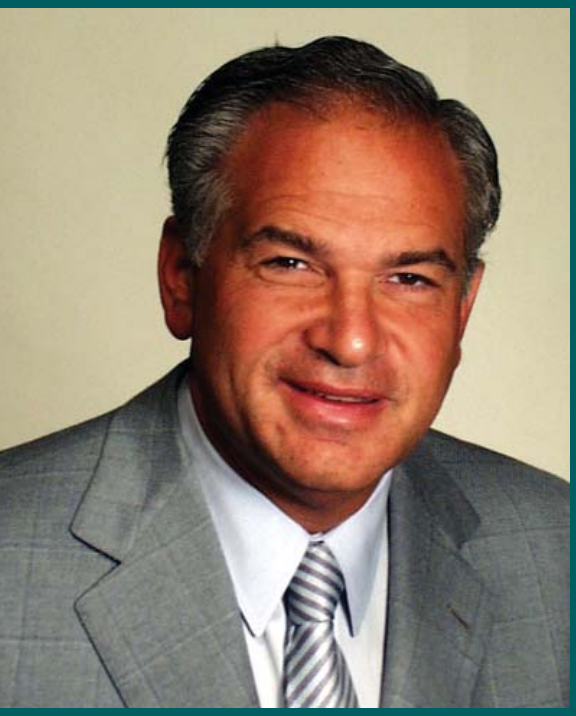
BJT: Here are a few thoughts. Each day, at least 250 people will die unnecessary deaths in US hospitals. Just think about that. If one airplane went down today, and 250 people were killed, and then one went down tomorrow, we would be shutting down the industry. But meanwhile, in the US, we are losing 250 patients per day who shouldn't die. Second, we have research and evidence that points to a healthcare delivery system that discriminates against people of color. We know now that the vicinity of care is a major issue. Third, we have the most expensive healthcare industry in the world, but we have 45 million people that are uninsured and millions of people who are underinsured. We have an industry that is growing 10-12% per year and that growth is dependent on the federal government and the employer. And we have a country where no one wants to die. All this suggests to me that over the next 10 years, continuing to build on this broken model is the wrong answer. There needs to be a fundamental retooling of the healthcare industry.

WHLE: Given Kaiser Permanente's success with an integrated model, why aren't we seeing for-profit companies emerge that try to replicate it?

BJT: I keep in mind a comment that one of my competitors made: "You've got to understand that Kaiser Permanente is an 'anomaly'." One of our biggest challenges is to figure out how to help the rest of the country replicate our model. It has great advantages when it is working in a market like Northern California, where we own 30% of the market. It gives us incredible competitive advantages. But there is an incredible price to be paid in investing in this model from scratch today to getting it up and running. Success is highly dependent on a marketplace that is willing to accept the model. So I think our biggest challenge is finding a way to replicate our model so that it will take hold and produce the results we want to produce.

We went through an incredible growth period in the 1990s where we bought a number of health plans and tried to "Kaiserize" them, and we have had several major failures in that attempt. Now we are on solid financial footing. Next year we'll be over $30 billion in revenue and will make $1 billion. Next year we predict 2% membership growth. What we haven't yet figured out is how to bring this model to new marketplaces. ■

THE POWER OF PATIENT CHOICE



Jonathan T. Lord, MD, joined Humana in 2000 as its Senior Vice President and Chief Medical Officer. His title changed to Chief Clinical Strategy and Innovation Officer during Humana's restructuring in January, 2001. Dr. Lord came to Humana from Health Dialog, a Boston-based Internet provider of health information to more than 5 million Americans, where he served as president and became a leader in e-enabled healthcare. Prior to joining Health Dialog, he served as Chief Operating Officer of the American Hospital Association in Washington, DC, Executive VP of Anne Arundel Medical Center in Annapolis, MD, and Executive VP of Sun Health in Charlotte, NC. A board-certified forensic pathologist, Dr. Lord also has 21 years experience in medical practice. In 2001, Lord was named president of the Disease Management Association of America. DMAA, a nonprofit membership organization, is dedicated to changing the way America manages chronic illness. Since its founding in 1999, it has become an important catalyst for change in healthcare delivery. He has also received numerous academic appointments in his career, most recently as an adjunct professor of community and family medicine at Dartmouth Medical College.

Here, Dr. Lord talks about the innovative solutions being pioneered at Humana to address the myriad challenges facing the healthcare system today. Rapid improvements in information technology and transparency will play an important role in helping both payors and providers modernize their businesses. The biggest gain, however, will come from systems and processes designed to empower the most important stakeholder of all: the patient.

WHLE: Please describe your experience at Humana.

JTL: I came to Humana with the sense of having a responsibility to fundamentally change the way the company and the industry does business. I've been at Humana since 2000, initially as Chief Medical Officer. My role has changed as we built out the Innovation Center and added more components. The idea was to try to more fully integrate product design, clinical programs, advanced analytics, and consumer understanding into one part of the enterprise so we can deliver more value to our consumers.

WHLE: How does the Humana model of consumer-directed healthcare improve quality of care and reduce cost?

JTL: One factor is that you need to have transparency in the marketplace. People need to be given a chance to understand what things cost and how things work, what the advantage is for one service over another and what different levels of performance exist in the marketplace among providers.

The second factor is choice. Choice is a fundamental power that affects peoples' minds and attitudes toward any product or service. Said differently, historically, health insurance has been a passive set of decisions. An employer made a decision about what to buy from whom and offered one plan choice. The lack of choice disengaged the consumer. Giving people choice, and allowing them to configure things the way they wanted to, was an important force to unleash. I always like to point out the difference between Denny's and Starbucks. You can order black coffee at Denny's and put cream and sugar in it. But if you go to Starbuck's, you basically have a way to customize and personalize. And when you do create customer choice, you end up creating a higher value and a more profitable product.

The final critical factor is the notion of independence, which is the idea that people need to be supported in an environment where their free will can be exercised in dealing with the healthcare system. An underpinning to all the things that we've been doing is a passionate, almost religious belief in emancipating people from the controls that exist in the healthcare system. We want to allow people to operate as independently as they want.

So how does that affect healthcare quality? Clearly, transparency is an important part of getting people to become engaged and allowing them to understand what is going on, as well as allowing providers to see what is happening in their own communities and benchmark their performance against others. And transparency in health benefits means letting people understand what they are spending and what they really need to spend over a plan year. That way, when they go to make a decision in the marketplace, they are actively making decisions that, like any other market, will improve the quality of the offerings available to people and will improve the underlying quality of healthcare.

"Healthcare has been steeped in a model of 'Father Knows Best.' There is a critical lack of information and transparency."

One of the things we've tried to do with our product set is to continue to place more of the marginal cost decision into the hands of the consumer, as opposed to just the front-end costs which ultimately mask real costs. Said differently, we are moving away from the idea of a $10 co-payment for a drug, where all drugs are treated the same and consumers don't have to shop around because it's only $10 and there's no difference whatever you choose and wherever you get the drug. We want to expose the true differences in cost between products and even between pharmacy chains, thereby creating more of a real market inside healthcare. Our bias is that a real market will have impact on both quality and cost.

WHLE: Why did healthcare evolve to today's current model without an emphasis on patient choice?

JTL: There are a number of reasons. Healthcare has been steeped in a model of 'Father Knows Best.' In terms of the preservation of income and status and autonomy, there's been a lot of effort put into preserving and protecting the differential power of physicians versus patients or other stakeholders in the healthcare system. There is a critical lack of information and transparency, and without transparency there is no such thing as choice.

WHLE: Aren't those physician attitudes a barrier to what Humana is trying to accomplish?

JTL: It's a barrier if you try to change physicians. It's not a barrier if you work on changing patients. Physicians, nurses and other providers have a great value system. They want to be helpful and responsive to patients' needs. They've generally rebelled or resisted things that came from institutions. But I believe physicians are responsive, and will be responsive, to any patient who asks them a question or asks about alternatives. So our strategy is to create change through consumers, as opposed to trying to change doctors.

WHLE: How do you think about measuring quality in healthcare?

