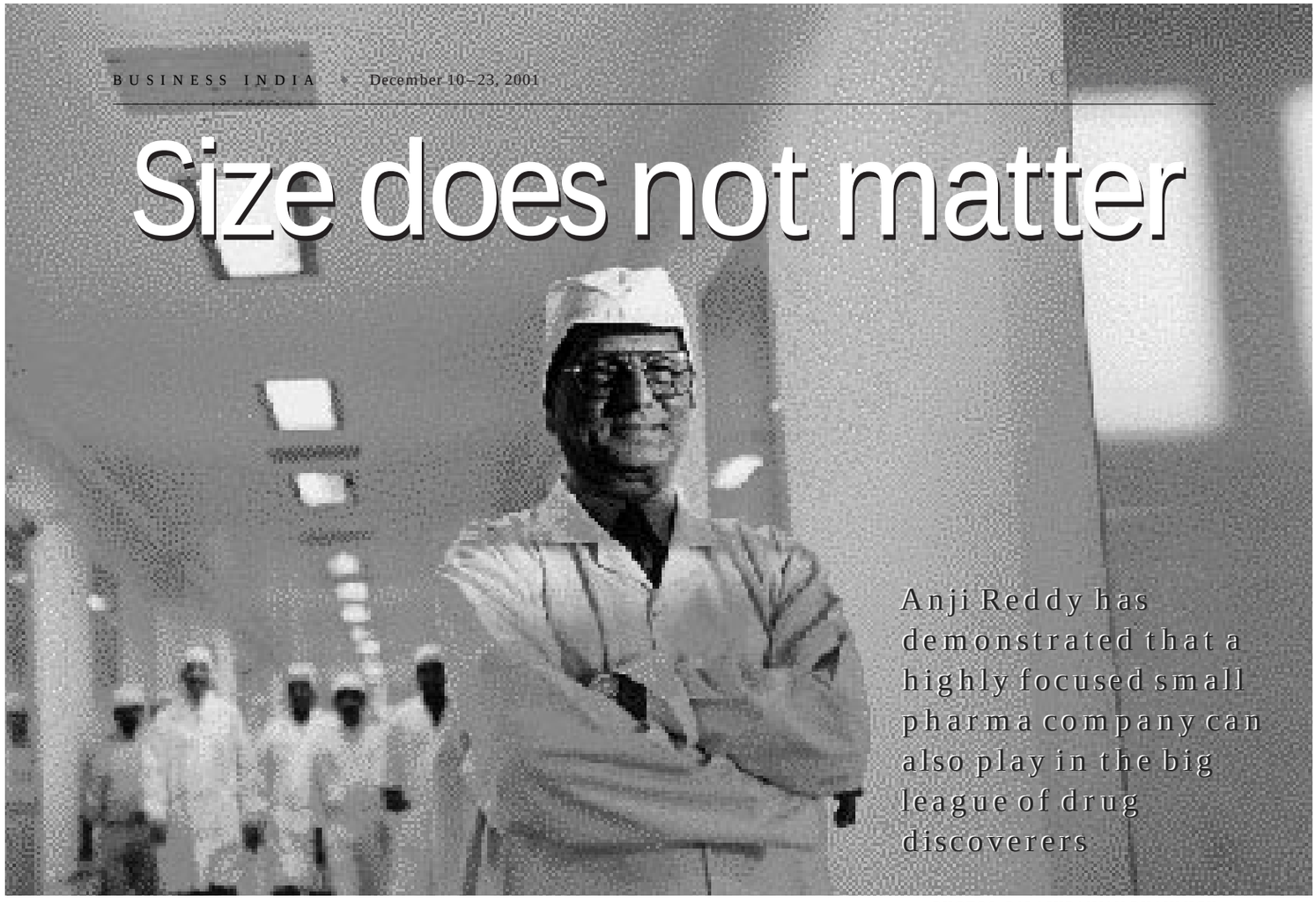
Size does not matter



Anji Reddy has demonstrated that a highly focused small pharma company can also play in the big league of drug discoverers

PHOTOS: PALASHRANJAN BHAUMICK

"Looking at the patents regime that has been accepted by 90 per cent of the nations of the world and the rapidly changing world scenario, the issue before us is not whether to accept the patent regime — it's a question of when, say 10 years, as suggested by the Dunkel draft. Basic research is an arduous task and is said to be expensive. The statistical data from Western countries are frightening. It is estimated to cost anywhere between $100 and 200 million, but it is my considered opinion that in the Indian context such an endeavour may be accomplished within Rs100 crore or so. Expenditure of this magnitude is within the reach of some companies in India."

