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More Delayed Recognition. Part 2. From Inhibin to Scanning Electron Microscopy

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Delayed recognition refers to significant research that is initially underappreciated and years later becomes widely acknowledged and highly regarded. Six possible cases of delayed recognition include (1) inhibin, the male antifertility factor, (2) central nervous system drugs, (3) adrenotropic receptors, (4) scanning electron microscopy, (5) alkaline phosphatase determination, and (6) aqueous electrolytes. The first two were suggested by *Current Contents*® readers. Four were identified quantitatively from the 1945-1988 *Science Citation Index*® database.

How Do We Recognize Delayed Recognition?

Delayed recognition refers to those "premature" discoveries that presumably are overlooked or underappreciated for a long time but that are eventually "rediscovered." Sociologists and historians of science have studied the phenomenon closely to understand better the dynamics of the discovery process. For example, delayed recognition may reveal instances of scientific conservatism or communal resistance to unorthodox concepts.[1] Or it may indicate cases where a new or improved method "hibernates" until a critical technical limitation is resolved, making the method suddenly popular.[2]

In an essay published 10 years ago, I suggested ISI® might develop a systematic, quantitative algorithm to identify possible examples of delayed recognition by tracing the citation histories of key papers associated with these discoveries.[3] We haven't yet reached that goal, but a recent survey of the 100 most-cited papers in the 1945-1988 *Science Citation Index*® (*SCI*®) demonstrates that we may now be in a better position to test the "theory."[4] To quantify a definition of delayed recognition, we set a threshold of 10 or fewer citations to a paper at age 10 as one criterion. A second criterion was a 10-fold increase in citations at age 20. Scanning a database of highly cited papers, we first ranked them by total citations. Then we tracked the year-by-year citation counts. In this way we identified about 20 that matched our definition of delayed recognition.

Data for several of these are discussed here and documented with graphs of their citation histories and *Citation Classic*® commentaries by the authors. The first two examples were suggested by *Current Contents*® (*CC*®) readers.

Inhibin, the Male Antifertility Factor

Anil R. Sheth, Institute for Research in Reproduction, Indian Council of Medical Research, Bombay, India, wrote us about his interest in the early work on the follicle-stimulating hormone (FSH) called inhibin:

> I write to you with reference to your *Current Comments*® on Delayed Recognition.... One other contribution...that comes to...mind is that of "INHIBIN".... The first known and published report of the concept...is that of J.C. Mottram and W. Cramer [1923],[5] [although] D.R. McCullagh coined the term "Inhibin" in 1932.[6] After a gap of more than 40 years, research on "Inhibin" has picked up again and [it] is now very much talked about as

> a male contraceptive.... Further analysis may reveal interesting dimensions hitherto not known. We are curious to know what citation analysis comes up with.[7]

The pituitary produces two gonadotropic hormones: luteinizing hormone (LH), which affects the testis in males, and FSH, which affects the ovary in females. Both LH and FSH are stimulated by a factor produced by the hypothalamus, hypothalamic decapeptide LH-releasing hormone. There is evidence of an additional hormone that regulates FSH more strongly than it regulates LH.[8] F.H. de Jong, Department of Biochemistry, Erasmus University, Rotterdam, The Netherlands, mentions four possible theories.[9] The role of inhibin, a protein originating in the gonad, is one.

De Jong describes three periods of inhibin research. The earliest, 1923-1940, saw the introduction of the inhibin concept with experiments in rats showing that the irradiation of testes and the removal of male and female gonads affected the pituitary, suppressing the secretion of hormones. However, some attempts to repeat the early experiments were unsuccessful and led to a general disinterest in the inhibin concept of J.C. Mottram and W. Cramer[5] and of D. Roy McCullagh, Cleveland Clinic Foundation, Ohio.[6]

De Jong calls the second period, 1940-1965, the "denial of the existence of inhibin."[8] From about 1965 on, direct evidence for the existence of inhibin has increased, particularly with the demonstration in 1976 by de Jong and R.M. Sharpe,[10] MRC Unit of Reproductive Biology, Edinburgh, UK, that a nonsteroidal component of ovarian follicular fluid could prevent the increase of FSH in castrated adult male rats.

