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Current Comments®

The Articles Most Cited in 1961-1982. 2. Another 100 *Citation Classics* Highlight the Technology of Science

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In last week's tribute to Derek Price, the importance of methods and instruments in the advance of science was stressed.[1] Before he died, Derek published several articles and books on this topic.[2] He argued that many conceptual breakthroughs would not have been possible without first developing techniques and instruments to approach basic problems. Indeed, the development of new instruments and methods often leads to unanticipated theoretical innovations.

The importance of technology and methodology in science is further reflected in studies of highly cited articles. We recently published a list of the 100 papers most cited from 1961 to 1982 in *Science Citation Index*® (*SCI*®).[3] We have now extended the list to include 100 additional articles.

Table 1 provides full bibliographic information for these papers. They are arranged in alphabetic order by first author. After the citation count for 1961-1982, we've also included, in parentheses, the number of cites for 1983. A single asterisk indicates that the paper was the subject of a *Citation Classic*™ commentary. The issue, year, and edition of *Current Contents*® (*CC*®) in which these commentaries were published follow the reference.

Many of these papers have appeared in earlier studies of most-cited papers. For example, 32 papers were included in a similar study covering 1961-1972.[4] They are indicated by a number symbol. In comparison, 44 of the 100 papers identified in the first part of this series[3] also appeared in the 1974 study.

These papers were published in 51 journals. Just four journals account for a third of the papers: *Journal of Biological Chemistry* (16 papers), *Biochemistry Journal* (7), *Journal of Chemical Physics* (5), and *Nature* (5). Other high-impact journals that repeatedly turn up in our citation studies include *Science, Lancet, Journal of the American Chemical Society,* etc. But a few "newcomers" are represented, including *Annales de Chimie*. The oldest paper on the list was published in this journal in 1928. P. Job described a method for studying inorganic complexes in solution. That 70 publications cited this paper in 1983 indicates that researchers still have the patience to use Job's method.

Although methods papers dominate these lists of most-cited articles, a large number of high-impact theoretical or conceptual papers are also included. These superstar "idea" papers are widely recognized to be primordial contributions to science. Highly cited methods papers, however, are only grudgingly acknowledged as "useful" even by their authors. Theoretical papers are more highly valued because they usually symbolize major "intellectual" achievements. Methods papers, on the other hand, are "blue collar" efforts, "inevitable" pre-

Table 1. The second 100 most-cited articles, 1961-1982 *SCI*®, arranged in alphabetic order by first author. A=1961-1982 citations. 1983 citations appear in parentheses. B=bibliographic data. An asterisk (*) indicates that the paper was the subject of a *Citation Classic*™ commentary. A number symbol(#) indicates that the paper appeared in the 1974 list of most-cited articles.

