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VI. CONCLUSIONS

Among the various adverse effects of drugs and other chemical agents, their potential action during intra-uterine life is of particular concern because of its irreversible nature.

In order to present a critical evaluation of the present methods of assessing teratogenicity, it was necessary to make as complete an analysis as possible of the various factors involved in the production of congenital malformations.

Although it was recognized that certain agents might act directly on the genetic material by inducing mutations which lead to developmental defects, the group did not discuss mutagenicity testing because this particular problem has recently been treated by a panel of the World Health Organization.

Therefore particular attention was devoted to the aetiology of congenital malformations with special reference to the role of genetic factors, the importance of the physiology of prenatal development, and placental function. This required an extensive review of the available methods for detecting teratogenic potential of drugs and other chemical agents to which the maternal organism may be exposed. Therefore, the conditions involved in teratogenic reactions, the selection of animal species, the choice of doses, the number of animals, and the predictive value of experimental data as well as the eventual priorities in teratogenic drug testing, were considered.

Malformations may be induced in man by external agents (especially by drugs) and they must be viewed against the background of spontaneous malformations. An appreciable number of them are considered to be of genetic origin, i.e. due to point mutations or chromosomal aberrations.

The nature and origin of spontaneous malformations occurring in man is of prime importance in formulating a general concept of methods that may be considered adequate to analyse the possible factors in the laboratory animal.

Chromosomal changes may be diagnosed by karyotypic studies. They represent about $^1/_{10}$ of the total number of human malformations. Point mutations are recognized by their hereditary transmission. Their incidence is estimated at less than $^1/_{10}$ of the total malformation rate. The majority of the malformations are considered to be of multifactorial origin to which exogenous factors may contribute, although at an unknown rate.

Two types of method are used in the study of the aetiology of congenital malformations: prospective or retrospective epidemiological studies, and animal experiments. Although epidemiological investigations have yielded a number of valuable results, the interpretation of the data is beset with difficulties because of the large number of potentially causal factors that might intervene in human pregnancy. By contrast, experimental investigations are performed on laboratory animals under strictly controlled conditions.

The basic principles of testing for teratogenicity are similar to those underlying the detection of general toxicity except that the action of an injurious agent on the embryo is more complex than its action on the adult. In terato-

genesis, one is dealing with two interdependent biological systems, the pregnant female and the embryo; the specific reactions of each may be entirely different.

The embryo encounters profoundly changing conditions as functions are assumed while the organs are developing. The initial stages of the growing conceptus are in fact governed by effects at the cellular level. Thereafter, morphogenetic movements determined by sequential induction processes mark the modelling of the early embryo. In this most critical period the specific organ functions have not yet developed and detoxification processes such as are present in the adult organism are not available. This is the phase of greatest sensitivity to teratogens. Specific enzyme functions characteristic of the future organs begin in the anlagen. The general metabolic functions are oriented to anaerobic glycolysis. Later on, when the embryo differentiates into a foetus, most metabolic functions are still taken care of by the maternal organism, the foetal functions being restricted to circulation and renal excretion. Certain organ systems which differentiate at later stages, like the external genitalia, or histogenetic processes which last for the entire prenatal period, like the nervous system, remain vulnerable to factors interfering with their development.

At birth, metabolic functions are switched to catabolism. All the energy previously stored as glycogen and lipid during foetal life is required for thermogenesis, the assumption of respiration, and motility. Early postnatal life is thus partly conditioned by the stage of maturation achieved.

The placental functions are very complex and little understood. Unfortunately this is particularly true of the early trophoblast stages, which coincide with the period of maximum teratogenesis.

Some of the modalities of active or passive transfer of chemical agents via the placenta have been investigated. Although placental transfer is important it is not the essential determinant of embryotoxicity or of teratogenicity. Direct effects on placental function or haemodynamics are possible and these may favour certain malformations, without any transplacental transfer of a chemical being implied.

To produce a congenital malformation, not only has the agent or its metabolites to be present in the appropriate amount, but it also has to act at a very precise moment in the course of morphogenesis. In addition, the embryo must have the suitable genetic susceptibility to react.

To a large extent these conditions can be made to prevail in experiments on laboratory animals. It may be assumed however that they are only exceptionally prevalent during the development of the human foetus. This may be one of the possible reasons why, of a rather large variety of agents that are known to produce congenital malformations in laboratory animals, only a few are suspected of having a teratogenic effect in humans.

Through analysis of the data available at present, an attempt was made to establish a generally acceptable methodology. The agent is administered by the route that is most relevant to human intake.

Several, usually three, dose levels are employed and for each dose 10 to 20 pregnant animals are considered sufficient to give interpretable results. The animals are treated during the entire period of organogenesis or for a limited amount of time when only a sequential method is used.

