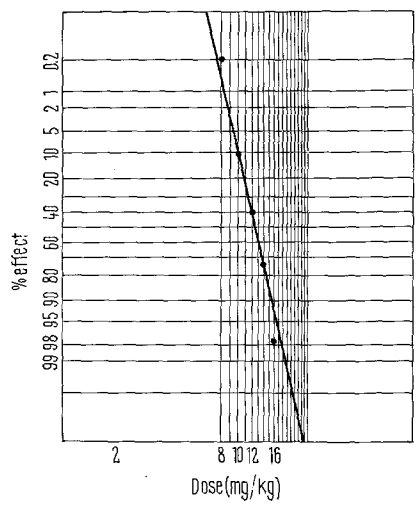
The animals were placed in 6 dosage levels from 2.0 mg/kg to 16.0 mg/kg. After intragastric intubation of the lead/oil solution, the subjects were observed, without handling, for a standard 14-day-period.

Results. The Table indicates the mortalities which resulted from the experiments. When plotted on logarithmic probability paper, the curve shown in the Figure was obtained. From the Figure it is possible to obtain the LD_{50} value (12.3). The 95% confidence limits, calculated according to the method of LITCHFIELD and WILCOXON[2], are 11.50 to 13.16. The slope function, S, is 1.2 (1.029 to 1.134).



Tetraethyl lead dose response curve.

Mortality data for all subjects

Experiment	Dosage (mg/kg) 2	8	10	12	14	16
1	0/1	0/3	1/5	3/7	5/5	2/2
2	0/1	0/3	0/5	4/6	4/5	2/2
3	0/1	0/3	1/4	2/7	2/5	2/2
4	0/2	0/5	0/4	2/7	4/5	2/2
Total	0/5	0/14	2/18	11/27	15/20	8/8
Percent	0	0	11	41	75	100

Conclusions. As in the previous research, 3 stages in the progress of the toxicity were noted: Stage 1: lethargy; Stage II: aggression and thrashing, and Stage III: convulsions and, in higher dosages, death. An interesting phenomenon observed in the third stage of the disease was that 14 of the animals exhibited self-cannibalization of the feet and tail. An additional 5 subjects rubbed the skin and hair completely off their snouts. Auditory seizures were particularly manifest during the second stage of the toxicity in virtually all the animals.

In an earlier experiment[1], the LD_{50} value was calculated to be 14.18 (12.62 to 15.93). The discrepancy between that value and the present one is most likely attributable to the small sample size which was previously utilized (16 subjects). There were 2 subjects in the first experiment which perished on the 15th day, 1 day after the end of the standard observation period. These 2 subjects, representing $12^1/_2$% of the population, could have had considerable impact on lowering the LD_{50} value since they were in group II which received 12.67 mg/kg.

Résumé. On a donné à 96 rats mâles albinos six doses différentes de plomb tétra-éthyle par intubation intragastrique. Une courbe dose-réaction a été établie à partir des résultats obtenus et les calculs ont donné une valeur LD_{50} de 12,3 mg/kg (11,50 à 13,15). Cette valeur diffère de celle qui a été obtenue précédemment. On croit que cette différence résulte du fait qu'un nombre plus grand d'échantillons a été utilisé dans cette série d'observations.

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Antagonism of 2-Br-α-Ergokryptine-Methanesulfonate (CB 154) to Certain Endocrine Actions of Centrally Active Drugs

It is known that in man several centrally acting drugs may induce galactorrhoea and amenorrhoea. WINNIK and TENNENBAUM[1] were the first to observe mammary enlargement and galactorrhoea with chlorpromazine. AUDIBERT et al.[2] soon showed that rabbits behaved similarly. A number of tranquillizers, but also psychomotor stimulants, antihistaminics and antihypertensives[3] have been found to increase prolactin secretion and by this mechanism to exert mammotropic actions. On the other hand several ergot alkaloids are known to inhibit prolactin secretion[4–6] and it was therefore interesting to test one of them whether it also inhibits a pharmacologically induced state of prolactin secretion in rats.

Methods. 2-Br-α-ergokryptine-methanesulfonate (CB 154) was chosen as the inhibitor[5,6], reserpine (R) chlorpromazine (CPZ) and α-methyl-*p*-tyrosine (AMT) were used as stimulators of prolactin secretion[7]. Virgin female rats with regular vaginal cycles of 4 days were used. 5 animals each received one of the following treatments: 1 mg/kg R s.c. on day P_1 (= metoestrus), or 50 mg/kg CPZ s.c. on day P_1, or 100 mg/kg AMT i.p. on 4 consecutive days, beginning on P_1. These animals formed the controls to the second set. Another set of animals (experimental) received the same treatment but in addition they were injected on day P_2 with 3 mg/kg CB 154 s.c. Vaginal cycles were followed for 14 days. The animals were kept in a room with controlled

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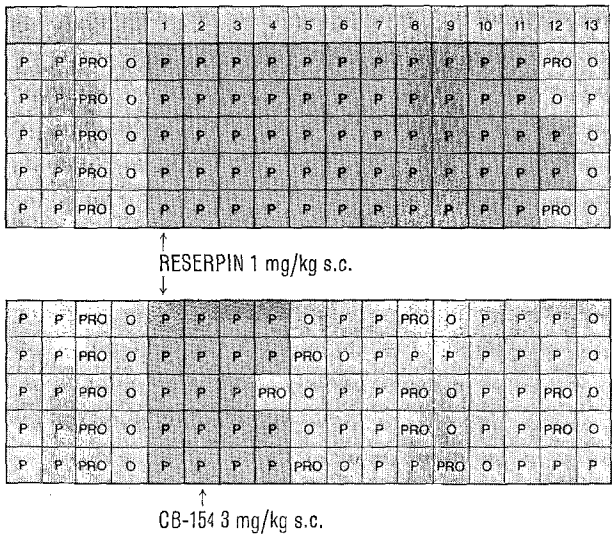

Table I. Vaginal smear patterns showing antagonism of CB 154 to reserpine (R). R controls above, combined treatment below.

