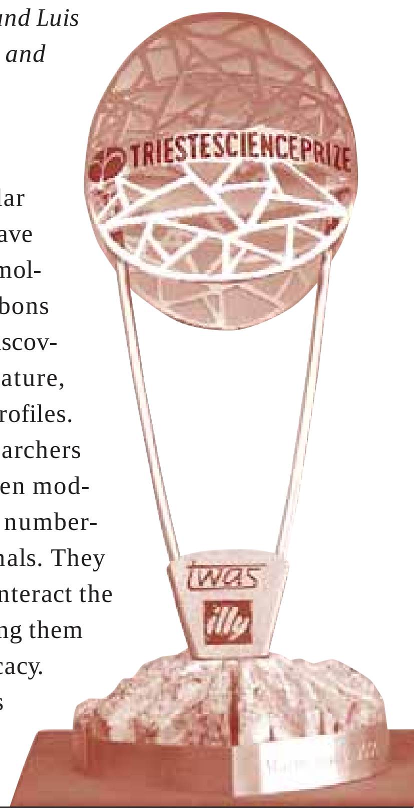
THE AWARDS CEREMONY FOR THE TRIESTE SCIENCE PRIZE TOOK PLACE IN THE POLITEAMA ROSSETTI THEATRE IN TRIESTE ON 19 MAY 2007 AS PART OF THE FIRST-EVER FEST, *FIERA DELL'EDITORIA SCIENTIFICA TRIESTE* (INTERNATIONAL SCIENCE MEDIA FAIR). OFFICIALS IN TRIESTE HOPE TO MAKE FEST A YEARLY EVENT AND TO HAVE THE ANNUAL CEREMONY OF THE TRIESTE SCIENCE PRIZE AS AN ONGOING PART OF THE FESTIVITIES.

PRIZE WINNERS TALK SHOP

During their visit to Trieste, the editor of the TWAS Newsletter had an opportunity to sit down and speak to the two winners of the 2007 Trieste Science Prize, Goverdhan Mehta, Bhatnagar fellow and honorary professor of organic chemistry at the Indian Institute of Science in Bangalore, and Luis Rafael Herrera-Estrella, professor of plant genetic engineering at the Centre of Research and Advanced Studies in Irapuato, Mexico. Excerpts of the interviews follow.



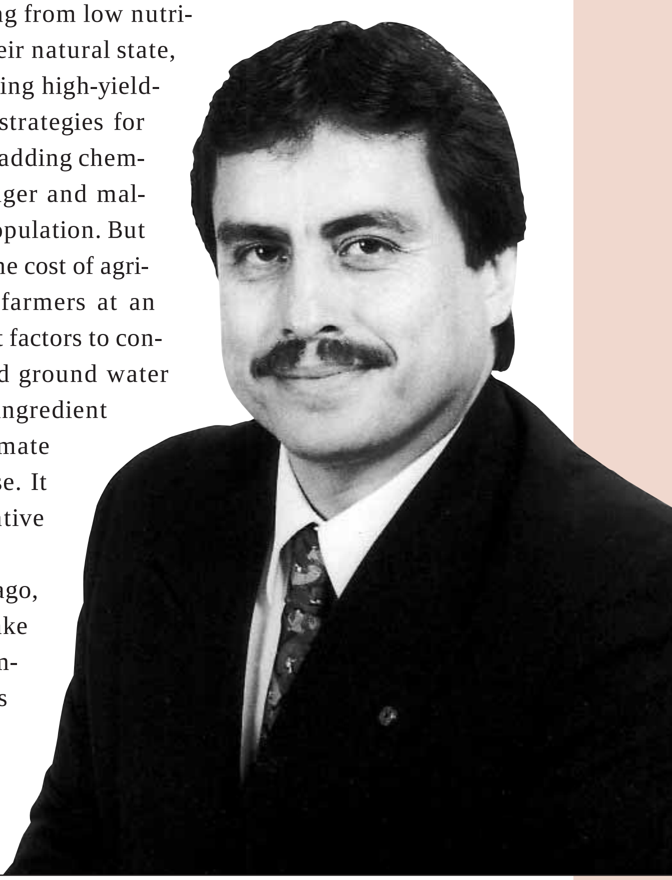
What is the nature of your research? What makes it unique?

