



Cyrus Mehta (left) and Nitin Patel (right) at Cytel's 25th anniversary banquet.

Creators of Pioneering Software and Clinical Services Company Look Back and to the Future

CHANCE magazine invited Cyrus Mehta and Nitin Patel of Cytel, Inc. to talk with Scott Evans, executive editor of CHANCE. Cytel is a pioneer in the development of software for exact methods, clinical trial design including adaptive designs, and statistical consulting and services. Mehta and Patel discuss their background, the challenges of developing and maintaining Cytel, and what they have learned on their journey.

Evans: Please tell me about your backgrounds and how you met.

Mehta: We are both from Bombay, India, and went to high school and undergraduate college in Bombay, followed by graduate studies at MIT. I got my bachelor's degree in Civil Engineering at the Indian Institute of Technology, Bombay, and my master's and PhD in Operations Research at MIT. I learned statistics on the job. Although I had met Nitin once or twice when

I was still a student in India, we really became friends at MIT. I've learned a lot from him both about how to conduct original research and about how to live well.

Patel: I obtained my bachelor's degree in Electrical Engineering at the Victoria Jubilee Technical Institute (VJTI) of Bombay University. VJTI was set up in 1887 to celebrate Queen Victoria's Golden Jubilee and is one of the oldest engineering colleges in India. On graduation, I joined MIT, which incidentally was

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Nitin Patel is co-founder, chair, and chief technology officer of Cytel and has been a visiting professor at MIT and at Harvard for several years. He has focused on research at the intersection of statistics, operations research, and computer science. He is a Fellow of the ASA and a Fellow of the Computer Society of India. He is a past president of the Operations Research Society of India and has also served as vice president of the International Federation of Operational Research Societies.

established in 1861. After earning a master's degree in Electrical Engineering and Computer Science and an MBA from the Sloan School there, I went to work at Bonner and Moore Associates, a consulting and software company in Houston, a company that pioneered in building operations research (OR) models for the oil and gas industry and developed some of the earliest commercial Linear Programming software.

It was there that I had my first experience of building statistical models for practical applications. I had the good fortune to work on a four-person team to develop a commercial Monte Carlo simulation software package in FORTRAN for analyzing risk in capital investments for the production and exploration of oil and gas.

I returned to India, where I was a member of the founding management team of Tata Consultancy Services. I came back to MIT after a six-year break to study for a PhD in OR alongside Cyrus. From those days up to today, his extraordinary drive and energy, and his gift for clarity and focus in writing, have been inspiring to me. I was at the British Museum last year when I came across an ancient Egyptian hieroglyphic which immediately brought Cyrus to mind. It said: "By day, write with your fingers; recite by night. Befriend the scroll and the palette—it's more fulfilling than wine!"

Evans: How did Cytel get started?

Patel: The key event that led to the creation of Cytel in 1987 actually occurred a decade earlier. In 1977, Cyrus was a young assistant professor in the business school at the University of Pittsburgh and I was a faculty member at the Indian Institute of Management,

Ahmedabad, or IIMA, as it's popularly known in India. We had become friends when we were doctoral students at the Operations Research Center at MIT.

In 1977, Professor Mosteller at Harvard recruited Marvin Zelen and the entire Department of Biostatistics at SUNY Buffalo (which I understand was referred to as "Marvin's Baseball Team"). Marvin went to Carnegie Mellon University to talk about the research he and his team were doing in biostatistics at the Harvard School of Public Health. Cyrus was blown away—he wanted to play on the baseball team! He was thrilled when Marvin invited him to join, but there was a hitch: Someone had to be found to teach the courses Cyrus was scheduled to teach in the coming semester.

Cyrus wrote to me, asking if I would like to come to Pittsburgh as visiting faculty to teach his courses. I readily agreed, as I thought it would be an interesting experience for me; my wife, Tehmi; and our three-year-old son Aneesh. During the semester, I made a trip to Cambridge and stayed with Cyrus and Satu.

At one point in our conversation, Cyrus described two problems in computational statistics that Marvin had suggested to him. We decided to work together to try to solve them. Fortuitously for us, these problems were ideally matched to our strengths. We were able to combine ideas from statistics, operations research, and computer science to develop solutions to them. I should point out that the operations research component drew heavily on the "branch-and-bound" method created by John Little, my doctoral dissertation adviser at MIT.