A	B
2032 (93)	#***Abell L L, Levy B B, Brodie B B & Kendall F E.** A simplified method for the estimation of total cholesterol in serum and demonstration of its specificity. *J. Biol. Chem.* 195:357-66, 1952. (34/79/LS)
1851 (74)	#***Ahlquist R P.** A study of the adrenotropic receptors. *Amer. J. Physiol.* 153:586-600, 1948. (45/78)
1916 (102)	***Anton A H & Sayre D F.** A study of the factors affecting the aluminum oxidetrihydroxy-indole procedure for the analysis of catecholamines. *J. Pharmacol. Exp. Ther.* 138:360-75, 1962. (34/77)
1558 (361)	**Aviv H & Leder P.** Purification of biologically active globin messenger RNA by chromatography on oligothymidylic acid-cellulose. *Proc. Nat. Acad. Sci. US* 69:1408-12, 1972.
1554 (90)	**Axen R, Porath J & Ernback S.** Chemical coupling of peptides and proteins to polysaccharides by means of cyanogen halides. *Nature* 214:1302-4, 1967.
1835 (174)	**Bauer A W, Kirby W M M, Sherris J C & Turck M.** Antibiotic susceptibility testing by a standardized single disk method. *Amer. J. Clin. Pathol.* 45:493-501, 1966.
1589 (79)	**Bessey O A, Lowry O H & Brock M J.** A method for the rapid determination of alkaline phosphatase with five cubic millimeters of serum. *J. Biol. Chem.* 164:321-9, 1946.
1691 (74)	#***Bloembergen N, Purcell E M & Pound R V.** Relaxation effects in nuclear magnetic resonance absorption. *Phys. Rev.* 73:679-712, 1948. (18/77)
1554 (127)	***Born G V R.** Aggregation of blood platelets by adenosine diphosphate and its reversal. *Nature* 194:927-9, 1962. (37/77)
1558 (36)	#**Boyden S V.** The adsorption of proteins on erythrocytes treated with tannic acid and subsequent hemagglutination by antiprotein sera. *J. Exp. Med.* 93:107-20, 1951.
1605 (25)	#***Boyer P D.** Spectrophotometric study of the reaction of protein sulfhydryl groups with organic mercurials. *J. Amer. Chem. Soc.* 76:4331-7, 1954. (25/79/LS)
1834 (38)	**Britten R J & Kohne D E.** Repeated sequences in DNA. *Science* 161:529-40, 1968.
1600 (97)	**Brunauer S, Emmett P H & Teller E.** Adsorption of gases in multimolecular layers. *J. Amer. Chem. Soc.* 60:309-21, 1938.
1823 (54)	**Butcher R W & Sutherland E W.** Adenosine 3′,5′-phosphate in biological materials. I. Purification and properties of cyclic 3′,5′-nucleotide phosphodiesterase and use of this enzyme to characterize the adenosine 3′,5′-phosphate in human urine. *J. Biol. Chem.* 237:1244-50, 1962.
1675 (65)	***Chance B & Williams G R.** The respiratory chain and oxidative phosphorylation. *Advan. Enzymol. Relat. Areas Mol.* 17:65-134, 1956. (49/83/LS)
1738 (144)	**Chandrasekhar S.** Stochastic problems in physics and astronomy. *Rev. Mod. Phys.* 15:1-89, 1943.
1744 (74)	#**Clarke D H & Casals J.** Techniques for hemagglutination and hemagglutination-inhibition with arthropod-borne viruses. *Amer. J. Trop. Med. Hyg.* 7:561-73, 1958.
1542 (37)	**Clementi E.** *Ab initio* computations in atoms and molecules. *IBM J. Res. Develop.* 9:2-19, 1965.
1571 (34)	#***Coons A H & Kaplan M H.** Localization of antigen in tissue cells. II. Improvements in a method for the detection of antigen by means of fluorescent antibody. *J. Exp. Med.* 91:1-13, 1950. (6/81/LS)
1687 (114)	**Crestfield A M, Moore S & Stein W H.** The preparation and enzymatic hydrolysis of reduced and S-carboxymethylated proteins. *J. Biol. Chem.* 238:622-7, 1963.
1881 (77)	#**Davis B D & Mingioli E S.** Mutants of *Escherichia coli* requiring methionine or vitamin B_{12}. *J. Bacteriol.* 60:17-28, 1950.
1657 (142)	**Davis R W, Simon M & Davidson N.** Electron microscope heteroduplex methods for mapping regions of base sequence homology in nucleic acids. *Meth. Enzymology* 21:413-28, 1971.
1714 (39)	#**Dische Z.** A new specific color reaction of hexuronic acids. *J. Biol. Chem.* 167:189-98, 1947.
2024 (119)	**Dixon M.** The determination of enzyme inhibitor constants. *Biochem. J.* 55:170-1, 1953.
1982 (161)	**Dodge J T, Mitchell C & Hanahan D J.** The preparation and chemical characteristics of hemoglobin-free ghosts of human erythrocytes. *Arch. Biochem. Biophys.* 100:119-30, 1963.

1901 (70) **#Dole V P & Meinertz H.** Microdetermination of long-chain fatty acids in plasma and tissues. *J. Biol. Chem.* 235:2595-9, 1960.

1608 (102) **•Edman P & Begg G.** A protein sequenator. *Eur. J. Biochem.* 1:80-91, 1967. (9/84/LS)

1480 (49) **Fahey J L & McKelvey E M.** Quantitative determination of serum immunoglobulins in antibody-agar plates. *J. Immunol.* 94:84-90, 1965.

1913 (75) **Falck B, Hillarp N-A, Thieme G & Torp A.** Fluorescence of catechol amines and related compounds condensed with formaldehyde. *J. Histochem. Cytochem.* 10:348-54, 1962.

1594 (34) **#Farquhar M G & Palade G E.** Junctional complexes in various epithelia. *J. Cell Biol.* 17:375-412, 1963.

