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Peer usage versus peer review

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Peer usage versus peer review

PERSONAL VIEW **Bruce G Charlton**

It is often asserted that peer review is the essence of scientific evaluation, but this is incorrect. Peer review is not specific to science but is employed by all academic subjects from English literature to theology. Neither is it necessary to science. Until a few decades ago—and during the scientific golden age of the mid-20th century—there was very little peer review in the modern sense. So peer review is neither necessary nor sufficient for scientific progress.

The truly definitive scientific evaluation is in fact "peer usage," which entails testing facts and theories not by opinion but in actual practice. This means that, even when published in the best journals, new science should never be regarded as valid until its predictions have been retrospectively validated by use in further relevant research by competent scientific peers.

True scientific validity can be established only after publication, by the slow and rigorous methods of peer usage

Peer usage is essential to science because it evaluates how research stands up when used for intervening in the natural world. This is often termed "replication"; however, it is not usually repetition but instead a process by which ideas and facts are incorporated into future successful research. As long as later research that is built on earlier research continues to grow and thrive, then that earlier science is provisionally regarded as valid.

But peer usage is a retrospective process, and testing science by usage is slow and expensive. It involves persuading other scientists that it is worth their while to expend energy and resources. Evaluation by peer usage has a timescale of years. Published research must be noticed, read, understood, incorporated; new work must be planned and executed, then published, noticed, read, etc. Peer usage is also incomplete, because more scientific theories and findings are published than can ever be checked in practice. Only a small percentage of published science ever actually gets evaluated by peer usage.

As a result, there has been a major shift away from retrospective peer usage towards the predictive process of peer review. Peer review is faster (taking weeks rather than years) and cheaper (because it asks only for opinions). In effect peer review is prospective filtering by a consensus of informed judgment.

Although peer review is not specifically scientific, in principle it can identify ideas and facts that are probably correct, so long as research is an incremental extrapolation of established knowledge, methods are standard and well established, and investigations are performed by researchers of validated competence. In other words, peer review usually works well for applied science or "research and development."

However, peer opinion becomes markedly less valid when research is more ambitious and radical. Many or most major scientific advances were initially rejected by peer review. This implies that there is a continuing need for other methods of evaluating radical and ambitious science.

Traditionally, editorial review is the main alternative to peer review. A scientist editor or editorial team applies a sieve, with varying degrees of selectivity, to research submissions. Strictly, this process should not attempt to predict whether ideas and facts are "true," because truth can be established only in retrospect. Instead, editorial selection works within constraints of subject matter on the basis of factors such as potential importance and interest, clarity and appropriateness of expression, and broad criteria of scientific plausibility. Even probably untrue papers may be judged worth publishing if they contain aspects (ideas, perspectives, data) that are potentially stimulating to the development of future science.

In my personal experience, editorial review remains a viable model for publishing in modern biomedical science. *Medical Hypotheses* explicitly uses editorial review and aims to publish bold and radical ideas; yet the journal has a 2006 impact factor of 1.299, and papers are downloaded an average of 26 000 times per month. This implies that the journal is being used by other scientists to a significant and worthwhile extent.

The most prestigious scientific journals like to imply that their publications are not just radical but also true. This is simply hype. When published science is (almost certainly) true then it cannot be important; and when science is potentially revolutionary then it cannot be regarded as true (until subjected to evaluation by peer usage).

Peer review is valuable for predicting the probable validity of modestly incremental science; but there remains an important role for journals that use editorial review, on the basis that true scientific validity can be established only after publication, by the slow and rigorous methods of peer usage.

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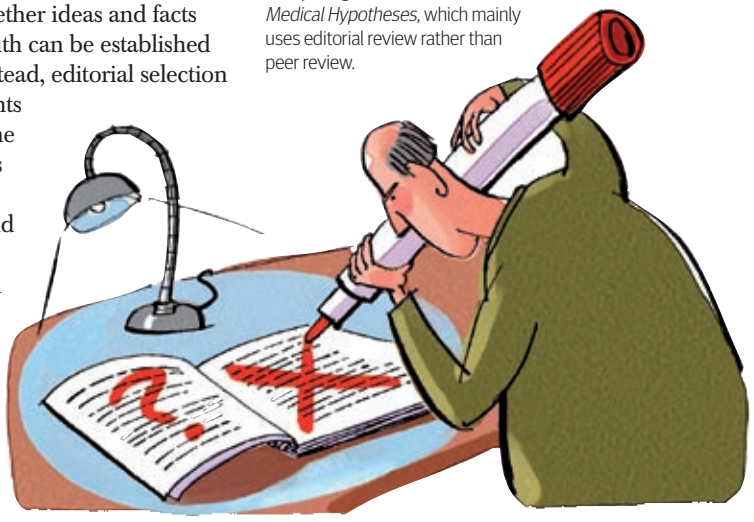
Competing interests: BGC is editor of *Medical Hypotheses*, which mainly uses editorial review rather than peer review.