Mehta: My research has focused largely on the creation of new and diverse molecular architecture. Like many of my colleagues working in the field of organic chemistry, I have devoted a good deal of time to the design of carbon-based structures (that is, organic molecules). The public knows about carbon-derived structures largely through hydrocarbons present in fossil fuels. But organic molecules have also proved invaluable in drug discovery. Almost all drugs are based on organic molecules. Many have been inspired by nature, which makes a vast array of organic molecules that exhibit interesting bioactivity profiles. Nature, in fact, provides a repository – a library, if you will – of molecules that researchers can explore for the purposes of replication, and, when possible, amplification and even modifications of their drug-related attributes. The approach works like this: molecules, numbering in the hundreds of thousands, are isolated from microorganisms, plants or animals. They are then characterized and examined to identify compounds with the potential to counteract the effects of human ailments and diseases. Synthetic chemists pick up these leads, preparing them in the laboratory. They also carry out modifications to enhance their therapeutic efficacy.

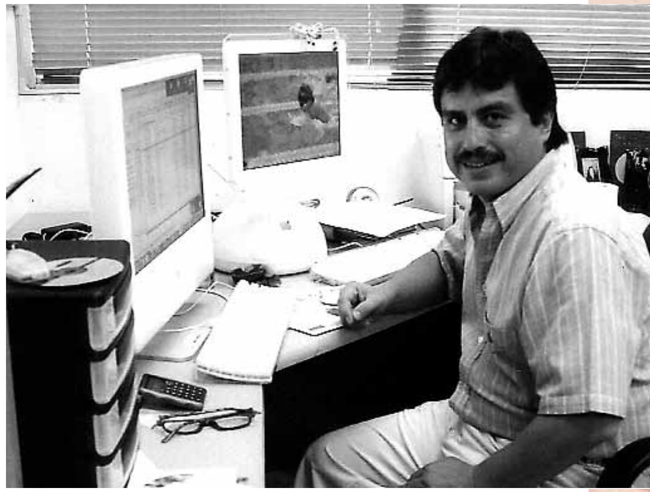
The study of natural products was – and remains – one of the primary strategies that scientists use to advance pharmaceutical research. Until recently, it was the main

strategy other than classical trial-and-error approaches. With the advent of molecular biology and, more specifically, with the unraveling of the human genome, scientists now have powerful new tools to conduct research in drug discovery. Every human disease is associated with a certain portion of the genome. The genome sequence, in fact, provides a biological roadmap that tells us which proteins are linked to which diseases. Once such an identification has been made, which is no easy task, the challenge is to inhibit or 'lock out' disease-inducing proteins or even 'switch off' the pathways leading to them. Such advanced scientific knowledge creates the potential both to uncover and create molecules to treat, for example, bacterial diseases, cancers and HIV/AIDS. My research aims to synthesize molecules that exhibit promising profiles against such disorders. What I do is not very unique. But it does advance knowledge about the art and craft of making new and useful molecules.

Herrera-Estrella: My research focuses on understanding the genetic mechanisms by which plants survive – and indeed thrive – in soils suffering from low nutrient levels. There are not many places with soils that, in their natural state, have sufficiently high levels of nutrients capable of nurturing high-yielding food crops. As a result, scientists have investigated strategies for boosting soil nutrient levels in a variety of ways, including adding chemical fertilizers. The latter effort has helped to reduce hunger and malnutrition in poor countries and to feed a growing global population. But it has come at a price. Fertilizers are expensive and add to the cost of agricultural production. That places poor people and poor farmers at an economic disadvantage. But there are even more important factors to consider. Pesticide-laced runoff has polluted both surface and ground water across the globe. Moreover, phosphate, which is a prime ingredient in many fertilizers, is a finite resource that soil experts estimate could be depleted within 50 years at current levels of use. It therefore makes sense for scientists to develop alternative strategies for helping to reduce the use of fertilizers.



