mutations and chromosome damage. The action of these irradiation by-products (indirect effect) is becoming increasingly important in explaining irradiation phenomena that were once attributed solely to a direct effect (target theory) of ionizing radiation.

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Larval Stages and Phylogeny as Exemplified by the Lung Fluke of Turtles

Embryonic and larval forms as clues to relationships have been criticized largely because their application to phylogeny has been misinterpreted as acceptance of the recapitulation hypothesis of Haeckel. That larval stages may be highly specialized has been well established but, as de Beer (*1*) has stated, "although it can in many cases be shown that these larval forms could not represent the adult ancestral forms, this does not detract from their value as evidence of affinity between the organisms that possess any particular type." That such value not only applies to relationships between phyla and classes but also may extend to less inclusive categories as well is shown in a striking manner by the digenetic trematodes. A larval stage common to all of them is the cercaria (cercariaeum, if tailless) of which there are several types. The discovery that certain very similar adult trematodes have utterly different types of cercariae and that very dissimilar adults may have the same larval type has required drastic revision of existing concepts of relationships and phylogeny within the group. For example, immature stages have demonstrated that trematodes once thought to form a single family, the Heterophyidae, actually belong to three families in two orders (*2*). On the other hand, life-history studies promise to consolidate major groups and, more importantly, indicate lines of descent among them.

It thus was particularly desirable to investigate the life-history of *Heronimus chelydrae,* a common parasite in the lungs of fresh-water turtles and so different from other trematodes that it has long been the sole occupant of a distinct family. It has been found that the miracidium penetrates *Physa* sp. and develops into a sporocyst which produces cercariae directly without the interpolation of an intermediate sporocyst or redial generation, as is the case in most known life-histories. The cercaria differs from the larvae of the paramphistomes only in lacking eyespots and possessing a pair of flame cell groups in the tail. However, these differences are known to occur in larvae belonging to the same superfamily, and the fundamental resemblances between the cercaria of *H. chelydrae* and that of the paramphistomes, especially in the embryology and form of the excretory system, justify the allocation of that species to the superfamily Paramphistomatoidea. The cercaria has a powerful ventral sucker which disappears before the adult stage is attained, and the unique features of that stage, notably the unusual position of the excretory pore and form of the genital glands, may be attributed to differential growth after the cercaria leaves the snail.

From the phylogenetic standpoint, the cercaria of the turtle lung fluke is of much interest. The presence of flame cells in the tail, the posterior position of the definitive excretory pores in that structure, the thin-walled excretory vesicle, and absence of an intermediate generation in the molluscan host are all characteristics that in combination have been reported only for certain fork-tailed cercariae, the larvae of the order Strigeatoidea. Although the amphistomes have been placed heretofore in the order Prosostomata, they thus may be the extant group closest to the trematodes from which the two orders evolved. Furthermore, the life-history of *H. chelydrae* lends support to the view that the fasciolids, echinostomes, and many monostomes, as well as the paramphistomes, trematodes that have never fitted comfortably into the Prosostomata, actually are closer to the Strigeatoidea.

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Effects of Certain 19-Nor Steroids on Reproductive Processes in Animals

In previous publications we have reported that progesterone and certain of its chemical relatives are effective inhibitors of ovulation in rabbits, rats, and women (*1–4*). Among the most potent of a large number of compounds tested in animals have been a series of 19-nor steroids. These have proved to be effective ovulation-inhibitors by both oral and parenteral routes of administration. We have recently concentrated our attention on four of these compounds in a series of studies designed to reveal their action in various mammalian reproductive processes (*5*). The compounds are 17α-ethinyl-19-nortestosterone (I), 17α-ethinyl-5(10)-estraeneolone (II), 17α-ethyl-19-nortestosterone (III), and 17α-methyl-19-nortestosterone (IV).

The following assays with progesterone and these compounds have been performed in female mammals: (A) the Clauberg assay for endometrial stimulation in immature female rabbits, (B) the Rubin assay for uterotrophic activity in immature mice, (C) the deciduomagenic activity in primed, ovariectomized rats, (D) the conception-inhibiting activity in mature female rats caged with fertile males, (E) the ovulation-inhibiting activity in postpartum female rabbits mated to fertile males, and (F) the ability to induce and sustain implantation of the fertilized ovum in female rabbits castrated 1 day after a fertile mating. The details of the methods employed in these assays are being published elsewhere (*6*). In Table 1 we present the calculated minimum effective dose (M.E.D.) in each of the tests. Except where noted in the table, subcutaneous administration of the compounds was practiced.

The data demonstrate, first of all, that each of these compounds possesses progestational activity by virtue of its ability to induce pseudopregnant proliferation in the Clauberg assay (A). Of them II has approximately one-half of the activity of progesterone, whereas I, III, and IV are 5 to 10 times as active.

All of the substances are uterotrophic (B), but they exhibit marked quantitative differences, II being approximately 350 to 400 times as active as progesterone, and III, I, and IV being intermediate in activity. Actually there is a qualitative difference between these compounds in this test in the sense that the slope of the dosage/response curve for I, III, and IV resembles that of progesterone, whereas that of II more nearly resembles that of estrone, and comparison of the curves gives II an activity equivalent to one-fortieth to one-eightieth of that of estrone (*6*). In the spayed female rat test

for estrogenic activity, II has this same order of activity, whereas III is inactive.

