

The Philosophical Basis of Peer Review and the Suppression of Innovation

David F. Horrobin, DPhil, BM

Peer review can be performed successfully only if those involved have a clear idea as to its fundamental purpose. Most authors of articles on the subject assume that the purpose of peer review is quality control. This is an inadequate answer. The fundamental purpose of peer review in the biomedical sciences must be consistent with that of medicine itself, to cure sometimes, to relieve often, to comfort always. Peer review must therefore aim to facilitate the introduction into medicine of improved ways of curing, relieving, and comforting patients. The fulfillment of this aim requires both quality control and the encouragement of innovation. If an appropriate balance between the two is lost, then peer review will fail to fulfill its purpose.

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THE QUESTION I will address is the fundamental one: what is peer review for? When reading the literature on peer review, I have been disappointed by the small amounts of space devoted to this issue. If we do not know why we are engaging in peer review, we are unlikely to be very good at it.

Explicit in many articles on peer review, and implicit in most, is the concept that the purpose of peer review is quality control. This is an unsatisfactory answer to the question I have posed. Quality control is one means of achieving an end, but it is not the end itself. The ultimate aim of peer review in biomedical science cannot be different from the ultimate aim of medicine. That has never been expressed more effectively than in the phrase "to cure sometimes, to relieve often, to comfort always." (*Guerir quelquefois, soulager souvent, consoler toujours*. This is inscribed on the statue of Edward Livingston Tru-

deau at Saranac Lake, NY, and is believed to be a French folk saying of medieval origin.) The purpose of peer review should be nothing less than to facilitate the introduction into medicine of improvements in curing, relieving, and comforting. Even in those many fields of biomedical research that are remote from clinical practice, the peer reviewer should always be asking the question, "Is this a possible innovation that should be encouraged because at some time it could lead to improvements in the treatment of patients?"

INNOVATION AND QUALITY CONTROL

Ten years ago, I left the university world to found a small pharmaceutical company. The purpose of the company is closely related to that of medicine itself, to develop new ways of curing, relieving, and comforting. The company will prosper only if it succeeds in improving patient care. While building the organization, I have become very conscious of the necessary creative tension between innovation and quality control. The innovators, who generate the future, are often impatient with the precision and the systematic approach of the

quality controllers. The quality controllers are often exasperated by the apparent indiscipline and unpredictability of the innovators. But a successful pharmaceutical company requires both types of people and also requires that their skills be evenly balanced. Dominance by either group will lead to failure.

Science in general, and the medical research enterprise in particular, is no different. As Polanyi¹ pointed out in 1958, there is a powerful tension in the history of science between, on the one hand, originality, creativity, and profundity and, on the other, accuracy and reliability. Success requires the balanced contribution of both.

PEER REVIEW, PUBLIC FUNDING, AND THE OUTCOMES OF MEDICAL RESEARCH

The public requires of the medical research community *success*. The public ultimately provides money for medical research for one purpose only—to generate improvements in patient care. Medical researchers, editors, and peer reviewers should be under no illusions: the public does not support research for the pleasure of watching a cultural event. If improved medical care is not delivered, support for medical research—and hence for medical journals—will dwindle and atrophy.

This is not to say that the public is unsophisticated in its understanding of the relationship between basic science and a practical outcome. Most people have some grasp of what is to scientists a truism, namely, that practical solutions may sometimes come unexpectedly from pure science. So long as an important disease problem remains unsolved, there is likely to be support for a broadly based and relatively unfo-

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Reprint requests to Efamol Research Institute, PO Box 818, Chipman Dr, Kentville, Nova Scotia, Canada B4N 4H8 (Dr Horrobin).

cused research effort. But researchers should not be under the illusion that this situation would continue if tomorrow there emerged dramatically effective solutions to major scourges such as cancer or acquired immunodeficiency syndrome. Much of the support would disappear rapidly. Those who doubt this should look at the history of problems that have been largely solved, such as poliomyelitis.

Prior to the successful introduction of immunization, both basic and applied research on anything that might conceivably be related to poliomyelitis flourished. Immunization provided answers to none of the problems that were being investigated, many of which remain unsolved (for example, see reference 2). Yet in the years after the introduction of immunization, funds available for basic or applied research related to poliomyelitis dried up. If cancer and acquired immunodeficiency syndrome could be cured by simple injections, much of our present medical research enterprise would disappear. Something similar may happen more insidiously if the public loses hope in the ability of the research effort to deliver.

And if we are to deliver results, quality control can be only one side of the editorial equation. The other must be the nourishment and encouragement of high innovation. There I think we have a problem. In all that is said and written about peer review, quality control appears overwhelmingly important and the encouragement of innovation receives little attention. That is a recipe for failure.