There are no citation data available for the period before 1945, so we can't really say much about the early recognition of the Mottram/Cramer or McCullagh papers. Figure 1 shows their annual citations compared to the year-by-year distribution of the 434 papers cited in the 1987 and 1988 reviews of inhibin research by de Jong.[8,9]

On the basis of the pattern in Figure 1, inhibin research began to flourish in the mid-1970s, when citations to McCullagh's 1932 paper began to grow. This corresponds to the increase in the number of papers on inhibin beginning in 1972. Interestingly, Figure 1 indicates that the 1923 Mottram/Cramer "concept paper" shows little change in annual citation frequency during the 1970s and 1980s. It is also clear that the 1932 McCullagh paper has enjoyed a surge of "recognition" since the mid-1970s, whatever its citation history for the period 1932-1944. While the McCullagh paper seems to be an example of delayed recognition, the Mottram/Cramer paper apparently is not, at least from the perspective of its citation history.

Central Amine Receptors and Chlorpromazine

G. Curzon, Institute of Neurology, University of London, UK, sent us his paper on the history of reserpine and chlorpromazine.[11] In his letter, Curzon notes:

Figure 1: Year-by-year distribution of *SCI*® citations to two early papers on inhibin, compared to the annual distribution of papers on inhibin identified by F.H. de Jong in his 1987 and 1988 reviews.

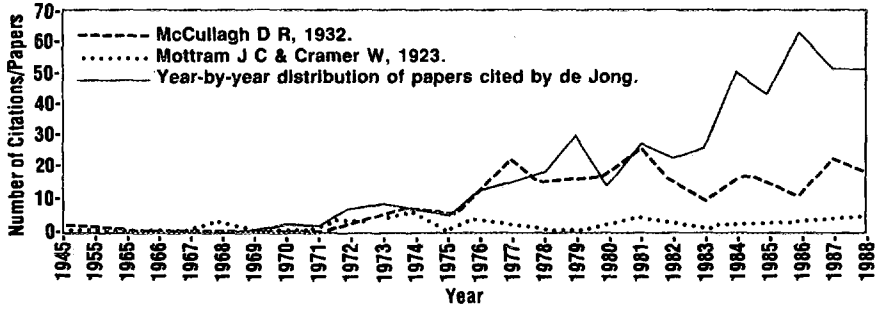
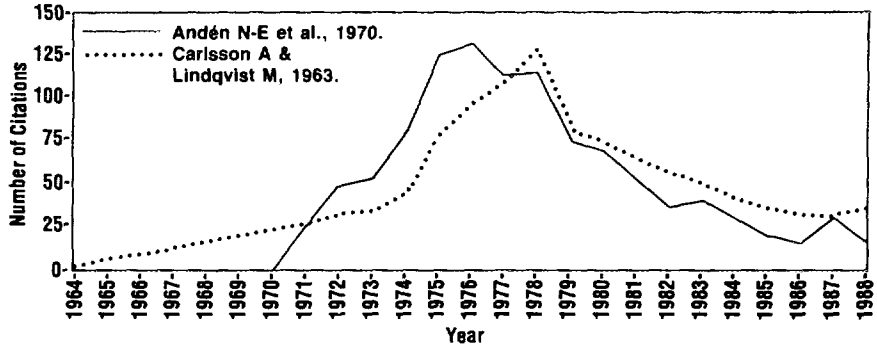


Figure 2: Year-by-year distribution of *SCI*® citations to the following papers:



> My interest in delayed recognition derives from a communication I gave at the International Society for Neurochemistry (ISN) meeting in Portugal earlier [in 1989] in which I discussed an example of delay. Subsequently I saw Dr. Garfield's essay...and applied to your Uxbridge [UK] office for the earlier article[3] as I was writing a paper derived from my ISN talk.... A copy is enclosed. You will note...the citation profile of the [1963] paper by Carlsson and Lindqvist[12] and its relationship to the subsequent [1970] paper of Andén *et al.*[13,14]