— K. ANJI REDDY in his presidential address to the Indian Pharmaceutical Congress

Interestingly, the year K. Anji Reddy delivered the address was 1992. It is a classic example of the much-touted word "vision". Dr Reddy's Laboratories had just crossed Rs100 crore in sales that year and here was its chairman saying he could invest Rs100 crore in the next 10 years and discover new drugs! It was not an empty boast, but contained a clear-cut roadmap of process development, lead molecule discovery, and co-development and co-marketing with global majors. Obviously not many in the audience believed this bluster. Even fewer had similar plans.

But Anji Reddy went about doggedly implementing his own recipe step by step and took the risks. As a result his company, Dr Reddy's Laboratories, stands tall in the Indian pharma sector in less than 10 years. Although no drug has yet come out in the market from Reddy's stable, many are in advanced trials all over the world and major pharma companies like Novartis and Novo Nordisk are co-developing the drugs with him. If the molecules pass muster in the trials then they might even become sizable revenue-earners. There's a chance that one of them might even be a blockbuster.

Reddy started with two companies in his group Dr Reddy's Labs and Cheminor. Recently they were merged. The group has grown from a sales of Rs103 crore in1991–92 to over 10 times that figure in less than 10 years. In fact this years' performance is amazing — over 150 per cent growth in the first half. Profits too have grown from Rs10 crore in 1991–92 to over Rs300 crore in the first half this year! Reddy calls them "indecent" profits and one of the main contributors is his exclusive marketing rights to sell the blockbuster Prozac, an antidepressant, for six months in the US market. But don't let the self-deprecation deceive you; after all, when Reddy listed his company on NYSE in April 2001, it became the first pharmaceutical concern from Asia–Pacific to do so. And amidst crashing markets it has been declared the best-performing IPO on NYSE and Nasdaq this year. According to Naina Lal of Morgan Stanley, one of the main reasons for this performance is the high level of disclosure norms

Reddy has adopted. It may be a family-owned business with himself, his son, and son-in-law controlling the management, but it is setting high professional standards.

One of the reasons for Reddy's spectacular performance is his agility. "He knows when to get into a bulk drug or formulation and when to get out and move on to new ones," says M.M. Sharma, FRS, former director of UDCT Mumbai and a doyen of Indian chemical engineers. From high-purity bulk drugs Reddy has moved into branded formulations and quickly made his mark. Nise, an anti-inflammatory formulation, has quickly become one of the largest-selling brands in the Indian market. He was a pioneer in exports and has maintained a strong position and increased value by filing Advanced New Drug Applications in the US market, as in the case of Prozac mentioned earlier. To top it all are his molecules for diabetes, which are in advanced trials. Reddy is very much a man on the move now with a $100-million war chest from his ADR issue on NYSE. He has earmarked $30 million for drug discovery and $75 million for acquisitions.

No wonder that when Anji Reddy addressed the recent Ficci CEO conference on 'Building a research-based pharmaceutical company', his theme was: "Size does not matter". This time every one in the audience took this diminutive and feisty technocrat seriously.

"There has been a tradition of innovation in Reddy and other Indian companies even in process chemistry," says R.A. Mashelkar, a champion for intellectual property rights in India. "That is why they can easily become a high-quality source of off-patent generics for the rest of the world. This achievement itself is non-trivial and the oft-used statement 'Indian companies used the Indian Patent Act 1971 and its non-recognition of product patents and prospered' does not tell the full story," he adds.

Clearly if it were so easy and trivial, then why are others not doing it with generics? Secondly, Reddy's process for Ibuprofen, a popular anti-inflammatory drug, was so advanced that Ethyl Corporation, US, had to accept its superiority in front of the US Trade Representative and ask for tariffs to be put against Reddy to achieve a level playing field! Later Ranbaxy's process for Cefeclor, an anti-infective, made Eli Lily, the discoverer of the molecule, take India seriously. Similarly with Cipla's anti-Aids, anti-asthma, and anti-cancer drugs, or Lupin's anti-TB drugs. Naturally when the anthrax fear psychosis took root in the American psyche, everyone looked at Indian companies to source Ciprofloxacin. One letter by a senator in this regard was enough for Bayer to drop the price per dose from over $4 to less than a dollar overnight.

