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Notes and Letters (continued)

● **ABSTRACT**

A set of 316 commentaries by authors of highly-cited papers was reviewed, to identify any difficulty encountered by the authors in producing or publishing their articles. The commentaries were selected from those published each week in the Citation Classic^a feature of Current Contents. According to their commentaries, a small proportion (5.7%) of the authors of these papers had some difficulty when doing the research, or when trying to publish the results. Three more highly-cited papers which had also encountered difficulties in getting published were identified from Citation Classic^a commentaries: one of them was co-authored by a Nobel Prize winner. Three of the papers which encountered publication problems are the most cited from their respective journals. In part, the problematic papers reported innovative methods or theories, or presented new interpretations of previous data. Those in the peer review system should have access to these findings, to improve their review of innovative work. Evaluative criteria that are too narrow can sometimes lead to the initial rejection of very important papers.

Consolation for the Scientist: Sometimes it is Hard to Publish Papers that are Later Highly-Cited

Juan Miguel Campanario

Legará una época en que nuestros descendientes se asombrarán de que ignoremos cosas que para ellos son tan claras. Muchos son los descubrimientos reservados para las épocas futuras, cuando se haya borrado el recuerdo de nosotros. [A time will come in which our descendants will be astonished to know we were not aware of things they will take for granted. A great many discoveries are lying ahead for future generations, when even our memories will have vanished.] (Seneca, *Cuestiones naturales*, libro 7)

As Barber points out,¹ the assertion that scientists sometimes resist scientific discovery clashes with the stereotype of the scientist as 'the open-minded man'. However, it is also commonly accepted that new

ideas and unexpected observations often have difficulty getting published. It is also a common idea that some discoveries are 'premature', and do not fit the current conceptual framework of a given discipline. Sometimes these considerations cause a delay between the discovery and acceptance of new ideas by the scientific community. Scientific journals play a crucial role in both the selection and the publication process of scientific ideas. Almost all leading journals use a peer review system in order to evaluate and select contributions. Manuscripts are reviewed by members of the editorial staff, or by one or more external referees who are supposedly experts in their fields.

The peer review system has frequently been criticized.² Flaws in the system have been documented. In a survey of manuscripts rejected by the *Journal of Clinical Investigation*, Jean Wilson found that 85% of these papers were subsequently published elsewhere.³ A study of the most cited manuscripts in chemistry indicates that graded referee judgements were negatively correlated with later judgements of merit, as measured by citations. Those manuscripts that later received the most citations also received more critical reviews and required more revision.⁴ Gottfredson compared reviewers' ratings of psychological research papers to the number of citations received by these papers in the first nine years following publication: he found only low to moderate correlations.⁵

The peer review system has been accused of delaying publication.⁶ Bias and unethical behaviour in the refereeing process have also been identified,⁷ and the reliability of the system has been strongly questioned. A study by William Goffman, editor of *The New England Journal of Medicine*, indicated that the possibility of two different referees agreeing was only slightly better than chance.⁸ Cicchetti has reviewed some studies on the reliability of peer review of manuscripts: he found that there is much more agreement on rejection than on acceptance.⁹ Peters and Ceci resubmitted twelve psychology articles to the journals that had originally published them. The original papers had been published by prestigious authors from important departments, but in this instance the names and affiliations were altered. Only three of the resubmissions were detected, eight were rejected and one was accepted.¹⁰ Singer analyzes these flaws in the peer review system as part of a general crisis of criteria in the academic world.¹¹

The most serious charge against the peer review system is made by Redner, who affirms that 'one of the roles of journals almost appears to be to sift out and reject really original contributions'.¹² Stephen

Lock, editor of the *British Medical Journal*, also thinks that peer review 'favours unadventurous nibblings at the margin of truth rather than quantum leaps'.¹³ However, a study on library journal referees found that the originality of papers and validity of claims were the evaluation criteria they most valued.¹⁴ Medical editor David F. Horrobin also accuses the peer review system of impeding the publication of innovative ideas, and he illustrates his accusations with a set of well-documented cases.¹⁵ More cases of resistance to new ideas and instances of important papers which have had difficulties in getting published can also be found in the literature. Some of them are given below.

1. Working with yeast, Professor Roger J. Williams discovered one of the B vitamins in 1919. His commentary recalls a letter from an editor of the *Journal of Biological Chemistry*, advising him to attack the subject of vitamins in a more realistic way, using laboratory animals. As Williams wrote, 'if I had followed his advice, many of the vitamins we have known for 30 years might still be undiscovered'.¹⁶ An account of scientific resistance to discovery of vitamins can be found in a paper by Aronson.¹⁷

2. A highly-cited paper by Raymond P. Ahlquist on adrenotropic receptors, published in the *American Journal of Physiology*,¹⁸ was originally rejected by the *Journal of Pharmacology and Experimental Therapeutics*. As Ahlquist has recognized,¹⁹ his paper was finally published in part due to his personal friendship with the physiologist W.F. Hamilton. Scientists ignored this paper for five years. As of 1958 the citations began to grow, and the paper has continued to receive 50 to 120 citations per year.²⁰ It has been cited over 2400 times since 1948.²¹

3. Another surprising instance is a letter to the editor by Sen-itiroh Hakomori which has been cited more than 3200 times — one of the 100 most-cited papers of all time.²² The paper was first submitted to the *Journal of Biochemistry (Toyko)* but received strong criticism from a pre-print reviewer. Hakomori withdrew it, but a colleague advised him to resubmit the manuscript; it was finally published as a letter.

