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Classic Papers from the *Proceedings of the National Academy of Sciences*. Part 2. Absolutely, the 50 Most Cited—Almost

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In the first part of this essay,[1] I discussed a list of highly cited and classic papers from the *Proceedings of the National Academy of Sciences of the United States of America* (*PNAS*). These were selected on a year-by-year basis. The essay included information about the history and membership procedures of the National Academy of Sciences (NAS) and gave a brief history of *PNAS* and its editorial policies. In this second part, a list of overall *Citation Classics*® published in the journal is provided along with a discussion of *PNAS* research fronts.

Bibliography 2 lists the most-cited *PNAS* papers from the 1955-1986 *Science Citation Index*® (*SCI*®) but excludes 30 of the articles that were listed in Part 1 of this essay. Unlike the papers in the chronological, or annual, Bibliography of Part 1, papers in this list were selected regardless of date. The 50 articles identified are those cited over 611 times during the 32-year period. The average number of cites is over 844.

Biological- Versus Physical-Sciences Articles

Although the purpose of the journal is to publish exceptional papers in *all* scientific disciplines, there have been interesting changes in the quantity of physical-sciences versus biological-sciences papers published during the journal's 72-year history.

A year-by-year account of the changing subject content of the journal for its first 50 years is detailed in the book *History of the Proceedings of the National Academy of Sciences 1914-1963*,[2] by Edwin Bidwell Wilson, the first managing editor of *PNAS*. Although he is known for managing the journal for its first 50 years until his death in 1964, Wilson is equally, if not better, known for his long and varied career in the physical sciences.[3]

Formally trained in mathematics and physics, Wilson contributed to many areas within these fields. He created the Department of Vital Statistics at the Harvard School of Public Health, Cambridge, Massachusetts, and established the first Department of Aerodynamics at the Massachusetts Institute of Technology, Cambridge. As a student of Josiah Willard Gibbs (1839-1903), one of America's greatest physicists, Wilson transferred Gibbs's lectures on vector analysis into a textbook.[4] Based on Wilson's firsthand account of *PNAS* history and telephone interviews with Frances Zwanzig, its current managing editor, we traced the shift in subject content of the journal.

During the first 40 years of its monthly publication (1915-1954), *PNAS* published articles in all scientific areas studied at that time, including chemistry, genetics, and paleontology, but most of the articles published were in the physical sciences. In 1955 and 1956, the physical sciences represented about 60 percent of *PNAS* articles and the biological sciences, about 40 percent. This dominance, however, did not last. In 1957 the reversal began. Articles in the physical sciences published in *PNAS* dropped to a little over 46 percent, and contributions from the biological sciences rose to over 53 percent. By 1958 the biological sciences dominated the journal, with over 67 percent of the published articles. Biochemistry was the strongest specialty, with over 36 percent. In that same year, the physical-sciences papers had dropped to nearly 33 percent. Mathematics articles, which had reached an all-

time high (48 percent) only seven years before, constituted only 17 percent.[2] (p. 31, 35)

According to Zwanzig, *PNAS*'s specialization in the biological sciences and concurrent decrease in physical-sciences articles occurred unintentionally. She attributes the decrease in the contributions from the physical sciences to the availability of alternative publications like *Physical Review Letters*, a specialty journal published by the American Physical Society.[5] By overcoming the publication-lag problems of *Physical Review*, the *Letters*, which began in 1958, became the journal for quick publication.

With regard to *PNAS*'s specialization in the biological sciences, Zwanzig believes that certain key players in DNA research focused biologists' attention on *PNAS*.[5] During the 1940s and early 1950s scientists were working to understand the molecular basis of heredity. In 1941 George W. Beadle and the late Edward L. Tatum, then at Stanford University, California, published a paper in *PNAS* on the "Genetic control of biochemical reactions in neurospora."[6] Although the paper is not listed in Bibliography 1 or 2, both Beadle and Tatum were awarded the 1958 Nobel Prize in physiology or medicine for their work. Later, Linus Pauling and Robert B. Corey, then at the California Institute of Technology (Caltech), Pasadena, developed a model (although not the correct one) of DNA's structure, which was published in *PNAS* in 1953.[7] Even though the J.D. Watson and F.H.C. Crick paper,[8] which was published in *Nature* in the same year, turned out to be the correct model that revolutionized biology,[9] it may be that the Pauling and Corey paper brought biologists' attention to *PNAS* as an outlet for publishing original research in the life sciences.[5] It is somewhat ironic that one of Pauling's most controversial papers (on the therapeutic value of vitamin C) would also be published in *PNAS*.[10]

