bly similar to that found in the hypothalamus of the rat[8], mouse or guinea-pig (3.4, 9.0 and 1.2 ng/g respectively).

Octopus ganglia contain relatively high concentrations of octopamine (1310 ng/g in the optic lobe, e.g.) and the administration of reserpine (4 mg/kg) produced a marked reduction (to about 10% of control value) in its concentration[6]. It has been reported that a similar dose of reserpine does not produce a reduction in the whole mammalian brain octopamine levels[13]; more recent work, however, has shown that reserpine (1–3 mg/kg) does indeed produce marked reductions (to 32% and 1% of controls) in the hypothalamic levels[7,8]. The present experiments show that the level of hypothalamic p-octopamine in the domestic fowl is indeed markedly reduced as a result of reserpine (1 mg/kg) administration and this suggests that the p-octopamine, or perhaps some of its precursors, are kept in a reserpine-sensitive storage compartment as has been shown to be the case in mammals for the catecholamines and tyramines[14–16].

The substantial increases in p-octopamine levels that follow after monoamine oxidase inhibition with tranylcypromine and pargyline respectively, strongly suggest that p-octopamine in the domestic fowl possesses an active turnover rate as has been shown in the case of the mammalian brain[4,5]. Dopamine-β-hydroxylase is the enzyme that catalyzes the β-hydroxylation of dopamine as well as that of p- and m-tyramine to yield respectively, noradrenaline, p-octopamine or m-octopamine[17]. Since the administration of fusaric acid (a dopamine-β-hydroxylase inhibitor) produced a marked decrease in the domestic fowl hypothalamic p-octopamine, this synthetic route would seem to be the one followed in this animal species as well.

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Prolactin secretion inhibition by a new 8α-amino-ergoline, CH 29-717

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Summary. In rats, CH 29-717 inhibits basal and physiologically or chemically stimulated prolactin secretion. It is more potent than the standard bromocriptine.

10 years ago we provided the first indirect evidence that a synthetic ergot derivative, 2-Br-α-ergokryptine-mesylate (CB 154, bromocriptine) inhibits prolactin secretion[1]. Since that time many new ergot derivatives have been found in various laboratories which also inhibit the secretion of this hormone[2]. Unfortunately, few of them have been adequately characterized[3]. We wish to report data obtained in the rat on the prolactin secretion inhibitory activity of a new synthetic ergot compound N,N-dimethyl-N'-(6-methyl-ergoline-8α-yl)-sulfamide hydrochloride, code number CH 29-717. Its effects were compared with those of bromocriptine.

In all experiments, CH 29-717 was dissolved in saline; bromocriptine was dissolved in acidified ethanol (70%) and then diluted with saline. All experiments were carried out with rats kept under a regimen of 14 h light, 10 h dark, at constant temperature and humidity. Food and water were freely available. The results reported for the 2 compounds are not from experiments run in parallel.

1. *Inhibition of ovum implantation. Method.* Adult proestrus

Table 1. Incidence (%) of milk-spots in the stomach of pups of treated and untreated lactating rats

Treatment	Dose ($mg \cdot kg^{-1} \cdot d^{-1}$ orally)	Number of nursing rats treated*	Pups showing milk-spots on day (%) 4	5	6	7	8	9	10	11
Vehicle	0	6	100	100	98	100	98	98	96	98
CH 29-717	0.0125	5	100	100	95	95	88	98	100	100
	0.0250	6	100	100	96	83	69	79	98	100
	0.0500	5	100	100	75	0	3	8	100	100
				Treatment period						

*7 or 8 pups per nursing rat.

rats (Ivanovas strain) were brought together with males of proven fertility. The next morning (day 1) the sperm-positive females were randomly allocated to the different treatment groups (10 animals per group). On day 5 a single dose of the drug was injected s.c. The rats were killed on day 15 and autopsied. The uteri were inspected for foetusses or implantation sites. If none were found, ovum implantation was considered to have been inhibited[1]. *Results.* CH 29-717 reduced the proportion of pregnant rats per group dose-dependently. Implantation inhibition was an all-or-none effect as for bromocriptine[4]. The calculated[5] ED_{50} for implantation inhibition was 0.0125 mg · kg^{-1} s.c. (95% confidence limits: 0.0087–0.018). The ED_{50} for bromocriptine is 0.75 mg · kg^{-1} s.c.[1,2].

In further experiments we were able to prevent the inhibitory effect of 0.1 or 1 mg/kg CH 29-717 by treating the rats until day 9 with exogenous prolactin (Ferring AB). This indicated that the inhibitory action of CH 29-717 on ovum implantation (nidation) was probably obtained by inhibition of prolactin secretion rather than by a peripheral action.