1646 (218) **Feighner J P, Robins E, Guze S B, Woodruff R A, Winokur G & Munoz R.** Diagnostic criteria for use in psychiatric research. *Arch. Gen. Psychiat.* 26:57-63, 1972.

1551 (16) **#Friedmann T E & Haugen G E.** Pyruvic acid. II. The determination of keto acids in blood and urine. *J. Biol. Chem.* 147:415-42, 1943.

1545 (7) **Gell-Mann M.** Symmetries of baryons and mesons. *Phys. Rev.* 125:1067-84, 1962.

1750 (48) **•Gillespie D & Spiegelman S.** A quantitative assay for DNA-RNA hybrids with DNA immobilized on a membrane. *J. Mol. Biol.* 12:829-42, 1965. (11/77)

1528 (189) **Glowinski J & Iversen L L.** Regional studies of catecholamines in the rat brain. I. The disposition of [^{3}H] norepinephrine, [^{3}H] dopamine, and [^{3}H] dopa in various regions of the brain. *J. Neurochem.* 13:655-69, 1966.

1656 (82) **Glynn I M & Chappell J B.** A simple method for the preparation of ^{32}P-labelled adenosine triphosphate of high specific activity. *Biochem. J.* 90:147-9, 1964.

1826 (180) **•Haber E, Koerner T, Page L B, Kliman B & Purnode A.** Application of a radioimmunoassay for angiotensin I to the physiologic measurements of plasma renin activity in normal human subjects. *J. Clin. Endocrinol. Metab.* 29:1349-55, 1969. (12/80/CP)

1979 (211) **•Hakomori S.** Letter to editor. (A rapid permethylation of glycolipid and polysaccharide catalyzed by methylsulfinyl carbanion in dimethyl sulfoxide.) *J. Biochem. Tokyo* 55:205-8, 1964. (23/80/LS)

1778 (125) **Hamilton W C.** Significance tests on the crystallographic *R* factor. *Acta Crystallogr.* 18:502-10, 1965.

1648 (21) **#Hanes C S & Isherwood F A.** Separation of the phosphoric esters on the filter paper chromatogram. *Nature* 164:1107-12, 1949.

1642 (16) **•Hanson H P, Herman F, Lea J D & Skillman S.** HFS atomic scattering factors. *Acta Crystallogr.* 17:1040-4, 1964. (30/77)

1531 (80) **Hatchard C G & Parker C A.** A new sensitive chemical actinometer. II. Potassium ferrioxalate as a standard chemical actinometer. *Proc. Roy. Soc. London Ser. A* 235:518-36, 1956.

2035 (210) **•Havel R J, Eder H A & Bragdon J H.** The distribution and chemical composition of ultracentrifugally separated lipoproteins in human serum. *J. Clin. Invest.* 34:1345-53, 1955. (46/83/LS)

1484 (76) **•Hayflick L & Moorhead P S.** The serial cultivation of human diploid cell strains. *Exp. Cell Res.* 25:585-621, 1961. (26/78)

1715 (184) **Hehre W J, Stewart R F & Pople J A.** Self-consistent molecular-orbital methods. I. Use of Gaussian expansions of Slater-type atomic orbitals. *J. Chem. Phys.* 51:2657-64, 1969.

1703 (142) **Herbert V, Lau K-S, Gottlieb C W & Bleicher S J.** Coated charcoal immunoassay of insulin. *J. Clin. Endocrinol. Metab.* 25:1375-84, 1965.

1717 (58) **#Hirs C H W.** The oxidation of ribonuclease with performic acid. *J. Biol. Chem.* 219:611-21, 1956.

1971 (32) **#Hoffman W S.** A rapid photoelectric process for the determination of glucose in blood and urine. *J. Biol. Chem.* 120:51-5, 1937.

1830 (127) **Hubel D H & Wiesel T N.** Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *J. Physiol.—London* 160:106-54, 1962.

1605 (160) **•Hughes J, Smith T W, Kosterlitz H W, Fothergill L A, Morgan B A & Morris H R.** Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature* 258:577-9, 1975. (38/82/LS)

1549 (156) **•Huzinaga S.** Gaussian-type functions for polyatomic systems. I. *J. Chem. Phys.* 42:1293-302, 1965. (17/80/PC)

2043 (130) **•Jerne N K & Nordin A A.** Plaque formation in agar by single antibody-producing cells. *Science* 140:405, 1963. (35/81/LS)

1546 (67) **Job P.** Formation and stability of inorganic complexes in solution. *Ann. Chim.—Paris* 9:113-203, 1928.

