

alter what is to be expected from either agent alone. Extensive experimental observations indicate certain interactions between estrogen and progestogens. These phenomena include synergistic as well as antagonistic effects of these two agents on the endometrium, on deciduoma formation, on premalignant metaplastic changes in the cervical glands, on fibroid tumor formation in the uterus, on carcinogen-induced endometrial carcinoma, and on many other biological end-points (51-54). The complexity of these interactions, varying as they do with different dosage ratios and with the critical effects of the timing of the administration of each agent creates many as yet poorly understood features of the tissue responses obtained.

Moreover, the naturally occurring substance, progesterone, as already noted, when given either following estrogenization of the endometrium or when given simultaneously with estrogen only rarely induces the degree of stromal change observed in the uteri of women given estrogen-progestogen mixtures. Such tissue effects in women are supplemented by extensive observations concerning the unique and anomalous qualitative effects of these compounds in animals as compared with progesterone (47, 48). Hence, it seems inadvisable to presume that the interaction of estrogen with these newer progestogens will necessarily parallel that which has been previously observed for progesterone itself, and the potentiality for substantially different long-term effects must be more completely analyzed by clinical as well as experimental observation.

Effects on Germ Cells

An unequivocal abnormality produced by estrogen-progestogen combinations is the suppression of ovulation itself. It is only reasonable to consider the ultimate fate of the ovum that would have been normally released from the ovary. We do not know whether this ovum dies or survives. If it survives, is it altered in any way? The only information we now have in this regard is that subsequent fertilization of some ova from the same ovaries readily occurs and that a limited number of newborn derived from such pregnancies appear normal at birth (1-4). The number of such infants thus far described in the literature is a minute fraction of that required to determine the relative frequency of congenital defects or related abnormalities of the newborn and no sig-

nificant pediatric followup of these children is yet available. Statistical and clinical considerations indicate that for an adequate analysis of this problem a population of 100,000 children would be required. Moreover, the delayed clinical manifestations of many congenital abnormalities requires that these children be followed for 6 to 9 years in order to completely appraise any possible effect upon them. It seems unjustified to assume that the suppression of the normal ovulatory mechanism of the ovary for a 4-year period may not be reflected in the quality of the ova subsequently released even from an ovary in which the histological findings appear to be normal. Interpretation of such findings after years of deferral of pregnancy would, of course, have to include a full appreciation of the spontaneous increment in the frequency of congenital abnormalities with advancing maternal age.

The foregoing considerations have been brought together to direct the attention of the medical profession to these aspects of our knowledge as well as of our ignorance which seem pertinent to an evaluation of some of the risks involved in the use of estrogen-progestogen combination for purposes of contraception in the completely normal, healthy, young woman over a 4-year period.

Each physician must evaluate these risks with an appreciation of the many undetermined factors involved and with due regard for the merits of alternative methods available to him and to his patients.

In view of the serious limitations in our knowledge of the potential long-term effects of estrogen-progestogen combinations, it is mandatory that further clinical experience be gained under properly controlled conditions of observation and followup.

Table I.—Latent period of some known carcinogens in man

Carcinogen	Site of cancer	Range of latency (years)
X-rays.....	Skin.....	10-30
Radioactive paints.....	Bone.....	10-30
Radioactive ores.....	Lung.....	5-20
Thorium dioxide.....	Liver.....	10-25
Ultraviolet exposure.....	Skin.....	10-40
Aromatic mines.....	Bladder.....	2-20
Coal tar (shale oil).....	Skin.....	10-25
Soot (chimney sweeps)....	Scrotum.....	11-17

Drawn from data of Hueper, W. C., chapter 24 in Homburger-Fishman "Physiopathology of Cancer," Hoeber-Harper, New York, 1959.