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A Tribute to Cold Spring Harbor Laboratory on Its 100th Birthday: Jan A. Witkowski Reviews Its History and the Highest Impact Symposia Publications

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In March of this year, *The Scientist*® presented a survey of small, independent research institutions in the US.[1] Twenty such institutions were ranked by the citation impact of their papers published between 1973 and 1987. Although the Salk Institute for Biological Studies and the Scripps Clinic and Research Foundation, both of San Diego, California, received the most citations (over 124,000 each), the institution that topped the list by citation impact was the Cold Spring Harbor Laboratory, New York. As David Pendlebury observed, papers published from Cold Spring Harbor had a citation impact more than five times greater than the average for the entire *Science Citation Index*® database. Furthermore, the impact factor for this lab was nearly twice that of the average for the 20 institutions listed.[1] (The entire list appears in Table 1.)

The following guest essay, however, does not really concern Cold Spring Harbor's current preeminence in life-sciences research, but rather its distinguished past—specifically, the yearly symposia in experimental biology that have taken place there for more than a half-century. Jan A. Witkowski, director of the laboratory's Banbury Center, discusses the 51 most-cited articles in the *Cold Spring Harbor Symposia on Quantitative Biology*. His account includes a brief history of the laboratory itself, from its beginnings as a summer school at the end of the last century to its current renown. The evolution of the symposia is also described, from the first meeting in 1933, with 16 scientists in attendance, to what Witkowski calls the "frenetic, action-packed meetings that we know today."

A native of Birmingham, UK, Witkowski received a BS degree in zoology from the University of Southampton in 1968 and a PhD in biochemistry from the University of London in 1972. Between 1972 and 1982 he was a research fellow at the Institute of Child Health, London, and at the Mayo Clinic, Rochester, Minnesota. From 1982 to 1986, he was a lecturer in the Department of Pediatrics, Royal Postgraduate Medical School, University of London. He then served as director, Kleberg DNA Diagnostic Laboratory, and assistant professor, Institute for Molecular Genetics, at Baylor College of Medicine, Houston, Texas.

Witkowski came to Cold Spring Harbor in 1987. As director of the Banbury Center, he determines topics for conferences at the center, arranges meetings for congressional staff and science journalists, and assists with the publication of meetings. His own major research interest is in human genetics, but Witkowski notes that he has a long-standing interest in the history of science—especially topics relating to the development of experimental biology in this century. He has also published papers discussing significant studies in biochemistry, embryology, tissue culture, and molecular biology.[2]

The papers discussed in this study span 40 years of research, from 1940 to 1982. Although there is a predominance of papers from the 1960s—the period Witkowski refers to as "the first golden age of molecular genetics"—this study demonstrates the consistency with which the symposia have produced highly cited works over the years. As Witkowski notes, this year marks Cold Spring Harbor's 100th birthday, and as the symposia continue to address the latest topics in biological research, this output of important and influential work is certain to continue.

Table 1: The top 20 high impact Association of Independent Research Institutes (AIRI) members (among those that published more than 100 papers, 1973-1987).

Name	Papers	Citations	Citation Impact
1. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY	839	49,217	58.7
2. Salk Institute for Biological Studies, San Diego, CA	2,834	124,942	44.1
3. Fred Hutchinson Cancer Research Center, Seattle, WA	1,756	59,800	34.1
4. Whitehead Institute for Biomedical Research, Cambridge, MA	208	6,624	31.8
5. Roche Institute of Molecular Biology, Nutley, NJ	1,731	53,450	30.9
6. Carnegie Institution of Washington, Baltimore, MD, and Washington, DC	1,695	51,896	30.6
7. Trudeau Institute, Saranac Lake, NY	288	8,358	29.0
8. Scripps Clinic and Research Foundation, La Jolla, CA*	4,972	124,323	25.0
9. Wistar Institute, Philadelphia, PA	1,586	38,758	24.4
10. New York Blood Center, New York, NY	734	17,620	24.0
11. La Jolla Cancer Research Foundation, La Jolla, CA	405	8,915	22.0
12. Joslin Diabetes Center, Boston, MA	304	6,437	21.2
13. American Health Foundation, New York, NY	820	17,127	20.9
14. Jackson Laboratory, Bar Harbor, ME	994	19,872	20.0
15. Worcester Foundation for Experimental Biology, Shrewsbury, MA	1,347	26,807	19.9
16. Public Health Research Institute of the City of New York, NY	796	15,769	19.8
17. Forsyth Dental Center, Boston, MA	617	11,270	18.3
18. Palo Alto Medical Foundation Research Institute, Palo Alto, CA	539	9,808	18.2
19. Boston Biomedical Research Institute, Boston, MA	696	12,075	17.3
20. Center for Blood Research, Boston, MA	180	3,088	17.2

*Scripps is no longer an AIRI member.

