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The 1989 Nobel Prize in Chemistry Goes to Sidney Altman and Thomas R. Cech for the Discovery of Enzymatic RNA

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The 1989 Nobel Prize in chemistry has been awarded to Sidney Altman and Thomas R. Cech for their discovery that RNA in living cells can function not only as a molecule of heredity, but also as a biocatalyst. A brief historical overview of the laureates' work is presented, and citation data for their most-cited publications are examined. Research-front analysis highlights both scientists' centrality to the field of RNA enzymology studies. The effect of the finding of RNA catalysis on origin-of-life theories is also covered.

In the late 1970s and early 1980s, two researchers, working independently, made a discovery that reversed a 50-year-old dogma in biochemistry—that the triggering and acceleration (catalysis) of chemical reactions within living cells were the exclusive domain of protein molecules called enzymes. Biophysicist Sidney Altman, Yale University, New Haven, Connecticut, and chemist Thomas R. Cech, University of Colorado, Boulder, found that ribonucleic acid (RNA), traditionally considered to be only a passive intracellular carrier of genetic information, can also act as an enzyme or biocatalyst. This unexpected and unprecedented discovery has been hailed as one of the most important scientific breakthroughs of the 1980s, and, in recognition of this, Altman and Cech were awarded the 1989 Nobel Prize in chemistry by the Royal Swedish Academy of Sciences.

Cech showed that the RNA molecule could cut and rejoin itself and thereby alter the material it produces, an operation that had previously been thought to be the sole property of proteins. Altman showed that RNA could have an independent catalytic function—that is, it could alter the makeup of RNAs other than itself, proving that RNA was indeed as much a catalyst as proteins. The work of Altman and Cech has led to a new scientific field called RNA enzymology, and old theories of the origin of life and cell function have had to be rethought. In the words of the Swedish Academy, "Many chapters in our textbooks have to be revised."[1]

Future applications of catalytic RNA could include its use as gene shears to destroy RNA molecules involved in viral infections such as the common cold or AIDS, in producing genetically engineered, disease-resistant agricultural plants, and, at some date, correcting certain hereditary diseases in both animals and humans.

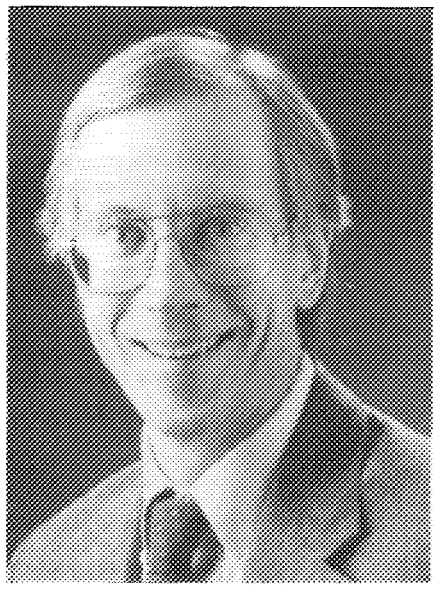
The chemistry prize carries an award of three million Swedish kronor, or about 470,000 US dollars. The 1989 award to the two Americans continued a trend of the chemistry prize throughout the 1980s, where 12 out of the 19 awards were given to US scientists. Altman and Cech became the 35th and 36th Americans to win the Nobel Prize in chemistry since it was first instituted in 1901. There have been 114 chemistry prize-winners through 1989.

Biographical Data

Sidney Altman

Sidney Altman was born May 8, 1939, in Montreal, Quebec, Canada. He spent his childhood in the west end Montreal district of Notre-Dame-de-Grace, where his father ran a grocery store. Altman left Montreal in 1956 to attend the Massachusetts Institute

Sidney Altman



Thomas R. Cech

of Technology (MIT), Cambridge, where he received a BS in physics in 1960. Seven years later, Altman earned a PhD in biophysics from the University of Colorado. Subsequently, he obtained research fellowships from Harvard University (1967-1969), Cambridge, and the Medical Research Council Laboratory of Molecular Biology (1969-1971), University of Cambridge, UK, where he worked with Sydney Brenner and Nobelist Francis H.C. Crick. Altman joined the faculty of Yale University as an assistant professor in 1971 and has been a professor of biology there from 1980 onwards. He also acted as a dean at Yale College from 1985 through last year. In 1984 Altman became a US citizen while retaining his Canadian citizenship.

