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I think that the type of work described by Dr. LUTWAK-MANN and by Dr. KEBERLE is of the greatest importance since it is only on the basis of studies such as these that we can expect to understand the mechanism of action of embryopathic agents.

To understand the mechanism of action of a chemical teratogen requires knowledge of two different sets of factors. Firstly, one should understand the pharmacodynamic properties of the noxious agent–its absorption, distribution, its metabolic fate, particularly whether it is metabolized to toxic metabolites, its penetration to the embryo and possible accumulation in the embryo. Our level of knowledge is such that we can usually determine these properties of a compound with relative ease. The second factor is knowledge of the biochemistry of the embryo. Devising a plausible mechanism of embryotoxicity requires knowledge of the biochemical architecture of the embryo and it is here that we are sadly lacking. I feel that if we are to understand better the mechanism of action of embryotoxic agents this will depend to some extent on our accumulating a more adequate picture of the 'chemical morphology' of the developing embryo.

Thalidomide, on which we have been working for the last three years, is a good case in point. Whereas I think we now know a great deal about the pharmacodynamic properties of thalidomide–its behaviour in the mother and the embryo–our lack of knowledge concerning the biochemistry of embryonic development does not permit the ready formulation of ideas on a biochemical basis regarding its mechanism of action.

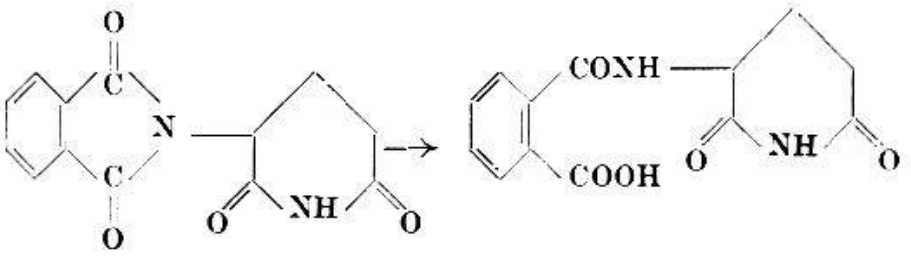
However, I think that a number of points may be made concerning the embryotoxic action of thalidomide.

1. We believe the effect is probably a direct one on the embryo and its membranes and contents and the embryotoxicity is not a secondary effect of a primary action on the mother. This fact is indicated by the embryotoxic action of thalidomide on the development of the hen's egg and the tadpole. The readiness with which maternally administered thalidomide penetrates the rabbit blastocyst also indicates the feasibility of a direct effect on the mammalian embryo.

2. The problem of which is the teratogenic agent—thalidomide or a metabolite? In the experiments of Dr. KEBERLE and his group and ourselves in which the metabolites were administered to pregnant rabbits, in no case did they appear to have embryopathic properties. However, whether this inactivity is real or is a reflection of the inability of the metabolites to penetrate to the embryo has been a polemical issue. We have found that the ^{14}C-labelled metabolites, following their maternal administration, are able to penetrate to the blastocyst and to persist. If the metabolites in the yolk-sac fluid are able to penetrate to the embryo—and we are at present carrying out experiments to check this—one must conclude that in all probability the embryopathic effects of thalidomide are due to the compound itself and not to a metabolite.

3. Regarding the embryotoxic mechanism of thalidomide, we are of the opinion that in all probability, the teratogen exerts its effect by influencing a mechanism which is specifically involved in morphogenesis. Otherwise its lack of effect on mature cells and on regenerating cells—even when applied in massive concentration—is difficult to explain.

Our own views concerning the mechanism of action of thalidomide have been stimulated by certain observations regarding the relationship between chemical structure and embryotoxic activity. Briefly, the results led us to the conclusion that the embryotoxic properties of the compound were determined by the phthalimide moiety of the molecule. The problem then arises as to the possible significance of the N-substituted phthalimide structure in biological systems. One interesting property of the phthalimide group of thalidomide is its high chemical reactivity. Thus, it readily reacts with water undergoing hydrolysis and in effect acylates the hydroxyl group of water to give α-(o-carboxy benzamido)glutarimide:



thalidomide

α-(o-carboxybenzamido) glutarimide

Spontaneous hydrolysis of thalidomide

This caused us to suspect that thalidomide may react with other compounds, particularly with substances containing groups capable of participating in nucleophilic reactions. We therefore examined the reactivity of thalidomide towards a range of compounds, particularly those containing hydroxyl and amino groups. It was found that thalidomide under certain conditions is able to interact with a number of amines, particularly the biogenic amines such as spermine, spermidine, putrescine and cadaverine. The reaction appears to involve an acylation of the diamine with splitting of the phthalimide ring.

The problem arises as to whether this reactivity of thalidomide is of significance for its embryotoxic effects. At present this is difficult to assess but it is a possibility that thalidomide is involved in acylating some embryonic component.

As far as the aliphatic diamines are concerned it is of interest that RAINA has reported (Acta chem. scand. *16*, 2463 [1962]) the appearance of spermine and spermidine in the developing chick embryo. In a very recent paper MORRUZZI et al. (Biochem. J. *97*, 84 [1965]) have described the appearance of the four polyamines, spermine, spermidine, putrescine and cadaverine in the chick embryo. Whether these polyamines occur in the developing mammalian embryo is not known and we are at present looking into this possibility.