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Are medical journals becoming component of a network financed by pharmaceutical companies? Marcia Angell on editorial autonomy, fraud in science and the purpose of peer reviewing.

The pharmaceutical branch is particularly well-known for being innovative in regards to their view on bringing things to the public through the media. With which strategies are these companies especially successful?

First of all to the keyword "innovative". In the USA alone, "Big Pharma" turns over $200 billion per year in prescription drugs from pharmacies and drug stores. A proud third of this, almost $60 billion, is spent on marketing – from TV and magazine ads to free medication or concert tickets for doctors. Despite – or rather because of – these high expenditures for advertising and publicity, the pharmaceutical industry advanced to a profitable branch in the 80s and 90s, whose scientific innovation, however, left something strongly to be desired. With capital investments in research and development, which comprise "only" one-third of the marketing expen-

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ditures, more often then not simply "me-too drugs" are developed, that is, trivial imitations of already existing mediums. In the meantime, strategies for the exertion of influence are multifaceted, but are at times followed in very indirect ways. We will take, for example, the US pharmaceutical organization Pharmaceutical Research and Manufacturers of America, for short PhRMA. They invested a million dollars in an "Intellectual Echo Chamber of Economists". Hidden behind this name lies a network of economic and leadership powers, who fulminate against the national price regulations for medications – be it in the form of full articles for the media, or statements that journalists integrate into their own texts. In addition to this, USD$ 550,000 is available to the media "for the placement of so-called Op-Eds, or opposing editorials and articles from third parties". And at least another two million dollars is at the disposal of research and political groups "to build up intellectual capital and to generate a larger number of statements stemming from credible sources". By this, 'statements' are intended to be those that support the pharmaceutical branch.

The British Medical Journal (BMJ) recently quoted the Lancent-editor Richard Horton with the comment that "the relationship of the medical journals to the pharmaceutical branch, meanwhile, is parasitic". He made this statement in front of an examining committee of the House of Commons. Didn't Horton exaggerate a bit there?

Horton was simply hinting at the fact that pharmaceutical firms exert a lot of pressure on the professional interest journals in order to get a study suitable to the company printed. The company says: "If you publish this or that analysis, we will buy many copies – or reprints – of the article in which the product appears to be the most favorable". Richard Horton was talking about this practice, which already almost amounts to bribery. References like this do not surprise me.

Do you consider this practice normal?

The sale of reprints to pharmaceutical companies, who then introduce the publication into their marketing and for example distribute to doctors, means an important source of revenue for the journals. And the pharmaceutically affiliated groups put on pressure. Editors like Horton receive regular calls from authors who inquire as to if the journal has the interests of a certain paper in mind – with the allusion that the company is then also willing to buy ten thousand reprints.

Horton is, after all, the editor of one of the leading scientific magazines world-wide.

Medical journals are owned by professional societies or for-profit publishing companies. Either way, they need to make enough money to survive, or else they have to be subsidized by their owners. Because of this many are dependent upon the goodwill of the pharmaceutical industry.

And how can they keep their objectivity and independence nevertheless?

That's difficult considering how strongly the magazines depend upon the advertisements from pharmaceutically affiliated groups. Many of these are little more than a vehicle for the transport of advertising messages.

The companies say: „If you publish this analysis, we will buy many reprints." This sale means an important source of revenue for the journals.

Are you speaking from personal experience?

That, which Horton gave an account of, never happened to me during my 20-year occupation as director of the New England Journal of Medicine (NEJM). We were probably the only ones worldwide who were also able to survive without ads.

How come the NEJM could afford this independence and not the others?

First of all, as far as I know, the *NEJM* was the only professional medical journal that could live entirely from subscription revenues. Secondly, the prestige of the *NEJM* was so high that the pharmaceutical companies wanted to run ads, even if they could

not exert influence on the editorial decisions. And thirdly, while the editors of most medical journals reported back to their publishers and because of this were unavoidably influenced by economic considerations, the proprietors of the *NEJM*, however, respected the unrestricted autonomy of the editor-in-chief. During my time at *NEJM*, no decisions were made based on commercial interests.

Lancet-director Horton also reported that many are trying to stop so-called "Ghost Writing". Here an author would claim that a certain article about a medication was written by him/herself – until it came out by accident that the complete text was composed with the help of the drug manufacturing pharmaceutical company. How can magazines protect themselves against this infiltration?

That is anything but easy. I have no secret weapon ready to fight against this form of fraud.

The scientific historian Horace Judson wrote in his book "The Great Betrayal. Fraud in Science": Fraud in science is just not – though still widely taken for granted – an exception. In fact, more often "research is penetrated with fraud". Would you agree with that?

Yes.

After all, drug companies have an enormous influence upon the origination and the data pool of research.

In Lancet, a reviewer wrote the following about Judson's book: "Scientists often have not just their egos and fellowships in mind – today the prospect exists, that the results of their research could make them into very well-to-do people [for example, one can thank the lucrative license fees of patents, the well-endowed consulting contracts, or the allotment of stock shares]. Judson paints a dark picture, but we will see even darker days if proof and profit get mixed together inseparably." Shouldn't scientific magazines guard themselves against this?