MALCOLM WILLETT

About the boys and the Bs

FROM THE FRONTLINE
Des Spence

The door burst open. "Midweek special," he shouted, clutching five *Star Trek* videos to his chest. We pulled the curtains; it was a Wednesday "Trek-athon." We were four boys sharing a flat and skiving lectures. Somehow *Star Trek* just seemed more important than the roots of the brachial plexus.

I wanted to study consistently but I couldn't. Each term I would carefully draw up a study plan, as my mum had suggested. But eight weeks into the term it stared blankly down at me, and not a stroke of reading had been done. I would grapple around in the dark of my head trying to find the work switch, but to no avail. Two weeks before the exams the lights would go on and I could pour in the information. However, when my brain thought it had enough to pass, the lights went out again.

My flat mates were the same. We were four Titans of mediocrity astride the top of the standard deviation curve—we knew that a slip either way would lead to folly and certain destruction.

This year's exam results are out and again boys are left floating in an educational void. No one seems to care too much. The male intake to medical school is declining, and is now roughly 40% of the total. Negativity towards male medical students as a group also seems acceptable and goes unchallenged. So does it matter if boys aren't entering the profession? The simple answer is no, as clearly admission committees must choose the best candidates, irrespective of gender.

But life is more complex. Discussions about gender are difficult and often dissolve into the stereotypes and rhetoric of past conflicts. But I suggest that the battle to get more women into medicine is over: now there is a pressing need to make sense of the peace. For women and men are surprisingly similar but also surprisingly different—in most areas of life it seems that we complement, depend on, and need each other. We need men in medicine not to restore some misguided sense of status but to bring balance to the workforce and choice to patients.

So until the education system wakes up to the current educational inequalities and locates those switches in our sons' heads, please, selection committees, try to look beyond the Bs of our stupid boys. One day they might grow up to be useful and even intelligent men.

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Slowly, the monster dies

DRUG TALES AND OTHER STORIES
Ike Iheanacho

Not quite 7 years old, the third millennium already has a lot to answer for. Too young to be considered just another time span, its novelty too often triggers anxious navel-gazing and the urge to exaggerate the significance of current events and preoccupations.

Thus all sorts of mundane challenges come to be seen as crises and every tiny step as leaving a giant footprint on history. And this spirit provides a cover for blatant air-brushing, an excuse to pretend that bad practice has suddenly become outdated, rather than never being right in the first place.

Politicians are peculiarly keen to make things "fit for purpose for the 21st century." This meaningless phrase appears in, and supposedly underlies, the UK government's recent announcement of its intention to reform the Pharmaceutical Price Regulation Scheme (PPRS). The key determinant of NHS spending on branded medicines, this arrangement is both complex and a stranger to public awareness. So although it's existed in various forms for around 50 years, the PPRS remains largely unknown or poorly understood by many affected by its operation.

This opacity partly explains how the PPRS has flourished for so long despite being fundamentally flawed. Whatever its name suggests, the scheme makes no real attempt to dictate, circumscribe, review or otherwise "regulate" the price of individual products according to society's valuation of these treatments. Instead, the scheme centres on regulating the profit drug companies can make, but largely leaves them to decide how to set the price of each medicine in pursuit of this money.

Like many monsters, the PPRS has a good side. By limiting company profits, it has helped to guard against a wholly uncontrolled national drugs bill—an even scarier beast. But this doesn't change the fact that the arbitrary pricing it leads to has always skewed assessments of cost effectiveness and judgments of affordability.

These anomalies are particularly glaring given that other countries have long been able to design, implement, and benefit from effective methods of value based pricing that are far better placed to secure worthwhile beneficial medicines at reasonable prices, while also ensuring that the pharmaceutical industry is rewarded for true innovation.

It has taken an excellent critique of the PPRS from the Office of Fair Trading to push the government into introducing a value based pricing system. Without such a prompt, the scheme might have lumbered on indefinitely. After all, its latest five year incarnation was negotiated with the pharmaceutical industry just three years ago, and was due to run until 2010.

Still, at least things are changing now. And all thanks to the not so new century.