I am at present involved in a research project that tries to identify, from the patient's point of view, the differences in outcome between the best medical care available in 1930, 1960, and 1990. The sorts of questions I am trying to pose include the following: For the major causes of death, what are the changes in age-adjusted mortality? For the major causes of morbidity, what are the changes in the course of the illness? What aspects of these changes can truly be attributed to medical innovations? Have the introductions of new diagnostic techniques, such as endoscopy, plasma analyses, and computed tomographic scanning, had demonstrable effects on the outcome of patient care? Have the changes in the cost of medical care produced commensurate improvements in patient welfare? When and how did those innovations that have been influential originate?

An initial overview of the literature leaves no doubt that during the last six decades the overall accuracy and reliability of medical articles have im-

proved substantially. But there may have been a trade-off in the relative failure of innovation.³ Between 1930 and 1960, the improvements in the best patient care were truly dramatic. Many infectious diseases were controlled by drugs or by immunization and the prototypes of many of the drugs that we use today were discovered. Since 1960, despite major developments, especially in the field of diagnostic techniques, the initial impression is that, from the patient's point of view, the improvements in medical care have been substantially smaller. It may be that the problems have become inherently more difficult, or that may be a self-serving answer that will be seen to be so when the problems are actually solved. We may just have been unlucky in that in the past 30 years the vast increases in research expenditure have not brought commensurate increases in patient care. But I think we must take seriously the possibility that we have traded innovation for quality control, not only in medical publishing but throughout medical science.

Here is a specific example. My particular historical interest is in the development of psychiatric therapy. There are five major types of drug in use in psychiatry: the neuroleptics, the benzodiazepines, the tricyclic antidepressants and related compounds, the monoamine oxidase inhibitors, and lithium.³ All five classes were discovered prior to 1960. Some new molecular variants have been introduced, but all the original compounds are still extensively used and no major new therapeutic principles have been developed and shown to be effective clinically. This is in spite of the incomparably greater expenditure on research into neurobiology and psychiatry since 1960.

Lithium is in some respects the most successful of these five classes of compounds. It is the only one that when properly used appears to bring about a true normalization of behavior. Yet modern peer review practices would certainly have blocked its introduction. Cade worked under primitive conditions in a psychiatric hospital in Australia in the period immediately following the Second World War.⁴ His animal experiments were crude and would not now be regarded as remotely adequate to justify a trial in humans. Yet more comprehensive and detailed animal studies would have been impossible because of a lack of resources. The article describing his completely uncontrolled clinical observations⁵ would almost certainly now have been rejected. If that had happened, it is very doubtful whether Cade would have been in a position to do the additional work that

would justify publication and lithium would have been lost to medicine. Cade's originality would probably not have overcome the current emphasis on accuracy and reliability.

The history of many innovations, both in medicine and in other areas of endeavor, indicates that the innovators are often erratic, unsystematic, and difficult to deal with. The quality controllers often regard the work as of poor quality and not worth publishing or noting. The only problem is that the quality controllers, while exquisite in their crossing of *t*'s and dotting of *i*'s, rarely discover anything that matters. The improvement in research quality over the past years is not all gain if it has occurred at the expense of innovation.

THE REVIEW OF INNOVATIVE WORK

I believe that the great majority of editorial decisions are fair. The quality controllers are right to congratulate themselves that the frequency of error is low. But unfortunately, from the point of view of innovation, that is irrelevant. The numbers of truly important, innovative articles presented to an editor are small. Yet it is this tiny minority of articles that is responsible for pushing medicine forward. Peer review must therefore be judged by how it handles those rare articles that genuinely offer the possibility of new approaches that might eventually lead to improvements in curing, caring, and comforting. Here I think we begin to run into problems.

I believe that all editors, even those operating in the basic sciences, should have antennae sensitive to the question, "If this article is right, is it conceivable that it could change patient care 5, 10, or 20 years from now?" Very few articles will come into this category, and those that do not can be safely consigned to the ordinary review process without too much loss of sleep. But if the said antennae do twitch when the editor reads the abstract, then the editor has a huge responsibility and must exercise great care, if only to avoid being lampooned 30 years later when the author wins a Nobel Prize for a rejected piece of work! It is my view that innovation is so rare, so valuable, and so central to the improvement of patient welfare that innovative articles should be deliberately encouraged and more readily published than conventional ones.

In the original version of this article, I wrote, "I do not think that anyone will need convincing that the reverse is now the case." Both of the anonymous reviewers disagreed and challenged me to provide examples. There are, of course, many cases in which the innovator has

been accepted and even acclaimed and where the work has rapidly entered the mainstream of science. Examples of the opposite, of the total suppression of an innovation that would have had a major impact, are by definition nonexistent. How can one know about them if they have been suppressed? One can therefore illustrate the case only in terms of either personal experience or near-failures, situations in which peer review tried to suppress an innovative concept but failed. That this is not rare is illustrated by the many examples that follow. They draw not only on the use of peer review by journals, but also on peer review in the choice of conference programs and in the award of grants. In my view, when discussing the philosophical basis of peer review it is artificial to separate the different contexts in which it occurs.