2. *Lactation inhibition. Method.* The method used earlier[1] to assess lactation inhibition is not very sensitive to the effects of depressed prolactin secretion[3]. We therefore adopted the method described by Auskova et al.[6] with minor alterations[7]. Groups of 5–6 lactating female rats (Ivanovas strain) were given daily oral doses of CH 29-717 or vehicle from day 5 to 8 post partum, and the regression coefficients to the growth rates of the pups in the different groups were calculated, taking the daily weight gain of the young as indicator of milk yield[7]. *Results.* The dose-response curve constructed from the regression coefficients of growth rates is shown in the figure. The oral dose of CH 29-717 necessary to reduce the control value by half (ID_{50}) was 0.026 mg · kg^{-1}. For bromocriptine this value is 5.9 mg · kg^{-1}. When inhibition of milk intake by the pups becomes pronounced the proportion of pups with empty stomachs increases. This can be observed through the abdominal wall as an absence of a 'milk-spot'. Table 1 shows the decreasing proportion of pups with milk-spots in the various treatment-groups and the return to normal at the end of treatment.

Table 2. ID_{50} values (µg · kg^{-1} s.c.) for serum prolactin suppression in male rats

Drug	Time after drug application (h)			
	2	4	8	24
CH 29-717	0.8	0.4	5	220
Bromocriptine	8.0	7.0	57	940

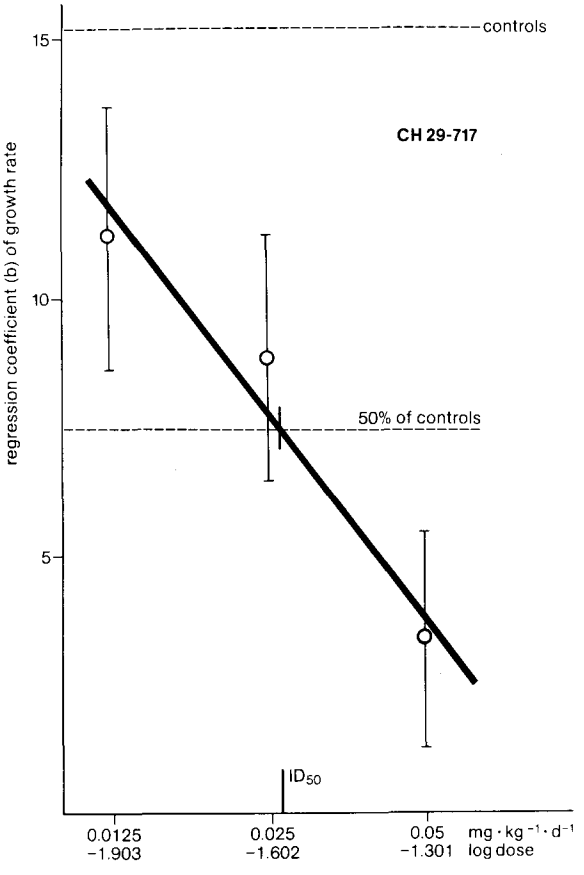
Table 3. Reduction of serum prolactin levels in rats with chemically induced hyperprolactinaemia

Dose of CH 29-717 (mg · kg^{-1} s.c.)	Serum prolactin (ng · ml^{-1}, mean ± SE) after	
	1 h	3 h
0	248.0 ± 48 (7)	382.0 ± 33.9 (6)
0.03	287.8 ± 98.5 (7)	28.9 ± 66.5** (5)
0.3	94.4 ± 31.1* (7)	32.3 ± 5.0** (6)

CH 29-717 was injected 24 h after 2 mg · kg^{-1} i.p. reserpine and 4 h after 250 mg · kg^{-1} i.p. α-methyl-p-tyrosine. Number of animals in parentheses. Significance of difference to control value: *$p < 0.01$, **$p < 0.001$.

3. *Inhibition of basal prolactin secretion. Method.* Male OFA-rats of about 250 g weight were installed singly in cages in the experimental room at least 24 h before the actual experiment. The compound or the vehicle were administered s.c. in various doses to groups of 3 rats. 2, 4, 8 or 24 h later the rats were killed by decapitation and blood was collected from the trunk, then centrifuged and the serum deep-frozen until assayed. The sera of the 3 animals per group were pooled in equal parts for the prolactin radio-immunoassay. The serum prolactin levels were expressed in ng/ml in terms of the prolactin standard NIAMDD-RPrl-RPl. These results were used to construct dose-response curves for the various times reducing basal prolactin serum levels by 50%. *Results.* The results are given in Table 2, together with the ID_{50} values previously obtained for bromocriptine. It is evident that CH 29-717 given s.c. is more potent in depressing serum prolactin levels in male rats than bromocriptine.