JTL: You could look at data, such as the readmission rate for a healthcare system in COPD or CHF, or whether there are differences between one place and another, that might suggest how well an episode of care is being managed. It's about better information driving the patient toward better providers and thus forcing all providers to improve. If people see different levels of performance and the market responds to those differences, then I think you'll see a shift of the performance curve. Right now, we don't have that occurring because the data are generally not available, useable or presented in an actionable manner for there to be pressure on a provider to get closer to the mean, or, better, a benchmark in quality. There will always be leaders, but you want to keep pressuring everybody to bring that mean up. The beauty is that this is right in line with every physician's core value set. I think physicians and nurses all live to make what they do tomorrow better than what they did yesterday. We just want to let the market expose all the facts and continue to push on that objective.

WHLE: Aren't there great challenges in getting hold of that data?

JTL: Certainly. There are two or three different forces at work. People, physicians and hospitals have been reluctant to just put out raw numbers. Their reluc-

tance may be valid from the standpoint that the data may not be meaningful or intelligible for people. But until you start taking initial steps to do that, you never find out what you might use or might not use and don't create a demand from those being measured to improve the measures. The second thing is there hasn't been enough consumer research done to say what data points are important when making a decision. Third, until you introduce a model where there is some form of explicit cost consequence for decisions that you make, making decisions independent of any type of economic factor is a flawed system.

WHLE: Are there specific initiatives that Humana has under way which will improve data capture?

JTL: We have initiatives on a number of fronts. We've been working with state legislatures to develop legislation that pushes for transparency from provider systems. On our own web site, we provide as much information as we can that is publicly available and in useful forms. If you're contemplating a procedure, you can put your zip code in and answer questions about your preferences (teaching hospital, proximity, etc.) and we let the technology apply your preferences to what's known about the healthcare systems around you, like a Google search, and rank them with a highest percentage match. This all comes with a message of still having to go back and talk with your doctor, but at least it makes the information more useable and more actionable.

WHLE: Wouldn't an integrated model like Kaiser Permanente have advantages in terms of capturing information?

JTL: If you lived a perfect world, integrated delivery systems (IDS) would be where you wanted to go and what you wanted to be. It would be a powerful combination of the aggregation of physicians, the development of dedicated technologies, and rational ways to work through tradeoffs in terms of investments and availability. Part of the reason that a Kaiser-like system is more efficient is because it's dealt with supplier-induced demand. By controlling the supply of both practitioners, technologies and beds, it can have a fundamental impact in terms of the efficiency of the delivery system. But the problem is that in the last ten years, the various IDS experiments that were formed in communities have all failed or are coming apart.

WHLE: Why did they fail?

JTL: They didn't have an understanding that was deep enough in terms of managing risk. At a simple level, these systems put billboards up around their communities that pictured a doctor and a nurse and it naturally attracted the sicker patients in the community. As a result, they got crushed on the risk side. At the same time, because primary care physicians weren't profitable for the most part, they paid a lot for the businesses they were aggregating and there was no margin to recover the capital costs they invested. Physicians were also not socialized to working in large groups.

> **"The critical belief is to trust people to be good decision makers."**

Kaiser has been around for a long time and pre-selects people by virtue of who wants to join Kaiser. But trying to go out now and buy practices of an assortment of 40-year-old independent doctors and pull them into a group. There's a whole change management project to that, and it is a lifetime of work. There are lots of different factors that went into why those efforts didn't work, but the bottom line is that they didn't work, and there is not much interest to go back.

WHLE: How does Humana ensure that consumers will make the right choice?

JTL: Our attitude is that people are smart and can act well in their own self interest. A lot of the reason that people have been reluctant to go down these paths is that they don't think everyone is smart enough to make the perfect decision. And that's true. But can many people make the right decision? Yes.

Some people also may not want to make decisions. So the issue isn't just to throw people out into a free fall, but to create an environment that is permissive so they can take on as much of the risk of decision making as they want, and have the tools to do so. Over time, based on different generational attitudes and skill sets in using technology, this will encompass more of the population over time rather than less. What we've tried to do is have a strategy that enables choice, but that doesn't force choice. It meets people where they are; we try to encourage people to take on more, but at the same time, we don't just abandon them. That's a really important distinction. This is a set of transitions that has to be well planned and choreographed, at every time providing people with the peace of mind that they can't get too far off the road if they are not used to taking bigger steps.

WHLE: What resources do you have in place to guide patients toward the right decision and provide that peace of mind?

JTL: That's part of the reason that we have a personal nurse program. The nurses guide patients toward the resources to help them make a better decision as opposed to creating another co-dependency model where people are relying on someone else to make a decision for them. In the case of most medical treatments, there are choices, and those choices are informed by who you are, what you do. But decisions are not currently taking into account the person's social needs or personal preferences and values. This suggests that you want to set up a system that helps people learn how to fish by exploring their own feelings and needs as opposed to doing the fishing for them.

Personal nurses are employed by Humana and are trained specifically in four psychological techniques to support behavioral change. Part of it is based on the notion that physicians have had neither the training nor the time to support behavioral change, which is really part of the solution, especially when dealing with chronic conditions. We need to have a systematic approach to helping people understand their choices. Patients need to feel more confident going into their physician's office and asking more questions. We don't want to create a relationship where the person feels they have to go to the nurse and ask what they should do.

In fact, what we have learned, clinically, is that when people are more active participants in choosing a particular treatment, their outcomes are better and their resource consumption along the way is lower. It's the power of your mind; knowing more about something acts as encouragement toward the best outcome, as opposed to the detrimental anxiety of uncertainty and helplessness.

WHLE: What is your vision for where Humana and the US healthcare system are headed over the next ten years?

JTL: For Humana, we're going to continue to push choice, transparency and independence. We'll continue to work on models that more fully integrate financial services and health benefits. An example is the integration of ID cards and credit cards. The whole idea is to create some parallels in terms of the metaphors of experiences so that they become more like the experiences people have in other areas of their lives as opposed to more specific to healthcare. And we will probably work to leverage two assets within the organization: the data that we collect and the fact that we maintain a relationship with people over time, so that we can create value for people. We want to learn and understand how people think and act and the differences in the way they approach healthcare and health behaviors.

At the highest level, at the employer level, health benefits will start to look a lot more like 401(k)s, portable types of funds that can be planned for in advance. Employers are becoming more explicit with their employees in saying, "Here's your compensation, here are the things you can do with some of the money we give you in terms of retirement and health benefits." There will be far less of the HMO and PPO types of strategies.

On the government level, there will be progressive looks at how to more actively manage the Medicare fee-for-service populations, because if you simply help organize people's care, you get rid of some of the inefficiencies and redundancies that exist in the system. Over time, our bias is that in terms of life and healthy behaviors, we'll start to see a merging and morphing of style, technology, and fashion to help people be healthier, deal with issues around obesity and take more control of their own lives and destiny from a health perspective.

WHLE: Do you think that the current system is sustainable?

JTL: From a physician's perspective, there will have to be changes to the model that has doctors seeing one patient at a time. That's not practical or sustainable. From the standpoint of technologies around physician practices, there will also have to be more organization into cohesive groups. And I think the effect of more women entering the profession will continue to transform the socialization among physician groups.

From a hospital's perspective, they'll have to redefine what they do and how they operate to focus on high intensity acute services at one level and also deal with chronic illness in a different way. I don't think we have yet established a good system for managing chronic illness, by which I mean that the nursing home world is not a sustainable model. It doesn't deal with a bulge of people between the ages of 40 and 60 who are picking up chronic illnesses.

WHLE: Kaiser Permanente used to face the accusation of being a socialist system. Humana, on the other hand, is proposing more of a capitalist market-based system. One criticism of such an approach might be that it is destined to benefit the middle and upper side of the social scale at the

expense of the poor and unemployed. Do you worry about people that don't have enough education or access to the information to take advantage of the system? Or that you will lure away the healthiest patients and cripple other payor networks?

