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The 1984 Nobel Prize in Physics Goes to Carlo Rubbia and Simon van der Meer; R. Bruce Merrifield Is Awarded the Chemistry Prize

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Last week we reviewed the 1984 Nobel laureates in medicine: immunologists Niels K. Jerne, Georges J.F. Köhler, and César Milstein.[1] In this week's essay the prizewinners in physics and chemistry are discussed.

The 1984 physics prize was shared by Carlo Rubbia, Harvard University and the European Center for Nuclear Research (CERN), Geneva, Switzerland, and Simon van der Meer, also of CERN. The Nobel committee honored "their decisive contributions...which led to the discovery of the field particles W and Z, communicators of the weak interaction."[2] The 1984 Nobel Prize in chemistry was awarded to R. Bruce Merrifield, Rockefeller University, New York, for his development of a "simple and ingenious" method for chemical synthesis on a solid matrix.[3]

Physics

Rubbia and van der Meer were selected less than two years after the identification of the W and Z particles, a remarkably short period for recognition by the Nobel committee. The scientific achievement of these two physicists and their colleagues culminated a half-century of theory and experiments on the so-called "weak force." Along with gravity, electromagnetism, and the "strong force" that binds together particles in the atomic nucleus, the weak force is one of the four fundamental forces in the universe. The weak force is responsible for certain kinds of radioactive decay. It also controls the reactions that result in the sun's generation of energy.[4]

Rubbia, van der Meer, and the hundreds of scientists and technicians at CERN were seeking the ultimate confirmation of what is known as the electroweak theory. This theory states that two of the fundamental forces—electromagnetism and the weak force—are actually facets of the same phenomenon. The 1979 Nobel Prize in physics was shared by Sheldon Glashow and Steven Weinberg, Harvard, and Abdus Salam, Imperial College of London, for their contributions to the electroweak theory. I discussed their work in my examination of the 1979 Nobel laureates.[5]

The daunting task facing the scientists at CERN was to find evidence of the subatomic exchange particles that communicate the weak force. Theorists speculated that, in the same way that tiny particles of light called photons communicate electromagnetism, the weak force is transmitted by another, related group of particles. These very dense communicators of the weak force—the so-called intermediate vector bosons designated W^+, W^-, and Z^0—had been predicted by Weinberg and Salam, independently of one another, in the late 1960s.[6,7] The task of actually finding these particles remained. Groups of scientists at CERN and at the National Accelerator Laboratory (Fermilab), Batavia, Illinois, had attempted to release the W particle. But the particle accelerators at these facilities did not have enough power to produce particles of the mass that Weinberg and Salam had predicted.[8]

Rubbia proposed the use of a collider, which would smash together two counter-rotating beams—one composed of protons, the other of antiprotons. The resulting collisions, according to Rubbia and his colleagues, would provide sufficient energy to reveal the W and Z particles. However, this idea presented formidable obstacles. Rubbia had proposed converting the existing accelerator at Fermilab into a proton-antiproton collider, but his idea was rejected. He then took his plan to the European scientific community and CERN. There, the idea was approved. In 1978 the tremendous effort began to convert CERN's four-mile, underground Super Proton Synchrotron into a proton-antiproton collider.

One of the most serious problems was the production and storage of antiprotons inside the collider. Antiprotons do not exist in ordinary matter and must be produced in high-energy particle collisions.[2] Accumulating the necessary millions of antiprotons and regulating their passage around the collider was a key experimental problem. Rubbia turned to a CERN colleague, Simon van der Meer. In 1968 van der Meer had written a paper (not published until 1972) that described "stochastic cooling"—a method for increasing the density of a beam of protons.[9] Work began at CERN to adapt van der Meer's technique to the accumulation of an unprecedented quantity of antiprotons.

The efforts of van der Meer and his coworkers led to the construction of the Antiproton Accumulator, a storage ring 154 feet in diameter in which millions of newly created antiprotons are "cooled" into a dense beam. Inside the ring, sensors detect deviations in the individual orbits of the antiprotons, and, in millionths of a second, an electronic signal is flashed across the chord of the circle to intercept and tighten the beam of antiprotons as it races around the ring. Both the beam and the correcting signal travel near the speed of light.[10] The process is repeated millions of times until, after approximately 24 hours, enough antiprotons have been accumulated to be fed into the larger ring, where they can be collided with the counter-rotating beam of protons.

