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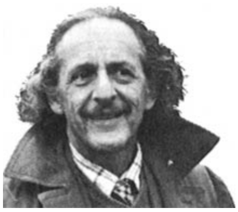

They Stand on the Shoulders of Giants: Sol Spiegelman, a Pioneer in Molecular Biology

Number 21 May 23, 1983

Science in our century has been marked by tremendous upheavals in understanding, brought about by momentous discoveries and extraordinary people. One such upheaval has occurred in biology. It began in the 1930s, when a new field, molecular biology, was born of the synthesis of five distinct disciplines: physical chemistry, crystallography, genetics, microbiology, and biochemistry.[1]

Molecular biologists try to explain biological phenomena at the molecular level. By the mid-twentieth century, they had settled several problems that plagued previous generations of biologists. For instance, proteins and nucleic acids had been known since the nineteenth century to be very large molecules, each consisting of long chains of subunits—amino acids in the case of protein, purines and pyrimidines in the case of nucleic acid. But it remained for molecular biologists to discover the long sought after *sequence* in which these subunits occurred. During the 1930s, however, answers to fundamental questions involving the structure of DNA, and the processes by which it regulates cell metabolism, still lay in the future.[1]

It was during this turbulent, revolutionary time that my friend Sol Spiegelman completed his undergraduate training and entered the field of molecular biology. He would become one of the major figures in the then infant science. Indeed, it is upon his widely acclaimed discoveries that much of the framework of the discipline now rests. Sol was still deeply involved in a number of projects when, tragically, he died following a brief illness on January 21, 1983.[2] This essay is dedicated to his memory, and to the surviving members of his family: his wife, Helen; his daughter, Marjorie; and his sons, Willard and George.

I deeply regret that Sol did not have the opportunity to read this long overdue discussion of his work. I had planned to do this as part of our series of essays on various awards in science—in particular, the Feltrinelli prize, mentioned later. Sol was one of the true giants of modern science. So it is with a mixed sense of pain and gratitude that I use this opportunity to pay tribute to a man whose genius was unique.

Sol was born on December 14, 1914, in New York City to Max and Eva (Kramer) Spiegelman. Even as a child, he exhibited a deep interest in biology.[3] But when he began his undergraduate career at the College of the City of New York in 1933, he found his biology courses so disappointing that he majored in mathematics and physics instead. However, he read biology on his own. And in 1936 and 1937, he interrupted his schooling to work as a researcher in the Richard Morton Koster Research Laboratory, Crown Heights Hospital, Brooklyn, New York. There he completed his first research pa-

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per—an analysis of the mutation of a bacterium,[4] written under the supervision of the lab's director, A. Shapiro. He returned to City College in 1938 to finish his undergraduate career, and graduated with a bachelor of science degree in 1939.

Spiegelman went on to begin graduate work in cellular physiology at Columbia University in 1940. After two years there, he continued his postgraduate studies from 1942 through 1944 at Washington University, St. Louis, Missouri. During this time, he also lectured in physics and in applied mathematics. He received his PhD from Washington University in cellular physiology and mathematics in 1944.

In his early investigations, Spiegelman wanted to describe how cells form their enzymes, and what factors determine the types of enzymes a cell has. Enzymes are proteins that stimulate, direct, and regulate the complex chemical reactions underlying the life processes of an organism. It was suspected that abnormalities in certain enzymes involved in the regulation of tissue building played a role in the development of cancer. Since it was known that the synthesis of enzymes is under direct genetic control,[5] Spiegelman felt that knowledge of how the genes themselves are controlled was vital to an understanding of malfunctioning enzymes. He began his investigations in the mid-1940s. The work occupied him for a full decade. But in the end, he and his colleagues were able to show clearly that enzymes could be altered without necessarily involving an accompanying mutation in the genes controlling them. Spiegelman suggested that changes or abnormalities in enzymes occurred when critical fractions of genes were inappropriately activated or deactivated—a phenomenon known familiarly today as switching a gene on or off.

The implications for cancer research were enormous. During most of the 1940s, the wild multiplication of some cells at the expense of others that is so characteristic of cancer had been ascribed to genetic mutation. Spiegelman's results, however, made it possible to test the idea that the genes of a cancerous cell might be intact, but that the control mechanism had gone berserk. And Spiegelman's suggestion that copies of the information encoded within DNA are transmitted into the cell's cytoplasm for protein synthesis[6,7] had great significance for future research into messenger RNA.

