stances that have been on the market for several years and in some instances decades. The toxic response in each instance is in the area of chronic toxicity and more specifically that area that I will refer to as genetic toxicity. Genetic toxicity may be defined as a toxic response where inferentially there is an alteration or modification of DNA or its functions. This alteration, if not lethal, may lead either to a carcinogenic, teratogenic, or mutagenic effect. Table 1 indicates the probable mechanisms and differences between these three types of genetic responses.

Never have so many healthy individuals of child-bearing age been exposed for a prolonged period to a drug for non-therapeutic use. The uniqueness of the hormonal contraceptives makes it important that a careful evaluation of potential hazards in the area of genetic toxicity be carried out. In 1965, one of every four married women under the age of 45 had used or was using oral contraceptives. Actual users in 1965 numbered 3.8 million and an additional 2.6 million had discontinued use. Almost three out of four American women starting oral contraceptives continued to use the method for at least one year and more than three out of five continued for at least two years (10). Estimates of the number of current users indicate an apparent doubling since 1965 (11).

What types of studies are required to give us greater assurance of minimal genetic effects? To answer this question, I will discuss certain general principles that apply to substances that are either mutagenic, 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.

GENERAL PRINCIPLES

The following are unique characteristics that distinguish genetic toxicity:

(*a*) *Irreversibility of Effects.* When non-lethal alteration of DNA occurs, and the lesion is not repaired or repaired erroneously, the effect at the molecular level persists.

(*b*) *Long Latent Period.* 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 makes it highly unlikely to establish a cause and effect relationship for a period of 10 or more years, and even for generations in the case of 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.

(*c*) *Statistical Rather Than Unique Response.* 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 caused congenital malformation, but simply because it was an exception to the rule of non-uniqueness 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.

(*d*) *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 as carried out with cigarette smokers would be required to indicate a possible relationship between oral contraceptives and cancer. Results of a mass study concerning carcinogenesis would probably not be of any value until well into the 1970's. In the area of mutagenicity, it is virtually impossible to determine a cause and effect relationship.

(*e*) *Animal Testing Probably the Only Practical Means for Determining the Relation Between Chemicals and Their Genetic Effects.* This conclusion can be inferred from the preceding statements. The need to rely on animal data is especially imperative with the oral contraceptives that have been in use for a comparatively short time. The universal nature of the hereditary material allows one to extrapolate between species with some assurance. In lieu of epidemiological