1502 (6) **Karnovsky M J.** Simple methods for "staining with lead" at high pH in electron microscopy. *J. Biophys. Biochem. Cytol.* 11:729-32, 1961.

1723 (66) **Kauzmann W.** Some factors in the interpretation of protein denaturation. *Advan. Prot. Chem.* 14:1-63, 1959.

1721 (639) **Kohler G & Milstein C.** Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* 256:495-7, 1975.

1640 (77) **Kubo R.** Statistical-mechanical theory of irreversible processes. I. General theory and simple applications to magnetic and conduction problems. *J. Phys. Soc. Jpn.* 12:570-86, 1957.

1999 (59) **Loening U E.** The fractionation of high-molecular-weight ribonucleic acid by polyacrylamide-gel electrophoresis. *Biochem. J.* 102:251-7, 1967.

1537 (63) **Lowry O H, Passonneau J V, Hasselberger F X & Schulz D W.** Effect of ischemia on known substrates and cofactors of the glycolytic pathway in brain. *J. Biol. Chem.* 239:18-30, 1964.

1564 (8) **#Mandell J D & Hershey A D.** A fractioning column for analysis of nucleic acids. *Anal. Biochem.* 1:66-77, 1960.

1654 (84) **Mans R J & Novelli G D.** Measurement of the incorporation of radioactive amino acids into protein by a filter-paper disk method. *Arch. Biochem. Biophys.* 94:48-53, 1961.

1527 (89) **Marmur J & Doty P.** Determination of the base composition of deoxyribonucleic acid from its thermal denaturation temperature. *J. Mol. Biol.* 5:109-18, 1962.

1620 (182) ***Marquardt D W.** An algorithm for least-squares estimation of nonlinear parameters. *J. Soc. Ind. Appl. Math.* 11:431-41, 1963. (27/79/ET)

1740 (144) **McConahey P J & Dixon F J.** A method of trace iodination of proteins for immunologic studies. *Int. Arch. Allergy Appl. Immunol.* 29:185-9, 1966.

1601 (181) ***McCord J M & Fridovich I.** Superoxide dismutase. *J. Biol. Chem.* 244:6049-55, 1969. (17/81/LS)

1766 (20) **Mejbaum W.** Uber die Bestimmung kleiner Pentosemengen insbesondere in Derivaten der Adenylsaure. (Estimation of small amounts of pentose especially in derivatives of adenylic acid.) *Hoppe-Seylers Z. Physiol. Chem.* 258:117-20, 1939.

1942 (38) **#Millonig G.** Advantages of a phosphate buffer for OsO_4 solutions in fixation. (Abstract.) *J. Appl. Phys.* 32:1637, 1961.

1759 (108) **Mishell R I & Dutton R W.** Immunization of dissociated spleen cell cultures from normal mice. *J. Exp. Med.* 126:423-42, 1967.

1896 (33) **#Moore S, Spackman D H & Stein W H.** Chromatography of amino acids on sulfonated polystyrene resins. *Anal. Chem.* 30:1185-90, 1958.

1802 (46) **#Moore S & Stein W H.** A modified ninhydrin reagent for the photometric determination of amino acids and related compounds. *J. Biol. Chem.* 211:907-13, 1954.

1811 (85) ***Morgan C R & Lazarow A.** Immunoassay of insulin: two antibody system. *Diabetes* 12:115-26, 1963. (52/77)

1782 (101) **Mulliken R S.** Electronic population analysis on LCAO-MO molecular wave functions. I. *J. Chem. Phys.* 23:1833-40, 1955.

