Cold Spring Harbor Turns 100

Director James Watson brought about a renaissance at the laboratory during his 22-year tenure. But the lab's friends worry about its future as its second century begins

WHEN JAMES WATSON, THEN 40, TOOK THE reins at Cold Spring Harbor Laboratory in 1968, the place was in financial shambles. Despite the valiant efforts of John Cairns, the previous director, the lab had a budget of just $600,000. And it was also in danger of losing its intellectual focus. Cold Spring Harbor's brilliant Phage Group, which had essentially ushered in the era of molecular genetics in the 1940s, was winding down, and a new research direction was badly needed. Things looked so bleak, the trustees were seriously talking of closing the lab.

Today, 22 years later, as Cold Spring Harbor turns 100, it has an operating budget of $28 million and a $45-million endowment, the envy of institutions twice its size. The scientific excellence of the lab is without question; indeed, papers by Cold Spring Harbor researchers are cited more often than papers emanating from any other research institution, according to *Science Citation Index*. A list of lab alumni reads like a Who's Who in molecular biology. In addition to the 125 Ph.D.'s who work there year-round, nearly 6000 more scientists pass through the lab each year to attend the meetings and summer courses, presenting their latest data, often for the first time. All of which makes Cold Spring Harbor one of the most exciting places in the world to do molecular biology.

"Jim made it all happen," says Phillip Sharp of the Massachusetts Institute of Technology, a leading molecular biologist who was one of Watson's earliest recruits. "What's there now, the style and substance of Cold Spring Harbor, is the creation of his energy over the past 20 years." Indeed, no other research institution is so clearly the reflection of one man's vision as is Cold Spring Harbor.

But that may be the lab's greatest problem as it enters its second century. People, both inside and outside the lab, are deeply worried about what will happen when Watson, now 62, retires or is drawn ever more frequently to Washington where, since 1988, he has also directed the genome project for the National Institutes of Health.

The lab is stronger financially than it has ever been, thanks to Watson's prodigious fund-raising talents. But it still relies precariously on soft money, as investigators live or die on their ability to bring in grants. And with the funding squeeze at NIH, that makes the lab "very vulnerable," says Bruce Stillman, the new assistant director of the lab. "I think about money all the time," admits Watson.

What's more, at a time when a more conservative director would hold a steady course, Watson has presided over an enormous expansion. He is soon to open the glittering $22-million neuroscience center, which will house 60 new scientists. To expand so massively in the midst of a funding crunch "is enough to give one sleepless nights," says former director Cairns, who is now at Harvard. Indeed, several other knowledgeable scientists worry that this time Watson may have bitten off more than he can chew.

"How will he populate that huge building?" asks Cairns. His point: some of the top guns in neurobiology have already turned down Watson's job feelers.

Perhaps the most troubling question to Cold Spring Harbor scientists—and to many of its unabashedly effusive alumni—is whether it can grow so much and still retain the quality that has made it unique. Cold Spring Harbor has been a place where young people, unencumbered by teaching or administration, can devote themselves to science—a place shaped by Watson's uncompromising demand for excellence and absolute intolerance for anything less. But with growth has come some of the bureaucracy Watson so studiously avoided through the early years. And while Cold Spring Harbor is still inhabited mostly by young people—only three scientists are over age 40—talk of continuity is creeping into a place that once prided itself on shedding its scientists every 5 years or so.

To Stephen Hughes, a National Cancer Institute researcher who spent more than 4 years there, whether you liked the lab or not—and many people did not—"there was no place on earth like what Cold Spring Harbor was; but there are lots of places like what it is becoming."

The current laboratory is the product of the 1962 merger of two facilities, the original Biological Laboratory, which was founded in 1890 by the Brooklyn Institute of Arts and Sciences as a summer camp for biologists, and a field station for experimental evolution established at Cold Spring Harbor several years later by the Carnegie Institution.

But Cold Spring Harbor really came into its own in the 1940s. That was when Barbara McClintock, who would win a Nobel Prize in 1983 for her discovery of transposable elements, joined the lab.