Altman's honors and awards include membership in the US Academy of Arts and Sciences (1988), the US National Academy of Sciences (NAS) (1990), and the American Philosophical Society (1990); the Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Research (given by Brandeis University, Waltham, Massachusetts) 1989; the Yale Science and Engineering Association Medal (1990); the Distinguished Service Medal, Teachers College, Columbia University, New York (1990); and honorary degrees from the University of Montreal and York University, Toronto, Ontario, Canada (1990). He has also been an associate editor of *Cell*, 1983-1987, and a consulting editor of *American Scientist*, 1972-1990. Through early 1990, Altman has authored 89 publications.

Thomas R. Cech

Thomas Robert Cech was born in Chicago, Illinois, on December 8, 1947. He received a BA in chemistry from Grinnell College, Iowa, in 1970 and a PhD in chemistry from the University of California, Berkeley, in 1975. After a stint at MIT as a National Cancer Institute fellow in molecular biology (1975-1977), he joined the faculty of the University of Colorado in 1978. Cech became a full professor there in 1983. From 1988 onwards he has been an investigator of the Howard Hughes Medical Institute at the university.

Cech received the 1985 Pfizer Award in Enzyme Chemistry and was elected to membership in NAS in 1987. In 1988 he received the American Association for the Advancement of Science Newcombe-Cleve-

Table 1: The most-cited works of Sidney Altman and Thomas R. Cech. Data are from the *SCI®/SSCI®*, 1945-1989. A = number of citations. Works that appear as core papers in the historiograph in Figure 2 are indicated with an asterisk (*); research-front numbers appear in parentheses after the bibliographic data.

A	Bibliographic Data
273	***Kruger K, Grabowski P J, Zaug A J, Sands J, Gottschling D E & Cech T R.** Self-splicing RNA: autoexcision and autocyclization of the ribosomal RNA intervening sequence of Tetrahymena. *Cell* 31:147-57, 1982. (84-1651, 85-3838, 86-1923, 87-7297)
252	**Altman S & Smith J D.** Tyrosine tRNA precursor molecule polynucleotide sequence. *Nature New Biol.* 233:35-9, 1971.
208	***Guerrier-Takada C, Gardiner K, Marsh T, Pace N & Altman S.** The RNA moiety of ribonuclease P is the catalytic subunit of the enzyme. *Cell* 35:849-57, 1983. (84-1651, 85-3838, 86-1923, 87-6317, 88-3760)
191	***Cech T R, Tanner N K, Tinoco I, Weir B R, Zuker M & Perlman P S.** Secondary structure of the Tetrahymena ribosomal-RNA intervening sequence: structural homology with fungal mitochondrial intervening sequences. *Proc. Nat. Acad. Sci. USA* 80:3903-7, 1983. (85-3838, 86-1923)
172	***Cech T R & Bass B L.** Biological catalysis by RNA. *Annu. Rev. Biochem.* 55:599-629, 1986. (87-1678, 88-3760)
172	**Cech T R, Zaug A J & Grabowski P J.** *In vitro* splicing of the ribosomal RNA precursor of Tetrahymena: involvement of a guanosine nucleotide in the excision of the intervening sequence. *Cell* 27:487-96, 1981.
142	***Cech T R.** RNA splicing: three themes with variations. *Cell* 34:713-6, 1983. (85-3838)
125	**Altman S.** Isolation of tyrosine tRNA precursor molecules. *Nature New Biol.* 229:19-20, 1971.
116	**Cech T R.** The generality of self-splicing RNA: relationship to nuclear messenger RNA splicing. *Cell* 44:207-10, 1986.
116	**Stark B C, Kole R, Bowman E J & Altman S.** Ribonuclease P: an enzyme with an essential RNA component. *Proc. Nat. Acad. Sci. USA* 75:3717-21, 1978.
109	**Cech T & Pardue M L.** Cross-linking of DNA with trimethylpsoralen is a probe for chromatin structure. *Cell* 11:631-40, 1977.
88	**Altman S.** Biosynthesis of transfer RNA in Escherichia coli. *Cell* 4:21-9, 1975.
81	**Cech T R & Hearst J E.** Electron microscopic study of mouse foldback DNA. *Cell* 5:429-46, 1975.
76	**Guthrie C, Seidman J G, Altman S, Barrell B G, Smith J D & McClain W H.** Identification of tRNA precursor molecules made by phage T4. *Nature New Biol.* 246:6-11, 1973.
72	**Cech T R & Pardue M L.** Electron microscopy of DNA crosslinked with trimethylpsoralen: test of secondary structure of eukaryotic inverted repeat sequences. *Proc. Nat. Acad. Sci. USA* 73:2644-8, 1976.
65	**Altman S & Lerman L S.** Kinetics and intermediates in intracellular synthesis of bacteriophage T4 deoxyribonucleic acid. *J. Mol. Biol.* 50:235-61, 1970.
61	**Cech T R, Rosenfeld A & Hearst J E.** Characterization of the most rapidly renaturing sequences in mouse main-band DNA. *J. Mol. Biol.* 81:299-325, 1973.
58	**Cech T R & Rio D C.** Localization of transcribed regions on extrachromosomal ribosomal RNA genes of Tetrahymena thermophila by R-loop mapping. *Proc. Nat. Acad. Sci. USA* 76:5051-5, 1979.