4. A report of Rosalind Yallow submitted to the *Journal of Clinical Investigation* was initially rejected, although it was based on the research that subsequently earned her the Nobel Prize. She is one of the few scientists who has since had the opportunity of writing to other editors who rejected her papers saying: 'You may not become as famous as [editor] in being identified in a Nobel lecture, but you are on the right track'.²³

5. In June 1937, *Nature* rejected Hans Krebs's letter describing the citric acid cycle, and a full article appeared two months later in *Enzymologia*.²⁴ Krebs won the 1953 Nobel Prize in physiology or medicine for this work, and has published an account of the episode.²⁵ As has since been pointed out, 'the rejection of Hans Krebs's discovery of the tricarboxylic acid (or Krebs's) cycle, a pivot of biochemical metabolism, remains *Nature's* most egregious error'.²⁶

6. *Nature* initially rejected a paper by the 1988 Nobel Prize winner Harmut Michel, based on that research, that has since been cited 140 times.²⁷ A cluster analysis has subsequently identified the paper as a core document in several research fronts.²⁸

7. A Royal Society referee rejected a paper by Waterston on a new molecular theory of gases, thinking that 'the paper is nothing but nonsense'. As a result,

Waterston's work lay in utter oblivion until rescued by Lord Rayleigh forty-five years later.²⁹

8. The most cited paper ever published in *Cytogenetics and Cell Genetics* was rejected when the author, Arthur D. Riggs, submitted it to one of the leading journals on molecular biology.³⁰ This paper proposed that DNA modification by enzymatic methylation was important for the X-inactivation process, and also suggested a new somatically heritable, information-coding system based on methylation patterns. A review on this topic by Riggs and Aharon Razin has been cited over 685 times.³¹

9. While his doctoral dissertation was being typed, Harland G. Wood discovered that CO₂ is used as a substrate by heterotrophic bacteria. He considers this discovery to be the most significant contribution of his scientific career, since it destroyed an erroneous dogma then held by biochemists. Wood told his thesis director, Professor C.H. Werkman, that he wanted to rewrite the thesis, only to be told: 'the thesis is all typed except the bibliography; we don't want to type it again' (!). The discovery was finally presented in a microbiology meeting in 1935.³²

10. In 1943, David Nachmansohn and A.L. Machado were the first researchers to observe the enzymic acetylation obtained in a soluble system in which the free energy of ATP hydrolysis was used. However, *Science*, *Journal of Biological Chemistry* and *Proceedings of the Society of Experimental and Biological Medicine* all refused to publish a paper reporting this crucial finding.³³

11. Peters and Ceci had problems in publishing their paper (cited in note 10). After a long delay, the paper was rejected by *Science*, and then by *American Psychologist*. Submission was encouraged by the editor of *Behavioral and Brain Sciences* and, after major revisions, was accepted for publication.³⁴ According to the *Social Sciences Citation Index* and the *Science Citation Index*, this paper has been cited over 110 times.

12. British biochemist Robert H. Michell developed the idea that receptor-triggered inositol lipid hydrolysis is a transmembrane-signalling reaction that causes the mobilization of Ca²⁺ within cells by hormones. This finding was sent to *Nature* and rejected. Michell then presented his new idea as the central conclusion of a review paper for *Biochimica et Biophysica Acta*,³⁵ since cited over 1835 times.³⁶ Another Michell article *Nature* did not want to publish appeared in an invited paper,³⁷ cited over 325 times since 1981.³⁸

13. W. Neal Burnette discovered a method whereby specific antigens can be distinguished in a complex protein mixture. He submitted a manuscript to *Analytical Biochemistry*, but reviewers rejected the paper. As Burnette tells us, 'the few pre-prints sent to colleagues seemed to have undergone logarithmic Xerox multiplication'.³⁹ He began receiving phone calls from researchers unable to read the umpteenth photocopied generation of the pre-print. Finally, *Analytical Biochemistry* agreed to publish the paper; it appeared in 1981,⁴⁰ and has been cited in more than 3810 publications.⁴¹

14. The law of the conservation of energy (the first law of thermodynamics) was reported by J.R. Mayer in 1842. Mayer's paper was rejected by the leading physics journal *Annalen der Physik*, and was eventually published in a relatively obscure chemical journal.⁴² According to Ziman,⁴³ the paper was almost entirely ignored by physicists and, possibly as a result of this, Mayer suffered a mental breakdown from which he never recovered.

