19th and 21st day of pregnancy is statistically significant. If we compare the concentration of DNA per 100 mg of the wet liver tissue, there is no difference between the two series.

Summarizing, we can say that the hepatectomy of the pregnant female rat slows down the growth of the embryo without any specific effect on the liver growth.

Résumé. Les auteurs ont utilisé deux lots des Rates portantes. L'un d'eux a été soumis à la laparotomie et l'autre à une hépatectomie partielle le 16ème jour de la gestation. Les animaux ont été sacrifiés à des dates échelonnées après l'intervention. Le poids des embryons et celui de leur foie, ainsi que la teneur en DNA du foie ont été mésurés.

L'hépatectomie de la mère ralentit la croissance des embryons sans aucun effet spécifique sur le foie embryonnaire.

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The Influence of Cocaine and Reserpine on the Effect of Several Sympathomimetic Amines on the Mouse Iris

The various sympathomimetic amines can have direct, indirect (releasing of catecholamines as transmitter agent) or mixed (direct and indirect) actions on the various effector organs. With regard to the fact that the sympathomimetic drugs show certain differences of action on various effector organs (Trendelenburg[1], Holtz[2]), the behaviour of the mouse iris to sympathomimetic drugs after pre-treatment with cocaine or reserpine was investigated for determining the mode of action of fifteen sympathomimetic amines on this system.

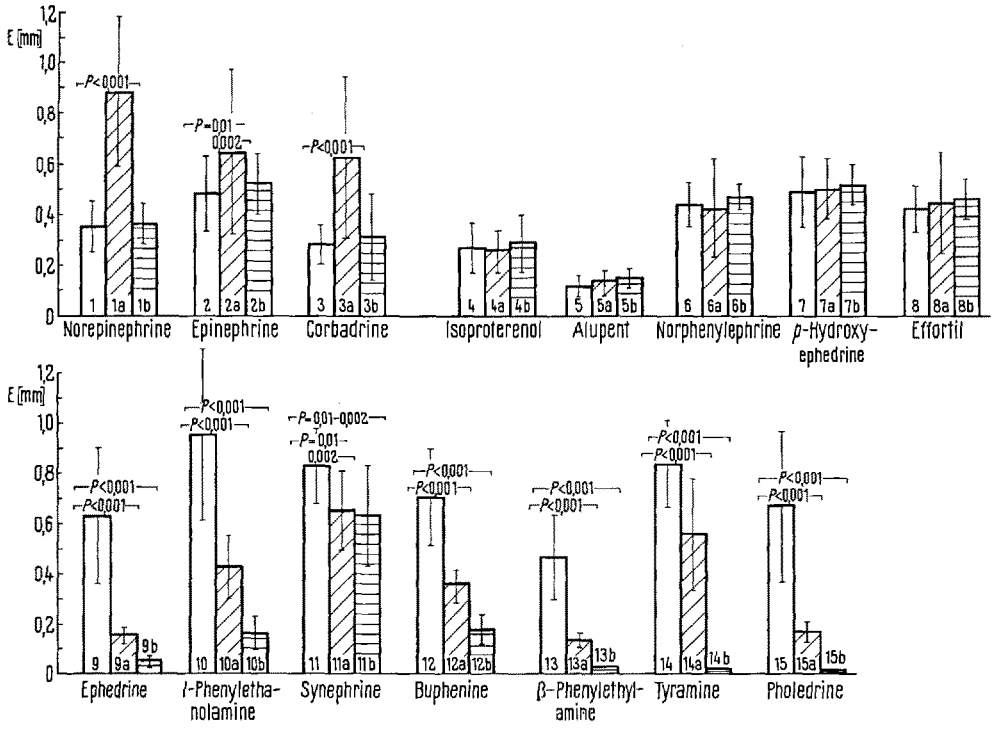
Method. Determination of the mydriatic effect [E = maximal mydriatic diameter minus diameter before treatment (d_{bt} = 0.24 ± 0.016 mm)] according to Pulewka[3] on male mice of an average weight of 25 g, breed NMRI-Tübingen.

Results (see Figure). (a) Preceding injection (30 min s.c.) of cocaine significantly increased the mydriasis produced by the i.v. injection of norepinephrine, epinephrine or corbadrine, but did not influence the pupillary dilatation produced by i.v. injection of isoproterenol, alupent, norphenylephrine, *p*-hydroxyephedrine or effortil, and decreased significantly the mydriasis produced by ephedrine, *l*-phenylethanolamine, synephrine, buphenine, β-phenylethylamine, tyramine or pholedrine. (b) Preceding injection (24 h s.c.) of reserpine did not significantly influence

[1] U. Trendelenburg, Pharmacol. Rev. *15*, 225 (1963).
[2] P. Holtz, Acta neuroveg. *21*, 445 (1960).
[3] P. Pulewka, Arch. exp. Path. Pharmak. *168*, 307 (1932).

