The years since have shown just how important the discovery of the structure of DNA was, not just in answering the ancient question of how like begets like, but in providing the key to a mechanistic understanding of processes that until then could only be described, not explained. And as researchers learned how to manipulate DNA, it became an indispensable tool for research — and for the creation of whole new classes of therapeutics.

To mark the 50th anniversary of the discovery of the structure of DNA, BioPharm International turned to a distinguished group of scientists, both academic researchers and the leaders of biotech companies, to ask what DNA has meant to them and what they think its future will be, both in science and in biotechnology. What follows is an edited version of their answers.

ESCAPED OUR NOTICE

There’s this famous sentence in Watson and Crick’s first DNA paper: “It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.”

There are a lot of things Jim and Francis couldn’t possibly have noticed at the time, things that were literally unimaginable at the time. Here are four:
One has to do with the DNA structure. At the time of the discovery of the double helix, no one had any idea there would be huge stretches of DNA that would have all these repeat elements. The assumption was that you’d have a stretch of DNA and that would be a gene, and then there would be another stretch of DNA and that would be another gene, and no one thought that there would be huge amounts of DNA that didn’t code for protein.

The second is related to that: RNA splicing—the idea that a gene can be split into different pieces that then have to be assembled by splicing. Of course that’s very important biologically—alternative splicing may be the factor that enables you to generate lots and lots of proteins from what seems to be a small number of genes. That was a complete bombshell when it was discovered in 1976.

The next two are things that you might have wanted to do at the time of the discovery of the double helix, but you would have been sent to a lunatic asylum if you’d seriously proposed them. One is the tremendous understanding we are now getting of the process of development. Then there’s the ability to manipulate genes. In the early 1950s you could move genes using bacteriophage from one bacterial cell to another. But the idea that you could use in vitro mutagenesis to change a single base in a gene would have been beyond belief. And the idea that you could create mice with a specific mutation in one specific place in a gene would have been beyond science fiction—much less credible than the idea that you could put a man on the moon.

— JAN WITKOWSKI, executive director of the Banbury Center at Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

EVERYTHING TALKS TO EVERYTHING

You can connect the dots all the way from Watson and Crick’s first paper to where we are today, but today the questions about DNA deal with genomes—human genomes and other genomes. Understanding genomes goes way beyond the double helix and involves important contributions from chemistry and computer science and physics. In my own world, that means using small molecules from chemistry to modulate the functions of the proteins to which these small molecules bind, and doing so across the genome so we can dissect the networks that are so critical to the organisms that result from these genomes.

It’s a bit like the Internet with proteins for servers. In the 1990s we heard a lot about signal-pathways. Today, I’m convinced that pathways are simply an artifact of a reductionist approach. If you try to simplify your experiment so you only see protein A talking to protein B and then B to C, it sort of looks like a pathway. But when you take a step back and look at the entire system, as most scientists have in recent years, you realize that in fact everything talks to everything. The key is to understand these networks with their nodes, or the servers, that are like CNN.com—that’s the protein that’s truly sitting at a critical node to which nearly every other protein is connected—versus the more obscure servers that are serving but one or two proteins encoded within the genome.

This network analysis is obviously going to be key to gaining a true understanding of genes and genomes. My own belief is that until recent years a kind of overlooked element of this had been the magical property of small molecules that unobtrusively permeate living systems and instantaneously modulate function. These are the rheostats we have that flip switches on and off—and even partly on and partly off. They are absolutely essential to understanding complex living networks, and they should have a profound effect on drug discovery.

— STUART SCHREIBER, a Morris Loeb Professor at Harvard University, where he is chair of the department of chemistry and chemical biology. He is also an investigator at the Howard Hughes Medical Institute, Chevy Chase, MD.

THE POLYMORPHISMS OF HUMANS

By knowing the mechanism of drug action—what the target is and how the target is manipulated by the presence of the drug—we have a better shot at making better, more specific drugs. That’s one part of the equation. The other part has to do with the polymorphisms of humans.
We're not all the same. We really haven't faced that fact yet, but we are starting to.