Source: ISI®'s *Science Indicators* file, 1973-1987.

Although the laboratory's research flourished under earlier directors, notably Milislav Demerec and John Cairns, it is the present director who has played the major role in the growth of the laboratory's influence. He is, of course, Nobel laureate James D. Watson, who has been director at Cold Spring Harbor since 1968. Previously, in a broad discussion of *Citation Classics*®, I've noted that perhaps the most influential paper of the century—Watson and Francis H.C. Crick's 1953 publication on the double-helix structure of DNA[3]—has been cited "only" about 1,000 times.[4] This seemed to me to indicate an upper limit on citations that one could expect for such a work. It is also understandable that neither Watson nor Crick would provide us with a commentary on this paper. You might say that with the publication of Watson's *The Double Helix*[5] and Crick's recent autobiography, *What Mad Pursuit*,[6] they have already provided the ultimate commentaries.

Although I am hopeful that other authors listed in the Bibliography that follows the essay will have contributed commentaries on their papers by the time we go to press, the main reason for their absence is our failure to invite them until now. Several of them have written commentaries on papers published in other journals. Success in obtaining commentaries depends upon the right timing—it is preferable to invite authors to write *Citation Classic* commentaries before they receive the Nobel Prize or other major recognition, lest they be too preoccupied with other pressing obligations.

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The 51 Most-Cited Articles in the *Cold Spring Harbor Symposia on Quantitative Biology*

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The Cold Spring Harbor Symposia on Quantitative Biology are a venerable and venerated part of experimental biology. Established in 1933, the symposia have since that time charted progress in research in a wide range of subjects, subjects chosen for their excitement, the need for dispassionate and critical review, and above all by the belief that they were the subjects that would continue to define the leading edge of research in biology. However, as John Cairns, director of Cold Spring Harbor Laboratory from 1963 to 1968, has written on the symposia: "any catalog of the virtues of the various Symposia, even if perfectly done and in the liveliest style, would miss the whole point of the exercise. These meetings have meant much more to many people than could possibly be guessed at from looking at the contents of the books.... When we look at the published volumes...we are looking at the history of a scientific era."[1] (p. 3) So before discussing the citation record of the symposia, some historical background is needed to appreciate the nature of the symposia and why they have continued with ever-increasing success for 57 years.

Quantitative Biology

The period at the beginning of the twentieth century was marked by the increasing employment of experimentation and quantitative methods in the biological sciences. This was most evident in the increasing numbers of physicochemical studies of living organisms, and the work of Jacques Loeb, The Rockefeller Institute for Medical Research, New York, exemplified this mechanistic, physicochemical analysis approach.[2] As Loeb wrote with Winthrop J.V. Osterhout, Harvard University, Cambridge, Massachusetts, and Thomas Hunt Morgan, Columbia University, New York, in the editors' announcement to the series Monographs on Experimental Biology, "Biology, which not long ago was purely descriptive and speculative, has begun to adopt the methods of the exact sciences, recognizing that for permanent progress not only experiments are required but quantitative experiments."[3] Indeed, Loeb went so far as to define "scientific biology" as the attempt to reduce life phenomena "completely to physicochemical terms."[4] Following the work of the physical chemists, a colloidal theory of living matter became very popular and experiments were performed to determine the effects of changes in the physical environment on organisms. Typical of these studies were investigations of osmosis and diffusion of molecules across membranes, the colloidal properties of proteins such as gelatin and albumin, and the effects of ions on developing embryos and of X rays on cells.