Direct, indirect, and mixed mode of action of various sympathomimetic amines

Agent	Substitution at						Mode of action	
	o	*p*	*m*	β	α	N	According to the chemical constitution (Fleckenstein et al.[4] etc.)	On the mouse iris
(a) Catecholamine derivatives								
Norepinephrine		OH	OH	OH			direct	direct
Epinephrine		OH	OH	OH		CH_3	direct	direct
Corbadrine		OH	OH	OH	CH_3		direct	direct
Isoproterenol		OH	OH	OH		$CH(CH_3)_2$		mixed
Alupent	OH		OH	OH		$CH(CH_3)_2$		mixed
(b) Intermediary agents								
Norphenylephrine			OH	OH			mixed	mixed
p-Hydroxyephedrine		OH		OH	CH_3	CH_3	mixed	mixed
Effortil			OH	OH		C_2H_5		mixed
Ephedrine				OH	CH_3	CH_3	mixed	indirect
l-Phenylethanolamine				OH			mixed	indirect
Synephrine		OH		OH		CH_3	mixed	indirect
Buphenine		OH		OH	CH_3	$CH(CH_3)CH_2CH_2$		indirect
(c) Neurosympatomimetic drugs								
β-Phenylethylamine							indirect	indirect
Tyramine		OH					indirect	indirect
Pholedrine		OH			CH_3	CH_3	indirect	indirect



The influence of (a) cocaine and (b) reserpine on the action of various sympathomimetic amines on the mouse iris. Columns a: Pretreatment (30 min) with 7.5 μg/g cocaine-HCl s.c. (for producing an optimal sensitizing action without mydriatic effect) Columns b: Pretreatment (24 h) with 10.0 μg/g reserpine s.c. (for achieving a strong and sufficient depletion of catecholamine stores). Columns 1: 0.1 μg/g norepinephrine-HCl i.v. Columns 2: 0.05 μg/g epinephrine-HCl i.v. Columns 3: 0.2 μg/g corbadrine-HCl i.v. Columns 4: 56.0 μg/g isoproterenol-HCl i.v. Columns 5: 40.0 μg/g alupent-H_2SO_4 i.v. Columns 6: 2.0 μg/g norphenylephrine-HCl i.v. Columns 7: 100.0 μg/g *p*-hydroxyephedrine-HCl i.v. Columns 8: 4.0 μg/g effortil-HCl i.v. Columns 9: 10.0 μg/g ephedrine-HCl i.v. Columns 10: 50.0 μg/g *l*-phenylethanolamine-H_2SO_4 i.v. Columns 11: 100.0 μg/g synephrine tartrate i.v. Columns 12: 20.0 μg/g buphenine-HCl i.v. Columns 13: 5.0 μg/g β-phenylethylamine-HCl i.v. Columns 14: 25.0 μg/g tyramine-HCl i.v. Columns 15: 6.25 μg/g pholedrine-H_2SO_4 i.v. Each column shows the average mydriatic effect E [mm] of ten mice.

the mydriasis produced by the i.v. injection of norepinephrine, epinephrine, corbadrine, isoproterenol, alupent, norphenylephrine, *p*-hydroxyephedrine or effortil, but significantly decreased the pupillary dilatation produced by i.v. injection of ephedrine, *l*-phenolethanolamine, synephrine or buphenine, and almost completely abolished the mydriasis produced by i.v. injection of β-phenylethylamine, tyramine or pholedrine.

Discussion (see Table). According to the observations made on denervated and cocainized nictitating membranes of cats, FLECKENSTEIN et al.[4] classify the sympathomimetic drugs as follows: (1) *Catecholamine derivatives*, chemically characterized by two OH-groups in the ring, have predominantly direct action on the effector organ. (2) *Intermediary agents* (Intermediärstoffe), chemically characterized by one OH-group on the β-C-atom, have predominantly mixed (direct and indirect) action on the effector organ. (3) *Neurosympathomimetic drugs*, chemically characterized by two H-atoms on the β-C-atom, have predominantly indirect action on the effector organ, i.e. they effect the release of the transmitter agent from the storage sites.

The results given above mean that not all sympathomimetic drugs act on the mouse iris precisely according to this classification. Of the sympathomimetic drugs with two OH-groups in the ring (catecholamine derivatives) only epinephrine, norepinephrine and corbadrine acted directly on the mouse iris, while isoproterenol and alupent obviously had the same effect as agents with mixed action. Of the sympathomimetic drugs with one OH-group on the β-C-atom (intermediary agents) only norphenylephrine, *p*-hydroxyephedrine, and effortil acted on the mouse iris according to the so-called mixed mode, while ephedrine, *l*-phenylethanolamine, synephrine, and buphenine acted according to the indirect mode, i.e. the indirect part of the action of these amines on the mouse iris was the predominant one. The action of β-phenylethylamine, tyramine, and pholedrine, sympathomimetic drugs with two H-atoms on the β-C-atom (neurosympathomimetic drugs), on the mouse iris was an indirect one.

The results of our investigations have demonstrated differences in the mode of action of sympathomimetic amines on the mouse iris and on the nictitating membrane of the cat (FLECKENSTEIN et al.[4]). This finding is comparable with HOLTZ's observation that dopamine acted on the nictitating membrane of the cat directly and on the isolated auricle of the guinea-pig indirectly.

Zusammenfassung. Der direkte, indirekte und gemischte Wirkungsmodus von fünfzehn sympathomimetischen Aminen an der Mäuseiris wurde an cocainisierten und reserpinisierten Tieren bestimmt, wobei sich gewisse Unterschiede gegenüber dem Wirkungsmodus an der Katzennickhaut zeigten.

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Institut für Toxikologie der Universität Tübingen (Germany), January 22, 1965.

[4] A. FLECKENSTEIN and H. BASS, Arch. exp. Path. Pharmak. *220*, 143 (1953). – A. FLECKENSTEIN and J. H. BURN, Brit. J. Pharmacol. *8*, 69 (1953). – A. FLECKENSTEIN and D. STÖCKLE, Arch. exp. Path. Pharmak. *224*, 401 (1955).