Of doctors and patents

	US Filed	US Granted	PCT*
Diabetes	40	17	15
Cancer	10	4	8
Peptic ulcer diseases	1	1	1
Inflamation	1	—	2
Bacterial infections	3	—	1
Process/polymorphs	7	1	22
Total	64	23	49

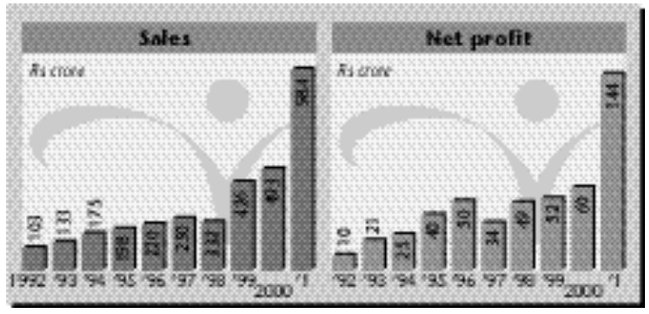
*PCT — Patent Cooperation Treaty (Headquartered in Geneva, Switzerland)

Executives at Dr Reddy's Laboratories (DRL) proudly recount an anecdote from the past about Reddy's drive towards quality and innovation even in the early days. At one time DRL was making Ibuprofen of a higher quality than Boots, the original discoverer of the molecule. When a foreign buyer came and asked if DRL could supply "Boots-quality stuff", Reddy is supposed to have replied that it would take a little time since it would need to introduce some impurities to achieve that!

That is quintessential Reddy; aggression and pride in the quality of his products. When he started making Methyldopa, a drug for hypertension, for the first time for exports in the 1980s, his goal was to at least achieve Merck's quality. Today, when his molecular hunt is yielding results, he has provided a new international profile to the Indian pharmaceutical industry, notes Kiran Mazumdar, a biotech pioneer herself.

Reddy himself travels tirelessly. At a recent medical conference in Atlanta at which he was present, his vice-president for research was asked a highly technical question. Before the V-P could compose an answer he had a Reddy cue "tell him about the *JAMA* article", referring to a complex medical article published in the Journal of the American Medical Association six months earlier. "He astonished others present by the speed at which he retrieved this highly technical information, considering that his expertise is in chemistry," says Uday Saxena, who heads Reddy's biotech research lab in the US.

Reddy is a man obsessed with his research. He looks very laid-back about everything else. "He never asks us about operations. Even when we are hard on ourselves for not achieving some target, he brushes it aside and gives the big picture, but as for research he drives them relentlessly," says G. Prasad, COO of DRL. "It's common to receive calls from him at 3 in the morning," says R. Rajgopal, who should know, since he is president of Dr Reddy's Research Foundation (DRF). Satish Reddy, MD and CEO of DRL, concurs. "He is extremely focused on research and delegates everything else to others," he says.



Satish is Reddy's son and Prasad is his son-in-law. Both joined the firm when it was in trouble in the early 1990s after an exodus of key personnel, but Reddy was planning his magnificent obsession

Reddy with son Satish (L) *and son-in-law Prasad: a perfect team*

– the molecular hunt – right back then and hence sent an SOS to both of them to come and take over operations. The temporary setback bothered him little. His ploy worked. The Reddy group grew at a record 30 per cent year-over-year for the next three years.