1464 (44) ***Nachlas M M, Tsou K-C, De Souza E, Cheng C-S & Seligman A M.** Cytochemical demonstration of succinic dehydrogenase by the use of a new p-nitrophenyl substituted ditetrazole. *J. Histochem. Cytochem.* 5:420-36, 1957. (17/79/LS)

1800 (181) ***Nash T.** The colorimetric estimation of formaldehyde by means of the Hantzsch reaction. *Biochem. J.* 55:416-21, 1953. (14/81/LS)

1713 (136) ***Panyim S & Chalkley R.** High resolution acrylamide gel electrophoresis of histones. *Arch. Biochem. Biophys.* 130:337-46, 1969. (33/81/LS)

1526 (31) **#*Pariser R & Parr R G.** A semi-empirical theory of the electronic spectra and electronic structure of complex unsaturated molecules. II. *J. Chem. Phys.* 21:767-76, 1953. (3/79/PC)

1936 (52) **Pople J A & Segal G A.** Approximate self-consistent molecular orbital theory. III. CNDO results for AB_2 and AB_3 systems. *J. Chem. Phys.* 44:3289-96, 1966.

1924 (77) **#Porter R R.** The hydrolysis of rabbit γ-globulin and antibodies with crystalline papain. *Biochem. J.* 73:119-27, 1959.

1694 (75) **#*Reitman S & Frankel S.** A colorimetric method for the determination of serum glutamic oxalacetic and glutamic pyruvic transaminases. *Amer. J. Clin. Pathol.* 28:56-63, 1957. (10/79/CP)

1623 (84) **Richardson K C, Jarett L & Finke E H.** Embedding in epoxy resins for ultrathin sectioning in electron microscopy. *Stain Technol.* 35:313-23, 1960.

1587 (894) **Rigby P W J, Dieckman M, Rhodes C & Berg P.** Labeling deoxyribonucleic acid to high specific activity *in vitro* by nick translation with DNA polymerase I. *J. Mol. Biol.* 113:237-51, 1977.

1885 (156) ***Rodbell M.** Metabolism of isolated fat cells. I. Effects of hormones on glucose metabolism and lipolysis. *J. Biol. Chem.* 239:375-80, 1964. (45/80/LS)

1843 (71) **#Roothaan C C J.** New developments in molecular orbital theory. *Rev. Mod. Phys.* 23:69-89, 1951.

1890 (46) **Schneider W C.** Determination of nucleic acids in tissues by pentose analysis. *Meth. Enzymology* 3:680-4, 1957.

1970 (37) **#*Schneider W C.** Phosphorus compounds in animal tissues. I. Extraction and estimation of desoxypentose nucleic acid and of pentose nucleic acid. *J. Biol. Chem.* 161:293-303, 1945. (8/77)

1474 (151) ***Seabright M.** Letter to editor. (A rapid banding technique for human chromosomes.) *Lancet* 2:971-2, 1971. (14/81/LS)

1478 (45) **#Seldinger S I.** Catheter replacement of the needle in percutaneous arteriography. *Acta Radiol.* 39:368-76, 1953.

1935 (40) **#Sever J L.** Application of a microtechnique to viral serological investigations. *J. Immunol.* 88:320-9, 1962.

1650 (131) ***Shannon R D & Prewitt C T.** Effective ionic radii in oxides and fluorides. *Acta Crystallogr. B—Struct. Sci.* 25:925-46, 1969. (21/81/PC)

1465 (91) ***Shore P A, Burkhalter A & Cohn V H.** A method for the fluorometric assay of histamine in tissues. *J. Pharmacol. Exp. Ther.* 127:182-6, 1959. (40/81/LS)

1720 (50) ***Skou J C.** Enzymatic basis for active transport of Na+ and K+ across cell membranes. *Physiol. Rev.* 45:596-617, 1965. (20/81/LS)

1562 (6) **#Smithies O.** An improved procedure for starch-gel electrophoresis: further variations in the serum proteins of normal individuals. *Biochem. J.* 71:585-7, 1959.

1646 (33) **#*Sperry W M & Webb M.** A revision of the Schoenheimer-Sperry method for cholesterol determination. *J. Biol. Chem.* 187:97-106, 1950. (22/83/LS)

1917 (70) **#*Sweeley C C, Bentley R, Makita M & Wells W W.** Gas-liquid chromatography of trimethylsilyl derivatives of sugars and related substances. *J. Amer. Chem. Soc.* 85:2497-507, 1963. (43/77)

2030 (128) ***Till J E & McCulloch E A.** A direct measurement of the radiation sensitivity of normal mouse bone marrow cells. *Radiat. Res.* 14:213-22, 1961. (43/79/LS)

1903 (25) **#*Van Handel E & Zilversmit D B.** Micromethod for the direct determination of serum triglycerides. *J. Lab. Clin. Med.* 50:152-7, 1957. (16/77)

1662 (148) **Vogel H J & Bonner D M.** Acetylornithinase of *Escherichia coli*: partial purification and some properties. *J. Biol. Chem.* 218:97-106, 1956.

