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Fifty Classics from the *Journal of Clinical Investigation*: Over 60 Years of Nobel-Class Research

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In recent years we have published a series of essays discussing the most-cited articles from high-impact journals. We have already discussed the classic articles from the *British Medical Journal*,[1] the *New England Journal of Medicine* (*NEJM*),[2] and the *Lancet*.[3] For this essay we selected 50 papers published in the *Journal of Clinical Investigation* (*JCI*) that were most cited in the *Science Citation Index*® (*SCI*®) from 1955 to 1985. The Bibliography that follows lists these papers alphabetically by first author.

Established by the American Society for Clinical Investigation (ASCI) in 1924, the *JCI* is a highly respected journal, publishing original papers on research pertinent to human biology and disease. Out of 4,300 journals covered in the 1985 *SCI Journal Citation Reports*® (*JCR*®), *JCI* ranks 16th by citations received. Of the nearly 10,000,000 references processed in 1985, 42,901 were to the *JCI*. Ranked by impact, the journal is 52d with an impact of 6.88. This unusual combination of size and quality is discussed later.

The "Young Turks" Society

At the time the ASCI was founded in 1907, the medical community had not yet realized the value of clinical research. John S. Fordtran, Department of Medicine, University of Texas Health Science Center, Dallas, describes the science of medical research during this time as "based almost entirely upon the correlation of bedside observations and autopsy findings."[4]

Samuel James Meltzer became the organization's first president in 1909. Meltzer was a physician who gave up his private practice in 1904 to head the Department of Physiology and Pharmacology at the then newly formed Rockefeller Institute for Medical Research. Meltzer was unique in that he strongly supported the development of clinical investigation as a separate entity from clinical practice. In his presidential address he called for American physicians to apply scientific principles towards the solution of clinical problems.[4]

During this same time period, young revolutionaries had deposed the sultan Abdul Hamid II of the Ottoman Empire in 1909. These revolutionaries went on to establish a new constitutional regime and to institute sweeping reforms in the declining empire. Someone recognized the parallel between these Turkish revolutionaries and their crusading counterparts in American medicine. Thus the nickname "Young Turks" was also applied to the active members of the ASCI.[5]

Active members in ASCI today have accomplished meritorious original investigations in the clinical or allied sciences of medicine, have a medical degree, are based in the US or Canada, and are under 45 years of age. Today the ASCI has 529 active members under 45 and over 1,700 emeritus members over 45.[6]

The ASCI has similarities to other professional organizations. It holds its annual meeting with the American Federation for Clinical Research (AFCR) and the Associa-

tion of American Physicians. The ASCI, like the AFCR and the European Society for Clinical Investigation (ESCI), requires that active members become emeritus at the age of 45 to promote continuous evolution and renewal of the society. Both the AFCR and ESCI also publish highly respected journals. The AFCR established *Clinical Research* in 1953 and the ESCI launched the *European Journal of Clinical Investigation* in 1970.

A prospective ASCI member must be nominated by two active members of the society. Less than 80 new members are accepted each year. Prospective members of the AFCR may apply for membership.

Jean D. Wilson, Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas, pointed out in his 1978 ASCI presidential address that when the ASCI established the journal over 60 years ago, "the *JCI* was envisioned by its founders as an interface between the basic biomedical sciences and clinical investigation...it was not meant to be a specialty journal but to be broadly based, encompassing all of biomedical science and clinical investigation."[7] Indeed, in a 1974 citation study of the *JCI*, we noted that the journal successfully integrates these two areas of research in a complementary fashion.[8]

Today William N. Kelley, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, considers the *JCI* the premier journal in the field of clinical investigation. He feels that the journal defines what is meant by clinical research at its finest. Kelley writes, "Consider how important this high standard is to individuals in our discipline who run the risk of being viewed as weaker scientists by the more basic investigator and as weaker clinicians by the practitioner."[5]

Editorial Policy

The first editor of the *JCI*, G.C. Robinson, used an editing system in which manuscripts were assigned to a member of an editorial committee. The chosen editor decided if the paper was suitable for publication. If the paper was accepted, the editor was then responsible for its editing.[7]

In 1942 James L. Gamble, then the editor of the *JCI*, realized that this system was unsuitable to handle the increased complexity of scientific papers sent to the *JCI* for publication. Gamble revised the procedures so that manuscripts were sent to scientists outside the editorial committee to obtain the advice of people with more diversified scientific expertise.[7]

