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Man At His Best

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50 Who Made the Difference

A Celebration of Fifty American Originals

Oswald Avery and the Cascade of Surprises

Future historians may remember this century for three scientific events: the splitting of the atom, the first exploration of outer space, and the discovery of the structure of DNA. This last marked the start of genetic engineering, a science with the potential for changing life as we know it. The discovery was by Watson and Crick, whose work on the double helix brought them the Nobel Prize. Without Oswald Avery, however, it might not have happened when it did.

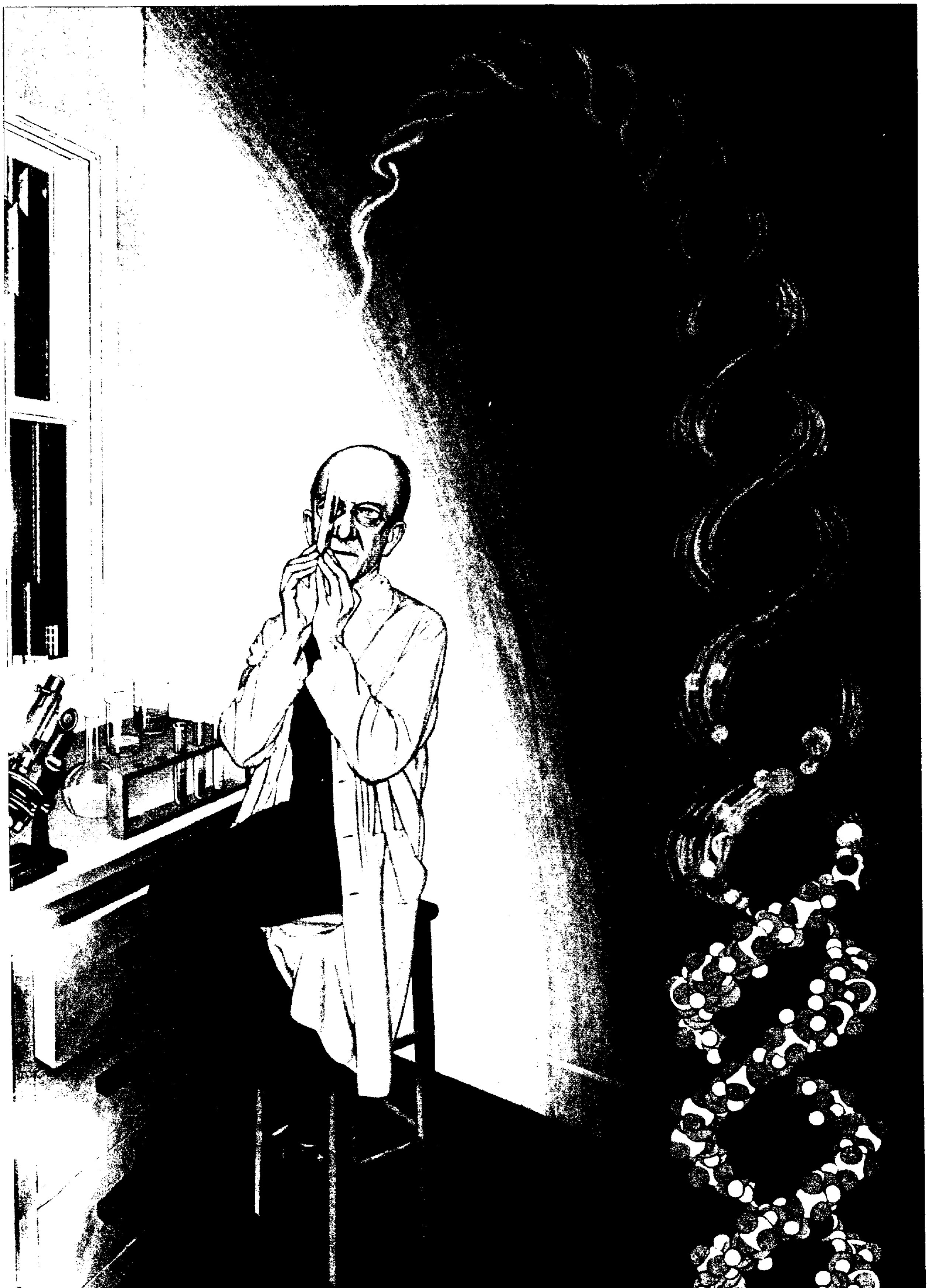
The Biological Revolution

In a laboratory forty years ago, an obscure researcher found the key that unlocked the secrets of the cell