1582 (61) **Wachstein M & Meisel E.** Histochemistry of hepatic phosphatases at a physiologic pH. *Amer. J. Clin. Pathol.* 27:13-23, 1957.

1880 (148) **Wilkinson G N.** Statistical estimations in enzyme kinetics. *Biochem. J.* 80:324-36, 1961.

1694 (60) **#*Yalow R S & Berson S A.** Immunoassay of endogenous plasma insulin in man. *J. Clin. Invest.* 39:1157-75, 1960. (14/77)

scriptions or recipes for getting the job done.

Ambiguous feelings about methodological works are often expressed in *Citation Classics* commentaries. Authors of high-impact work usually are pleased to learn that one or more of their papers have become "classics" in their field. But they sometimes are disappointed if their most-cited work is not one of the more theoretical articles they value most.

Although all 100 papers listed in Table 1 are *Citation Classics*, only 37 have been the subject of commentaries published in *CC*. In these commentaries, authors provide interesting background on their work—sources of inspiration, difficulties in obtaining materials or funding, publication delays and rejections, etc. The discussion which follows is based on these commentaries.

As mentioned earlier, many researchers underrate the value of methodological efforts. For example, David Gillespie, National Institutes of Health, Bethesda, Maryland, and the late Sol Spiegelman[5] developed an assay for DNA-RNA hybrids. Gillespie commented on their 1965 paper: "I must admit that...I didn't recognize the potential of what I was doing at the time.... I looked upon the method primarily as a neat trick that would allow me to discover some 'really important' facts of biological interest."[6] The attitude that methods are "neat tricks" while facts and theories are "really important" is echoed in a commentary by S. Hakomori, University of Washington, Seattle: "Life as a scientist is totally unpredictable. Frankly, I have mixed feelings as the paper cited is in my subsidiary interest.... I would be happier if some of my other papers, such as...discovery of cell surface fibronectin, would have been selected...."[7]

Even though researchers tend to trivialize methods papers, they do recognize in hindsight the wide impact these papers have on science. Richard J. Havel, University of California, San Francisco, and colleagues devised a method for isolating lipoproteins from blood serum. Havel commented on this 1955 paper: "None of the authors...felt that it represented a major conceptual advance and we were initially surprised by the wide attention that it received. Evidently, even rather straightforward methodological efforts can sometimes help to open up a fruitful field of research."[8] Havel's method is now routinely used in clinical and epidemiological research.

Devising methods for specific research problems can result in profound advances in basic scientific knowledge. Leonard Hayflick, Children's Hospital Medical Center, Oakland, California, and P.S. Moorhead worked on cultivating human diploid cell strains to study differences between cancerous and normal cells. To their surprise, the normal cell strain died after about 50 population doublings. They suggested that this newly observed phenomenon indicated cellular aging. But their paper was rejected by the *Journal of Experimental Medicine* because the findings conflicted with 50 years of tissue culture research showing that cells multiply *indefinitely*. Hayflick commented: "Our original suggestion...seems even more tenable today. It has given rise to the new field of 'cytogerontology.' The cells were found to have other properties of immediate practical importance.... [In] 1973, the first poliomyelitis vaccine produced on our normal human cell strain...was distributed...."[9]

A characteristic of classic methods is that they are used by researchers from many different fields. Multidisciplinary methods that can be applied to a variety of research problems will accrue a large number of citations. N. Bloembergen, Harvard University, makes this point in a commentary on a classic 1948 paper he coauthored with E.M. Purcell and R.V. Pound. The paper discussed relaxation effects in nuclear magnetic resonance (NMR) absorption. Commenting on this paper, Bloembergen said: "The exploitation of [NMR spectroscopy] by the chemists and biochemists, who are more numerous...and more prolific in authoring papers than physicists, is...responsible for the higher incidence of citations."[10] D.W. Marquardt, DuPont Company, Wilmington, Delaware, also attributes the large number of citations to his 1963 classic on computing procedures for nonlinear models to its multidisciplinary application: "The growing use of nonlinear models in both the sciences and social sciences...must be a factor in the citation history of this paper."[11]

Another characteristic of classic biomedical methods is that they are applied in clinical practice as well as in basic research laboratories. Albert H. Coons, Harvard Medical School, and Melvin H. Kaplan developed a fluorescent method to localize antigens in tissue cells for basic histological research. In a commentary on this 1950 classic, Coons said: "[The method] also has been applied to the study of autoimmune disease...and in the detection of autoantibodies against tissue components. Immunofluorescence...therefore, became a feature of the diagnostic, as well as the research, laboratory."[12] Many other classic authors attribute the high citation rates of their methods papers to their successful exploitation by clinicians and basic researchers.