This system of refereeing is still used by the *JCI*'s current editor, Thomas P. Stossel, Hematology-Oncology Unit, Massachusetts General Hospital, Boston, and will presumably be continued under the supervision of the editor-elect, Bruce F. Scharschmidt, Department of Medicine, University of California, San Francisco. Refereeing not only provides reliable advice to assist the editors in making decisions, but it also helps an author make a good or potentially suitable paper even better. We have discussed the refereeing process in some detail.[9]

Article Information

To develop the list of most-cited articles for the Bibliography, we examined the articles from the *JCI* cited at least 50 times from 1955 to 1985 in the *SCI*. A strict listing of the top 50 *JCI* papers by citation frequency would have included several pairs of papers written by the same authors about closely related subjects. These pairs of papers are generally highly co-cited. So we chose to list only the most cited of the two in order to cover other authors and topics.

As shown in Table 1, the top 50 papers constitute only 1 percent of the 4,320 items cited 50 or more times. However, these papers received about 41,000 citations, or 8 percent of the 515,000 citations to *JCI* papers cited 50 or more times. The average for the top 50 papers was 818 as compared with 119 for the overall group. It should be noted that this is a remarkable record since the *JCI* has published about 20,000 papers in its entire history—almost 14,000 in the past 30 years. In the near future we will

Table 1: Citation-frequency distribution for the 4,320 articles published in the *Journal of Clinical Investigation* with 50 or more citations, 1955-1985 *SCI®*.

Citation Level	Number of Items at Level	Percent of Total Items
≥1,000	7	0.2
700-999	13	0.3
500-699	23	0.5
400-499	34	0.8
350-399	37	0.9
300-349	55	1.3
250-299	102	2.4
200-249	200	4.6
150-199	401	9.3
100-149	925	21.4
75-99	953	22.1
50-74	1,570	36.4
Total	**4,320**	**100.0**

lated by dividing the number of 1985 citations (6,323) to 1984 articles in the *JCI* by the number of articles (919) published in the journal in 1983 and 1984. However, Table 2 covers a six-year period to provide a longer-term perspective. We divided the number of 1980-1985 citations to 1980-1983 articles published in the *JCI* by the number of items published in the journal between 1980 and 1983.

In order to make a valid comparison of impacts, Table 3 presents the impact data for five "comparable" journals. The standard two-year 1980 *JCR* impact is shown (items published in 1978 and 1979). The six-

Table 2: Analysis based on an article-by-article audit of the *Journal of Clinical Investigation* source items, 1980-1983, and their 1980-1985 *SCI®* citations.

	Total Items	Percent Total Items	Number Cited 1980-1985	Percent Cited	1980-1985 Citations	Percent Total Citations	Cited Impact	Total Impact
Articles	1,220	78.4	1,205	98.8	30,962	78.2	25.7	25.4
Editorials	4	0.3	3	75.0	9	—	3.0	2.3
Letters	—	—	—	—	—	—	—	—
Notes	98	6.3	97	99.0	3,191	8.1	32.9	32.6
Reviews	—	—	—	—	—	—	—	—
Proceedings	219	14.1	218	99.5	5,437	13.7	24.9	24.8
Discussions	—	—	—	—	—	—	—	—
All Others	15	1.0	—	—	—	—	—	—
Total	**1,556**	**100.0**	**1,523**	**97.9**	**39,599**	**100.0**	**26.0**	**25.5**

NOTE: Combining four years of source data with only six years of citation data reduces the long-term impact of the items. This occurs because the articles published more recently, in 1983, have had less time for citations to accumulate. As seen in Table 3, the impact for 1980 research articles is 37.9, while the 1980-1983 research-article impact is 25.4 in the table above. The earlier articles have had the time to achieve a longer-term impact.

compare the performances of several high-impact journals. By any reasonable standard we could and will invite authors of over 100 articles in the *JCI* to write commentaries on their *Citation Classics®*.

While we generally refer to all items published in journals as articles, they really must be divided into many categories including original research articles, editorials, notes, proceedings, and so on. Table 2 provides data on the categories of journal items published in the *JCI* from 1980 to 1983. Citation totals from 1980 through 1985 are provided. At the outset I stated that the 1985 impact of the *JCI* was 6.88. This is calculated by dividing the number of 1985 citations (6,323) to 1984 articles in the *JCI* by the number of articles (919) published in the journal in 1983 and 1984. However, Table 2 covers a six-year period to provide a longer-term perspective. We divided the number of 1980-1985 citations to 1980-1983 articles published in the *JCI* by the number of items published in the journal between 1980 and 1983.