15. In 1983, a paper by Michael J. Berridge on inositol triphosphate and diacylglycerol as second messengers was rejected by *Nature*; it was accepted by the *Biochemical Journal*, published in 1984,⁴⁴ and has been identified in a study of 'hot'

articles that were highly cited within two years of their publication.⁴⁵ With a citation tally of 1938, the paper ranks number 275 of the most-cited papers of all time.⁴⁶ Berridge later received the Feldberg Award in 1984, the King Faisal International Prize in Science in 1986, the Louis Jeantet Prize in Medicine in 1986, and he shared the 1989 Lasker Award for basic research with Alfred G. Gilman and Yasutomi Nishizuka.⁴⁷

16. The most cited paper in the story of science is that by Oliver H. Lowry, N.J. Rosebrough, A.L. Farr and R.J. Randall on protein measurement with the Folin phenol reagent.⁴⁸ This paper has been cited more than 187,000 times (!); the next most cited paper only scores 59,000.⁴⁹ Lowry's paper was not rejected but, in an autobiographical account, Lowry recalls that, after its first submission to the *Journal of Biological Chemistry*, it was returned by the editors for drastic shortening. According to Lowry, 'this shortening may have improved the paper, but forced us to omit some details that perhaps would have lessened the plethora of papers by others describing improvements and precautions'.⁵⁰

Although there is a well-documented body of instances of very important papers which have encountered difficulties in getting published, no systematic research has been carried out in this area. In this Note, I suggest a new approach to this topic. A set of authors' commentaries on important and highly-cited papers can be found in the Citation Classic^R feature of *Current Contents*. I have examined a subset of these essays on highly-cited papers, to identify papers which had difficulty in getting produced or published. I have extended this analysis to identify not only papers which had difficulty in getting produced, but also those whose authors have noted difficulty in doing the research. Sometimes, difficulties in producing important papers arise even before scientists try to publish their results. Funding agencies rarely risk money on innovative projects, and department heads, not always aware of the importance of an original paper, may pose difficulties.⁵¹

What is a Citation Classic^R?

Derek de Solla Price used to speak of a hypothetical *Journal of Really Important Papers*,⁵² and Garfield introduced the idea of a *Journal of Citation Classics*^R.⁵³ A Citation Classic^R is a paper or book which, by definition, is extraordinary in the relatively large number of citations it has received. Citation Classics^R have been identified from the Institute of Scientific Information (ISI) database since 1977. ISI uses citation frequency as the major criterion for selecting Citation Classic^R candidates. However, this invariably gives an advantage to

articles published in well-known leading journals.⁵⁴ To avoid this domination by high-impact journals, ISI limits its initial choices to the top ten or twenty papers from each journal.⁵⁵ Alternative sources of candidates are also identified from cluster analyses of citations, to identify annual or biannual research fronts, whose core papers can be Citation Classic^R candidates. Readers of *Current Contents* can also make nominations. While any paper cited over 400 times is a candidate, the necessary citation frequencies vary from field to field: over 50 citations can confer classic status in a small field, such as radio astronomy or mathematics.⁵⁶ It must be kept in mind that ISI statistics indicate that 55% of the papers published between 1981 and 1985 received no citations at all in their first five years after publication.⁵⁷ Only 2% of over 32 million papers which were cited at least once between 1945 and 1988 were cited more than 50 times, just 0.05% of all cited papers more than 500 times.⁵⁸

Authors of Citation Classic^R candidates are invited to write a short essay on the highly-cited publication. When an author agrees to write this retrospective, the paper becomes a Citation Classic^R. About 40% of authors of Citation Classic^R candidates have written commentaries.⁵⁹ Authors explain the work, detail what prompted the research, the contributions of their co-authors and, sometimes, the obstacles encountered in both research and publication. In Garfield's words, a Citation Classics^R essay presents 'the human side of science'.⁶⁰ It must be pointed out that, due to the peculiar selection method, the Citation Classic^R collection is neither a random selection nor a representative set of highly-cited published papers; and, although the authors of highly-cited papers do correctly assume that their papers were cited for positive reasons, in at least one case, a Citation Classic^R (not involved in this study) was often cited for negative reasons.⁶¹

Citation Classic^R essays have been used as a data source in, among others, research on the delayed recognition of innovative ideas,⁶² an evaluation of German scientific production,⁶³ and an investigation of interdisciplinary research.⁶⁴

Procedure

Current Contents is published in six editions per week,⁶⁵ and one more each two weeks.⁶⁶ Excepting the Life Sciences edition, which publishes two Citation Classics^R per week, all the other editions publish one weekly commentary. Many of these are repeated in different

editions in the same week, or in different editions in other weeks. It is therefore sufficient to examine four editions to explore all the essays published. The editions examined were *Agriculture, Biology & Environmental Sciences*; *Life Sciences*; *Physical, Chemical & Earth Sciences*; and *Social & Behavioral Sciences*.

As pointed out above, a Citation Classic^R can be a paper or a book. Books were excluded, for my analysis focuses on papers which encountered difficulties during research and/or publication. Books usually summarize many investigations, and are often compiled by an editor; it is rare for authors to encounter serious difficulties once they have been contacted.⁶⁷

All the commentaries from 1989 and 1990 were examined: 316 different items were read (see Table 1). Sixty-seven of these referred to books and hence were excluded from further analysis. Citation Classic^R papers in which authors explicitly recognized having had some difficulty during research or publication were recorded, as were the number of citations which the paper had already received when the commentary was published.

