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.

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

[8] G. FALCONI and G. BRUNI, J. Endocrinol. *25*, 169 (1962).
[9] R. I. DORFMAN, Abstracts of the Proceedings of the International Congress on Hormonal Steroids, Milano (May 1962), Excerpta Medica Foundation, paper no. 4.
[10] G. FALCONI and A. ERCOLI, Proc. Soc. exp. Biol. Med. *108*, 3 (1961).

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).

[1] J. BOURDILLON, C. R. Acad. Sci. *255*, 512 (1962); Exper. *18*, 530 (1962).

The graph represents a tube of unit capacity and unit length, connected to a reservoir at $x = 0$, and ideally extended into space beyond its real end at $x = 1$.

The system is first filled with water, a solution then replaces the water in the reservoir, and the solution is pushed into the tube. The solution penetrates the water in the shape of a paraboloid and its distribution is given by the line $\overline{ax}$, its amount by the area $\overline{a0x}^2$. Since x moves forward at twice the mean velocity of the water, it will always be numerically equal to $2U$, if U is the total amount of fluid collected. When $x = 1$, $(U = 0.5)$, the solution just appears at the end, and the effluent will henceforth contain, when $x = x_2$, x_3 and so on, increasing amounts of solution.

One must now distinguish between the relative content of solute at the outlet and the relative concentration of the effluent. The relative content at the outlet is obviously equal to y, determined by the position of line $\overline{ax}$. With the restriction that $x \geq 1$, or $U \geq 0.5$, $(x - 1)/y = x/1$, $y = 1 - (1/x)$; or $y = 1 - (1/2U)$. With the same restriction, the concentration c of the effluent is as follows: The amount of solution expelled is the area $A = (x-1)y/2$, or $A = U + (1/4U) - 1$, since $x = 2U$ and $y = 1 - (1/2U)$. By differentiation, $(dA/dU) = 1 - (1/4U^2) = c$. Thus, for the same value of U, the concentration of the effluent is always higher than the relative content at the end. Note that $c/y = 1 + (1/2U)$. For $U = 0.5$, or $x = 1$, $c/y = 2$; in other words, the concentration of the first small sample collected equals exactly twice the relative amount at the end of the tube. The two curves are shown in Figure 2.

Consider now two extreme cases: rapid flow with negligible diffusion and slow flow with diffusion sufficient to offset the effects of laminar flow. In the first case, results should fit curve I. In the second, TAYLOR's[2] work shows that a steep sigmoid curve should be obtained in which, for $U = 1$, c should approach 0.5 and thus become identical with y.

The flow of a hemoglobin solution is given to illustrate the point (Figure 2). It conformed to expectation in slow, but not in fast flow. Neither did the profiles of other high molecular weight solutes or suspensions of red cells ever reach curve I, regardless of concentration or velocity of flow. They were always blunter than expected, the area under the curves below $U = 1$ smaller than expected. With red cells, if not with protein, this discrepancy cannot be due to diffusion and its cause must lie elsewhere. Although complications due to gravity cannot be ruled out, they would probably not account for the regularity of the phenomenon under varying conditions.

Figure 1 can be used also to estimate the theoretical profile when a small specimen of solution is placed between two sections of water. Assume that the x's on the graph are equidistant and that a solution specimen having volume fraction f has reached the position of triangle $\overline{ax}\overline{x}_1$, whose base $x_1 - x$ is then numerically equal to $2f$. By the time the specimen reaches position $\overline{ax_1}\overline{x_2}$, it has lost $\overline{ax}\overline{x}_1 - \overline{ax_1}\overline{y_2} = \overline{x_1}\overline{x_2}\overline{y_2}$, which is the amount collected in a volume of fluid equal to $\overline{bx_1}\overline{x_2}$. In the next position $\overline{ax_2}\overline{x_3}$, the amount collected is $\overline{ax_1}\overline{y_2} - \overline{ay_2}\overline{y_3}$ in fluid volume $\overline{bx_2}\overline{x_3}$, and so on.

