in its toxic action, as may be suggested from the EEG-changes (Figure), which seem to be more pronounced in rabbits pretreated with the xylitol solution than with the fat emulsion. The survival of animals would be due to an uptake of CPZ by the emulsified fat as the i.v. infusion of a fat emulsion leads to a temporary lipemia[7,8]. Furthermore, additional effects of the fat emulsion might decrease the acute toxicity of CPZ. Surfactants like the phospholipids of the fat emulsion used can reduce the diffusion of drugs into the tissue[9]. In addition, it could be demonstrated that the capillary flow in the mesentery of rabbits is lowered in the presence of emulsified fat[10]; a decrease of the capillary flow in brain would reduce the CPZ uptake into the CNS.

Infused fat emulsions hardly enter the brain[11] but can be taken up by phagocytosis by the liver[12]; this means a further pathway of elimination for CPZ. The latter effect, however, is probably of less importance to the acute toxicity of CPZ. From the present results it might be concluded that a fat emulsion in blood can take up lipophilic drugs, reduce their fraction dissolved in plasma water and thus decrease their actual availability at the sites of action. Whether this effect may be used for therapeutical management of poisoning due to CPZ or other lipophilic drugs remains to be shown.

Zusammenfassung. Kaninchen überlebten die letale Dosis von 30 mg/kg Chlorpromazin (i.v.) nur zusammen mit einer Fettinfusion (0,5 ml/kg/min Lipofundin S 10®). Es konnte in vitro gezeigt werden, dass der Zusatz einer Fettemulsion (Lipofundin S 10®) zu Kaninchenblut (25 mg Fett/ml) den Anteil an freiem Chlorpromazin (Gesamtkonzentration 10^{-4} *M*) von 2,05% auf 0,87% herabsetzt.

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The Effects of Nicotinamide on Mouse Sleep

We have previously reported[1] that methionine administered to rats or mice induced behavioral disruption and that the administration of nicotinamide simultaneously with methionine[2] did not prevent disruption of mouse sleep/wake cycles. However, we did observe that nicotinamide when administered alone appeared to increase the amount of paradoxical or rapid eye movement sleep (REM) which the mice had in a 10 h period. This present study describes the effects of nicotinamide on mouse sleep.

Methods. 30 adult, male, random bred Swiss mice weighing between 27 and 35 g were used. The mice were housed randomly 5 per cage in a sound-attenuated room, with continuous diffuse lighting. Half of the animals were injected daily with saline and the other half with 250 mg/kg nicotinamide. The volume injected was 0.01 ml/g body weight, given s.c. in the back. The pH of the nicotinamide solution was adjusted to approximately 7.4. The injections were administered at 09.00 h. On day 19 of injection the animals were anesthetized with diabutal and implanted with 4 cortical electrodes, 2 over the frontal and 2 over the occipital regions of the cortex. A small surgical clip was also fixed to the skull of each mouse. Dental acrylic was built up around the clip and electrodes to hold them in place. The mice were then placed individually in small cages. They were allowed to recover on day 20, but were injected at the normal times. On day 21 they were injected and habituated to the small recording leads which were connected from the implanted electrodes to a polygraph. On day 22 after injection the polygraph was started at 09.30 h and run at a speed of 6 mm sec continuously until 700 pages of electroencephalogram (EEG) record had been collected (this was approximately 10 h later).

Results. VAN TWYVER[3] and others[4–6] have shown that mouse EEG can be classified into 3 categories: awake-low amplitude, high frequency waves; sleep – high amplitude, low frequency waves; and paradoxical or REM

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The effects of nicotinamide on the percentages of the total recording time for slow wave sleep and rapid eye movement sleep (REM) and the percentage of REM of total sleep time

Compound	Slow wave sleep (%)		REM (%)		REM of total sleep time (%)	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Saline	49.8	6.91	6.8	1.35	12.0	2.39
Nicotinamide	43.1	7.73	7.6	1.50	14.9	2.37

sleep – constant amplitude, high frequency θ-waves. The record for each mouse was analyzed into all 3 categories and the overall percentage of each was obtained. The Table shows the mean and standard deviation for the percentages of slow wave sleep and REM, and the percentage REM of total sleep time for both groups. Mann Whitney U-tests were carried out on the data for the percentage of REM (significant at 0.05 level, one-tailed test) and for the percentage REM of total sleep time (significant at 0.01 level, one-tailed test), showing significant increases in both measures for the group treated with nicotinamide. Comparisons between the percentage of REM for the first 300 pages of EEG record and the percentage of REM for the last 300 pages were not significant for either group, indicating that the increase seen after nicotinamide was present for the full 10 h period. We have confirmed these results in a second experiment using inbred C57 mice. All showed a 25%, or more, increase in percentage REM. Further experiments are being conducted with this strain.