1. The article by Glick et al⁶ on the identification of B lymphocytes as separate entities is one of the seminal papers in immunology. It was rejected by leading general and specialist journals and eventually appeared in *Poultry Science* because of the species on which the work was done. *Poultry Science* is a respectable and respected journal, but perhaps not the place where one would expect to find such a fundamental article.

2. Krebs⁷ article on the citric acid cycle, possibly the most important single article in modern biochemistry, was initially rejected by the peer review process.

3. The work of S. A. Berson, MD, and Yalow⁸ on radioimmunoassay, which, like Krebs' studies, eventually led to a Nobel Prize, was initially rejected for publication.

4. In the 1950s and 1960s, in the United Kingdom, grant proposals for research directed at renal transplantation and based on United Kingdom-originated work on immunological tolerance were repeatedly turned down by the Medical Research Council. Key peer reviewers who were opposed to the clinical concept were those heavily involved in the relevant basic science (oral communication, June 23, 1988, from a scientist who was a member of the Medical Research Council at the time and whose name has been deposited with the editorial office of *JAMA*).

5. Requests for funding for research on in vitro fertilization were repeatedly turned down by the peer review process. Steptoe⁹ and R. Edwards, PhD, funded the research personally and as everyone knows it ended in practical success.

6. Hillman is a distinguished microscopist who for many years has been try-

ing to report in the specialist journals observations that challenge many current interpretations of electron micrographs. He has totally failed to get these published in appropriate journals and they have ended up in *The School Science Review*¹⁰ and *Medical Hypotheses*,¹¹ a journal that I edit. I am pleased to have Hillman's articles in the journal, but they would be much more appropriate in a specialist experimental publication.

7. R. Drummond, MB, ChB, on the basis of careful experimentation, has developed the concept that neutrophil leukocytes may be derived from the discarded nuclei of red blood cells (oral communications, 1984 through 1987). This is an unlikely proposition, but it is based on solid observation and deserves an airing. He has totally failed to get the work published.

8. Ling, over many years, has developed the brilliant concept that the movements into and out of cells of ions and small molecules are based not on membranes and pumps but on a state of intracellular ordered water. Some of the work has been published,¹² but Ling's articles have been repeatedly rejected by mainstream journals because they are so out of tune with the dominant membrane concept.

9. Facial eczema is an epidemic disease of sheep that used to cost the New Zealand economy tens of millions of dollars annually. It appears to be due to infection with a fungus that proliferates wildly under certain conditions. A farmer, Gladys Reid, suggested that the cause might be marginal zinc deficiency, which allowed the fungus to multiply. She could not get her observations published in any reputable journal and was subjected to an extraordinary campaign of vilification in the New Zealand press by scientists researching the fungal origin of the disease. Eventually, in small part because I published her article in *Medical Hypotheses*¹³ and therefore gave her the respectability of a publication in an *Index Medicus*-listed journal, her observations were taken note of and confirmed and led to the effective elimination of the disease. She was then awarded a decoration for services to agriculture in New Zealand.

10. In the mid-1970s, a researcher obtained experimental results and made theoretical proposals that challenged some of the work of an eminent scientist. This senior scientist mounted an extraordinary campaign of vilification designed to block publication of the researcher's work, to prevent him speaking at scientific meetings, and to stop the award of grants. The campaign degenerated to a level that included the

sending by the senior scientist of anonymous letters to journal publishers. For legal reasons details of this case cannot be published, but materials that I feel support my assertions have been deposited with the editorial office of *JAMA*. The senior scientist's behavior can only be described as psychopathological. His willingness to be ruthlessly unfair in the pursuit of his own ends is known to many members of the scientific community, yet no one has had the courage to try to put a stop to it, such is the power and influence he wields. He is still used as a consultant, as a member of meeting program committees, and as a peer reviewer for articles and grant applications. Behavior as extreme as this is perhaps unusual, but lesser degrees of the same syndrome are not uncommon. How can the peer review system operate fairly and in the best interests of both science and the public when science itself does nothing to curb such excesses?

11. Peer review in the grant-giving process is so restrictive that most innovative scientists know they would never receive funding if they actually said what they were going to do. Scientists therefore have to tell lies in their grant applications. Such views have been explicitly stated by at least two Nobel laureates.¹⁴⁻¹⁶

12. Rous¹⁷ received the Nobel Prize more than 60 years after his original observation on viral transmission of tumors. Although the original article was published, he then totally failed to receive support for the work and had to stop researching in that field.