From 1955 to 1963, the overall number of biochemistry articles published in *PNAS* increased by over 370 percent while mathematics articles decreased by more than 42 percent.[2] (p. 35) "Now," Zwanzig said, "nonbiologists don't care to publish in *PNAS* because of its overwhelming concentration of biological-sciences articles."[5] In order to solicit more physical-sciences papers, from 1980 through 1984 *PNAS* was divided, publishing the biological- and physical-sciences papers separately. In 1982 the biological-sciences issues were published on a semimonthly basis while the physical-sciences issues remained monthly. This experiment, however, was unsuccessful in attracting more physical-sciences articles, so the two parts were rejoined in 1985 and have been published on a semimonthly basis since. (It is interesting to note that *Nature* also experimented with specialized life-sciences and physical-sciences editions from 1971 through 1973 before rejoining them in 1974.)

Although the quantity of physical-sciences papers published in *PNAS* has risen modestly during the last year—from 2 percent to 2.5 percent—many academy members would like to see more physical-sciences articles contributed to more closely reflect the subject distribution of NAS membership. However, as Zwanzig says, "We can't go out and generate these papers ourselves. They will have to come by the desire of the authors."[5]

Some *PNAS* Classic Papers

As mentioned above, the journal is dominated by biological-sciences articles, and our Bibliography also shows that about 30 percent of the papers describe methodologies. Lists of *Citation Classics* usually include many methods papers, even though not all methodology papers prove to be highly cited.

One that is highly cited, with almost 2,000 citations, is a 1975 paper by Tom Maniatis, Andrea Jeffrey, and Dennis G. Kleid, Biological Laboratories, Harvard University. The paper describes a method for deciphering the DNA sequence for a bacteriophage. Another methods paper by James C. Alwine, David J. Kemp, and George R. Stark, Department of Biochemistry, Stanford University School of Medicine, discusses a technique for transferring bands of RNA from an agarose gel to paper strips. Published in 1977, it was cited 1,265 times.

Table 1 lists the distribution of articles in Bibliography 2 according to their publica-

tion dates. Many papers—34 percent, or 17 of the 50 papers in the Bibliography—were published between 1970 and 1974. The oldest paper, published in 1953 by Max Alfert and Irving I. Geschwind, Department of Zoology, University of California, Berkeley, describes a staining technique for nuclear proteins. The most recent paper, coauthored by M.D. Biggin, T.J. Gibson, and G.F. Hong, Laboratory of Molecular Biology, Medical Research Council (MRC), Cambridge, UK, and published in 1983, describes two methods that allow scientists to read longer DNA sequences using polyacrylamide gels.

Table 1: Chronologic distribution of publication dates for the papers listed in Bibliography 2.

Publication Date	Number of Articles
1950-1954	1
1955-1959	3
1960-1964	4
1965-1969	9
1970-1974	17
1975-1979	12
1980-1984	4

Table 2: Geographic areas represented by the institutional affiliations given by authors in Bibliography 2, listed in descending order by the number of papers produced.

Geographic Location of Institutions		Number of Articles
United States		39
Maryland	8	
New York	8	
Massachusetts	7	
California	6	
New Jersey	4	
Colorado	3	
Pennsylvania	3	
Washington	2	
Connecticut	1	
Missouri	1	
Wisconsin	1	
Sweden		3
UK		3
Canada		2
Israel		2
Switzerland		1

Nobelists and Author Information

Many ISI® citation studies have demonstrated that Nobel laureates frequently publish *Citation Classics*. A recent essay discussed this relationship.[11] Five papers in Bibliography 2 were written or coauthored by Nobel Prize winners. Aaron Klug, Laboratory of Molecular Biology, MRC, won the 1982 Nobel Prize in chemistry for his work with crystallographic electron microscopy and nucleic acid-protein complexes.

The remaining four Nobelists were honored for their contributions to physiology or medicine. As mentioned previously, Tatum and Beadle, then at The Rockefeller University, New York, and Caltech, respectively, shared the 1958 prize for their work in genetics. In 1960 Peter B. Medawar (now Sir Peter), University College, London, and Frank Macfarlane Burnet (now Sir Macfarlane), Walter and Eliza Hall Institute for Medical Research, Melbourne, Australia, won the Nobel for their work in immunology. Recognized for their work on antibodies, Gerald M. Edelman, The Rockefeller University, and Rodney Porter, University of Oxford, UK, won the prize in 1972.