Another problem facing the scientists at CERN was detecting the effects of these proton-antiproton collisions. In 1978 Rubbia turned his efforts to the creation of a detector in which the collision experiments would actually take place. This 2,000-ton device, named Underground Area 1 (UA1), took three years and $20 million to build.[11] Designed essentially as a series of boxes within boxes, UA1 comprised an intricate collection of sensing devices and processors that enabled the scientists to detect the fleeting presence of the W and Z particles in the midst of all the particles created in the collision of the two beams. An immensely complicated device, UA1 set new standards for detectors in colliding-beam experiments. A second, somewhat simpler detector, UA2, was added as a backup.[2]

Collision experiments began in 1981, but much of the key data were taken from collider runs late the next year. After examining information from millions of collision "events," the scientists focused their attention on a handful of collisions that seemed significant. Analysis of the data showed signs of the predicted "signature" of the W particle: a single electron shooting off at a wide angle from the colliding beams. Measurements of the energy expended during these collisions—the so-called "missing energy"—pointed to the existence of another signature particle, a neutrino. This all-but-invisible particle veered off from the collision in the opposite direction with force equal to that of the electron. Calculations showed that the mass of the W particle was equivalent to that predicted by theoretical models. Rubbia's UA1 group announced the discovery of the W particle in 1983, closely followed by the UA2 group.[12,13] The discovery of the Z particle came a few months later.[14,15]

Rubbia

Rubbia was born in Gorizia, Italy, in 1934 and attended the University of Pisa.

His graduate work in physics was completed at Columbia University, New York. In 1961 Rubbia returned to Europe to join CERN.[16] Since 1970 he has divided his time between CERN, where he is senior physicist, and Harvard University, where he is a professor of physics.

Using the *Science Citation Index®* (*SCI®*), we have determined Rubbia's most-cited works for the period 1955-1984. The list is based on ISI®'s internal "all-author" data, since Rubbia does not appear as first author in any of the papers. The fifth most-cited work is the *Physics Letters B* paper in which Rubbia and colleagues announced the discovery of the W particle.[12] Although only two years old, this paper has already been cited over 170 times—a dramatic demonstration of its immediacy and impact. The bimonthly *SCI*s show that the paper also was cited in 56 publications in the first six months of 1985. Also highly cited is the paper by Rubbia and colleagues that discusses the identification of the Z particle.[14] This work has been cited over 160 times in the two years since publication—and over 80 times in the first half of 1985. Both papers will be included in our forthcoming study of the most-cited 1983 articles in the physical sciences.

The most-cited paper, "Observation of new-particle production by high-energy neutrinos and antineutrinos," has received over 300 citations since its publication in 1975.[17] Another highly cited paper is "Small-angle proton-proton elastic scattering at very high energies (460 $GeV^2 < s < 2900$ GeV^2)," published in 1972.[18] The work has been cited 249 times.

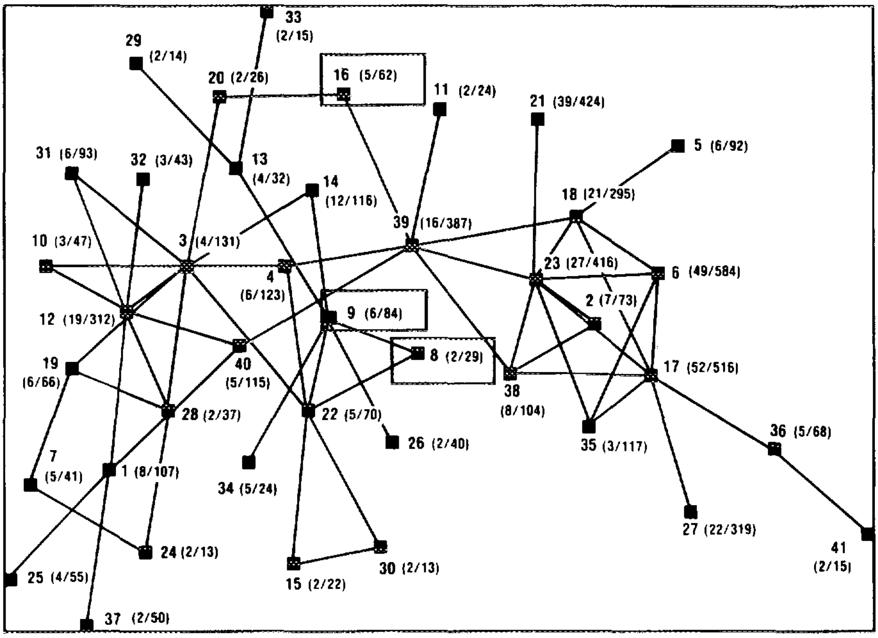
Table 1 lists some of the ISI research fronts in which works by Rubbia, van der Meer, and colleagues are core documents. The fronts cover 10 years of research in high-energy particle physics. Some of these papers appear regularly in our annual inventory of research fronts. A 1974 paper from *Physical Review Letters*, for example, "Observation of muonless neutrino-induced inelastic interactions,"[19] is core to six fronts, covering the years 1974 to 1980.

