Developmental neurotoxicity of industrial chemicals

In asserting the existence of a "silent pandemic" of developmental neurotoxicity, P Grandjean and P J Landrigan (Dec 16, p 2167)[1] have apparently forgotten or ignored dose-response principles in their zeal to promote their opinions. In compiling their list of "chemicals known to be neurotoxic in man", they derive much of their information from occupational exposure studies done when hygiene measures were much less stringent than they are now. Therefore, those results are of limited relevance to assessing general population risks, including those of sensitive populations (pregnant women, infants, children) in whom exposures are much lower.

Grandjean and Landrigan's faulty logic is exemplified by ethanol. Abuse during pregnancy causes fetal alcohol syndrome, a developmental syndrome with neurological manifestations. However, there are no data to show that maternal exposure to low, environmentally relevant levels of ethanol (ie, concentration in foods) places the fetus at any risk of fetal alcohol syndrome. Risk is a function of dose, even for developmental neurotoxicity.

With drugs, to see efficacy, a critical concentration at the target site is needed. The same principle applies to toxicity. Effects at high doses will not be realised at lower doses if the concentration falls below the target site threshold level. If Grandjean and Landrigan's logic is applied to drugs, an "outbreak of cures" would be predicted to be triggered by any dose of any therapeutic agent. Evidence-based medical practice would reject such a homoeopathic belief. Evidence-based toxicology and epidemiology dictates a similar conclusion with respect to Grandjean and Landrigan's allegations of a "pandemic" of developmental neurotoxicity.

I am an independent scientific consultant, and have served as a consultant on toxicology and risk assessment issues to the American Chemistry Council, a trade organisation that represents chemical manufacturers.

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1 Grandjean P, Landrigan P. Developmental neurotoxicity of industrial chemicals. *Lancet* 2006; **368:** 2167–78.

P Grandjean and P J Landrigan[1] provide a valuable and timely review of industrial chemicals that are thought to have damaging effects if they reach the developing brain. In discussing possible mechanisms that might account for the vulnerability of the developing brain to these agents, Grandjean and Landrigan state "The blood–brain barrier is not completely formed until about 6 months after birth", citing a paper by Adinolfi.[2] This perpetuates the long-standing misconception that "the" blood–brain barrier in the fetus and newborn is immature.

The term blood–brain barrier is used to describe a series of physiological mechanisms (inward and outward transport mechanisms) that control the composition and stability of the internal environment of the brain. Underlying these physiological mechanisms is the presence of intercellular tight junctions between cerebral endothelial cells (blood–brain barrier) and between choroid plexus epithelial cells (blood–CSF barrier). The presence of tight junctions is essential for the functional effectiveness of all the physiological barrier mechanisms. Tight junctions between cerebral endothelial and between choroid plexus epithelial cells have been known for decades to exclude the intercellular passage of proteins from blood into brain and CSF.[3]

The tight junctions at both blood–brain and blood–CSF interfaces are well formed from early embryonic life.[4] However, there is a transcellular mechanism in a subpopulation of choroid plexus epithelial cells that transfers proteins from blood to CSF.[5] This protein transfer mechanism might be relevant for the entry of some neurotoxic agents into the immature brain. For example, some of the heavy metals listed by Grandjean and Landrigan bind to proteins in plasma and could thus be transported into the brain via the choroid plexus. However, this is a reflection of a developmental specialisation rather than of immaturity.

We declare that we have no conflict of interest.

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1 Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. *Lancet* 2006; **368:** 2167–78.
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5 Johansson PA, Dziegielewska KM, Ek CJ, et al. Blood-CSF barrier function in the rat embryo. *Eur J Neurosci* 2006; **24:** 65–76.

Authors' reply

Laura Plunkett seems to have missed a main point of our review—ie, that during prenatal and early postnatal development the timing of exposure is at least as crucial as the dose. It is the unique sensitivity of the developing human brain during windows of early vulnerability that accounts for the profound damage caused by minute doses of lead, methylmercury, ethyl alcohol, and probably many other industrial chemicals that have never been properly tested. As we show with the few chemicals that are known to damage brain development, waiting for the production of detailed dose-response relations will promote the continued exposure of developing brains to toxic risks.

