Medical Research Council

Institute for Environment and Health

IEH report on

PERINATAL DEVELOPMENTAL NEUROTOXICITY

From contributions by Jennifer Court, Vincenzo Cuomo, Per Eriksson, Elaine Perry, Andrew Pickles, David Ray, Patricia Rodier, Mark Stanton, Eric Taylor and Faraneh Varga-Khadem

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This report incorporates the output of a workshop held in March 1995, and has been prepared by the Institute for Environment and Health under the auspices of the Medical Research Council's Neurosciences Approach to Human Health initiative. The workshop was chaired by Trevor Robbins from the Department of Experimental Psychology at the University of Cambridge. The Institute gratefully acknowledges the contribution of all those who attended the workshop and provided material for inclusion in the Report, but assumes no endorsement from these scientists for the conclusions and recommendations contained here.

The views expressed here do not necessarily represent those of any Government Department or Agency.

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Preface

This report, which is based on a workshop hosted by the Institute for Environment and Health in Leicester in March 1995, has been prepared under the auspices of the Medical Research Council's Neurosciences Approach to Human Health (NAHH) initiative. The NAHH initiative aims to encourage high quality innovative research that meets at least one of the following criteria: '(i) uses novel approaches that may lead to an understanding of causation, or to clinical advances in the medium-term in under-researched areas; (ii) exploits opportunities to apply molecular and cellular biology to the understanding of neural mechanisms commonly affected by disease; or (iii) bridges psychological and clinical disciplines within the framework of neurobiology'.

The main text of the report is based on written contributions prepared by a number of authors in advance of the workshop; these contributions have been amended based on the discussions during the workshop.

The report presents an evaluation of the nature and significance of the developmental neurotoxicity of environmental and pharmaceutical agents in the perinatal period and recommends a general strategy for the development of future research.

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Summary

Much of our present knowledge of the adverse effects of chemical agents on human brain development relates to actions at early stages of development, during gestation. However, developmental neuroscience clearly indicates that many potentially sensitive processes (such as cell migration and apoptosis, or synaptic formation and trimming) occur during the post-natal period of brain maturation in both humans and animals. There is also experimental evidence from studies with rats and mice that post-natal exposure to certain environmental and pharmaceutical agents, acting either directly or indirectly on the nervous system, can lead to persisting changes in adult neurochemistry and behaviour. Often these effects are more subtle than classical teratogenic effects, and are seen at dose levels producing no acute toxicity.

There are however a number of problems in extrapolating these experimental studies to man. The first relates to study design. A number of investigations have shown that there are clear developmental time windows of vulnerability to toxic agents, yet most studies involve potentially insensitive conception to weaning exposure schedules. The second is that those researchers who have demonstrated adverse developmental effects in experimental animals have as yet used endpoints (such as open field behaviour) that are either too crude to yield information about mechanisms or are too limited in scope (such as changes in a single receptor type). Better understanding of the mechanisms involved is needed for prediction of risks to humans. In addition, clinical studies have been hampered by the difficulty of defining dose and period of exposure retrospectively, and of eliminating confounding variables.

Before further progress can be made, a more integrated and multidisciplinary approach is needed, drawing on a wider range of applied and fundamental scientific expertise. Standardised behavioural and other indices capable of being used in both animals and humans are available from the general neurosciences, and should be applied in toxicologically appropriate study designs. In clinical research a prospective cohort study of a defined population, such as neonates given analgesics, would be of value.