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Developmental Pharmacology: Overview

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Developmental pharmacology is an area of research with which I have been associated since 1955. My major interests have concerned the processes of chemical and drug metabolism and how these change from fetus, to newborn, to adult, to the aged; all of my work has been done in animals. The discipline of developmental pharmacology, if we can refer to it as that, is an outgrowth of a very real therapeutic dilemma—how to treat illness and disease with drugs in the very young or very old patient.

When I first began my work in this area in the early 1950's, few data were available about the reasons for differences in drug response between newborns, young adult, and aged animals. Outside a few research-oriented centers there was little awareness that very young patients were perhaps not just very small adults for purposes of calculating drug dosage.

It has been fairly easy to propose reasons for drug actions being different in fetus and newborn and to test some of these hypotheses. This was not so easily done in the very old animal, and even today, developmental pharmacology almost always uses young, not aged, subjects.

Major determinants of drug effects include the processes of disposition—absorption, distribution including storage, metabolism, and excretion—as well as interaction between drug and receptor sites.

Drug-receptor site interactions at the time I first entered the field were relatively difficult to isolate, identify, and quantify. The result of drug-receptor interactions—namely, drug response—is not what I am talking about, though in very young animals, even this latter is often not easy to study. At present, this interaction of drug and receptor is the most neglected area of developmental pharmacology, in my opinion. We now have some elegant new tools for carrying out such drug-receptor interaction studies and I hope they will soon be made in increasing numbers. The relative lack of research in this area is emphasized by the program of this session: no one is scheduled to talk about it and I doubt that it will be more than a peripheral issue of any speaker at this conference.

Yet we know that receptor sites for drugs and chemicals are different in the fetus, newborn, and adult and are probably different in the aged. We know these differences are quantitative and probably qualitative as well. Myriad examples can be given for almost all classes of drugs—these are not often remembered and even less explained or subjected to experimental study.

Even in the areas where we have spent most of our efforts—disposition—there is a lot of uncovered territory. We now have considerable information about drug metabolism in the liver of fetus, newborn, and adult. We do not know to what extent the changes seen in hepatic drug metabolism in the aged are the result of liver damage and to what extent they are due to uncomplicated senescence (if there is such a thing). We know very little about drug metabolism in organs other than the liver. My own laboratory has done quite a bit of work on drug and chemical metabolism by extrahepatic tissues, but there is much left to do, especially with humans. Considerable controversy has arisen as to the development of drug-metabolism enzymes in human ver-

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sus animal livers. In all animal species examined thus far, drug metabolism by liver is very low or absent in the fetus until just before birth. In a variety of studies done on abortuses both here and in Scandinavia there appears to be measurable drug metabolism in mid- and late-term fetuses. Perhaps Dr. Lucier will speak to this problem, but, suffice to say, at this point—in drug metabolism—the area where more work has been done than any other—we still have large gaps in our knowledge of differences in function between fetal, newborn, adult, and aged animals and humans, and outside of one organ—the liver—we have virtually no knowledge at all.

Other processes of disposition have been even less studied. Recently some good studies on renal and biliary excretion of drugs and chemicals in newborn and adult animals have been made. A few studies on distribution and storage of chemicals in fetal, newborn, and adult animals have indicated differences in these processes with age as well. Whole body autoradiography has been especially helpful in these studies of chemical distribution and storage at different ages.

Occasionally a report has been made of differences between adult and young animals in the binding of drugs. Most of these studies deal with serum protein—drug interactions and are often confounded by both the qualitative and quantitative differences between adult and fetal blood constituents and proteins. Few if any studies have been made on differences between adult and fetal or newborn tissue binding of drugs; this also gets back to the original consideration I made concerning drug-receptor interactions, since receptors for most drugs are in tissues, not blood.

Pharmacokinetics can tell us much about processes of disposition, so I look forward to hearing from Dr. Singh about the developmental pharmacokinetics. I think the application of this tool to developmental pharmacology is long overdue, and I hope the results of these studies will be as useful as I feel they will be.

Finally, the role of both environment and heredity in the development of all systems interacting with drugs has been very much neglected until recently. From all we know, it seems likely that both environment and heredity will have determining roles at all ages in how a drug is handled, as well as what drug receptors are available, what their affinity for the drug will be, and what will be their intrinsic power to cause effects after they have reacted with the drug. It seems reasonable to expect that subsets of our population will have drug handling and drug receptor mechanisms that are different, both qualitatively and quantitatively, as determined by genetics. It also seems probable that environmental factors can influence these drug handling and drug receptor systems differently in genetically different subsets of a population. I look forward to hearing what Dr. Nebert has to say about this aspect of the field.

In short, we will consider a few of the very active areas of research in developmental pharmacology. We certainly need to remember that our knowledge even in the best-researched aspects is only rudimentary. I hope this session can clearly identify where future work may be most productive.