The Biological Laboratory and the Station for Experimental Evolution at Cold Spring Harbor

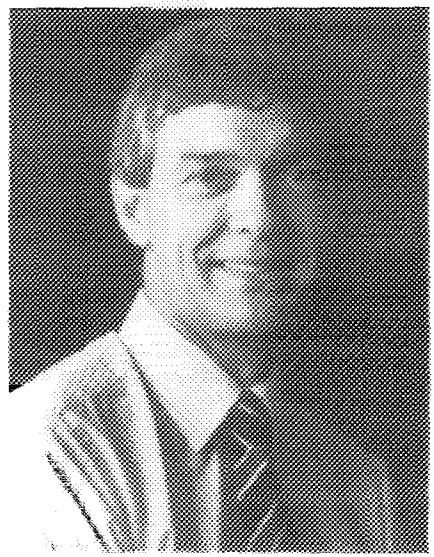
In the late nineteenth century, the Naples Zoological Station, Italy, founded in 1872, was the mecca for experimental biology.[5,6] Such luminaries as British biologist Thomas H. Huxley; Louis Agassiz, Harvard University; Charles M. Child, University of Chicago, Illinois; Edmund B. Wilson, Columbia University; and Morgan all visited there to carry out research on the marine organisms abundant in the bay. Morgan was

so impressed by the Naples Station that he became a prime mover in promoting the Marine Biological Station at Woods Hole, Massachusetts, (1888) as the American equivalent.[7] (However, not everyone subscribes to the view that the station had such an impact on the development of US biology.[8]) Later, when Morgan went to the California Institute of Technology (Caltech), Pasadena, he established the institute's marine station at Corona del Mar, California, in 1936.

In 1890 the Brooklyn Institute of Arts and Science, New York, created the Biological Laboratory at the southwest corner of Cold Spring Harbor, an inlet on the north shore of Long Island, New York.[9] The Biological Laboratory began by teaching courses in zoology, botany, comparative anatomy, and nature study to biology teachers and students through the summer months. In 1898 Charles B. Davenport was appointed director of the Biological Laboratory. Davenport had been professor of evolutionary biology at Harvard University, and he is remembered especially for his interest in eugenics and for establishing the Eugenics Record Office.[10] In 1904 he applied to the Carnegie Institution of Washington, DC, for support of a program to carry out research on genetics. The Carnegie Institution established the Station for Experimental Evolution on the same site as the Biological Laboratory, and Davenport became director of both. The history of these institutions is complex and the two were not formally amalgamated until 1962 when they became Cold Spring Harbor Laboratory.

Thus began a long and distinguished research program at Cold Spring Harbor. George H. Shull began work on corn genetics at the station in 1905. He produced pure lines of corn by self-pollination over several seasons and found that when these pure lines were crossed, the hybrid progeny were healthy and produced more corn strains. This was the first demonstration of hybrid vigor.

The laboratory's long association with cancer research began in 1916 when Clarence C. Little demonstrated that mouse



Jan A. Witkowski

strains varied in their susceptibility to transplanted tumors, work continued by E. Carleton MacDowell. (Little went on to found the Jackson Laboratory at Bar Harbor, Maine.) Both Alfred D. Hershey and Barbara McClintock carried out their research at the station. Hershey is best known for the famous "Waring blender" experiment that helped demonstrate that DNA is the molecule of heredity,[11] and McClintock for her cytogenetic studies and the discovery of movable genes in maize.[12] They were awarded the Nobel Prize in physiology or medicine in 1969 and 1983, respectively.

The Symposia on Quantitative Biology

While the Station for Experimental Evolution at Cold Spring Harbor flourished, the Biological Laboratory fared less well, remaining a summer camp for teaching. It underwent a rejuvenation in 1924 when it was taken over by a group of scientists and local citizens who formed the Long Island Biological Association (LIBA). In that same year, Davenport's son-in-law, Reginald Harris, became director. He began building a research program with the support of LIBA and instituted year-round research.

The vogue was still for physicochemical studies in biology, and Harris's determination to make the laboratory a center for modern biological research was evident in his appointment of Hugo Fricke, former director of biophysics at the Cleveland Clinic Foundation, Ohio, as the laboratory's first full-time investigator. Within a few years of Harris's appointment as director, there were research programs in biophysics, endocrinology, and pharmacology.