BY LEWIS THOMAS

One of the liveliest problems in cancer research these days is the behavior of oncogenes, strings of nucleic acid that were originally found in several of the viruses responsible for cancer in laboratory animals, later discovered to exist in all normal cells. By itself, an oncogene appears to be a harmless bit of DNA, maybe even a useful one, but when it is moved from its normal spot to a new one on another chromosome, it switches the cell into the unrestrained growth of cancer. It is not yet known how it does this, but no one doubts that an answer is within reach. Some of the protein products of oncogenes have already been isolated and identified, and the site of their action within the cell, probably just beneath the cell membrane, is now being worked on. The work is moving so fast that most recent issues of *Science* and *Nature* contain several papers on oncogenes and their products.

But cancer is only one among dozens of new problems for the scientists who work on DNA. The intimate details of genetically determined diseases of childhood are coming under close scrutiny, and the precise nature of the error in the DNA molecule has been observed in several, sickle-cell disease, for example, with more to come. The immunologists, embryologists, cell biologists, and, recently, even the endocrinologists have observed the ways in which small modifications of DNA affect the behavior of the systems that they study. *Observed* is exactly the right word here: the DNA molecule can be inspected visually, purified absolutely, analyzed chemically, cut into whatever lengths you like, transferred from one cell to another or into a test tube for the manufacture of specific proteins. The techniques and instruments now available for studying DNA have become so sophisticated that I recently heard a young colleague, one of the new breed of molecular geneticists, complain



February 1944
Avery's paper on DNA opened the door to the new biology.

that "even a dumb researcher can do a perfectly beautiful experiment."

It is indeed a biological revolution, unquestionably the greatest upheaval in biology and medicine ever.

It began just fifty years ago in a small laboratory on the sixth floor of the Hospital of the Rockefeller Institute for Medical Research, overlooking the East River at Sixty-sixth Street in New York. Professor Oswald T. Avery, a small, vanishingly thin man with a constantly startled expression and a very large and agile brain, had been working on the pneumococcus—the bacterium causing lobar pneumonia—since the early years of World War I.

Avery and his colleagues had discovered that the virulence of pneumococci was determined by the polysaccharides (complex sugars) contained in the capsules of the organisms and that different strains of pneumococci possessed different types of polysaccharide, which were readily distinguished from one another by specific antibodies. It was not clear at that time that the type of polysaccharide was a genetic property of the bacterial cells—it was not even clear that genes *existed* in bacteria—but it was known that the organisms bred true; all generations of progeny from a pneumococcus of one type were always of that same type. This was a solid rule, and like a good many rules in biology there was an exception.

An English bacteriologist, Fred Griffith, had discovered in 1923 that pneumococci could be induced to lose their polysaccharides and then to switch types under special circumstances. When mice were injected with a mixture of live bacteria that had lost their capsules (and were therefore avirulent), together with heat-killed pneumococci of a different type, the animals died of the infection, and the bacteria recovered from their blood were now the same type as the heat-killed foreign organisms.

Avery became interested in the phenomenon and went to work on it. By the early 1930s it had become the main preoccupation of his laboratory. Ten years later, with his colleagues Colin M. MacLeod and Maclyn McCarty, the work was completed, and in 1944 the now-classic paper was published in the *Journal of Experimental Medicine*, formidably entitled "Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types: Induction of Transformation by a Desoxyribonucleic Acid Fraction Isolated from Pneumococcus Type III."

The work meant that the genes of pneumococci are made of DNA, and this came as a stunning surprise to everyone—not just the bacteriologists but all biologists. Up until the announcement, the concept of the gene was a sort of abstraction. It was known that genes existed, but nobody had the faintest idea what they were made of or how they worked. Here, at last, was chemical evidence for their identity and, more importantly, a working model for examining their functions.