When the theoretical curve is thus estimated for our previous experiments (Figures 2 and 3 in reference 1b), the initial hump occupies the same position but is higher than shown and the relative areas up to $U = 1$ are as follows:

Theoretical area	0.75	Polysaccharide	0.61
RBC (in 30% sucrose)	0.75	Thiocyanate	0.49
RBC (in saline)	0.62	Phosphate	0.49
Protein	0.64		

The two salts yield the expected result (0.50). The other areas are below theoretical except for red cells in sucrose. The position of the protein and polysaccharide areas may be partly due to diffusion, which would displace their apex toward the right; but the position of the red cell curve cannot be explained in this manner. Chicken red cells, which are nucleated, elongated and larger than sheep cells, gave a profile that was even further displaced to the right than that of sheep cells.

Blunting of the red cell profile in blood flow has been recently recorded by a photographic procedure[3]. According to one observer[4], particles in laminar flow undergo an outward displacement if they rotate, an inward displacement if they do not. According to others[5], centripetal displacement exists only when particles are deformed. Other evidence[6] shows both inward and outward displacement, resulting in an accumulation of the material in an annular region.

In the experiments discussed here, radial displacement may have existed and may have been responsible for the unexpected positions of the curves, but it was not of such a nature as to cause an overall increase in velocity.

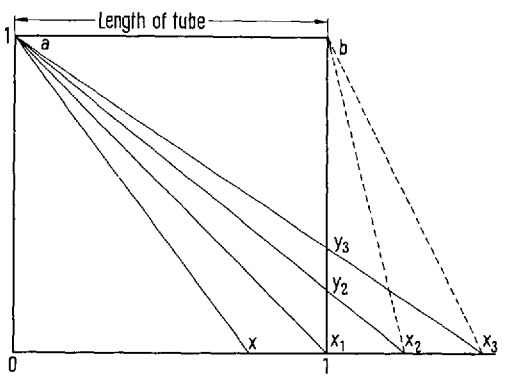

Fig. 1. Diagram to illustrate laminar flow of a solution.

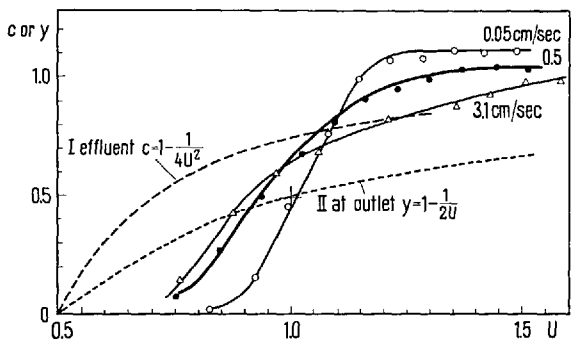

Fig. 2. Flow of a 1% hemoglobin solution into a water filled capillary tube, capacity 1 ml, diameter 0.7 mm, length 261 cm.

[2] B. TAYLOR, Proc. Roy. Soc. A. *219*, 186 (1953).
[3] G. BUGLIARELLO and J. W. HAYDEN, Science *138*, 981 (1962).
[4] D. R. OLIVER, Nature *194*, 1269 (1962).
[5] H. L. GOLDSMITH and S. G. MASON, Nature *190*, 1095 (1961).
[6] G. SEGRÉ and A. SILBERBERG, Nature *189*, 209 (1961).

These considerations do not apply to the evidence obtained with low molecular weight solutes in the capillary tube or in porous media, and should not affect the conclusions that were drawn from them.

Résumé. Quand une solution s'écoule par un tube capillaire préalablement rempli d'eau, le calcul montre que la concentration du liquide effluent est toujours plus élevée que la proportion de soluté au point de sortie. On a reéxaminé, à la lumière de ce fait, certains résultats expérimentaux publiés récemment sur le comportement de suspensions de globules rouges et de solutés à poids moléculaire élevé.