Surely the marriage of science and commerce represents a big threat. But the fact that the natural sciences are based upon a line of reason offers a certain protection against total corruption – a protection that other areas of society do not have. Although I am not optimistic, I don't see things quite as darkly as Judson.

Many of the so-called arguments are considered highly questionable because the survey methods are questionable. Above all, publicly-effective headlines about supposed life-prolonging effects of tested supplements are often alarming, not only because the long-term study does not exist, but also because no comparative tests were done. Take for example, Lipobay and Vioxx: They only mentioned much later on that the supplements were no good, and were even destructive. Two corresponding FDA surveys stated that placebos should be introduced as a control. It could very well be true that the trial matter has no effect or is even – when compared to a neutral placebo – damaging. For this, placebo testing would confront the problem of when a medication study, which officially is considered to be correctly conducted but is in fact unclean, is used as a basis in order to test the consequences of the supplement. They even wrote in their book "The Truth About the Drug Companies": "If there really is any doubt as to whether a standard treatment is effective or not, the FDA should conduct clinical studies to find new methods of treatment using three comparison groups: the new substance, the original substance, and a placebo". Do you think it is ok that professional papers often publish studies that were not controlled with a placebo?

Basically I worry about the overwhelming trust in the high value of the clinical studies, which are published in even the best professional publications. These studies can be based on biased research or can be incomplete – after all, drug companies have an enormous influence upon the origination and the data pool of the operation. But I do not totally agree with the premises that placebo-controlled studies are necessary. Many might believe that, but it is more important to find out if a substance is better than the original. If uncertainty rules over the acceptance of a medication, then higher research standards should be introduced, not placebo controls.

How well does the control through the so-called editorial peer reviewing – also called refereeing – actually function for the scientists in the respective area of expertise, when examining the presented article and through this determine if it will be published or not?

In the meantime there are around 50,000 peer-

reviewed journals that are examined by experts kept anonymous. And I think that the best researchers and the best science magazines are still good.

Elizabeth Knoll, former the science editor of the University of California Press, wrote that peer reviewing has "molted itself into a powerful social system". She asserted a "remarkable noncritical trust in peer review". The effectiveness of peer review has never been proven, other critics also say. It is threatened with corruption. It is often the case that the expert, the person whose job is to determine the value of a research assignment or the merit of a presented article, is the biggest competitor of the person whose article he/she is supposed to evaluate. It is like if a new BMW has to be approved by other anonymous car manufacturers right before it is to enter the market. In doing so here, the peer reviewer remains not only anonymous but is also not rendered accountable from anyone, which endows the reviewer with more of a wealth of power than a judge. How do scientific magazines confront this problem?

Yet, profuse confusion rules over what the editors and peer reviewers can do and cannot do. If fraud is covered up smoothly and suggests the appearance of consistency, it is difficult for it to be detected. Peer review would not be able to protect against fraud, or more so, to weed out bad science – which is decidedly something different.

And as to the control over the methods and plausibility?

The editor or reviewer is not in the laboratory, watching over the shoulders of the researchers to see if the data is recorded honestly. In the world of science, the reviewers as well as the editors responsible have to have trust that the authors honestly report what they discovered or did not find. They can, however, check to see whether the design and methods of the study measure up in relation to the question or not and whether this analysis and interpretation are sound. And if bias is present, they can often detect that.

In Lancet for instance someone wrote: "It is particularly disturbing in the case of Darsee [a Harvard researcher, who published falsified cardiology data] and many other cases that they weren't exposed through the safety measures of the research establishment, like peer review". Or take the sensational case of the Nobel Prize winner David Baltimore, whose study on the immune system printed in Cell – next to Science and nature the magazine with the most influence – in 1986 later emerged as fraud. One of the referees, the renowned immunologist Klaus Rajewsky, put his finger on the weak spot of the study during its examination, without even suspecting fraud. But his concerns were simply blown off by the editors.

In Darsee's case, other fallback systems were of greater meaning. At that time, it was not required that the authors bear witness as to if the study presented under their name was in fact composed by them. Medicine is, as a matter of fact, based very strongly upon competition. But I have also had the experience that it functions like a council – and whenever possible is respectful. I found that reviewers are often too nice rather than too critical.

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Richard Smith, chief editor of the BMJ until July 2004, said that peer reviewing is "slow, expensive, prone to bias, easily misused, hardly effective in uncovering crass defects, and almost useless in the exposure of fraud". In the summer of 2002 he installed the one-of-a-kind online discussion forum "Rapid Responses". There anyone can take a stand on articles according to the bylaws, whereby one responds for example scathing or confused. Authors also have access to the examinations with names of the referees given. Starting in 2006, referees' reports should be accessible to the public online. The accredited professional magazine Medical Hypotheses, for example, is published without any peer review.

Angell: What Winston Churchill said about democracy is also true for peer reviewing: It is a terrible system, but better than any other one we know.