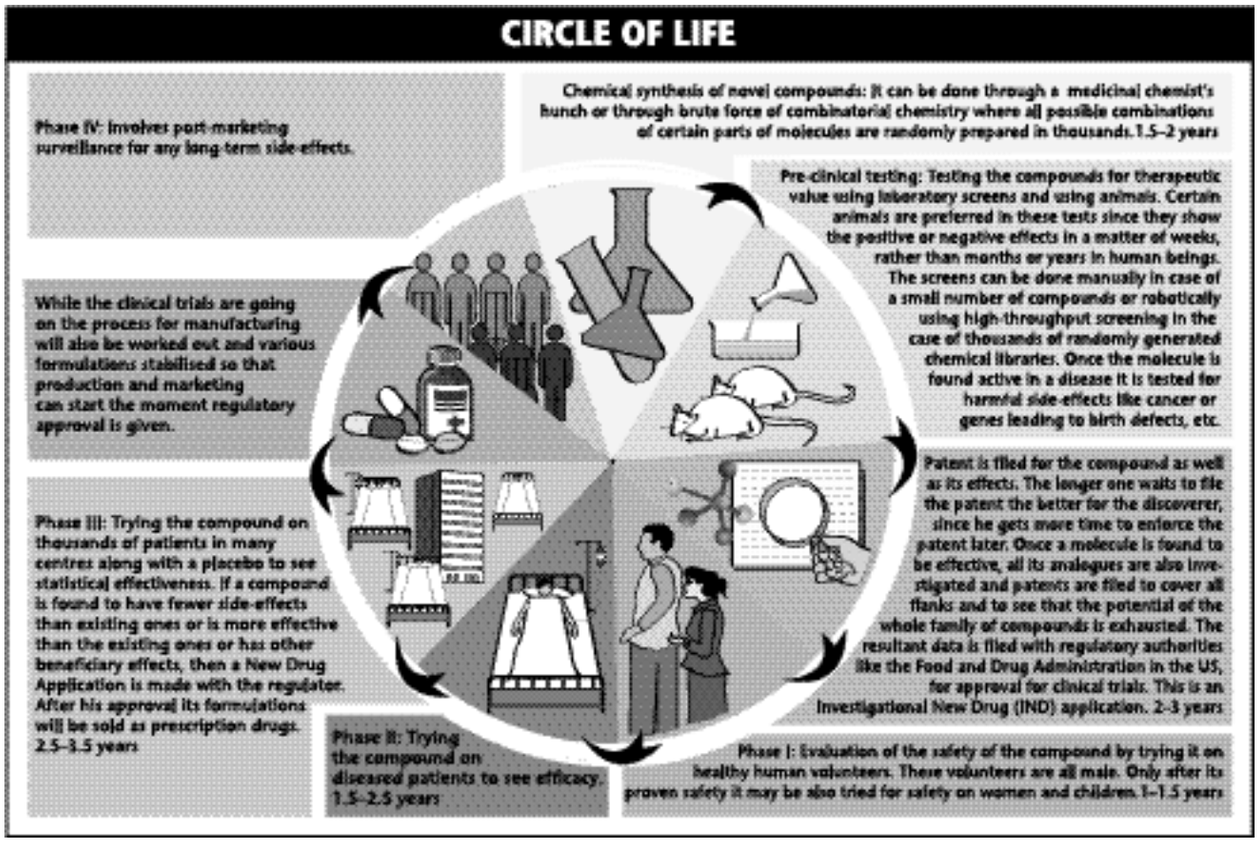
Whenever we at *Business India* have met him in the last seven years there has always been talk about a new molecule. He just assumes that you know the difference between DRF 2725 and DRF 2593. "His excitement about research is childlike. He spends hours with his grandchildren explaining to them what he is doing in the labs," says daughter Anuradha.

Sweet pain

Dr Reddy's Research Foundation today is abuzz with research on diabetes. Though it has developed other molecules which have shown anti-cancer properties, what has brought it fame and confidence, and a few million dollars besides, is diabetes.

Diabetes has been known since 1500 BC (Eber's papyrus of Egypt). Aretaeus gave it the name 'diabetes' in the second century AD. Interestingly, the main symptom of diabetes, namely a high level of sugar in urine, was described by an Indian physician of the 6th century AD who called it honeyed urine (*madhu meh*). The medical name *Diabetes mellitus* – meaning honeyed – comes from that.

There are two kinds of diabetes. Type I affects about 5–10 per cent of diabetics and is characterised by a lack of insulin production in the pancreas (a small organ behind the stomach). This condition is created by the body destroying its own beta cells in the pancreas which produce insulin. People suffering from this disease take human insulin injections. Insulin is a



hormone which helps in the absorption of glucose by liver, fat, and muscle cells. The lack of insulin leads to excess glucose in the blood, which is then passed into the urine through the kidneys. There are several dangerous effects of a high level of glucose in the blood. It can lead to deterioration of the kidney, retinal damage, early formation of cataract, and even coma. It has appropriately been called a silent killer.