JTL: You always have to be sensitive to having safety nets in place. It's a question of what your attitudes are. Do you create systems that are designed to be focused on the people who are going to be challenged as your primary objective, even if by doing so, you end up constraining everyone else? Or do you design systems for the top end of the curve where you are focused on enabling people to do more and better things. Our attitude is probably the latter, to be an enabler, but to be an enabler with a safety net in place.

A lot depends on how you come at this. In healthcare, because there has been a prevailing fact that doctors know more than patients, you have always had to work on protecting people. But what we haven't taken into account is that people know more about themselves than their doctor does. So our attitude has been to push toward that enabler mode, because when it truly comes down to understanding preferences and value sets, the social needs not only of a person but of an entire family, the doctor is not positioned well because he or she is not aware of all the variables. The patient is aware, assuming they can be educated enough to weigh them correctly.

Neither extreme is right. But the critical belief is to trust people to be good decision makers. Look at our society. If you believe that child rearing is the most important societal job, we have very few rules around it. We have a lot of rules about how to drive a car, for instance, but we have a tendency to create a free-for-all with regards to child rearing, believing that this will create the best results. There is no perfect system or single best approach, but you have to strive to create a system that gets you to the best set of outcomes overall, and for us that means empowering our patients to participate in their own choices in the healthcare arena. ■

Global Health

Private sector responses to a crisis in public health

The vast majority of the pharmaceutical market exists within the established economies of the US, Europe, and Japan, but the rest of the world carries an oppressive disease burden of its own. Every year, millions in the developing world die of infectious diseases that have been eradicated or contained in the developed world. **Dr. G. Lynn Marks** of GlaxoSmithKline talks about his company's commitment to creating new medicines for developing world diseases and ensuring that those in need have access to medical care. But the assault on developing world diseases is not the domain of pharmaceutical companies alone. **Dr. Carol Nacy** of Sequella, Inc. shows that small biotechnology companies and not-for-profit organizations also have important roles to play in addressing threats to global health.

A LEADER IN THE FIGHT

G. Lynn Marks, MD, is a Senior Vice President with GlaxoSmithKline and head of the Infectious Diseases Medicine Development Center. He is responsible for the development of medicines ranging across areas such as HIV/AIDS, antibiotics, and diseases of the developing world such as malaria and tuberculosis. He is board certified in infectious diseases and worked in academic medicine prior to joining the pharmaceutical industry.

Here, he discusses GlaxoSmithKline's commitment to providing the research and development, medicines, and educational outreach required to address developing world disease such as HIV/AIDS, malaria, and tuberculosis. Conquering these diseases requires the coordinated efforts of non-profits, governments, and pharmaceutical companies. He also speaks about the origins of GlaxoSmithKline's work in the developing world and the importance of those initiatives to the character of the company.

WHLE: Can you provide a description of your role within the Medicine Development Centers at GlaxoSmithKline (GSK)?

GLM: My official group is called the Medicine Development Center for Infectious Diseases. Inside of GSK we have what we call CEDDs, Centers of Excellence for Drug Discovery. Once molecules get to the point where they look like they have proof-of-concept (i.e., they look like they might work in people) they are transferred over to Medicine Development Centers. This usually occurs around Phase II or so in development. My group and I take them from there on. There are six Medicine Development Centers around the major disease areas: Cardiovascular, Infectious Diseases, Neurosciences, Oncology, Respiratory, and Musculoskeletal / Inflammation / Genitourinary.

WHLE: GSK has received a lot of attention for a position paper called "Facing the Challenge," which outlines the company's strategy for approaching developing world diseases. Can you delineate some of the main points of that document?

GLM: Facing the Challenge has three prongs. The first is drug research and development into diseases of the developing world. This is the focal point of what I do. The second is the preferential pricing of anti-retrovirals, anti-malarials, and vaccines for countries in the developing world. That program tries to cover our costs of drug manufacturing and transport, but we do not return profit back to the company. We have a not-for-profit mindset instead of a donation mindset because we need to be able to provide these drugs forever and the program needs to be sustainable. The third prong of the program consists of community investment activities. A lot of that is educational.

To try to put that in a concrete example, you cannot just show up in a village in Africa with a bunch of different anti-retrovirals that a patient is supposed to take in combination for the rest of his or her life. These drugs need to be taken with or without food. They have various side effects. If people do not understand why they are taking the medicine and they do not understand the disease, showing up in a village with a handful of pills is not going to have the kind of effect that is needed. We work with community-based leaders to help understand the local issues associated with treatment rather than going in and saying, "Hey, this is right for

you, swallow the pill and you will be OK." That is not a thoughtful, respectful, engaging way to deal with the problem. Fundamentally, our efforts are about education and support at the local level.

It is a mindset of improving healthcare in the developing world rather than just dropping off a barrel of pills at the local train station. It is getting into the community. It is sharing why you need to do this, what will the side effects look like, what can you hope for. What are the educational activities around how HIV is spread? What does it mean for your child? What should you look out for?

This is extremely important work because, for me, the rate-limiting step in the advancement of the world is the control and management of infectious diseases. After food, clothing, and shelter have been addressed the next thing a society needs to deal with in order to flourish is the control of infectious diseases. That is why HIV is just devastating to Africa because it is wiping out the productive middle age group, orphaning millions of children and just destroying the society. If you look at HIV, malaria, and tuberculosis, a future mother, father, doctor, lawyer, president, scientist dies every 5 to 6 seconds.

"If you look at HIV, malaria, and tuberculosis, a future mother, father, doctor, lawyer, president, scientist dies every 5 to 6 seconds."

WHLE: This is a very large undertaking on the part of the company. From where did this commitment arise?

GLM: I think that the uppermost management of this company, the Board of Directors, the executive management team, has an understanding that they need to do something about the issues facing the developing world. Now this is probably not commonly shared, but it is in my mind the first sort of juncture in terms of defining the culture of GSK and the way the company wants to be viewed in the world. Our Board of Directors, our corporate executive team, our CEO, J.P. Garnier, believe that we cannot just take from the world in terms of putting profits first. We have to have principles, we have to understand the challenges around the planet and try to participate in those by doing what it is we do.

We cannot solve clean water issues, we cannot solve housing and put new technologies in, but we can find medicines and try to come up with ways to enable people to have access to those medicines. We can participate in disease education programs and help people understand the medicines and vaccines that we make. All of that starts from the top. If that were not true, it would be impossible for us to maintain the programs that we have.

WHLE: How does GSK balance these programs with the fact that it is a for-profit company?

GLM: Now, obviously we are a for-profit company, so we do sell our products, except for those that are related to HIV/AIDS and malaria in the least developed countries, at a profit in order to fund research and development so that we can find new medicines and new solutions. You have seen our ads on TV: today's money finances the miracles of the future. That is true.

Beyond GSK, the industry, broadly, has many issues to address. However, our management understands that major pharmaceutical companies, major corporations in general, ran through a period where they began to lose their way. They made decisions that were in the interests of making money, not necessarily in the interests of what we would like for people. All the corporate scandals of late are a reminder of this coming from other industries. People wonder whether companies are making decisions that are balanced in terms of doing what is right and what is just for profit.

I think that our efforts in the developing world are part of a philosophic change, and I do not think that every company 'gets it.' But I do think that more and more companies are getting it and not just getting it from a public relations perspective that it is a good headline flash to do something for the developing world. We understand that our efforts are a fundamental motivating factor for people who work for the company, they are a motivating factor for people to invest in a company that recognizes these needs and has done something about them overtly, and they are a motivating factor for the management as they look at what they accomplish with the corporation.

For example, we have been watching people die of malaria and tuberculosis for as long as I can remember. Now we have begun to change the way we think of that. Now there are public private partnerships (PPPs) pulling together funds, there are pharmaceutical companies

linking up with the World Bank, the World Health Organization, and the Gates Foundation to try to find ways to get new medicines developed and get them into the hands of people in the developing world. I am happy to see it change, and it makes me more excited about the work. It makes me more excited about the potential for what we can do with new medicines because we can get them into the hands of people who need them around the world.

WHLE: You mention these hybrid public private partnerships between non-profits and for-profits. How have these organizations helped pharmaceutical companies address the issues in the developing world?