Discussion. Much controversy surrounds the use of niacin in the treatment of schizophrenia. LIPTON[7] allows that there may be a small subgroup of schizophrenics who do respond to niacin balanced by an equal number who get worse (see further SMYTHIES[8]). Schizophrenia is clearly a heterogenous syndrome with probably many different biochemical lesions involved in different subgroups. HOFFER[9] began treating patients with nicotinic acid because of its alleged role as a methyl acceptor. It should therefore, theoretically, lower the levels of the available methyl groups which may be contributing to the illness via a transmethylated psychotoxin. HOFFER et al.[9] have repeatedly reported the effectiveness of nicotinic acid in treating schizophrenics; however, many other investigators have failed to do so (these studies are reviewed by WYATT et al.[10]). It has not been shown that nicotinic acid can reverse the exacerbations observed in schizophrenics after the administration of methionine[11], nor is there any reported evidence that it impairs the methylation capacity of the body. Furthermore BALDESSARINI[12] reports that nicotinamide is not a good methyl group acceptor in the rat and does not lower levels of S-adenosyl methionine.

The results of this study show that high doses of nicotinamide may have behavioral effects unconnected with its role as a vitamin. The best known drug that increases REM is reserpine[13]. This suggests that a further pharmacological study of nicotinamide in this light might be of interest.

Résumé. Après avoir reçu pendant 21 jours une injection quotidienne de 250 mg/kg nicotinamide, des souris ont été examinées chroniquement par l'EEG. La nicotinamide prolonge la phase de sommeil et fait augmenter les mouvements oculaires.

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Beta-Adrenergic Dilatory Responses in Isolated, Saline Perfused Arteries of an Elasmobranch Fish, *Squalus acanthias*

Adrenergic receptors have been shown to mediate vasodilation in isolated saline perfused gills of teleosts[1] and elasmobranchs[2]. The sites of adrenergic vasodilation can not be localized in isolated perfused gills and the possibility exists that both shunts within the gill vasculature[3] and tonal changes in the arteries, afferent and efferent to them, contribute to the regulation of branchial circulation. KIRBY and BURNSTOCK[4] were unable to demonstrate any inhibitory responses in lower vertebrate arterial strip preparation including teleost ventral aortae. This communication reports inhibitory reponses to catecholamines in the ventral aorta and afferent branchial arteries of the dogfish, *Squalus acanthias*.

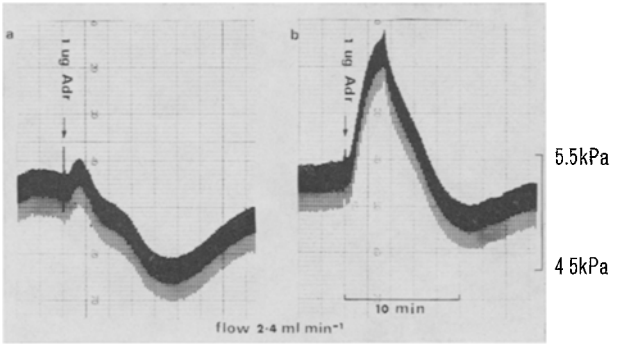

Fig. 1. a) The biphasic response to 1 μg adrenaline in a perfused 1st afferent branchial artery of *Squalus acanthias*. b) The response to 1 μg adrenaline 20 min after the administration of 100 μg of propranolol; the α-component of the biphasic response has been potentiated and the β-component diminished. Ordinate: pressure in kilopascals.

Segments of prebranchial arteries were cannulated in situ in freshly pithed dogfish (1–2 kg); then excized and perfused with an elasmobranch ringer at 10 °C. The ventral aorta and 1–2 cm segments of the 1st (hyoidean), 2nd and 3rd afferent branchial arteries were used. Ventral aortae were cannulated anterior to the conus arteriosus and all the afferent arteries were tied off except an innominate

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