Three of the research fronts in Table 1 appear in Figure 1, which presents the higher level map of cluster #83-0021, "Gauge theory of quark interactions and jet production in high-energy collisions at the CERN Collider." This map shows

Table 1: ISI® research fronts in which works by Rubbia and van der Meer occur as core documents. A = year and number. B = name. C = number of core papers. D = number of citing papers.

A	B	C	D
74-0039	Gauge theory	85	604
75-0203	Analysis of weak currents in neutrino scattering, construction of charmed quark models and related studies in hadronic weak interactions	2	32
76-0120	Large transverse momentum	22	231
77-0031	Neutral currents	41	480
77-0316	Studies of quark-parton models in deep inelastic scattering processes and scaling in charged-current neutrino scattering.	4	61
77-0412	Observation of trimuon, dimuon and other multilepton events in neutrino interactions and search for heavy leptons	3	36
78-0024	Weak neutral current reactions	49	368
78-0463	Neutrino interactions	3	75
80-0481	Weinberg-Salam unified theory of weak and electromagnetic interactions, gauge unification of fundamental forces and spontaneous symmetry breaking	21	276
82-0022	Particle production in high-energy collisions at the CERN-SPS Collider	3	35
83-0639	Transverse momentum spectra of hadron and jet production at high energies at the CERN Collider	2	29
83-0645	Koba-Nielsen-Olesen distributions and other types of multiplicity scaling in high-energy collisions	6	84
83-1158	Experimental evidence for bosons from colliders	5	62
84-0022	Weak boson production, electroweak interactions and Higgs masses	23	468

Figure 1: Higher level map for cluster #83-0021, "Gauge theory of quark interactions and jet production in high-energy collisions at the CERN Collider," showing links between research fronts. A = 1983 research-front number. B = research-front title. Numbers in parentheses indicate core/published papers.



Key

A **B**

1 0027 Methods of renormalization and quantization of gauge theories
2 0029 Composite models of quarks and leptons
3 0119 Quantum-chromodynamic studies of particle production from high-energy collisions
4 0120 Electron-positron annihilation and jet production at high energy
5 0258 Chiral supergravity and axial anomalies in higher dimensions
6 0319 Magnetic monopoles in a supersymmetric inflationary universe; quantum model of grand unification theory and cosmology
7 0612 Relativistic electron scattering and muon scattering from nuclei at high energy
8 0639 Transverse momentum spectra of hadron and jet production at high energies at the CERN Collider
9 0645 Koba-Nielsen-Olesen distributions and other types of multiplicity scaling in high-energy collisions
10 0649 Quantum-chromodynamic corrections and the Drell-Yan model of lepton pair production
11 0650 Models for nonleptonic decays
12 0702 Quantum-chromodynamic analysis and renormalization-group approach to annihilation processes and quark production
13 0887 Multiparticle production in high-energy hadron-nucleus collisions
14 0971 Parton and other model predictions and the determination of particle production during hadron collisions
15 1021 Hadron and other large particle production from nuclei p and other nuclear collisions at high energy
16 1158 Experimental evidence for bosons from colliders
17 1184 Yang-Mills and other supersymmetric grand unification theories with supergravity effects
18 1236 Invisible axions and symmetry
19 1371 Measurement of nucleon structure by deep inelastic lepton scattering from iron, deuterium and other nuclei
20 1482 Photoproduction of hadrons and other heavy charmed particles
21 1720 Massive neutrinos and beta decay in galaxy formation and universe models
22 1757 Hadron and jet production and fragmentation at CERN Collider