Harris realized that the laboratory's aims could be promoted, and the general course of research advanced, by holding special meetings at Cold Spring Harbor. As noted in the 1934 annual report,

> Now it happens in modern biological research that the problem of a given biologist, or group of biologists, may have much more in common with that of a given chemist or physicist, or a small group of either, than with that of a second group of biologists.... Yet the meetings of the various learned societies in this country still fail to take this into account.... The primary motive of the conference-symposia is to consider a given biological problem from its chemical, physical and mathematical, as well as from its biological aspects.[13]

In 1933 Harris organized the first of the Cold Spring Harbor Symposia on Quantitative Biology on "Surface Phenomena." These early meetings were not the frenetic, action-packed meetings that we know today. Instead a small group of 16 scientists stayed for one month at the laboratory, and 31 participants came periodically to present papers and to participate in symposia. The meetings were recognized immediately as being a unique contribution to science. The Rockefeller Foundation provided $5,000 towards the cost of the second symposium and continued to make an annual grant for the following 12 years.

Despite having to edit a vast amount of discussion, of which 30,000 words were published, Harris managed to bring the book out in the same year as the meeting. Publication of the first volume of the *Cold Spring Harbor Symposia on Quantitative Biology* (*CSHSQB*) series was also remarkable for the establishment of the format of the papers. They were, and have continued to be, a very successful hybrid of research paper and review article. Authors are given an opportunity to set their experimental results in a wider context, and the importance of papers in the *CSHSQB* series is undoubtedly due to this. Harris died in 1936 at the age of 35, supposedly of exhaustion from the burden of bringing out the *CSHSQB* volume within six months of the meeting. Cairns remarked that, when he read of Harris's experience, "I resolved never to get the book out before the New Year, and I notice that Jim Watson [the current director] takes even greater precautions in this regard!"[1] (p. 5-6) Harris was succeeded in 1936 by Eric Ponder, a biophysicist, who continued to hold meetings on physicochemical aspects of biology, including such topics as "Protein Chemistry" (1938), "Biological Oxidations" (1939), and "Permeability and the Nature of Cell Membranes" (1940).

Molecular Biology and Genetics

In 1941 there was an abrupt shift in symposium topics when Demerec became director of the Carnegie Institution's Department of Genetics (as the Station for Experimental Evolution was now called) and the Biological Laboratory. Demerec had come to the Carnegie Institution of Washington at Cold Spring Harbor in 1923 and became director in 1941. He was originally a *Drosophila* geneticist, but his interests changed to bacterial and phage genetics. It was during Demerec's tenure as director that the laboratory established its reputation as one of the world's centers for research on bacterial and phage genetics. Salvador Luria, at that time a research assistant at the College of Physicians and Surgeons of Columbia University, and Max Delbrück, then at Vanderbilt University, Nashville, Tennessee, worked together at the laboratory for the first time in the summer of 1941, and Delbrück began teaching the legendary phage course in 1945. (The two men shared the 1969 Nobel Prize in physiology or medicine with Hershey.) James D. Watson

Table 1: Citation-frequency distribution for the 705 articles published in the *Cold Spring Harbor Symposia on Quantitative Biology* with 50 or more citations, 1945-1988 *SCI®*.

Citation Level	Number of Items at Level	Percent of Total Items
1,000	2	0.3
900-999	1	0.1
800-899	0	0.0
700-799	1	0.1
600-699	2	0.3
500-599	2	0.3
400-499	7	1.0
300-399	10	1.4
200-299	36	5.1
100-199	180	25.5
50-99	464	65.8

came as a student to Cold Spring Harbor Laboratory in 1948.

The first of Demerec's symposia was a landmark meeting on "Genes and Chromosomes: Structure and Organization" and the first of the post-World War II meetings was on "Heredity and Variation in Microorganisms." These symposia were signposts for research in genetics through the decades spanning the 1950s and 1960s. This was a golden age of molecular genetics, and the list of participants in the symposia of that period is a roll call of those who established molecular genetics. This is reflected in the citation analysis discussed below. At the same time that bacterial and phage genetics were the dominating themes, the symposia have covered a remarkable variety of topics. These have included "The Mammalian Fetus" (1954), "Biological Clocks" (1960), "The Synapse" (1975), and "Evolution of Catalytic Function" (1987).