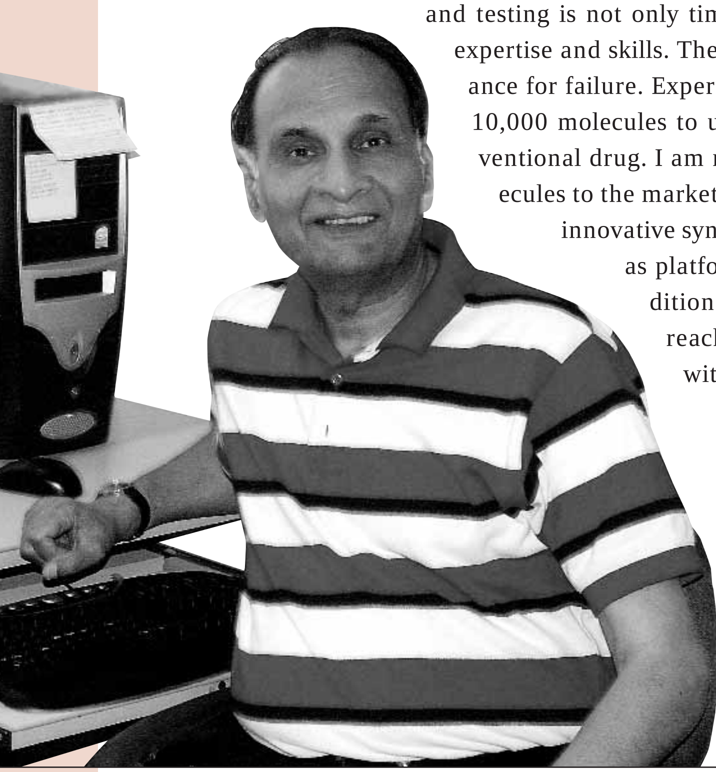
From the very outset of biotechnology several decades ago, scientists hoped to engineer plants in ways that would make them more hardy and productive without resorting to chemical interventions. But the science, not surprisingly, was difficult. As a consequence, research in the 1970s and 1980s focused mainly on microbes because of their relative simplicity. The laboratory I worked in as a graduate student in the mid 1980s, under the tutelage of professors Marc Van Montagu (TWAS Associate Fellow 2001) and Jeff Schell in Belgium, was the world's first laboratory to transfer the DNA of a soil bacterium (*Agrobacterium*) to plant chromosomes. Our research made it possible to introduce foreign protein into existing plant organisms. In effect, we produced the first genetically engineered plants.



Our research focused exclusively on tobacco. Tobacco possesses a property that is rare among plants: a single cell can be induced to develop into a normal tobacco plant. Because it is relatively easy to regulate and modify single cells, and because, in the case of tobacco, these cells can be transformed into a complete plant, tobacco is often the plant of choice among researchers. Only after I decided to return to Mexico in 1986 did I turn my attention to other plants – beans, chili peppers, husk tomatoes, sorghum, tropical maize and papaya – that are important to food production and food security in developing countries, particularly in Central and South America.

What are the current research challenges that you face?

Mehta: There is often a 10- to 15-year time lag between the identification of a molecule that has the potential to develop into a drug and the actual commercialization of a drug. The screening and testing is not only time-consuming and expensive, it also requires diverse expertise and skills. The process is not easy and requires a great deal of tolerance for failure. Experts estimate that scientists must investigate more than 10,000 molecules to uncover just one with the potential to become a conventional drug. I am not directly involved in efforts to bring potential molecules to the marketplace as drugs. My research is more basic. I try to take innovative synthetic routes to make natural molecules that can serve as platforms for 'diversity creation', which is a necessary condition for drug development research. Once this stage is reached, I pass the work to others who take it forward with their eyes set on the pharmaceutical marketplace.