	A	B
23	2071	Proton decay, left-right symmetry and other aspects of grand unification models; quarks, leptons, and supersymmetric generalizations
24	2087	Photon structure, photoproduction and high-energy physics
25	2188	Gauge theories, superspace and quantization
26	2382	High-energy hadron interactions of cosmic-ray multiplicity collisions
27	2796	Characterization of supergravity and supersymmetric Kaluza-Klein theories
28	2857	Application of quantum chromodynamics for quark production from heavy-particle scattering
29	3073	Studies of high-energy hadron-nucleus interactions
30	3221	Hadron and other particle production from $\bar{p}p$ collisions in CERN ISR
31	3528	Quantum-chromodynamic mechanisms for particle production from photon collisions
32	3779	One-loop renormalization of the theory for vacuum energy of a scalar field in curved space-time
33	4075	Particle production and cross sections of high-energy hadron-nucleus collisions
34	4499	Analysis of products formed in cosmic-ray showers
35	4624	Higgs effect and the calculation of supersymmetric effective potentials
36	5282	Supergravity and grand unification theories
37	5319	Quantum gravity, the Kaluza-Klein theory, and other gauge theories of curved space-time
38	5361	Aspects of supersymmetric technicolor models in unification theories
39	5733	Quark mixing and gauge models of electroweak interactions
40	6469	Gauge theory approaches to quantum chromodynamics and quark interactions
41	9365	Acausality of standard relativistic wave equations with Harish-Chandra degree four and spin 3/2

the citation links between the 41 1983 research fronts dealing with collision experiments at the CERN facility.

Not surprisingly, our previous studies of most-cited works in the physical sciences have included papers by Rubbia and his collaborators.[20-23] Rubbia, furthermore, was one of the 77 physicists we identified in our study of the 1,000 most-cited contemporary scientists from 1965 to 1978.[24,25]

van der Meer

Simon van der Meer was born in The Hague, The Netherlands, in 1925. He obtained a degree in physical engineering from the University of Technology, Delft, in 1952 and joined the staff of CERN in 1956. There, van der Meer became involved in the design and construction of various components for CERN's proton-synchrotron accelerator. However, his interest was growing in "matters more directly concerned with the handling of particles."[26] His projects during the 1960s included the design of a "neutrino horn," a focusing device for increasing the density of a beam of neutrinos. Van der Meer also designed a storage ring for an experiment that investigated the properties of an elementary particle known as a muon. In the early 1970s, van der Meer was responsible for magnet power supplies for the Super Proton Synchrotron (SPS) accelerator.[26]

It was van der Meer's concept of stochastic cooling, however, that proved crucial in the search for the W and Z particles. The accumulation of antiprotons, as I have mentioned, presented difficult obstacles. A general law known as Liouville's theorem predicted that electromagnetic fields would be unable to reduce the oscillations and energy spread of a particle beam in a storage ring. Seeing beyond this theorem, van der Meer based his ideas on statistical studies of large numbers of particles in accelerators. He concluded that, with proper placement of electrodes and amplifiers, it would be possible to monitor and modify the orbit of each particle and thus drive all the particles toward a common trajectory.[2] As noted earlier, van der Meer formulated the theory of stochastic cooling in 1968 but considered the idea too farfetched to justify publication.[8] By the mid-1970s, electronics technology had improved sufficiently to make the idea feasible. With subsequent refinements by van der Meer and his colleagues at CERN, stochastic cooling served as the basis for the Antiproton Accumulator ring, without which the W and Z particles could not have been found.