Science goes through these different phases. For 15 or 20 years, a lot of the focus was on the universality of genetic information and the double strand DNA. We were fascinated by the fact that everything worked more or less the same. I could do a reaction in fruit flies. I could do it in a worm, or in mice, or in humans. But as you look at any system with finer and finer detail you start to see difference. As we get into finer granularity of the picture of what's going on with gene expression, we're going to focus more and more on the differences.

Here's a practical example: Drug approvals are difficult partly because we have to do animal studies, and the animal studies don't always reflect what we want to know about what's going on in humans. That's because of the differences. We kind of know that on a basic level, but we don't know what those differences are. If we knew in detail the differences between a mouse and a human for a particular problem, then at least it would be more predictable. Right now we don't quite have that, other than knowing there probably is a difference. Or maybe sometimes there isn't much difference. Wouldn't it be nice to know, so you could say, "This animal model really makes sense because it really is working exactly the way it's supposed to in humans, whereas that animal model doesn't."

I think we're right in that transition. More and more, pharmaceutical and biotech companies are taking deep biological information as their starting point. I think that anyone who's going into drug discovery and product development without that kind of information is stepping on soft ground.

In most diseases either you're making too much of something, you're making too little, or it's the wrong version. The question is how do you flip these biological switches back and forth so you don't get into a situation where you're making too much of something or too little. Conceptually it's pretty clear where we have to go. In practice you're talking about a much more complicated issue — not just the science itself but the regulatory aspects and what you might call the Wall Street component. Because all three of those things have to coincide in order for a company to succeed. I think that's a very tall order.

I tend to be optimistic, because I think when you have more information, your chances of success go up. I see it all the time in my laboratory. There are so many pathways and so many possible points of intervention. Which ones are you going to choose? The biggest problem is figuring out what you don't want to do.

— ROBERT TJIAN, professor of biochemistry and molecular biology at the University of California–Berkeley and an investigator at the Howard Hughes Medical Institute, Chevy Chase, MD. He is a founder of Tularik, a biopharmaceutical company based in South San Francisco.

WHO LIKES TO LOAD THE PCR MACHINE?

I'm sort of a romantic at heart. The fact that there's lots and lots of money out there to be made is interesting to me because I have to make a living, but it's not a driving factor the way that intellectual curiosity is. It's kind of cruel to say I don't care about diseases — and kind of stupid, because one of these days you're going to get one and you're going to wish there was some kind of nice biochemical answer for it. But for the general practitioner of the field, like I think of myself, a lot of the excitement has passed out of DNA research.

Today, we have an immensity of techniques available to approach just about any kind of problem you can define. The machines are there. It's a matter of getting the grants or the investment, hiring the people, getting the machines, and doing it. It does have its moments, because you do find things every now and then. But you don't really find things that blow you away. You find things you've been looking for already. Who likes to load up the PCR machine? You kind of know what you're going to get.

What I'm more interested in today is arranging chemicals to do things that you might want them to. Right now I'm interested in the immune system because there's a whole lot of stuff there that nobody has figured out yet. It's a field where the words don't really tell you what the things are because they really haven't known until recently what a lot of the things they have words for are.

I just discovered that everyone — humans, old world monkeys, and apes — has an antibody for a particular epitope, alpha(1,3) galactosyl. That epitope probably was on the surface of some parasite that was giving us a lot of trouble and caused everything that led to human and old world moneys and apes to drop an enzyme called alpha(1,3)galactosyl transferase. That affected a whole lot of stuff we made but allowed us to make antibodies to that epitope. About one percent of our immune response is directed toward that, and no one knows exactly what it's for. That's been known in a way for 70 years, but the real details were only discovered in the 1990s.

"Science goes through phases. For 15 or 20 years, the focus was on the universality of genetic information. We’re going to focus a lot more on the differences."

Robert Tjian
"It's always good to be a novice, not just because you have the luck of the novice, but because it's fun.”
Kary Mullis

It’s a whole part of the body that I don’t know about, that I’m learning about. It’s always good to be a novice, not just because you have the luck of the novice, but because it’s fun.
— KARY MULLIS, 1993 Nobel Prize winner for the invention of the polymerase chain reaction. He has consulted on nucleic acid chemistry for more than a dozen corporations, including Angenics, Cytometrics, Abbott Labs, and Milligen/Biosearch. He is currently vice president and director of molecular biology at Burstein Technologies in Irvine, CA.