The nature of the symposia changed with Demerec. The average number of participants at the first eight meetings had been 56. The same figure for the first eight of Demerec's meetings was 160, with 305 at the 1951 symposium on "Genes and Mutations." Demerec also instituted one of the hallmarks of the *CSHSQB*, the collection of photographs of participants appearing in each volume. These began in 1949, and Demerec took many of the early photographs himself. The early pictures show small groups of scientists conversing, and the earnest faces of Hermann J. Muller, Indiana University, Bloomington; Leo Szilard, University of Chicago; Jacques Monod, Pasteur Institute, Paris, France; and others look out at us. The scenes reflect an unhurried style of meeting that has now disappeared, but the organization of the week-long meeting, with the afternoons free and a picnic on the lawn of the director's house, still contrives to provide opportunities for quiet conversations.

The Impact of the *CSHSQB*

Publication of the *CSHSQB* began in 1933, but we begin our analysis in 1945, currently the earliest date in the *Science Citation Index®* (*SCI®*), and end with 1988. Table 1 gives the citation frequency distribution for the 705 articles with 50 or more citations published in that period, in absolute numbers and as a percentage of the total papers in the *CSHSQB*. These figures make an interesting comparison with those for the entire *SCI* file. Only 1.53 percent of papers in the *SCI* are cited 50 times or more, compared with about 20 percent for those published in the *CSHSQB* volumes. For the 51 most-cited papers published in the *CSHSQB*, the citations range from 218 to 1,495. The mean and median values are 389 and 299, respectively. These figures are much higher than for research journals and comparable with those for review journals. This reflects the hybrid nature of the symposia papers, that they give the authors an opportunity to develop their case as well as present data.

One estimate of the importance of scientific papers is their *SCI* impact factor. For 1988, this figure is the number of 1988 citations to a paper published in the period 1986-1987. The impact factor for the papers published in a journal is obtained by averaging the number of citations for all papers in the journal, and this figure for *CSHSQB* papers is 2.25. This compares with the figure of 1.49 for all publications in the *SCI* database, and the *CSHSQB* ranks 418th out of the 4,232 journals that were used to calculate this impact factor.

Table 2: Chronological distribution of publication dates for the 51 most-cited articles from the *Cold Spring Harbor Symposia on Quantitative Biology*, 1945-1988 *SCI®*.

Publication Year	Number of Papers
1940-1944	1
1945-1949	2
1950-1954	3
1955-1959	3
1960-1964	15
1965-1969	9
1970-1974	10
1975-1979	7
1980-1984	1

An indication of how well articles published in the *CSHSQB* "age" is given by the 1988 six-year impact factor. This is the average number of 1983-1988 citations to 1983 articles, and for the *CSHSQB* the figure is 43.12. This is far higher than the estimated figure of less than eight for the entire *SCI* file and suggests that those papers published in the 1983 *CSHSQB* have continued to be cited for longer than most papers. This reflects the data of Table 1 that show that *CSHSQB* papers are cited much more frequently than other papers in the *SCI* file.

The cited half-life of a journal is the median age of the journal's articles that were cited in a particular year. For the entire 1988 *SCI* data file, the cited half-life for a journal was 5.9. The value for the *CSHSQB* was 7.2 for the same period, again showing that the articles retain their value for longer.

Overall Citation Record

The chronological distribution of publication dates for the 51 most-cited articles is shown in Table 2. The oldest paper is that by Merkel H. Jacobs, University of Pennsylvania School of Medicine, Philadelphia, published in the 1940 volume and deals with cell permeability to ions, a classical subject in biophysics. The most recent paper was published by Werner W. Franke, German Cancer Research Center, Heidelberg, Federal Republic of Germany (FRG), and colleagues in 1982.