These commentators also express surprise that their works are still being cited "after all these years." Indeed, more than half of the classic papers in Table 1 are at least 20 years old. Table 2 shows the age distribution for the 100 most-cited papers in this essay. As you can see, 58 papers were published in the 1960s and 1970s. Exactly the same number of papers in the first part of this series[3] were published in these two decades. It will be interesting to learn whether this pattern holds when we extend these lists in future essays.

Gillespie suggests that classic methods papers continue to be highly cited even after 30 or 40 years because they are "unimprovable."[6] He explained: "[While] attempting to decide why a 'classic' becomes one, especially in...methodology, I keep returning to the notion of developing an unimprovable method.... [The] distinction between a classic and a quickly outmoded method lies in the ability of the investigators to see the uses to which [it] will be put...and, as important, to take heed of the little incongruities that lead to significant improvements."[6]

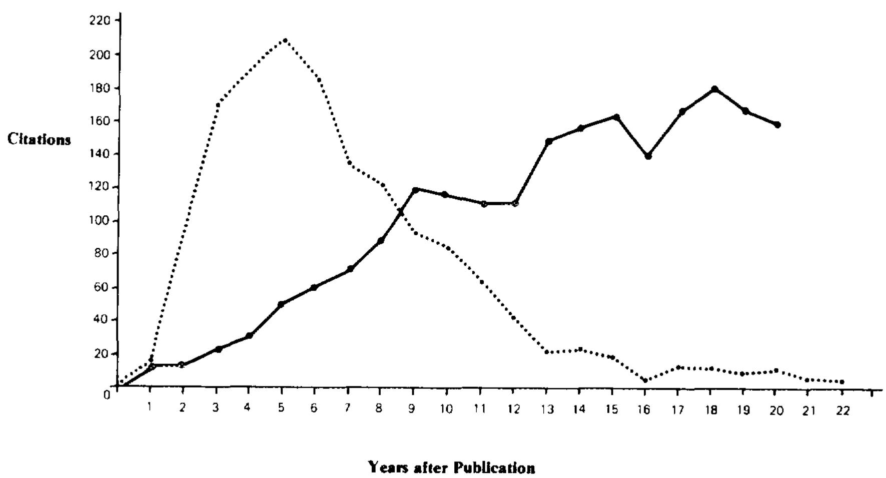
Table 2: Chronological distribution of publication dates of the second 100 most-cited articles, 1961-1982 *SCI*®. A=publication date. B=number of papers.

A	B
1920s	1
1930s	3
1940s	8
1950s	30
1960s	51
1970s	7
	100

However, other authors acknowledge that their classic methods have been improved by other researchers, yet the original method is still highly cited for a variety of reasons. Bloembergen commented: "[Many subsequent publications] certainly constitute an improvement on [our] naive experimental and theoretical discussions.... Perhaps new workers, confronted with the complexities of modern NMR and its applications, like the account of our early wrestling with some basic problems...."[10]

In addition, some authors suggest that fewer currently active scientists bother to *explicitly* cite their classic methods because they have become firmly incorporated into the "common knowledge" of their fields. Rosalyn Yalow, Veterans Administration Hospital, Bronx, New York, and the late Solomon Berson developed radioimmunoassay (RIA) in 1960 to measure minute amounts of insulin in plasma and tissue. Yalow commented on this classic: "At present RIA is considered so classic a method that relatively few of the scientific papers based on RIA refer to the original detailed description of the methodology presented in this 1960 paper...."[13] We commented on this "obliteration phenomenon" in 1973 in connection with the work of Albert Wollenberger, German Academy of Sciences, Berlin,[14] and have discussed it in other essays.[15] Nevertheless, the Yalow and Berson paper was explicitly cited in 60 publications in 1983, as can be seen in Table 1, in parentheses. A careful analysis of the number of *implicit*, unreferenced uses of this article is needed before we can determine the degree of its obliteration. Obliteration is probably one of the greatest compliments a researcher can receive.[14]

Figure 1: Chronological distribution of citations to two classic papers listed in Table 1. The solid line represents citations to J.T. Dodge's 1963 paper. Dotted line represents citations to M.J. Karnovsky's 1961 paper.