In 1963 Arvid Carlsson and Margit Lindqvist, Department of Pharmacology, University of Göteborg, Sweden, suggested that chlorpromazine blocks monoamine receptors in the brain while reserpine depletes the amines themselves.[12] However, according to Curzon,[11] the way chlorpromazine and similar drugs work was not entirely clear until Nils-Erik Andén, who had worked in Carlsson's laboratory, and colleagues reported in 1970 that chlorpromazine and similar drugs (neuroleptics) block dopamine receptors but not noradrenaline receptors.[13]

Figure 2 shows citation graphs for the 1963 Carlsson and Lindqvist and 1970 Andén *et al.* papers. As Curzon has pointed out, there is a 14-year gap between the publication of the earlier paper and its citation peak.[11] There is only a six-year gap between the publication and citation peak of the Andén *et al.* paper. Most noticeable is the remarkable similarity of the curves of the two papers after 1970, the date of publication of the Andén paper. Is this a case of delayed recognition where a later breakthrough paper makes an earlier cited paper much more important by association?

It may be questioned whether these papers are indeed examples of delayed recognition. The Carlsson paper seems not to have suffered from lack of recognition. By the time the 1970 Andén paper was published, Carlsson's 1963 paper was being cited over 20 times per year. It subsequently became the most-cited paper ever published in *Acta Pharmacologica et Toxicologica*, with 1,130 citations through 1988. It is also clear that the Andén *et al.* paper affected later citations to the Carlsson paper. Andén *et al.*'s 1970 paper has received 1,055 citations, making it the most-cited paper published in the *European Journal of Pharmacology*. However, it is remarkable that, during 1986-1988, 145 papers referred to either of these two papers but only 7 cited both.

In a 1985 *Citation Classic* commentary on his 1963 paper, Carlsson wrote:

> This, I believe, was the first time that a receptor-mediated feedback control of neuronal activity was proposed.... In the following year, three of my students discovered the neuroleptic-induced increase in the concentrations of deaminated dopamine metabolites.[15] Despite confirmatory work by others, our findings did not receive much attention until several years later. A possible explanation for this was that in the 1960s most workers in this field were focusing on other aspects of neurotransmission. However, a fairly dramatic

change occurred in the early 1970s. Since then receptors have attracted an ever-increasing interest.[16]

The 1964 paper by Carlsson's students, Andén, B.-E. Roos, and B. Werdinius,[15] mentioned in his *Citation Classic* commentary, had been cited 450 times through 1988. But it is actually Andén *et al.*'s 1970 paper[13] that has received wider recognition by citations as a breakthrough concept.

Toward a Quantitative Indicator of Delayed Recognition

While interesting and sometimes provocative, anecdotal examples are ambiguous because there is no handy yardstick to measure delayed recognition. However, as stated at the outset, citation data may be applied systematically to identify papers that conform to a defined citation pattern for delayed recognition.

In recent essays on the most-cited papers in the 1945-1988 *SCI*,[4] I commented on this possibility. In the ISI database, the number of times each paper has been cited explicitly is shown. That facilitates the creation of a putative "citation profile" for delayed recognition. A computer algorithm then can be created to search for such papers, but the work mentioned in this essay was in fact done manually.

To reiterate, delayed recognition was simply defined as 10 or fewer citations per year at age 10 and at least 10 times as many citations at age 20. About 20 papers among the top 750 publications in the 1945-1988 *SCI* file fit this definition. Each of the top 750 was cited over 1,300 times in the 44-year file. Figure 3 shows a graph of the annual citations to the first three possible cases of delayed recognition discussed here.

