140 mEq/l (total daily amount: 4.2 mEq) containing 2% sucrose. This solution was administered 2 more days, later the phenobarbital solution was reinstituted.

Every day the animals were weighed and the drink and food intake measured. Clean urine was collected under mineral oil in graduated cylinders. Sodium was measured by flame photometry. All the animals consumed all the amount of food and drink (when limited) administered, therefore, daily sodium intake was the same for all the animals.

The increase in sodium excretion after bilateral ADX or sham procedure and the handling of sodium load are shown in the table. The following deduction can be made: bilateral ADX on normal rats produced, in the 3 days after surgical procedures, a significant increase in sodium excretion (more than twice the basal values). This increase was not observed in the cirrhotic animals.

Cirrhotic ADX rats were able to eliminate during 3-day period 64% of a 2-day 8.4 mEq sodium overload, an amount significantly greater than in the sham-operated cirrhotic rats, but significantly less than the excretion percentage of ADX or sham-operated control rats.

Adrenalectomy in the rat strain used does not abolish the aldosterone production but induces a transient aldosterone depletion. The lack of natriuretic response after ADX in cirrhotic rats supports the hypothesis that factors others than aldosterone play a primary role in sodium and water retention by the kidney of cirrhotic rats. However this observation must be regarded with caution because of the possibility of an increase in the half-life of aldosterone in the liver-damaged animals. When sodium-loaded, the ADX cirrhotic rats excreted more sodium than sham-operated animals, but did not reach the sodium excretion of control animals.

From the above experiment, it can be deduced that aldosterone does not play a primary role in the water and sodium retention in this model of experimental liver cirrhosis in the rat, although it might contribute to increase the distal tubular reabsorption of an already decreased sodium load.

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Prolonged action of drugs in rats with flavonoid-deficiency

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Summary. In flavonoid-deficient Wistar-rats, the action of caffeine, harmine, hexobarbital, morphine and pentobarbital is enhanced. In contrast, the thiopental sleeping time is shortened. These observations may indicate impaired drug metabolism as a consequence of the flavonoid-deficiency state.

Flavonoids are a class of compounds widely distributed in plants and all having the 2-phenylbenzo-γ-pyrone structure[1]. However, the physiological role of these substances, in plants as well as in animals, has not been totally elucidated. There are some indications that, in rats at least, flavonoids are related to vitamins[2].

In flavonoid-deficient rats, pentobarbital- and hexobarbital-induced sleeping times are prolonged. This results from impaired metabolism of barbiturates.[3].

The question arose as to whether other types of drugs, eliminated by different metabolic pathways, also have a prolonged action. Therefore, rats given a diet lacking flavonoids[4], for a period in excess of 25 weeks, were treated with caffeine, harmine, morphine or thiopental. Motor activity, tremor duration, duration of response to a pain stimulus and sleeping time were then estimated and compared with controls. In addition, hexobarbital and pentobarbital were used, since the present results deal with a different strain of rat than those described in a former publication[3].

Materials and methods. Male Wistar rats (Bäumler/Wolfratshausen, BRD) weighing approximately 240 g, were given a flavonoid-deficient diet[4] for in excess of 25 weeks. Following this treatment, 1 group of 5 rats was dosed with caffeine (50 mg/kg i.p.). Motor activity was followed 15 min after injection by counting the interruptions of a light beam from a suspended lamp falling on photosensitive cells. A 2nd group of 5 flavonoid-deficient rats was treated with harmine hydrochloride (10 mg/kg i.v.). The rats immediately went into tremor, the duration of which was followed as previously described[5]. A 3rd group of 10 rats was treated with morphine hydrochloride (5 mg/kg

Action of different drugs in flavonoid-deficient rats in comparison to controls

Drug	Control rats	Deficient rats
Caffeine	354 ±51 (5)	501 ±34 (5)
Harmine	78 ± 3 (5)	95 ± 4 (5)
Morphine 20 min	9.1± 1.3 (10)	12.6± 1.5 (10)
30 min	7.1± 1.0 (10)	10.5± 1.4 (10)
Hexobarbital	12.3± 0.7 (10)	16.7± 1.0 (10)
Pentobarbital	25.3± 2.2 (10)	37.5± 2.7 (10)
Thiopental	2.6± 0.3 (10)	1.9± 0.2 (10)

Units of measurement: Caffeine, interruptions of light beams; harmine, hexobarbital, pentobarbital and thiopental, min; morphine, sec. (n)=rats/group. For detail see Materials and methods.

i.p.); 20 and 30 min after the injection, the rats were placed on a hot plate (56 °C). The morphine effect was measured by the response of the rat to the hot plate in terms of time taken (sec) to raise the hind paw. A 4th group of 10 rats was treated with thiopental (20 mg/kg i.v.), 2 further groups of 10 rats each with hexobarbital (50 mg/kg i.v.) and pentobarbital (25 mg/kg i.v.), respectively. The sleeping time was estimated as the time taken following injections for the animals to rise from a reclining to a standing position.

