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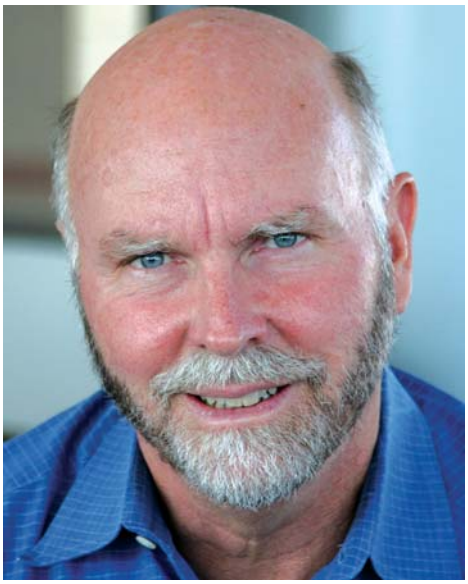
CRITICAL FOCUS

Brian J. Ford

Inventing Life or Reality?

If there's a subject of conversation for microscopists this summer it must be the synthesized cell. "Artificial life" has reportedly been created in a test tube by Dr. J. Craig Venter, that archvillain or inspired genius, depending on where you stand. The newspapers are reporting that Venter has created synthetic cells. Radio news is calling this as astonishing as splitting the atom. Science magazines are professing that this momentous development will allow us to create microbes that could perform miracles, like digesting the BP oil spill in the Gulf of Mexico. And television is proclaiming that we could even create – think of this! – entirely new species. Search on YouTube for "Venter synthetic life" for a flavor of what I am saying.

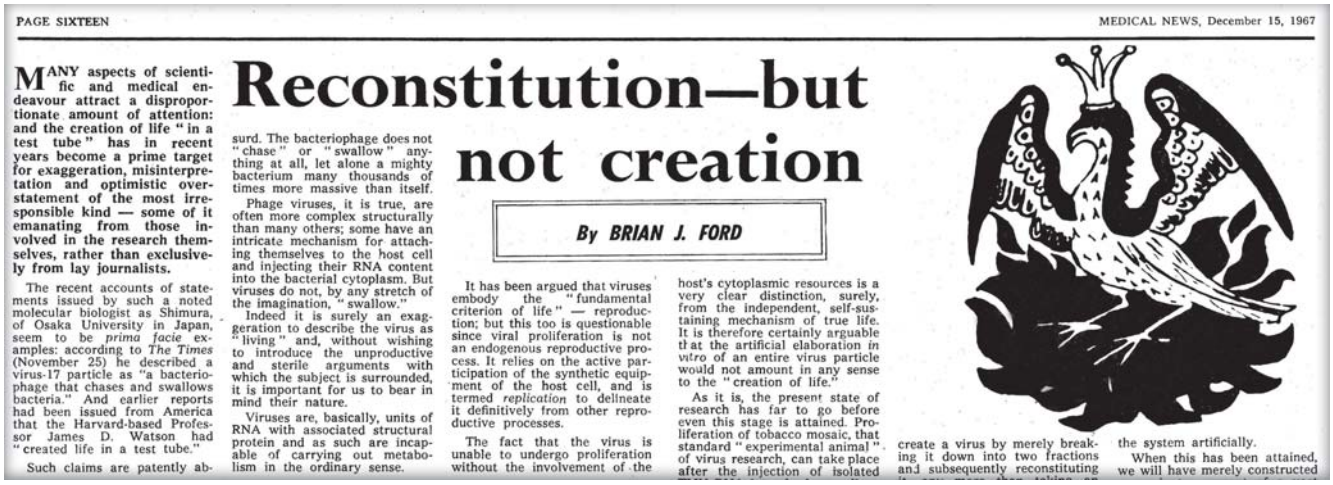
Creation of life in a test tube has in recent years become a prime target for exaggeration of the most irresponsible kind.



Dr. J. Craig Venter

Here is an antidote that says: "The creation of life 'in a test-tube' has in recent years become a prime target for exaggeration, misinterpretation and optimistic overstatement of the most irresponsible kind – some of it emanating from those involved in the research themselves, rather than exclusively from lay journalists." This comes from my article for the British magazine *Medical News*, for the issue dated December 15, 1967. Not much has changed over the past 43 years. The *Medical News* article was a response to research by Dr. Arthur Kornberg of Stanford University who took DNA from the phage virus φX174 and used purified DNA polymerase to replicate the DNA and produce synthetic infective viruses. Although the virus he obtained was indeed infective, it was not a synthesis *de novo*; it was reconstitution.