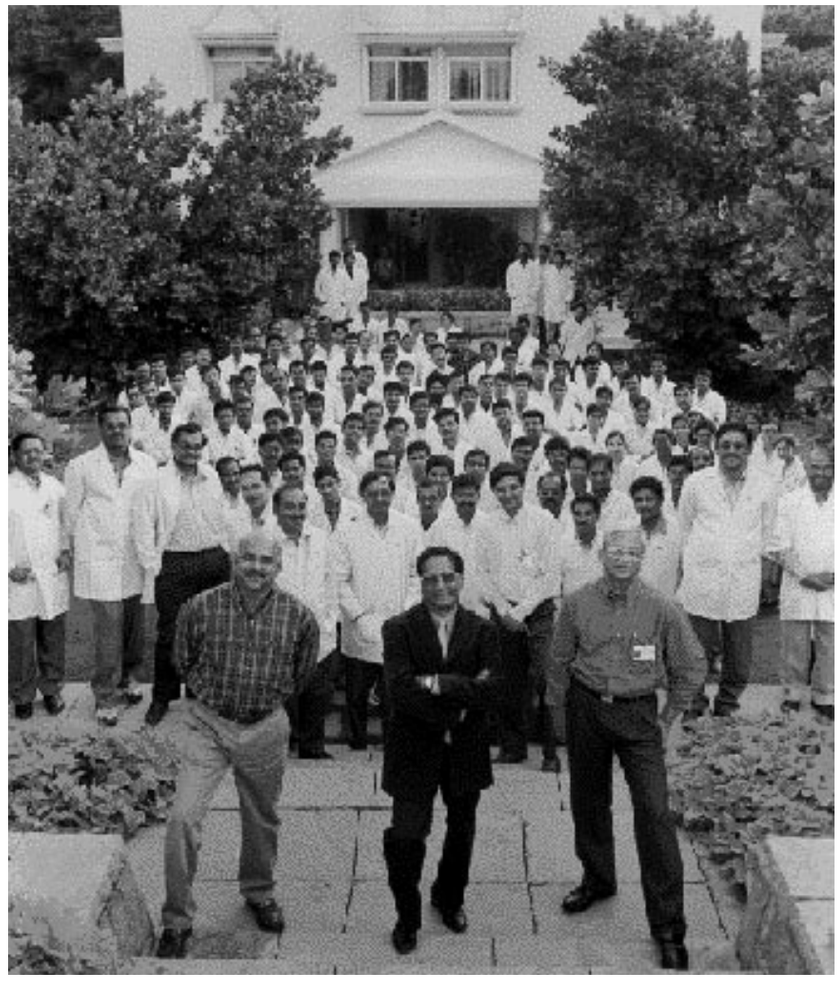
Type II diabetes is a condition where there is enough insulin produced by the pancreas but the body is able to absorb only a part of that. This affects 90 per cent of diabetics. So one therapy available is to increase the production of insulin in the body. However, if we can make the cells absorb insulin, then glucose oxidation or burning in these cells will increase. It has been discovered that there are some Peroxisone Proliferator Activator Receptors (PPARs) and those molecules that bind to PPAR gamma sensitise the body for insulin absorption. Those that bind to PPAR alpha help in reducing the triglycerides – unwanted fat in the blood – and increase the level of HDL, the so-called good cholesterol.

A Japanese company Sankyo discovered a class of compounds called troglitazones that sensitise the body for insulin. However, the molecule was withdrawn after it was found have side-effects on liver enzymes. Dr Reddy, who himself suffers from type II diabetes, was interested when he saw the activity of troglitazones and pushed his team to come up with better molecules. He had a hunch that activity could be increased with some clever substitutions within the molecule.

The result was a new molecule DRF 2593, which was at least 40 times more potent than the existent insulin sensitisers, but it too had a side-effect on liver enzymes. This molecule was licensed to Novo Nordisk, a leading player in diabetes. However, when better drugs by other companies with hardly any effect on the liver came into the market, Novo put DRF 2593 on the backburner.

When Novo representatives came to DRF, again, before making his presentation, Rajgopal asked them to write down a wishlist. The Novo people said, "We would love to have a insulin sensitiser which does not have side effects on the liver and which lowers lipids in the blood." Rajgopal said "We've got it" and presented data about a new compound codenamed DRF 2725!

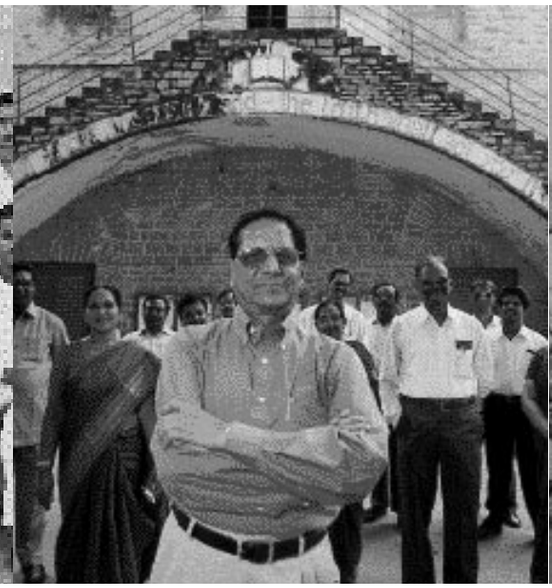
This new molecule not only sensitised the body to insulin absorption but also reduced the triglycerides in blood, thus hitting two targets with one arrow. It caused a stir and Novo Nordisk double-checked the data in its labs and signed a licensing agreement forthwith. Today it has passed the first two phases and is in a global Phase III trials in which nearly 4,000 patients are involved in about 35 centres. If all goes well, this molecule can come out as a drug for diabetes and cholesterol patients by 2003. It has been estimated that this class of dual-active drugs can increase the life expectancy of diabetics by 10–15 years.



