Seeman has suggested that D2 receptors exist in more than one form (as monomers, dimers, and oligomers), which have differing properties and may exist in an altered proportion in schizophrenia. Clearly, more work is needed to clarify the key cellular events and aetiological triggers explaining aberrant dopaminergic function in schizophrenia.

Dopamine and schizophrenia have long been inextricably, but inexplicably, linked. Although the details of their relation may continue to be elusive, the recent findings together mean that its existence and importance should not be doubted. This proof of principle of the biochemical candidate approach will provide welcome encouragement to researchers working on equivalent theories of other psychiatric disorders. It also raises several interesting questions. Why does the dopaminergic abnormality come and go? Are there differential changes in mesolimbic or mesocortical compared with nigrostriatal dopamine pathways (the former being important for psychotic symptoms and the latter for the parkinsonian side-effects of antipsychotic agents)? Do similar alterations occur in other types of psychosis? There are important clinical implications too. It may enable the predictive value of increased dopamine stimulation for drug response, or the relation of D2-receptor occupancy with therapeutic response and side-effects, to improve the routine use of antipsychotic medication. Finally, the potential of non-dopaminergic antipsychotics should be pursued for the subgroup of patients who do not seem to have any dopamine wind fanning their psychotic fire. These various considerations ensure that the roles of dopamine in schizophrenia and in its treatment will continue to be both topical and entwined, though fortunately no longer indistinguishable.

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The less acceptable face of bias

A clinical investigator is, to paraphrase Whitney Balliett, a bundle of biases held loosely together by a sense of method. Bias and biomedical research are firm and rowdy partners. Some scientists have set out to make the collection of biases their life’s work: David Sackett achieved something of a record by cataloguing 56 of them. Bias—any systematic deviation of an observation from the true clinical state—is accepted provided researchers do their best to diminish it or, as a last resort, to admit its presence. But there are biases, generally more distorting than those commonly acknowledged in textbooks of epidemiology, that medical research prefers to ignore, perhaps because they point to unsettling and unflattering facts about the research process itself.

Editors hardly help matters. Opening up the peer-review process to investigation has revealed uncomfortable questions about positive-outcome bias, geographical and gender bias among reviewers, citation bias, and sex bias in appointing editors. The fundamental problem with much published research into journal peer review is that it fails to get to grips with the way decisions are actually made at journals, decisions that investigators may feel are marked by inconsistency, compromise, caprice, base personal rivalry, pique, passion, and plain unscrupulousness. Unfortunately editors are human, and they could be much better. That ill-defined human element is crucial in the production of three additional and less acceptable biases concerning investigators, industry, and the identity of research.

Investigators continue to discriminate against women in clinical trials. David Harris and Pamela Douglas studied 126 trials funded by the US National Heart, Lung, and Blood Institute between 1965 and 1998. When two large single-sex studies were excluded, women made up only 38% of patients enrolled, despite a 49% prevalence of cardiovascular disease in the general population. That proportion of women participants did not change over time. This imbalance was especially prominent in trials including patients with heart failure. Harris and Douglas concluded that “The successful resolution of this difficult problem is critical for the prevention and management of cardiovascular disease in women and men”.

A related bias affects research questions being posed by investigators. Deborah Tallon and colleagues found a mismatch between what interested clinical scientists studying osteoarthritis of the knee (drugs and surgery) and what concerned patients (surgery and education). The products of the pharmaceutical industry, together with their accompanying enticements, hold far too powerful a sway over the interests of clinical investigators.

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workers make hard to produce practice guidelines and educate the public is the persistent failure of either effort to make an impact. The continuing gap between patients and their doctors was illustrated in an expression of acute frustration by the editor of a cardiac-patients’ journal. After new research seemed to question the use of aspirin, Michael Knight wrote, “How do we expect patients to make sound decisions and achieve concordance when the experts cannot agree for more than two minutes?”

Pharmaceutical industry bias is hard to study with any rigour. However, Benjamin Djulbegovic and colleagues found that these from studying sponsored symposia in their published cardiologists is given over to industry? An answer emerges a fifth of the main annual meeting content for European commercially sponsored. Should anyone care that almost increasing. In 1999, 56 of 342 (16%) sessions were programmes.”

Identity bias concerns frequently commercially driven agendas that are allowed expression under cover of reputable organisations and their associated meetings. Sponsored satellite symposia are widely accepted to be a necessary trade-off that academic societies must make to pay for expensive annual meetings. These conferences are the lifeblood of many specialties. For instance, the European Society of Cardiology meets annually each summer; it is the central event not only for European cardiologists to report new data but also for important clinical updates across all aspects of heart disease. The organisers work hard to promote these features of the conference to the public. But is the price too great? A parallel exhibition enables about 200 drug companies, device manufacturers, and publishers, together with a few non-governmental organisations, to promote their products and activities alongside the conference. There is a clear separation between the intellectual and commercial aspects of the meeting. But satellite symposia blur that important distinction.

The ESC programme underlines the importance of satellite symposia to its meeting: “Co-operation between clinicians, researchers and the pharmaceutical and technical industries has significantly contributed to a better understanding and management of patients with cardiovascular diseases. This is reflected in a series of symposia organised by industries as part of the congress programme.”

Of the 361 sessions held over 5 days, 65 (18%) were commercially sponsored satellites. This proportion is increasing. In 1999, 56 of 342 (16%) sessions were commercially sponsored. Should anyone care that almost a fifth of the main annual meeting content for European cardiologists is given over to industry? An answer emerges from studying sponsored symposia in their published form. Lisa Bero and colleagues found that these symposia were more likely to have misleading titles and to use brand-named drugs, and less likely to be as carefully peer-reviewed as other journal content. They concluded that sponsored symposia have strong “promotional attributes” and that readers should “approach symposium issues that are sponsored by a single pharmaceutical company with scepticism”. The same seems to be applicable to the actual symposia themselves.

At one satellite meeting organised by Bayer, the ESC imprint was placed on the company’s leaflet promoting the evening event. The ESC logo also appeared on a promotional booklet published by Bayer, which advertised its three main cardiovascular products. At the symposium, speakers presented data and arguments in favour of one of these three drugs. In one case, the summary of the INSIGHT trial in a company pamphlet (with ESC logo) accompanying the meeting emphasised a non-primary endpoint, provided an unbalanced account of adverse events, and overinterpreted the beneficial effects of the new drug. If the ESC is willing to lend its name to such satellite symposia, should the society not pay more attention to the quality of presentations going out under its name? And if Bero and colleagues’ journal-supplement data are correct, and no evidence has been presented to refute them, the identity and reputation of societies such as the ESC and those that pursue the same symposium policy are in grave danger.

How might these three biases be minimised? Investigator bias could be diminished by building up a collaborative research agenda with patients. The most mature example of such an approach is to be found in the HIV-AIDS community, where activists play a decisive part in shaping research culture. This participatory model might also help to bridge the widening gap between research and practice, both for improving public education and for lessening residual confusion among patients. Industry bias within clinical trials can be tackled only by more rigorous ethics-committee review of study protocols. The elimination of identity bias depends on recognition by societies that their public reputation rests on their real and perceived independence. Once given up, that independence will be impossible to reclaim. A first step might be to reduce the proportion of meeting content that is given over to industry-sponsored satellites (say, to below 5%), and for the conference organisers to review more carefully the printed materials that are provided to delegates under their name. The relations between industry and trialists and specialist societies need to be carefully readjusted.

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