GLM: I think PPPs begin to bolt together critical mass of funding in an area. Inside of a company I can put together 50 chemists and biologists working on trying to find a solution for a disease like malaria. I know that the medicine is certainly not going to pay for the R&D invested in it, but it is the right thing to do. I have to try to pull the funding together from inside the company. But, if I can link up with the Medicines for Malaria Venture public private partnership and get money from the World Bank and from Gates, perhaps now I can bolt on to it another 50 chemists and biologists as well as extensions into academia and policy groups and the government.

You begin to take that nidus and build upon it to create a critical mass that can come up with drugs. The reason I am using that example is because out of a similar effort we developed the pyridone class of antimalarials. I cannot tell you that it would have never happened with those original 50 chemists and biologists trying to pull together the resources they need. However, I cannot help but believe that the infusion of additional people and money accelerated that and made it a reality a lot sooner.

WHLE: GSK has pioneered the supply of antiretrovirals to the developing world, but the pharmaceutical industry has received some criticism for not donating medicines for HIV/AIDS. What are some of the issues?

GLM: I would like to back up for a moment and give you an example of one of our donation programs. We have a program to donate our drug albendazole which is part of the global alliance to eliminate lymphatic filariasis over 20 years. We will give away 6 billion tablets worth approximately $1 billion. This is a situation in which donation might actually be the right way to do it. We are trying to eliminate this disease. We are hoping that at the end of those 20 years, we do not have the disease anymore. Therefore, the donation, even though it is a long time, is finite. It has a way to stop.

The HIV epidemic has 5 million new people infected every year and 40 million people infected around the globe. This is not going away. This is not a short term situation, and we do not believe that donation with as many anti-retrovirals as we have and we hope to bring to bear on the disease through our research is the sustainable thing to do. It is just not something that is sustainable for us to do.

The risk associated with it is that well-meaning people can be criticized and have things happen as unintended negative consequences of trying to do good things. I think we have to do it responsibly, I think we have to do it openly so that people understand what we are trying to accomplish. We also have to be clear where the risks lie.

We have to make sure that people are on the right drugs in the right combinations. We have to continue research and development for new drugs to deal with resistance down the road. If you try to overcome all the objections and all the problems that might occur somewhere down the road before you start doing something like this, you would never start doing it. I think that is where the highest levels of the company have to be committed to understanding that going down this path is important and critical, risky, but the right thing to do. And you try to make sure that your critics as well as your supporters understand that what you are trying to do is the right thing.

WHLE: What are some of the other challenges that you expect to face in combating developing world disease going forward?

GLM: As I said, the management of infectious diseases is a rate limiting step for society, and it is something that we constantly battle. Every time we think that we have beaten infectious diseases we either have resistance emerge or we find new infectious diseases. As I look into the future I feel a need to maintain companies in the field of infectious diseases, which is harder and harder to do. A lot of companies have elected to get out of infectious diseases. That is one major piece of the puzzle, the other that is frightening to me is the number of major companies that are not moving into infectious diseases. So the attrition over time is fine, companies change their direction, but with no entry, the attrition hurts more and more each time it occurs.

WHLE: With a lack of new companies participating in infectious disease, is the fight against developing world disease the domain of large pharmaceutical companies with existing programs?

GLM: I think a lot of the things we do probably are for medium-sized and large companies. I spoke to our CEO a couple of years ago about this. I said that when GSK has double digit growth and the stock market is up and life is good and profits are flowing, we can feel pretty good about being philanthropic. Now what happens when we get into flat, no growth scenarios, or we get into more difficult times, how do we continue on these avenues? He said two important things: 1) the sustainability of the models has to take into consideration those scenarios, and 2) that is when we define the character of the company.

WHLE: Looking forward to the next couple years, do you think that pricing pressure is going make it more difficult for GSK to complete its mandate in the developing world?

GLM: The pharmaceutical sector is going to continue to come under more and more pricing pressure, driving us to make really hard decisions about what we are doing and how we are doing it and the cost of doing it. I think there is only so much mileage about talking to people about the price of pharmaceuticals rather than the value of pharmaceuticals. I would like to talk to people about the fact that they are living longer and doing better, and I would like to talk about the fact that they are not in the hospital as frequently, their standard and their quality of life is better. That is what we are trying to accomplish with anti-retrovirals.

Back when I trained in infectious diseases, when the AIDS epidemic was just starting, the care of an HIV-infected patient was just to try to help them deal with dying. It is very different now. It is about dealing with living and what the anti-retroviral regimen is going to look like 20, 30, 40, 50 years from now. It is just a very, very different dialog. Without HAART (Highly Active Anti-Retroviral Therapy), they had horrible quality of life, chronically ill, chronically in and out of the hospital, and it was just a miserable way to exist. And now those conversations are very different, those clinics are very different.

I am sure that people wish that anti-retrovirals were less expensive, but I would like for the conversation to include the value of having that option and that medicine versus not having it. I do not think that people stop and think that if we fund these programs where we give away or heavily discount drugs it might actually increase the cost of the medicine for them. But that is a reasonable thing to have happen.

WHLE: Is it your hope that the developing world will get to the point in ten years where HIV/AIDS is a manageable infection as opposed to an uncontrolled pandemic?

GLM: I think that when I look out into the future, I would love for every man, woman and child in Africa to have the fundamentals of healthcare that I enjoy. By that I mean the ability, when you are ill or have a major disease, to have access to medicines and healthcare professionals. I think that comes from people engaging and participating in the developing world. In order for that to occur throughout Africa, you need roads and electricity and housing and refrigeration and clean water. That is the part that I think does not get enough attention because I do not know of any industry that could not participate in a different way for the developing world. Hopefully they will, because that is what will lead to the environment I am talking about where people have classrooms and schools and can read and can understand adverse events and can understand what we are trying to do with these medicines. ■

"What happens when we get into flat, no growth scenarios, or we get into more difficult times... That is when we define the character of the company."

AN ENTREPRENEUR SHOWS THE WAY

Carol A. Nacy, PhD, is the Founder and Chief Executive Officer of Sequella, Inc, a privately-held biopharmaceutical company that commercializes new and more effective products for diagnosis and treatment of tuberculosis. Prior to Sequella, Dr. Nacy was Executive Vice President and Chief Scientific Officer at EntreMed, Inc., from 1993 through its successful public offering in June 1996. She is a member of the Board of Directors of several Companies (ASM Resources, TolerGenics, Social and Scientific Systems) and non-profit agencies (Sequella Foundation, Women in BIO) and serves on a number of committees in global health organizations.

Here, she articulates the importance of breaking down the myths that have restrained drug development for tuberculosis, an infectious disease that affects billions worldwide. More importantly, Dr. Nacy is proof that the mission to provide new drugs to address global health is not the domain of Big Pharma alone. Small companies and non-profits can take the risks required to make real progress against neglected diseases.

WHLE: How did you become interested in developing diagnostics and therapeutics for tuberculosis (TB)?

CAN: I have a PhD in microbiology with a specialty in immunology. I spent 17 years in an academic setting at the Walter Reed Army Institute of Research (Washington DC) working on bacteria, viruses and parasites for which there are still no drug therapies or vaccines. These infections are devastating global health problems.

I left academia in 1993 and helped start a company called EntreMed, which began with three technologies that were infectious disease-oriented and three that were cancer-oriented. By the time we took the company public, we were labeled 'the Angiogenesis Company' and were specifically focused on cancer. I began looking for opportunities to get back into the research that gets me up in the morning: infectious diseases.

In late 1996, the NIH convened a panel to review the previous five years' work in TB research. They asked if I would be the immunologist on that team. I agreed because I figured, 'Well, we cured TB, how long could this take?' It turned out to be a three day meeting, and I was introduced to TB as a global health threat and a huge problem with an unmet medical need: products that were outrageously outdated and ineffective and a growing epidemic worldwide, with 2 billion people infected and 9 million new patients every year. Even more concerning was that multi-drug resistance was growing in this population. It didn't take me more than a minute after learning those statistics to realize that the technologies clinicians used to control the disease were outdated and no one else in industry was paying attention to this problem. That sparked my interest.