It is striking that 47 percent of the 51 most-cited papers were published in the 1960s. As this period might be regarded as the first golden age of molecular genetics, and given the laboratory's historically important role in this area, it is not surprising to find that symposia papers from this period are among the most highly cited; 4 of the top 5, and 12 of the top 20 papers appear in volumes published between 1960 and 1969. The 1963 symposium on "Synthesis and Structure of Macromolecules" accounts for 4 of these top 20 papers. However, it is something of an oversimplification to assume that highly cited papers come just from symposia on molecular genetics. I mentioned that symposia topics were chosen for their timeliness and importance, and not necessarily because of their relevance to research going on at the laboratory. For example, symposia topics other than molecular genetics include subjects as diverse as "Biological Clocks" (1960), "Antibodies" (1967), "The Mechanism of Muscle Contraction" (1972), and "The Synapse" (1975). All these gave rise to highly cited papers. Furthermore, when these figures are broken down by year, it is remarkable to find that 18 of the 20 symposia held between 1960 and 1979 have at least one highly cited paper. It is testimony to the laboratory directors' knowledge of what is going on in the world of biology that they have picked winners so consistently.

The recent decline in cited papers is more likely to reflect the short time that has elapsed for citations to accumulate rather than any fall in the value of symposia contributions. A glance at the titles of the symposia held through the 1980s shows that there is every reason to believe that they will continue to generate highly cited papers.

The Five Most-Cited Papers

Of the five most-cited papers in the *CSHSQB* volumes, four come from the 1960s and represent the two major fields of research in molecular biology in that period. Three papers are examples of classical molecular genetic analysis in the prere-

combinant DNA era, analysis that was characterized by the elegant exploitation of bacterial and viral genetic behavior. The other paper is an example from the field of structural molecular biology. The fifth paper comes from the late 1970s and shows how rapidly molecular genetics moved from indirect inferences based on genetic analysis to direct analysis of nucleotide sequences.

Sutcliffe

The most highly cited paper in the *CSHSQB* comes from the 1979 symposium on "DNA: Replication and Recombination." It is a technical tour de force—the determination by Greg Sutcliffe, Harvard University, of the entire 4,362 base pair sequence of the cloning plasmid pBR322. The plasmid had been developed by Francisco Bolivar and colleagues in Herbert W. Boyer's laboratory at the University of California, San Francisco, and rapidly became one of the most widely used vectors.[14,15] The continuing citation of Sutcliffe's paper reflects the fact that pBR322 is the basis for many modern vectors and his work remains the primary reference for its sequence. Sutcliffe was working in Walter Gilbert's laboratory at Harvard Medical School, Boston, Massachusetts, and used the DNA sequencing method devised by Allan M. Maxam and Gilbert.[16] Sutcliffe's comments on the project make interesting reading in relation to the current efforts to map and sequence the larger genomes of *Escherichia coli, Caenorhabditis elegans,* and humans. He found that "chemical problems were minor compared with the clerical problems of handling the data."[17] The sequence data were read on three separate occasions and the final printed sequence checked extensively against the master handwritten copy by "many people."[17] Nowadays, handwritten notes have been replaced by computer hard discs, and sequencing films are read using digitizer tablets. Sutcliffe took 13 months to sequence 4,362 base pairs of pBR322. Automated sequencing machines are now capable of generating 12,000 base pairs of sequence per day, but handling and analyzing this amount of data are becoming increasingly serious problems for large-scale sequencing and mapping.

Jacob and Monod

The symposium in 1961 was on "Cellular Regulatory Mechanisms" and the paper François Jacob and Jacques Monod, Pasteur Institute, presented is the fifth most cited (643 citations) in the *CSHSQB*. In it they reviewed the data on the regulation of protein synthesis in bacteria and discussed mRNA and operators and the operon as the unit of coordinated gene expression. It makes a striking contrast with the paper of Sutcliffe. Jacob and Monod's analysis of the elements controlling gene expression involved elegant reasoning based on genetic experimental evidence. In contrast, Sutcliffe's discussion of the origin of replication, the structures of the amp^r and tet^r, and protein coding regions of pBR322 is based on knowledge of the exact structure (nucleotide sequence) of the DNA. This paper by Jacob and Monod would probably have had a much higher citation rate but for the publication of their great review "Genetic regulatory mechanisms in the synthesis of proteins" in the *Journal of Molecular Biology*[18] just one week before the symposium. However, they were able to incorporate into the *CSHSQB* paper a discussion of McClintock's work that had been omitted from the *Journal of Molecular Biology* paper. Another highly cited symposium paper, on "The structure of DNA" by Watson and Francis H.C. Crick, was also "scooped" by publication elsewhere.[19] This talk by Watson at the 1953 symposium on "Viruses" was the first presentation of the double helix at a public meeting. It is ranked 16th among the *CSHSQB* papers.