Another aspect of my research is devoted to exploring and manipulating the architecture of molecules – a process that can only be 'seen' by using advanced spectroscopic and nuclear magnetic resonance techniques. Such efforts to design organic molecules are not only scientifically challenging; they also have extraordinary artistic and aesthetic appeal. I first conceptualize the shape of familiar objects, for example, a football, a bowl or a ladder – much as geometricians create their own symbolic forms and shapes. I then try to build the molecular equivalents of what I have seen in my mind's eye. The construction can take the form of chemical expressions, carrying the elegance that mathematicians find in formulae and proofs. What's created may be of no obvious or immediate use. But it is eminently pleasing to me and others who have invested a life's work in creating diverse molecular architecture. What we can't yet see, we can create with our imagination at a molecular level. It is often a thing of beauty.

Herrera-Estrella: I don't seek to replicate molecular architecture at the basic scale that professor Mehta just described. But I do seek to genetically engineer plants to make them more hardy and productive. There are two basic avenues of research I have pursued since I returned to Mexico. First, I have studied plant biology with the goal of transferring genes from other organisms into plant cells. The usual intent is to enable the engineered plants to absorb nutrients more efficiently. In this effort, my laboratory colleagues and I have studied broccoli and cauliflower, two food plants that grow well in low-nutrient soils. In broad terms, we seek to dissect the biological mechanisms that give these plants such an enviable trait and then to apply this knowledge – as well as our technical skills in genetic engineering – to produce plants with more efficient rates of nutrient uptake. Second, with the help of recent breakthroughs in genetics, we try to determine the regions of the DNA in plants where protein functions are expressed. Such knowledge, based on our growing expertise in genomics and genome mapping facilities, has enabled us to conduct new experiments that were not possible a few years ago. These experiments not only enhance basic scientific knowledge but also lead to strategies that allow plants to trigger reactions only when an external danger is present. Such a targeted approach is not much different than that outlined by professor Mehta in his description of efforts to identify drugs that are able to fight human diseases. In plants, however, we are dealing with the use of insecticides, for example, that would only be activated when a plant is attacked by a particular insect. Such a strategy would obviously reduce the amount of chemicals needed to protect a plant from the ravages of pests. This would be good not only for crop productivity but also for the environment.

What is the current state of science in your country, particularly when compared to the state of science when you began your career?

Mehta: There has been a sea change in science in India during the course of my career. Funding has increased enormously and facilities have improved markedly, especially over the past decade. When I first began my research in the 1960s, there was virtually no ready access to equipment in my field (or in any other field, for that matter) to carry out competitive level research in India. Reagents and chemicals, so critical for the kind of research I do, were not available and foreign exchange restrictions and import controls made it difficult and time-consuming to purchase them from abroad. Under these circumstances, I had no choice but to ship my samples to colleagues in other countries who would make spectroscopic measurements and send me the results. This was very time-consuming and frustrating. I sometimes feel that I should be launching my research career now when things are so much better. But, I don't have much to regret. I'm glad things are easier now. But I sometimes think the difficulties faced by my generation of scientists forced us to be more innovative and enterprising.