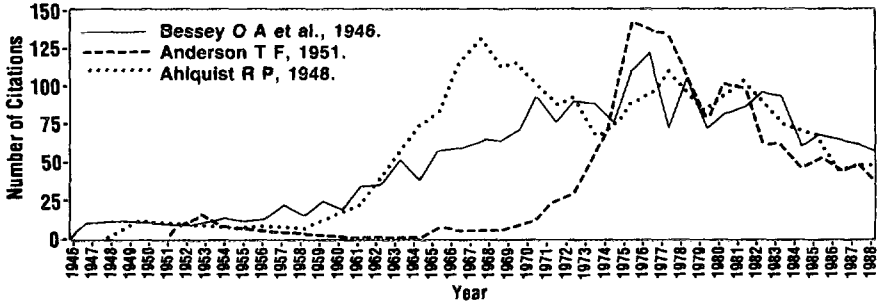
R.P. Ahlquist: Adrenotropic Receptors

A 1948 paper by Raymond P. Ahlquist, University of Georgia School of Medicine, Augusta, on adrenotropic receptors in the *American Journal of Physiology*[17] averaged 8 citations per year until 1958, when it began to grow, peaking at 134 citations in 1967 at age 20. In his *Citation Classic* commentary,[18] Ahlquist quotes his own 1973 essay on alpha and beta receptors, in which he notes the resistance of entrenched opinion as a possible cause of his work's delayed recognition:

> The original paper was rejected by the *Journal of Pharmacology and Experimental Therapeutics*, was a loser in the Abel Award competition, and was finally published in the *American Journal of Physiology* due to my personal friendship with the great physiologist W.F. Hamilton. It was ignored for five years. The reasons for this are obvious today. The concept did not fit with ideas developed since 1890 on the actions of epinephrine.[19]

Ahlquist says the paper was ignored for five years. The *SCI* data in Figure 3 suggest it was effectively overlooked at least twice as long. He also explains why the paper has continued to receive 50 to 120 citations per year since the early 1960s:

Figure 3: Year-by-year distribution of *SCI*® citations to the following papers:



> In my opinion, the most important contribution of my concept was to repopularize the idea of receptors. These had been described in the early part of this century but for some reason had been forgotten. Now there are receptors for hormones, peptides, and drugs.[18]

Ahlquist's paper may also have benefited from the return to the concept of receptors that Carlsson discussed.[16]

T.F. Anderson: Electron Microscopy Specimens

Citations to the 1951 paper by Thomas F. Anderson, Johnson Foundation, University of Pennsylvania, Philadelphia, "Techniques for the preservation of three-dimensional structure in preparing specimens for the electron microscope,"[20] exceeded 10 per year only in the 19th year after its publication. It reached a high of 142 citations in 1975 at age 30. In a 1982 *Citation Classic* commentary, Anderson, now at Fox Chase Cancer Center, Philadelphia, indicated a reason for this long delay:

> Electron microscopists were very slow to adopt the method, even though everyone knew about it from the beautiful stereoscopic pictures of critical point-dried specimens I showed at meetings in both the US and Europe.... It wasn't until late 1960, when scanning electron microscopes became practical and useful, that the method became popular.[21]

The scanning electron microscope greatly increased the flexibility of electron microscope use. Anderson's paper benefited from a technical development and a wave of converts to the electron microscope in its improved form. This is a good example of the delayed *application* of a method.

O.A. Bessey, O.H. Lowry, and M.J. Brock: Measuring Alkaline Phosphatase

A 1946 paper coauthored by Otto A. Bessey, Oliver H. Lowry, and M.J. Brock, Division of Nutrition and Public Health, Public Health Research Institute of the City of New York, on alkaline phosphatase measurement, published in the *Journal of Biological Chemistry*, is another possible case of delayed recognition.[22] It received 11 citations in 1955 at age 10. At age 31 in 1976, it reached a peak citation level of 123. The paper received over 2,200 citations through 1988.

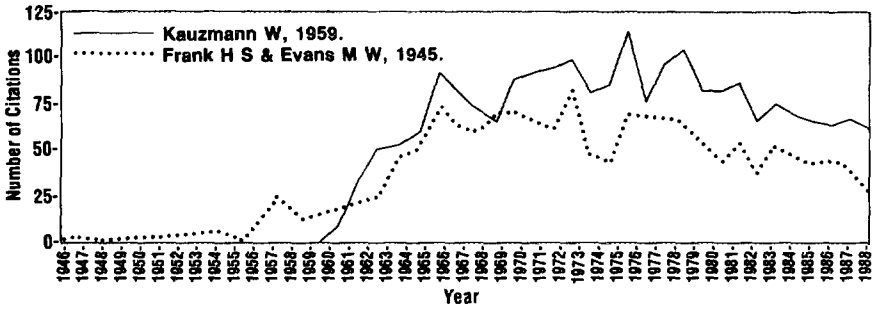
Lowry is the author of the first *Citation Classic* commentary published in *CC*,[23] which described his phenomenally cited method for protein determination.[24] In a 1985 commentary on the 1946 paper with Bessey and Brock describing a method for determining alkaline phosphatase in blood serum, Lowry noted an interesting relationship between research and commerce:

> Before publishing, we fortunately discovered that Ohmori[25] and Fujita[26] had used p-nitrophenyl phosphate for the same purpose and clearly had priority. Nevertheless, we published anyway, because our procedure was simpler, required less plasma, and the *Journal of Biological Chemistry* had a much wider circulation in those days than the *Journal of Biochemistry* (Japan) or *Enzymologia*.... After the war, Eastman stopped making p-nitrophenyl phosphate.... I mentioned this to Dan Broida, who was just cranking up Sigma, and suggested he might like to make it instead. He obliged (and made a more stable product) and used to say that this was a factor in his really getting involved in manufacturing top-notch biochemicals.[27]

It would be interesting to know exactly when Sigma began manufacturing p-nitrophenyl phosphate—perhaps the lack of a high-quality, stable form of the compound may have contributed to the delayed application of the Bessey methods paper.

The paper by Hiroshi Fujita, Medical Chemical Institute, Medical Academy of Chiba, Japan,[26] received fewer than 50 citations through 1988 while the paper by Yoshihisa Ohmori, also of the Medical Chemical Institute, Medical Academy of Chiba,[25] received 66. Both were published in German, which may account for their lower citation rate compared to the Bessey paper.

Figure 4: Year-by-year distribution of *SCI*® citations to the following papers:



H.S. Frank and M.W. Evans: Aqueous Electrolytes

A 1945 paper by Henry S. Frank and Marjorie W. Evans, Department of Chemistry, University of California, Berkeley, in the *Journal of Chemical Physics* represents an advance in the understanding of aqueous solutions.[28] Frank, now at Pomona College, Claremont, California, recalled in a 1983 *Citation Classic* commentary that the idea resulted from

> a "double-take" while walking the deck in June 1939 on the *S.S. President Coolidge*.... The sudden realization [came to me] that the thermochemistry of an aqueous salt solution is dominated by changes in the local entropy of the solvent water in the immediate neighborhood of the ions....[29]

The paper received no more than 7 citations per year during its first 10 years, then peaked at 81 citations in 1972 at age 28. It was cited in over 1,600 publications through 1988. Frank noted the significance of the aqueous systems to many kinds of research and pointed to resistance to new ideas about structure:

> Since the properties of aqueous solutions are fundamental to so many areas, any advance in understanding them will have to be "used by everybody".... For a long time the only aqueous systems [in] which the solution properties had been intensively studied had been electrolytes.... From about 1920 on, electrolyte theory had been "doing so well"...that an establishment had grown up which, for the most part, was neither accustomed nor hospitable to [new ideas about structure]. This made all the more effective the positive influence of...favorable notice and practical application in...influential new works [such as] Kauzmann.[29,30]

Figure 4 shows a graph comparing annual citations to the papers by Frank and Evans and by W. Kauzmann, Department of Chemistry, Princeton University, New Jersey. The *SCISEARCH*® online database for 1974-1990 shows over 1,940 citations to the Frank/Evans and Kauzmann papers, with 158 papers citing both papers in their references.

Questions for Future Consideration

In the months ahead, we are planning to continue the series of essays on the Most-Cited Papers of All Time, 1945-1988. Each group of 100 papers will be reviewed with delayed recognition in mind. There are some interesting questions that come to mind: Is delayed recognition more prevalent among methods or concepts papers? Are delayed recognition citation patterns typical of paradigm-busting papers in chemistry but not in physics or biology? And is there a difference over the past few decades, where the existence of improved information retrieval methods has ostensibly made it more difficult to be unaware of relevant work? Or is there some fundamental delay

factor that must inevitably affect the acceptance of new ideas via the education-research process? The human brain can only deal with so much information. In the competition of ideas, it may well be research that is commercialized (and hence "advertised") that more easily penetrates the innate brain barrier through redundancy.

* * * * *

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