Geneticists and molecular biologists are prone to exaggeration. That's where their funding comes from. Reporters were told that sequencing the human genome heralded an era of miraculous cures and the "ultimate answer" to the nature of life. The era has not arrived, and the public feel disillusioned. Since the committees who grant the finance are also members of the public, the funders are increasingly inclined to pull the plug. Cutting-edge research is measured in terms of column inches in a newspaper. Half a century ago it was not considered correct to court comment, and research scientists who found their work in the media were embarrassed. Not any



PAGE SIXTEEN MEDICAL NEWS, December 15, 1967

Reconstitution—but not creation

By BRIAN J. FORD

MANY aspects of scientific and medical endeavour attract a disproportionate amount of attention: and the creation of life "in a test tube" has in recent years become a prime target for exaggeration, misinterpretation and optimistic overstatement of the most irresponsible kind — some of it emanating from those involved in the research themselves, rather than exclusively from lay journalists.

The recent accounts of statements issued by such a noted molecular biologist as Shimura, of Osaka University in Japan, seem to be *prima facie* examples: according to *The Times* (November 25) he described a virus-17 particle as "a bacteriophage that chases and swallows bacteria." And earlier reports had been issued from America that the Harvard-based Professor James D. Watson had "created life in a test tube."

Such claims are patently absurd. The bacteriophage does not "chase" or "swallow" anything at all, let alone a mighty bacterium many thousands of times more massive than itself.

Phage viruses, it is true, are often more complex structurally than many others; some have an intricate mechanism for attaching themselves to the host cell and injecting their RNA content into the bacterial cytoplasm. But viruses do not, by any stretch of the imagination, "swallow."

Indeed it is surely an exaggeration to describe the virus as "living" and, without wishing to introduce the unproductive and sterile arguments with which the subject is surrounded, it is important for us to bear in mind their nature.

Viruses are, basically, units of RNA with associated structural protein and as such are incapable of carrying out metabolism in the ordinary sense.

It has been argued that viruses embody the "fundamental criterion of life" — reproduction; but this too is questionable since viral proliferation is not an endogenous reproductive process. It relies on the active participation of the synthetic equipment of the host cell, and is termed *replication* to delineate it definitively from other reproductive processes.

The fact that the virus is unable to undergo proliferation without the involvement of the host's cytoplasmic resources is a very clear distinction, surely, from the independent, self-sustaining mechanism of true life. It is therefore certainly arguable that at the artificial elaboration *in vitro* of an entire virus particle would not amount in any sense to the "creation of life."

As it is, the present state of research has far to go before even this stage is attained. Proliferation of tobacco mosaic, that standard "experimental animal" of virus research, can take place after the injection of isolated

create a virus by merely breaking it down into two fractions and subsequently reconstituting

the system artificially.

When this has been attained, we will have merely constructed

Medical News published this essay in 1967, and, surprisingly, much of it remains relevant today. The article took geneticists to task for overstating the implications of their work, and reminded the reader that the study of genes was only a minor part of our understanding of life. Because of its size, the article was filed in two halves, and was re-assembled for publication in this paper 43 years later.

longer – since your career in scientific research is now measured in terms of impact, researchers encourage the media to report their work. It encourages overstatement at every turn and "synthetic life" is one of the catch-phrases of the age.

It is not new. There was a flurry of "life creation" stories in 1899, when the German biologist Dr. Jacques Loeb induced an unfertilized sea urchin egg to divide and develop into a larva by treating it with salt solution. Loeb went on to talk about "the artificial production of living matter," and the *Boston Herald* ran a story about his research: "Creation of Life. Lower Animals Produced by Chemical Means." At the 1912 meeting of the British Association for the Advancement of Science, the president, Dr. Edward Albert Sharpey-Schäfer, said that this work raised the possibility of the "synthesis of living matter."

DAWN OF GENETICS

The next big year for synthetic biology was 1953. At the University of Chicago, Dr. Stanley L. Miller and Dr. Harold C. Urey carried out their ground-breaking experiment in which they heated inorganic chemicals in a chamber fitted with electrodes that emitted sparks. They began with water, methane, ammonia and hydrogen, and detected eight amino acids in the result. An analysis of the resulting soup two years ago found traces of 22 amino acids. It was a resounding success and showed that prebiotic molecules could be manufactured without the intervention of life. Naturally, it made headlines.

It was also in 1953 that the era of genetics was triggered from Cambridge, England. The young British physicist Francis Crick and the American would-be ornithologist James D. Watson – who first attracted media attention as 12-year-old contestant on the Quiz Kids radio show in Chicago – were always aware of the need publicly to promulgate their work.

I never met Crick, though I was introduced to Watson in London. He was a crisp and opinionated figure, not the kind of person to whom you might immediately warm. He and Crick had worked privately on the structure of DNA because they knew that this project had the lure of major celebrity, and even a Nobel Prize. Watson had attended a seminar by the brilliant Rosalind Franklin in November 1951, when she showed her X-ray diffraction experiments revealing that DNA had a helical structure. At Cambridge, Watson and Crick began to build a model of the molecule but their head of department, Sir Lawrence Bragg, told them to stop as the work was being done elsewhere by people with established track records and it was considered unethical for the Cambridge duo to gatecrash the field.