Cyrus and I kept up our research collaboration for several years after I returned to India. In those days, there was no Internet and the telecom service to India was expensive and of poor quality, so we had to use snail mail. Fortunately, thanks to the generous support of Harvard and IIMA, we were able to schedule visits by me to Cambridge during summer breaks, and by Cyrus to Ahmedabad during the December holiday.

Pralay Senchaudhuri and Yogesh Gajjar were then on the staff of the IIMA computer center and provided us with excellent programming support. This arrangement worked only because of the exceptional patience and understanding of our families, who had to put up with drastic reductions in holiday time with us.

We were able to publish papers on a range of non-parametric problems in computational statistics. A number of statisticians urged Cyrus to develop an industrial strength software product based on our work. They suggested applying for a Small Business Innovation Research Grant and offered to write letters of support. This led Cyrus to ask me if I was willing to move to Cambridge to start a company with him.

For Tehmi and me, it meant settling far away from our aging parents. For me, it would be a major career

change to switch from teaching at a management school in India to developing software in the U.S. On the other hand, it was a unique opportunity that also held promise for a much better education for our sons Aneesh and Arjun; particularly Aneesh, who had muscular dystrophy. We decided we would go.

Pralay was happy to join the team while working for his doctoral degree at Harvard. Yogesh decided to enroll at Northeastern as a master's student in Computer Science and work with us under their apprenticeship program. We adopted Tehmi's suggestion of Cytel for the company's name ("Cy" from Cyrus and "tel" from Patel), and we were ready to roll!

Cytel started in the ground-floor apartment of Cyrus's house in Cambridge. Tehmi and I, with our two sons, inaugurated the location by sleeping there on our first night after arriving in Cambridge, with Aneesh on a folding bed and the rest of us in sleeping bags.

Mehta: I belong to the Zoroastrian community, a tiny ethnic group that migrated to India from Persia in the 10th century. Our community has a tradition of starting and owning businesses. I had this ambition from my early boyhood. My opportunity came in 1987 when I heard about the Federal Government's Small Business Innovation Research (SBIR) program.

Between 1983 and 1987, Nitin and I had published some innovative papers on exact permutational inference that were motivated by various types of discrete data situations arising in clinical trials. I remember when one of our papers on exact inference was published in *JASA*. Carl Morris was then the editor. He accepted the paper but wondered how practical it would be without accompanying software.

The SBIR program was a way to convert the fruits of our research into professional, robust and well-documented software that would address this concern, so we applied for SBIR funding, won an award, and launched Cytel with the blessings of our mentor, Marvin Zelen. We had families with young children, but it is easy to be fearless when you are young, full of optimism, and totally ignorant of what the future holds in store for you.

Evans: What were the early years at Cytel like? What were the biggest challenges?

Mehta: For the first half of our history, we were a software company, primarily devoted to developing and upgrading our core software packages, StatXact, LogXact, and East. StatXact performs exact nonparametric inference for categorical data models expressed as contingency tables, while LogXact extends the exact inference to logistic and polytomous regression models to incorporate covariate adjustments.

Both packages rely on network algorithms that Nitin and I pioneered and published in the 1980s. The software produces valid inferences for small, sparse, and imbalanced datasets, where conventional large-sample methods may be unreliable.

East is a package for the design and interim monitoring of group sequential and adaptive clinical trials. All three packages are widely used in the biopharmaceutical industry.

This phase gave us a solid foundation for future success. Our software was innovative and our manuals were well-written, so we won the respect of our statistical colleagues and were able to penetrate into most major pharmaceutical companies, academic centers, and government organizations both in the U.S. and overseas.

Now, you must understand that getting well-known and respected is not the same as making a profit. We relied on the SBIR grant program to fund much of our R&D. There were severe challenges to staying solvent and meeting payroll. We'd be flush with cash as soon as a new version of one of our products came out, since our customers were eager to upgrade. Then, once everyone had upgraded, we were left with the more-difficult problem of finding new customers in a fairly specialized market.