At the cutting edge: Reddy with his platoon of scientists at the DRF campus in Hyderabad

Having tasted success once, the DRF team is charged up and has come out with another molecule DRF 4158, which is even more potent than DRF 2725 and is dual-active. This molecule has been licensed to Novartis and is undergoing Phase I trials.

Just a few weeks ago DRF announced a new molecule DRF 4832 at the American Heart Association's conference and caused quite a flutter since this new molecule is in fact triple-active — that is, it also increases HDL (good cholesterol)! Clearly, world pharma majors are looking at DRF as a possible source of novel molecules and exciting drug candidates. Today the Camelot the DRF team is chasing is



A class photograph at Andhra Christian College. Reddy received his early grooming here — With the principal and staff on a recent visit

a triple-active molecule effective in type II diabetes which elevates good cholesterol and also lowers the bad cholesterol effectively like the statins.

Paradigm shift

The paradigm of secretive pharma research under one roof at a giant company has changed considerably as pharma majors go shopping to shore up their drug pipelines. They want to have several drugs under trial and be sure of the sustainability of revenue growth. The old "not invented here" syndrome is very much in the decline. They are scouring labs, universities, and research-based companies worldwide for new and interesting molecules. One of the reasons for a spate of mergers in global big pharma is this hunt for pipelines and synergies in R&D. Meanwhile, some companies like Sankyo and DRF are showing that small companies can come up with very interesting molecules.

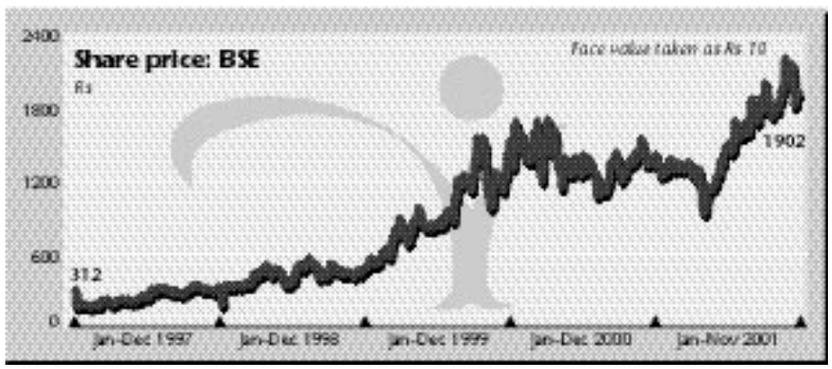
Many molecules of DRF may be 'me-too' molecules — that is, they may not have extended the boundaries of medical research and might have followed somebody else's pioneering work. But that hardly matters. If a me-too is more effective or less toxic or has other beneficial effects, it may turn out to be a bigger hit than the original. For example ranitidine – brand name Zantac – by Glaxo was a me-too after the original cemetidine by another company. But it contributed over $2 billion to Glaxo's bottomline for several years. Similarly Enalapril, an ACE inhibitor, and Atenolol, a beta-blocker, were also me-toos that became blockbusters.

Me-too molecules may not get you the Nobel Prize, but the research involved in finding them successfully is non-trivial. Once a molecule is found to be effective, all its analogues – lookalikes (siblings and cousins) – are also investigated and patents filed to cover all the flanks and to see that the potential of the whole family of compounds is exhausted. Thus an original discoverer would have already covered all his flanks when another hopeful like DRF starts looking at it.

The good news for 40 million Indian diabetics is that Reddy's molecules may be available in India at an affordable price when they come into the market despite being the latest patented drugs, since Reddy holds the marketing rights for India.

Today DRF has applied for over 65 patents and is making presentations to several drug majors. Dr Janardhan Reddy, a professor at Northwestern University and one of the leading experts in PPAR, says: "Anji Reddy has a childlike curiosity which is reflected in a twinkle in his eye and a twitch of mischief in his smile. He is a maverick and an iconoclast." It is this curiosity and iconoclasm that have taken Reddy where he is.

