Cobalt concentrations in ppm (dry matter) ± SD of the mean

	Cortex				Caudate nuclei		Raphe nuclei
	Frontal		Occipital				
	Lesion	Contralateral	Ipsi-	Contralateral	Ipsi-	Contralateral	
Day 6	>50 ppm	10.5±5.5	16.8±7.5	12.1±6.2	19.9±5.3	10.0±6.6	3.0±1.9
Day 21	>50 ppm	1.8±1.4	7.9±4.7	5.3±4.7	6.1±3.9	1.98±0.8	2.4±1.6
Day 97	No detectable cobalt						

There were 5 rats in each group. In all cases the glial capsule and any visible traces of cobalt-gelatine were removed from primary lesion samples. It was often not possible to remove all traces of the cobalt-gelatine, however, and therefore physiologically inactive cobalt may well have been assayed in the primary lesion. Excess values referred to represent values of over 50 ppm and were not quantified. Control rats and 97 day rats were assayed under the same conditions as the day 6 and 21 rats (see text) and under these condition no cobalt could be detected.

still significant cobalt in the brain outside the implant. However by day 97 there is no longer detectable cobalt in brain areas outside the glial capsule.

The implication of these results, for this and related models of epilepsy, are profound. Although the in vitro levels of cobalt (2–10 μM) which would be obtained in preparing a conventional brain homogenate (e.g. 1 mg brain tissue in 10 µl buffer) from an animal with a cobalt implant would not be sufficient to inhibit in vitro the enzymes we have previously studied (e.g. tyrosine hydroxylase choline acetyltransferase, glutamic acid decarboxylase)[12]. However, the levels in vivo (20–100 μM) will undoubtedly interfere with a wide range of metabolic process. In fact the wide spread of the cobalt ions and the possibilities of their concentration in different cellular compartments, such as nerve terminals suggests that a large area of the brain may become epileptogenic rather than just a small area around the original implant. These results indicate the need for caution in using heavy metal implants as models of epilepsy and suggest that the basis for cobalt induced epilepsy probably lies in a certain selectivity of cells, terminals and enzymes to the toxic effects of this ion in vivo. Certainly the secondary focus produced in this model of epilepsy although very interesting biochemically cannot be regarded as being untouched by the toxic effects of cobalt.

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Increased Aggression in Rats after Withdrawal of Long Term Used Oxazepam

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Summary. The withdrawal of oxazepam (5 mg/kg i.p.) applied for 1 year in rats, increased shock-induced aggression of animals. This phenomenon is interpreted as a sign of abstinence and suggests that long-term treatment causes dependence to oxazepam in rats.

Oxazepam has a central pharmacological profile consisting primarily of anticonvulsant, sedative-hypnotic, muscle relaxant and anxiolytic activities[2–4]. It is an effective ataractic benzodiazepine drug for treating anxiety in patients[5]. The data in the literature concerning its antiaggressive effects are controversial. In this report we present evidence that oxazepam given for 1 year to rats had no antiaggressive action, but withdrawal of long-term drugs intensifies instrumentally induced aggression.

Methods. Experiments were carried out on male rats of Wistar strain from the Central Animal Farm of Silesian School of Medicine. The weight of animals at the beginning of the experiment was 135–145 g; 5 rats were housed in a cage of dimensions 33 × 40 × 26 cm. During the whole experiment the animals had free access to standard laboratory diet and water. Rats were treated for 1 year with oxazepam (Polfa) at a dose of 5 mg/kg i.p. every day except Sundays. Control animals were injected i.p. with 0.9% NaCl solution, used as a solvent. Drug or solvent were applied in the volume of 1 ml/kg. Aggressive behaviour of rats was induced by applying electrical foot-shock according to Eichelman[6]. The pair of rats was placed in Plexiglas box of dimensions 32 × 25.5 × 30.5 cm with stainless-steel grid floor. Shock was delivered by a constant current at 2 mA for a duration of 0.4 sec every 7.5 sec. For the evaluation of shock-induced-aggression, rats were subjected to daily sessions of testing consisting of 50 foot shocks to each pair of rats. The pairs of the same treated or control rats were examined always be-