Herrera-Estrella: For the most part, conditions for scientists in Mexico have essentially held steady since I began my career in the mid 1980s. There have been some fluctuations in spending levels but overall the level of funding has remained about the same. In 1986, Mexico spent about 0.3 percent of its gross domestic product on research and development; in 2006, the figure was 0.36 percent. The nation's economy has grown though. So that means there is more money. There has also been a slight increase in the number of scientists. Surveys show that there are currently about 30,000 scientists actively publishing in peer-reviewed international journals. This upward trend is indeed welcome. But we should not forget that the figure remains extremely low for a country with 100 million people. My institution has been extremely fortunate to have received generous and consistent support from the government. We have enjoyed a privileged position under difficult conditions. In 2004, we received a US$14 million grant from the government to launch a new genomics institute dedicated to studying Mexico's unique biodiversity. Mexico ranks among the top five countries in terms of biodiversity and its status as a 'biodiversity hotspot' represents a huge scientific opportunity that could have enormous economic impacts extending well beyond the scientific community. Our job is to sequence the genomes of Mexico's plants and microbes to determine whether some of their genes could ultimately find commercial applications. The project began three years ago and the first new laboratory building should be ready for occupancy by the end of this year. In the interim, we have begun sequencing several plants, including agave (used in the production of tequila) and chili peppers. We have also sequenced a desert microbe that has survived for 8 million years to try to determine the biological mechanisms that have allowed it to exist in such an arid environment. Although the government has generously supported our research, there is a dark side to our efforts to create a world-class laboratory. Nearly a quarter century after the discovery of transgenic plants, the potential impact of this technology has been severely impaired by controversies fuelled by environmental groups that, without any scientific basis, have claimed that transgenic plants are dangerous to human health and the environment. In Mexico, an internationally orchestrated campaign has lead the government to impose a nationwide moratorium that extends not just to the commercialization of transgenic plants but also to experimental field testing for techniques developed in our country. This represents a serious impediment to Mexico's efforts to join the ranks of Brazil, China and India as a scientifically proficient

developing country. Ultimately, it handicaps national efforts to ensure adequate supplies of food commodities both for domestic consumption and foreign export.

Who inspired you to become a scientist?

Mehta: I had two major influences. First, my parents (my mother was a housewife and my father a senior government officer) always wanted me be to a scientist. To this day, I still don't know why they had such strong feelings about my career choice. I do believe, however, that they believed science to be an honourable profession that brought out a person's best instincts. Second, I had excellent early education and sound mentoring at the university and research level. I was taught by teachers who not only made learning exciting but also instilled a sense of values and dedication. The significance that my teachers and parents placed on education is part of a great Indian tradition – a tradition that has recently begun to pay significant economic dividends for my nation.

Herrera-Estrella: Since I was a child, I've been interested in discovery and during my adolescence and teenage years I dreamed of becoming an inventor. That dream only began to be transformed into reality after I entered university. There I took a course in molecular biology during my freshman year. The teacher did a wonderful job explaining how research was done and how knowledge could be applied to address critical societal needs. I've been hooked ever since and I don't expect the sense of wonder is something that will ever leave me.

How did you learn about winning the Trieste Science Prize and what does the prize mean to you?

Mehta: I was at an executive board meeting of the International Council for Science (ICSU) in Rome, Italy, where I currently serve as president, when I received a phone call from Mohamed Hassan, TWAS's executive director. I had known about the Trieste Science Prize from the press articles and was aware of the previous winners from India (T.V. Ramakrishnan who won the prize in physics and C.S. Seshadri who won the prize in mathematics). But I was nevertheless completely surprised by the news. The award brought me a feeling of great satisfaction at being recognized by peers and honoured by a leading professional body like TWAS. However, I must say that I derive equal – if not greater – satisfaction and joy from doing research, especially when a project is going well. It is the reason that led me to become a scientist in the first place and it is the reason that drives me in my work today.