In order to make a valid comparison of impacts, Table 3 presents the impact data for five "comparable" journals. The standard two-year 1980 *JCR* impact is shown (items published in 1978 and 1979). The six-year impact for all items published in 1980 is shown as well as separate impacts for research articles. The number of published items for journals like the *British Medical Journal* and *Lancet* is six times greater than the number of items published in the *JCI*. Alternatively, the six-year impact for the *JCI* is 39.4, which greatly exceeds the overall impact of the other journals. One reason for this wide discrepancy is simply that journals like *Lancet* and *JAMA—Journal of the American Medical Association* include letters that are substantive enough to be indexed by ISI®. However, the longer-term impact of research articles is apparent for

Table 3: Impact factors for five medical journals, comparing *SCI®* *Journal Citation Reports®* (*JCR®*) impact factors to impact factors calculated using six years of *SCI* citation data.

Journal Title	1980 *JCR* Impact	1980-1985 Impact for All Items Published 1980	Number of 1980 Items Published	1980-1985 Impact for 1980 Research Articles	Number of 1980 Research Articles
British Medical Journal	2.9	2.7	3,135	10.6	467
Journal of the American Medical Association	2.4	4.4	1,444	12.0	299
Journal of Clinical Investigation	6.9	39.4	363	37.9	285
Lancet	8.7	7.5	2,982	29.6	448
New England Journal of Medicine	14.2	14.7	1,791	57.0	282

Table 4: Geographic areas represented by the institutional affiliations of the authors of the 50 most-cited articles published in the *Journal of Clinical Investigation*, 1955-1985 *SCI®*, listed in descending order of the number of papers produced.

Geographic Location of Institutions		Number of Articles
United States		46
Massachusetts	11	
New York	11	
Maryland	6	
Pennsylvania	4	
California	3	
Minnesota	3	
Texas	3	
Colorado	2	
Iowa	2	
Missouri	1	
North Carolina	1	
Ohio	1	
Oregon	1	
Washington	1	
Sweden		1
Canada		1
Switzerland		1
United Kingdom		1

Table 5: Frequency distribution of publication dates for the 50 most-cited articles from the *Journal of Clinical Investigation*, 1955-1985 *SCI®*.

Publication Date	Number of Articles
1945-1949	3
1950-1954	2
1955-1959	13
1960-1964	4
1965-1969	15
1970-1974	11
1975-1979	2

most journals but especially *NEJM*, *JCI*, and *Lancet*.

Table 2 shows that the *JCI* items coded as notes, which are called "Rapid Publications," have the highest impact, perhaps due to their immediacy. The *JCI* defines "Rapid Publications" as concise papers of unusual scientific importance that represent definitive and original study. These papers are expeditiously reviewed and if accepted are published two months before regular manuscripts accepted on the same date.[10]

Regular articles and proceedings differ only in that the proceeding papers are categorized separately because the latter were first presented at a professional meeting, such as the annual ASCI meeting. Apparently this type of public previewing does not change their impact significantly. Both types of articles have almost equal impact.

Ten articles in this study have already been featured in *Citation Classic* commentaries, indicated by an asterisk in the Bibliography. Two authors from the Bibliography, Roger H. Unger, Department of Internal Medicine, University of Texas Health Science Center, and Stephen E. Epstein, National Heart, Lung, and Blood Institute, National Institutes of Health (NIH), Bethesda, Maryland, provided *Citation Classic* commentaries that are included in *Contemporary Classics in Clinical Medicine*.[11,12]

Author Information

One hundred sixty unique authors appear in this study. G.F. Cahill, Howard Hughes Medical Institute, Boston, appears three times, while 10 authors appear twice in the Bibliography. Solomon A. Berson and Rosalyn S. Yalow, Radioisotope Service, Veterans Administration Hospital, New York, coauthored two papers appearing in the list, including the third most-cited article. This landmark paper, which describes the then-new method of radioimmunoassay, was highlighted in the second part of our series on the 1,000 articles most cited between 1961 and 1982.[13]

The authors of the papers in the Bibliography are affiliated with institutions in five countries listed in Table 4. Since the majority of papers were published by authors affiliated with institutions in the US, we have shown the number of affiliations from individual states. Forty-two institutions are represented in the Bibliography. Harvard University Medical School, Boston, Massachusetts; the NIH; and the University of Pennsylvania, Philadelphia, lead the list.