What does a "visionary" mean? Is it that others around him are blind? No, most people can only see what is around them. They cannot see what is not there or what is in the distant



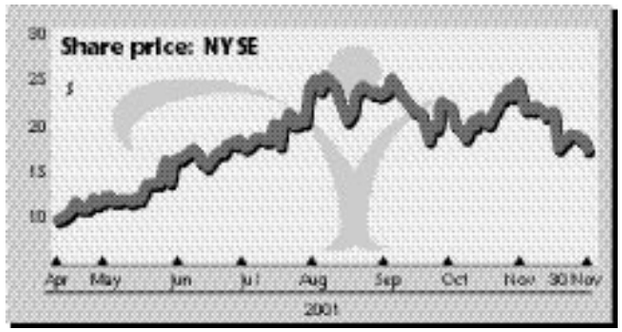
From the family album — With his mother in Tadapalle, the village of his childhood

future. A visionary can. "My father took me to their farmhouse on the outskirts of Hyderabad one day and said, 'Here will be a modern research lab for drug discovery'. It was barren land. I also knew as a medicinal chemist at Purdue University, how complex the process of drug discovery is since I myself was involved in some projects. I was sceptical to say the least," recalls Satish Reddy. Satish was not alone; many in the pharma industry too weren't willing to believe. But today all he receives is accolades for his vision and drive. A proud M.M. Sharma beams about his distinguished alumnus: "He has made the impossible possible through his R&D."

His peers in the pharma industry acknowledge his leap. "He has successfully turned his company into a research-based pharma company, says Habil Khorakiwala of Wockhardt. "Dr Anji Reddy has been a pathbreaker for the Indian pharma industry in this millennium. He has demonstrated that the Indian pharma industry is capable of holding its own in global markets with high-quality revenue streams that can be reinvested for research. I also admire his fortitude in quietly handling risk and uncertainty; and for ably guiding his company in an increasingly exacting international marketplace," says Dalip Shanghvi of Sun Pharma.

Praise from peers in other sectors too is plentiful. "Dr Reddy's Laboratories is one of the few companies in India with a strong focus on drug discovery, and a track record of success in global markets," says Mukesh Ambani of Reliance Industries. "He is passionate about whatever he does and pursues a clear vision," says Ramalinga Raju of Satyam Computers.

For Andhra Pradesh Chief Minister Chandrababu Naidu, Reddy is a showpiece to promote Hyderabad as a new centre for knowledge-based industries. "It's a matter of pride for us that Dr Reddy's Laboratories was the first non-Japanese Asian/Pacific pharma company to be listed on the New York Stock Exchange. Dr Anji Reddy belongs to that rare breed of people who dare to dream and make their dreams come true," says Naidu.



Reddy showed promise in research long ago. According to his elder sister Rajamma, he used to open up germinating beans when he was four to see how the seedling was coming out. Reddy spent his childhood in a small village across the Krishna river near Vijayawada, where his father was a prosperous farmer growing turmeric. His early education took place in Hindu College and Andhra Christian College, Guntur. He has really fond memories of his days there. When we accompanied him to these places he was distressed to find that his chemistry lab had been shifted from its old premises at Andhra Christian College. A sentimental Reddy told the principal and head of the department there, "I will give you all the modern equipment to build a modern analytical lab. My only request is that you restore my old lab to the same premises."

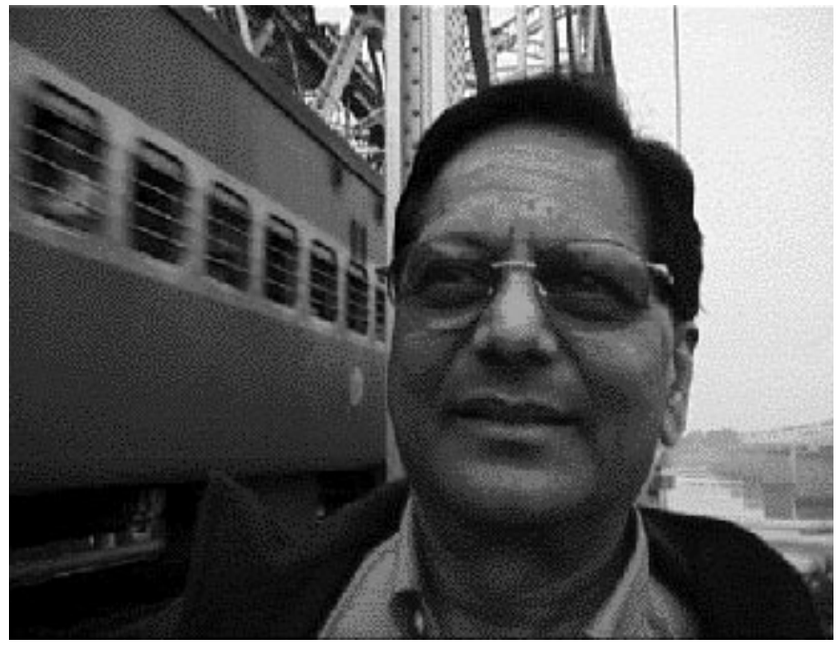
After his BSc in Guntur, Reddy joined UDCT in Mumbai to study pharmacy. He was greatly influenced by the atmosphere at UDCT. "The academia there was very close to industry. I liked it," recalls the entrepreneur in him. However, he then