TIME TO MOVE BEYOND PROTEINS

I don’t think people understood what the DNA code would turn out to be as simple, straightforward, and universal as it is. One of the first really great surprises about DNA was its universality, that all organisms use the same code, and therefore all organisms are fundamentally made of interchangeable parts. Another major surprise was the fact that RNA could be turned into DNA. A third major surprise was how plastic genomes are — that they seem to be able to expand, contract, and invert, in response to real-time selection. Certainly in cancers that happens, and it happens in our immune system.

Another major surprise in the whole world of nucleic acids came from the realization that very likely RNA preceded DNA, as the stuff of life. The best theory for the origin of life today is that there was an RNA world before there was a DNA world, and we can see the effects of that in many aspects of what we thought were relatively passive molecules playing very active roles in the nucleic acid life of a cell. We have come to appreciate that it is almost certain that DNA arose from living structures patterned on RNA as a genetic material, not DNA, and that was a real paradigm shift in the way we think about origins of life and evolution.

The biggest useful surprise about DNA was that the code of life is shared among all organisms. That has given rise to the biotechnology industry, where we can produce human proteins and human antibodies or other substances such as human peptides in bacteria, yeast, and other organisms.

Now, though, it’s time for the pharmaceutical industry to move beyond just proteins and antibodies. It’s time to seriously consider medicines based on cells and stem cells.

I believe that the most exciting discoveries and the most exciting area of biology in the next 50 years will be human embryology and stem cell research. If I were a young scientist today that’s where I would work, because I think the era of DNA as the cutting edge science is drawing to a close and the era of embryology and stem cell research is just beginning.

The discovery of DNA solved an ancient mystery, why like begets like. But there are remaining great mysteries of life. One is the process of memory and thought. Today we exist in the same state of ignorance of the fundamental processes of memory and thought that we existed in with respect to the physical basis for inheritance before the discovery of the structure of DNA. The second is the intricate means by which the unfolding takes place from the fertilized egg to an adult human being. Those are the remaining two great mysteries of life, which I believe we will have the answers to 50 years hence.
— WILLIAM HASELTINE, chairman and CEO of Human Genome Sciences in Rockville, MD, a biopharmaceutical company he founded in 1992. Haseltine was a professor at Dana-Farber Cancer Institute, Harvard Medical School and Harvard School of Public Health from 1976 to 1993 and has founded seven biotechnology companies, each in a different area of medicine.
BILOGY IS AN INFORMATION SCIENCE

The structure of DNA gave us insights into the biological functioning of DNA as a molecule and how it replicated itself and copied messenger RNA and corrected errors and so forth. Even more fundamental was the observation that the information in chromosomes, the core genomic information of organisms, was digital — it was linear and had a four-letter code rather than the two-letter code of information technology.

We’ve made enormous strides in understanding the mechanisms by which DNA operates and ultimately in defining the source code — the sequence of the genome. The essential challenge now is taking DNA sequence information and translating it into knowledge about how the organism actually works, deciphering the digital code, and coming to understand how it operates in the context of the rich environment of the biology of living creatures.

We have the digital source code that’s become available for humans and other organisms, a genetic parts list. We’ve gained some fundamental insights into the fact that biology is really an informational science. And we can now employ the global high throughput tools of genomics and proteomics and start gathering information in a hypothesis-driven sense about biological systems.

The ultimate objective is to be able to take various types of biological information — DNA, RNA, protein–protein interactions, protein–DNA interactions, and so forth — integrate it into graphical pictures about how systems operate, and ultimately translate these graphical pictures into mathematical constructs that describe the behavior of systems and give us the ability to do two things: predict what the behavior of a system would be given any particular genetic or environmental perturbation, and redesign the system so it has completely different properties.