land Award, the Royal Netherlands Academy of Sciences Heineken Prize, the Gairdner International Award for Outstanding Achievement in Medical Science (given by the Gairdner Foundation, Willowdale, Ontario), and the Albert Lasker Basic Medical Research Award (given by the Albert and Mary Lasker Foundation, New York). In 1989 Cech received the Lewis S. Rosenstiel Award, which he shared with Altman. Cech also has been an associate editor for *Cell* (1986-1987) and serves on the editorial board of *Genes and Development* (1987 onwards). Cech has authored 105 publications through early 1990.

Sidney Altman: RNase-P and the Overturning of a Dictum

Altman's early research focused on RNA processing, in particular that of transfer RNA (tRNA). The tRNAs are the nucleic acid molecules responsible for delivering individual amino acids to the protein-synthesizing machinery of a cell. In 1970 Altman and his colleagues isolated a tRNA-processing enzyme found both in bacteria and higher cells and named it RNase-P.[2] The characteristics of the enzyme are unusual in that it contains RNA and protein in a single

package. This enzyme is responsible for one of the reactions that produces tRNA.

RNase-P is found in human intestinal bacteria, *Escherichia coli*, and participates in the activation of tRNA by removing a portion of the precursor to tRNA, which is unnecessary for the function of the mature tRNA molecule. Altman's early work in observing and characterizing enzymatic activity affecting tRNA resulted in a series of papers in the early 1970s. Several of these appear in Table 1, a listing of the two Nobel laureates' highly cited works. Altman's most-cited work, "Tyrosine tRNA precursor molecule polynucleotide sequence,"[3] coauthored with J.D. Smith, Medical Research Council Laboratory of Molecular Biology, and published in *Nature New Biology* in 1971, dates from this period.

In 1976 one of Altman's graduate students at Yale University, Ben C. Stark, showed that *both* the RNA and protein were essential components of the active enzyme.[2]

Altman and his colleagues at Yale also found that RNase-P seemed to lose its enzymatic abilities when the RNA portion was destroyed or removed. Originally, Altman thought that the RNA component of the enzyme RNase-P did not serve any active enzymatic function because of the well-established "fact" that only proteins could serve as catalysts.

The finding that RNA plays an essential role in an enzyme directly challenged the long-held biochemical dogma of "proteins only as catalysts." Not surprisingly, Altman's work met with some resistance in the biochemical community.[2,4,5] Altman's colleague, Yale biologist Joel Rosenbaum, observed to a *Washington Post* reporter: "It was heresy.... What Sidney was saying was so revolutionary he had trouble getting his papers published."[4]

Indeed, it was two years after the Yale group's experiments were completed that the paper "Ribonuclease P: an enzyme with an essential RNA component" was published in the *Proceedings of the National Academy of Sciences of the USA* (*PNAS*) in 1978.[6] Altman himself acknowledged personal reluctance to accept the revolutionary finding that RNA was a necessary, if not sufficient, component of RNase-P. In his Nobel lecture, he recalled: "When Stark's experiments were published we did not have the temerity to suggest, nor did we suspect, that the RNA component alone of RNase-P could be responsible for its catalytic activity. The fact that a simple enzyme had an essential RNA subunit, in itself, seemed heretical enough."[7]

