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The Future Of Medicine

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We OWE THE MOST EXCITING VISION OF THE FUTURE OF MEDICINE TO AN Austrian monk, Gregor Mendel, whose laboratory was the garden of his monastery. About 150 years ago, using the pollen of one plant to fertilise others, he observed that traits are passed on to successive generations. This sowed the seeds of a new discipline, which came to be called genetics.

We know that the traits we inherit from our ancestors are determined by our genes, which are part of our DNA, shorthand for deoxyribonucleic acid. Genes trigger the production of proteins that are essential for life processes, like insulin, which helps transform sugar in the body into energy, or erythropoietin, which is essential for the proliferation of red blood cells. DNA is the code of all life and is incredibly complex, as anything so wondrous as life should be.

It took a hundred years after Mendel for James Watson and Francis Crick to discover the structure of the DNA. We now know our DNA consists of three billion letters, each letter denoting a pair of substances that replicate twice within each one of our tens of trillions of cells. By the end of the 20th century, thanks to the labours of over 1,000 scientists in six nations across the globe, we were able to read the entire genetic code of a human being, otherwise

known as the human genome.

Announcing the completion of the Human Genome Project on June 26, 2000, the then US President Bill Clinton termed this learning of "the language in which God created life" as a profound new knowledge that would "revolutionise the diagnosis, prevention and treatment of most, if not all, human diseases".

We know now that minute genetic differences explain why among people with the same disease, some respond to certain drugs and others don't. We also know that more complex differences are, at least, partly responsible for some people being prone to a whole host of diseases including cancer, sleep disorders, Alzheimer's, atherosclerosis and diabetes. As of now, more than a quarter of the drugs that are under development are biotech products. And many more drugs of conventional chemistry are based on the increasing understanding of molecular biology (the branch of biology that studies the structure and activity of macromolecules essential to life, particularly their genetic role), which has been an integral part of drug discovery for several decades prior to the completion of the sequencing of the human genome.

If unravelling the human genome was a momentous scientific advance of the 20th century, the application of this learning to cure and, more importantly, prevent disease, will be the challenge of the 21st century. The pundits of post-genomic medicine believe, as Philip Kotler and Françoise Simon have noted, that the future of medicine will be marked by two paradigm shifts: from diagnosis and treatment to prediction and prevention, and from a mass-produced drug for a population to a designer drug tailored to an individual, based on our emerging understanding of the genetic code of humans and diseases that afflict them.

One cannot, however, ignore the complexity of achieving this vision. Our genes—30,000 of them—produce three lakh proteins, and different genes can produce different proteins at different stages in life. The rate at which these are produced could change to make them inappropriate for the complex reactions that they participate in. And there could be mutations that complicate issues further. It will necessarily take decades of scientific research to comprehend the complexities and develop effective therapies, particularly for degenerative diseases like Alzheimer's and atherosclerosis.

It is not just the lay person who gets carried away by the undoubtedly immense potential of spectacular scientific advances and genuinely believes that the future is now. Take the example of penicillin. It was so effective against the staphylococcus bacteria that no less than the then Surgeon General of the United States, William Stewart, declared in 1962: "The time has come to close the book on infectious diseases. We have basically wiped out infection from the United States." Within a decade of this assertion, 90 per cent of the staphylococci had developed resistance to penicillin.

Triumphs are sometimes temporary, but there is enough evidence that rigorous scientific research will yield notable successes. The success of science is perhaps best evidenced by the changing causes of mortality over time.

At the beginning of the 20th century, the leading causes of mortality were communicable diseases: pneumonia, tuberculosis and diarrhoea. The war against communicable diseases has not been won; AIDS and SARS are grim and sobering reminders that we have a long way to go. But the leading causes of mortality now are the non-communicable diseases led by cardiovascular diseases (CVD), which afflict 200 million people globally. Heart disease and stroke, the two principal cardiovascular diseases, kill 17 million people a year, compared to the three million who die from HIV/AIDS. 80 per cent of CVD deaths and an even greater percentage of CVD-related disability are in low and middle-income countries. As Dr. K. Srinath Reddy notes, the CVD epidemic means "that the poor among nations and the poor within nations would be the most vulnerable victims in the 21st century".