Van der Meer's most-cited work is the 1983 paper from the UA1 group discussing the discovery of the W particle.[12] As noted earlier, this paper has been cited over 170 times. Also among the most-cited works of van der Meer and colleagues are papers dealing with the magnetic properties of the muon.[27,28] Interestingly, these papers, and van der Meer's other most-cited works that we identified, have not received an unusually high number of citations. The 1972 paper on the muon,[28] for example, and van der Meer's original paper on stochastic cooling[9] have each received around 30 citations. This demonstrates, as noted in our analysis of the 1979 prizewinners, that the importance of a scientist's work is not always reflected by citation frequency.[5]

Figure 2 presents a historiograph, or microhistory, of research leading to the discovery of the W and Z particles. Each box indicates an annual research front and the number of core (cited) and published (citing) papers. As I've noted previously, these flowcharts demonstrate the continuity as well as branching of research fronts from year to year.[29]

Chemistry

In 1959 Bruce Merrifield wrote in his research notebook, " 'There is a need for a rapid, quantitative, automatic method for the synthesis of long-chain peptides.' "[3] Twenty-five years later, Merrifield's innovations in this area were rewarded with the Nobel Prize.

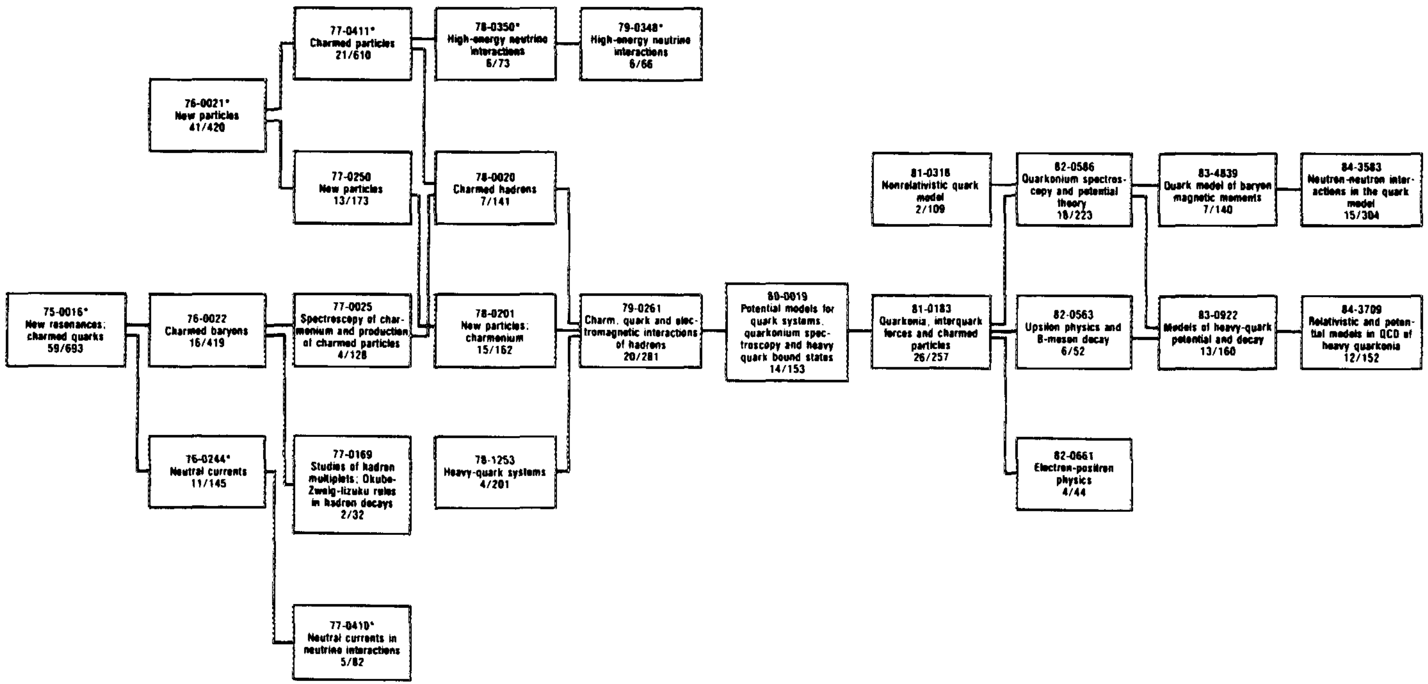
Proteins, the key components of living organisms, are made up of long chains of peptides. These peptide chains consist of amino acid subunits joined together by what are known as peptide bonds. The major problem in peptide synthesis lies in the formation of these bonds that couple amino acids. Amino acids contain several different reactive groups: a carboxyl group, an amino group, and often another group on a side chain. To prevent unwanted combinations in the formation of a peptide chain, all but one of these groups must be chemically protected, or "blocked."[30] Further additions to the peptide chain must be preceded by this system of protecting and "de-protecting" the various amino acid groups. With conventional methods of peptide synthesis, it is necessary to isolate and purify the products of these reactions each time a new amino acid is added to the chain. However, crystallization, the usual method for purifying organic compounds, often leads to still more unwanted by-products, requiring further purification through a complicated series of procedures. In short, the formation of a long peptide chain is a laborious and time-consuming procedure.