WHLE: This is a very large threat to global health, but public opinion in the developed world still does not acknowledge a TB problem. Why?

CAN: I talked to 26 business development executives about TB, and they had an amazing response. They said, 'There is no unmet medical need, we have all the tools we need.' Looking at the growing epidemic, that made absolutely no sense. The second thing they said was that there is no market for TB, that it only strikes poor people. Given that 2 billion people are infected and the disease is present on every continent and in every country, including the US, that stance didn't make any sense to me either.

We busted all those myths and generated substan-

tiated and verifiable numbers that would enable us to honestly say to angel and venture investors that there is a market opportunity here that can be accessed by a company, and that market opportunity is bigger than anyone suspected. It is certainly bigger than that for most anti-cancer drugs that have to compete with many other drugs for the same purpose. Anything we did would stand out as unique because there are no TB products on the market that work efficiently.

WHLE: Just to clarify, we are talking about a US market in addition to the developing world market.

CAN: Right. US, Europe, and Japan. There is definitely TB in these countries. In fact, London, England has a TB epidemic that is bigger than the numbers you see in China. It's a huge problem everywhere, with substandard technologies available for control of the disease.

"2 billion people are infected and the disease is present on every continent and in every country, including the US."

WHLE: Many people might find it hard to believe that TB is not just a disease of the most impoverished like malaria and river blindness.

CAN: Yes, even the most privileged among us are susceptible. The Prince and Princess of Japan were exposed to TB recently by one of the workers in the palace. No one is immune.

One classic example of transmission dynamics is the gentleman who boarded a plane from Paris, France, and traveled to New York City, US. In his eight hour travel across the Atlantic, he managed to infect thirteen of the forty people in his jumbo jet compartment with TB. Unfortunately, he had profoundly multi-drug resistant TB, resistant to seven of the eight drugs available to cure this disease. Now we have thirteen people, American citizens just sitting on an airplane, who are infected with multi-drug resistant TB.

It is certainly true that in impoverished villages or areas of cities where people are living in very close proximity with one another one can transmit TB more easily. Thus, poor communities suffer TB at a higher rate than affluent communities. It is not poverty, however, it is crowding.

WHLE: What did you decide to do based on this NIH meeting?

CAN: I told the NIH that it would take substantial work to change the current paradigm from one in which there is no acknowledged unmet medical need or market to one in which the market and the need is recognized. That would take too long to do *de novo*, so we started a company ourselves focused on TB.

The first person I talked to was Barry Bloom, who at that time was at the Albert Einstein College of Medicine and has since become the Dean of the School of Public Health at Harvard. We talked about developing a company focused on TB and he said, "That's great, but what happens when you are successful? Big Pharma is going to come in and just run you over." I said, "Won't we have solved the problem then?"

The concept from the get-go was essentially to do a business experiment: could we generate interest in and understanding of TB and rehabilitate TB in both the Pharma community and in the financial community? Through my contacts in the TB research community, we could begin licensing technologies from academia to develop as potential new products for use in the clinic. At the same time, we would initiate market research to help us articulate in a verifiable way the actual market for a new TB drug, diagnostic, or vaccine.

When we actually went out and started looking at what technologies were available for licensure, we discovered a major issue. Because most universities lacked BioSafety Level 3 (BSL-3) facilities for handling an airborne microorganism like TB, many of the really cool, interesting new concepts about TB diagnosis and treatment had no proof of principle experiments in TB. In order to do their experiments, they used mock TB that was not hazardous. As a result, this area was too early and too risky for investors. We debated for about six months on how to help the research community build their story.

WHLE: What was the solution?

CAN: We ended up putting together two organizations: The Sequella Global Tuberculosis Foundation and Sequella, Inc.

The Foundation's mission was to help people get over the barriers of new product development for TB. The Foundation's role was to (1) promote proof of principle experiments for academics who thought they had a product and (2) facilitate industry movement of products into the clinic, all with free resources.

A unique aspect of Sequella Global TB Foundation

was that we did not attach interest in IP to the work that we did. Many foundations working with companies want to own the technology wholly or in part in order to bring in revenues downstream. Our idea was that the Sequella Foundation was a stopgap measure to help everybody move their products along. Absent intellectual property issues, we could work with anybody, academics, companies, government, without fear of compromising their IP position.

We allowed our sister institution, Sequella, Inc. (the company), to use Foundation facilities and resources, but only if it competed scientifically and commercially with everyone else at the table. Sequella, Inc. had no preferential rights to anything that the Sequella Foundation did or any Foundation resources.

One grant the Foundation received was from the Bill and Melinda Gates Foundation to facilitate the development of a new TB vaccine: $25 million over five years. By the end of four years of the Gates grant, we had a dozen vaccines being prepped to go into human clinical trials. It was astonishing that in four years we could actually turn this whole industry around. Now there are three new TB vaccines in Phase I and Phase II trials. We stimulated both the academics and industry to get their vaccines moving. The Gates Foundation support was an amazing asset.

WHLE: How does the mission of Sequella, Inc. differ from that of the Foundation?

CAN: Sequella, Inc., the company, was actually set up to in-license or develop technologies in-house that already had the potential to be products, that had the proof of principle experiments and had significant biology behind the product to enable us to move it into product development. We picked six different technologies in the early days of the company, and not one of them has fallen by the wayside. The good news is that we picked our technologies well, the bad news is that we have to generate the money to develop each properly.

Our technologies include:

(1) A device that can identify bacteria in sputum as *M. tuberculosis* and give an antibiotic profile of that clinical isolate in two days. This is a huge advance over the six to twelve weeks to do the same set of studies today.

(2) A Patch Test diagnostic that transdermally delivers a protein only produced during active replication of *M. tuberculosis*. The Patch Test has been in four Phase II clinical trials in South Africa and the Philippines and has a remarkable 90% sensitivity and 100% specificity. The Patch is waiting for the close of our current financing round for the pivotal Phase III trial.

(3) New TB drugs with novel mechanisms of action. We filed the IND for SQ109 on December 30, 2004, and we expect to initiate human clinical trials of this first new TB drug in 30 years in March 2005. From that same program, we also discovered a whole new class of drugs, dipiperidines, and we recently selected the lead drug candidate, SQ609. This new antibiotic is about 12 months behind SQ109.

"Someone has to take the first step, and that is a very risky proposition."

(4) A new natural product TB drug. We recently licensed in a drug from Sankyo, also a new class of antibiotics that affect a translocase 1 inhibitor in *M. tuberculosis*. We have worldwide rights with all indications, and the drug has activity on *M. tuberculosis*, *M. avium*, and *Candida albicans*.

WHLE: So Sequella intends to develop these products all the way through commercialization?

CAN: Absolutely. For the Patch, we defined the market with the help of our consultants, L.E.K. Consulting. We have a corporate partner for marketing and sales of the Patch in Europe, we have another corporate partner for the Patch in all RoW territories. The Japan BCG Laboratories, which licensed us the rights to the patch, is going to market and sell in Japan. We reserved the US marketing and distribution for ourselves or a corporate partner, depending on decisions of our new Board after our financing is complete. We have a wealth of interesting and unusual products and all we need is money, about $10 million to get us into marketing and sales of the Patch and a substantial revenue stream.

WHLE: You are a small company in a niche market. In terms of fundraising, are you able to convince investors that Sequella is on the right track?

CAN: I think we have rehabilitated TB in a way that is astonishing. We have lots of venture investors who are interested in the concept and who are excited about Sequella. Getting them to write the check is the trick. Nobody wants to be the first venture capital firm to fund a TB company. They all believe in it, they are excited about it, but they just can't be the first.

I don't think we've had any problem convincing people we are going to make money or that TB is a good therapeutic area to be in. The biggest problem is that they will have to stand up and declare themselves different from the others. That is the hurdle.

Yes, we are a small company. We are still only 15 people in-house, although we have a regulatory group from RRD International, an engineering design firm, M-Biosystems, and an investment bank, Friedman Billings Ramsey. We are small in number of employees, but we have lots of people who we work with on the outside. I would characterize us as more virtual than small.