Results and Discussion

Table 1 gives a statistical summary of results. Authors of eighteen Citation Classic^R commentaries on papers (5.7%) admitted having encountered some difficulty during the investigation, or during their attempts to publish. We could speculate that other authors of commentaries may have encountered some difficulties that they did not mention, for whatever reason; this might add some additional instances. However, I believe that this is not likely because, as noted above, authors of Citation Classic^R candidates are required to explain any difficulties they may have encountered.

Table 2 shows the bibliographic data of Citation Classic^R papers which encountered difficulties in getting produced or published. Three additional highly-cited papers which had such problems were identified when reading the commentaries. These papers are included in Table 2. Interestingly, a Citation Classic^R essay by Grunberg-Manago led to the identification of a highly-cited paper co-authored by the Nobel Prize winner Severo Ochoa which initially had problems in getting published. Table 2 also shows the number of citations received by each paper when its corresponding commentary was published, and the number, year and edition of *Current Contents* in which the

TABLE 1
Statistical Data from Examined Citation Classic^R Essays

Year	Examined essays			Papers that Had Problems		
	Books	Papers	Total	Citation Classics ^R	Other Papers ^a	Total
1989	39	157	196	8	1	9
1990	28	159	187	10	2	12
Total	67	316	383	18	3	21

a. Other highly-cited papers which encountered difficulties in getting published (not Citation Classics^R), identified when reading Citation Classics^R commentaries. See text for details.

TABLE 2
Bibliography of Highly-Cited Papers which have been Identified as having Problems in being Produced or Published

(Current Contents Editions: LS/Life Sciences; S&BS/Social and Behavioral Sciences; PC&ES/Physical, Chemical & Earth Sciences; AB&ES/Agriculture, Biology & Environmental Sciences)

Item	Cit. ^a	Current Classic ^R Comment Issue, Year and Edition	Bibliographic data
(a) Authors encountered some resistance during research phase.			
1:	370	(14/90/LS)	V.J. Balcar and G.A.R. Johnston, 'The Natural Specificity of the High Affinity Uptake of L-glutamate and L-aspartate by Rat Brain Slices', <i>Journal of Neurochemistry</i> , Vol. 19 (1972), 2657-66.
2:	105	(39/89/PC&ES)	I. Gupta and J.C.M. Li, 'Stress Relaxation, Internal Stress, and Work Hardening in Some Bcc Metals and Alloys', <i>Metal Transactions</i> , Vol. 1 (1970), 2323-30.
(b) Authors encountered some resistance to publication by the journal which finally published the paper.			
3:	285	(8/89/PC&ES)	M.S. Paterson, 'X-ray Diffraction by Face-Centered Cubic Crystals with Deformation Faults', <i>Journal of Applied Physics</i> , Vol. 23 (1952), 805-11.
4:	345 ^b	(5/90/PC&ES)	L.B. Robinson and E.J. Wampler, 'The Lick Observatory Image-Dissector Scanner', <i>Publications of the Astronomical Society of the Pacific</i> , Vol. 84 (1972), 161-66.

continued

Table 2 continued

Item	Cit. ^a	Current Classic ^b Comment Issue, Year and Edition	Bibliographic data
5:	130	(26/90/PC&ES)	H.J. Hsü, 'Principles of Mélanges and their Bearing on the Franciscan-Knoxville Paradox', <i>Geological Society of America: Bulletin</i> , Vol. 79 (1968), 1063-74.
6:	210 ^c		M. Grunberg-Manago and S. Ochoa, 'Enzymatic Synthesis and Breakdown of Polynucleotides: Polynucleotide Phosphorylase', <i>Journal of the American Chemical Society</i> , Vol. 77 (1955), 3165-66.
7:	530	(12/90/LS)	W.D.M. Paton and E.S. Vizi, 'The Inhibitory Action of Noradrenaline and Adrenaline on Acetylcholine Output by Guinea-Pig Ileum Longitudinal Muscle Strip', <i>British Journal of Pharmacology</i> , Vol. 35 (1969), 10-28.
8:	415	(42/90/LS)	K.M. Anderson and S. Liao, 'Selective Retention of Dihydrotestosterone by Prostatic Nuclei', <i>Nature</i> , Vol. 219 (20 July 1968), 277-79.
	225 ^d		S. Liao and S. Fang, 'Receptor Proteins for Androgens and Mode of Action of Androgens on Gene Transcription in Ventral Prostate', <i>Vitamins and Hormone-Advances Research Applications</i> , Vol. 27 (1979), 17-90.
9:	195	(27/89/AB&ES)	J.P. Sutherland, 'Multiple Stable Points in Natural Communities', <i>American Naturalist</i> , Vol. 108 (1974), 859-73.
(c) Authors encountered resistance so strong as to cause them to withdraw the paper, or else the paper was rejected outright.			
10:	260	(7/89/S&BS)	W.R. Gove, 'The Relationship between Sex Roles, Marital Status, and Mental Illness', <i>Social Forces</i> , Vol. 51 (1972), 34-44.
11:	210	(50/90/LS)	J.G. Vos, J.H. Koeman, H.L. van der Maas, M.C. ten Noever de Brauw and R.H. de Vos, 'Identification and Toxicological Evaluation of Chlorinated Dibenzofuran and Chlorinated Naphthalene in Two Commercial Polychlorinated Biphenyls', <i>Food and Cosmetics Toxicology</i> , Vol. 8 (1970), 625-33.