We had to rely on making phone calls, placing ads in *Amstat News*, and direct mail. It was expensive, and the returns were always disappointing; below our expectations. I did cultivate a detached attitude to making cold sales calls and having people hang up on me.

The hardest period was in the mid-'90s when the MS-DOS Operating System was being replaced by MS-Windows. This was a time when many small software companies folded because they could not adapt quickly. Our software engineers had to learn how to develop Windows software on the fly so StatXact-for-Windows could come out before we ran out of cash.

We were extremely fortunate to receive timely financial help from Marvin Zelen, one of the most generous, positive, and exceptional people I've known. He made us a loan on the spot with no questions and no security. "Just pay me back when you can," was all he said. With that timely loan, we completed the product and watched with delight as the orders rolled in and a huge mountain of packages piled up in the office, waiting to be shipped.

Patel: One of the initiatives we started 15 years ago was setting up a software development team in India. The Indian Statistical Institute was established in 1931 by Professor P.C. Mahalanobis and since then, there has been a strong academic tradition in statistics in India.

Also, I had been a member of the management team that set up and ran Tata Consultancy Services (TCS), a software services company in Bombay in 1966. By

1998, TCS had gained global recognition as a high-quality custom software developer. Although Cytel was a small company then, we wanted to explore how we might tap into the statistical and software talent in India to give us an edge in competing with big statistical software companies.

We began with a few contract software projects in the '90s with companies that I knew from my days in India. For example, we had a pilot project to explore the idea of porting StatXact to the Apple Macintosh. However, we found that our needs were different from the strengths of the Indian software industry as it was then. We needed depth in algorithms and statistics, as well as a product orientation to building software.

The focus of software companies in India was on data processing and services. We came to the conclusion that we would need to set up our own company. I contacted my former student from IIMA, Ajay Sathe, who had developed algorithms to create a successful software product for the Indian market. He agreed to head up our Indian company and we decided to locate it in Pune. The university there has a strong statistics department. Mukund Altekar, another former student at IIMA, helped us launch the company in 1998.

A major project was to develop the first Windows version of East under the guidance of Cytel USA. I don't have any siblings, but some friends whom I have known for decades are basically brothers to me. In fact, they are more than brothers in the sense that they do things for me which they are not obliged, in any way, to do.

Cytel India's chairman for 25 years, Mahendra Shah, is such a friend. He agreed to help me after his retirement from setting up and heading a large manufacturing company in Pune. He did this for no other reason than the fact that I was requesting his help. His wise guidance has been a key factor in the growth of Cytel India from the earliest days up to the present time.

Evans: You are no longer an exclusively software product company. What made you go into services? And what were the challenges?

Mehta: After about 15 years of exclusive reliance on software and NIH grants for our revenues, it became evident to me that we had to expand our business model if we wanted to grow.

We had built up a loyal following of biostatisticians in industry and our software was also being used by the FDA, NIH, and universities. It seemed to me that we should attempt to leverage these connections to build up a consulting business. This would add to our

revenue stream, bring us closer to our customers, and give us fresh insights for further software development.

We had no track record as a consulting organization and the space was crowded with large and small contract research organizations (CROs), as well as with seasoned statistical consultants who had spent years working for or consulting to the biopharmaceutical industry. Our experience with software had taught us that it is possible to compete with the big guys (SAS, SPSS) by creating special products that add value but are not available in standard packages. We felt the same strategy would work to get our foot in the door with consulting.

We decided to pick the niche area of adaptive clinical trial design, and become experts in it. The first papers on adaptive design were just coming out and the pharmaceutical industry was showing interest in this nascent movement. It seemed to be a natural fit for us, since an adaptive design could be viewed as an extension of group sequential design, where we already had a strong presence through our East software.

Adaptive designs were slow to catch on in the first five years of the 21st century. There was a wariness about being the first to use these designs in a regulated industry. The slow growth was to our advantage, since it gave us time to digest the emerging methodological literature and add the new methods to East. Then, in 2005, we met Per Lofberg, the CEO of Merck Capital Ventures (MCV), an investment arm of Merck Pharmaceuticals.

Per wanted to invest in businesses that could improve efficiencies in the pharmaceutical industry. He believed that adaptive designs would grow in importance as clinical drug development became increasingly expensive, and it became evident that the lack of flexibility for making mid-course design corrections to conventional designs was resulting in failed trials. He expressed interest in Cytel, and we felt the time was right to take in an investment and use it to grow our consulting services business.