If you look at the digital core of the genome, there are really two major languages, one is the language of the genes that make the molecular machines, that catalyze chemistry of life. The other is the language of gene regulatory networks that actually specify the behavior of the genes.

It is these gene regulatory networks that really are going to hold the keys to understanding evolution, differentiation, development, and finally physiology. Although we know a great deal about genes and can define many if not most of them and we still know very little about the regulatory networks that operate to control their behavior.

— LEROY HOOD, a pioneer of the automated sequencing of DNA. He is president and director of the Institute for Systems Biology in Seattle, professor-at-large at the Keck Graduate Institute of Applied Life Sciences in Claremont, CA, and former affiliate professor in the departments of bioengineering, computer science, immunology, and molecular biotechnology at the University of Washington, Seattle.

YOU’VE FINALLY GOT THE PARTS LIST

In my research, we try to understand how packets move in neurons and how that movement process might fail in diseases such as Alzheimer’s and Huntington’s and perhaps Parkinson’s. So, while in some ways you might say what we do is cellular neuroscience, we couldn’t live without recombinant DNA technology. We routinely make knockout mutants in embryonic stem cells. We sequence mutant genes in fruit flies. Everything we do is based in genetics, and genetics can’t exist anymore without the ability to manipulate DNA. It’s all part of the revolution that was touched off by the discovery of the structure.

Prior to recombinant DNA there were 80 zillion mutants made in fruit flies, but you didn’t know what components were encoded by those genes.

— Lawrence Goldstein

"Prior to recombinant DNA there were 80 zillion mutants made in fruit flies, but you didn’t know what components were encoded by those genes.”

Lawrence Goldstein
Throughout 2003, a wide variety of events will commemorate the 50th anniversary of the discovery of the double helix structure of DNA. The following are just a sampling. For a comprehensive look at the history and the current events, visit Cold Spring Harbor Laboratory’s dedicated website, www.DNA50.org.

26 February–2 March 2003 The Biology of DNA. Cold Spring Harbor, NY. A scientific meeting organized by Jan Witkowski and David Stewart and cosponsored by Columbia University and Rockefeller University. Sessions will cover replication, recombination, mutagenesis, DNA repair, genomes, DNA topology, and chromosome dynamics. Speakers will include leaders of the biotechnology industry.

http://meetings.cshl.org/2003helix.htm

3 March 2003 Exploiting Genetic Knowledge: 50 Years on from Crick and Watson. Newcastle-upon-Tyne, UK. A British Council International Networking Event organized by Professor John Burn and Dr. Tom Shakespeare. Speakers will include Sir Richard Sykes, Sir John Sulston, Professor Dorothy Wertz, and Ms. Suzi Leather. Topics will include the state of the science, regulation, commercialization, ethical dilemmas, and public engagement.

www.britishcouncil.org

6 March 2003 DNA and Culture: Out of the Test Tube and Into the Limelight. London, UK. On the 50th anniversary of Crick and Watson's breakthrough, Matt Ridley, Jon Turney, Alexander F. Markham, and Marek Kohn investigate the wider impact of the discovery of DNA on areas outside the life sciences. How have physics, technology, arts and letters, popular culture, the law, and the social sciences responded to this momentous development?

www.dna50.org.uk

14–15 April 2003 50 Years of DNA: From Double Helix to Health. webcast. A two day scientific symposium on DNA organized by The National Human Genome Research Institute (NHGRI). Participants including James Watson, Francis Collins, and members of the International Human Genome Sequencing Consortium will describe the science and history of the Human Genome Project and explore the future of science and medicine made possible by breakthroughs in genomic science. As part of the event, NHGRI will unveil its new scientific plan.

www.genome.gov

23–24 April 2003 Replicating and Reshaping DNA: A Celebration of the Jubilee of the Double Helix. London, UK. Sessions will address the processes that replicate, recombine, and repair DNA, and discuss their interrelationships and how they contribute to genome instability and tumorigenesis.

www.royalsoc.ac.uk

25 April 2003 DNA Day. Various locations across the United States. High schools throughout the United States will utilize such tools as a taped educational event with high school biology students, the National Human Genome Research Institute (NHGRI) multimedia education kit, and the American Society of Human Genetics mentors network. High schools are encouraged to make this the culmination of a month-long focus on genetics.