Results are given as mean±SEM ($\bar{x}\pm S_{\bar{x}}$). Statistical analysis of experimental values in comparison to controls was carried out using Student's t-test. Differences are denoted as significant when $p<0.05$.

Results. Feeding the rats for 25 weeks with the flavonoid-deficient diet increased their b.wt from 248±3 g (n=60) to 430±5 g (n=60), whereas the controls showed a significantly lower increase i.e. from 240±2 g (n=60) to only 391±5 g (n=60). In flavonoid-deficient rats, caffeine, harmine, morphine, hexobarbital and pentobarbital acted significantly longer than in normally fed animals. In contrast, thiopental was found to cause a decreased sleeping time (table).

Discussion. The prolonged action of metabolically inactivated barbiturates such as hexobarbital and pentobarbital[6] in flavonoid-deficient rats, as already demonstrated in animals of the Sprague-Dawley strain[3,4], has now been found to be a more general phenomenon, since, in the present experiments, similar results were obtained in Wistar rats. In contrast, thiopental, which is well known to be inactivated by redistribution phenomena[6], showed a decreased duration of action. The shortened action of thiopental may be related to a possible elevation of the lipid content in the deficient rats which, indeed, showed a greater increase of b.wt during the feeding period than did the controls.

Hexobarbital is also partially inactivated by redistribution. Nevertheless, it caused a prolonged sleeping time in the deficient animals. The prolonged effect of hexobarbital could be explained if an impairement in its metabolism counteracted the inactivation caused by redistribution. In rats, as in other species, caffeine, harmine and morphine are all eliminated mainly by metabolic degradation[7-9].

In order to explain the prolonged effects of these drugs in a flavonoid-deficiency state, the assumption is made that the metabolic inactivation of all these compounds in the liver is impaired, as seems to be the case with the metabolically eliminated barbiturates. Recently, it was shown that a flavonoid-free diet in rats caused distinct changes of the hepatic enzyme profile[10]. This may also be related to a general impairment of drug metabolism. These results support the concept that flavonoids have a vitamin-like character[2].

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Effect of non-steroidal anti-inflammatory drugs on Moloney sarcoma virus inoculated mice

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Summary. Chronic administration of phenylbutazone, flufenamic acid and a new, potent non-steroidal anti-inflammatory agent ITF (3-methyl-5-benzoyl-amino-isothiazole-4-carboxy-p-ethoxyphenylamine) to BALB/c mice inoculated with a Moloney sarcoma virus resulted in a stimulation of tumor growth and increased severity of disease. This treatment, however, had no effect on the spontaneous regression of tumors. Indomethacin in a dose of 5.0 or 2.5 mg per kg suppressed the MSV-induced tumor growth, but this effect was apparently connected with the high toxicity of this drug for mice.

The Moloney sarcoma virus (MSV) tumor in the mouse 'is at the same time a malignant disease and an infectious disease, with spreading of the virus from producer cells to surrounding normal cells'[1]. It has frequently been used as a model in tumor immunology, since large tumors develop rapidly at the site of virus inoculation, and in the mature animals the neoplasms regress in almost all instances. The regression process is immunologically mediated[1-3]. The tumor mass in the MSV-infected animals consists mainly of the neoplastic cells and infiltrating inflammatory cells, which in turn consist principally of T lymphocytes and macrophages[2,3].

Recently, Humes and Strausser et al.[4-7] reported that chronic administration of indomethacin, a potent prostaglandin synthetase inhibitor, to BALB/c mice inoculated with MSV, delayed the onset of the tumor and suppressed the tumor growth. The authors suggested that indomethacin may act by inhibiting prostaglandins synthesized in large amounts in tumors, and that this process may help to restore the depressed immune response of sarcoma-bearing mice[6,7].

Independently, Seifter et al.[8] showed that the feeding of laboratory chow containing 325 mg of aspirin per kg diet, to CBA mice inoculated with MSV, resulted in the decrease in tumor incidence and severity of disease. The authors characterized the action of aspirin as being anti-viral rather than antitumor. These observations and suggestions were intriguing, but at the same time they were difficult to reconcile with several facts. First of all, since the anti-inflammatory drugs inhibit influx as well as reactivity of