continued

Table 2 continued

Item	Cit. ^a	Current Classic ^R Comment Issue, Year and Edition	Bibliographic data
12:	170	(33/90/S&BS)	R.J. Gelles, 'Child Abuse as Psychopathology: A Sociological Critique and Reformulation', <i>American Journal of Orthopsychiatry</i> , Vol. 43 (1973), 611-21.
13:	400	(51-52/89/LS)	M. Cohn and T.R. Hughes, 'Nuclear Magnetic Resonance Spectra of Adenosine Di- and Triphosphate, II: Effect of Complexing with Divalent Metal Ions', <i>Journal of Biological Chemistry</i> , Vol. 237 (1962), 176-81.
	130 ^c		M. Cohn and T.R. Hughes, 'Phosphorus Magnetic Resonance Spectra of Adenosine Di- and Triphosphate, I: Effect of pH', <i>Journal of Biological Chemistry</i> , Vol. 235 (1960), 3250-53.
14:	180 ^b	(20/90/S&BS)	A.D. Baddeley, 'Short-term Memory for Word Sequences as a Function of Acoustic, Semantic and Formal Similarity', <i>Quarterly Journal of Experimental Psychology</i> , Vol. 18 (1966), 362-65.
15:	175 ^b	(20/90/PC&ES)	J.D. Rowley, 'Identification of a Translocation with Quinacrine Fluorescence in a Patient with Acute Leukemia', <i>Annales Génétiques de Paris</i> , Vol. 16 (1973), 109-12.
16:	400	(10/90/LS)	G. Pontecorvo, 'Production of Mammalian Somatic Cell Hybrids by Means of Polyethylene Glycol Treatment', <i>Somatic Cellular Genetics</i> , Vol. 1 (1975), 397-400.
17:	330	(35/89/LS)	I. Ofek, D. Mirelman and N. Sharon, 'Adherence of <i>Escherichia coli</i> to Human Mucosal Cells by Mannose Receptors', <i>Nature</i> , Vol. 265 (17 February 1977), 623-35.
18:	125	(34/89/AB&ES)	P.A. Werner, 'Predictions of Fate from Rosette Size in Teasel (<i>Dipsacus fullonum L.</i>)', <i>Oecologia</i> , Vol. 20 (1975), 197-201.

continued

Table 2 continued

Item	Cit. ^a	Current Classic ^R Comment Issue, Year and Edition	Bibliographic data
19:	130	(49/89/LS)	H.C. Ellinghausen and W.G. McCullough, 'Nutrition of <i>Leptospira pomona</i> and Growth of 13 other Serotypes: Fractionation of Oleic Albumin Complex and a Medium of Bovine Albumin and Polysorbate 80', <i>American Journal of Veterinary Research</i> , Vol. 26 (1965), 45-51.

a. Number of citations received when the Citation Classic^R commentary was published.

b. This is the most cited paper from its journal.

c. Mentioned in the Citation Classic^R commentary on the paper by M. Grunberg-Manago, P.J. Ortiz and S. Ochoa, 'Enzymatic Synthesis of Polynucleotides, I: Polynucleotide Phosphorylase of *Azotobacter vinelandii*', *Biochimica and Biophysica Acta*, Vol. 20 (1956), 269-85. (Citation Classic^R commentary appeared in 15/90/LS.)

d. Mentioned in the Citation Classic^R commentary on the paper by K.M. Anderson and S. Liao, listed above.

e. Mentioned in the Citation Classic^R commentary on the paper by M. Cohn and T.R. Hughes, listed above.

commentary appeared. The number of citations received ranges from 105 to 530 (mean = 253.3). Three of the articles listed in Table 2 were the most cited papers from the journals which published them!

Next, each of the papers shown in Table 2 is analyzed in more detail. In order to avoid boring citations, I note that data on these papers were obtained from the ISI prologue to each commentary, and from the commentary itself. As can be seen, at least some of these problematic papers reported innovative methods or theories, or presented new interpretations of previous data.

(a) *Pre-publication difficulties*. In two cases the highly-cited paper encountered some difficulty or difficulties before the publication process.

1. In 1972, Vladimir J. Balcar and his PhD supervisor, Graham A.R. Johnston, published a study on about two-hundred compounds, selected on the basis of their pharmacological characteristics and chemical structure. These compounds were tested against high affinity uptake of L-glutamate by brain slices. This work demonstrated that glutamate uptake and glutamate receptors were two distinct entities (not obvious in 1972). In his commentary Balcar recalls that 'some difficulties were encountered with

getting the manuscript past the head of the department', although it was quickly accepted by the *Journal of Neurochemistry*.