www.genome.gov

6–11 July 2003 XIX International Congress of Genetics. Melbourne, Australia. 280 speakers will address the Congress and 54 symposia will be held. The annual conferences of the Association for the Advancement of Animal Breeding and Genetics, the Genetics Society of Australia, and the Human Genetics Society of Australasia will be incorporated into the Congress. A celebration of the 50th anniversary of the discovery of the structure of DNA will feature James D. Watson and other luminaries who made seminal discoveries in molecular genetics, including Seymour Benzer, Sydney Brenner, Robin Holliday, H. Gobind Khorana, and Charles Yanofsky.

www.geneticscongress2003.com

20–24 July 2003 Annual Meeting of the International Congress of Biochemistry and Molecular Biology. Toronto, Canada. The meeting will include a public session, “DNA: The Next 50 Years.” Speakers will include DNA pioneer Sydney Brenner; Lap-Chee Tsui, Geneticist-in-Chief at the Hospital for Sick Children, Toronto; and Timothy Caulfield, director of the Health Law Institute, University of Alberta.

www.iubmb2003.org

I think the future offers an opportunity for small companies because they can respond to changing needs much better than big companies can. They’re the nimble, aggressive, creative force in the industry. My friends and I started a company; from a standing start, it got its first product into the clinic in four and a half years. It took a lot of hard work and probably a little luck, too. But my view is that things can work and work pretty well, especially if you use all these technologies appropriately. I’m a real optimist about this stuff. The expectations are higher today, but the kinds of things you can do are better, and why would we not want that?

— LAWRENCE GOLDSTEIN, a professor in the department of cellular and molecular medicine at the University of California–San Diego and an investigator at the Howard Hughes Medical Institute, Chevy Chase, MD. He is a cofounder of the biopharmaceutical firm Cytokinetics in South San Francisco, CA.

A TIME FRAME WE CAN’T MEET
In the 1960s and 70s when I was a student, and then a graduate student, interested in the brain — how it was put together, how it wired itself up, how it worked — in those days, one had all these dreams about what one would like to know without knowing exactly how we were going to get...
there. And then, during the 1970s, came the whole revolution of recombinant DNA, which gradually spilled over into neuroscience. It was an exciting time, to be among the first wave to ask how nerve cells are specified, how they hook up with one another and find one another, at a real mechanistic kind of level.

I was a professor for 25 years between Stanford and Berkeley, and I could have kept doing that for the rest of my career. But I like the thrill of new things. I saw the private sector as the chance to see whether the science can really be translated into therapeutics and into the clinic and into patients, and to see if I could really do it rather than just talk about it. So here I am, the CEO of a company, and every day I’m learning about things I vaguely knew anything about before — clinical trials, direct discovery, how to make compounds, how to actually get them with the right properties to take to FDA so you can take them into humans, thinking about and enjoying immensely all of things I never knew anything about a few years ago.

I’ve learned that one danger we face is that we — the whole scientific community — get so excited about discoveries and their potential that we effectively promise society that something’s going to happen on a time frame we can’t meet. Look at the history since the molecular biology revolution. Was the discovery of oncogenes important? Of course. But the promise was made to society that cancer was going to be cured within 10 years. It’s 25 years later. Has cancer been cured? No. Are any of us surprised?

We’re going through the same thing right now with stem cells. When I read about it in the paper, I often almost get embarrassed, because society is being led to believe that we might have Parkinson’s patients or patients who need a new hunk of liver cured in a couple of years. When you think how far we’ve come since the discovery of the double helix, it’s clear that all of this stuff is going to have a huge impact, but it’s just going to take time

— Corey Goodman, cofounder, president, and CEO of Renovis, a South San Francisco, CA-based biopharmaceutical company focused on neurological diseases. He was a professor of neuroscience at the University of California–Berkeley, an investigator at the Howard Hughes Medical Institute in Chevy Chase, MD, and a cofounder of the genomics-based drug discovery company Exelixis in South San Francisco, CA.