WHLE: Sequella has accomplished quite a lot in changing perceptions and advancing products in TB, things that Pharma companies have not been able to do over the past 20 years. What capability do you add that Pharma doesn't have?

CAN: Pharma is not any different than the venture community or any other large group. They tend to follow the pack. If Pfizer comes out with a penile erection drug, everyone is out looking for erection drugs. If someone comes out with a new drug for diabetes, then all of the sudden everyone is interested in diabetes.

Someone has to take the first step, and that is a very risky proposition. I think small companies are very beneficial for niche disease opportunities because of their ability to take risks and their inability to see obstacles until they've already passed them.

Knowing now what I know about development of a company focused on global infectious diseases, would I have started in the first place? Would I have had the fortitude to make it though all the obstacles that were put in my path? I don't think so. I think it is better to not know what is going to happen, and just make the first step and let other people follow you. If you focus on the problems and the issues and the market and this and that, you will never make the first step. There is a place for ignorance in the world.

For all large organizations, whether pharmaceutical companies or government organizations, change is scary, taking the first step is risky, and risk is something that nobody wants to do when there is a bottom line to defend. The entrepreneurial attitude of people who start small companies can be very useful to Pharma. That said, I don't think we replace Pharma's structural advantages on clinical development. They have massive skills and expertise once you get a product to the clinic. Sequella could never acquire those skills and remain as entrepreneurial as it is: we'd have to develop a bureaucracy, and bureaucracy trumps entrepreneurship.

WHLE: When you look at companies like GSK and Novartis, companies that have made a public commitment to malaria and HIV research, how do you feel those programs fit into this picture?

CAN: Glaxo Wellcome made a commitment to TB many years ago using a program called Action TB. Action TB was actually set up to provide money into academic centers, with no expectation of products. It was a way to stimulate the underlying academic research of new product development. Since the merger with SmithKline Beecham, that program has had more of a product focus. GSK did open a new drug discovery unit in Madrid. It is important for Big Pharma to be involved in discovery.

AstraZeneca and Novartis also have drug discovery units in tropical diseases. Novartis has a Research Institute in Singapore, but it is actually interested in licensing out discovered drugs to other companies, not Novartis. The AstraZeneca TB drug discovery facility in Bangalore, India, is at the very earliest stages of discovery, selecting drug targets.

Interestingly, Johnson & Johnson (Tibotek) announced a new TB drug at ICAAC that is going into human clinical trials. They've been working on it for seven years without saying a word. They recognize that TB will never be treated with a single drug, and they announced this publicly. They don't see Sequella as a competitor but rather as a collaborator. And that is good news for us.

WHLE: What do you expect over the next ten years? Obviously, from a clinical development perspective, products like the patch and the drug could be on the market in ten years.

CAN: I think these products will change the way people think about TB, especially if Sequella makes money. Revenues from TB products will change the way people think about the market opportunity. And I am very pleased that Johnson & Johnson has, for the past seven years, been developing a new TB drug. They are an important example that Big Pharma is interested in new TB products.

I think the climate for global health products is going to change. Sequella will pave the way and provide the market information for TB, will show how to access the right people and the right technologies. And if this goes in the right direction, Barry Bloom's comment will eventually come true: Big Pharma is going to run Sequella over, which is great. Then we've solved the TB problem and we can get onto something easier…like malaria. ■

Art Collins, Chairman & CEO Medtronic, Inc.

Art Collins has spent 13 years at Medtronic, including seven years as COO and four years as CEO. Under his CEO leadership, Medtronic has enjoyed solid double-digit growth, nearly doubling its revenues to more than $10 billion. Prior to assuming leadership of the company, he was Corporate Executive Vice President and President of Medtronic International. He came to Medtronic after a 14-year career with Abbott Laboratories. He also has worked as a consultant with Booz Allen Hamilton and served as an Officer in the US Navy.

Art graduated with an MBA from the Wharton School of Business in 1973, and was also a member of the undergraduate faculty while attending the school. Today, he is a member of the Board of Overseers of the Wharton School. He also serves as the Chairman of AdvaMed, the medical device industry association, and is a board member of US Bancorp and Cargill, Inc.

WHLE: Briefly describe the progression of your career.

AC: I graduated from undergraduate school in 1969 and, at that point in time, unless one had a medical or educational deferment, the decision was what branch of the service to join and in what capacity. So after graduating, I entered officer's candidate school and was commissioned as an ensign in the United States Navy. And while I didn't want to make the Navy a long-term career, the experience provided me an opportunity at a very early age to obtain responsibility for leading a division of men who had very diverse backgrounds and ages. In retrospect, I was very fortunate to have that leadership experience at the beginning of my career. After the Navy, I came to Wharton.

When I graduated from Wharton in 1973, I elected to join Booz Allen Hamilton in Chicago. In many ways my four years in consulting equated to a practical doctoral degree in business. During that time, I was exposed to a wide variety of industries and functional disciplines, and my learning experience continued at a rapid pace. However, I knew I didn't want to be a consultant for the rest of my life. What I did want was the opportunity to lead an organization and implement the kinds of recommendations I was making as a consultant, and then live with the results.

When I left Booz Allen, I chose to go to work for Abbott Laboratories. I come from a medical family. My father, who died the year I graduated from college, was a medical doctor. My mother, who is 88, was a registered nurse. I always had an interest in medicine, although my father gave me good advice early on when he said that if I didn't have the calling to be a doctor, then I shouldn't do it. While I didn't have that calling, I ultimately gravitated back to the medical industry.

After an initial stint in corporate planning at Abbott, I was fortunate to be assigned outside the United States. I first lived in Brussels, Belgium, and then ultimately in Frankfurt, Germany. My initial responsibilities included a group of countries in Europe, and ultimately I assumed responsibility for all of Abbott's country operations in diagnostic products for Europe, Middle East and Africa.

WHLE: Was that international experience crucial as well?

AC: Very much so. During my time in Europe, I

was exposed to a number of different cultures and ways of doing business. During that time, I also traveled extensively.

When I returned to the United States, I moved through a series of general management roles, first taking over one global business unit and then multiple business units. In the late 1970s and 1980s the diagnostics business at Abbott was growing very rapidly. When I started, the business had revenues of a few hundred million dollars. When I left Abbott to join Medtronic in 1992, my responsibilities included all of the business units that made up Abbott's diagnostic business, and revenues had grown to about $2 billion.

WHLE: Why did you select Medtronic, and was it a good choice?

AC: Joining Medtronic was a great move. Medtronic at the time I joined was just beginning to grow very rapidly and expand its product offerings through internal R&D and acquisitions. The technology was very interesting, the business was global, and my experience at Abbott was very applicable for Medtronic at that stage in the company's evolution. I was also very intrigued with the mission of Medtronic, which has continued to be a significant differentiating factor for the corporation.

After serving as President of International, I became COO in early 1994. I was in that role until being named CEO about four years ago. I just named a COO last year who is now responsible for managing the day-to-day operations. Because I am now serving as the Chairman of our industry association, AdvaMed, I am increasingly involved in a number of policy decisions affecting Medtronic and our industry inside and outside the United States. In this regard, one of our goals is to help improve patient access to medical technology. This involves efforts to improve the worldwide regulatory and reimbursement environment, together with a number of other important initiatives.

WHLE: What would you say were the most formative experiences that shaped the skill set that has allowed you to succeed? What advice would you give to someone who was hoping to follow a similar path to leadership?

AC: The ability to obtain early leadership experience in some capacity is a major plus. For me, the experience in the Navy was very important. The international experience, including the opportunity to both live and work abroad, has been particularly important since Abbott and Medtronic operate in a global marketplace. While working internationally, I've been fortunate to be associated with companies that have high-tech products that change rapidly and that are impacted by a constantly evolving external environment. As a result, the pace of business and decision-making has been very rapid and, at the same time, very rewarding. I've also had the pleasure of working with a number of very talented people over the years.

"If you're not making some mistakes along the way, you're not pushing the envelope enough."

WHLE: Do you strive to provide those experiences for the people you now manage?