Norman Saunders and Katarzyna Dziegielewska provide important

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information on the early development of the blood–brain barrier. Given that intercellular tight junctions between cerebral endothelial cells in the blood–brain barrier are already well developed from early embryonal life, any incomplete development of this barrier will have at most a partial role in the genesis of developmental neurotoxicity. The industrial chemicals that we identified as toxic to the adult brain are obviously capable of passing the mature blood–brain barrier. With regard to these substances, the risk of developmental neurotoxicity would not depend on any assumption of incomplete barrier development.

PG has testified on behalf of the Natural Resources Defense Council in a court case in regard to mercury pollution from a chemical plant in Maine, USA. PJL has testified on behalf of the State of Rhode Island, USA, in a lawsuit against the manufacturers of lead-based paint.

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Direct-to-consumer drug information in Europe

In your Jan 6 Editorial (p 1),[1] you claim that "European Commissioners are considering proposals to loosen Europe's ban on direct-to-consumer advertising for prescription drugs." Your general conclusion is that "it would be better to fund independent information sources, free of industry influence, to provide the public with unbiased evidence-based information."

On behalf of the European Federation of Pharmaceutical Industries and Associations (EFPIA), the representative voice of the research-based pharmaceutical industry in Europe, I would like to make the following comments.

To our knowledge, the European Commission has no such plans to remove the current ban in Europe. However, there is widespread agreement among EU institutions and the public that communication with patients and the public on prescription medicines should be improved, with the objective of having better informed patients. But the ban is so inclusive that it largely prevents industry providing any information on its products, ironically while allowing anyone else to do so. As pointed out by Vice-President Günter Verheugen at the Ministerial EU Pharmaceutical Forum on Sept 29, 2006, the current restrictive position in many Member States, and EU citizens' uneven access to information, are "unsatisfactory and… even unacceptable".

We do not advocate US-style direct-to-consumer advertising as an appropriate model for Europe. Instead, we call on the European institutions to improve access for all patients and citizens in Europe to health and medicines information in their own language. We firmly believe that better informed patients will lead to safer and more successful health outcomes, a more efficient use of health-care resources, and ultimately to healthier societies.

Clearly no single source can provide all the available information, but pharmaceutical companies have much knowledge and information to share about health and medicines, having researched and developed their products over an average of 10–12 years each. The industry should be enabled (among other sources) to supply non-promotional, high-quality disease-related and health-related information to EU citizens. In our view, information should be deemed "acceptable" on the basis of its quality rather than the source providing it. EFPIA has developed a set of principles for good quality information and invites all other information providers to apply the same criteria.

The industry stands ready to play a responsible part in the provision of health information and thus respond to citizens' legitimate right to receive such information.

I declare that I have no conflict of interest.

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1 The Lancet. The direct-to-consumer advertising genie. *Lancet* 2007; **369:** 1.

Age-proofing hospital surge capacity

During major catastrophes, older people suffer disproportionately. It would be unfortunate if an interesting project on hospital surge capacity (Dec 2, p 1984)[1] were to add to the difficulties facing older people in such crises.[2] Older people are the key client group of hospitals, and it is not always clear that the system has adapted to measure and treat the complexity of care that they need. Complexity, functional loss (often undetected), and chronic disease are hallmarks of their presentation to hospitals,[3] and adapting the hospital to cater to these needs can be highly effective. A meta-analysis suggests that the acute geriatric medicine approach gives a benefit similar to that associated with stroke units for stroke.[4]

The absence of a geriatrician on the expert panel in Gabor Kelen and colleagues' study[1] is unfortunate, and a reminder of the task still facing the health-care system to recognise that standard measures of acuity are likely to miss much of the acute health needs of older people, for whom serious illness might present as functional loss or delirium. The low priority given to support for activities of daily living in the study might be yet another manifestation of an agnosia to the expression of illness through functional loss.[5] Kelen and colleagues' suggestion that this model of reverse triage might be used in everyday hospital practice should not be adopted until the system has been shown to support the health and wellbeing of older people to the same extent as younger people.