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Drug-Induced Teratogenesis

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ABSTRACT

The probability that a teratogen, applied to a pregnant mammal, will produce malformations in the embryo depends on the agent, the dose, the species, the genetic constitution of mother and embryo, and the developmental stage of the embryo. Several drugs (including salicylates and antibiotics) now being used in medical practice are teratogenic in experimental animals, some at doses comparable, on a body-weight basis, to those used therapeutically. Demonstration of teratogenicity in experimental animals can serve as a warning of possible teratogenic effects in man, and as a guide to the types of malformations the drug might produce, but failure to demonstrate teratogenic effects experimentally does not prove the drug's harmlessness to the human embryo. If thalidomide had produced only common malformations, such as cleft lip, its teratogenic nature might still be unrecognized. The final test must be careful follow-up of babies born to mothers who have taken the drug in question.

IT HAS been known for some time that congenital malformations can be produced in mammalian embryos by exposing their mothers to a variety of physical or chemical agents (teratogens) during pregnancy.[1] A number of such agents are known to affect man, but the problem has recently become prominent because of the discovery that thalidomide, widely used in some countries as a "sleeping pill" or antinauseant, is highly teratogenic to human beings.[2-4] Questions are now being asked about possible measures to ensure that medications likely to be taken by pregnant women will not harm the embryo. The following principles, established in experimental teratology, are relevant to the problem.[5, 10]

It is probable that each teratogen produces developmental errors by specific pharmacological actions on particular embryonic tissues. Thus each teratogen produces a characteristic array of defects, presumably depending on what metabolic pathways it interferes with at a given stage of development. This array is often similar, but not by any means identical, in different species. Little is known, as yet, of the specific developmental mechanisms involved, which may range from death of certain groups of cells at sensitive stages, to mitotic aberrations, to altered embryonic inductive relationships, to cell surface or other changes altering cell migrations or tissue movements, to interference with other aspects of morphogenetic mechanisms such as the properties of acid mucopolysaccharides or enzymatic activities.

Virtually all types of malformation known in man can be produced experimentally in animals. Furthermore, evidence is accumulating that drugs administered prenatally may also have harmful postnatal effects. For instance, adrenaline given during pregnancy may influence the behaviour of the offspring in rats and mice,[7] and hypertensive agents (aldosterone, desoxycorticosterone acetate (DCA), low potassium diet; etc.) given during pregnancy may produce hypertension in the offspring of rats.[8]

Agents that cause malformations will usually, at the same or somewhat higher dosages, kill embryos. However, some agents that will cause abortion or resorption of embryos have not been shown to be teratogenic, and the ratio of teratogenic, to embryonic-lethal, to maternal-lethal dose varies widely from agent to agent.[9]

The types of malformations produced depend on the stage of embryonic development at which the agent is applied. Malformations are, in general, not produced in organs that have completed their development at the time when the agent is given. For a particular organ, the stage at which its de-

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velopment is most likely to be deranged by a teratogen (the "critical period") may be at the time when organogenesis is proceeding rapidly, or at some earlier stage, perhaps even before there is a visible primordium of the organ. The critical period for a particular organ may be different for different teratogens. Therefore one cannot predict for a teratogen what stage of development must be treated to obtain a given malformation, or predict from a malformation the stage at which the embryo had been exposed to the teratogen.

The frequency with which a malformation is produced by a teratogen may vary with a variety of environmental (as far as the embryo is concerned) factors such as maternal weight, and position of the embryo in the uterus. Moreover, two teratogens, used at doses at which neither would produce malformations when used singly, may cause a high frequency of malformations when given together.

The frequency with which malformations are produced by a teratogen varies with the genetic constitution of the treated animal.[6, 10] There are marked species differences in teratogenicity—for instance, cortisone given during pregnancy will produce cleft palate in the mouse and rabbit, but not in the rat. The mouse appears to be one of the species most sensitive to teratogens. Even within a species the genotype influences markedly the frequency of induced malformations, e.g. the same dose of cortisone in the mouse may produce cleft palate in anywhere from 4% to 100% of cases, depending on the genotype of the animals studied. Both the embryo's and the mother's genes are involved, and the genetic differences are specific to particular organs. Thus in one mouse strain a maternal riboflavin deficiency may produce a high frequency of cleft palate and a low frequency of limb defects, and in another strain the reverse situation may occur. Perhaps this accounts, at least in part, for the fact that substances which are teratogenic for humans, such as thalidomide, may affect some embryos and not others. In any case, the existence of inter- and intra-species differences in drug response complicates the problem of testing new drugs for possible teratogenicity in man.

There are already a number of drugs in medical use that are known to be teratogenic in animals, including adrenaline, androgens, antileukemic agents, corticosteroids, estrogens, insulin, penicillin plus streptomycin, posterior pituitary extract, progestins, salicylates, oxytetracycline, tetracycline, thalidomide and tolbutamide.[1-4] Of these, the antileukemic agents (busulfan, aminopterin), estrogens, androgens and progestins, and thalidomide are known to be teratogenic in man as well. Others are only suspected.

It should be emphasized that the teratogenic nature of thalidomide was recognized only because it produced a rare and rather specific combination of defects. A sudden increase in frequency of this unusual syndrome led Lenz[2] to search for its cause. If thalidomide (or aspirin, for that matter) produced a more common type of defect such as cleft lip and palate or spina bifida in, say, 5% of cases where it was taken in the first trimester, it would probably not have been suspected.

The ratio of teratogenic dose in animals to therapeutic dose in man, on a per unit body weight basis, varies widely from drug to drug, and species to species. The dose of cortisone required to produce cleft palate in the mouse is roughly 400 times the therapeutic dose in man. For cortisone in the rabbit the ratio is about 20, and for tetracycline in the rat it is about 1.

A screening procedure to detect teratogenic properties of new drugs in experimental animals would not, of course, permit extrapolation of results of such studies to man, but nevertheless would indicate some of the possible dangers. The drug should be tested on several species, including the mouse, at dosages that will reduce litter size somewhat, and should probably be given for a period of about two days, rather than continuously throughout pregnancy. A series of such trials should be arranged to cover the period at least from implantation to term.

Failure to demonstrate that a drug produces malformations under these circumstances is not a guarantee that it will be harmless to all human embryos, but a drug that was found to be not demonstrably teratogenic in animals would occasion less cause for concern than one that was. Conversely, a drug that was teratogenic in animals would not necessarily be so in man, but one would be alerted to this possibility, and would have some idea of the types of defect that it might produce.

There is need for a program in which all drugs given to a population of pregnant women are recorded at the time of treatment, and the babies of these women are examined at birth, and again later in life, for malformations and other possible harmful effects. This is particularly important in the case of new drugs. In any case it is clear that medications should not be given to pregnant women without a definite medical indication and a reasonable expectation of benefit to the mother.

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