Basic and Therapeutic Aspects of Perinatal Pharmacology

Editors
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F. Sereni

MONOGRAPHS OF THE MARIO NEGRI INSTITUTE
FOR PHARMACOLOGICAL RESEARCH, MILAN

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PREFACE

It has become increasingly evident in recent years that extrapolation of pharmacologic data from adults to infants, corrected only for differences in size, is frequently meaningless and occasionally dangerous.

The importance of the *qualitative* differences between infants and adults has been shown by many studies. These differences are particularly significant in regard to specific pharmacologic processes including the absorption, distribution, biotransformation, and excretion of drugs. Drug protein binding is also affected by age. Sensitivity of newborn organisms to certain drugs can vary considerably from that of the adult.

Furthermore, the transfer of drugs or their metabolites, or both, through the placenta to the fetus or through maternal milk to the breast-fed infant is a problem unique to perinatal pharmacology. Very little is known about the long-term effects that such transfer or direct drug administration has on the development of the infant's various organs, resulting in physical and behavioral changes.

Most of these problems can be solved only through a concerted multidisciplinary effort, involving close cooperation and an exchange of information among scientists engaged in both basic and clinical research.

It is hoped that this volume, based on a symposium held in Milan on June 17 to 19, 1974, that brought together distinguished scientists from many countries and many disciplines, will contribute to this effort.

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Perinatal Pharmacology: An Introduction

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Perinatal pharmacology as a subdivision of developmental pharmacology should include studies of that period of life before and shortly after birth. The goals of the field are similar to all of pharmacology: the examination of the adverse and therapeutic effects of pharmaceutical agents. This study should consist not only of these mission-oriented goals, but must also include a scholarly examination of basic physiologic and biochemical phenomena. Most important is that the realistic biologic responsibilities of perinatal pharmacology include the complex integrated physiologic unit consisting of mother, uterus, placenta, and fetus. All organs and organisms in this unit are at different stages of development, and the system truly presents a pharmacologic challenge. The neonate, although less complex physiologically, manifests a number of very special pharmacologic problems not encountered in the mature organism. It is deplorable that the overt appreciation of the general medical and legislative public for the special considerations of drug usage in mother and child required the clinical calamities of chloramphenicol, thalidomide, and other drugs. As with many startling events, there were derived benefits in knowledge and caution, intertwined with overt hysteria and restrictive action. However, the possibility for creative advance in this field is great, with an eventual benefit to mother and child.

I would like to consider a few aspects of perinatal pharmacology and particularly concentrate on (1) the general action of drugs in the perinatal environment; (2) some specific examples of these actions directly on metabolic and genetic systems, as well as interaction with other environmental factors, such as nutrients; and finally (3) the potentiality for future practical contributions of perinatal pharmacology to clinical medicine.

A drug, when administered, can act directly on a metabolic system and thereby stimulate or inhibit a set of reactions which result in a predetermined physiologic effect. The potentiality for a drug to be toxic is related to the perturbation of the physiology so severely that the individual demonstrates disease. This effect can either be direct or result from interference with other specific pathways, or by interaction with other agents. Also, it has been shown

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that a number of agents, particularly steroids, phenobarbital, and thyroxin, exert their pharmacologic effect by determination of the rate of synthesis or degradation of an enzyme.

In the case of the fetus or infant, we encounter a system in the kinetic state of development where one metabolic time period of observation does not necessarily resemble the next. This kinetic biologic state makes perinatal biology a difficult but most exciting field. It is a biology of constant change, constituting a flow from immaturity to maturity.

The general cellular phenomena of proliferation and differentiation of cells is most prevalent in the immature organism, but continues throughout life in many specific organs. Proliferation is carried on by all cells sometime during their life span, and differentiation endows these cells with a specialness. All cells are not the same during proliferation; and although there must be some molecular degree of predetermination, there are basic distinctive biologic mechanisms of cell division which are shared by all proliferating cells. All differentiated cells are dissimilar, but they share some similar life-preserving processes. Both differentiation and proliferation are genetically controlled. The fetus or neonate not only differs from the adult in that the development of certain cells occurs at different stages, but also in the general functional aspects of the organisms that emanate from these major differences in cellular biology. The adult and the fetus are the same in that, regardless of their differences, their biology is appropriate to their particular environment and both have specific metabolic needs which are required for adaptation. In the case of the fetus or neonate, there is particular sensitivity to disruption of environment, and ability to adapt is fleeting since we are dealing with an exquisitely time-dependent system.

A number of these thoughts have been incorporated into reviews on teratology and perinatal medication (Pomerance and Yaffe, 1973). It has been clearly shown that some drugs or macromolecules (viruses) have specific deleterious actions on particular organ systems at certain distinct times during embryogenesis. The teratologic effect of a drug is dependent on its ability to cross the placenta and upon the specific period of development during which it is administered. A most fascinating example for me is the recent data that have accumulated regarding diphenylhydantoin.

Diphenylhydantoin (DPH) traverses the placenta with ease, and, as shown by Mirkin (1971) and others, the concentration in cord blood is approximately that found in maternal blood. There are a number of congenital malformations associated with anticonvulsant therapy, particularly those involving the palate (Hill, Horning, and Horning, 1973). Data from Hauser and Kurland (1975) indicate that in a total group of 284 children from 138 women with epilepsy, there were 141 children born from mothers who received one or more anticonvulsants. Of these 141, there were 10 or more with serious malformations; 5 had congenital cardiac malformation, 2 had cleft palate, and the remainder had a variety of anomalies. In contrast, there