The paper reported the authors' findings in cautious and circumspect language. While stating that "the presence of a discrete RNA component in RNase-P appears to be essential for enzymatic function," the authors acknowledged that "we do not know if the RNA component...is needed for stabilization of the protein moiety [of RNase-P] or if it plays a more active role in substrate recognition."[6] Although the authors offered a "model...for enzyme-substrate recognition in which this RNA component plays an important role," they also stressed that "this scheme is hypothetical: we have no direct evidence that the critical positioning of RNase-P on precursor tRNA substrates is determined by RNA-RNA rather than by protein-RNA interactions."[6]

According to *Science Citation Index®* (*SCI®*) data, the paper excited significant—but not extraordinary—initial interest as judged by citations. It was cited once in 1978 and 13 times in 1979. Citations nearly doubled to 23 in 1980 and 21 in 1981. They declined sharply to six in 1982, and the paper continued to be cited at about this level through 1988. Clearly, the paper reported an intriguing and even sensational hypothesis. But the impact of this hypothesis was perhaps limited by the lack of hard experimental evidence to convince researchers of RNA's enzymatic properties. Experimental verification was indeed reported four years later in 1982, and it came about serendipitously from the work of Cech.

Thomas R. Cech: Ribosomal RNA and Serendipitous Discovery

Cech's research concentrated on understanding how introns (or intervening se-

quences) are removed from RNA. Introns were first seen in the mid-1970s, when methods for determining nucleotide sequences were introduced.[8] Researchers found that genetic material in some animal viruses as well as genes encoding proteins in hemoglobin and antibody molecules have extra stretches of DNA in their interiors.

In 1977 Cech became interested in the regulation of gene expression. He initiated efforts to isolate the protein enzyme that was presumed to control a splicing reaction in which certain extraneous segments are selectively removed from RNA molecules. Cech and his group of researchers at the University of Colorado developed an *in vitro* transcription system using a ribosomal RNA (rRNA) gene from the single-celled microorganism *Tetrahymena thermophila*. The gene from the microorganism happens to contain a 400 base pair intron sequence.[2]

Some of Cech's early results with *in vitro* splicing of *Tetrahymena* rRNA appeared in a paper entitled "*In vitro* splicing of the ribosomal RNA precursor of Tetrahymena: involvement of a guanosine nucleotide in the excision of the intervening sequence."[9] This 1981 *Cell* paper, Cech's third most-cited publication, can be seen as the penultimate work—"on the doorstep" as it were—to the experimental verification of RNA as a catalyst that was to be published the following year by Cech and colleagues.[10]

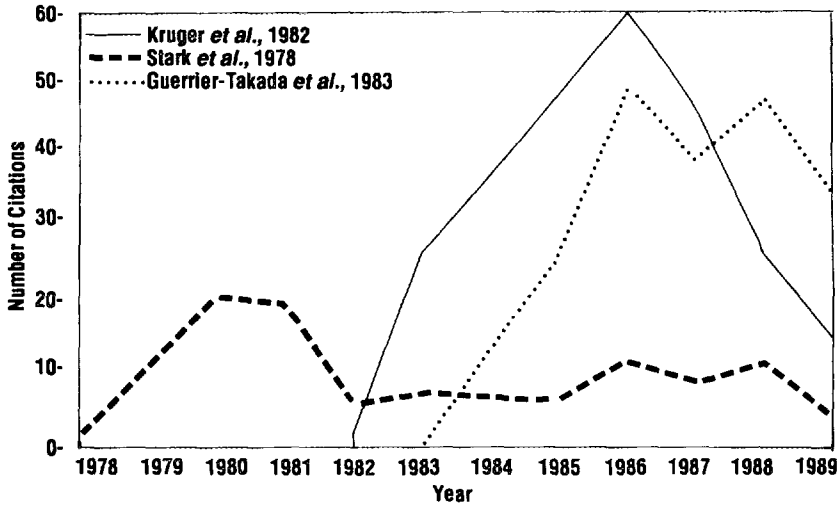
During development of the *in vitro* transcription system, the Boulder group made the surprising discovery that RNA splicing also was occurring.[2] This unexpected result led Cech to attempt the isolation and definition of the enzyme responsible for the splicing reaction. An experiment was set up where precursor rRNA was to be used with cell-nuclei extract-containing enzymes, as was an enzyme-free control without the extract. After incubation, the enzyme with cell-nuclei extract experiment worked. But so did the control experiment—it, too, showed that splicing was occurring. Cech's initial reaction was to suspect that the result was due to a methodological error that may have contaminated the control experiment. He recalled the comment he made to his colleague Art Zaug and the painstaking follow-up experiments: " 'Well Art, this looks very encouraging, except you must have made some mistake mixing up the control sample.' Yet several careful repetitions [five times] of the experiment gave the same result: [RNA splicing had] occurred independent of the addition of nuclear extract, and therefore apparently independent of any enzyme."[11]