2. Another paper which had difficulty before publication was the Gupta and Li paper on stress relaxation, internal stress and work-hardening in metals and alloys. In 1940, E. Orowan had proposed an equation relating the strain rate to dislocation velocity, but in 1970 this equation still had not been verified experimentally. As part of Gupta's thesis, the authors attempted to verify it. In their paper, the stress-time relation during stress relaxation is interpreted in terms of a power relation between dislocation velocity and effective stress. The work was supported by US Steel and, before publication, all papers had to be approved by their scientific advisors. The US Steel management advised Gupta and Li to shorten the manuscript, and make changes in the section on materials and specimen preparation. Since they did not follow all these suggestions, the manuscript was not approved. US Steel then suggested that the authors submit the manuscript without mentioning the company, and without its approval. The paper was finally submitted with the approval of Columbia University, and it was published without revisions.

(b) *Difficulties during the revision phase.* The journal referees raised questions and posed problems, but the paper was finally published.

3. In 1951, while he was spending a year at the Institute for the Study of Metals of the University of Chicago, Mervyn S. Paterson proposed to sort out the theory of stacking faults in deformed metals. In his 1952 paper, the X-ray diffraction effects were calculated for face-centred cubic crystals with stacking faults. The positions, widths and intensities of the X-ray diffraction lines were predicted as a function of fault density. The referee from the *Journal of Applied Physics* told Paterson many years later that he had thought of recommending rejection, believing that the predicted effects of the theory would not be observable. Curiously, he and one of his students were the first to publish experimental observations that fitted the theory.

4. A reviewer of the *Publications of the Astronomical Society of the Pacific* almost rejected the most cited paper from this journal. It was co-authored by L.B. Robinson and E.J. Wampler (Lick Observatory, University of California), who were trying to increase the effectiveness of a telescope. Two expensive ways of doing this are to increase the size of the telescope, and to improve the associated optics. Instead, Robinson and Wampler developed a less expensive computer-controlled device that can simultaneously examine several hundred wavelength intervals, improving the performance of the detector that records the photons collected by the telescope. They experimented with image-intensifier tubes, but the reviewer thought that image tubes could not provide quantitative data, and initially rejected the paper. Some colleagues also suggested that Robinson and Wampler should 'stop developing new gadgets and do some real astronomy'. Eventually, their device became the most-used instrument at Lick, until the new sensors became competitive. The authors believe that the high number of citations represents those astronomers who have used these scanners at various observatories.

5. Although it is hard to believe, in 1984, Kenneth J. Hsü received the highest award of the American Geological Society, the Wollanston Medal, for a 1979 paper initially rejected by a reviewer of *The Geological Society of America Bulletin*. It was accepted only after the author agreed to publish it in a section for trivial communications.

In his paper Hsü formulates new principles and proposes a non-Smithian stratigraphy to guide students of the *mélanges* that are found in mountain ranges all over the world. His new ideas were not easily accepted by the establishment. Hsü points out, 'for more than a decade, I was pictured as a Don Quixote waving my lance against a windmill that was the US Geological Survey'. But young geologists adopted Hsü's principles and, ironically, the non-acceptance of his ideas increased the number of citations to the paper, because the word *mélange* appeared in few textbooks.

6. The Spanish Nobel Prize winner Severo Ochoa had difficulties in publishing a paper with M. Grunberg-Manago on polynucleotide phosphorylase (PNPase). This is revealed by Grunberg-Manago in his commentary on a 1956 paper published in *Biochimica and Biophysica Acta*. The problematic paper was the first report of the existence of the PNPase, and was published in the *Journal of the American Chemical Society* while Grunberg-Manago was working with Ochoa in the Department for Biochemistry of the New York University of Medicine. As can be seen from Table 2, this paper has also been highly cited. However, the reviewer was strongly critical and Ochoa had to argue for the paper to be published. PNPase was the key to the development of modern molecular biology, and it is still used in medical studies on interferon, cancer, AIDS and to synthesize long polymers in protein synthesis. The Nobel Prize in 1959 awarded to Ochoa, and the Charles-Leopold Mayer prize awarded to Grunberg-Manago, finally recognized its importance. An account of this episode can be found in a paper by Ochoa.⁶⁸

7. W. Feldberg, chief editor of the *British Journal of Pharmacology*, allowed publication of the first paper reporting neurochemical evidence for a fundamental type of 'cross talk' between neurones. A referee was sceptical of the findings of W.D.M. Paton and his Hungarian postdoctoral assistant, E. Sylvester Vizi, which provided neurochemical evidence for the existence of presynaptic alpha-receptors and for functional interaction between neurons. But this paper laid the ground for later studies of physiological control by disinhibition and by negative feedback, and several drugs have been developed according its findings.

8. Shutsung Liao and his graduate student, Kenning M. Anderson, at the University of Chicago, also encountered difficulty in convincing the reviewers of *Nature*. Their work addressed the retention of dihydrotestosterone (DHT) in rat prostate cell nuclei. DHT comes from testosterone that is converted by a reductase. Selective binding of DHT to an androgen receptor explains its retention. As Liao and Anderson say in their commentary, the finding was unusual and very important, but reviewers did not agree on its significance. Nor did they approve the use of the term 'steroid receptor'. In fact, a section of another paper of S. Liao and S. Fang on DHT and androgen receptor was removed (one could say 'censored') at the editor's suggestion. This paper is also listed in Table 2. The importance of the relation testosterone–DHT–receptor is now well-known. New drugs based on these findings are being developed for treatment of acne, prostate diseases, female hirsutism and male pattern baldness.