In America, Linus Pauling had been working on DNA for years and sent a draft of his paper to his son Peter, who was studying in England and was a friend of Watson's, to whom he passed on the results in January 1953. Two days later, Watson was shown a print of Franklin's latest X-ray diffraction image. Watson wrote in his book *The Double Helix* (1968): "The instant I saw the picture my mouth fell open and my pulse began to race." The main laboratory research work on DNA in England was being carried out by Franklin

Photo courtesy of Ruth Duskin Feldman

James Watson (center) attracted media attention as a 12-year-old contestant on the Quiz Kids radio show in Chicago. As a youngster, he aspired to be an ornithologist.

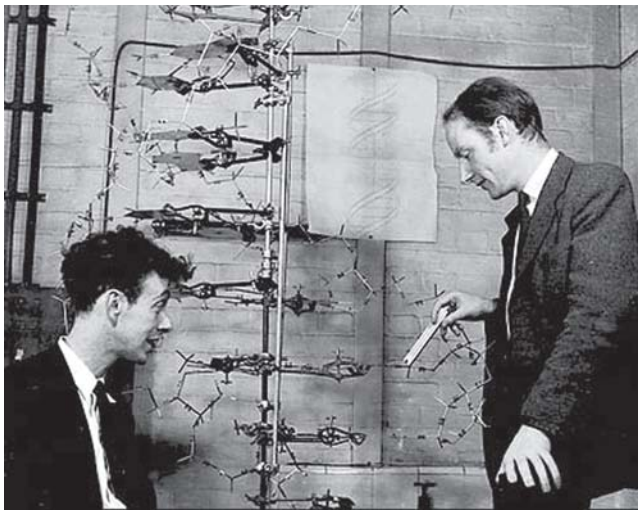


Photo by Antony Barrington Brown

This is one of several popular images of Watson (left) and Crick admiring their new molecular model. The scientists were eager for publicity, but an early news report for *Time* magazine was rejected.

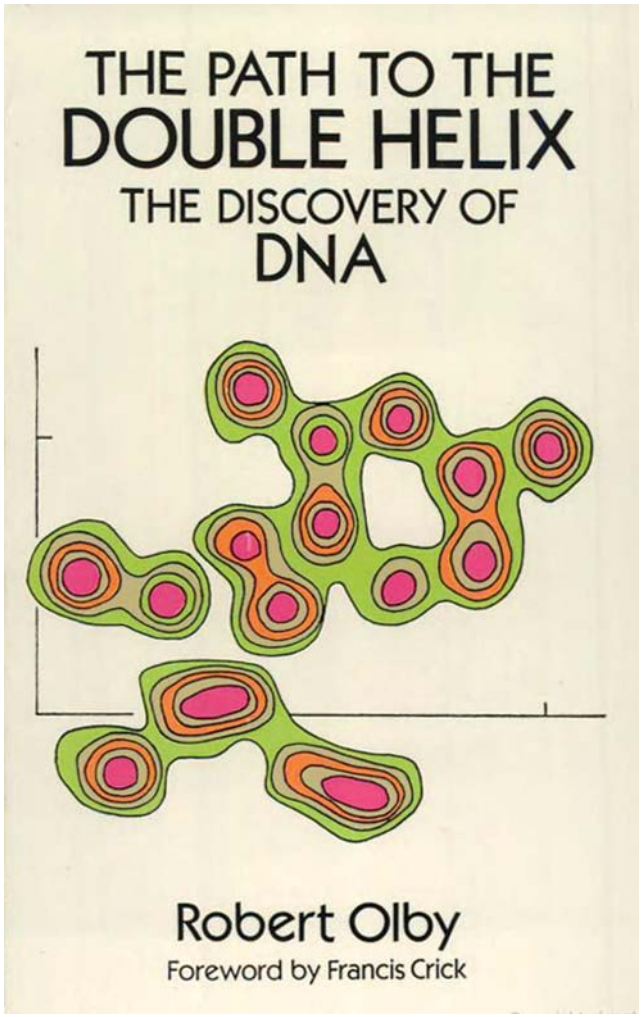
and Maurice Wilkins. The final clues that solved the problem of the structure were passed to Crick in an unpublished research report by Professor Max Perutz, the man who founded molecular biology. Once Watson and Crick had all the data they needed they finished building their model of DNA and went to the Cambridge pub, the Eagle, where Crick announced in the bar: "We have found the secret of life."

