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LETTERS

Chirality and Drug Development

In his article "Looking glass chemistry" (Research News, 15 May, p. 964), Ivan Amato predicts, on the basis of statements by some industry researchers, the demise of racemates as viable new drug candidates. While few would argue that a single purified enantiomer is the better drug substance candidate in many cases, attaining this goal is not always technologically or economically practical.

Amato states that "regulatory incentives . . . are . . . pushing drug companies toward single-enantiomer chemistry." However, the Food and Drug Administration (FDA) policy statement he cites (*1*), which was issued after the article appeared, actually says, "Although it is now technologically feasible to prepare purified enantiomers, development of racemates may continue to be appropriate." A 1990 paper (*2*) by a Pharmaceutical Manufacturers Association committee agreed with this view, concluding, "The sponsor should decide whether to market one enantiomer or the racemate on a case-by-case basis, considering all available data, and provide regulatory bodies with information that delineates the safety and efficacy of the proposed drug substance."

There are several situations in which development of a racemate may be preferred. For example, each enantiomer may exhibit pharmacological and toxicological profiles similar to those of the racemate or be rapidly interconverted in vivo. Ibuprofen, pictured in the article, is a case in point. The less active R enantiomer of ibuprofen is metabolically converted to the active S enantiomer in the body; therefore, administering the racemate to a patient offers no disadvantage relative to the active enantiomer alone (*3*). With other compounds, one enantiomer may be found to be pharmacologically inactive, while the racemate is demonstrated to be safe and effective. Also, a separation of enantiomers that can be performed on drug quantities sufficient for laboratory testing cannot always survive the scale-up process to production volumes. In some cases, the enantiomers may even produce different therapeutic effects. As noted in the FDA policy statement, this situation occurs with sotalol (*1*).

It now takes 12 years and an investment of $231 million before the average new molecular entity reaches the pharmacy shelf (*4*). A pharmaceutical company will carefully consider the expected benefit before embarking on a course that may substantially increase the cost of a new medicine or delay its availability to patients who need it.

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In the boxed piece "Government smiles on one-handed drugs" (Research News, 15 May, p. 965), it is mentioned that I expected that a forthcoming policy statement would officially make single enantiomer the standard in drug development. The policy statement to which I referred does not mandate development of single isomers and is flexible enough to allow for the development of racemates when adequate data are available to ensure the safety and effectiveness of resulting drug products.

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Thrombin and Its Inhibitors

With respect to Jean Marx's interesting article "A new link in the brain's defense" (Research News, 29 May, p. 1278), I would like to say that the work performed in my laboratory during the past 20 years would not have been possible without the dedication of a number of students and postdocs who made contributions that were decisive in the characterization of glia-derived nexin or protease nexin–1 (PN-1) and in suggesting the importance of the regulation of thrombin-like activity in the nervous system. These include the first authors of the publications referred to in Marx's article:

Joachim Guenther (*1*), Sergio Gloor (*2*), Jurg Sommer (*3*), Melitta Dihanich (*4*), and Hana Suidan (*5*), who are past or present collaborators at the Friedrich Miescher Institute, and Marie-Charlotte Hoffmann (*6*), who is associated with Cordula Nitsch's group at the University of Basel.

The demonstration that thrombin acts on neuronal cells by activation of a specific receptor (*5*), initiating still unknown cascades, possibly through a linkage with a G protein (*7*), indicates that the classical coagulation pathway may not be the primary mode of action in the nervous system, as Marx points out. Similar results supporting this concept were recently obtained by Wouter Moolenaar and his colleagues in Amsterdam (*8*). In addition, David Small and his collaborators at the University of Melbourne have demonstrated that PN-1 is a potent inhibitor of a secretase of the amyloid precursor protein which can be associated with acetylcholinesterase and is thought to process the protein from the cell surface or from the extracellular matrix (*9*). Together with the presence of messenger RNA for prothrombin (*4*) and thrombin receptor (*10*) in neural structures, these results indicate that these proteins are not only involved as safeguard components to prevent serious damage from local rupture of the blood-brain barrier, but that they could have additional functions important for the development and plasticity of the nervous system. These novel aspects will render research in this field even more exciting in the years to come.