9. In contrast to the above, John P. Sutherland's difficulties were not particularly important. Sutherland investigated the way in which some events, which determine the presence or absence of important consumers, influence structure in natural communities. He submitted a paper to *American Naturalist*, and it was provisionally accepted. However, the editor suggested that Sutherland replace the data tables with a diagram. In his commentary, Sutherland says that he resisted because he couldn't think of a way to plot percentage data that had been transformed into arcsines. The

solution was to transform the y axis, and the manuscript was finally accepted.

(c) *Authors encountered strong resistance* – so strong as to cause them to withdraw the paper, or else the paper was rejected outright.

10. As Walter R. Gove recognizes, his 1972 paper on differences in rates of mental illness between men and women ran counter to accepted notions in the social-science community. At that time, it was assumed that there were no such differences. Gove personally interviewed 458 mental patients. He concluded that women did have higher rates of mental illness than men, and married women than married men. He also found that among the non-married, divorced and widowed, rates of mental illness were as high or higher in men than in women: women's higher rates can thus be due to the married women's role. However, it was generally believed that higher rates of reported symptoms among women only reflected their willingness to report them. As Gove remarks in his commentary, these preconceptions may have accounted for his difficulties. He feels that the negative critiques of some reviewers did not reflect the paper's quality. Its hypothesis is now largely accepted.

11. A paper published by Jan Koeman's research team at the University of Utrecht reported the high toxicity of polychlorinated dibenzofurans (PCDFs) in two commercial polychlorinated biphenyls (PCB) mixtures. This paper was submitted to *Nature* as an article, but journal staff informed the authors that they should write a short letter to the editor, examining just one aspect, because they could not offer space for the full report. The authors preferred to send their paper to *Food and Cosmetics Toxicology*. Curiously, *Nature* later published a paper by other authors that confirmed the findings of Koeman's team.⁶⁹ The latter has been cited 105 times.

12. When he was a fourth-year graduate student in sociology at the University of New Hampshire, Richard J. Gelles took a course on family violence with the sociologist Murray A. Strauss. Strauss assigned Gelles to review some articles on child abuse which used a psychopathological explanation. Gelles was not convinced, and Strauss encouraged him to write a critical article. Using the same data on child abuse, Gelles suggested a multi-dimensional social-psychological explanation. It was not easy to communicate his new interpretation. First, Gelles submitted his paper to an American Sociological Association meeting. It was accepted, but scheduled for a final catch-all session on the last day, and only Gelles's wife was present. The paper was then rejected by the first journal to which Gelles submitted it. The *American Journal of Orthopsychiatry* eventually accepted the paper, and it has been much cited. As Gelles points out, these difficulties are not surprising, given the extent of his re-interpretation of data on a sensitive topic.

13. In this case, a paper's rejection led the authors to publish two reports. Mildred Cohn and the physics graduate student Tom Hughes obtained high-resolution ¹H and ³¹P-NMR spectra of some diamagnetic ions complexes of both ADP and ATP, showing a change in chemical shift for the β -P of ATP. They also investigated the effect of pH in NMR spectra of ATP. They submitted a paper to the prestigious *Journal of the American Chemical Society*, but the manuscript was rejected. They then published two papers in the *Journal of Biological Chemistry* (see Table 2). The chemical shift change in β -P of ATP has been widely used to determine the free Mg²⁺ concentration *in vivo* in cells and in animal organs.

14. The most-cited paper from the *Quarterly Journal of Experimental Psychology* was first rejected by the *Journal of Experimental Psychology*. It was written by A.D. Baddeley while he was working at a Medical Research Council centre, on a grant from the British Telephone authorities. He was trying to contrast the effect of acoustic similarity with that of similarity of meaning in the short-term recall of words. He found that memory performance was lower when words were similar in sound, but that meaning similarity had no effect; he suggested that short-term memory, in contrast to long-term memory, relies on acoustic coding. His findings were rejected by the *Journal of Experimental Psychology*. The referee suggested that the 'author should do more parametric studies'. Baddeley's later work continued to focus on short-term memory. He proposed the very important concept of working memory, and it is now widely used.⁷⁰

15. Again, the most-cited paper of one journal was first rejected by another journal. In this case, Janet D. Rowley's paper on chromosome translocation was submitted as a short letter to the prestigious *New England Journal of Medicine*, which rejected it. As she just received a form letter, Rowley decided to phone and ask why the paper had been rejected. She was told that it was unimportant. Luckily, Jean de Grouchy, editor of *Annales de Génétique*, did not think so, and agreed to publish the paper. It was one of the very first reports of the discovery of a translocation in malignant cells.