EAGER FOR PUBLICITY

Franklin and Wilkins knew nothing of it and carried on with their projects. Meanwhile, Watson and Crick were excited about their success and the quarrel they had with the department was forgotten. Indeed, Sir Lawrence Bragg, director of the Cavendish Laboratory, made the first formal announcement of their results at the Solvay Conference on proteins in Belgium on April 8, 1953. It produced a little interest among the delegates and was not reported further. Watson and Crick submitted a paper to *Nature*, published on April 25, 1953. Without doing any of the laboratory research, the pair scooped the news.

They were eager for publicity, and a young photographer named Antony Barrington Brown photographed them with their molecular model. It is reported that he was a reporter from *Time* magazine, but the truth is more prosaic. He had a friend who was hoping to sell the story to the magazine, but they didn't use it. Brown said: "My 'snaps' came out well enough and my friend fired them with his story off to *Time*, but they never used it and sent me half a guinea [about one dollar] for my pains." His picture is one of the most widely reprinted images from the period, yet nobody has discovered where it was first published.

The unraveling of the molecule is a complex story of success that has been told in detail by Robert Olby in his celebrated book *The Path to the Double Helix – The Discovery of DNA* (published in 1974 and reissued by Dover in 1994). Olby took pains to investigate all sides of the story, and his book remains a classic. Their success did not make Watson and Crick popular with fellow scientists. The most acerbic comment at the time came from the pen of Erwin Chargaff, who had laid the groundwork for DNA analysis. He met both men and wrote of them in terms that are far from flattering. First Crick and then Watson: "One 35 years old, with the looks of a fading racing tout . . . an incessant falsetto voice, with occasional nuggets gleaming in the turbid stream of prattle. The other quite undeveloped . . . a grin, more sly than sheepish . . . a gawky young figure. I never met two men who knew so little and aspired to so much. They told me they wanted to construct a helix, a polynucleotide to rival Pauling's helix. They talked so much about "pitch" that I remember I wrote it down afterwards, 'Two pitchmen in search of a helix'." In later life he viewed them in a more considered light: "Crick and Watson are very different. Watson is now a very able, effective administrator. In that respect he represents the American entrepreneurial type very

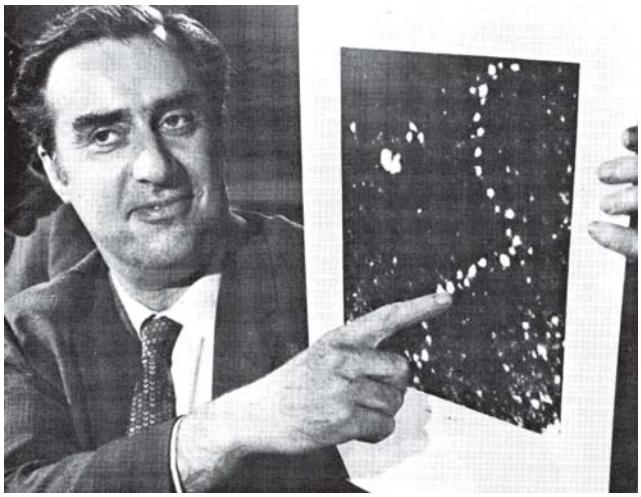


Dover Publications

First published in 1974, *The Path to the Double Helix – The Discovery of DNA* by Dr. Robert Olby candidly recounts the rivalry and opportunism that surrounded the unraveling of the double-helix molecule.

well. Crick is very different: brighter than Watson, but he talks a lot, and so he talks a lot of nonsense." Watson was certainly bright – he went to the University of Chicago aged just 15.

It proved that what matters more than the quality of the research is the way it is presented. That great British microscopist Albert Crewe was quick to jump upon the bandwagon when working on his high-voltage electron microscope at the University of Chicago. Crewe was born in Bradford, England, in 1927 and came to the University of Chicago at the age of 31, moving to Argonne National Laboratory in 1958. Three years later he became its director. He moved back to the University of Chicago in 1967 to work on his field



Dr. Albert Crewe's imaging of individual thorium atoms with his field emmission scanning transmission electron microscope attracted worldwide attention after it was heralded as the "tool to be useful in research on a cure for cancer."

emission scanning microscope, and in 1970 he succeeded in taking images of individual atoms of thorium. This was immediately featured in the press.

COURTING THE MEDIA

Individual atoms had first been imaged by Erwin Muller and his Ph.D. student Kanwar Bahadurin at Penn State as long ago as 1955. Their famous picture of the atoms in a tungsten needle tip had been published around the world. How did Crewe capture the headlines, since imaging atoms was by that time old news? It was simple. "Professor Crewe," reported the university, "believes that his discovery may be useful in finding a cure for cancer." Bingo. Atoms? Cancer? There is no greater connection between imaging atoms and curing cancer than between plotting protozoa and banishing acne, but this unique concatenation of buzzwords was all the press needed, and journalists rallied to the cause. Crewe sent me one of his first prints and I published it as an example of how exaggeration can allow the scientist to claim headlines. It appeared in my satirical book *Nonscience (or How to Rule the World)*, published in London and Buenos Aires in 1971.