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Estimating Biomass

Estimates of global and continental biomass and carbon storage are rarely based on data intended for that purpose. This is the case with the data used as a baseline by Pekka E. Kauppi *et al.* (Articles, 3 Apr., p. 70). The source they cite for baseline biomass estimates of European forests (*1*) is a compilation of many unrelated estimates of timber stocks. They convert these estimates to assess biomass and carbon storage and include no estimates of error, without which it is difficult to evaluate discrepancies among estimates or test the significance of suggested trends. Examination of this source and others (*2*) cited by Kauppi *et al.* reveals that the data they contain are not well documented, and it is difficult to evaluate their merit.

Under the heading of "Universal-global tendencies" Kauppi *et al.* cite a source (*3*) that states that growing stock and timber growth potential in the United States have been repeatedly underestimated. M. Clawson, however, states at the outset of (*3*) that his study, like many other historical reviews, is "limited by the paucity, suspected inaccuracy, and noncomparability of available data." Kauppi *et al.* cite this study and conclude that underestimation may be common. On the contrary, it has been shown recently that the biomass and carbon storage of North American boreal and Eastern deciduous forests have been vastly overestimated (*4*). Whether this is true for Europe we do not know, but it is a question that should be examined. In addition, a recent publication about North American forests (*5*) from the source of the authors' primary data (*1*, *2*) suggests that in Canada growing stock is declining, which apparently contradicts the same data source. How valid are the results and conclusions of a study that depends on questionable data with no independent measures or confirmation?

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Response: We appreciate the comment by Botkin *et al.*, which we think supports the recommendation we made in our article about research priorities with regard to estimating the carbon budget of ecosystems. Confidence limits can only be calculated when the primary measurements are taken from sample plots located randomly or with a systematic grid.

Botkin and Simpson have estimated the carbon storage of aboveground forest vegetation on a continental scale with unbiased sampling (*1*). Their study area covered 5.1 million square kilometers. Y. Ilvessalo published an early corresponding national study, an unbiased forest inventory covering 0.38 million square kilometers (*2*). Although his study and subsequent forest resource surveys in Europe were not designed for carbon assessments, they can be used in this context because all trees reaching breast height (1.3 meters) were included in the samples. The large pool of belowground carbon was not measured in either (*1*) or (*2*).

It is useful to distinguish between carbon storage and the *change* of carbon storage. It is the change that counts in budget calculations. Therefore, we need periodically repeated, statistically representative measurements. Forest inventories have been repeated periodically since the 1920s and are probably the only relevant studies providing unbiased time series data for carbon storage in forest vegetation. The sampling grid in these inventories has extended at best to national geographic scale.

In Europe, forest inventories have been carried out and repeated in Finland, Sweden, and Austria and, with some interruptions and shortcomings, in France. They cover a total of 14% of the European forests area (18% if France is included). The growing stock, an indicator of aboveground carbon storage, increased from 1971 to 1990 by 28 ± 2.0% in Finland, 14 ± 2.0% in Sweden, and 24 ± 2.5% in Austria (*3*). The development was similar in France.

Our conclusions were based on five kinds of references: (i) complete forest inventory records (from Finland, Sweden, Austria, and, with reservation, France); (ii) incomplete forest inventory records (from Germany and Switzerland); (iii) official statistics on forest resources from the remaining countries; (iv) reviews and primary research articles on growth and yield; and (v) forest products statistics. The data consistently showed a trend of increasing forest biomass, forest growth potential, and accumulation of forest products. The criticism of Botkin *et al.* applies only to category (iii).

Official forestry statistics can be biased. For some countries (in the worst cases) the information is based on expert opinion. However, we believe that listing and reviewing results from different studies from different countries represents scientific progress as compared with the state of the