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I. INTRODUCTION

Twelve years ago, an unexpected side effect of a drug on the conceptus was suddenly revealed. The dramatic circumstances of this discovery, and the limited scientific knowledge that was available at that time about developmental physiology and foetal pharmacology, led to a rather pessimistic appraisal of this type of adverse and irreversible action on the growing embryo. The possibility of a teratogenic hazard, particularly one caused by drugs, tended to be overemphasized, almost to the extent of jeopardizing any further therapeutic progress. It seemed that the only way to escape the potential danger of drugs for the growing embryo, was to deprive women for half of their lifetime of the benefit of efficient therapeutic agents.

To meet the most urgent needs, the World Health Organization convened a scientific group to devise appropriate methods for the testing of drugs for teratogenicity (1967). General principles were elaborated. These recommendations still constitute the framework of the experimental methods in teratogenicity testing as well as the point of reference of many basic research programmes.

However, many difficulties still exist in teratogenic drug screening and in the interpretation of experimental results.

The Swiss Academy of Medical Sciences was aware of the fact that, in recent years, a deeper insight into the nature of teratogenic effects has been gained and the reliability of the experimental methods used in their detection has been enhanced. In the hope of using this knowledge to augment the predictive force of teratological studies and formulate a realistic policy towards the evaluation of teratogenicity of drugs and other chemicals, an expert committee has been convened.

The aim of the group was to analyse the circumstances in which a teratogenic accident can occur and to define the most accurate experimental methods likely to disclose noxious agents.

It was understood that any recommendations emerging as a result of the work of the committee should remain flexible enough to be amended following further progress in reproductive physiology and foetal pharmacology.

Practical screening methods are based on the available scientific knowledge. Therefore it was felt that the recommendations of the group should be elaborated in the light of the basic principles of teratology.

A critical analysis was made of the various aspects of teratology, from the genetic, the epidemiological, the physiological and the pharmacological points of view.

This survey revealed the complexity of the aetiology of congenital malformations and hence the difficulties encountered in epidemiological investigation of demonstrating a causal relationship between an environmental factor and a birth defect.

Since such investigations require very large samples and long-term studies, the experimental methods, despite their limitations, probably constitute a more realistic and efficient approach to the detection of the teratogenic potential of environmental agents, particularly of drugs and other chemical agents.

It is often very difficult to make a clear distinction in the aetiology of many malformations between environmental and genetic causes, since some genetic dispositions display a greater susceptibility to the teratogenic agents of the environment than others.

The basic principles of testing for teratogenicity are similar to those underlying the detection of toxicity in general, except that the action of an injurious agent on the embryo is more complex than its action on the mature organism. In teratogenesis one is dealing with two biological systems – the pregnant female and the embryo – the specific reactions of which may be completely different. For instance, a drug innocuous to the female may be apt to kill the embryo or produce congenital malformations. The problem is further complicated by the fact that all types of disturbed development may occur through spontaneous mutation. An effect of treatment can therefore only be assumed if the incidence of the particular change is significantly higher than that observed in controls, or in a large population suitable for comparison. Furthermore, a dose-response relationship has to be established.

Embryolethality, embryotoxicity and foetotoxicity are changes that result from entirely non-specific interference with intra-uterine development and growth. Effects of this kind are not indicative of a teratogenic action; they may be induced by a large variety of chemical substances provided that sufficiently high doses are administered. Non-characteristic effects in the young are frequently observed at dose levels that cause symptoms and toxicity in the mother animal.

The significance of results obtained in such conditions, the high dose effects, the statistical evaluation of experimental data, and the particular problems raised by certain drugs have been discussed in the light of the experience gained in various research centres.

Although there are still many gaps in our knowledge of teratogenic mechanisms, and it might consequently seem hazardous to predict drug effects on man from data on laboratory animals, there is at the present time no satisfactory alternative.

From the present experience it might be assumed that there is no basic difference in susceptibility to a given teratogenic agent between man and the various mammalian species. Nevertheless if a teratogenic effect is observed as a result of treatment under the conditions of a particular experiment, it must be borne in mind that such effects are very often species-specific.

For this reason great caution must be exercised in extrapolating from animal experiments to man. However, it cannot be excluded, *a priori*, that a compound found to be teratogenic in laboratory animals may have similar effects in the human being. This fact is set forth in a report of the World

Health Organization (1972): "Modern animal toxicity studies even when supplemented by careful human pharmacology studies and clinical trials, still fail to detect certain delayed effects, novel types of toxicity effects that may be unpredictable owing to genetic variables, interactions between disease and drugs, and interactions among drugs themselves".

Despite the complexity of the problems involved in teratogenicity, the results obtained with the teratogenic screening methods, which were devised only a few years ago, compare favourably with those of general toxicology.

Although the ideal animal species whose embryo would react in all circumstances like the human embryo is non-existent, there are good reasons to think that the present difficulties in the evaluation of experimental data will be overcome by a better knowledge of teratogenic mechanisms and future progress in foetal pharmacology.