Several years later a new working model was devised in other laboratories, involving viruses as the source of DNA, and in 1953 the famous paper by James Watson and Francis Crick was published, delineating the double-helix structure of DNA. Many biologists track the biological revolution back to the Watson-Crick discovery, but Watson himself wrote, "Given the fact that DNA was known to occur in the chromosomes of all cells, Avery's experiments strongly suggested that future experiments would show that all genes were composed of DNA."

Looking back, whether back to the Watson-Crick paper or all the way back to Avery, the progress of science can be made to seem an orderly succession of logical steps, a discovery in one laboratory leading to a new hypothesis and a new experiment elsewhere, one thing leading neatly to another.

It was not really like that, not at all. Almost every important experiment that moved the field forward, from Avery's "transforming principle" to today's "jumping genes" and cancer biology, has come as a total surprise, most of all surprising to the investigators doing the work. Moreover, the occasions have been exceedingly rare when the scientists working on one line of research have been able to predict, with any accuracy, what was going to happen next. A few years ago certain enzymes were discovered that will cut DNA into neat sections, selectively and precisely, but it could not have been predicted then that this work would lead directly, within just a few more years, to the capacity to insert individual genes from one creature into the genetic apparatus of another—even though this is essentially what Avery accomplished, more crudely, to be sure, a half century ago.

Good basic science is impossible to predict. By its very nature, it must rely on surprise, and when it is going very well, as is the case for molecular genetics today, it is a cascade of surprises.

And there is another sort of surprise that is essential for good basic science, not so exhilarating, enough to drive many student investigators clean out of science. This is the surprise of being wrong, which is a workaday part of every scientist's life. Avery endured ten years of it, one experiment gone wrong after another, variables in the system that frequently made it impossible to move from one question to the next. Reading the accounts of those ten years in René Dubos's book *The Professor, The Institute, and DNA*, one wonders how Avery, MacLeod, and McCarty had the patience and stubbornness to keep at it.

Being wrong, guessing wrong, setting up an elegant experiment intended to ask one kind of question and getting back an answer to another unrelated, irrelevant, unasked question, can be frustrating and dispiriting, but it can, with luck, also be the way the work moves ahead. Avery was especially good at capitalizing on mistaken ideas and miscast experiments in his laboratory. He is quoted by some of his associates as having said, more than once, "Whenever you fall, pick something up."

This is the way good science is done: not by looking around for gleaming negotiable bits of truth and picking them up and pocketing them like game birds, nor by any gift of infallible hunch of where to look and what to find. Good science is done by being curious *in general*, by asking questions all around, by acknowledging the likelihood of being wrong and taking this in good humor for granted, by having a deep fondness for nature, and by being made nervous and jumpy by ignorance. Avery was like this, a familiar figure, fallible but beyond question a *good* man, the kind of man you would wish to have in the family. Accident-prone, error-prone, but right on the mark at the end, when it counted.

One thing for a good basic scientist to have on his mind, and worry about, is how his work will be viewed by his peers. If the work is very good, very new, and looks as if it's opening up brand-new territory, he can be quite sure that he will be criticized down to his socks. If he is onto something revolutionary, never thought of before, contradicting fixed notions within the community of science involved, he tends to keep his head down. When he writes, he writes as Avery wrote, a cautious paper, as noncommittal as possible, avoiding big extrapolations to other fields.

Not all scientists with great discoveries to their credit receive the Nobel Prize, and Avery did not. This spectacular omission continues to mystify the scientific community and has never been explained. René Dubos thinks that the Nobel committee was not convinced that Avery knew the significance of his own work, perhaps because of the low-key restraint with which the manuscript was written; the paper did not lay out claims for opening the gate into a new epoch in biology, although this is certainly what it did accomplish.

I doubt very much that Oswald Avery was ever troubled by the absence of a Nobel Prize or even thought much about it. He was not in any sense a disappointed man. He understood clearly, while the work was going on, what its implications were, and when it was finished he was deeply pleased and satisfied by what it meant for the future. He had set the stage for the new biology, and he knew that.

Contrary to the general view, not all scientists do their best work in their thirties, peak in their forties, and then slide. Avery was sixty-seven years old when his DNA paper was published. He retired four years later and died of cancer at the age of seventy-seven, at peace with the world.