Merrifield's "simple and ingenious" idea was to chemically anchor the first amino acid in the chain to a solid support and then add the rest of the amino acid units one at a time.[3] With the growing chain anchored to an insoluble matrix, all intermediate peptide products would also be insoluble. Therefore, any undesired reactants or by-products, which would still be in solution, could be eliminated through regular filtering and washing rather than through tedious crystallization methods.[31] When the required amino acids were assembled, the peptide chain could be separated from its support.[30] This method promised to be much faster than conventional peptide synthesis, with greater yields at each step in the building of the peptide chain.

The first requirement was to find a suitable matrix on which to anchor the peptide chain. Merrifield experimented with a number of polymers before settling on a polystyrene resin in the form of beads about 0.002 inch in diameter. One such bead was capable of holding about one trillion peptide chains.[30] Even though he had found a viable support substance, Merrifield still had to determine the proper reagents and conditions to ensure that the coupling of the amino acids would be rapid and complete. The development of Merrifield's solid-phase technique took about three years.

In 1962 Merrifield succeeded in using his method to form a four-unit peptide chain, a tetrapeptide. He published his

Figure 2: Historiograph of fronts leading to the discovery of field particles W and Z, communicators of the weak interaction. Numbers at the bottom of each box refer to the number of core/published papers for that year. Asterisks indicate fronts that include Rubbia and van der Meer core papers.



results early the following year in the *Journal of the American Chemical Society* (*JACS*).[32] In 1964 he used the solid-phase method to synthesize bradykinin, a hormone with nine amino acids.[33] He then turned his efforts to automating solid-phase synthesis. Working with colleagues at Rockefeller University, he developed the first automated peptide synthesizer in 1965.[34] The device included vessels for storing and mixing the amino acids and other required reaction chemicals, and a "programmer" for controlling the reactions.

Using the automated synthesizer, Merrifield was able to assemble more complicated peptide chains. In 1966 he and Arnold Marglin, a colleague at Rockefeller University, synthesized a simple protein, bovine insulin.[35] The process took about 20 days, much shorter than the time required by conventional methods. Another key achievement for Merrifield, with colleague Bernd Gutte, also at Rockefeller, was the first synthesis of an enzyme, the catalytic protein ribonuclease A, in 1969.[36]

Merrifield and his colleagues at Rockefeller continued to refine and improve the solid-phase method, seeking ever-greater speed and purity in the synthesis of increasingly complex peptides and proteins. And in the years since the synthesis of ribonuclease, the Merrifield technique has found worldwide acceptance and application in the production of many important peptides. Two examples are the thyroid hormone calcitonin and the pituitary hormone ACTH (adrenocorticotropic hormone), which are produced on a commercial scale using solid-phase synthesis.[3] The technique is also being used in the study of synthetic antigenic proteins and their effect on the production of specific antibodies. This research may lead to synthetic vaccines against such viral diseases as influenza, rabies, and polio. Furthermore, the solid-phase synthesis of neuropeptides has aided human-brain research.[30]

Figure 3: Chronological distribution of articles citing Merrifield's 1963 *Journal of the American Chemical Society* paper.