During 1945 and 1946, Spiegelman served as an instructor in bacteriology at Washington University School of Medicine. He was then promoted to assistant professor of bacteriology, a post he held for more than two years, until 1948. He became so widely known and admired for the elegance of his experiments that the American Cancer Society offered to set him up in his own research program with an annual budget of $25,000—a sum greater than the budget of the entire biology department.[3] Spiegelman accepted the offer. In 1948 he left St. Louis, taking the grant with him, and went to work with the US Public Health

Service at the University of Minnesota, Minneapolis. When the money ran out a year later, he left Minneapolis for the University of Illinois, Urbana. There he was named professor of microbiology, and there he would remain for the next 20 years.

By the mid-1950s, a few years after his arrival at Illinois, Spiegelman began the work that eventually led to the discovery for which he is best known. While studying the synthesis of nucleic acids, he and an associate, Benjamin D. Hall, found it necessary to pair a strand of viral DNA with a strand of matching viral RNA.[8] This was possibly the most important technique in molecular biology, then or now—RNA/DNA hybridization. The new technique led Spiegelman and his colleagues directly to the discovery that only one strand of DNA's double helix transmits the genetic information to the cell's protein-making machinery.[9]

In 1961, Spiegelman turned his attention to those viruses which contain RNA rather than DNA. The central biological dogma of the time held that the direction of transmission of genetic information was always from DNA to RNA. Thus, it was relatively easy to understand how a DNA virus used a bacterium to reproduce itself: it simply injected the cell with its own DNA, which interposed between the cell's DNA and the cellular RNA. However, in the case of viruses containing RNA rather than DNA, the problem was to describe how an RNA virus completes its life cycle in a cell dominated by DNA. Spiegelman seemed to confirm the view of RNA as subordinate to DNA when he failed to find evidence that viral RNA could somehow usurp a bacterium's genetic machinery to produce copies of itself that were made of DNA, rather than RNA.[10] However, as we shall see, just such a reverse transcription of RNA to DNA would be discovered nine years later.[11] In the meantime, Spiegelman began to search for an enzyme that would duplicate, or replicate, the viral RNA directly.

In 1963, Spiegelman and several colleagues found the enzyme they were looking for: one capable of specifically recognizing viral RNA among all the other bacterial RNA within a cell.[12] It was the first of the nucleic acid polymerases—enzymes aiding in the formation of nucleic acid—discovered to possess such a quality, which was later named template specificity.[13] Spiegelman's announcement of the discovery at a Cold Spring Harbor symposium in New York was greeted with skepticism.[14] But within two years he demonstrated, together with I. Haruna, that an enzyme coded for by still another virus, known as phage Qβ, was also template specific.[13] The enzyme proved relatively easy to isolate and purify. Within the year, Spiegelman was using Qβ's RNA replicating enzyme—or RNA replicase—to manufacture RNA in test tubes.[15]

The "artificial" RNA proved as viable and infectious as its "natural" counterpart. Spiegelman used it to observe Darwinian selection at the relatively simple molecular level, a stage removed from the complexities of evolution at the cellular level.[16,17] His experiments culminated in 1968 with the discovery of a type of RNA that was a fraction of the original Qβ phage—a "little" Qβ.[18-20] It could do little more than grab the appropriate replicase enzyme and copy itself. Presumably, this extremely limited capacity for simple replication is all that primeval nucleic acid molecules were able to achieve. Why, then, had they ever evolved beyond that capacity, to the point where they were capable of directing the synthesis and functioning of something as complicated as a cell? Spiegelman's work made possible some hypotheses and further work concerning the environmental pressures that had forced primordial nucleic acids to become increasingly complex in order to survive. Cells were evolved by nucleic acids in an attempt to create a safe, controlled environment for replication. Without the pressure to create such an environment, cellular evolution would have been a totally unnecessary complication. Spiegelman's work in this area is being continued today by his colleagues at Columbia.