Noteworthy Articles

Over half (64 percent) of the articles in the Bibliography were published between 1960 and 1977, as shown in the frequency distribution of publication dates (Table 5). The most recent paper in this study, published in 1977, is authored by Barry Bresnihan and Hugo E. Jasin, Department of Internal Medicine, University of Texas Southwestern Medical School. This paper describes suppressor cell activity in human peripheral blood mononuclear cells.

Two articles published in 1945 are the oldest articles in this study. S.E. Bradley, Evans Memorial Hospital and Boston University School of Medicine, and colleagues developed a method for measuring hepatic blood flow. This measurement is necessary to differentiate changes in hepatic function due to blood circulation factors from those due to cellular activity. Previous methods used on animals required surgical manipulation that was inapplicable to humans.

Franz J. Ingelfinger is a coauthor of this paper. As a past editor of *NEJM*, Ingelfinger established the controversial "Ingelfinger Rule," which prohibits prior disclosure to the media of papers submitted to *NEJM*, discussed earlier.

The other 1945 article in the Bibliography was published by a team from the Department of Physiology, New York University College of Medicine. Homer W. Smith and colleagues devised a method for studying to what extent organically bound iodine aids the excretion process. Diodrast and hippuran, two iodine-bound chemicals that are swiftly excreted, were compared with a substitute derivative of hippuric acid that does not contain organically bound iodine. Smith and colleagues found that the excretion rates were identical, indicating that the efficiency of excretion is not dependent on iodine. Cited over 1,500 times, this paper is the fourth most-cited paper in this study.

The second most-cited article deals with lipoprotein differentiation. Recently we discussed lipoprotein research when describing Michael S. Brown and Joseph L. Goldstein's Nobel-winning contribution to cholesterol research.[14] The paper by Richard J. Havel, National Heart, Lung, and Blood Institute, and colleagues describes an accurate and efficient method for determining the composition of the different types of lipoproteins. Havel wrote in a 1983 *Citation Classic* commentary, "although we referred in the laboratory to the fraction that we separated at a nonprotein (background) solvent density of 1.019 g/ml as *very low density lipoproteins* to distinguish them from those subsequently separated at 1.063 g/ml (*low density lipoproteins*), such terminology was not permitted by the editors of the *Journal of Clinical Investigation* until 1957. Since then, this terminology has stuck, and VLDL, LDL, and HDL have become the standard jargon of the field."[15] Cited over 2,800 times, the methods described in this article indirectly helped determine the mode of cholesterol metabolism.

The 1956 article by Vincent P. Dole, Rockefeller Institute for Medical Research, New York, is the most-cited article published in the *JCI*, cited over 3,800 times. Dole developed a new, efficient method to measure the concentration in plasma of non-esterified fatty acids (NEFA), those fatty acids bound to protein. This paper was highlighted in our essay on the 250 most-cited articles from 1955 to 1964.[16]

Seymour S. Kety and Carl F. Schmidt, then of the Department of Pharmacology, University of Pennsylvania, published a study in 1948 describing a quantitative method for measuring cerebral blood flow in humans using nitrous oxide. The method was based upon the uptake by the brain of the diffusible nitrous oxide supplied by way of the arterial blood. This paper has been cited over 860 times. In a 1981 *Citation Classic* commentary, Kety, who is now at the Harvard Medical School Mailman Research Center, McLean Hospital, Belmont, Massachusetts, wrote that "this early work has been [highly] cited...because the theory on which it was based led directly or indirectly to the development of current methods for the measurement of regional blood flow, metabolism, and the visualization of functional activity throughout the human brain."[17]

Conclusion

The challenges facing the clinical investigator are quite different today than they were for Samuel Meltzer and his colleagues, who had to commit themselves to establishing experimental clinical research as a necessary and integral part of medical science. Today Kelley notes that "the very success of medical science has transformed the clinical investigator. Rather than dedicating himself to conducting controlled clinical observations and experimental medicine, the contemporary physician scientist must be able to master and apply concepts and techniques in molecular and cellular biology to answer the questions of interest."[5] Judging by the remarkably large number of *Citation Classics* it has published, the continued high impact of the *JCI* successfully reflects this transformation. A detailed examination of *JCR* shows that citations to and from journals in physiology and other preclinical areas are the rule rather than the exception for *JCI*. It serves as a model of the synergism between basic and clinical research.

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