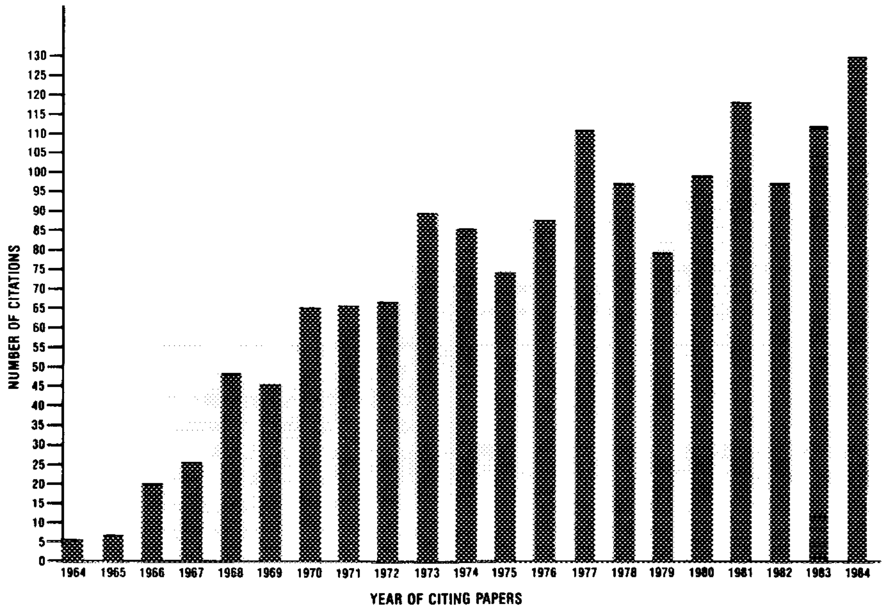
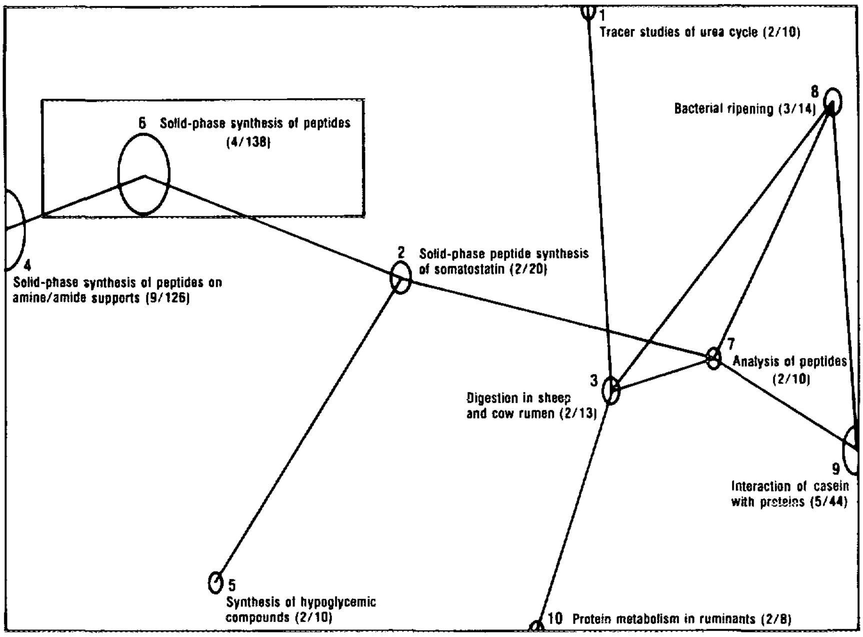


Figure 4: Second-level cluster map for front #83-0283, "Solid-phase peptide synthesis of enzymes." A = research-front number. B = research-front name.



Key

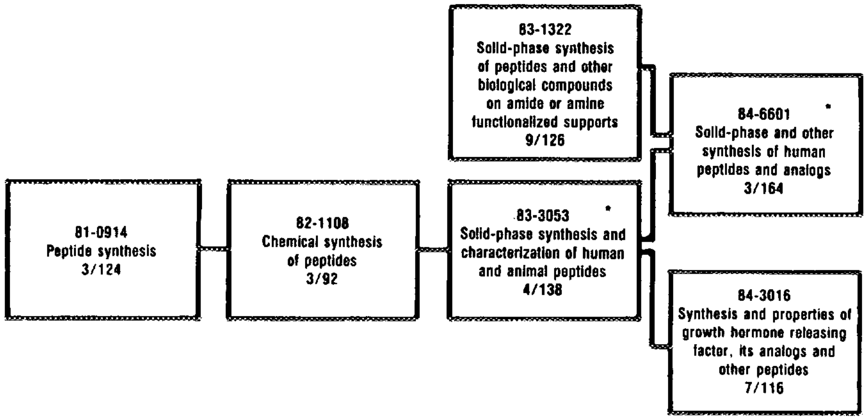
	A	B
1	0546	Nitrogen-15 tracer studies of the urea cycle
2	0814	Solid-phase peptide synthesis of somatostatin
3	1256	Influence of free and protected oils and other dietary supplements on digestion in sheep and dairy cow rumen
4	1322	Solid-phase synthesis of peptides and other biological compounds on amine or amide functionalized supports
5	1911	Synthesis and properties of hypoglycemic compounds including sulfonylurea derivatives
6	3053	Solid-phase synthesis and characterization of human and animal peptides
7	6169	Analysis of peptides, casein and related components contributing to the bitter flavor in cheese and milk
8	6861	Bacterial ripening of cheese and the production of skim-milk yogurt
9	7605	Interaction of casein with lipid micelles and other proteins in milk and cheese
10	8813	Dietary effects, blood plasma amino acids and nitrogen metabolism in ruminants

