mination of glomerular filtration rate and physiologically active extracellular fluid space in man.

Zusammenfassung. Es wird über die renale Clearance und das Verteilungsvolumen einer neuen inulinartigen Substanz, Polyfructosan-S, die gegenüber Inulin einige Vorteile hat berichtet. Renale Clearance und Verteilungsvolumen von Polyfructosan-S entsprechen bei nierengesunden und nierenkranken nichtödematösen Personen den mit Inulin ermittelten Vergleichswerten.

D. P. MERTZ

Medizinische Universitätspoliklinik, Freiburg i. Br. (Germany), February 4, 1963.

3-Cyclopentyl Ether of 17α-Ethynylestradiol: A Potent Anti-Gonadotrophic and Contraceptive Agent in Rodents

It has been reported in recent papers from our laboratory[1-3] that 3-etherification of various estrogenic steroids with cyclopentyl alcohol gives rise to compounds which, upon oral administration, are outstandingly potent in animal assays compared with their parent compounds.

Particularly noteworthy from a quantitative point of view is the activity of 3-cyclopentyl ether of 17α-ethynylestradiol (EE c-5). This compound, if evaluated for its growth-promoting effect on uterus of immature mice[3], appears to be the most potent estrogenic agent, described so far, which is effective by mouth. Since estrogens are also known to be strong pituitary inhibitors, we have been led to study EE c-5 for the ability to prevent the ovarian hypertrophy arising in parabiotic animals following gonadectomy of the male partners.

A first assay was based on the use of *parabiotic rats* according to the method of MEYER and HERTZ[4]. 17α-Ethynylestradiol (EE) and its 3-methyl ether (EEME) were also employed for comparative purposes. All compounds, dissolved in 0.2 ml of sesame oil, were administered orally via a stomach tube to the male partners for 10 days. Three dosage levels were chosen. The results, presented in Table I, show that EE c-5, at the two lower doses, was more effective than EE in preventing stimulation of ovaries. EEME, on the other hand, did not succeed at any dose in depressing ovarian weight below the range of controls. The uterine weight curves were similar in trend to the ovarian ones, except that they lagged somewhat behind. Dosage levels which were already able to inhibit ovarian response did not yet depress uterine weight, and at times even enhanced it.

A second set of experiments was based on the use of *parabiotic mice* according to the method of MIYAKE[5], all the technical procedures being the same as in the assay made formerly in rats. As shown in Table II, extremely low daily doses of EE c-5 (of the order of one hundred thousandth of microgram) succeeded in suppressing ovarian hypertrophy. Such doses appear to be much lower than those reported to be effective by MIYAKE[6] for EEME in the same test. Another finding is worth noting in Table II: that is the reversal of uterine weight at the highest dose of estrogen. This fact is likely to be interpreted as a direct stimulation by a transfer of steroid across parabiotic union[7], all the more so as the test compound is extremely potent in the Rubin test[3].

Although as far as we know it cannot be said what correlation exists between the ability of a steroid to inhibit gonadotrophic hormone secretion (as evaluated in para-

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Table I. Gonadotrophic-hormone-inhibiting activity in parabiotic rats

Compound	Dose/animal/day µMoles	µg	Average body weight of pairs in g initial	final	Average organ weights in mg ± S.E ovaries	uterus
Sesame oil (intact males)	—	—	99	157 (6)[a]	40.7 ± 2.9	65.3 ± 20.4
Sesame oil (castrated males)	—	—	100	144 (7)	118.1 ± 26.5	109.7 ± 19.9
17α-Ethynylestradiol	0.00005	0.0148	100	155 (9)	146.1 ± 19.2	147.4 ± 11.8
	0.0005	0.148	98	153 (9)	124.4 ± 19.7	153.2 ± 20.9
	0.005	1.48	99	153 (8)	39.5 ± 4.6	87.9 ± 20.9
17α-Ethynylestradiol 3-methyl ether	0.00005	0.0155	101	154 (6)	162.2 ± 23.4	140.9 ± 17.4
	0.0005	0.155	99	142 (9)	143.5 ± 15.9	161.8 ± 15.0
	0.005	1.55	100	162 (7)	111.2 ± 18.9	139.4 ± 23.3
17α-Ethynylestradiol 3-cyclopentyl ether	0.00005	0.0182	95	142 (9)	72.9 ± 20.8	142.3 ± 12.3
	0.0005	0.182	101	149 (7)	87.8 ± 16.7	105.4 ± 19.0
	0.005	1.82	102	154 (9)	40.0 ± 7.7	90.5 ± 11.3

[a] Number of couples in parentheses.