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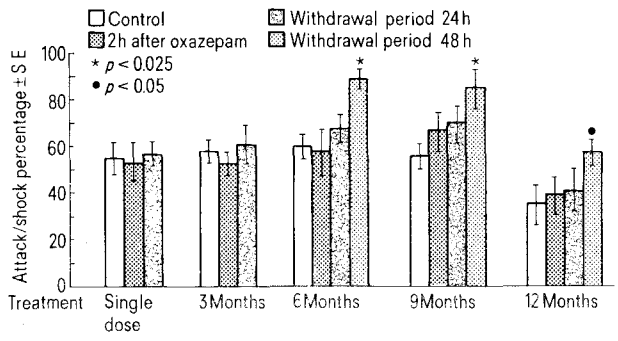
tween 11.00 h and 13.00 h. Animals were divided into groups: 1. 15 rats were treated with a single dose of oxazepam and aggressive behaviour was measured 2 and 24 h later. 2. 9 rats treated chronically with oxazepam were subjected to foot shock 2, 24 and 48 h after the last injection of the drug applied 3, 6, 9 or 12 month.

Corresponding control groups consisted of the same number of animals injected with 0.9% NaCl solution i.p. were handled identically. The extent of foot-shock-induced behaviour was calculated as an attack (shock percentage / the number of attacks divided by the number of shocks administered × 100) according to EICHELMAN[6]. Statistical significance was calculated using Student's *t*-test.



Effect of withdrawal of oxazepam (5 mg/kg i. p.) after the long-term treatment on the foot-shock-induced aggression in rats.

Results. Oxazepam, in a dose of 5 mg/kg i.p. administered only once or 6 times weekly for 3, 6, 9 or 12 months, had no influence on the shock-induced-aggressive behaviour 2 and 24 h after drug injection. The withdrawal of the drug for 48 h in rats treated for half 1 year and up to the one year caused an evident increase of foot-shock-induced aggression of rats (Figure).

Discussion. The antiaggressive action of oxazepam depends upon the used experimental model of aggression. Oxazepam did not reduce aggression elicited by grouping of male mice[7], but suppressed this phenomenon induced in mice by isolation[8], or by administration of D,L-DOPA[9]. Used in our experiments, shock-induced aggression is the most common model for irritable aggression. Oxazepam applied chronically did not affect this type of aggression in rats. The phenomenon which we observed of evident increase of foot-shock-induced aggression of rats during the period of withdrawal of oxazepam after the long-term treatment with the drug, we interprete as a sign of abstinence. This suggests that long-term treatment with oxazepam causes dependence on the drug in rats.

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Distribution of H^3-Dimetacrine in Rat Cerebral Cortex by Electron Microscopic Autoradiography

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Summary. The cellular distribution of H^3-dimetacrine in rat cerebral cortex was studied by electron microscopic autoradiography. A considerable proportion of autoradiographic grains (40.6%) was located over the synaptic areas, while the other structures (i.e., dendrites, axons, glial and neuronal cells) contained less autoradiographic activity.

Dimetacrine[2], 10-[3-(dimethylamino)propyl]-9,9-dimethyl-acridan, is a tricyclic compound with a hexagonal ring instead of the heptagonal ring common to most antidepressants. Clinical superiorities of this drug in the treatment of depressive states and other psychic disorders have been well established[3]. Recent works[4,5] on the subcellular fractionation of brain tissue permitted the isolation of pinched-off nerve endings or synaptosomes, and it has been observed that the bound form of putative central transmitters (acetylcholine, noradrenaline, 5-hydroxytryptamine and dopamine) and the enzymes related to those transmitters are highly concentrated in the synaptosomal fraction. Previous paper[6] demonstrated that the highest concentration of dimetacrine consistently occurred in the synaptosomes-rich fraction. However, biochemical procedures used in the previous study were not sufficient to explain the subcellular distribution of dimetacrine in the central nervous system because of the contamination of each of the subcellular organelles. The objective of the present paper is to visualize the distribution of dimetacrine in undisrupted tissue by electron microscopic autoradiography.

Materials and methods. 3-H^3-dimetacrine (1.92 mCi/mg) was prepared from 3-bromo-dimetacrine. Male Wistar rats (200–250 g) were given 960 μCi/500 μg of H^3-dimetacrine by the direct lateral intraventricular injection method of NOBLE et al.[7]. The animals were sacrificed by decapitation 1 h after administration and cerebral cortices were fixed in cold 4% glutaraldehyde (MILLONIG's buf-

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