13. In 1879 the Marquis of Sautuola, an extremely distinguished amateur archaeologist, discovered the spectacular cave paintings of Altamira. He privately circulated news of his find and was promptly labeled a fraud and a forger.¹⁸ He was not only not allowed to present his findings at international congresses of archaeology, but he was actually banned from attending them and died in 1888, a disappointed man. Only in 1903 did any colleague decide to check the story and demonstrate that the paintings were indeed by early humans and not by a modern forger.

14. A whole series of examples of intellectual suppression, some of them involving peer review, have been documented in the Australian scientific community.¹⁹

15. Ivanhoe is a medically qualified archaeologist working in an important department. He has collected a large amount of detailed evidence showing a correlation between tooth size of Neanderthal humans and variations in the strength of the geomagnetic field. The

meaning of the correlation is uncertain, but there can be no doubt that it exists. Three journals in the field have refused to publish the article without giving any adequate reasons. The article will now appear in *Medical Hypotheses*.²⁰

16. Setala is a Finnish pathologist who in the 1940s and 1950s had a distinguished publication record in American journals. He then made observations that upset certain prominent Americans and found himself unable to publish as a result of statements in the peer review process such as "I do not believe Dr Setala's observations." His abstracts were not accepted for presentation at conferences, even for meetings where almost all abstracts were taken. Again, some of his work has now been published in *Medical Hypotheses*.²¹ I do not know whether Setala is right or wrong; I do know that he deserves a hearing.

17. I have documented several cases of poor-quality peer reviewing that occurred in the United Kingdom in the 1970s.²² For example, they include referee statements such as "I cannot explain the findings but I do not feel that they represent anything but experimental artifact." As with Setala, no objective criticisms were provided.

18. The story of vitamin C and cancer has received a great deal of publicity and many might believe that they know the full story. Richards²³ has recently documented in great detail the failure of either of the two Mayo Clinic studies to test the use of vitamin C in the way proposed by Pauling and Cameron. She has also discussed the repeated refusal of *The New England Journal of Medicine* to publish either articles or letters by L. Pauling, PhD, and E. Cameron, MB, ChB, demonstrating just why the second Mayo trial was not a test of their

hypotheses. Furthermore, she has shown that highly toxic treatments for cancer, including fluorouracil for colon cancer, continue to be used in the United States in spite of a failure to demonstrate their efficacy in placebo-controlled trials.²⁴ One may wonder why the full weight of disapproval has landed on vitamin C, which everyone acknowledges is of low toxicity, when toxic drugs that are certainly of no greater efficacy are widely used.

This is by no means a complete list of all the examples of which I am aware of situations in which peer review has delayed, emasculated, or totally prevented the publication and investigation of potentially important findings. The list is extensive enough to demonstrate that while antagonism to innovation during the peer review process may not be the norm, it is far from being exceptional. The examples I have given, together with the numerous cases of scientific fraud that have been documented in a book²⁴ and described ad nauseam in the pages of *Nature* and *Science*, demonstrate that what some might call psychopathology is not rare in the scientific community. Most decent scientists are reluctant to admit this and therefore reluctant to take it into consideration when assessing peer review. There can be little doubt that this wish to believe that all is for the best in the best possible world has led to serious injustice. If the shepherds do not believe that wolves exist, then some of the sheep are going to have a bad time.

CONCLUSIONS

I cannot put my conclusions too strongly. To further the cause of improving patient care, it is the duty of editors to encourage innovation as well as to ensure quality control. This re-

quires a conscious effort of will to look askance at hypercritical reviews of innovative articles. It also requires an awareness that even some of the most distinguished of scientists may display sophisticated behavior that can only be described as pathological. Editors must be conscious that, despite public protestations to the contrary, many scientist-reviewers are against innovation unless it is *their* innovation. Innovation from others may be a threat because it diminishes the importance of the scientist's own work.

So what is an editor to do when it does appear that an article may possibly be highly innovative? First, think a lot harder than usual about to whom the article should be sent for review. The idea that all scientists are peers simply will not do. Second, try to ensure that the reviewer is of the highest possible quality in terms of either the absence of vested interest or, equally valid, the open recognition that such an interest is present. Third, find a reviewer with generosity of spirit who will not recommend rejection because of those faults that can be found in any article but that do not challenge the fundamentals of what is being said. Fourth, never forget the possibility that even the most eminent and urbane of reviewers may occasionally be corrupt or malign or that lesser folk may be acting under duress. Fifth, be an editor, read the article carefully, and make an informed judgment on the basis both of what it says and of what the reviewers say. And finally, remember that while an editor has a duty both to ensure quality and to encourage innovation, both of these things are means not ends.

The true aim of peer review in biomedical science must be to improve the quality of patient care.

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