And it was in 1941 that the Phage Group was born at Cold Spring Harbor. At a meeting that summer, Salvador Luria of Indiana University and Max Delbruck of Vanderbilt University got the idea of studying bacteriophages, tiny viruses that infect bacteria, to get at the mechanisms of

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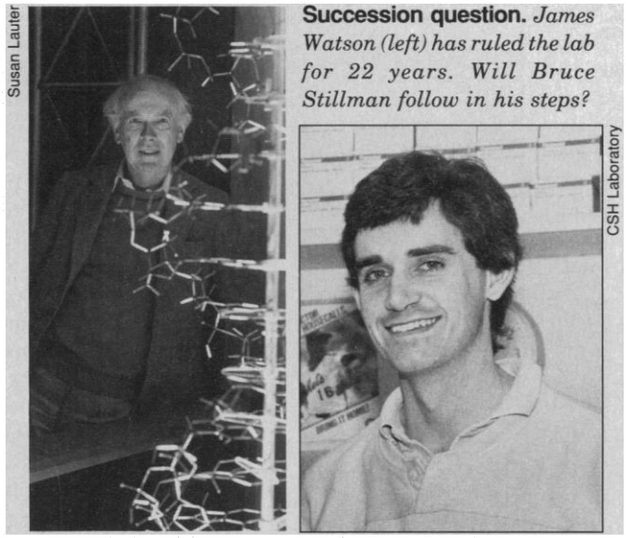
Bucolic Setting. *Cold Spring Harbor's tranquil, park-like campus belies the intensity of the work there.*

heredity. Joined by Alfred Hershey of the still independent Carnegie lab at Cold Spring Harbor, they pioneered the study of the phages, producing many of the insights and techniques that would guide molecular genetics over the coming decades. (Luria, Delbruck, and Hershey eventually received a Nobel Prize for their phage work.)

Although Luria and Delbruck kept their appointments elsewhere, they met every summer at Cold Spring Harbor, which became the intellectual center of the phage field. An ever-expanding number of biologists and physicists coalesced around the three researchers, returning summer after summer for 26 years. One of those scientists was James Watson, then a graduate student in Luria's Indiana lab, who first visited Cold Spring Harbor in 1948. "It was the most exciting place in the world to do molecular biology," he recalls.



Susan Lauter

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Succession question. *James Watson (left) has ruled the lab for 22 years. Will Bruce Stillman follow in his steps?*

It was that vitality that Watson set out to rebuild 20 years later when he took on the directorship of the then foundering lab. The financial situation was so precarious, though, that he hedged his bets, splitting his efforts between Harvard, where he had essentially created the molecular biology department, and Cold Spring Harbor until the first big gift—$7.5 million—from the late financier Charles Robertson came through in 1973.

But well before achieving financial stability, Watson had reestablished Cold Spring Harbor's scientific credentials as *the* place to do molecular biology. "We rescued it by doing good science," he says. Then as now, Watson's formula for good science was to identify a problem difficult enough to attract the best minds and central enough to attract funds—and then to recruit the best people to work on it.

The problem he picked was tumor viruses, through which he proposed to get at the molecular mechanisms of cancer. It was, by all accounts, a brilliant choice. When President Nixon launched the War on Cancer in 1971, Cold Spring Harbor was well positioned to take advantage of that massive infusion of federal funds into biology. And although tumor viruses did not turn out to have a central role in human cancer, work done at Cold Spring Harbor and elsewhere led to the discovery in the early 1980s of the malfunctioning genes at the root of cancer.

If one thing has clearly set Cold Spring Harbor apart from other research institutions, it was Watson's decision, right from the start, to put his faith—and limited resources—in young scientists rather than established ones. Watson used to say that after age 30, scientists were finished—they were "rusty old hulks who ought to go off to a university to be comfortable," recalls NCI's Hughes. Watson now says the cutoff point was always 40, his age at the time. "At 40, you realize you have other obligations. At 30 you can work all the time."

Thus, Cold Spring Harbor became a place where relatively unproven young investigators came for 3, 5, or maybe 7 years to make a name for themselves and then move on. The high turnover, which had its roots in necessity, became the core of the lab's strength. "The place is invigorated by young scientists coming in and working at maximum intensity," says Sharp.

One of his first recruits was Joseph Sambrook, then a 29-year-old postdoc with Renato Dulbecco at the Salk Institute, who Watson brought in, along with Henry Westphal and Carel Mulder, to study the monkey tumor virus SV40. Sambrook, who soon emerged as the leader, ran the tumor virus effort for years, eventually becoming Watson's assistant director and the second dominant force to shape the lab until he left in 1985 for the University of Texas Southwestern Medical Center at Dallas.

Many of today's leading lights in molecular biology cut their eye teeth at Cold Spring Harbor in the 1970s, working on SV40 with Sambrook or on adenovirus, another animal tumor virus, with Raymond Gesteland—researchers like Sharp, now director of MIT's Center for Cancer Research, Robert Pollock, professor and former dean at Columbia University, and Tom Maniatis, head of the biochemistry department at Harvard, to name a few.