Bengt I. Samuelsson, Karolinska Institute, Stockholm, Sweden, and his colleague, Sune K. Bergström, shared the 1982 award with John R. Vane, Wellcome Research Laboratories, Beckenham, UK, for their work on prostaglandins and other related biologically active substances. Samuelsson is a coauthor with Mats Hamberg and J. Svensson, also of the Karolinska Institute, of a paper about thromboxanes. These substances regulate cellular reactions in platelets. This 1975 paper was the subject of a *Citation Classic* commentary,[12] as were 13 other papers in the list.

For all their overwhelming prestige, the Nobel Prizes are the most visible among numerous other distinguished awards that recognize the achievements of scientists. Many of the authors in Bibliography 2 are winners of some of these awards, which include the Charles Stewart Mott Award for Distinguished Education Reporting, John and Alice Tyler Ecology-Energy Prize, Gairdner Foundation International Award of Merit, and Albert Lasker Awards. Although it would be interesting to highlight the awards won by each of the 136 authors appearing in Bibliography 2, this would re-

Table 3: The 1986 life-sciences research fronts including 60 or more citing papers published in the *Proceedings of the National Academy of Sciences of the United States of America (PNAS)*. A = number of *PNAS* articles citing the core of each front. B = total number of citing documents. C = total number of core documents.

Number	Name	A	B	C
86-1382	Viruses, nucleotide-sequence analysis, transcription of genes, and cDNA cloning	720	7,995	36
86-6423	Isolation, purification, and characterization of proteins and antigens using monoclonal antibodies and other methods	304	8,512	3
86-1674	Transcriptional enhancer genes, adenoviruses, regulation of late promoters, and gene expression	129	1,189	28
86-2283	Pre-messenger and messenger RNA splicing and small nuclear RNAs	119	1,200	32
86-0547	C-*myc* proto-oncogene expression, cellular and c-*fos* oncogenes, and n-*myc* gene	77	945	41
86-0633	T-cell antigen receptor genes, murine systemic lupus erythematosus, and major histocompatibility complex	77	1,234	59
86-1983	Protein kinase-C, inositol triphosphate, phorbol esters, and intracellular Ca-2+	64	2,093	45
86-4303	Platelet-derived growth factor, receptor proto-oncogene FMS, and transforming growth factors	61	694	13
86-8517	Isolation, cloning, expression, and sequencing of cDNA for enzymes and proteins	61	248	2
86-3728	*Ras* proteins, expression of the c-Ha-*ras* oncogene, and transforming genes in human leukemia cells	60	569	26

quire another essay. A sizable number of authors have received well-known awards and serve as members of foreign academies.

The geographic distribution of authors appearing in Bibliography 2, according to their institutional affiliations, is listed in Table 2. Six countries representing 30 institutions are listed. The National Institutes of Health, Bethesda, Maryland, and Harvard University and Medical School occur most frequently, with five papers each. Five other institutions are listed three times: Johns Hopkins University and Medical School, Baltimore, Maryland; Karolinska Institute; The Rockefeller University; University of California, Berkeley; and University of Colorado and Medical Center, Boulder.

Research-Front Analysis

As mentioned previously, *PNAS* publishes mostly biological-sciences articles. Both Bibliographies in this two-part study demonstrate this preponderance. As expected, a research-front analysis of *PNAS* also confirms its emphasis in these areas. We identified about 8,500 research fronts in 1986. Of these, about 1,150 fronts involved articles published in *PNAS*. The 10 fronts containing at least 60 citing papers published in *PNAS* are listed in Table 3. The fronts are mostly related to biochemistry and genetics.

Over 700 *PNAS* articles have been published in 1986 on the first research front listed, "Viruses, nucleotide-sequence analysis, transcription of genes, and cDNA cloning" (#86-1382). Of the 7,995 articles published on this topic in 1986, only 36 papers constitute its core. Five articles listed in both Bibliographies are core documents in this research front. In Bibliography 1 the following four first authors produced core papers to this front: Haim Aviv, Frederick Sanger, Patricia S. Thomas, and Geoffrey M. Wahl. The fifth author, Biggin, is listed in Bibliography 2. All of these core papers have been published within the past 16 years.