Although we had managed somehow, all these years, neither Nitin nor I were really business people. We enjoyed doing methodological research, writing papers, and developing software, but if we were going to take in venture capital, we would need a solid business plan and a commitment to creating a management team that could take full advantage of the investment to grow the business and make it more profitable. Otherwise, why would MCV invest in us?

We therefore began to look around for a CEO who could negotiate with MCV, build up the marketing and sales organization, and create a formal management structure that would facilitate growth. We found just the person. Ranganath Nayak, was a colleague of ours from our MIT days with many years of management

experience at Arthur D. Little and at Boston Consulting Group. He had been in the same high school and engineering college in Bombay as Nitin and was someone we could respect and trust.

He became our CEO. He made a number of strategic hires, including heads of clinical development, sales, and functional outsourcing from the CRO world, and he brought a razor-sharp focus to ensuring that every business unit was profitable.

The result was a spectacular growth spurt in all aspects of our business—software, strategic consulting, biostatistics, and data management. In the 10 years since we took the investment from MCV, we grew in size from about 50 employees to 500, with offices in the United States, Europe, and India.

Nitin and I have the best of both worlds. We provide the scientific leadership for software development and strategic consulting while the business side of the company, including the CRO services, is handled by our management team.

Patel: Two pivotal contracts sparked the growth of our statistical and programming services abroad.

The first was a large multi-year project for Merck USA for statistical and programming services. We set up a large, dedicated team for this work by recruiting Professor Anil Gore, a distinguished statistician, who is a Fellow of the Indian Academy of Science. The project required rapidly ramping up our capability in programming and statistical services with rigorous quality and productivity standards.

Ajay Sathe, CEO of our India operations, used this landmark experience as a launch pad to dramatically grow our India-based services. He provided extraordinary leadership in the challenging task of both developing business and managing rapid growth while maintaining quality.

The second contract led us to establish our European office. Merck-Serono had an experienced internal team with expertise in statistical and programming services, located in Geneva. When they decided to close that office, they asked if we would like to take over much of the work there. We had been planning to have a European office to better serve our European clients. The Merck-Serono opportunity enabled us to jump-start our presence in Europe by hiring most of their staff.

Evans: What lessons have you learned?

Mehta: I am an ordinary man who got this extraordinary opportunity to start a company with my colleague Nitin Patel, and grow it over a period of 28 years into a thriving organization which now has more than 600 employees spread out over the United States, Europe,

and India. Along the way, I learned many things about running and growing a business.

The three most important lessons I learned are these: Constantly reinvent yourself; get out of the way; be thankful.

Lesson 1 is to constantly reinvent yourself.

Having a goal is important, no doubt, for as the saying goes, “If you don’t know where you are going, any road will get you there.” I would add to that, “Be prepared to adapt to circumstances.” You select the goal with only partial knowledge of its worth. To have a successful and sustaining business, you must constantly reposition your business model. We positioned and repositioned Cytel at crucial times.

Cytel was initially a provider of software for exact tests. Twenty-eight years ago, Nitin and I published a series of papers on the use of network algorithms for performing permutation tests quickly. Such tests were useful for analyzing categorical data without making any distributional or sample size assumptions.

The IBM PC had just come out and the amount of computational power available to individual statisticians was increasing exponentially. On the strength of these developments and with encouragement from Marvin Zelen, then the chair of my department at the Harvard School of Public Health, we were awarded a small business innovation research grant from the NIH. With that award, we launched Cytel.

Our first products were StatXact and LogXact. The business had a highly specialized focus. We sold the following idea: “Why should you rely on approximate answers when you can get exact answers from Cytel?”

We enjoyed early success. The software took off and gave us valuable name recognition in pharmaceutical companies, medical research centers, the NIH, and the FDA. As time went on, though, we noticed that SAS had read our papers and begun to introduce exact tests into its offerings. We were vulnerable. To fend off that threat, we developed our own SAS Procedures for StatXact and LogXact, and sold them directly to SAS users.