In 1969, Spiegelman left Illinois to return to his native city of New York to become director of Columbia's Institute of Cancer Research and professor of human genetics and development in the university's College of Physicians & Surgeons. By the early months of 1970, Spiegelman's new lab was functioning smoothly. But in May, at the 10th International Cancer Congress in Houston, Texas, Howard Temin announced his discovery of an enzyme within RNA viruses that was capable of reverse transcription, or manufacturing DNA from RNA.[11] It was just the sort of enzyme Spiegelman himself had looked for years earlier, but had not found. Spiegelman immediately set his team to work putting Temin's results to use. They soon demonstrated that a number of other RNA viruses also carried the reverse enzyme, and that the DNA produced within the infected cell by the enzyme was a copy of the viral RNA.[21-25] The viral DNA then invaded the bacterium's nucleus. Most importantly, however, Spiegelman and his colleagues developed a "simultaneous detection test,"[25] with which they could identify the presence of RNA, reverse transcriptase, or DNA in tumor tissue. The technique made it possible for the first time to examine cancerous human tissue for evidence of viral agents.

The groundwork was laid for Spiegelman's next series of experiments: the attempt to prove a link between human cancer and viruses. An epidemiological survey by Dan Moore and colleagues had found particles identical to a mouse mammary tumor virus in the milk and breast cancers of 60 percent of American women with family histories of breast cancer.[26] Moore and Spiegelman collaborated to show that the virus contained the reverse transcription enzyme.[23] Spiegelman then derived DNA copies from the mouse tumor RNA. He reasoned that if human breast cancer *did* involve a virus, the RNA of that virus might be similar in structure to that of the mouse tumor virus. Thus, the human RNA would be attracted to the DNA derived from the mouse tumor RNA. The experiment worked. The viral DNA neatly hybridized with the RNA of a high proportion of the cancerous human tissue he tested.[27] Moreover, the association was tumor-specific, meaning that the viral DNA failed to hybridize with the human RNA from any other type of human tumor. Experiments using various types of human cancers continued to occupy him until his death. Indeed, a method of detecting cancer by assaying plasma samples for the presence of viral-related proteins, invented by Spiegelman, was recently granted a US patent.[28]

Spiegelman's achievements have been recognized with a long list of honors and awards. In 1974, for instance, he received the prestigious Albert Lasker Basic Medical Research Award for his 1965 synthesis, in collaboration with Haruna, of the infectious viral phage Qβ's RNA.[15] In 1981, he was awarded the Antonio Feltrinelli International Prize in Biology for his contributions over the previous 45 years to molecular biology, bacterial and molecular genetics, and experimental biology. The Feltrinelli prize is administered by the Italian National Academy of Sciences for the Feltrinelli Foundation, and includes a cash award of 100 million lire, approximately $83,000.[29] And in addition to holding ten honorary doctorates, Spiegelman was a member of the American Society of Biological Chemists, the American Society for Microbiology, the

Genetics Society of America, the National Academy of Sciences (NAS), and several foreign societies, to name just a few of his affiliations.

The importance and relevance of Spiegelman's work is reflected in many of ISI®'s citation studies. For example, in our recent study of the 1,000 most-cited authors publishing between 1965 and 1978,[30] he appeared as the thirtieth most-cited author. Our earlier study of the top 300 scientists cited between 1961 and 1976 revealed that Spiegelman ranked first among microbiologists and virologists.[31] When we publish the 1955-1964 *Science Citation Index*® (*SCI*®), we will have more data on the crucial 1950s.[32] But even now one can estimate that there were probably over 15,000 citations to the more than 350 papers he published during his career. The 25 most cited of his papers are presented in Table 1. Among them is an article published in *Nature*, "Characterization of the products of RNA-directed DNA polymerases in oncogenic RNA viruses."[21] It appeared on ISI's list of the 30 1970 papers most cited from 1970 to 1973.[33] And his paper, "Electrophoretic separation of viral nucleic acids on polyacrylamide gels,"[34] produced in 1967 at the International Laboratory of Genetics and Biophysics in Naples, Italy, appeared in our 1977 study of highly cited articles from Italian journals and laboratories.[35]

Spiegelman was perhaps best known for the technique of RNA/DNA hybridization. The method of cajoling DNA to seek out and pair with RNA was originally developed in 1961 in collaboration with Hall.[8] The paper reporting the original technique has been explicitly cited about 300 times. But in 1965, the technique was improved upon by Spiegelman and David Gillespie, then a graduate student at the University of Illinois. The paper reporting the improved technique[36] was quoted over 1,700 times by the end of 1982. One of the most-cited articles of the 1960s,[37] it was already selected as a *Citation Classic* for *Current Contents*® (*CC*®) in 1977.[38] Another paper by Spiegelman and colleagues[39] is featured as a *Citation Classic* in this week's *CC/Life Sciences*.

