teratogenic, or carcinogenic. A review of teratogenic and mutagenic studies with the hormonal contraceptives will then be presented. I will conclude this presentation by indicating the types of studies that I believe need to be undertaken. I understand there will be subsequent testimony on potential carcinogenic effects of the oral contraceptives.

I would initially like to discuss certain general principles that apply not only to oral contraceptives——

Senator NELSON. May I interrupt just a moment? There is an undertone of conversation going on in this hearing which makes it difficult to hear the witness. For those of you who want to carry on a conversation I would appreciate it if you would step outside. It is very difficult to hear the witness up here.

Dr. LEGATOR. I would like to discuss some general principles that apply to this general area of toxicity, and not specifically to the oral contraceptives and point out some of the difficulties inherent in this area. First of all when we talk about genetic response, mutagenicity, teratogenicity or carcinogenicity we are talking about a response that is usually irreversible. We don't really know how to turn off the pump once we get it started. When we have altered the hereditary material, DNA, and it is not repaired, or repaired erroneously, this change is perpetuated. In terms of a mutagenic or carcinogenic response, a latent period of several generations or years, respectively, would be anticipated. This long latent period with either a mutagenic or carcinogenic response make it highly unlikely to establish a cause and effect relationship for a period of 10 or more years in the case of carcinogenicity, and even for generations with a mutagenic response. For example, the earliest period for detecting an increase in genital or mammary tumors among users of the oral contraceptives would be the mid-1970's. With a teratogenic effect the latent period will not be as long.

But when we talk about mutations and when we talk about carcinogenicity we are talking about a latent period of many years if indeed not generations.

Another, I think, important problem in this area is that most of the responses we see are statistical rather than unique. Cancer, teratological effects, and inherited syndromes are all too common in our population. A new compound that increases the rate of genetic damage simply adds to an already existing burden. The non-unique nature of the problem is an additional factor that obscures determining a cause and effect relationship in the human population. Thalidomide serves as an excellent illustration of detecting a teratogen, not because it causes congenital malformation, but simply because it was an exception to the rule of nonuniqueness of genetically active compounds. If thalidomide had produced an increase in mental retardation or other genetic abnormalities, that are quite common, it might have gone unnoticed, and we would probably be using it now. So this is one of the very definite problems we have, the fact that we always have as high background of genetic injury as long as we can't define a unique response such as was the case with thalidomide.

The next point which follows the preceding points is, that long term use cannot be equated with safety. The two preceding points combined with the present deficiencies in our population monitoring systems leads to the inescapable conclusion that usage does not insure safety in the area of genetic effects. An exhaustive epidemiological study such