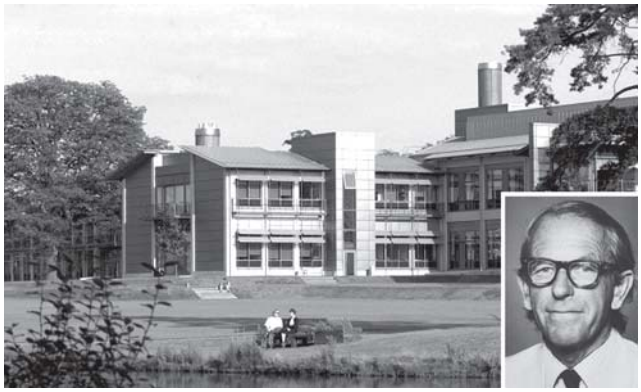
"Creating life in a test tube" continued to be a surefire way to seize the attention. Back in 1967, I was writing about research on phage virus φX174, where, as we have seen, teams had found how to disassemble the genome and reassemble it. The title of my article was "Reconstitution, but not Creation" and I concluded by arguing that: "One does not create a virus by merely

breaking it down into two fractions and subsequently reconstituting it, any more than taking an alarm clock to pieces and reassembling it is equivalent to designing and constructing a timepiece." In 1964, a French biologist named Rostand described the fertilization of ova in vitro as the "creation of embryonic life." During the following year, I noted that the *Sunday Times* of London reported work by an American scientist named Spiegelman that was headlined "Man-made life." Forty years ago there was a lot of life being "created in test tubes" by ingenious scientists – but only by those who manipulated the media.

Others are far more circumspect. The key to analyzing DNA was unraveled by Fred Sanger who was modest, wise, yet unassuming. He developed the "Sanger Reagent," fluorodinitrobenzene (FDNB). It reacted with exposed amino groups in the insulin molecule and in particular with the amino group at one end of the polypeptide chain. He then partially hydrolyzed the protein into short peptides with an acid or enzyme. This mixture was ingeniously fractionated on a sheet of filter paper: first by electrophoresis running up the sheet and then by chromatography across the separated components.

The fractions ended up well-spread across the paper sheet giving Sanger the locations he called "fingerprints." From a series of these procedures he could build up the structure of insulin, which won him a Nobel Prize in 1958. He moved on to apply similar reasoning to DNA, and by 1975 had developed the dideoxy technique for sequencing DNA, known as the "Sanger Method." It was the familiar phage virus φX174 that was the first to be sequenced, and the result was announced in 1977. It was so significant that it won him a second Nobel Prize for chemistry in 1980, and automated versions of this technique led to the decoding of the human genome.

When Sanger retired, he did not embark on the worldwide lecture tour you might expect, but settled back home to cultivate his garden in Swaffham Bulbeck near Cambridge, England. Sanger shunned the high life and knew where his priorities lay. Although his work was crucially important, it was never designed to catch the public attention. So great is the esteem in which he is held, that his fellow scientists were determined to recognize his contribution. His name was immortalized through the Sanger Institute at Cambridge, England, which was one of the main partners in the international Human Genome Project. The BRCA2 gene, which is related to human breast cancer, was one of their early discoveries, and the center is a leading source of genomic research.



Dr. Frederick Sanger developed the dideoxy technique for sequencing DNA, known as the Sanger Method. His work is perpetuated through the Wellcome Trust Sanger Institute, a center of human genome research in Cambridge, England.

VENTER TRIUMPHANT

But let us return to Craig Venter. He ran a rival version of the Human Genome Project, using private capital that funded his own Institute for Genomic Research of Rockville, Maryland, and produced a result that showed how a single, driven individual could match the greatest global enterprise. He used a "shotgun" sequencing approach that split DNA into large numbers of small fragments, which could be analyzed simultaneously and later reassembled. This gave him the edge in terms of speed and economy, so that Venter was able to announce his research at the same time as the global consortium. It was a triumphant moment for private enterprise genetics, and Venter went on to found his own establishment, the J. Craig Venter Institute.

Such an organization demands large sums of money to operate, and Venter patents new developments whenever they have the potential to become a commercial commodity. At the Sanger Institute, by contrast, the base-pair sequences light up on a scrolling digital screen in reception as they are read by the machines, thus providing instant publication and preventing anyone from patenting new genes. This whole area is fraught with confusion. Some six years ago, Myriad Genetics of Salt Lake City obtained the exclusive rights to test for the BRCA1 and BRCA2 mutations. They marketed their combined test under the name BRACAnalysis and charged $350 for a single test (which was useful for families where there was a specific known mutation) up to $2,975 for a full sequence of both genes.