Even as one contemplates the future of medicine with the optimism born of the astounding explosion of

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knowledge, the celebration of scientific triumph, when it comes, will be of no consequence to the vast majority of people if they have no access to the medicines they need. The future of medicine has two challenges that are equally important: to harness science, and to do it at an affordable cost. Astonishing as it may seem, India is uniquely positioned to show the way before the end of the next decade.

The Indian pharmaceutical industry has already demonstrated its potential on both these dimensions. Just about thirty years ago, we were struggling to make the most basic drugs. At that time, few would have thought that India would emerge as the leading manufacturer of low-cost active pharmaceutical ingredients and generics for the world.

Today, India has the largest number of FDA-approved manufacturing facilities outside the US. Over the last several years, India has consistently made the largest number of drug master file submissions for bulk actives for generics, and over a third of the submissions are now from India. Last year, close to 20 per cent of the total filings of abbreviated new drug applications for finished dosage forms in the US were from India.

In biotechnology products, too, Indian companies have succeeded in bringing generic versions of insulin, erythropoietin and granulocyte colony stimulating factor to the market, apart from vaccines.

From generics to new drugs, from imitation to innovation, is a big leap but there is growing optimism that Indian companies have an opportunity in the R&D space.

Let me draw from my own experience and review

the progress we have made in approaching the problem of atherosclerosis, a condition where fatty deposits on arterial walls form plaque that could interfere with blood circulation. Atherosclerosis is, by far, the most important cause of heart attacks and strokes. Atherosclerosis starts early in life, indeed from childhood, progresses slowly and presents itself dramatically in middle age or later.

Atherosclerosis is currently managed by lowering low-density lipoprotein (LDL), the 'bad' cholesterol. Yet, almost half of all heart attacks and strokes occur in people with total cholesterol of less than 200 ml/dL. There is as yet no therapy that actually reverses the formation of atherosclerotic plaque, though research is going on in laboratories around the world to find a drug that can act directly on the disease process, rather than merely lowering LDL, a risk factor.

The drug farthest into clinical development is a molecule discovered by AtheroGenics, which is based on the theory that the inflammation of the arteries stimulates the production of a protein that, in turn, induces the formation of plaque. Results from Phase II clinical trials released in November 2004 evidence the reduction of plaque by an average of 2.3 per cent.

Glaxo is placing its bets on preventing the build-up of plaque by preventing the production of an enzyme believed to be responsible for the production of fatty acids from LDL, which are deposited on arterial walls and form atherosclerotic plaque. Its molecule is now in Phase II clinical trials.

Dr. Reddy's is working on a novel target based on the hypothesis that plaque build-up consists of three steps: inflammation, cell proliferation and thrombosis. This molecule is now in pre-clinical development and has shown remarkable activity in animal models on all the three steps of plaque formation, as also the regression of atherosclerotic plaque.

There are no insurmountable barriers for Indian companies acquiring the scientific expertise to make the leap from generics to innovation. The issue is one of cost, and therein lies the rub as well as the opportunity for India.

Drug discovery and development are the exclusive preserve of big pharma companies in the developed world—US, Europe and Japan—and is incredibly expensive. Big Pharma has steadily increased R&D spending to over $30 billion (Rs 1,32,000 crore) every year, up from $2 billion (Rs 8,800 crore) in 1980. On the other hand, there has been a decline in the total number of drug approvals by the FDA in recent years, with just about 20 drugs approved annually, significantly lower than the number in the 1990s. The often-quoted Tufts study estimates the pre-tax cost of developing a new drug to be $800 million (Rs 3,520 crore)—a six-fold increase in 25 years. Another study concludes that only about three out of 10 new drugs recoup the post-tax R&D spend of close to $500 million (Rs 2,200 crore).

The fundamental issue is one of containing the cost of development of new drugs. The 20th century model for drug development is not sustainable.

India is already uniquely positioned to undertake the initial phase of discovery and pre-clinical development, which is estimated to cost Big Pharma a third of their R&D spend. And this is substantiated by the experience of Dr. Reddy's Laboratories itself. Our first eight molecules in the pre-clinical stage cost us $57 million (Rs 250.8 crore).

Dwell for a minute on the costs incurred by the Big Pharma at the pre-clinical stage; make any assumption you like about the actual costs, and you will still find that we are hugely productive and cost-effective in comparison. We need to find a model that will enable the realisation of similar cost efficiencies in clinical development.

If the world's burden of disease is to be diminished, it needs science that is both good and cost-effective. India has the potential to deliver on science that is both. bt

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