BORN OCTOBER 21, 1877

An accomplished musician, Oswald Avery played the cornet in church during his childhood. At Colgate University, he joined the college band (in photo Avery is in the first row, third from left) and eventually became its leader.

Dossier

Oswald Theodore Avery

was born in Halifax, Nova Scotia, on October 21, 1877, four years after his parents emigrated from England. His father started out as a paper-maker; but discontented with that trade and possessed of a mystical nature, he became a Baptist minister.

When his father established his ministry in New York, the Baptist community helped the family live on a meager salary. After a fire destroyed the Avery home in December 1890, Mrs. John D. Rockefeller sent a check for one hundred dollars.

In 1892 both his father and his older brother, Ernest, died, and Oswald became the man of the family. His mother went to work for the Baptist City Mission Society. Her work allowed her to mingle with the Rockefellers, Vanderbilts, and Sloans, who took an interest in her sons and invited them to their estates; and Avery acquired sophisticated tastes unusual for his background.

As an undergraduate at Colgate, he earned excellent grades. His yearbook said that only the accident of his being born in Canada prevented him from fulfilling "his aspirations for the presidency." He majored in the humanities and took only those science courses that were required. Nevertheless he went on to Columbia University's medical school.

At Columbia he was called Babe, because of his small size and youthful demeanor. One classmate said he had an "aristocratic daintiness."

After receiving his medical degree in 1904, he practiced general surgery in New York for about three years. But he found it upsetting to deal with patients suffering from chronic pulmonary diseases and intractable asthma, for whom he could do nothing useful. Although he was successful in his relations with patients, clinical practice did not satisfy him intellectually or emotionally.

His favorite haunt was Deer Isle, Maine. He never missed a chance to go sailing. He also walked through the Maine woods collecting wild flowers.

He left clinical medicine when, in 1907, the Hoagland Laboratory in Brooklyn appointed him associate director at a salary of $1,200 a year.

His next important move—to the Rockefeller Institute in 1913—almost didn't occur because, in keeping with his neglectful attitude toward correspondence, he failed to answer two letters offering him the job.

He walked to work every day and, from 1913 to 1948, occupied the same small, immaculate office.

He ate very little—he probably never weighed more than one hundred pounds—but was fastidious about the food he did eat. He was immensely popular and received many dinner invitations, but seldom did he accept.

After joining the Institute, he shunned large gatherings and gave up public speaking. But his office door was always open to people needing advice, and he was an effective lecturer. In college his best grades had been in public speaking, and decades later, he still enjoyed declaiming the graceful phrases of a speech on Chinese civilization, one of his early oratorical triumphs.

His shirts, shoes, suits, and ties were always impeccable and always subdued. His voice was soft and his manner retiring, but his handwriting displayed a daring, enthusiastic flourish.

He traveled little, outside of his trips to Maine. When he won the Paul Ehrlich Gold Medal in 1933, he did not go to Germany to receive it; nor did he go to Sweden to receive the Pasteur Gold Medal awarded him in 1950.

He wouldn't hurry; he used to quote an old black patient who, upon watching the doctors rush by, said, "What's your hurry, Doc? By rushing that way you passes by much more than you catches up with."

On rare moments when he was alone in the lab, he was prone to move slowly, whistling the lonely shepherd's song from *Tristan und Isolde.*

In 1948 he moved to a stone house in Nashville, near the home of his brother, Roy. Six years later, while at Deer Isle, he felt pain that was eventually diagnosed as cancer of the liver. His terminal illness was painful; he bore it with characteristic patience. He died at the age of seventy-seven on February 20, 1955, at Vanderbilt Hospital.

"[Avery is] a doctor's doctor wholly devoted to the progress of the profession; redoubtable pioneer in the chemistry of immunology, whose laboratory conquests have quelled the ravages of dread pneumonia; he is a professor without portfolio to a host of the country's leading medical teachers and researchers, and himself one of the truly great scientists of modern times...."

—HAROLD O. VOORHIS
VICE-CHANCELLOR OF NEW YORK UNIVERSITY, UPON AWARDING AVERY AN HONORARY DOCTORATE IN 1947

DIED FEBRUARY 20, 1955