As they left, more young hot shots moved in to take their places, often turning out stunning science. Richard Roberts, who went to the lab in 1972, isolated about half the known restriction enzymes and then, along with Sharp's group at MIT, discovered "RNA splicing," or editing—a "once-in-a-lifetime" discovery, says Watson. In the late 1970s, James Hicks, Jeffrey Strathern, and Amar Klar worked out the puzzle of yeast mating type—finding that yeast could essentially change sex by inserting a different DNA cassette into its chromosome. Michael Wigler was one of the first researchers to isolate a human oncogene in 1981. More recently, Edward Harlow's group helped show that certain tumor viruses work by blocking the effects of a cellular gene that puts the brakes on cancer. And David Beach has been at the forefront of the work leading to the identification of the genes that control the cell cycle.

But despite its position in the center of the molecular biology universe, Cold Spring Harbor was not for everyone. Along with the scientific rigor came an atmosphere of intense competition in which people either thrived or perished.

"It was a terrible place to work," says Roberts, now assistant director for research. "It was destructive for a lot of people. Many did not do the best science they could because of it," says Roberts, who suspects that those who wax nostalgic for the golden days of the 1970s have forgotten how cutthroat it really was then.

And still is, according to Andrew Hiatt, a plant biologist who recently left the lab for Scripps Research Institute in La Jolla. "It works if you are not married, don't have kids, and are willing to work 12 hours in the lab and do nothing else. That is what Cold Spring Harbor is about," he says.

Even Cold Spring Harbor's greatest fans, like James Feramisco, concede that "it is not a place to grow old." Watson's personality is too dominant, he says, and the place is too narrow, both scientifically and personally. Feramisco, who headed the cell biology group there, is now at the University of California at San Diego.

What's more, the lab's rapid turnover was, and remains, a high-risk strategy, says Maniatis. "Periodically the lab gives up the basis of its strength. People leave at the peak of their productivity, and that is risky because you are constantly in a situation of making the right decision, hiring the right people." Until recently, Watson had a role in hiring every scientist at the lab, and he rarely erred. And that is what makes people worry as he begins to step back.

For better or worse, Cold Spring Harbor is changing—becoming bigger, more impersonal, a bit less in Watson's image and more like a conventional research institute. In Watson's 22 years, it has grown from a

staff of 50 to 460—though, as he says, "we are still tiny compared to MIT. Even Whitehead is bigger." Once run like an extended family, "more forms are creeping in," says Harlow, who just left after 8 years for Massachusetts General Hospital. Principal investigators don't necessarily work at the bench anymore—quite a switch from the early days, recalls Hughes, when "everyone was a spear carrier—even Sambrook was in the lab in the middle of the night."

And while turnover is still high, investigators are sticking around longer than they used to; a hierarchy is even developing. In 1979 Wat-son created a new senior scientist position, in part because he kept losing his top researchers to places that offered more security. And in 1985, when Wigler, one of the unquestioned stars at Cold Spring Harbor, told Watson he was leaving for Princeton, Watson created the first tenured slot at the lab for him.

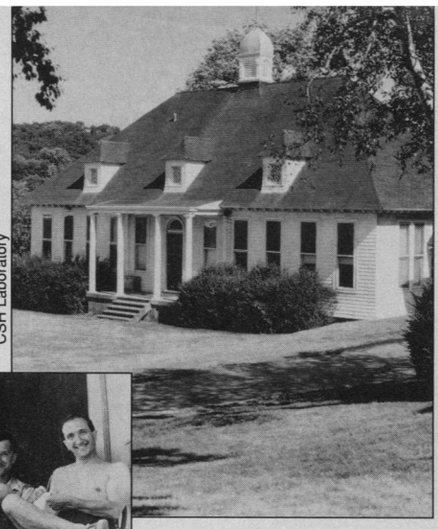
Watson is now talking about starting a small Ph.D. program, which would bring in cheap labor in the form of graduate students, who are now available only through Stony Brook. And, in a nod to the current funding squeeze at NIH, he is seeking funds to support the research of senior scientists in case their grants don't come through.

"We are not against stability," says Watson. "What we are afraid of is being in a position, like the Rockefeller, where the average age of the professors is 60. That means you have enormous competence and distinction, but it is not very exciting."

But in opting for growth and stability, Watson is giving up the electricity that has characterized the lab, say Hughes and others. Feramisco agrees. One reason he left Cold Spring Harbor for San Diego, he says, is because he wanted greater diversity than he could get there—to be around "real" biologists, even clinicians. But there was another reason, too. "I left partly because it was getting larger, and that was giving it a different feeling," Feramisco says. "Now it has the drawbacks of being larger but not the diversity."