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Der Einfluss von α-Methyl-Dopa auf die Tyraminwirkung an mit Reserpin vorbehandelten Katzen

α-Methyl-Dopa hemmt die Dopadecarboxylase *in vivo* nur einige Stunden (WESTERMANN, BALZER und KNELL[1]), während seine blutdrucksenkende Wirkung 12–24 h und die Verarmung der Gewebe an Noradrenalin sogar mehrere Tage andauert (GOLDBERG, DA COSTA und OZAKI[2], HESS et al.[3]). Es wird vermutet, dass die Blutdrucksenkung und die Noradrenalinverarmung nicht durch die Decarboxylasehemmung, sondern durch einen Eingriff von α-Methyl-Dopa oder eines seiner Stoffwechselprodukte in die Mechanismen der Noradrenalinbindung und -speicherung bedingt sind (HESS et al.[3], STONE et al.[4], GESSA et al.[5]). Da der sympathicomimetischen Wirkung des Tyramins eine Freisetzung von Noradrenalin aus den Aminspeichern der Gewebe zugrunde liegt (BURN und RAND[6], SCHÜMANN[7]), können aus der Beeinflussung seiner Wirksamkeit Rückschlüsse auf Amingehalt und Aminbindung in den Speichern gezogen werden.

Wir haben deshalb den Einfluss von α-Methyl-Dopa auf die Tyraminwirkung am Blutdruck und an der Nickhaut der Katze untersucht.

Aus den in Tabelle I zusammengestellten Ergebnissen ist zu ersehen, dass die blutdrucksteigernde Wirkung von

[1] E. WESTERMANN, H. BALZER und J. KNELL, Arch. exp. Path. Pharmak. *234*, 185 (1958).
[2] L. I. GOLDBERG, F. M. DACOSTA und M. OZAKI, Nature *188*, 502 (1960).
[3] S. M. HESS, R. H. CONNAMACHER, M. OZAKI und S. UDENFRIEND, J. Pharmacol. exp. Therap. *134*, 129 (1961).
[4] C. A. STONE, C. A. ROSS, H. C. WENGER, C. T. LUDDEN, J. A. BLESSING und C. C. PORTER, J. Pharmacol. exp. Therap. *136*, 80 (1962).
[5] G. L. GESSA, E. COSTA, R. KUNTZMAN und B. B. BRODIE, Life Sciences *1962*, 353.
[6] J. H. BURN und M. J. RAND, J. Physiol. (Lond.) *144*, 314 (1958).
[7] H. J. SCHÜMANN, Arch. exp. Path. Pharmak. *238*, 41 (1960).

Blutdrucksteigernde Wirkung von Tyramin an normalen und reserpinvorbehandelten Katzen

	Zeit in min nach Infusionsende (nach Versuchsbeginn für Zeile (3)) 2	30	60	90	Zahl der Versuche
Kontrollen ohne Reserpin (1) 10 ml 0,9%ige NaCl-Lösung, 1 ml/min	36 ± 9	35 ± 11	30 ± 10	27 ± 9	3
l-α-Methyl-Dopa (2) 500 mg/Tier 5%ige Lösung, 1 ml/min	35 ± 9	33 ± 9	31 ± 7	30 ± 6	3
2 mg/kg Reserpin s.c. 24 h vorher (3) ohne Infusion	20 ± 5	18 ± 6	—	—	5
(4) 10 ml 0,9%ige NaCl-Lösung, 1 ml/min	—	23 ± 3	15 ± 3	15 ± 3	5
l-α-Methyl-Dopa (5) 500 mg/Tier 5%ige Lösung, 1 ml/min	28 ± 3	38 ± 4	47 ± 4	53 ± 3	5
(6) Höhe des Ausgangsblutdrucks der Versuche unter (5) in mm Hg	zu Versuchsbeginn	nach α-Methyl-Dopa 5	30	90 min	
	86 ± 9	97 ± 8	106 ± 15	96 ± 8	

Katzen 1,75–2,25 kg, Chloralose-Urethannarkose, Reserpintiere künstlich beatmet. Tyramintestdosis 300 µg i.v. Die Zahlen sind Mittelwerte und geben das Maximum der Tyraminblutdruckwirkung in Prozent des Ausgangswertes mit mittlerem Fehler (standard error) an. Tyramininjektionen in Abständen von 6–10 min. Infusionen in die V. jugularis. Die nach Vorbehandlung mit Reserpin abgeschwächte Tyraminwirkung wird durch α-Methyl-Dopa verstärkt.