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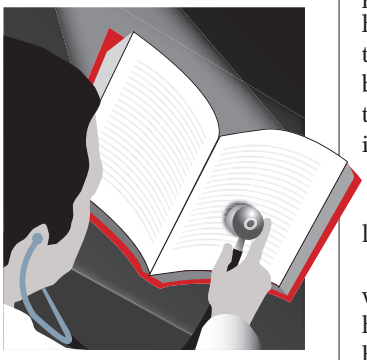
Arms and the man

BETWEEN THE LINES
Theodore Dalrymple



His father, when practising, went to sleep with a revolver within reach. The revolver kept the more violent patients from becoming too violent

Many writers were also doctors, of course, and some were medical students who never qualified. Yet others were the children of doctors, as if the literary advantages of a medical career were heritable. Among them was John O'Hara, an American writer often dismissed because of his irascibility, self promotion, and reactionary political ideas as just a pulp writer.

His long story "The Doctor's Son" was written for a short story competition in 1931 whose prize money disappeared in the great depression. It is set in the middle of the Spanish influenza epidemic of 1918-9, in which many more people died than in the first world war. The story is narrated by the 15 year old doctor's son of the title, who acts as a chauffeur for the medical student "Doc" Myers. The student has come from Philadelphia to a coal mining town in Pennsylvania to replace the boy's father, who has fallen ill with the flu. The town, Collierville, is eerie during the epidemic: the streets so deserted that it seemed as if the epidemic had brought about "a new kind of holiday."

The most interesting thing about the story is the unquestioned faith the patients show in doctors and their ministrations. Evidence based medicine, if it had then been in existence, would surely have demonstrated the impotence of medicine to affect the clinical course of the disease. Yet patients queued to see the doctor as if for salvation. So many were ill in their families that they described the symptoms of each member, and Doc Myers prescribed en masse for them.

At one point the manager of the mine, one of the three notables of the town, asks Doc Myers to attend his wife at home and asks whether the hour's delay that Doc Myers proposes because he has other patients to attend will not be fatal. What does the mine manager imagine that Doc Myers could do to save his wife's life?

The one time when speed might have saved a life, however, is when Doc Myers and the doctor's son visit a Polish miner's home and find a child there dying from diphtheria. Doc Myers sends the doctor's son to the car for instruments to perform a tracheotomy, but they arrive too late: the child has died. The doctor's son is then given 20 000 units of antitoxin as prophylaxis.

"I was stiff the next morning," he writes, "but it had not been so bad as the other times I had taken it." I suppose he was fortunate not to have suffered from serum sickness.

I discovered from the story that, contrary to my belief, violence against doctors is not an entirely new phenomenon. The narrator tells us how his father, when practising, went to sleep with a revolver within reach. "He had to have the revolver, because here and there among the people who would come to his office, there would be a wild man or woman, threatening him, shouting that he would not leave until he left with them, and that if their baby died they would come back and kill him. The revolver . . . kept the more violent patients from becoming too violent."

There is a lesson here, surely, for British casualty departments and GPs.

Theodore Dalrymple is a writer and retired doctor

MEDICAL CLASSICS

The Book of Job

Many of the books in the Hebrew Bible take the form of histories, while some are collections of poetry or prophecy, and a few are like short novels. The Book of Job, uniquely, is a play. Its brief prologue tells of the catastrophes inflicted by God on the hero, a wealthy and virtuous farmer. These include the deaths of all his children and servants, the loss of his entire livestock, and affliction with a vile skin disease. In the verse drama that then follows, Job bemoans his fate in a series of chilling suicidal laments: "Let the day perish wherein I was born, and the night in which it was said 'there is a man child conceived'."

Job is not by himself. Three of his friends set upon him—there is no better phrase—with successive attempts at counselling. The three men are models of piety. They are scarcely less eloquent than Job. Their reasoning and sincerity are a match for the millions of homilies that must have been delivered to the bereaved and despairing over the centuries since then. Job will have none of this. He rails against the men with as much vehemence as he does against his misfortunes, God, and life itself. His friends, undeterred, inflict a second round of counselling on him, and then a third. (At this point, the biblical text becomes confusing, with gaps and interpolations, including the arrival of a fourth comforter. The drama probably makes more sense if you skip chapters 23 to 37, and then read these later for their poetry alone.)

Enter God, in a whirlwind. In three chapters of terrifying poetic power, God makes no apologies, and no excuses for himself. Instead, he describes creation in all its beauty, its cruelty, and its utter unfathomability: "Doth the eagle mount up at thy command, and make her nest on high? Her young ones also suck up blood: and where the slain are, there is she." We are no longer in the world of infantile religion, or naive therapy for the survivors of trauma. "The grand vista of nature opens before Job," writes one commentator, "and it reveals the working of God in a realm other than man's moral order."