There was, however, a limit to growth in the exact line. Working in this field was intellectually rewarding but narrow; it did not solve a mission-critical business problem. We had to broaden our offerings.

An opportunity to broaden our offerings to a provider of software for efficient trial design and analysis arose when, around 1994, the Harvard Biostatistics Department and Schering-Plough Corporation formed a partnership with an annual workshop featuring cutting-edge statistical methods of importance to industry.

The first workshop in this series was on group sequential design. All the major players in this

field—Chris Jennison, Bruce Turnbull, Butch Tsiatis, Dave DeMets, and many others—gave talks. I listened carefully and realized that here was an opportunity for Cytel to offer a software solution for a really important business and public health problem: saving time and patient resources in clinical trials for serious diseases.

In collaboration with my Harvard colleagues, Butch Tsiatis, Kyungmann Kim, and Sandro Pampallona, we developed East, the first commercial software package for group sequential design and interim monitoring. East is now firmly established in all the major biopharmaceutical companies and at regulatory agencies as the industry-standard software for the design, monitoring, and simulation of early and late-stage adaptive clinical trials.

We now had two major software lines to maintain and enhance. Highly trained software engineers were scarce and expensive. A possible way out of this problem was to look to India, where our roots originated.

It was the mid 1990s. India was undergoing a transformation. The Indian government was encouraging new businesses with favorable tax incentives. Nitin, having been a professor at the Indian Institute of Management, Ahmedabad, had many contacts in the IT industry in India. We leveraged these contacts to start Cytel India, thereby opening up a pipeline to the finest software engineers and statisticians from places like the Indian Institute of Technology, the Indian Statistical Institute, and the Department of Statistics at the University of Pune. Long before Bangalore became known to the west, we had opened our first India office in Pune. We have subsequently also opened offices in Bangalore, Hyderabad, and Mumbai.

For the first 15 years of our life, we were entirely a software company. We relied on StatXact, LogXact, East, and SBIR grants from the NIH for revenue and R&D support. Here again, it became evident that we were vulnerable. How could we continue to innovate our software? How could we find new customers for it? How could we fend off competitors who would surely develop software for group sequential design sooner or later?

The answer became obvious. We had to start a statistical consulting arm of Cytel. That would get us closer to our customers and enable us to understand what they really needed. We sensed an opportunity to create a valuable feedback loop; relationships built on software sales could be leveraged to win consulting contracts and in turn, the new ideas generated by the consulting assignments could be incorporated into new versions of our software.

This would keep us ahead of the game. None of our competitors were playing both the software and consulting games. But how to get started? We needed to transform the organization, and learn how to run a

consulting business without disrupting our successful software business.

We were lucky. In 2001, we hired Hillary Hedges, a smart young MBA from Harvard Business School who understood that we had a tremendous opportunity to expand our role in clinical trial design. She signed me up to visit companies all along the New Jersey/Philadelphia corridor, thus getting me out of the comfort of my Cambridge office and into the real world. Then she introduced us to Merck Capital Ventures (MCV), an investment arm of Merck Corporation. Taking an investment from MCV was what enabled us to transform Cytel from a software company into a software plus services company.

Lesson 2 is to get out of the way.

There comes a time when you realize that, for the company to grow further, you must take a back seat. It can be a painful lesson if you have become accustomed to having your own way in all matters, but it is necessary. To generate fresh ideas, move in a new direction, others with a different set of skills and experience must be brought in with the authority to make decisions, even if you don't agree with the decisions.

The move from software to services required a different set of leadership skills. It required closing on a venture capital deal, building a management team, creating an outside sales force, and developing stricter financial controls and a more formal reporting structure. In short, a transformation from what had been more like an academic research center into a business with a stricter watch over the bottom line.

I was not the right person to lead that transition, and Nitin was not interested in it, either. We turned to our long-time friend, Dr. Ranganath Nayak, to become Cytel's first CEO. He had extensive business experience as a senior executive at Arthur D. Little and Boston Consulting Group. He ran the business side and was responsible for several strategic hires and mergers that deepened our ties to the biopharmaceutical industry, while Nitin and I continued to focus on providing technical leadership of consulting, research collaboration, and software.