AC: One of the things that I learned early on is that your job becomes much easier if you have good people around you, and much more difficult if you don't. In today's fast-paced, complex business world, no one can successfully answer all the questions or make all the decisions. Once you get the right people in place, it is important to help foster an environment where people can grow and learn and feel excited about coming to work each day.

WHLE: Hearing the biography of CEOs, one often gets the sense that nothing has ever gone wrong for them. What's your perspective on the role of failure in a career?

AC: I was fortunate to have been put into some very difficult situations early in my career and, candidly, before I was completely qualified for what lay ahead. You grow by living through difficult situations where everything isn't working the way it should. These experiences teach you a lot about yourself, while forcing you to learn quickly if you are to survive, let alone succeed.

People are going to make mistakes. I don't know of anyone who learns, grows and progresses in their career who hasn't made mistakes. The key is to quickly recognize when you have made a mistake and then immediately move to take corrective action. You should learn from your missteps, while not making too many serious errors or making the same mistake repeatedly. Remember, if you're not making some mistakes along the way, you're not pushing the envelope enough.

WHLE: Please reflect on the device industry as a whole. Where is it in its lifecycle, and how will it evolve in the next 10 years?

AC: First of all, if one looks at the broad range of medical products, from pharmaceuticals to capital equipment to commodity products, there isn't a more rapidly changing segment of the medical industry than medical technology. For example, about two-thirds of Medtronic's current revenues are generated from products introduced within the last two years. At the present time, significant advances in information technology and biotechnology are being incorporated into medical devices in order to improve patient outcomes and provide more cost-effective delivery of care. While the rate of change has increased significantly over the past decade, I believe that rate will only accelerate in the decade to come.

"Every six seconds, someone, somewhere in the world is either alive or living a more full life as a result of a Medtronic product or therapy."

WHLE: How will industry structure evolve to adapt to that change?

AC: Over the past decade, the industry has consolidated as a number of companies have merged or been acquired. This consolidation trend continues today. Having said that, the industry still has room for start-up companies and for R&D partnerships with leading medical institutions and academia. In this sense, the medical technology industry is very different from the pharmaceutical industry. In medical technology, you don't put a group of bright scientists in a lab to come up with a new device or indication that then is tested for safety and efficacy. R&D is much more applied, involving close collaboration among company engineers and scientists and with key medical doctors who are delivering cutting edge therapy. In this sense, medical technology R&D is very iterative, fast-paced and extremely collaborative.

Medical technology is also very different in the economics of how product value is derived. Unlike pharmaceuticals, where a prescription is refilled and paid for every month, medical devices have an upfront cost but significant value is delivered over an extended period of time, often measured in years and even decades. Many of these devices are very cost-effective, but that value needs to be viewed over the life of the therapy. Most of our markets are also significantly underserved or underpenetrated. If you look at the number of patients who are indicated for existing medical technologies compared to the number of patients who have actually received these therapies, the percentages are very low. As a result, there is a tremendous opportunity both inside and outside the United States to expand patient access and coverage.

The most important statistic that I quoted in our most recent annual report is the fact that about every six seconds, someone, somewhere in the world is either alive or living a more full life as a result of a Medtronic product or therapy. At Medtronic, our objective is to keep moving that six-second statistic lower.

WHLE: What are the challenges that you see ahead from an industry standpoint and for Medtronic?

AC: There is no question that medical technology will continue to evolve and advance. The industry has a major responsibility to continue to move new products through the regulatory cycle in a timely fashion, while ensuring proper testing is done to ensure safety and efficacy. We also need to ensure that proper reimbursement is available for our products around the world. Once a product is available, it is important that physicians who refer patients and deliver care are made aware of available products and therapies. In addition, it is increasingly important for patients and their families to receive access to this information in a responsible way. Finally, the industry needs to do a better job of calculating and communicating the value of medical technology. I firmly believe that when one looks for ways to improve the cost-effective delivery of healthcare to an increasing number of people around the world, medical technology will be viewed as part of the solution, rather than part of the problem. At Medtronic, we're committed to being an even larger part of the solution going forward. ■

Patricia M. Danzon, PhD on Pharmaceutical Reimportation

Patricia M. Danzon, PhD, is the Celia Moh Professor of Health Care Systems, and Insurance and Risk Management at The Wharton School of Management, University of Pennsylvania. She is also Chair of the Health Care Systems Department. Professor Danzon received a BA First Class, in Politics, Philosophy and Economics, from Oxford University, England, and a PhD in Economics from the University of Chicago. Dr. Danzon's previous positions include Associate Professor at Duke University, Research Economist at The Rand Corporation, and Visiting Professor at the University of Chicago.

Professor Danzon is an internationally recognized expert in the fields of healthcare, pharmaceuticals, insurance, and liability systems. She has served as a consultant on international healthcare issues to the World Bank, the European Commission Working Group on Pharmaceuticals, the New Zealand Treasury, the Asian Development Bank, and US Agency for International Development. In the US her consulting experience includes work for the American Medical Association, the American Hospital Association, the Insurance Services Office, the Institute for Civil Justice, the Alliance of American Insurers and the Pharmaceutical Manufacturers' Association. Professor Danzon is an Associate Editor of the Journal of Health Economics and the International Journal of Health Care Finance and Economics. She has published widely in scholarly journals on a broad range of subjects related to medical care, pharmaceuticals, insurance, and the economics of law.

WHLE: Drug reimportation is a critical issue right now within the larger context of price discrepancies between the US and the rest of the world. Do you see reimportation as a valid response to those price discrepancies?

PMD: No. To start off with, we have to consider if it is a sound policy from the perspective of both the US and global policy, because I think we have to take a global perspective. Right now, there's a broad consensus that the most efficient and equitable way to pay for R&D is through differential pricing, by which I mean that prices relative to marginal cost differ across countries in ways that roughly reflect income differences. Importation attempts to undermine that, because it attempts to import the cheaper prices from other countries. Faced with that threat, pharmaceutical companies respond by pricing based on a uniform or at least a narrow band of prices across countries. Because of the dominance of the US in terms of market size and relatively inelastic demand, the price that is optimal for the US market is likely to dominate that calculation.

WHLE: Do you think pharmaceutical companies could feasibly raise their prices abroad to preserve that US price level?

PMD: An effort to raise prices in other countries would run up against those countries' cost control systems and against the fact that other countries are already paying prices that are roughly proportional to their per capita income levels. Both in terms of how other countries strive to control their pharmaceutical spending and in terms of what they feel they can reasonably afford, there's going to be a lot of resistance to raising prices. And so the likely effect is that they'll either ration the use of the drugs, or they'll simply refuse to reimburse most new drugs and focus only on the ones they consider most innovative. That will mean less access, so that the pharmaceutical companies will be faced with launching at a price that they consider too low, choosing not to launch at all in those countries, or delaying the launch for several years in low price markets compared to higher price markets.

WHLE: At which point the arbitrage opportunity has disappeared.

PMD: That's right. It will mean lower sales for the

pharmaceutical companies, loss of access for foreigners, and no real improvement in drug costs for the US. It's lose-lose-lose.

Obviously, that's the extreme scenario. But that's why I think drug importation is a bad idea from a policy perspective, because it's going to undermine differential pricing. I also think it's ineffective from a US perspective in that it won't have an effect on prices, for two reasons. First, there will be a tendency for price differentials to narrow and for there to be a drying up of availability abroad. Second, the main actors in the importation game are going to be wholesalers, not individuals. The game will be played by the McKessons and the Bergen Brunswicks and even the big pharmacy chains, all of whom will go out and try to buy directly huge volumes of products. This will have a much bigger impact on demand in these foreign countries than we currently experience. It's very unlikely that those wholesalers will be able to source enough foreign products at low prices to really bring prices down in the US.

"[Reimportation] will mean lower sales for pharmaceutical companies, less access for foreigners, and no real improvement in drug costs for the US. It's lose-lose-lose."

