most implicated in masculinization, norethindrone, has been found to be most rapidly transferred across the placenta when compared to certain other progestins.

Information from animal studies that is published reports, on the teratogenic effects of oral contraceptives is scarce but suggests potential activity in humans.

A major target for the steroids would be the reproductive system which includes the last organs to undergo differentiation (10–12 weeks after conception) during embryogenesis. Ordinarily the user of the steroids should be aware of pregnancy before the period of greatest risk is present. Current labeling of oral contraceptives emphasizes discontinuation of oral contraceptive therapy after missing one or possibly two periods. Presently available hormonal contraceptives contain these drugs at a considerably lower dose than that at which teratogenic effects have been recorded. However, the effect of steroids on organs other than sex organs, and the chance of inadvertently taking the contraceptive during pregnancy could mean that some women are exposed to possible teratogenic effects of hormonal contraceptives. It must be emphasized that large doses in experimental animals are routinely employed to compensate for the unavoidable differences between limited numbers of animals treated, and widespread use in the human population.

Senator NELSON. May I interrupt a moment? Are you saying that you can draw a valid conclusion about whatever systemic effect occurs or tissue damage occurs in human beings from a large dosage in a small animal?

Dr. LEGATOR. Well, as an example of this particular point of extrapolation from animal attitude to humans, let's assume we have an effect in our animal population of 0.2 of a percent in the induction of a specific neoplasm. This means that one out of 500 animals would have a neoplasm and this would mean then to do a proper experiment we would need perhaps 5,000 or more animals which is usually impossible.

If we can use 50 animals say at a particular dosage of a compound this is usually considered quite adequate.

If you take the same figure of 0.2 percent and extend it to the human population where you have mass use, as in the case of a food additive, several hundreds of thousand individuals would be involved in terms of the induction of a neoplasm. From an experimental point of view, how does one compensate for the limited exposure to experimental in animals compared to this wide exposure in the human population? One of the methods of doing this is simply to substantially increase the dosage. Animal tests using a limited population are highly insensitive indicators in terms of mass human exposure and high concentrations, even maximally tolerated doses, must be used to give us any assurance of safety.

Senator NELSON. This argument, as you know, is frequently raised with respect to the cyclamates. It is claimed that the cyclamates were given to the animals far in excess of what they would ever be consumed by the human species.

Is that a valid objection?

Dr. LEGATOR. No.

Senator NELSON. With reference to cyclamates, I was simply using the argument that was made at the time. We could use any other example.