This was a huge strategic move and resulted in our [growth]. In many companies, the founders continue to hang onto the controls for far too long and, as a result, the business stagnates. I remember the words of Arthur J. Levitt (chair of the SEC) in the *Wall Street Journal* some years back: "Unlike in a large company, stagnancy in a small company can lead, not only to a diminished paycheck, but to extinction."

Lesson 3 is to be thankful.

We always keep in mind that we did not build the organization ourselves. Many people worked directly to build Cytel or helped us in different ways along the way.

We thank them all, our families first and foremost, but also Pralay Senchaudhuri and Yogesh Gajjar, who took a big risk in moving from India to join us as co-founders.

We will always be grateful to Marvin Zelen for his unflagging support, both moral and financial. We thank our wonderful group of loyal employees, both in the USA and in India, who have really created an atmosphere in which it is fun to work at Cytel.

We thank the National Institutes of Health for backing us through their Small Business Innovation Research programs. Others to whom we owe our gratitude are our customers, our board of directors, and our many research collaborators at Harvard and elsewhere. It is impossible to name all the people who have helped us to reach where we are today.

Evans: Any final thoughts or suggestions to others considering entrepreneurial endeavors in statistics?

Mehta: To those of you who are contemplating taking the plunge and starting out on your own, I would say this: Start out by playing to your strength, but don't relax; don't become complacent if you enjoy rapid early success. Rather, be alert for new opportunities.

As you grow, don't be afraid to bring in others who know more than you do. Encourage them to take charge; give away parts of your company to them. They will make you rich. A small share in a large pie can be worth considerably more than having a small pie all to yourself.

What you can do, how much you can grow, how much you influence the profession—all these are limited only by the size of your vision, and your vision will grow over time if you keep your mind alert and open.

Patel: I think entrepreneurs come in all shapes and sizes and hues. However, I learned that there are some fundamental factors for them to succeed.

First, they have to forego pursuit of a well-defined path for career growth in favor of a riskier, uncertain future. They must be willing to take risks. This willingness can arise in many different ways. In my case, a major impetus was the prospect of providing a stimulating education to my physically handicapped son. This, along with my discomfort with the relentless pressure and uninspiring environment in most Indian schools that my younger son was experiencing, led me to decide to take the risk.

Second, it requires a core team that is committed to the idea behind the start-up and has the mix of skills required to actually implement it. We were fortunate to have Pralay and Yogesh on our starting team. We did not have much experience in developing commercial

statistical software, but between us, we had just the right skill set and great enthusiasm to learn that enabled us to develop StatXact and obtain SBIR grants that were critical for survival in Cytel's early days.

Third and most important, in my opinion, one needs a good measure of luck, in particular being at the right place at the right time. Cyrus and I were fortunate to have the extraordinary opportunity to move from the research papers and prototype software to producing commercial software products because of the rapid strides that computer technology was making. In particular, it was the fact that personal computers (as desktops were called then) were becoming powerful and inexpensive that made it possible to conceive of products like StatXact and LogXact.

I agree with all the points Cyrus has made. I would like to add to the point he made about having to select the goal with only partial knowledge of its worth. In a small company, there will be several opportunities from which a single main focus has to be chosen because of lack of bandwidth and resources. This can be difficult to do.

An example, in our case, was the area of data mining. With Professor Dimitris Bertsimas of MIT, I had developed and taught a data mining course for MBA students for a few years. This experience gave me the idea of developing an Excel-based data mining package. We developed the XLMiner package at Cytel and I co-authored a book that has been successful as an MBA textbook in data mining.

I felt that, as first movers, we would gain an advantageous position in a rapidly growing market. However, we found we did not have the resources to develop in this field in addition to the adaptive trials initiative that Cyrus mentioned. We had to sell XLMiner to Frontline Systems, a major player in the Excel add-in market. They have successfully re-launched it in newer versions and have incorporated it into their popular Analytics Solver Suite.

Finally, I learned the truth of a maxim that I came across in reading an autobiography several years ago when we were starting Cytel. I think it was by Akio Morita, the founder of Sony, but am not sure. To paraphrase, it was: "When you start a company, you lead from the front; when it is growing, you lead from the middle; and when it has grown to maturity, the best you can do is stand at the back and applaud." 🗨

About the Author

Scott Evans is the executive editor of *CHANCE*.