Of course, citations tend to "decay" over time even for classic papers, whether due to obliteration, obsolescence, or other factors. Many classic papers reach a citation "plateau" and continue to be cited above average for many years. But other high-impact papers enjoy a huge burst of citations soon after publication, followed by a precipitous decline. Figure 1 illustrates the citation patterns for two high-impact papers in this study. The solid line represents 1963-1983 citations to the paper by J.T. Dodge and colleagues describing the preparation and characteristics of hemoglobin-free ghosts of human erythrocytes. The use of this method seems to have peaked in 1981. On the other hand, 1961-1983 citations to M.J. Karnovsky's method for lead staining at high pH in electron microscopy (dotted line) indicate that the method is rarely used anymore.

Before we conclude this study, a few points made by the classic authors on current science policy and funding deserve to be highlighted. Hayflick revealed that his classic method "resulted from the use of resources 'bootlegged' from grants having entirely different purposes. If our work has had any value, it is a tribute to the then prevailing freedom to pursue interesting leads unfettered by preconceived expectations written into grant proposals. Regrettably, in recent years, such opportunities have become increasingly compromised by myopic administrative demands for strict accountability."[9]

Paul D. Boyer, University of California, Los Angeles, also described the restrictions placed on him by narrow-minded administrators. He was to present his now classic method of spectrophotometric analysis of organic mercury compounds at a meeting. Boyer's grant provided for travel to the meeting, but a university administrator forbade him to use the funds because another staff member from a different department had already signed up for the meeting. Boyer commented: "My objections were of no avail, and the paper was presented at my personal expense.... [Such] action was a forerunner of the present condition of science support where the time expended and restrictions required for conformity to regulation often stifle progress."[16]

But the most telling example of administrative neglect is related by Charles C. Sweeley, Michigan State University, East Lansing. In 1963, Sweeley and colleagues innovated a chromatographic method to analyze sugar derivatives that is now a classic. Sweeley said: "It is perhaps noteworthy that we never had any direct support from any source for this research. In retrospect, it is remarkable that such a highly cited paper should not have received direct grant support from any federal agency."[17] Until researchers themselves overcome their bias against methods research, funding will continue to be a low priority for government administrators. I suspect, however, that industrial research directors are quicker to support methods research because innovative processes are often the key to successfully implementing new products.

The fact that 16 Nobel laureates appear in Table 1, many as authors of methods papers, further indicates that the bias against methodological research is misplaced. I am pleased to point out that "Citation Laureate" Oliver Lowry[18] appears twice in Table 1. He is the primary author of an article on the metabolic effects of ischemia, and a coauthor with O.A. Bessey and M.J. Brock of a paper describing a method for the determination of alkaline phosphatases.

As a final note, we would like to invite authors of the papers in Table 1 to contribute *Citation Classics* commentaries, if they have not done so already. We'll follow up this open invitation with letters to the individual authors involved. In the near future, we hope to collect the more than 1,800 commentaries already published in *CC* into a set of bound volumes. Thus, they will be more conveniently available to researchers, students, administrators, and the public.

We plan to continue this series in the weeks to come. At present, we have identified papers cited about 1,500 times or more in 1961-1982. No qualitative value is attributed to these citation data. Citations indicate various types of scientific activity, and they are affected by age, journal coverage in *SCI*, and other factors too numerous to discuss here.

When we extend the list of most-cited articles beyond the top 200 in future essays, the proportion of methods papers probably will decline. Life sciences papers will continue to dominate. This is due to many factors, not the least of which is the amount of publication in the life sciences. This phenomenon is also encountered in our studies of high-impact papers published each year. As pointed out on many occasions, most milestone papers in some fields—biochemistry or molecular biology, for example—are cited very soon after publication. The same is not generally true for papers in other fields, such as mathematics or geosciences. But by basing citation studies on 20 or more years of data, we can overcome the "time lag" that affects such fields.

* * * * *

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