4. *Mechanism and site of action. Method.* Female adult rats (Ivanovas strain) were pretreated with reserpine (R) (2 mg · kg^{-1} i.p.) and 20 h later with α-methyl-p-tyrosine (AMPT) (250 mg · kg^{-1} i.p.). 24 h after R, CH 29-717 (0.03 or 0.3 mg · kg^{-1}) or vehicle was injected s.c.[10]. Blood was collected from the trunk after decapitation 1 or 3 h later. Individual serum prolactin levels were determined with the same assay system used above. *Results.* Data given in Table 2 show that the high serum levels of prolactin produced by the pretreatment with R + AMPT were



Dose-response relationship for the inhibitory action of CH 29-717 on growth rate of suckling rat pups. 4 groups of lactating rats were treated orally 4 times on days 5 to 8 postpartum. The regression coefficients b of daily weight gains of the pups are used as an indicator of milk uptake[7]. CH 29-717 suppressed daily weight gain by 50% at 0.026 mg · kg^{-1} · d^{-1} per os.

reduced by CH 29-717. Effects obtained in response to 0.3 $mg \cdot kg^{-1}$ s.c. were significant at 1 and 3 h, and to 0.03 $mg \cdot kg^{-1}$ s.c. at 3 h after drug administration. These results suggest that prolactin secretion inhibition induced by CH 29-717 is not dependent on intact biogenic amine stores and amine synthesis in the hypothalamic neuronal system controlling prolactin secretion. This suggests that the compound acts directly at the pituitary level.

Discussion. The results presented indicate that CH 29-717 is a potent inhibitor of prolactin secretion in female and in male rats under different conditions. Basal secretion as well as physiologically and chemically stimulated secretion are inhibited when CH 29-717 is given by the s.c. or by the oral route. In the different test systems used, the potency of the new compound compared with bromocriptine varies. In the test for implantation inhibition (experiment 1) the new compound is about 60 times more active than the standard, while in male rats (experiment 3) it is between 17 times (4 h after drug administration) and 4 times (24 h after drug administration) more potent. This large difference between relative activities in experiments with female and male rats is difficult to explain. The diminution in relative activities observed in the male with CH 29-717 between 8 and 24 h after drug administration (Table 2) seems to indicate a shorter duration of action of the new compound compared with bromocriptine. In the experiments assessing lactation inhibitory activity after oral administration, a comparison of the ID_{50} values indicates that CH 29-717 is 220 times more potent than bromocriptine. This figure reflects more a rather low oral activity of bromocriptine in the rat than an unexpected high activity of the new compound. This becomes clear when the ID_{50} values (oral) from experiment 2 and the ED_{50} values (s.c.) from experiment 1 are compared. As to the site and mechanism of action of CH 29-717, the results of experiment 4 indicate that prolactin secretion inhibition is probably due to a direct action on the prolactin secreting cells. In analogy to what is known of the mechanism of action of bromocriptine[3,8,9], it may be assumed that CH 29-717 acts by stimulating inhibitory dopamine receptors on the prolactin secreting cells. The assumption that CH 29-717 is a dopaminomimetic drug is supported by results from studies on non-endocrine systems, the results of which will be reported elsewhere.

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Foetal growth retardation in the rat following chronic exposure to the inhalation anaesthetic enflurane

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Summary. Chronic exposure of pregnant rats to high subanaesthetic concentration of the inhalation anaesthetic agent enflurane led to foetal growth retardation. No significant foetal loss or abnormalities occurred.

Recent epidemiological studies suggest that chronic exposure to an operating room environment may have an adverse influence on pregnant women and their unborn children. It would appear that these women have a greater chance of spontaneous abortion or of having a child with congenital abnormalities than women in the same profession but in a different working environment[1-4]. Moreover, the results of animal studies are conflicting. Some have implicated inhalation anaesthetics as the possible cause for the teratogenic effects[5-8], whereas other investigations indicated that the danger of foetal toxicity from chronic exposure to the inhalation anaesthetic agents nitrous oxide, halothane and methoxyflurane may not be as great as had previously been feared[9-11]. We report here the results of a preliminary study of the effects of chronic exposure of pregnant rats to the volatile inhalation anaesthetic agent enflurane.

Materials and methods. Female virgin Sprague-Dawley rats (250–300 g) were placed overnight with males of proven fertility, and the morning on which spermatozoa were found in the vaginal smear was designated the first day of gestation. The pregnant animals were weighed, marked and randomly assigned to either a control or a treatment group. Both groups of animals were exposed for 8 h daily throughout gestation (days 1–21) in separate perspex exposure chambers at constant ambient temperature with careful

Fetotoxicity of the inhalation anaesthetic enflurane

	No. of animals	Implantations	Resorptions	Fetal weight (g)* (mean ± SE)	Placental weight (mg)* (mean ± SE)
Experimental	8	88	1	4.5 ± 0.07	631.3 ± 65.7
Control	5	68	1	5.3 ± 0.06	586.7 ± 11.1
				$p < 0.001$	NS

* Significance of difference between values of the control and the experimental groups was analyzed by means of the Student t-test.