William Blake's depiction of the story of Job

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A friend of mine, a Catholic priest, once described to me how he had to perform the funeral of a small child. He told me that there was only one way that it was possible for him to do it with any degree of honesty or authenticity: to offer no explanations, no pretence of understanding, no defence of his faith. Good doctors, and good counsellors, do likewise. The God of the book of Job is not the reasonable, bland God of wishful liberals, nor the vengeful and punishing God of fundamentalists. He is as he is. That is what makes this book possibly the most challenging in the whole Bible, and the most enduring handbook for any of us who have to deal professionally with tragedy, loss, and despair.

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REVIEW OF THE WEEK

Should we loosen the grip on drug companies?

It costs $40bn a year to produce just a handful of new drugs. **Richard Smith** reviews a highly publicised new book that claims over-regulation is holding the drug industry back

The American drug industry is over-regulated and consequently innovation is stifled and patients are denied drugs that could help them. This conclusion of Richard Epstein, a professor of law from Chicago, probably sounds shocking to many *BMJ* readers. The more familiar story is that the US Food and Drug Administration (FDA) is in the pay of an industry that makes excessive profits, spends more on marketing than research, produces mostly "me too" drugs, medicalises much of life's problems, and is a malign and excessive influence in all of health care. That story was well told by Marcia Angell, former editor of the *New England Journal of Medicine*, in her best selling book *The Truth about Drug Companies: How They Deceive Us and What to Do About it* (review *BMJ* 2004;329:862). Epstein's book might be regarded as the antidote, and he is scornful of what he sees as the shallow thinking of Angell and many other critics of the industry.

Epstein examines the regulation of every stage of the process of producing and marketing drugs, and his arguments are dense and driven by economic, business, and legal thinking. Passionately pro-market and libertarian, he has consulted extensively for drug companies and so has experienced first hand much of what he writes about. The differences between him and Angell are probably driven by their different perspectives and most doctors unsurprisingly will find themselves on the side of Angell. The biggest difference may be that Epstein seems to believe that almost all drugs, including me toos, have something important to offer, whereas doctors are unimpressed with many new drugs. But Epstein is not to be brushed aside. Over-regulation can be as bad as under-regulation, and it's far from simple to get the balance right. Some of the changes Epstein advocates might improve the system.

The first problem that Epstein sees in the United States is that "overreactive conflict of interest regulations" have driven researchers in academia and the private sector apart, so reducing chances of cross fertilisation. Then "the ever wider net of regulation" at all stages has made it tougher to get a drug to market, and "constant attacks on . . . intellectual property rights" threaten to undermine the whole system. The FDA is much more worried about letting through a bad drug than it is denying patients access to a drug that may help them, and price restrictions, far from making drugs more available, will make them less available. Finally, the liability system has gone nuts—potentially compensating people with hundreds of millions of dollars for problems that they probably would have developed anyway.

I may have been asked to review this book because I'm a "known critic of the drug industry," but I find that I agree with some of Epstein's arguments. For example, he points out that a licensing body like the FDA can make two sorts of errors—a type I error when a drug that should be kept off the market is allowed onto the market and a type II error where a valuable drug is kept off the market. One criticism is that regulatory bodies are much more concerned about type I errors, but a more cogent criticism is that taking a drug off the market means that it cannot be available to people who might benefit from it. It would be better—and more modern and less paternalistic—to allow individuals and their doctors to assess the risks and benefits for themselves. Such a system would, however, depend on a reliable flow of uncorrupted evidence, which may not be easy to achieve.

The fundamental problem for the drug industry is that it is spending more to produce fewer new drugs—and many of those drugs provide only marginal benefit. In 1996 the industry spent just over $15bn (£7.5bn; €11bn) and produced nearly 60 new molecular entities; in 2006 it spent over $40bn for just over 20 new entities. Only five of the major drug companies make more than 10% of their revenues from drugs launched in the past five years. "The road to progress has gotten steeper," writes Epstein. But is the answer lighter regulation when companies have become more aggressive in their marketing (illustrated best perhaps by what even Epstein concedes was the overpromotion of Vioxx (rofecoxib)), are devoting themselves to developing drugs for lifestyle problems, and are failing to produce major new drugs for important conditions? It's more of a problem of science than law.

Anybody who wants to enter seriously into the debate around regulation of the drug industry should read this book. It will infuriate some, but I like to believe that rationality, paying close attention to argument and evidence rather than polemic and emotion, will best take us forward—and many others believe so as well. Unfortunately we're probably all wrong.

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Overdose: How Excessive Government Regulation Stifles Pharmaceutical Innovation
Richard A Epstein
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The Food and Drug Administration is much more worried about letting through a bad drug than it is denying patients access to a drug that may help them