went to National Chemical Laboratory, Pune, to study for a doctoral degree. This time he decided to switch his field from pharmacy to chemical engineering, since bulk drug manufacture was mostly chemical engineering. Not an easy switch. "In fact I was very hesitant to take him on as a student," recalls L.K. Doraiswamy, a distinguished chemical engineer who later became the director of NCL and is currently Anson Marston Distinguished Professor in Engineering Emeritus at Iowa State University.

But Reddy did not disappoint him. "Indeed, I have rarely taken a better decision in recruiting students, and even scientists. He not only produced a very fine thesis, but also worked on a side problem to produce a paper in a matter of weeks which to this day is quoted in practically all books and reviews on Properties Estimation. The Reddy–Doraiswamy equation developed by him (with little assistance from me) for predicting liquid diffusivities has lost none of its original flavour," he declares.

However Reddy was a very focused man: his eyes were set on industry and not academe. He joined IDPL, the newly established bulk drug manufacturing unit in the public sector in Hyderabad. After a few years there he could not stand the non-entrepreneurial culture and quit to form a company with little seed money called Uniloyds. It made a successful foray into pharma, but his partner wanted control though he had no idea about the business. Reddy quickly cashed his share and joined an old classmate C.R. Reddy to found Standard Organics (SOL). SOL under Reddy's leadership soon became the largest producer of sulfamethaxazole and even won an R&D award from the Indian Chemical Manufacturers Association. But his partner had other plans on diversification and Reddy came out of it to establish Dr Reddy's Lab and Cheminor for bulk drug manufacture in the mid-1980s.

The early 1990s, however, saw an upheaval in both DRL and Cheminor. "Probably he is too trusting [in delegating responsibility] for his own good," says Prasad, who was asked to take over leadership at Cheminor. "It was tough. Leading people had left to start another company and there was a legal battle with Ethyl Corporation. I wish I had some handholding," recalls Prasad. But Prasad soon brought things under control and the rest is history. "He is a forest man and I am a trees man," he comments. "Now I see that one needs to see both the forest and the trees."



A bridge to the future, a journey of continual transformation

Looks like Reddy too knew his weaknesses and that's why brought in two excellent operational people, Prasad and Satish. Though they happen to be his son-in-law and son, they have built a genuinely professional team around him and there is none of the family business syndrome. Reddy is free to pursue his obsession with research and proving all the Cassandras, who were saying that only big pharma companies with research budgets of a billion dollars could do drug discovery, dead wrong. He's well on his way to doing it.

Anji is a short form for *Anjaneya* or Hanuman, who was the village deity of Tadapalle and every family had an Anji in it. According to the epic *Ramayan*, Anjaneya carried the mountain of *gandhamadan* to cure the battle-wounded Laxman, since he did not know the taxonomy of the herb *sanjeevini* that was needed. Anji Reddy, however, does very focused research into molecules and does not bring a mountain. When we visited his village he showed us the railway bridge he used to cross over the Krishna in spate to reach Vijayawada on the other side. The old bridge has vanished and modern bridges are in place. As we walked with him across the bridge he was able to recall many an old story with brief intermissions for conversation with his research teams in Hyderabad and Atlanta on his mobile phone. His executive assistant meanwhile informed him about his appearance in a cover story in *Forbes Global*, the first Indian businessman to be spotlighted by that magazine.

"The word 'visionary' is overused, but if it applies to anyone applies to Dr Reddy. I have little doubt that he will, step by step, build one of the most important international pharmaceutical companies in the world," says Bruce Carter, formerly of Novo Nordisk and now at Zymo Genetics.

As we walked with him we realised that Reddy is truly crossing a bridge in his career. From a generics manufacturer to a research-based company, from an Indian footprint to a global one.

◆ SHIVANAND KANAVI with MEERA SHENOY