It would have been fun to ask Sol to rank each of his papers and to comment on those he considered the most important. Putting numbers on his varied accomplishments may even trivialize them, if not seen in the proper context. But it is always of interest to the public to learn how creative people view their own accomplishments.

I first met Spiegelman when he became a member of the advisory committee of the *Genetics Citation Index* (*GCI*) project. Together with L.L. Cavalli-Sforza, Joshua Lederberg, Gordon Allen, George Lefevre, Joseph Melnick, and Victor McKusick, we worked out the design for *GCI*. In the years that followed, I met Sol occasionally and was always impressed by his willingness and patience to explain to me, in terms a layperson could understand, the progress of the research in which he was currently involved. I last saw him on the occasion of the NAS award ceremonies where we congratulated Victor McKusick on receiving the NAS Award for Excellence in Scientific Reviewing.[40] We had agreed that I would come visit his lab to demonstrate and talk about our new microcomputer system for managing reprints.[41,42]

But scientists pay a price for having so many talented friends. Often, we know them best through their writings. But because we are all so caught up with our own day-to-day concerns, we may miss much along the way. Then we grow older, and good friends die unexpectedly. You remember their sparkling eyes and their enthusiasm for new projects. And you regret the lost opportunity to get to know them better.

Throughout his career, Sol always wanted to do something "useful." He tried to work on problems whose solu-

Table 1: The 25 most-cited articles by Sol Spiegelman.

