Zusammenfassung. Die Depolarisation der Ia Nervenfasern, welche durch eine Entladung in Ia Fasern eines Flexormuskelnerven reflektorisch ausgelöst werden kann, wird durch Reizung der sensorisch-motorischen Grosshirnrinde oder der Flexor-Reflex-Afferenten gehemmt.

Es wird vorausgesetzt, dass der Mechanismus dieser Hemmung präsynaptisch ist, und zwar durch eine Depolarisation der Endigungen der Interneuronen, welche die Wirkung von Ia- zu Ia-Afferenten übertragen.

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Observations on the Renal Clearance and the Volume of Distribution of Polyfructosan-S, a New Inulin-Like Substance

It is well known that inulin is the only substance at present, the clearance of which is independent of its plasma concentration in all vertebrates investigated (SMITH[1]). Therefore inulin represents a standard for all other clearance substances.

Recently, we received a new inulin-like substance, Polyfructosan-S (producer: Laevosan Company, Linz, Donau, Austria), to examine the conditions of its renal excretion and the volume of distribution in man. Informative studies in dogs and rats by HARTH[2] have shown that the renal clearance and the 'space' of Polyfructosan-S (PFS) are in agreement with the corresponding values of inulin.

According to the manufacturer, PFS is a starch-like polymer, which contains about 15 to 18 fructose molecules especially. Similar to inulin the molecule is elongated, presumably with ramifications. The molecular weight is given as almost 3000. In comparison with inulin, there are a number of advantages: (1) PFS is totally soluble in cold water, (2) it is alkali-stable and (3) with weak acids it hydrolyzes only half as fast as inulin, a circumstance which is desirable insofar as inulin sometimes slightly hydrolyzes into smaller products during the dissolution of the ampuls in boiling water.

Methods and Materials. Since PFS and inulin form the same products by hydrolysis, the chemical analysis of both substances in plasma and urine is identical. Consequently, only successive studies in comparing PFS to inulin, with an interval of at least 1 day (for a complete removal) were possible. To diminish the limit of experimental error, the basal conditions in water and salt metabolism were kept constant in each case. Three days before the clearance studies were performed, the persons to be examined were put on a diet, which contained either 40 to 60 or about 150 mval sodium per day, and 0.5 to 1.0 g protein per kg body weight per day; the water balance was compensated. The clearance and 'space' ratios PFS/inulin were determined in 12 subjects (3 normal, 1 with healing acute glomerulonephritis, 4 with chronic glomerulonephritis, 3 with chronic pyelenophritis, 1 with essential hypertension), whereas the behaviour of PFS clearance after elevation of PFS plasma level was studied in 6 other subjects (2 normal, 1 with healing acute glomerulonephritis, 3 with chronic glomerulonephritis). No person examined had evidence of hypoproteinemia, endocrinopathy, heart failure or fluid retention. Determinations of the clearance and the volume of distribution of PFS and inulin, respectively, were performed simultaneously in 2 or 3 consecutive periods, lasting always 30 min. We used an 'inflow' procedure[3,4] with physiologically active extracellular fluid volume calculated by difference method. By means of a modified calibrated infusion technique, an equilibration of the clearance substances between plasma water and rapidly diffusible interstitial fluid (NICHOLS et al.[5], COTLOVE[6], MERTZ[7], MERTZ and EPPLER[8]) was hastened by a constant priming infusion over 20 min. Then the infusion rate was reduced and maintained constant at a value amounting to 1/4 of the initial rate for the continuous infusion. Equilibration was achieved about 40 to 50 min after the continuous infusion was started. In experiments in which the plasma level of PFS was elevated, we measured the clearance values as soon as a new equilibrium was reached.

For PFS and inulin analyses in urine and plasma, we used the method described by ROE et al.[9].

Results and Conclusions. In spite of the fact that only the successive method of comparison could be used, the clearance (C) and volume of distribution (VD) values of both substances are in good agreement. The mean values of C_{PFS} and C_{In} amounted to 101.6 ± 27.7 (range from 62 to 152) and 100.8 ± 23.5 (range from 64 to 142) ml/min and 1.73 m^2 body surface, respectively. We found a clearance ratio PFS/inulin of 1.016 ± 0.099. There is no difference in the variation of the values between normals and persons with renal diseases. We calculated a VD ratio PFS/inulin for the entire group of 1.005 ± 0.093. PFS clearances of patients with renal disease and of normal controls are independent of PFS plasma concentration over a range from 21.5 to 85.2 mg/100 ml. The mean deviation amounted to $-0.8 \pm 4.0\%$ of the control value. In all experiments PFS was non-toxic and produced no pyrogenic action.

Considering the standardization of the experimental conditions in each individual, the variability of the clearance ratio and of the 'space' ratio PFS/inulin has to be related mainly to endogenously changing glomerular filtration rate and extracellular fluid volume, respectively. Further studies about the usefulness of the PFS clearance are necessary. A complete description will be presented elsewhere[10]. According to the present data, it is suggested that PFS may be qualified as a substance for the deter-

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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.

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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	Dose/animal/day μg	Average body weight of pairs in g initial	Average body weight of pairs in g final	Average organ weights in mg ± S.E ovaries	Average organ weights in mg ± S.E 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.