In Europe, the authorities are less inclined to allow patents for naturally occurring phenomena, yet after

The author with Nobel Prize-winning biologist Sir Paul Nurse (right). Commenting on the Venter Institute's work on synthesized DNA, Nurse told the BBC, "I don't think it is a major breakthrough. It is not the creation of synthetic life."

years of argument they did allow a patent for Myriad Genetics. The Institut Curie in Paris said: "This is disappointing after our seven-year fight even though we have managed to reduce the scope of the patents. We had all been freely testing the BRCA genes since they were first described in the early 1990s." Clinics across Europe simply ignored the new patent. Matters became more interesting on March 29, 2010 when a New York decision declared that the patents invalid. A syndicate headed by the Association for Molecular Pathology challenged Myriad Genetics, and New York District Judge Robert Sweet ruled that genes do not constitute patentable subject matter. The patents issued are "directed to a law of nature and were therefore improperly granted." This is a small decision with large implications. About 20% of known human genes have been patented, and those may now be rescinded. Although this has not made much impact in the media, this is a major revolution and it imposes dramatic changes on independent genetics laboratories. A major tranche of their funding is set to evaporate like gasoline on a hot sidewalk.

Venter has, meanwhile, pressed ahead with research into synthetic DNA and has now announced a microorganism with a human-made genome. The news is full of breathless announcements about synthetic biology and its potential impact. This is all so new, they say. Or is it? For years we have been moving towards synthesizing oligonucleotides (short lengths of DNA with 20 or so base pairs). Hundreds of scientists are working on this research around the world, indeed the First International Meeting on Synthetic Biology (it was called "Synthetic Biology 1.0") took place in Cambridge, Massachusetts, as long ago as June 2004. By that time people were using bubble-jet techniques to print microarrays, and in the following year, Bio-Rad Laboratories of Hercules, California, launched their BioOdyssey Calligrapher, which could print oligonucleotides, proteins or cell lysates at will (*Nature* vol. 437 p. 1198, October 20, 2005). By June 2007, when the Synthetic Biology 3.0 meeting was held in Zurich, Switzerland, Dr. Ham Smith from the Venter Institute was there with a paper entitled, "The Quest for a Minimal Cell: a Synthetic Genomics Approach."

DNA FOR THE MASSES

So we have been able to mass-produce DNA for years. It is a tremendous advance, and the research teams who have achieved these things are worthy of admiration; but it is not the latest news. And although Venter has claimed the headlines, we must bear in mind the many teams who have been working towards this common goal. We can use the cold objectivity of Google to gain an immediate insight into "market penetration." There are now nearly 400,000 hits on Google for "synthetic biology," but add "Venter" to the search and the total falls to 148,000. This is very obviously a worldwide venture, not a one-man show.

Software and equipment is now widely available to add base pairs in a chosen sequence, so that home-made DNA strands have become available to all. In September 2008, Carolyn V. Johnson wrote a report for MIT's newspaper *The Tech* entitled "As Synthetic Biology Becomes Affordable, Amateur Labs Thrive," and she described people with equipment sourced through Craigslist setting up home labs to try it. Also in 2008, TED.com published the video of a lecture headlined: "Craig Venter is on the verge of creating synthetic life." He wasn't, but the report did show that synthetic DNA was clearly becoming closer. *Science Express* marked a milestone event in February 2008, when they published a paper from Venter and his colleagues (with 17 authors!) entitled "Complete Chemical Synthesis, Assembly, and Cloning of a *Mycoplasma genitalium* Genome."

Everyone seems to be doing it, for it is now a million times cheaper to sequence genes than it was 10 years ago. Last year, *Nucleic Acids Research* (Vol. 37, No. 20, pp. 6984-6990) featured a paper from the Venter Institute's Dr. Daniel G. Gibson showing that *Saccharo-*

syntheticbiology.org

The Synthetic Biology Web site features this graphic of amoeboid cells transmuting into gear wheels. This is a relic of the Cartesian philosophy of living organisms as machines. A similar mechanistic concept underpins modern genetics and molecular biology, but living cells have complex capacities for cognition and decision-making and are far more refined than this simple image implies.

myces cerevisiae can assemble more than 38 overlapping oligonucleotides in a single event. These oligonucleotides, which can overlap by 20 base pairs, can comprise as many as 200 nucleotides. It was only a matter of time before further steps were taken, and now the team has announced that they have reproduced a version of synthesized DNA that functions in a donor cell. It is a further step along the way, but was presented as earth-shattering.