Total Citations 1961-1982	Bibliographic Data
1,718	**Gillespie D & Spiegelman S.** A quantitative assay for DNA-RNA hybrids with DNA immobilized on a membrane. *J. Mol. Biol.* 12:829-42, 1965.
751	**Bishop D H L, Claybrook J R & Spiegelman S.** Electrophoretic separation of viral nucleic acids on polyacrylamide gels. *J. Mol. Biol.* 26:373-87, 1967.
475	**Ritossa F M & Spiegelman S.** Localization of DNA complementary to ribosomal RNA in the nucleolus organizer region of *Drosophila melanogaster.* *Proc. Nat. Acad. Sci. US* 53:737-45, 1965.
312	**Spiegelman S, Burny A, Das M R, Keydar J, Schlom J, Travnicek M & Watson K.** Characterization of the products of RNA-directed DNA polymerases in oncogenic RNA viruses. *Nature* 227:563-7, 1970.
305	**Kacian D L, Watson K F, Burny A & Spiegelman S.** Purification of the DNA polymerase of avian myeloblastosis virus. *Biochim. Biophys. Acta* 246:365-83, 1971.
290	**Hall B D & Spiegelman S.** Sequence complementarity of T2-DNA and T2-specific RNA. *Proc. Nat. Acad. Sci. US* 47:137-46, 1961.
268	**Hayashi M & Spiegelman S.** The selective synthesis of informational RNA in bacteria. *Proc. Nat. Acad. Sci. US* 47:1564-80, 1961.
263	**Nomura M, Hall B D & Spiegelman S.** Characterization of RNA synthesized in *Escherichia coli* after bacteriophage T2 infection. *J. Mol. Biol.* 2:306-26, 1960.
225	**Haruna I & Spiegelman S.** Specific template requirements of RNA replicases. *Proc. Nat. Acad. Sci. US* 54:579-87, 1965.
217	**Schlom J & Spiegelman S.** Simultaneous detection of reverse transcriptase and high molecular weight RNA unique to oncogenic RNA viruses. *Science* 174:840-3, 1971.
204	**Kacian D L, Spiegelman S, Bank A, Terada M, Metafora S, Dow L & Marks P A.** *In vitro* synthesis of DNA components of human genes for globins. *Nature New Biol.* 235:167-9, 1972.
202	**Spiegelman S, Burny A, Das M R, Keydar J, Schlom J, Travnicek M & Watson K.** Synthetic DNA-RNA hybrids and RNA-RNA duplexes as templates for the polymerases of the oncogenic RNA viruses. *Nature* 228:430-2, 1970.
192	**Ritossa F M, Atwood K C & Spiegelman S.** A molecular explanation of the bobbed mutants of *Drosophila* as partial deficiencies of "ribosomal" DNA. *Genetics* 54:819-34, 1966.
184	**Goodman N C & Spiegelman S.** Distinguishing reverse transcriptase of an RNA tumor virus from other known DNA polymerases. *Proc. Nat. Acad. Sci. US* 68:2203-6, 1971.
181	**Hayashi M, Hayashi M N & Spiegelman S.** Restriction of *in vivo* genetic transcription to one of the complementary strands of DNA. *Proc. Nat. Acad. Sci. US* 50:664-72, 1963.
170	**Yankofsky S A & Spiegelman S.** The identification of the ribosomal RNA cistron by sequence complementarity, II. Saturation of and competitive interaction at the RNA cistron. *Proc. Nat. Acad. Sci. US* 48:1466-72, 1962.
169	**Baxt W, Hehlmann R & Spiegelman S.** Human leukaemic cells contain reverse transcriptase associated with a high molecular weight virus-related RNA. *Nature New Biol.* 240:72-5, 1972.
161	**Yankofsky S A & Spiegelman S.** Distinct cistrons for the two ribosomal RNA components. *Proc. Nat. Acad. Sci. US* 49:538-44, 1963.
159	**Haruna I, Nozu K, Ohtaka Y & Spiegelman S.** An RNA "replicase" induced by and selective for a viral RNA: isolation and properties. *Proc. Nat. Acad. Sci. US* 50:905-11, 1963.
158	**Schlom J, Spiegelman S & Moore D.** RNA-dependent DNA polymerase activity in virus-like particles isolated from human milk. *Nature* 231:97-100, 1971.
158	**Yankofsky S A & Spiegelman S.** The identification of the ribosomal RNA cistron by sequence complementarity, I. Specificity of complex formation. *Proc. Nat. Acad. Sci. US* 48:1069-78, 1962.
140	**Ritossa F M, Atwood K C, Lindsley D L & Spiegelman S.** On the chromosomal distribution of DNA complementary to ribosomal and soluble RNA. *Nat. Cancer Inst. Monogr.* 23:449-72, 1966.
139	**Axel R, Schlom J & Spiegelman S.** Presence in human breast cancer of RNA homologous to mouse mammary tumour virus RNA. *Nature* 235:32-6, 1972.
135	**Spiegelman S, Burny A, Das M R, Keydar J, Schlom J, Travnicek M & Watson K.** DNA-directed DNA polymerase activity in oncogenic RNA viruses. *Nature* 227:1029-31, 1970.
130	**Giacomoni D & Spiegelman S.** Origin and biologic individuality of the genetic dictionary. *Science* 138:1328-31, 1962.

tions would explain big chunks of a field, rather than just a particular phenomenon. He didn't want to waste his time searching for explanations that would not be worth his efforts once he had them in hand.[43] Although his first allegiance was to basic research, he deplored the lag time between the obtaining of results and their application. "The days of the gentleman scientist are over," he once remarked. "We're professionals, we're paid well, our activities are costly, and we're going to have to listen to the people paying the bills."[44] His work stands as a monument to his determination to live up to this philosophy. A poem he wrote in tribute to a fellow cancer researcher Anna Goldfeder[45] is as applicable to Sol as it was to her. He said that her life that sang praises to the wonder of our universe, and added honor to the human condition. I can think of no better tribute to Sol himself than his own poem:

The Gentle Giants

There are the gentle giants
Who walk softly through our lives.

No shrill demand for early recognition
Commands our attentive admiration.

No blinding glare of brilliance
Announces their presence among us.

They are the quietly courageous ones
Who plant for future generations.

They are the creators and searchers
Who teach and celebrate the truth.

* * * * *

My thanks to Stephen A. Bonaduce and Terri Freedman for their help in the preparation of this essay.

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