The second front listed, "Isolation, purification, and characterization of proteins and antigens using monoclonal antibodies and other methods" (#86-6423), is the largest. Over 8,500 articles cited into this front in 1986; over 300 of them were published in *PNAS*. Remarkably, there are only three core papers in this front. The paper by Harry Towbin and Julian Gordon, Friedrich Miescher Institute, Basel, Switzerland, and Theophil Staehelin, Hoffmann-La Roche Pharmaceutical Research Department, Basel, listed in Bibliography 1 is one of these core papers. The other two papers are by R. Hawkes and colleagues,[13] also of the Friedrich Miescher Institute, and U.K. Laemmli,[14] Laboratory of Molecular Biology, MRC.

The Hawkes paper, entitled "A dot-immunobinding assay for monoclonal and other antibodies," was published in 1982 in *Analytical Biochemistry*.[13] The Laemmli paper, published in 1970 in *Nature*, is entitled "Cleavage of structural proteins during the assembly of the head of bacteriophage T4."[14] Laemmli's paper is the most-cited paper ever published in *Nature*, with over 42,000 cites, according to the 1955-1986 *SCI*. Other papers in Bibliographies 1 and 2 that are core papers in any of ISI's research fronts are identified by their corresponding research-front number.

Conclusion

From the lists of most-cited *PNAS* papers identified in this two-part essay, we have shown that *PNAS* is a significant contributor to the biological sciences. Although the journal originated as a publisher of original research papers in all scientific disciplines, it has become a prominent and well-respected journal for biologists. The results of our two-part citation study on most-cited *PNAS* papers, which contains papers identified by two different sets of criteria, show *PNAS*'s emphasis in biochemistry. Yet, it is important to keep in mind that biochemistry is a broad area of research and many of the articles could easily be classified into a biological subspecialty.

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Bibliography 2: Absolute list of most-cited papers from the *Proceedings of the National Academy of Sciences of the United States of America*, according to the 1955-1986 *SCI*®, **excluding** those articles that appeared in Part 1 of this essay. Articles are listed in alphabetic order by first author. Asterisks (*) indicate articles with *Citation Classic*® commentaries. The issue number, year, and edition of *Current Contents*® in which these commentaries appeared are in parentheses. Daggers (†) indicate first authors who have authored or coauthored other *Citation Classic* commentaries. The issue number, year, and edition of *Current Contents* in which these commentaries appeared are in brackets. Research-front numbers are listed for those papers that are core to 1986 *SCI/SSCI*® research-front specialties.

Number of 1955-1986 *SCI* Citations	Bibliographic Data
692	*†**Alfert M & Geschwind I I.** A selective staining method for the basic proteins of cell nuclei. *Proc. Nat. Acad. Sci. USA* 39:991-8, 1953. (6/79/LS) [34/80/AB&ES]
1,265	**Alwine J C, Kemp D J & Stark G R.** Method for detection of specific RNAs in agarose gels by transfer to diazobenzyloxymethyl-paper and hybridization with DNA probes. *Proc. Nat. Acad. Sci. USA* 74:5350-4, 1977.

(*continued*)

Number of 1955-1986 *SCI* Citations	Bibliographic Data (*continued*)
845	†**Ames B N, Lee F D & Durston W E.** An improved bacterial test system for the detection and classification of mutagens and carcinogens. *Proc. Nat. Acad. Sci. USA* 70:782-6, 1973. [12/84/LS] 86-0746
611	**Biggin M D, Gibson T J & Hong G F.** Buffer gradient gels and S-35 label as an aid to rapid DNA sequence determination. *Proc. Nat. Acad. Sci. USA* 80:3963-5, 1983. 86-1382
697	**Burger M M.** A difference in the architecture of the surface membrane of normal and virally transformed cells. *Proc. Nat. Acad. Sci. USA* 62:994-1001, 1969.
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958	†**Hamberg M, Svensson J, Wakabayashi T & Samuelsson B.** Isolation and structure of two prostaglandin endoperoxides that cause platelet aggregation. *Proc. Nat. Acad. Sci. USA* 71:345-9, 1974. [2/83/LS; 48/84/LS] 86-3499
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612	***Hsie A W & Puck T T.** Morphological transformation of Chinese hamster cells by dibutyryl adenosine cyclic 3′:5′-monophosphate and testosterone. *Proc. Nat. Acad. Sci. USA* 68:358-61, 1971. (35/83/LS)
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1,009	**Hunter T & Sefton B M.** Transforming gene product of Rous sarcoma virus phosphorylates tyrosine. *Proc. Nat. Acad. Sci. USA* 77:1311-5, 1980.
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