With refreshing objectivity, National Public Radio reporter Joe Palca (in "Something Understood" on May 20, 2010) put it in context: "This isn't really a new life form, says Jim Collins, a synthetic biologist at Boston University. Its genome is a stitched-together copy of the DNA of an organism that exists in nature. Collins says Venter has created something remarkable, but it's not creating life. 'We don't know enough biology to create or synthesize life,' says Collins. 'I think we're far removed from understanding how [you would] build a truly artificial genome from scratch.'"

The best commentary to put it all in context came the next day from British biologist Sir Paul Nurse, who won a Nobel Prize in 2001 and became the ninth president of Rockefeller University, New York, in 2003. I know Nurse as a dynamic, thoughtful and immensely insightful cell biologist. He set the reports into perspective. "I don't think it is a major breakthrough," he told the BBC. "It is not the creation of synthetic life." Even so, the commentator added the possibility of creating cells that could "eat waste oil."

A program discussing it all is on the BBC as I write these words, and it is being heralded as a major revolution that will allow us to (among other things) make hydrocarbon fuel for the centuries ahead. Wherever you look, people are claiming that synthetic organisms could perform miracles, and the news is full of reports of "creating new species". In a 2007 interview with Venter, *New Scientist* had asked, "Assuming you can make synthetic bacteria, what will you do with them?" Venter replied, "Over the next 20 years, synthetic genomics is going to become the standard for making anything. The chemical industry will depend on it. Hopefully, a large part of the energy industry will depend on it. We really need to find an alternative to taking carbon out of the ground, burning it, and putting it into the atmosphere. That is the single biggest contribution I could make." Chargaff had made a typically acidic comment in an interview that appeared in the science magazine *Omni* (June 1985). He told their reporter: "In my opinion present-day science, especially biological science, is a direct symptom of the decline of the west – all this shameless talk about creating and multiplying will be put down as the barbarism of the 20th century."

A REALITY CHECK

Somewhere between the brash boasting, the crisp criticism and the meticulous research lies the truth, and it is important for all of us who work with the microscope that we set the situation into context. These developments are steps up a ladder. They are not isolated, brain-bending explosions of new knowledge. Venter has produced some impressive research but still makes the mistake of seeing cells as nothing more than little factories. You can see resonances of this attitude in the artwork that the Synthetic Biology conferences have on their Web site, syntheticbiology.org. This shows amoeboid cells transmuting into the gear wheels of a machine.

As we have seen, Venter's team is busily looking at minimal cells and how one might perhaps create cells to order, but this is misconceived. As well as performing chemical transformations, cells sense their surroundings, make decisions and live lives of surprising complexity. Venter, like so many modern cell biologists, is trapped in the Cartesian philosophy of the organism as machine.

The second error is in the talk of creating new organisms to dispose of oil, create food or generate fuel. Cells have been doing that since long before humans were a spark in evolution's eye. Where do these people assume our food and fuels came from? Our oil is the legacy of living microorganisms that existed 100 million years ago. My own belief is that algae, like diatoms, synthesized oil droplets that have come down to us as crude oil. One can observe golden-hued droplets within diatoms today, though there is next to none remaining in the diatomaceous rocks of Lompoc, California, where geologists discovered vast deposits of the glassy frustules.

People are so attracted by the idea of creating something new that they never consider what abounds in nature.

In any event, cells have made the fuels that we are squandering. The conversion of plant remains to rock-hard, shiny deposits of coal was done by living cells that reduced the carbohydrates to carbon. We do not need modern synthetic DNA to produce the organisms of which everyone is dreaming; they already exist. It is just that we continue to ignore them. People are so attracted by the idea of creating something new that they have never troubled to consider those that abound in nature.

If cells can make oil, what about creating cells that could dispose of it? Once more, nature has got there first. Oil-degrading bacteria exist in abundance. Many species of genera including *Micrococcus, Bacillus, Pseudomonas, Corynebacterium* and *Flavobacterium* have been shown to degrade oil under the right circumstances. There's a good paper in *Journal of Basic Microbiology* (Vol. 42:4, July 2002), but the idea is much older than that. Back in 1967, I took part in discussions with a team of BP scientists. We evolved an intriguing idea of mixing oil-degrading bacterial cultures with light ash of the kind that comes from coal-burning power plants. The microbe-bearing ash would be treated with silicone and nutriments, and then tipped out onto the sea upwind of a spillage. The hydrophobic nature of the treated dust would bind it to the oil so it would form heavy lumps that would sink to the sea-bed, out of the way of the surface waters, to be digested by the bacteria. The pollution would disappear and the problem was solved – at least on paper.