Merrifield

Bruce Merrifield was born in Fort Worth, Texas, in 1921. He received his BA and PhD degrees from the University of California at Los Angeles. He joined the staff of the Rockefeller University (then known as the Rockefeller Institute for Medical Research) in 1949. He has received several awards for his work, most notably the Lasker Award for Basic Medical Research in 1969. As noted previously, the Lasker Awards are often "predictors" of Nobel winners.[37]

Merrifield's most-cited paper for 1955-1984 is the article from *JACS* in

Figure 5: Historiograph of research fronts relating to synthesis on a solid matrix. Numbers at the bottom of each box refer to the number of core/published papers for that year. Asterisks indicate research fronts in which Merrifield is a core author. A note about co-citation thresholds: The reader may well wonder why a heavily cited paper is not included in the core for a relevant research front. Co-citation thresholds are set so that methods papers do not drown out emerging core papers. While Merrifield's work was co-cited at the correct threshold in 1974, its popularity reduced its co-citation strength for many years. When, subsequently, the technique itself became the subject of investigation, the level of co-citation increased. Similar effects are observed in the work of Rubbia and van der Meer.



which he first published the solid-phase peptide synthesis technique.[32] This work has received over 1,500 citations since publication in 1963. It was included in our study of the most-cited papers of the 1960s.[38] This citation classic is increasingly cited each year—about 95 times in 1982, 110 in 1983, 130 in 1984, and more than 75 times in the first six months of 1985. Figure 3 is a bar graph showing the year-by-year citation history of this paper. A paper, published in *Biochemistry*, that describes the synthesis of the hormone bradykinin,[33] has been cited over 450 times since 1964. His 1965 *Science* paper, in which he published his automated method for peptide synthesis,[34] has been cited over 200 times. The 1969 *JACS* paper describing the synthesis of ribonuclease A (coauthored with Gutte)[36] has been cited over 170 times.

We have identified four ISI research fronts in which works by Merrifield occur as core documents. One such annual front, #74-1284, with 4 core documents and 28 citing papers, is appropriately named "Solid-phase peptide synthesis." Another front, #81-1117 from 1981, is "Solid-phase and liquid-phase peptide synthesis." There are 5 core papers and 156 citing papers in this front. Merrifield's work is also core to a 1983 research front, "Solid-phase synthesis and characterization of human and animal peptides" (#83-3053). Figure 4, another higher level map, shows how 10 C1 fronts are linked through co-citation to #83-3053. This C2-level map for research front #83-0283 "Solid-phase peptide synthesis of enzymes," links many more clusters on somatostatin, casein, and so on, to the large clusters on the left.

A more recent research front is "Solid-phase and other synthesis of human peptides and analogs" (#84-6601). Merrifield's 1963 *JACS* paper is the most cited for this front, demonstrating the continuing impact of the solid-phase technique on research in synthetic vaccines and antigens. Figure 5 shows how these research fronts are linked to earlier clusters of papers reporting chemical synthesis on a solid matrix.

Incidentally, I recently visited Rockefeller University and had the pleasure of meeting Dr. Merrifield and discussing some of this citation data with him.

In a few weeks our examination of the 1984 Nobel awards will conclude with a discussion of British economist Sir Richard Stone, recognized for his development of a national accounting system, and Czechoslovakian poet Jaroslav Seifert, winner of the prize in literature.

* * * * *

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