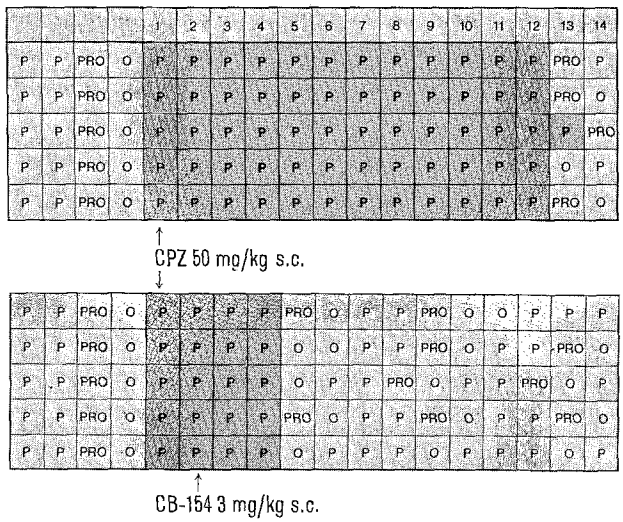

Table II. Vaginal smear patterns showing antagonism of CB 154 to Chlorpromazine (CPZ). CPZ controls above, combined treatment below.

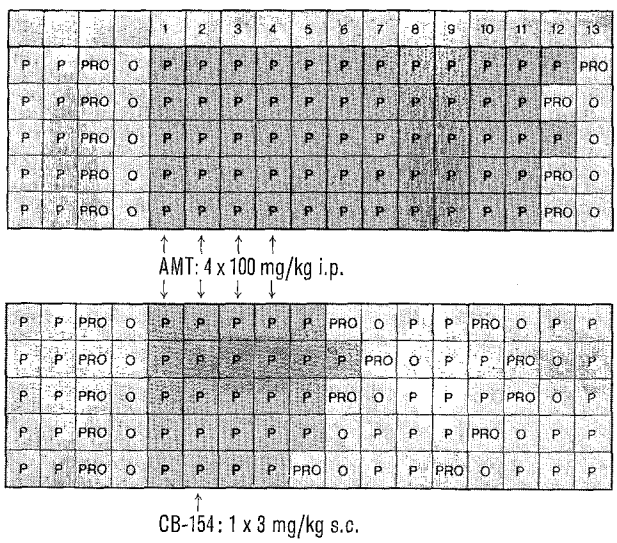

Table III. Vaginal smear patterns showing antagonism of CB 154 to α-methyl-*p*-tyrosine (AMT). AMT controls above, combined treatment below.

temperature (23–24 °C) and constant day light (14 h). They had free access to food and water.

Results. The readings of the vaginal smears of the individual rats are given in Tables I, II and III, where the control and experimental groups belonging to a particular prolactin stimulator are assembled. In the tables the different daily vaginal smear patterns are symbolyzed by the following letters: P, for leucocyte dominance; Pro, for Prooestrus; O, for oestrus. The numbers at the head of the tables count the days since the beginning of treatment.

All three basic treatments (R, CPZ, AMT) suppressed the cyclic-changes of vaginal smear pattern for 11 to 13 days and induced a leucocyte dominance in the smears instead. This vaginal smear picture is characteristic of active corpora lutea, which means under the conditions of the experiment: pseudopregnancy. In a different set of experiments not reported here the same treatment schedule supported scratch induced deciduomas.

If in addition to the basic treatment CB 154 was injected on day P_2 the suppression of cyclicity did not last as long. Instead in all three groups a new prooestrus to oestrus smear appeared within 4 days after CB 154 application.

Discussion. CB 154 interrupted in rats a pharmacologically induced prolactin dominated state and thereby prevented the development of pseudopregnancy. It is known that the three prolactin stimulators have different mechanisms of action in the CNS. R deplets monoamine stores, CPZ acts at synapses and AMT interferes with the synthesis of the transmitter amines. Independently of their primary action all three induce a qualitatively similar state of prolactin secretion, and this is counteracted by CB 154. It is thus probable, that the antagonism between the ergot alkaloid and R, CPZ or AMT does not take place at their primary site of action but somewhere more peripherally. This site could still be at a hypothalamic level[8] or it could be at the pituitary level[6]. The results show that not only physiologically induced states of increased prolactin secretion can be inhibited by CB 154, but that it acts also in experimental models of drug induced prolactin secretion. It is known clinically that CB 154 inhibits postpartum lactation[9] as well as non-puerperal galactorrhoea[10].

Zusammenfassung. Bei Ratten mit drei verschiedenen Modellen pharmakologisch induzierter Pseudogravidität wird gezeigt, dass 2-Br-α-ergokryptin-methansulfonat (CB 154) auch die durch Pharmaka stimulierte Prolactinsekretion zu hemmen vermag.

E. Flückiger, P. M. Lutterbeck, H. R. Wagner and E. Billeter

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