tives, but more generally with all of the drugs and food additives to which we are continuously exposed. I would like to mention the major tests that can be used, and attach a supplement to my written document that will describe the details of the various test methods. Mammalian tests which should be considered as the bases for evaluating potentially mutagenic agents are the host-mediated assay, dominant-lethal test, and *in vivo* cytogenetic tests. In addition to these three mammalian tests a number of ancillary tests in microbial systems, preferably those detecting both single nucleotide changes and effects involving more than one gene should be carried out.

The following is a brief description of the available methodologies:

(*a*) *Host-Mediated Assay.* This is an assay which detects point mutation in microorganisms implanted into a mammalian host. In this assay the mammal, during treatment with a potential chemical mutagen, is injected with an indicator microorganism in which mutation frequencies can be measured. It is important to note that the mutagen and the organism are always administered by different routes. After a sufficient time period, the microorganism is recovered from the animal and the induction of mutants is determined. The comparison between [a] the mutagenic action of the compound on the microorganism directly, and [b] in the host-mediated assay, will indcate (1) how fast the host can detoxify the compound or (2) if the host forms mutagenic products during the metabolism of the compound. This is a quick, simple method that is ideally suited for screening the various commercial steroids.

(*b*) *Dominant Lethal Test.* Dominant lethal is defined as a dominant genetic change which is incompatible with the survival of the conceptus. Dominant lethal mutants are convenient indicators of genetic damage which have been used in mammals for measuring effects of X-rays (18) and more recently of chemical mutagens (19). The mutagenic effects are evidenced by early deaths of the developing embryo. Associations between mutagenic and antifertility effects can also be studied in this system. In the usual dominant lethal protocol, untreated female rodents are bred to males previously injected with the test agent, and the stage in spermatogenesis that is effected can be determined. With the oral contraceptives, it would be of interest to carry out the usual protocol where males are treated, but the most relevant procedure, would be to treat female mice, either before or in early pregnancy and determine the effects of the steroids on meiotic germinal cells of the female.

(*c*) *In Vivo Cytogenetic Studies.* Production of chromosome abnormalities by various agents should be viewed as an indication of subvisible changes in the genetic material. Contrary to popular belief, the production of chromosome abnormalities by chemical agents in animals or man is a comparatively rare event. The agents that cause cytogenetic effects in either germinal or somatic cells have usually been known to produce viable mutations in biological systems. It has long been known, for example, that X-ray induced chromosome breakage is correlated with the incidence of mutations produced by irradiation (20).

There are two basic abnormalities that can be produced by mutagenic agents: (1) a numerical abnormality and (2) structural abnormality.

Numerical abnormalities were reported in 6 or 8 abortuses collected from women who became pregnant after taking oral contraceptives (21); an increased incidence (38.4%) of polyploidy was found in spontaneously aborted fetuses of women who became pregnant within six months after discontinuing use of oral contraceptives as compared to a 5% polyploidy in a non-treated random control group (22); progesterone after six weeks of daily I.M. administration produced aneuploidy and polyploidy in 50% of a limited number of dogs studied (23).

The possibility of structural abnormalities, chromosome breaks, might be inferred from two independent studies. Goh, reported an increase in frequency of breaks in 5 women who had been taking oral contraceptives for at least 6 weeks (24); McQuarrie *et al.*, reported an increase in break frequency in 50 babies born to mothers after oral contraceptive use (25).

The papers cited above certainly suggest that oral contraceptives may induce chromosome abnormalities. An additional paper of Beaconsfield and Ginsburg suggests that oral contraceptives interfere with meiotic division and induce polyploidy (26).

Well planned definitive studies in several species of animals, evaluating both somatic and germinal cells with the commercially used steroids are certainly indicated. Cytogenetic studies in rats with various commercial preparations of oral contraceptives is presently in progress at the FDA laboratories.