conductance in the absence of any effect on the electrochemical gradient. Further studies using specific constituents isolated from the crude mixture are underway.

Riassunto. La tassina cruda, ottenuta del tasso *Taxus baccata L.* ha dimostrato di ridurre l'influsso Na^+ dell'azione potenziale di singole preparazioni axon dal nervo sciatico della rana. La tassina cruda contiene una miscela di composti chimici e noi suggeriamo che la tassicina è il composto chimico responsabile per questo effetto.

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The Effect of Cold and Diazepam on the Toxicity of Fenfluramine in Mice

Fenfluramine is an amphetamine derivative and an antiobesity drug. Fenfluramine intoxications, especially in children, have often been described in literature[1–5]; 8–10 tablets (160–200 mg) alone have caused a severe intoxication in a 2.5-year-old child[5]. There exists evidence that fenfluramine has been used for hallucinogenic purposes[6], which adds to the risk of fenfluramine intoxications.

The treatment of fenfluramine overdose is primarily symptomatic, as no specific antidote exists[5]. Forced diuresis is probably of doubtful value[1]. Pyrexia, convulsions and tachycardia are characteristic of fenfluramine intoxication. Using controlled animal tests, we intend to examine whether cold treatment, diazepam and practolol have any positive effect on the treatment of fenfluramine intoxication.

Materials and methods. Male NMRI-mice used in the test were about 2 months old. The mice were bred in conventional laboratory circumstances, 9–10 of them in 1 box. The fenfluramine hydrochloride dose used in all the tests was 75 mg/kg i.p. because according to the preliminary tests it killed 0.75 of the aggregated mice. The final mortality figures were recorded in 24 h.

In cold treatment tests we used 7 groups of mice, each group consisting of 9–10 mice. The fenfluramine injection was administered at 1 min intervals to different mice of the group. The mice of the 1st group were removed to the same cold box (0 °C) instantly after the injection. The mice of the 2nd group were removed to the same cold box (0 °C) 5 min, those of the 3rd group 10 min and the mice of the 4th group 15 min after the injection. After the injection, before the removal to the cold, the animals of the group were also kept in the same box at room temperature (22 °C). 1 h after the injection the mice were brought to room temperature. The test consisted of 3 control groups. The mice of the 1st group were removed to another box at room temperature 5 min, those of the 2nd group 10 min and the mice of the 3rd group 15 min after the injection.

The effect of diazepam and practolol was examined with 9 groups of mice, each of which consisted of 9–10 mice. The fenfluramine injection was administered at 2 min intervals to different mice of the group. 1.50 min after the administration of fenfluramine the mice received i.v. either diazepam, practolol or physiological saline solution. The mice of each group were put in the same box after the injection.

Results. As soon as 5 min after the fenfluramine injection, the animals jerked and had clonic convulsions. Increased salivation and the rigidity of the limbs occurred as well. Occasional jumping attacks were developed after 7–8 min. Most animals went into a coma before death. Most lethal cases were produced 15–30 min after the injection, rarely any sooner or later. Those animals which survived were in good condition after 24 h. Increased aggressiveness was a frequent symptom.

Cold treatment decreased or abolished the hyperactivity and the convulsions caused by fenfluramine. The effect of cold treatment on the toxicity of fenfluramine has been described in Table I. It can be observed that when the

Table I. The effect of cold treatment on mortality caused by fenfluramine (75 mg/kg i.p.) in mice

Removed to cold (0 °C) after	*n*	Mortality (%)	Significance (p)
Control	29	83	
0 min	10	0	< 0.001
5 min	10	0	< 0.001
10 min	9	11	< 0.001
15 min	10	40	< 0.05

Table II. The effect of diazepam and practolol on mortality caused by fenfluramine (75 mg/kg i.p.) in mice

Post-treatment after fenfluramine	*n*	Mortality (%)	Significance (p)
Saline	28	71	
Diazepam (2 mg/kg)	10	0	< 0.001
Diazepam (0.5 mg/kg)	10	0	< 0.001
Diazepam (0.2 mg/kg)	19	21	< 0.01
Practolol (2 mg/kg)	10	60	n.s.
Practolol (5 mg/kg)	9	11	< 0.01

Diazepam, practolol and physiological saline solution were administered into the tail vein 1.5 min after the fenfluramine injection.