We have been unable to demonstrate deciduomagenic activity (C) of I in doses up to 10 mg and of II in doses up to 15 mg. Compound III is about 4 times as active as progesterone, and IV has the same activity as progesterone.

Our best means of comparing the conception-inhibiting action of these compounds in rats (D) is on the basis of oral administration. Compound II is the most active of the substances studied. It should be pointed out, however, that progesterone given by mouth does not exhibit a true dosage/response curve over the range 2 to 50 mg (*2*, *4*), whereas by subcutaneous injection it does and exhibits an M.E.D. of less than 5 mg. The means whereby conception is inhibited by II in the rat appears to be dual in nature. In certain animals a clear inhibition of ovulation has been determined by inspection of the ovaries and noting the failure to form corpora lutea. In other animals ovulation was observed, but fertilization failed to occur. This is reminiscent of the inhibition of fertilization by progesterone administration in artificially ovulated rabbits reported by Dutt and Casida (*8*).

All of these compounds are effective inhibitors of ovulation in the rabbit. Although accurate quantification of this effect is difficult, the data of Table 1 (E) suggest that I and II are the most active in this test and that III and IV have the order of magnitude of activity of progesterone. We have previously reported that certain compounds active in this test in the rabbit may be inactive as conception-inhibitors in the rat (*4*). In this instance activity is exhibited in both species.

By their activity in the Clauberg test, these 19-nor compounds would be classed as progestins. One would expect, therefore, that they, like progesterone, should be effective in maintaining pregnancy. Actually, as is evident from the data of Table 1 (F), this is not completely demonstrable. Thus in doses up to 2 mg per day per rabbit II fails to induce implantation; III acts very much like progesterone, but a somewhat higher dosage is required. Compound I has behaved very peculiarly in this test. Tested at the 0.25-mg-per-day level it has induced implantation, albeit accompanied by much fetal degeneration. At dosages up to 10 mg per day very limited implantation has occurred in one-fourth of the animals and no implantation in the remaining three-fourths. We have no adequate explanation for this phenomenon but have considered the possibility that among the various effects exerted there may be combined in one molecule both progestational and antiprogestational potentialities. We have not been able to test this with I, but certain experiments conducted with II are suggestive. Rabbits pretreated with II for 3 days were mated to fertile bucks; at the same time ovulation was insured by the intravenous injection of a pituitary gonadotrophic extract. Examination of the tubal ova of several females indicated that most of the ova were fertilized. Nonetheless, in no instance were young born of such rabbits, and palpation failed to disclose normal implantation.

When administered to fertile female rats in 2-mg dose every other day for 70 days, II completely inhibited fertility during the period of administration, although matings occurred with males kept with the females. Following withdrawal of administration, a sterile period ensued which averaged 26 days in length. Examination of the daily vaginal smears disclosed fairly regular vaginal cycles as well as mating, suggesting that II did not alter completely the fundamental endogenous secretory rhythm but affected either ovulation or ovum development.

On the basis of these animal studies, we find here a group of substances which, by reason of certain similarities to progesterone, may be classified as progestins. Only one of them, 17α-ethyl-19-nortestosterone (III), appears to have typical progesteronelike activity in all of the tests employed, but it is quantitatively more active than progesterone in certain tests (for example, A and C) and less active than progesterone in others (for example, F). With these compounds one may inhibit normal reproductive processes in one aspect (for example, ovulation) or stimulate them in others (for example, endometrial proliferation). The fact that certain of them are active at quite low concentrations suggests potential therapeutic usefulness.

Table 1. A comparison of estimated minimal active doses of progesterone and the 19-nor steroids in six tests of activity.

Compound	(A) M.E.D. in Clauberg assays (mg)	(B) Minimum uterotrophic dose in mice (μg)	(C) Minimum deciduomagenic dose in rats (mg)	(D) Minimum oral antifertility dose in fertile rats (mg)	(E) Minimum ovulation-inhibiting dose (mg)	(F) Minimum implantation sustaining dose in rabbits (mg/day)
Progesterone	1–2	87	2	5–10+	1–2	0.5–1.5
I	0.1–0.2	29	> 10	5	0.25	0.25*
II	2–4	0.24	> 15	2	> 0.2 < 1.0	> 2.0
III	0.1–0.2	± 100†	0.5	5	> 1.0 < 5.0	2.0
IV	0.1+	19	2	Not studied	0.5–2.0	Not studied

* Less active at higher dose. † Data of Drill, Saunders, and Edgren (*7*).

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Effects of Certain 19-Nor Steroids on the Normal Human Menstrual Cycle

In an accompanying paper (*1*) are described the effects evoked by certain 19-nor steroids on the reproductive processes of rodents. The present report deals with three of these compounds, 17α-ethinyl-19-nortestosterone (I), 17α-ethinyl-5(10)-estraeneolone (II), and 17α-ethyl-19-nortestosterone (III) (*2*). These were administered by mouth in dosages of 5 to 50 mg per day to 50 women from days 5 through 25 of the menstrual cycle. The subjects' ages ranged from 22 to 39 years (average, mean, and mode, all about 29 years).

During treatment, only rare instances of moderate side-effects occurred. Medication was given for inexplicable childlessness, since previous use of progesterone in high dosages had been helpful (*3*). On the basis of past history, these patients were known to ovulate regularly and, hence, to menstruate regularly and normally. During most con-