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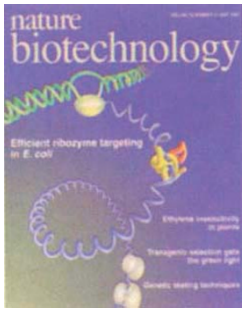
Discoveries in complex biosystems

To the editor:

I note with interest that Bains[1] and Strohman[2] agree on the fallacy of the paradigm of genetic determinism for many common diseases. The genetic research that has promised cure of complex disease conditions is thus reduced by Bains[1] to a science that generates tools with little predictable properties. Like other products of medicinal chemistry, the genetically discovered molecules may produce no effects, unexpected effects, unwanted or harmful effects, but also, occasionally, a useful effect, although not necessarily along the lines that were planned[1]. This confession by a consultant to the biotechnology industry may worry those who are now trying to reduce all diseases to simple molecular disorders amenable to molecular cures[3].



With reference to the medical history of drug introductions, Bains further argues that this new insight "does not matter"[1]. The pragmatic examples given by Bains include steroid anti-inflammatory drugs. He states quite correctly that the efficacy of these drugs (like that of numerous other drugs, including recent additions such as omeprazole) were discovered before anything was known about their mode of action[4,5]. Indeed, for many established drugs the essential mechanisms of actions may now remain conjectural. The heart of the matter then would be how novel drugs' efficacies actually were discovered. However, this question is disposed of by Bains in one line stating that "The paradigms of the day threw them up"[1]. One wonders how well defined and understood those drug-producing "paradigms of the day" were, by academic opinion leaders, scientific directors, their consultants. . .?

I think we easily forget the individual, rebellious researchers who made the original and important observations, frequently in complex biosystems[4,5], and who bravely (perhaps as brave as a scientist that today may deviate from the "centrality of the genes"[1]) believed in their data whatever the current paradigms had to say[4]. The history of drug discoveries may thus be endowed with examples where the true story is not told and where credit, instead of going to those who made the key iconoclastic observations, may go to those who came up with the best retrofit explanations (the best story for pharmacological textbooks and drug marketing alike).

Since Bains brought up the steroids, it might be worthwhile to mention that the first demonstration of "anti-inflammatory" efficacy of these drugs was reported at the last turn of the century[6]: The astute observer Solis-Cohen[7] then gave his patients, who suffered from severe asthma, desiccated adrenal glands by the oral route. Solis-Cohen[7] noted several features of the clinical efficacy of this steroid preparation in asthma, distinct from the effects of adrenaline and in excellent agreement with current knowledge of glucocorticoid actions in this disease[8]. Had Solis-Cohen's report arrived today it would not have taken 50 years to identify and produce the active compounds. Hopefully, his work would also have been understood and his pioneering contribution acknowledged. Solis-Cohen's work teaches the success of exploring off-label compound actions in complex disease or disease-like in vivo systems.

If astute observations of particular efficacies in complex biosystems (of compounds emanating from any source; and there may be no shortage of interesting compounds) is the crucial part of drug discovery, several questions emerge. For example, where is training going on to produce scientists who are experts on increasingly disease-relevant, in vivo research? (In the asthma field, I am not primarily thinking of experts on the popular mouse in vivo models, since the airways of these allergic mice apparently lack central features of real asthma, such as activated eosinophils, epithelial injury-repair processes, and microvascular-mucosal exudation of plasma[6]). And who, these days, teaches that complex in vivo biosystems may be the most significant experimental systems to be explored for leap progress discoveries, including such observations that will lead to truly innovative treatments?

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5. Wurtman, R.J. and Bettiker, R.L. 1995. The slowing of treatment discovery, 1965–1995. *Nature Medicine* **1**:1122–1125.
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Corrections

Because of an oversight, the reference for the crystal structure determination of bovine angiogenin was omitted from the review article on ribonucleases by Catherine Schein (*Nature Biotechnology* **15**:529–536, June 1997). The relevant paper can be found in *PNAS* (Acharya, K.R., Shapiro, R., Riordan, J.F., and Vallee, B.L. 1995. Crystal structure of bovine angiogenin at 1.5-Å resolution. *Proc. Natl. Acad. Sci. USA* **92**:2949–2953).

The article "Looking at thermocyclers" (*Nature Biotechnology* 15:685–687, July 1997) incorrectly stated the price of Idaho Technology's thermal cyclers, services offered to purchasers, and the terms of the machine's manufacturer. Idaho Technology is the sole manufacturer of the LightCycler LC24 and the RapidCycler 1002. Prices for the machines are as follows: LightCycler, $39,000 (US) and RapidCycler, $3,900 (US). Idaho Technology offers a two-day training course for purchasers of the LightCycler and a thirty day in-house trial for the RapidCycler. Users may be required to obtain a license for certain amplification reactions that are covered by patents. For more information or questions, please contact: Customer Service, Idaho Technology, Inc., PO Box 50819, 149 Chestnut Street, Idaho Falls, ID 83402. Phone: (800) 735-6544 or (208) 524-6354; Fax: (208) 524-1605; E-mail: it@idahotec.com.