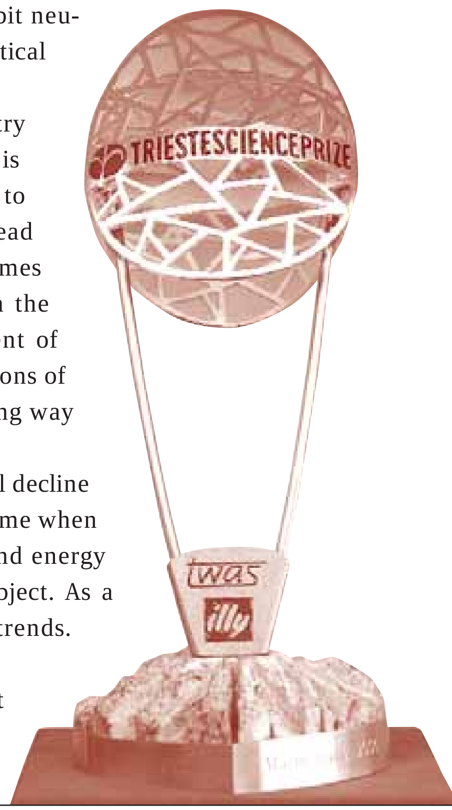
Herrera-Estrella: I too had heard of the prize and I was also completely surprised when I received an early morning call from Mohamed Hassan telling me that I had won. It is indeed a great honour to receive the Trieste Science Prize, and it is as much a tribute to my research team as it is to me. In Mexico, you often don't receive public recognition for your work until you are recognized abroad. The prize brings attention to my research and lets policy makers in Mexico know that I am doing world-class research. As a result, it likely means that I will be listened to more carefully when I speak in public about the importance of science to the nation's economic and social well being. My hope is that it will help make me a more effective spokesperson for science and that this, in turn, will help gain greater support for Mexico's scientific community.

What does the future hold for your work?

Mehta: I have recently devoted much of my research to issues related to neurodegenerative disorders. Little is understood about this age-related phenomena. Yet, it is likely to become increasingly important in the future as the world's population grows older. There is indisputable medical evidence that neuron connectivity grows weaker – and, in some cases, is lost – as people age. There is hope that new medicines could slow and perhaps reverse this process and that studies involving organic synthesis could help provide a platform for understanding the process of degeneration, and, more importantly, for doing something about it. Success won't be easy. But we have started working on the synthesis of natural products that exhibit neurotrophic activity and create 'diversity' around them for possible therapeutical development.

I also hope to spend time helping to reinvigorate interest in chemistry among young people not just in India but also around the world. India is doing well in some aspects related to chemistry, especially when it comes to drug-related process research and development. It has, for example, taken a lead role in developing and distributing generic HIV/AIDS drugs that cost 100 times less than similar drugs produced by international pharmaceutical firms in the developed world. This effort has had a profound impact on the treatment of HIV/AIDS in the developing world and has given both life and hope to millions of HIV-infected persons who had neither. However, we in India have to go a long way to become a major force in the world of chemical research.

There are some troubling developments in the field. Most notably, a global decline in enrollment in chemistry. India is no exception to what is happening. At a time when chemistry's importance to public health and well being, the environment and energy has never been greater, we are finding fewer and fewer takers on the subject. As a chemist I feel we have an obligation to try and help reverse these ominous trends.



Herrera-Estrella: I hope to deepen my research by continuing to analyse plant genomes that could be useful in increasing the efficiency of phosphorous uptake and thus limiting the amount of fertilizers necessary to grow high-yielding food crops. I also hope the same techniques can be successfully used to create food crops that are more resistant to drought. We have witnessed a remarkable increase in crop yields over the past half-century, thanks largely to the impact of the Green Revolution and its emphasis on the creation of new varieties of maize, rice and wheat through conventional plant breeding. But the impact of the Green Revolution in terms of increasing plant yields has been slowing for some time. At the same time, global population, especially in the developing world, continues to rise. Consequently, the ability to feed the world's population may well depend on advances in our understanding of the plant genome and plant genetics, and on our ability to engineer new plant varieties that can meet the environmental and climatic challenges that farmers are likely to face in the future. Scientists working in these areas face two major challenges: one is scientific – that is, to continue to conduct the research that is necessary to make advances in the field. The other is to convince the public that the work of scientists is not only safe but also necessary, and that good, not harm, can come from these efforts. These are the two areas in which I have concentrated in the past and these are the two areas that I plan to concentrate on in the future, hopefully with increasingly positive results, thanks, in some measure, to the boost in recognition that I have received by winning the Trieste Science Prize.

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