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animals were removed to cold only 15 min after the injection the mortality figures decreased significantly ($p < 0.05$). The mortality levels of 2 control groups showed that 5% had died before 15 min, 21% before 18 min, 37% before 20 min, 53% before 25 min and 74% before 30 min after the injection. Thus it seemed that if an intoxicated mouse was taken into cold a few min before it would otherwise die, it could survive.

The effect of diazepam and practolol on the toxicity of fenfluramine is described in Table II. It can be seen that a diazepam dose of only 0.2 mg/kg decreased the toxicity of fenfluramine significantly ($p < 0.01$). Practolol, on the other hand, had a less important effect. Only a very high practolol dose (5 mg/kg) could decrease the toxicity of fenfluramine. Neither the practolol nor the diazepam dose of 0.2 mg/kg had a clearly noticeable effect on the behaviour phenomena caused by fenfluramine. A diazepam dose of 0.5 mg/kg slightly decreased the convulsions and the jumping attacks. A diazepam dose of 2 mg/kg abolished the convulsions and motor activity.

Discussion. The results established indicate that cold treatment efficiently decreases the fenfluramine toxicity in mice. According to YEHUDA and WURTMAN[7], the toxic fenfluramine dose (50 mg/kg i.p.) raises the rat's temperature at room temperature but causes a 7–8 degrees' (°C) sudden fall at a temperature of 4 °C. It is unclear whether a mere decrease in temperature, or any secondary change caused by it, protects smaller mammals against the toxicity of fenfluramine. It is quite possible that cold treatment in fenfluramine poisoning decreases also man's and especially a child's temperature, or at least prevents it from rising dangerously high.

Only high doses of practolol decrease the toxicity of fenfluramine. Thus it may have no clinical use. On the other hand, diazepam doses, which are equal to human doses, decrease the toxicity of fenfluramine very efficiently. In these tests diazepam was administered after the fenfluramine injection but before the toxic symptoms appeared. These results suggest that diazepam and cold treatment given as early as possible decrease the toxicity of fenfluramine also in men and especially in children.

Zusammenfassung. Kaltbehandlung und i.v. Injektion von Diazepam reduzierten die Toxizität des Fenfluramins bei der Maus beträchtlich.

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Placental Transfer of Fluoride During Methoxyflurane Anaesthesia for Cesarean Section

After the discovery of the prophylactic action of systemic fluoride against dental caries, several studies on the placental transfer of this halide have been carried out. Placental transfer of fluoride has been shown to occur in animals and in humans[1–4]. It is known that the maternal fluoride concentration is dependant on the fluoride content of water and food[5,6]. It was also demonstrated that increased feeding of fluoride to animals and humans causes a rise of F^- concentration in maternal and fetal blood[7]. BAWDEN et al.[8], who administered radiofluoride (18 F) to pregnant ewes, found a relatively low fetal blood plasma radiofluoride level compared to the maternal concentration. ERICSSON and MALMNÖ[9] obtained similar results in their 18 F studies with rabbits as well as in women submitted to therapeutic abortions. However, ARMSTRONG[10] in a series of patients undergoing Cesarean section, found that the fluoride concentration in maternal and fetal blood were quite similar. This result was confirmed in a recent similar study by SHEN and TAVES[11].

The situation seems to be different in the presence of high maternal fluoride levels. For instance, GEDALIA[12] found that the cord fluoride values of babies, born in fluoridated areas, was consistently lower than the mother fluoride levels, whereas this was not the case when the mothers had not been submitted to fluoride supplements (water or tablets).

In a recent study, FRY and TAVES[13] reported on measurements of fluoride containing metabolites in maternal and cord blood associated with Methoxyflurane (MOF) analgesia during labor.

Already during anaesthesia, a metabolic break-down of MOF takes place[14]. This break-down into inorganic fluoride and an organic acid-labile fluoride, presumably methoxydifluoracetic acid, starts within 10 to 15 min after the administration of the anesthetic[13,15]. Thus, high fluoride blood concentrations can be demonstrated, presumably responsible for the observed nephrotoxicity after MOF anaesthesia[16]. FRY and TAVES[13] reported that during analgesia with MOF, the maternal serum inorganic

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