data, which usually cannot be accumulated until a compound has been on the market for a prolonged period, heavy reliance must be placed on definitive and extensive animal studies in this area.

PRODUCTION OF DEVELOPMENTAL ABNORMALITIES (TERATOGENICITY)

The steroid hormones (e.g. corticosteroids) are known to have a number of effects on the developing embyro in both animal and man. Women using hormones for contraceptive purposes may become pregnant either during the course of treatment or shortly after discontinuing the pill. The number of women who use the drug during pregnancy or shortly after becoming pregnant, may be sufficiently high enough to warrant careful consideration of the potential teratogenic effects of oral contraceptives.

The progestin, chlormadinone acetate, produced cleft palate in mice and contracture of the wrist joint, defect of the abdominal wall and cleft palate in rabbits at high concentrations. These concentrations are considerably higher than those required to inhibit ovulation in rabbits and humans. High doses of norethynodrel with 2% mestranol also produced cleft palate in mice. Norethisterone with 1% mestranol showed no teratogenic effects. An increase in dead or reabsorbed fetuses with the two progestins that produced malformations was also reported in this study (12).

In studies with rhesus monkeys, high doses of norethindrone were administered orally for 5 days per week from approximately 30 days to term. Eight of ten fetuses were still born; all five females were virilized: males showed a greater degree of cryptorchidism than expected. However, six rhesus mothers treated with 50 mg. progesterone I.M. daily during the same period of pregnancy suffered no deleterious effect (13).

In humans, two investigators have shown, in studies that progestins increase the risk of masculinization of female embryos during the first 16–18 weeks of inadvertent pregnancy (14, 15). In certain instances a dose-related response was recorded.

The steroids vary as to their teratogenic potency and the compound most implicated in masculinization, norethindrone, has been found to be most rapidly transferred across the placenta when compared to certain other progestins (16).

Information from animal studies 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 potential 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.

MUTAGENCITY

We define mutations as any inherited alteration in the genetic material. Such changes can lead to a wide range of abnormalities, mental retardation, physical and mental disease and all the other inherited weaknesses and debilities to which man is susceptible (17). The concern here is not only for the present generations, but for generations yet to come. The widespread use of oral contraceptives by women of child-bearing age, makes it especially imperative that the contraceptive steroids, singly and in combination be evaluated for mutagenic effects. With the exception of limited cytogenetic studies, there is a void of experimental animal data in this area. The methodology needed to characterize potential mutagenic substances is of comparatively recent origin, and simply has not been applied to the evaluation of oral contraceptives. Possibly as few as three laboratories in this country (Dr. H. I. Adler's at Oak Ridge, Dr. S. S. Epstein's at the Children's Cancer Foundation, Boston, and Dr. M. Legator's at the Food and Drug Administration, Washington, D.C.) are specifically equipped to evaluate potential mutagenicity of chemicals such as the oral contraceptives. There is a pressing need for program development in this area, certainly with the oral contracep-