The experimental data made Cech realize that RNA was itself closely associated with RNA splicing activity. Further experiments established that no protein was required for the splicing reaction to take place. When a nonsense segment is removed from the RNA molecule, the loose ends thus formed are then joined together. Still, the self-splicing RNA molecule could not be considered a true enzyme because it could perform the operation only once and was itself changed in the process. (True enzymes can catalyze a reaction repeatedly while emerging from the activity unchanged.) Later, in 1986, Cech and his colleagues reported that the portion of the RNA molecule that had been removed then modifies itself subsequently so that it can function as an RNA-synthesizing enzyme—meaning that catalytic RNA could also make new RNA.[2]

In 1982, when Cech and his group of researchers published their findings in *Cell* that RNA indeed was a biochemical catalyst, it created a sensation, as well as instant acclaim for Cech from his peers. According to *SCI* data, "Self-splicing RNA: autoexcision and autocyclization of the ribosomal RNA intervening sequence of Tetrahymena" has garnered over 270 citations through 1989, making the paper Cech's most-cited work.[10]

The following year Altman and his group at Yale, in collaboration with Norman Pace and his group at the University of Colorado Medical Center, Denver, published a paper that announced the discovery of the enzymatic activity of the RNA molecule associated with RNase-P. The 1983 *Cell* paper, entitled "The RNA moiety of ribonuclease P is the catalytic subunit of the enzyme,"[12] demonstrated that under non-

Figure 1: Distribution of year-by-year citations to three of the papers in Table 1.



physiological conditions, the RNA subunit of RNase-P alone cleaves tRNA precursors. It received 14 citations in 1984, 26 in 1985, and 51 in 1986. Through 1989, the paper accumulated over 200 explicit citations, making it Altman's second most-cited paper.

The graph in Figure 1 shows the citation records of these two landmark papers, which provide convincing experimental verification of RNA's catalytic properties. Also shown are annual citations to Altman's 1978 *PNAS* paper, discussed earlier, that first hypothesized an essential role for RNA in an enzymatic reaction.

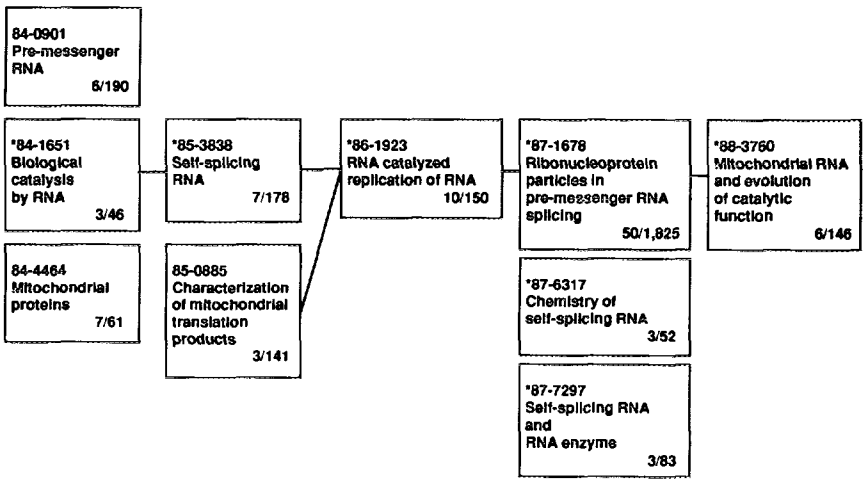
Catalytic RNA segments quickly came to be known as "ribozymes," and researchers all over the world turned to finding out how widespread these ribozymes really are. Today, nearly 100 ribozymes have been identified. Work continues on identifying the structure of enzymatic RNA, where there are clear indications that catalytic RNA possesses a specific three-dimensional framework in the same manner as proteins. According to Altman, efforts are under way to crystallize RNase-P for X-ray crystallographic studies.[2]

Historiographic Data Reveal Centrality of Laureates' Research

Figure 2 is a historiograph of ISI® research fronts on RNA catalysis from 1984 through 1988. A research front (specialty) is formed by the connections made by scientists in their referencing patterns. Using a method called co-citation clustering, it is possible to order automatically the scientific literature into bibliographically distinct and intellectually coherent units. Articles that are frequently cited together by current papers constitute the "core" of the specialty. The research front, in part, is composed of citing articles and is named from phrases co-occurring in these citing titles.

