Mr. GORDON. Is it possible to ascertain in advance whether a person is predisposed to react adversely to amphetamines?

Dr. NORA. This is an area for the next couple of decades of work, determining who is at risk for development of the various birth defects, who is at risk to respond adversely to certain agents.

I think that one area where it has been pursued a great deal, and must be pursued a great deal more, is to find those things in the environment that will produce coronary heart disease.

It is not quite as far advanced in the areas of birth defects, and in identifying the individuals at risk.

Unfortunately, there is no simple skin test or blood test that would help us identify who would be at risk in taking amphetamines.

Fortunately, there are few agents in our environment that possess the disastrous teratogenic potential of thalidomide or rubella virus. And, conversely, under the right combination of genetic predisposition and exposure at a vulnerable period of development, one could project that almost any agent that has pharmacologic activity could be teratogenic.

Between these extremes, I believe there exists a number of agents causing birth defects in enough susceptible individuals to constitute a significant health hazard. It is in this latter category that I believe dextroamphetamine may belong.

Some of my coworkers and I have devoted a not inconsequential portion of our research activity to investigating such teratogens, which are difficult to identify in the epidemiologic sense.

To give an example: Thalidomide causes malformations, including a rare sentinel anomaly, phocomelia, in 50 to 80 percent of infants who have had a maternal exposure during the vulnerable period of embryogenesis.

With these factors in favor of prompt detection of the teratogen, thalidomide was on the market for over 2 years before the first suspicions about its safety were voiced.

How much more difficult is it to implicate a "low risk agent" that causes maldevelopment in only 1 percent of exposures?

Yet, if the exposures are frequent, say, in 10 percent of pregnancies, then 3,000 malformed infants would be delivered in the United States each year as a result of taking such a "low risk agent."

The pitfalls in conducting epidemiologic studies that will yield a confident answer as to whether or not an agent is teratogenic are many.

In brief, precise verification is essential in both retrospective and prospective studies. But, even with careful verification, the possibilities for systematic bias and the limitation in the type of data obtained—no population frequency rates—make retrospective studies less conclusive than prospective ones.

The published studies of the potential teratogenicity of amphetamines are retrospective.

Prospective studies, in which one could be more confident, have not been done. The reason is simply this: Prospective studies require many more patients and no one to date has accumulated a large enough series to address this question prospectively.

Senator NELSON. Have there not been animal studies?