16. Resistance to new ideas is also illustrated by the response of a referee to a paper describing some experiments carried out by Guido Pontecorvo at the Imperial Cancer Research Fund Laboratories. In short, Pontecorvo's idea was to use polyethylene glycol (PEG) for fusion of mammalian somatic cells in culture. It was well-known that PEG promoted fusion between plant protoplast, and Pontecorvo thought that this botanical technique could also work with animal cells. He was right, and PEG is now used generally for (*inter alia*) monoclonal antibody development. However, his short note was rejected by the *Proceedings of the Royal Society*, because the referee did not accept the significance of Pontecorvo's new idea: 'the paper submitted does not permit one to decide whether PEG will prove to be no better than others that have been tried and rejected'.

17. In this case, *Nature* rescued a paper that was first rejected by *Science*. It was co-authored by I. Ofek, D. Mirelman and Nathan Sharon, and it demonstrates that *Escherichia coli* binds to epithelial cells by a mannose-specific lectin present on the bacterial surface. It also points out the importance of lectin-carbohydrate interactions in the initiation of infection. However, the *Science* referee thought that there was nothing new in it, and recommended rejection. It was then submitted to *Nature*, quickly published, and its findings confirmed in other laboratories. The authors believe that the paper has been highly cited because it stimulated much research on bacterial adherence. Unfortunately, no human application has yet been found.

18. Pursuing her doctoral research at the Kellogg Biological Station of Michigan State University, Patricia A. Werner published her 1975 paper on field populations of a biennial plant species. Its main conclusion was that the probability that an individual either died, remained vegetative or flowered in any growing season is highly correlated with the size of its vegetative rosette in the preceding year. These ideas, new in 1975, are well known and fully accepted today. The referee for the first journal to which Werner sent her paper thought that her findings were trivial, and advised rejection. *Oecologia* finally accepted the paper, although their referee asked Werner to cite a prestigious plant ecologist who was actually using her own unpublished work!

19. Practically all leptospiral bacteria producers use bovine albumin polysorbate 80

as a growth medium. It was first proposed by Herman C. Ellinghausen and W.C. McCullough, in a paper published in 1965 in the *American Journal of Veterinary Research*. It was earlier rejected by a major bacteriological journal, on the grounds that it was insignificant and lacking originality. The referee argued that bovine albumin had been used in studies fifteen years before. This growth medium, in the US in 1964, made the first isolation of *Leptospira grippotyphosa* possible, and led to great progress in the isolation of *Leptospira Hardjo*, which it is almost impossible to cultivate in other media.

Conclusions

The use of the Citation Classic^R database in historical and sociological studies of science can be useful and fruitful. Re-examination of the whole database in search of important papers that had difficulties in getting published could open a new research front, offering a fresh approach to the study of scientists' resistance to new discoveries.

It is difficult to define 'resistance' and 'difficulty'. Authors can encounter resistance before or after the publication of a paper. Sometimes a paper can be ignored by the scientific community for years. Eugene Garfield has studied delayed recognition in scientific discovery,⁷¹ where papers are initially unappreciated or unused, but are later recognized as significant. I am addressing a very different problem: I am interested in accounts by authors of difficulties and problems experienced in getting their papers published. What can we learn from the above stories?

First, there are very few Citation Classic^R papers which had problems in being published, but, precisely because of the great impact and importance of the papers involved, their rejection or delayed publication can have pernicious effects in a given discipline. However, due to the peculiar selection method of Citation Classic^R papers, we cannot generalize the results obtained in this study to all scientific literature.

Second, it is clear that new ideas and theories, or reinterpretations of previous data, can encounter some difficulty in being published. Authors are sometimes aware of this. For example, the Japanese biochemist Setsuro Ebashi admits that he submits most of his papers to the *Journal of Biochemistry (Tokyo)*. In a Citation Classic^R commentary on such a paper, cited 525 times, he wrote that 'this paper might not have been accepted by a journal in the US or Europe, and, even if accepted, many portions . . . would probably have been altered or deleted by authoritative reviewers'.⁷²

Third, referees must be aware of these findings in order to avoid the 'reviewer's nightmare' of rejected papers that are later highly cited. As Horrobin points out, referees must balance quality control with the encouragement of innovative work.⁷³

However, it is necessary to remember that, as the sociological literature on retrospective and ceremonial accounts of scientific practice shows, scientists' later accounts of their work should be interpreted, not as an accurate reflection of what happened, but as a carefully reconstructed representation.⁷⁴ Sometimes, such accounts follow context-dependent, implicit rhetorical rules. Maybe other participants would have described things differently.

●NOTES

I would like to thank Dr David F. Horrobin, editor of *Medical Hypotheses*, for his advice and encouragement, Miguel Angel Andrade for his commentaries and Carol F. Warren, from the Instituto de Ciencias de la Educación at the Universidad de Alcalá, for her help. The Institute for Scientific Information (ISI) does not vouch for the accuracy of this paper, or the use of the data, or for the interpretations of the data. I would like to thank two anonymous referees and Eugene Garfield and Paul R. Ryan (both from the ISI) for their advice and help and for giving permission to use ISI's data. My thanks to Angela Grito Manzanares, from the University of Colorado at Boulder, for her advice and friendship during the cold winter of 1991.

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