Jacob and Colleagues

Ten years after Watson's presentation, the symposium was on "Synthesis and Structure of Macromolecules," and Jacob, now in collaboration with Sydney Brenner, Medical Research Council Laboratory of Molecular Biology, Cambridge, UK, and François Cuzin, Pasteur Institute, presented what is

the second most-cited *CSHSQB* paper with 1,216 citations. They reviewed the experimental work on DNA replication in bacteria and presented a detailed discussion of the "replicon" model that Jacob and Brenner had outlined in a brief publication in *Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences*.[20] They defined a replicon as a genetic element capable of replication and gave episomes and bacterial chromosomes as examples. The replicon is formally similar to the operon and has remained a useful concept. Jacob *et al.* discussed how the concept might relate DNA replication in eukaryotes. The name is also used to describe the many individual regions of replicated DNA in the chromosomes of higher eukaryotes.

Epstein and Colleagues

The third most-cited paper at 929 citations also comes from the 1963 symposium on the "Synthesis and Structure of Macromolecules" and shows how genetic and structural studies were beginning to come together in an analysis of the assembly of the complex T4 bacteriophage. The great advances in molecular genetics in the 1950s and 1960s depended on the choice of organism and the availability of mutants that could be selected for and mapped. Ideally the phenotypes of the mutants should reveal something of the function of the genes involved. This paper by R.H. Epstein and his colleagues, University of Geneva, Switzerland, listed the 47 genes of phage T4 for which temperature sensitive (*ts*) and amber (*am*) mutations were available and described their phenotypes. Thirty-seven of these were associated with the assembly of the virus particles, affecting, for example, the tails of the phage. A notable feature of the analysis is the realization that genes affecting particular functions were grouped together and that the sequential expression of these genes contributed to the orderly assembly of the virus particles. (The origin of the strange name "amber" for these mutations is an interesting footnote in the history of molecular biology and deserves to be better known. Robert S. Edgar, University of California, Santa Cruz, recounts that Epstein and C.M. Steinberg, then at Caltech, had promised Harris Bernstein, then at Yale University, New Haven, Connecticut, that the mutants, if any were found, would be named after his mother. They were found and "amber" is the English equivalent of "Bernstein."[21])

Table 3: The number of authors per paper for the 51 most-cited articles from the *Cold Spring Harbor Symposia on Quantitative Biology*, 1945-1988 *SCI*®.

Number of Authors per Paper	Number of Papers
10	1
9	1
8	2
7	3
5	2
4	2
3	4
2	13
1	23

Caspar and Klug

"Structural" molecular biology led to the discovery of the DNA double helix and continued to flourish in the following years, even as it seemed that the "informational" approach was in the limelight. Indeed it is often forgotten that in 1956 the Crick and Watson team made a second major contribution to molecular biology with their discussion of the structures of small or simple viruses.[22] The paper by D.L.D. Caspar and Aaron Klug, Harvard Medical School, from the 1962 symposium on "Basic Mechanisms in Animal Virus Biology," is a lucid and definitive review of their elegant studies on the structure and assembly of simple helical viruses like tobacco mosaic virus and small regular viruses like turnip mosaic virus and adenovirus. Caspar and Klug's icosahedral model for the latter group of viruses had been inspired by the designs of Buckminster Fuller and a photograph of the geodesic dome illustrated the article. The paper ranks fourth on the list with 765 citations.

Authors

There are 135 authors of these 51 papers. As shown in Table 3, one paper has 10

Table 4: Nobel laureates listed as authors of the 51 most-cited articles from the *Cold Spring Harbor Symposia on Quantitative Biology*, 1945-1988 *SCI®*, showing the field and year of their awards.

