When is a drug 'safe'?

SIR—The Food and Drug Administration (FDA) is often criticized (as in a recent leading article in *Nature* **343**, 494; 1990) for its handling of various issues or specific products. While some criticism implies that the agency is too lenient on regulatory policies or decisions, other criticism takes us to task for being too slow. A favoured theme, one implicitly endorsed in the leading article, is "once any amount of possible effectiveness has been demonstrated, the FDA should approve the product immediately, making it available to patients who need it" (although *Nature* expressed more concern about the health of the manufacturers than about that of the patients). These critics are right to be critical of any genuine delay in bringing a safe and effective drug to market, and the FDA shares their eagerness for a streamlined drug-approval process: there is, indeed, a genuine cost of regulatory delays. However, any patient — even one with a fatal disease — can be made acutely worse. Thus, the costs of time in the review process must be weighed against the hazards of approval of an unsafe, ineffective drug.

The FDA's regulatory approach will do far more to bring safe and effective new drugs sooner to patients who need them than if it were to grant marketing approvals based on initial results. In fact, this latter path would have it ignore both the laws that ensure the safety of new drugs and the realities of clinical research.

Clinical researchers are aware that the earliest reports on a new drug are often over-positive. That is, initial reports can be more optimistic about how safe the drug is and how well it performs its intended purpose than later studies prove it to be. Consequently, the FDA and the medical community usually withhold judgement until some verification is obtained.

The FDA has already used its existing regulatory procedures to evaluate and approve numerous products of the new biotechnology, with many more in the pipeline; some 400 (the majority of which are diagnostic test kits) are approved for marketing, and more than 700 drugs and biologicals are in clinical trials. Marketing approval times for the new biotechnology-derived drugs and biologicals have averaged approximately half the 33 months required for new products generally; we do not, indeed, mindlessly crank each and every product "through the same rigorous and probably over-rigorous mill". The agency is committed to refining further its procedures for new drug evaluation. Recent changes in FDA regulations should make investigational drugs available to patients who require them at an earlier time than previously and should shorten review times. The FDA's decisions exert a profound impact on both patient care and commercial development, and it is imperative that the agency's actions be based on — and only on — solid scientific analysis. A high-quality, predictable review process fuelled by a strong research base can encourage the development of promising new therapies and speed the appearance of new, safe products. The drug review process is a complex and difficult one, and approval of an unsafe drug, or unnecessary delay of a good drug, can each have disastrous consequences. The FDA must avoid both.

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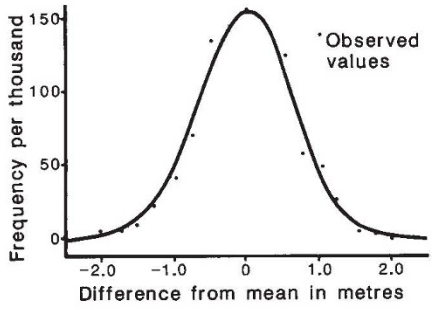
Identifying trends

SIR—In his leading article entitled "Two gales do not make a greenhouse", John Maddox (*Nature* **343**, 407; 1990) made the cautionary comment that "even indirect and properly qualified assertions that transitory events are evidence for more durable physical phenomena may backfire". H. E. Hurst[1] made just such a point as scientific consultant to the Ministry of Public Works, Egypt, in 1950 when he studied the discharge of the Nile river at Aswan. It appears that the Egyptians were particularly diligent about keeping records of the annual flood levels of the Nile at Cairo. The distribution of over one thousand readings (see figure) is well fitted by a normal curve, suggesting that the magnitude of the flood level was a random event. However, this long series of records of flood levels at Cairo showed a tendency[2] for groups of high or low values to occur. Hurst remarked that such a tendency is greater for natural than for truly random events.



Maximum annual gauge reading at Roda Gage, Cairo, Egypt for 1,080 years between AD 641 and AD 1946.

I have no knowledge of the reaction of the Egyptians to a series of high annual flood levels at Cairo but it is possible that they regarded them as a trend to a permanent state of affairs. The figure, however, clearly demonstrates that such trends were accommodated within a normal distribution of events and so occurred by chance. Clearly, disaster of increasing magnitude or a recurring nature did not overtake them, as witnessed by their ability to continue to record the flood level at the Roda Gage, Cairo, for over a thousand years.

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Blind reviews

SIR—I was recently sent a manuscript to review (not from *Nature*) written by an individual whom I had never met, but whom I knew by (negative) reputation. I found the task of trying to ignore this knowledge in order objectively to review the manuscript to be difficult and disturbing. Recent discussions in the literature[1], in correspondence to *Nature* and at the First International Congress on Peer Review in Biomedical Publication (*JAMA* **263**, 1311–1444; 1990) confirm that the issue of biased reviews is of general concern to the scientific community. Peer review of manuscripts is a critical step in the maintenance of quality and integrity in scientific communications. Reviews should be based solely on the merits of the research performed and the validity of the conclusions; the reputation, sex, race and institutional affiliations of the author(s) should not be allowed to bias the objective evaluation of manuscripts. However, the potential for bias is unavoidable unless reviews are blind, that is, the authors' names and institutional affiliations are removed before being sent to reviewers. Empirical studies[2,3] indicate that reviewer bias can affect the publication of manuscripts, and that blind review does improve the quality of peer review. Blind review is commonly used in fields such as education, sociology, agricultural economics and psychology, but is uncommon in the physical, Earth and life sciences. In the interest of improving objectivity in the review process, I propose that blind review should be adopted as a general practice by scientific journals.

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