Book Reviews

Teratogenicity: An Epidemiological Study

Birth Defects and Drugs in Pregnancy. OLLI P. HEINONEN, DENNIS SLONE, and SAMUEL SHAPIRO with seven others. Publishing Sciences Group, Littleton, Mass., 1977. xii, 516 pp. $75.

The harm that the drug thalidomide can do to the human embryo when taken in early pregnancy was not recognized until thousands of affected children had been born. Yet thalidomide was almost as easy a teratogen to recognize as one could wish for: restricted to certain countries, becoming very popular in some of them within a few years of its introduction, and causing a very high proportion of exposed embryos to develop malformations of types that are very obvious and in the unexposed very rare. A teratogenic drug that did not meet these conditions would not necessarily be recognized as such even by the more elaborate teratogenicity testing of new products in the laboratory and the monitoring of malformation rates in human populations that are routine today. Studies relating the frequency of human birth defects to drug use in early pregnancy, preferably recorded prospectively, are therefore needed as well, especially as evidence whether there are any teratogens among the drugs whose use was well established before routine testing and monitoring started.

This book is the definitive account of probably the most successful attempt so far made to meet the need for relating the use of drugs of all kinds to pregnancy outcome in humans. The data studied were those of the Collaborative Perinatal Project, an investigation based on more than 50,000 pregnancies that came under the care of 12 medical centers in the United States during 1959–1965. Drug use and numerous other particulars of these pregnancies were recorded antenatally and linked to details of the offspring's condition at birth and later.

In the first half of the book, the frequency with which 18 classes and subclasses of malformations occurred in these children is examined in relation to a variety of factors other than drug use, including attributes of the conceptus, the mother, and other relatives. Most of the 18 malformation categories refer to particular systems of the body or to specific types of defects. Estimates are included of the extent to which the malformations in each category would vary in frequency with each attribute if the rest of the attributes were held constant.

The second half of the book deals mainly with the relation of drug use to the frequency of malformations in each category. For 14 main groups of drugs and for the more important subgroups and individual drugs they include, the numbers of malformations in each category that were observed in children whose mothers used the drugs in early pregnancy are given, together with the numbers to be expected in each category (calculated on the assumption that the drugs did not affect risk but taking the drug users' other attributes into account) and the ratios between the observed and expected numbers. The book concludes by enumerating selected associations between drugs used in early pregnancy and *specific* malformations and between drugs taken at any time in pregnancy and certain defects that could arise late in intrauterine life.

Both the methodology and the results merit attention. The methodology used in adjusting the drug-related risks to allow for the effects of other attributes was unusually rigorous and deserves to be considered by all students of risk factors in human populations. Its main feature was the computation of multiple logistic risk functions (estimates of risk that can take any number of attributes into account) for each child. The risk functions of the children in each drug user group were then summed to give the group's "expected" number of malformations for comparison with the number observed. This approach does not correct all biases—its results could be falsely negative for a teratogen that was always given for the same disease and falsely positive for a harmless drug that tended to be taken with teratogenic ones—but for most drugs it can provide estimates of risk that are likely to be relatively undistorted by associations with other attributes. However, it may sometimes be misleading to control, as these authors did, for attributes such as hydramnios and low birth weight that are more likely to result from malformations than to cause them. Controlling for hydramnios, for example, may well have resulted in underestimation of the relative risk of central nervous system defects in the offspring of diabetics, since hydramnios is associated with both diabetes and central nervous system defects.

Perhaps because of such overcontrolling of the so-called "expected" numbers of malformations in the various drug user groups, the proportion of observed to expected ratios that exhibited differences from unity significant at the 5 percent level was remarkably low—no more than 3.8 percent (63 of the 1662 ratios examined), less than the 5 percent to be expected by chance alone. Fifty-six of the 63 ratios were greater than unity, which, like the possibility of overcontrolling, may rather weaken the support that the overall deficiency of statistically significant results provides for the view that few if any of the drugs considered are demonstrably teratogenic; but the findings are entirely compatible with this view.

It would clearly be unwise, however, to dismiss all 63 significant results as chance findings—or for that matter to accept as nonteratogenic every drug for which the results were not significant—without looking at other data. There is already some independent evidence that human malformations are occasionally caused by some drugs (exogenous female sex hormones) that were significantly associated with certain defects in the study under review, and also by one drug (the anticonvulsant phenytoin) that was not. The data in the book suggest various other etiological hypotheses that need independent testing; they will also be useful for testing hypotheses generated elsewhere. The latter may well be their most important function if past experience is any guide; the first hint that a drug or disease is teratogenic has generally come from one or more alert clinicians reflecting on their experience, rather than from any systematic epidemiological study of the type reported here, but such studies have contributed substantially by enabling clinical hunches to be tested, refined, and quantified. One hopes this study will do the same.

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