Special problems are raised by certain chemicals, such as antibiotics capable of altering the intestinal flora, compounds with enzymatic activity, psychotropic drugs which are lactogenic hormone releasers, and steroid hormones. In these cases, primary and secondary effects have to be distinguished.

One of the main difficulties in extrapolating experimental results is due to the fact that the various animal species, or strains of the same species, or even individuals, may vary in their reaction to an injurious agent. To some extent, these difficulties can be overcome by using several species and a large enough number of test animals to produce statistically valid data with respect to the parameter(s) under study.

According to present knowledge, rodents and/or lagomorphs can be expected to yield results that are of relevance to man. The predictive value of studies in these species seems to be at least as great as that of experiments in other species, including non-human primates.

For routine teratogenicity screening at least two species, a rodent species (the rat or the mouse) and a lagomorph (the rabbit), should be used.

The use of more than one species seems necessary because many known teratogens produce a positive effect in only one species. Difficulty in interpretation may emerge, however, when a potential drug or other new chemical substance produces a teratogenic effect in this way. Unless it is possible to explain the factor(s) implicated in this effect and it can be confidently stated that it has no bearing on the situation of the human, possible relevance for man must be assumed.

Until the basic mechanisms of teratogenicity are better understood, it will be impossible to design more relevant testing procedures. Neither the chemical structure nor the biological activities of a compound give a valid indication of its teratogenic potential.

The predictive value with regard to man of results obtained by teratogenic testing is not known at present. In spite of this, there is no alternative way of obtaining some guidance when a possible hazard is to be assessed.

The evaluation of a possible teratogenic risk should be made by taking into consideration all the circumstances under which the results were obtained; e.g. frequency of the anomalies, dose-response relationship, number of species in which anomalies occur, and similarities with reference compounds.

Provided teratogenicity experiments are performed by an experienced investigator under standard laboratory conditions and on a sufficiently large scale, the results may be considered to give a valid and relevant indication of the possibility of interference with important developmental processes. The present testing methods therefore appear to be satisfactory as far as safety evaluation is concerned. It must be borne in mind, however, that

animals may have a specific teratogenic susceptibility and may yield "false positive" results. Therefore the interpretation of positive laboratory data can only be attempted by taking all the known aspects of the biological activity of a compound into consideration.

From the experimental data gained in recent years it is concluded that suspected noxious actions of drugs on the embryo were detected by proper experimentation.

The characteristics of a compound must be taken into account when discussing priorities of testing, e.g. chemical structure and intended use.

In general, animal tests for teratogenicity should be performed in support of clinical trials of a new drug.

Tests should also be extended to known drugs in widespread use. Compounds of that sort offer the advantage of the large experience gained in a large human population for a comparatively long period of time. Therefore it is of considerable scientific interest to evaluate such compounds in teratogenicity studies on animals. Such information may form the basis for future attempts to estimate the predictive value with regard to humans of animal experiments in this field.

The prospects of identifying teratogenic agents seem favourable and as more experience is gained by animal experiments and human epidemiological studies, preventive measures may become a possibility.

Since, among many predisposing factors, the genetic component may be an important determinant in experimental teratogenicity experiments using particularly susceptible species or strains of laboratory animals, it may be useful to elucidate the importance of different genetic mechanisms in the development of congenital malformations.

The development of these different lines of investigation may lead in the future to a better insight into teratological mechanisms and consequently to valuable improvements in teratogenic drug testing.

REFERENCES

Barrow, M. V. and Taylor, W. J. (1969), J. Morph. *127*, 291.

Boué, J., Boué, A., Philippe, E., Giroud, A. and Deluchat, C. (1973), Bull. Europ. Soc. Hum. Genet. *32*.

Chaube, S. and Murphy, M. L. (1968), in: Advances in Teratology, D. H. M. Woollam ed., vol. 3, p. 181.

Dawson, A. B. (1926), Stain Tech. *1*, 123.

Degenhardt, K. and Koller, S. (1973), personal communication.

Fraser F. C., Kalter, H., Walker, B. E. and Fainstat, T. D. (1954), J. Cell Comp. Physiol. *43*, suppl. 1, 237.

Fritz, H. and Hess, R. (1970), Teratology *3*, 331.

Gregg, N. (1941), Trans. Ophthal. Soc. Aust. *3*, 35.

Jacobs, P. A., Frankiewicz, A. and Law, Z. (1972), Ann. Human Genet. *35*, 301.

Kohler, E. (1970), in: Metabolic Pathways in Mammalian Embryos During Organogenesis and its Modification by Drugs, Freie Universität Berlin, p. 17.