It is not so simple in practice. First, the presence of the glutinous globs across the seabed would have a destructive effect on marine life and would prevent trawlers from fishing the beds by clogging their nets. Secondly, the bacteria – though well able to degrade the oil in theory – would find it too cold down there to act rapidly, and oxygen tensions would also be reduced at depth. Without copious supplies of oxygen there would be little chance to oxidize the oil. And so the idea was flawed from the start. BP hoped to patent the process, but I published an account of it which amounted to a prior declaration, and this prevented the patent application from proceeding. Better versions of the "miraculous" cells that Venter hopes to construct are readily available in nature, without the need for them to be produced by geneticists. Synthetic cells won't necessarily do the job. Finding cells to perform a task is one thing – getting the right conditions in which they can operate is something else entirely.

PREHISTORIC GENETICS

And finally, what about the creation of new life – or even a completely new species? Many reporters have claimed this as the greatest potential breakthrough. They are way behind the times – up to 10,000 years too late. Humans have been creating new species since the dawn of civilization, and they did it by crossbreeding their crops and their farm animals. The animals and plants that we farm today were created by human endeavor, not nature. They are all genetically modified – not in the modern sense of transplanting specified strands of DNA from cell to cell, but by using careful selection and crossbreeding in controlled conditions.

Our prehistoric ancestors created artificial life forms like the domesticated pig, with more vertebrae in the spine than wild boars and with smooth and almost hairless pink skin in contrast to the wiry bristles of their forebears. Can you imagine the headlines, were a genetic engineer to add vertebrae to the pig backbone in order to produce more bacon? It would be a miracle (to the producers) and an affront to the gods (to people buying bacon in the store). Yet it was done, about 7,000 years ago, in the former Yugoslavia. What about your family dog, *Canis familiaris*? It was evolved from the gray wolf *Canis lupus* tens of thousands of

years ago, and was eventually bred to produce the vast range of dogs that we now know and love. Even though dogs are so different from wolves, through human intervention, we can still observe wolf-like traits in their behavior. Yet dogs are a different species. What was that? Yes, dogs are a different species from wolves – a new species made by humans in prehistoric times.

Here is another example. After maize and rice, wheat is the third most common staple food in the world. Our wheat is *Triticum aestivum* and it is a human-made species. It was derived from wild emmer, *Triticum dicoccoides*. But emmer is itself is a crossbreed between two wild grasses, *T. urartu* and wild goatgrass *Aegilops searsii* or perhaps *Ae. speltoides*. Today's wheat began to be created by prehistoric farmers in southeastern Turkey many millennia ago. The impetus for crossbreeding was to find wheat that didn't shed its seeds to the ground. This impetus still drives today's agriculture – for example, the main difference between wild brassicas and domesticated canola is that the wild species shed their seeds, whereas canola has been bred to retain them. This makes it so much easier to harvest. Wild grasses have a brittle rachis connecting the seed to the stem, which snaps in half as the grain ripens, spilling the seed on the soil. Domesticated types have been selected to have a rachis that doesn't break so easily and this – together with larger and fatter grains of a polyploid plant – gave rise to the types of wheat we cultivate today. About 10,000 years ago we find the first traces of einkorn, *Triticum monococcumone*, one of the earliest of wheats. It was Neolithic tribes that bequeathed to us spelt wheat, *T. spelta*. Try it. You can still buy spelt flour in specialty stores who tell you it was made into bread by the Romans. But it's more ancient than that, for spelt was perfected and first grown by stone-age people.

So just look anew at the astonishing developments in the genetic composition of crops and domesticated animals that were made possible by our prehistoric ancestors. Don't boast about the possibility of producing a "human-made species" of microbe. Humans, using traditional techniques, created a great realm of artificial species for our use today and these have given us a fundamental improvement on our ability to survive. Today's genetics should be set in perspective alongside those achievements. The hyperbole surrounding modern molecular biology is misplaced. We are trudging along, nudging new nuggets of knowledge from a vast universe; but what we are doing is often less impressive than what our forebears attained. And before we start to make new cells, we should step back and look at the organisms that already exist. They

Spelt wheat was one of the first domesticated grain crops to be developed by our Stone Age ancestors more than 10,000 years ago. Early attempts at "genetic modification" may have relied on crossbreeding rather than gene transfer, but the results they achieved remain impressive.

can do pretty much anything you want. Rushing ahead into strange new territories, impelled by self-aggrandizement or the quest for a fast buck, is not the answer. Looking at life as it already exists and harnessing the powers that already lie around us in abundance, makes a lot more sense.

I was thinking about this when I retrieved the file for 1967 and read further what I'd published: "There is, though we very often tend to forget it, very much more to the process of life than the molecular configuration of the nucleic acids." That still seems to be true. When the article appeared in print, the editors spread it right across the page. As a result, it had been cut in half and mounted on two separate pages in the file before being stored away. I was reassembling scans of the cuttings when my wife called in. "What are you doing?" she asked. "Creating something new?" I smiled back and glanced up momentarily from the computer screen. "Not creation" I said, as I slid the two halves of the article together and saved the file. "Just reconstitution."