It may well be the case that some of the most powerful buyers like Pharmaceutical Benefits Managers (PBMs) may be able to negotiate lower prices for some products, though the odds are that the intermediaries are going to capture a large part of the differential. But the cash-paying customers are not going to see any reduction in prices. To really bring down the retail price to cash-paying patients, you need enough supply to flood the market with cheap products. That's not going to happen, particularly if the pharmaceutical companies try to reduce supply of existing products or raise prices of new products and if other countries try to slow down exports once they see what's happening.

I'm not alone in making these predictions. My estimates of at most a 10% price savings in the US are independently made but similar to those of the Congressional Budget Office. And that is at manufacturing level prices. If we are interested in retail level prices, it's going to be an even smaller effect on average.

WHLE: What do you think about the general arguments made around safety and the threat of counterfeit or expired drugs?

PMD: Those are very important issues. There may be technologies developed that make it easier to verify where particular packages came from, but it will be much more difficult to find a way to put a tracking mechanism on each individual pill, which is what would be required to completely combat fraud using fake or expired products. Certainly, if there is, as people widely allege, a 40-50% price differential that could be arbitraged away by middlemen, the potential for fraud and counterfeit and the like is huge. So safety is a legitimate concern. It's unfortunate that it's the only one that gets raised in the debate, though, as opposed to the economic considerations.

WHLE: The repetition of the safety argument makes it seem like a diversionary delay tactic by the industry to forestall a movement that will impact their profits.

PMD: That's right. It's very hard for anybody, but particularly for the pharmaceutical industry, to make an argument that Americans should be paying higher prices because on average we have higher incomes. It doesn't sell well in Washington.

WHLE: Looking forward, what do you see as the likely outcome of the current struggle? What policy do you see taking shape?

PMD: Well, that is a political question, which I don't claim to be an expert on. But it's probably going to hinge to some degree on the extent to which safety tracking mechanisms can be developed, and also the extent to which there is going to be a push to reduce the cost of the Medicare drug bill. If there is increasing pressure for budget deficit reduction and reducing the unfunded liabilities associated with the Medicare drug benefit, then that will increase the pressures for allowing at least a toe in the door for importation, starting off with certain types of drugs just from Canada. That would presumably open up the potential for ultimately permitting importation for a wide range of drugs and from a larger number of countries.

WHLE: Let's return to the general issue of perceived high prices in the US and the discrepancy in prices around the world. You said earlier that you

believe that prices by country are roughly in line with per capita income.

PMD: That's right. In 1999, Professor Michael Furukawa and I did a study of prices for the 250 leading compounds in the US, based on unit volume. These drugs accounted for just over 60% of sales in the US. We found that differences in prices based on 1999 prices and exchange rates were, on average, roughly comparable to differences in income. Since then price levels in local currencies have changed and exchange rates have changed, and this could affect the conclusions. We are just starting a new study to update this earlier study.

WHLE: And that includes Europe and Japan?

PMD: Yes. It did not include the middle-income countries, so Mexico and Chile in our study had prices that were way too high relative to their per capita income. But for the European countries, Canada, and Japan, things were roughly in line relative to the US, after adjusting for income differences.

WHLE: That's certainly not the perception among the industry or the public.

PMD: That's true. Most people ignore the differences in per capita income. They assume that Canadians, Europeans, and Americans all have the same income levels, and that's not true. The average per capita income in Canada the last time I looked was over 20% lower than in the US. In most European countries that's true, too. That's the piece that most people ignore.

The other point is that the drugs that get the most publicity are the ones for which there are the biggest price differences. What we were looking at was a broad market basket including the leading 250 molecules. And that's a much broader sample than is used for most studies.

Finally, most of the comparisons that people are basing their general perceptions on are at the retail level. When you compare retail prices, you are including the differences not just between manufacturer prices, but also between pharmacy markups and wholesaler markups across countries.

This is particularly true for the uninsured. If one is looking at the prices to the cash-paying customer in the US, those are the highest prices that anyone pays, which will exaggerate average price differences. The reality is, most Americans have drug insurance and are getting discounts off that retail price of at least 20% because the PBMs are negotiating discounts on the manufacturer price component and on the retail markup. As a result, the difference between what the cash-paying customer is paying in the US and what the average insured citizen ends up paying is very significant. People lose sight of that because they don't see directly the discounts the PBMs are negotiating.

WHLE: Would you argue that, if not for the growing political pressure for change, the current differential pricing scheme is actually a stable situation that could continue economically?

PMD: Well, with a certain probability, yes. I believe that if the Medicare drug benefit moves ahead such that the problem of uninsured seniors becomes significantly diminished, and if the private PBMs have enough flexibility to negotiate big discounts for the Medicare program, then the magnitude of discounts in the US could actually increase. We could in fact see a narrowing of the price differences, in terms of net price, that the insured consumer is paying in the US compared to other countries, because there will be increased competitive pressures and more people covered by insurance in the US. That could be a stable environment, though the problem still remains of the segment of the population that doesn't have health insurance.

WHLE: Is there a movement abroad for the loosening of regulatory restrictions on pricing in Europe or Japan?

PMD: I certainly don't see it happening without a lot of political pressure from the US. If anything, most of the other countries that have a government-run or social insurance system try to keep their healthcare spending to a fixed percentage of their GDP. As new innovations come along, that puts pressure on that percentage, and so they are continually under more and more pressure to reduce prices because they're trying to cover more and more benefits and more technology. In the US, the percentage of GDP we spend on health rises to cover new technology. Other countries try to do it without much increase, and that means restraining prices. ■

Wharton Health Care Business Conference

The Wharton Health Care Business Conference will celebrate its 10th anniversary by reflecting on the industry's evolution as we move ahead into the next decade. As the leading healthcare business forum for industry professionals, academics, and students, the conference is at the forefront of industry thought leadership. The annual two-day event takes place every February in Philadelphia, PA, and typically draws over 500 attendees including students, professionals, and academics from across the nation. Corporate sponsors fund the industry's operations. The 2005 conference was held on February 17th-18th at the Park Hyatt Bellevue in downtown Philadelphia. A full description of that event's agenda and participants can be found at www.whcbc.org.

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Wharton Health Care Club

The Wharton Health Care Club organizes professional, academic, and social activities for all Wharton graduate students who are interested in exploring opportunities in the healthcare industry. Members share their curiosity and experiences regarding current issues facing hospital, physician, managed care, pharmaceutical, biotechnology, and medical device organizations. The Club seeks to educate the Wharton community about the different areas and functions within the healthcare community, provide a social outlet for those interested in healthcare, and assist Wharton community members seeking healthcare-related careers.

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Wharton Healthcare International Volunteer Project

The Wharton Healthcare International Volunteer Project (WHIVP) has a mission to provide management assistance to health institutions in developing countries that are grappling with the resource burden of fighting infectious disease epidemics. In the summer of 2004, a group of students and alumni went to Cape Town, South Africa to continue projects aimed at improving the city's public health clinics. Teams worked diligently to improve access to, and quality of care in a health system faced with overwhelming HIV and TB epidemics. This winter, a Wharton team initiated an HIV project in India in collaboration with the Bill and Melinda Gates Foundation. The team visited public clinics and hospitals in a district in Andhra Pradesh to gather HIV patient data and study the process of HIV testing and counseling. They created an HIV epidemiologic profile and presented their study, along with recommendations for monitoring the epidemic, to the state AIDS control office. In 2005, WHIVP will continue efforts to support management and business functions of health institutions in developing countries.

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Wharton Health Care Management Program

The Wharton School's MBA in Health Care Management is a full-time, two-year program that combines the core MBA requirements with an interdisciplinary healthcare major. Students thus gain the full range of managerial and technical expertise as well as addressing comprehensively the complex and multi-faceted aspects of the US healthcare system. The Program's graduates are exceptionally well prepared to play leading roles in the diverse organizations and specialties that make up this vitally important industry, one that is constantly changing as a result of innovations in science and technology, economic forces, human demand, and government and social policy. Alumni have established careers in pharmaceutical and medical product companies, financial services, hospitals and other medical institutions, entrepreneurial ventures, consulting firms, foundations, industry, and government, many of them holding positions as chief executive officers, directors, and other key decision makers.

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