The historiograph in Figure 2 is a graphic display of citation data that can be used to show key scientific events: their chronology, their interrelationships, and their relative importance.[13] Of special interest in the historiograph is the linkages between fronts, showing antecedent and follow-up research. These linkages are based on the percentage of similarity of the core documents that each front cites.

Figure 2: Historiograph of work in biological catalysis by RNA. The number of core/citing papers is given at the bottom of each box. An asterisk (*) next to the research-front number indicates that Thomas R. Cech and/or Sidney Altman are core authors.



Seven of the nine research fronts in Figure 2 contain core papers by Cech and Altman—specifically, the pathbreaking *Cell* papers that experimentally demonstrated that RNA is an enzyme, which are discussed earlier. Both appear in research fronts #84-1651, "Biological catalysis by RNA," #85-3838, "Self-splicing RNA," and #86-1923, "RNA catalyzed replication of RNA." In addition, Cech's 1982 *Cell* paper is a core document in research front #87-7297, "Self-splicing RNA and RNA enzyme," while Altman's 1983 *Cell* paper also appears in research front #88-3760, "Mitochondrial RNA and evolution of catalytic function," and #87-6317, "Chemistry of self-splicing RNA." Other papers by the authors are also core documents in research fronts #85-3838, #86-1923, and #88-3760 as well as #87-1678, "Ribonucleoprotein particles in pre-messenger RNA splicing."

It is interesting to note that two of the linked research fronts, #86-1923 and #87-1678, indicate an explosion of research on RNA enzymology. The number of core papers increased fivefold, from 10 in 1986 to 50 in 1987. The number of citing works increased 12-fold during this two-year period, from 150 to more than 1,800.

It should also be pointed out that both laureates appear as core authors in research fronts prior to those shown in Figure 2. Two of Altman's most-cited works—"Tyrosine tRNA precursor molecule polynucleotide sequence,"[3] and "Biosynthesis of transfer RNA in Escherichia coli"[14]—appeared in research fronts during the years 1975-1977 and 1980; one of Cech's papers, entitled "Characterization of the most rapidly renaturing sequences in mouse main-band DNA," is a core paper in a 1976 research front.[15]

Conclusion: Catalytic RNA and the Origins of Life

The scientific community has long been fascinated by the origins of life and has attempted to elucidate the conditions and mechanisms that gave rise to the incredible diversity of living organisms. For some time there had been a dilemma—how could life have arisen if the DNA molecules of the genetic material could only multiply and be deciphered with the help of proteins, whereas proteins can only be built up with genetic information from DNA? In the words of Cech, "Which came first, the nucleic acid or the protein, the information or the function?"[11]

With the discovery that RNA can be both genetic material and enzyme at the same time, the dilemma appears to have been solved—neither DNA nor proteins came first. RNA is the "grandfather" molecule from which DNA and proteins descended.[1]

There appears to be some corroborating evidence for this. Ribozymes are excellent catalysts, although at present scientists find that enzymatic RNA remains limited in versatility. There are also indications that ribozymes can recognize and manipulate amino acids directly (RNA can form a specific binding site for at least one amino acid[16]). More research needs to be done before a consensus can be reached, but all these findings point to a prebiotic, primordial soup on Earth four billion years ago that was ruled by RNA.

But a big question remains: From what did RNA itself evolve? RNA is not a simple molecule, and some life scientists feel that it is too elaborate to come into being just by random reactions, so researchers are looking for more likely candidates. There have been discussions recently in the scientific press as to what chemical processes or alternative molecules to RNA might have "kick-started" life on Earth.[17]

This concludes our examination of the 1989 Nobel Prize in chemistry. In a forthcoming essay, as is our custom, we will look at 1989 Nobelists in physics from a citationist perspective.

* * * * *

My thanks to C.J. Fiscus and Peter Pesavento for their help in the preparation of this essay.

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