Nobelist	Prize	Year
Baltimore, David	Medicine	1975
Crick, Francis H.C.	Medicine	1962
Gilbert, Walter	Chemistry	1980
Jacob, François	Medicine	1965
Klug, Aaron	Chemistry	1982
McClintock, Barbara	Medicine	1983
Monod, Jacques	Medicine	1965
Perutz, Max F.	Chemistry	1962
Watson, James D.	Medicine	1962

authors (Epstein *et al.*) followed by Franke *et al.* with 9 authors and the papers by F.L. Graham, University of Leiden, The Netherlands, *et al.* and Wolfram Zillig, Max Planck Institute for Biochemistry, Munich, FRG, *et al.* with 8 authors. Nevertheless, 71 percent of the papers have one or two authors, giving an average of 2.6 authors per paper compared with the value of 5.1 authors per paper for the 101 most-cited life-sciences papers in 1987.[23] This may reflect the fact that *CSHSQB* articles resemble review articles and so have small numbers of authors or may indicate the style of an era when research was performed by small groups. The most frequently occurring author is Jacob, who appears four times, appropriately coauthoring two of those papers with Monod. The remaining three authors who appear twice are David Baltimore, Massachusetts Institute of Technology, Cambridge; D.S. Hogness, Stanford University School of Medicine, California; and McClintock.

Nobel Laureates

In his 1934 annual report, Harris pointed out that one of the participants in the 1934 symposium had received the Nobel Prize for chemistry. Rather disingenuously prefacing his remarks with "While we do not wish to stress the fact unduly," Harris suggested that this could be taken as an indication of the quality of the meetings.[13] This has continued to be a feature of the symposia and over 70 Nobel laureates have attended the 54 meetings held since 1933. Given this attendance record and that Nobel laureates consistently publish classic papers as judged by their citation record, it is hardly surprising that Nobel laureates should feature strongly in the most-cited papers from the *CSHSQB* (Table 4). There are nine Nobel laureates listed as authors on 12 of the top 51 papers.

However, this emphasis on Nobel laureates tends to overshadow the remarkable quality of all the scientists who attend the symposia and the quality of the science they present. The contents pages of any volume list the names of those who created molecular biology, one of the triumphs of twentieth-century science, and each new volume shows those who continue to advance that work.

Table 5: Geographic areas represented by the institutional affiliations given by authors in the Bibliography, listed in descending order by the number of papers produced (column A). B=number of papers coauthored with researchers affiliated with institutions in other countries. C=national locations of institutions listed by coauthors.

Location of Institutions		A	B	C
US		35	5	Belgium, Japan, The Netherlands, Switzerland, UK
New York	11			
California	7			
Massachusetts	6			
New Jersey	3			
Oregon	2			
Wisconsin	2			
Colorado	1			
Connecticut	1			
Maryland	1			
Minnesota	1			
Pennsylvania	1			
Tennessee	1			
UK		8	4	Denmark, France, US
France		6	1	UK
FRG		3	1	Austria, Switzerland
Japan		2	1	US
Switzerland		2	2	Austria, US
Austria		1	1	FRG, Switzerland
Belgium		1	1	The Netherlands, US
Denmark		1	1	UK
The Netherlands		1	1	Belgium, US

Geographical Distribution of Authors and Institutions

These papers came from 49 unique institutions in 10 countries and the majority of papers have US authors (35). (See Table 5.) Remarkably, however, a US institute does not head the list of institutions with the most number of papers. Instead, the Pasteur Institute leads, reflecting its position as one of the great centers for molecular biology and genetics throughout the period covered by this analysis. There are five papers from the Pasteur, authored by J.-P. Changeux, Y. Hirota, Jacob, Cuzin, and Monod. There are five institutions each with three appearances in this list: Caltech; Cold Spring Harbor Laboratory; Medical Research Council; Princeton University, New Jersey; and The Rockefeller Institute.

Conclusion

The *CSHSQB* continues to thrive as reflected in the titles of the individual volumes. "Organization of the Cytoplasm," "Molecular Neurobiology," "Molecular Biology of *Homo sapiens*"—the broad sweep of these topics reflects the confidence of the organizers and participants that molecular biology is the key to a deep understanding of the nature of living organisms. Harris left a legacy that has stimulated the generations of molecular biologists that have come each year to talk, argue, and gossip at the symposium. He is quoted in the introduction to the first volume as saying that the meetings, like the laboratory itself, "should be centers of growth and dissemination of new methods and ideas in biology."[24] The citation record of the volumes shows that Harris's aspirations have been well served by the directors who followed him. As the laboratory enters its second century with the 1990 symposium on "The Brain," there is every reason to believe that the *CSHSQB* will continue to occupy a special place in experimental biology.

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