Table II. Gonadotrophic-hormone-inhibiting activity in parabiotic mice

Compound	Dose/animal/day µMoles	µg	Average body weight of pairs in g initial	final	Average organ weights in mg ± S.E. ovaries	uterus
Sesame oil (intact males)	—	—	32	35 (8)[a]	9.4 ± 0.7	9.4 ± 1.2
Sesame oil (castrated males)	—		32	35 (6)	16.7 ± 1.8	43.8 ± 8.2
17α-Ethynylestradiol 3-cyclopentyl ether	0.0000005	0.000000182	31	33 (7)	17.3 ± 3.9	27.6 ± 8.4
	0.000005	0.00000182	31	31 (6)	14.7 ± 3.6	30.4 ± 10.3
	0.00005	0.0000182	31	35 (6)	10.7 ± 1.9	20.6 ± 6.5
	0.0005	0.000182	30	29 (6)	8.4 ± 0.4	13.4 ± 1.4
	0.005	0.00182	29	32 (5)	9.6 ± 0.9	40.4 ± 2.0

[a] Number of couples in parentheses.

Table III. Contraceptive activity in female rats

Compound	Dose/animal/day µMoles	µg	No. of rats[a] with estrous cycle maintained	inhibited	No. of rats mated	No. of matings per rat in 10 days mean	range	No. of deliveries
Sesame oil	—	—	10	0	10	1.1	(1–2)	10
17α-Ethynylestradiol 3-methyl ether	0.015	4.65	6	3	7	0.8	(0–1)	5
	0.030	9.3	8	2	7	0.7	(0–1)	6
17α-Ethynylestradiol 3-cyclopentyl ether	0.015	5.46	3	7	9	1.6	(0–3)	0
	0.030	10.92	0	10	7	1.7	(0–3)	0

[a] 10 animals per group. One animal from the group treated with the lower dose of 17α-ethynylestradiol 3-methyl ether died during treatment.

biotic animals) and its fertility controlling capacity[8,9], the outstanding effectiveness of EE c-5 as pituitary suppressant in the previous experiments prompted us to study this compound also for *contraceptive activity*. The assay was performed on female rats, according to a method described previously[10]. Briefly, female albino rats, weighing 160–180 g, and presenting regular estrous cycles, were put on steroid treatment for 30 days. From 16th to 25th day the animals were caged with males (5 females with 2 males) and then observed until the assumed time of delivery. Daily vaginal smears were obtained until pregnancy was evident. Cornified epithelial cells without leucocytes were regarded as evidence of estrus, and the presence of spermatozoa was considered an indication of mating. Table III shows that, at the doses employed, EE c-5 was markedly more effective than EEME in blocking estrus and fertility, although it did not substantially interfere, in most instances, with mating.

The observations made in the present experiments justify the conclusion that in animal tests orally administered EE c-5 is a highly potent antigonadotrophic and contraceptive agent. In both these activities it far surpasses EEME, which is now largely employed in medical practice in combination with progestins for contraceptive purposes.

Riassunto. Esperienze condotte in ratti e topi parabionti hanno permesso di stabilire che il 3-ciclopentil etere del 17α-etinilestradiolo, estrogeno dotato di elevatissima attività uterotrofica per via orale, è parimenti fornito di forte potere inibente sulla secrezione gonadotropa ipofisaria. Pure a dosi minime esso rivela chiare proprietà anticoncezionali nei ratti femmine. Sia come inibitore ipofisario che come inibitore della fertilità, tale composto si dimostra notevolmente più attivo del 3-metil etere del 17α-etinilestradiolo.

G. FALCONI and A. ERCOLI

Vister Research Laboratories, Casatenovo (Como, Italy), December 21, 1962.

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The Capillary Flow of Solutions
A Re-evaluation of Experimental Evidence

In a recent contribution[1] on the capillary and porous flow of solutions, the results obtained with suspensions of red blood cells and solutions of two high molecular weight solutes flowing in a fine tube were taken as evidence of an increase in the overall velocity of the suspended material, and tentatively ascribed to axial migration. A closer examination of the theoretical conditions postulated in these experiments shows that a different interpretion is in order (consider Figure 1).

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