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Tip of The Iceberg

Why journalists shouldn't blindly rely on even reputable science magazines.

Science magazines, such as nature or the *New England Journal of Medicine* (*NEJM*), serve as blueprints for popular scientific media. But just how risky it is to pass their contents on to the public without evalutation was shown in the case of the arthritis medication Vioxx. At the end of 1999, half a year after the market approval of Vioxx, the *Frankfurter Rundschau* and the *Hamburger Abendblatt* newspapers euphorically reported, based on the studies from *Lancet* and *Gastroenterology*, on the "success of this new substance" that promised to "relieve millions of people from their joint pains". But a great disillusionment came about in 2004: Vioxx had to be taken off the market because it was held accountable for heart attacks and strokes as well as almost 40,000 deaths.

The deep trust of journalists in scientific professional journals cannot even be shaken through scandals like these. Experts, such as scientific historian Horace Judson, explain that this phenomenon occurs because medical authorities are generally accepted as altruistic truth seekers [Judson 2004:23-25]. Hence fraud cases are interpreted as rare, inadvertent "accidents". And more so the journalists are convinced that the professional journals have peer reviewers - anonymous experts who decide whether presented contributions are serious and should be printed or not - at their disposal to take appropriate measures to guard the journal and assure that only professional top-quality contributions find a place in the realm of "*nature&Co*". But in fact, this conviction proves often enough to be a superstition.

"In science as well", said Judson, "we are bombarded, saturated, and tormented by fraud." This is one perception that was confirmed through a study published by *nature*; the currently acknowledged dishonesties are just the tip of the iceberg [Martinson, 2005:738]. Just recently it came out that hundreds of scientists from the US health department NIH received millions of dollars of financial contributions from the pharmaceutical industry. These financial conflicts of interests in the meantime have undercut the whole research industry and its reviewers – and with that also the credibility of professional magazines, whose articles appear through the glory of unbiased science through the reviewing process.

In the USA in the meantime, it has gotten extraordinarily difficult to find a leading medical researcher without financial dependence to "Big Pharma" [Moynihan, 2003:1189]. According to a recent study from the British House of Commons, it does not look much better in Europe. "The state of medical occupations has been bought by the pharmaceutical industry – in regards to its practice, training, and research", complained Arnold Relman, Harvard professor and former chief editor of the *NEJM* [Moynihan, 2003:1190]. Vioxx-manufacturer Merck is said to have installed a surveillance system and exerted its influence on universities to find and silence Vioxx-critical physicians [Prakash, 2005]. Critics allude to the fact that publicized works, which are sponsored by the industry, bear pro-industrial results [Bekelman, 2003:454; Angell, 2000:1517]. Through this the results are distorted, for instance by being left out in critical questionings or silenced in the case of negative conclusions.

"It is impossible to say how many manipulated papers slip through the peer review and editorial processes", as stated recently in *Lancet*. "But as Judson would argue, there are probably quite a few" [McCarthy, 2004:1657]. And yet

Relman's successor Jeffrey Drazen did not allow himself to be kept from revising the guidelines for *NEJM* authors so that reviews and editorials are also allowed to be written by experts who take in payments of up to 10,000 dollars per year – as well as from companies whose products are mentioned in the articles in question. Drazen's reasoning: Unfortunately, it is not otherwise possible to win qualified authors. Drazen's direct predecessor, Marcia Angell, warned: "Scientists tend to believe that they can remain objective even if they are paid by pharmaceutical corporations. But actually the opposite is true" [Angell, 2005].

"Selective reporting" is also risky, whereby the entire study is sorted out so that only the ones with "desired" results are left over. Nevertheless: In order to take measures against this manipulation, Drazen as well as ten other editorial colleagues at Lancet want to print only such papers in the future that are entered in a special registry, which must be made publicly accessible free of charge, and whose data will need to be electronically screenable.

The initiators realize this just means the first step toward transparence [Drazen, 2005:1251]. Furthermore, there are in fact quite a few options for publicizing manipulated studies. One of these research tricks occurs when for the comparison of a test substance and a placebo, a placebo is chosen that can be recognized as such by the test persons; of course nothing is mentioned in print. The professional magazine editors do not see themselves in a position to weed out or correct such studies. Also in relation to this: "An important element of science gets lost: The verification of study results", said Judson [Judson, 2004: 39]. With this another negative effect exists: The established research industry oppresses something that is new as soon as it contradicts established theories – thereby supporting mainstream research [Judson, 2004: 266-267]. The review of professional journals strengthens this trend. But what peer reviewers, ask critics, would support innovative entries that refute his/her own work, upon which his/her career or reputation depends? "Peer review is not in the position to adequately filter out conflicts of interests in medical science", said Bruce Charlton, editor from Medical Hypotheses. He recommended the institution of "Conflict of Interest Consultancy Services". The experts from these independent "Col-Consultancies" – composed of various organizations – would assess the conflicts of interest as well as other distortions, and before the results of the publicized articles can be attained for use. A ray of hope?

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