"We have to expand," counters Watson, who believes that to stand still would be to crumble. "That is the only way to maintain our relative position. We are certainly three times bigger than we were 12 years ago, but I don't think we're less exciting. We made the transition so far."

Perhaps the biggest change at Cold Spring Harbor is in Watson himself. Although he is not talking about retiring, after 22 years of intensive—some would say obsessive—involvement in almost every decision, he is stepping back from the lab's day-to-day activities, delegating, and even, it seems, grooming a successor.



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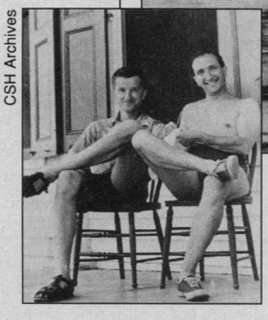

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Science by the bay. *Jones Laboratory dates to 1893. Max Delbruck and Salvador Luria relax in the summer of 1953.*

Watson has been disengaging for some time, but the real switch came in 1988, when he took on the job as director of the genome project for NIH. Since then he has spent about half his time in Washington or on the road, and he is admittedly stretched thin. "I never saw his anger until last year," says Wigler. Indeed, people inside and outside the lab wonder how long he can keep both jobs—and which he will give up, if one has to go. "No matter what happens, it is good for Cold Spring Harbor, because it will make them deal with the lack of Jim's attention, which will come anyway," says Sharp.

"I have no desire to leave this place," answers Watson. But he says he is ready to hand over the scientific responsibility while he continues fund-raising, at which he excels. Indeed, in the past 2 years he has raised almost $44 million for new facilities.

There is no clearer sign of Watson's frame of mind than his recent appointment of Bruce Stillman as assistant director of the lab, a slot Watson created to keep Stillman from leaving for Berkeley. Watson has asked Stillman to oversee scientific activities at the lab and has given him chief responsibility for recruiting—which instantly fueled speculation that Stillman is the heir apparent.

Watson doesn't deny it. "I have given Bruce a role in recruiting, which I consider the most important job in the institution. I wouldn't do it lightly." And when the neuroscience building is completed later this year, Watson will move into an office there, and Stillman will move into Watson's old office. "That is symbolic," concedes Watson.

Stillman is in many ways a radical choice, in the Cold Spring Harbor tradition, given his age—just 36—and experience. But everyone admits that he is the logical choice, with his scientific credentials, flair for management, and broad interests in science. But in terms of running the entire place, he is still untested. Says Roberts: "Much of that will depend on interpersonal interactions, and Bruce still has some rough edges." The bigger unknown, says Roberts, is whether Watson will back off enough to give Stillman a chance. "If Bruce ends up just being Jim's yes man, it is not going to work."

The test, in many ways, will be how much freedom Watson gives Stillman in recruiting scientists to run the six labs planned for the neuroscience center. It won't be an easy task. The problem, as Watson found out during his first attempt to move into neurobiology in the late 1970s, is how to build up an intellectual center from scratch, when there is no existing neuroscience expertise in house. "Because it is a complicated discipline, most neurobiologists require other neurobiologists around," says Thomas Jessell of Columbia University, one of the neurobiologists who is now advising Watson. "The problem is to build up a critical mass."

Over the past several months Watson has approached a half dozen or so of the leading lights in neurobiology, including Jessell, Gerald Rubin of Berkeley, and Richard Aldrich of Stanford, to see if they would run the new center. All turned him down—mostly, they say, because they are happy where they are, though at least one admitted to being worried about long-term security at the lab once Watson retires.

Now Watson and Stillman are returning to the formula that has always worked in the past: they are looking for six promising young researchers, probably at the assistant professor level—"people working on related questions who can interact," says Stillman, and who can also mesh with the molecular biologists at the lab.

Again, says Watson, "the main thing is to pick the right problem. There are two choices. We could go developmental or cognitive. Everyone will admit that cognition is the more exciting one but no one knows quite how to pull it off. I think you can't avoid cognition if you want to do neuroscience, otherwise you are doing molecular biology. If you don't focus on difficult problems you are not going to be exciting."

Watson says he is not losing sleep over it. "Can we somehow start it up in a way that works? Until we do it I can't say we will. But I don't worry about it. [We'll be alright] if we stay in the center of the field and never settle for a minor role."

■ LESLIE ROBERTS