Die Messung der Gesamt-^{3}H-Aktivität (DDT + Metaboliten) bei der relativ hohen Dosierung der Serie 1 zeigte, dass in Blut und Gehirn bei Mutter und Fetus dieselben Konzentrationen von 1–1,5 bzw. 0,5–0,8 ppm nach 24–72 h auftreten; eine Plazentarschranke existiert also zumindest in diesem Stadium der Fetogenese nicht. In der Leber treten beim Muttertier etwa 3–4fach höhere Konzentrationen (3–4 ppm) auf als beim Fetus (0,6–1,0 ppm); die Hauptmenge wird erwartungsgemäss im Fett gespeichert (maximal bis zu 90 ppm). In den ersten 10 Tagen nach der Geburt sinken die pränatalen Werte der Feten von 0,5–1,5 ppm um mehr als 90% ab; daraus ist zu erkennen, dass zumindest unter der hier gewählten relativ hohen Dosierung von 1 mg die transplazentare Kontamination des Fetus beachtliche Werte erreicht. ENGST et al.[6] konnten zeigen, dass auch beim Menschen unter Umweltbedingungen die pränatale Kontamination mit DDT + DDE wesentlich höher liegt als die durch die spätere Nahrungsaufnahme sich ergebenden Rückstände.

Unter Hungerbelastung treten in allen untersuchten Organen eindeutig höhere Rückstandswerte auf; auch hier sind die Konzentrationen im maternalen und fetalen Blut mit und ohne Hungerbelastung gleich. Die gefundenen Metaboliten und ihre Konzentrationen (Serie 3) wurden in der Tabelle zusammengestellt. In der fetalen Leber werden nur sehr geringe Mengen DDD gebildet. Unter Hungerbelastung nimmt der Anteil an DDE in der Leber und im Fett in geringem Umfange zu, während das Verhältnis der anderen Metaboliten im wesentlichen konstant bleibt. DDE entsteht in grösseren Mengen nur bei chronischer DDT-Aufnahme, während bei kurzen Versuchszeiten nur geringe Mengen DDE gebildet werden[10].

Summary. After i.p. application of 1, 0,5 and 0,1 mg p,p′ DDT, labelled with ^{3}H or ^{14}C, to pregnant mice in different stages of pregnancy, the same level of radioactivity was found in the fetal and maternal blood. Starvation for 2 days caused a significant increase of residues, especially in the liver. Residue levels of DDT and its metabolites DDE, DDD, DCB and (DDOH + DDA) are found in fetal and maternal blood, brain, liver and fat.

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On the Effect of Amantadine on Monoamines and Their Metabolites in the Brain and Cerebrospinal Fluid[1]

Since a beneficial effect of amantadine in Parkinson's disease was first demonstrated[2], it has been confirmed in many subsequent trials [3–9]. But little is known about the exact mechanism of action of the drug in improving patients with Parkinson's disease. However, the most recent evidence on experimental animals points to some interrelationship between amantadine and monoamines[10–14]. To further clarify this possibility, we have studied the effect of amantadine on the concentrations of homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF) of parkinsonian patients, as these concentrations give some indication of the metabolism of dopamine and 5-hydroxytryptamine in the brain[15]. In addition, the concentration of dopamine, HVA, noradrenaline, 5-hydroxytryptamine and 5-HIAA of autopsy brain samples of a parkinsonian patient treated with amantadine was studied. The effect of amantadine on these biogenic amines in the rat brain was investigated in the same connection.

Material and methods. A sample of cerebrospinal fluid (CSF) was collected by lumbar puncture from 13 hospitalized patients with Parkinson's disease prior to and at 1 and 3 months of amantadine treatment. All the patients had idiopathic Parkinson's disease. 5 patients were female and 8 male; their age ranged from 47 to 76 years (mean 62 ± 4 years). The duration of the disease was from 1 to 8 years, average 4 ± 0.5 years. The dose was 300 mg daily. The CSF samples were taken between 08.00 h and 10.00 h with the patients recumbent.

The autopsy brain samples were obtained from a 76-year-old male patient who had suffered from Parkinson's disease for 12 years. The disability of the patient was stage 5 according to the scale described by HOEHN and YAHR[16]. The clinical picture of the patient was characterized by a very marked akinesia and rigidity associated with moderate tremor in the left hand. Prior to his death, the patient was treated with amantadine for 2 months with a daily dosage of 200 mg. The last dose of 100 mg of amanta-

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Table I. Concentrations of HVA and 5-HIAA in the CSF of control subjects and parkinsonian patients prior to and during amantadine treatment

Patients	Homovanillic acid (ng/ml) (Mean ± S.E.M.)	5-Hydroxyindoleacetic acid (ng/ml) (Mean ± S.E.M.)
Control subjects	34.6 ± 1.9 (63)	24.4 ± 1.9 (10)
Parkinsonian patients		
Prior to amantadine	13.5 ± 2.2[a] (13)	12.8 ± 2.4[b] (13)
1 month on amantadine	11.4 ± 1.8 (13)	12.9 ± 3.0 (13)
3 months on amantadine	12.7 ± 2.8 (8)	16.7 ± 1.5 (8)

[a] Control/pretreatment ($P < 0.001$). [b] Control/pretreatment ($P < 0.01$).

dine was given 7 h prior to death. The patient also had trihexyphenidyl 12 mg daily as anticholinergic treatment. The autopsy was carried out 24 h after death and it showed that the cause of death was bronchopneumonia. Various regions of the brain were dissected out and immediately deep-frozen for biochemical analyses. Control samples of corresponding brain regions were obtained from 4 parkinsonian patients who had not been treated with amantadine, as well as from 17 patients of the same age without extrapyramidal disorders.

Adult male rats were injected with amantadine 25 mg/kg i.p. daily for 9 days. Control rats were injected with the same volume of saline daily. The rats were killed 60 min after the last injection.

Biochemical analyses of dopamine and noradrenaline were carried out according to CARLSSON and LINDQVIST[17], HVA by the method of ANDÉN et al.[18], 5-hydroxytryptamine according to MAICKEL et al.[19] and 5-HIAA in tissue as described by CURSON and GREEN[20] and in the CSF by ASCHROFT and SHARMAN[21].

Results. Table I shows that the mean concentration of HVA and 5-HIAA in the CSF was significantly lower in parkinsonian patients before amantadine treatment than that of non-parkinsonian control subjects. But amantadine treatment did not cause any significant changes in the mean concentration of either metabolite. Nor was there a clear relationship between the concentration of these amines and the clinical improvement, which was moderate in 6 patients and none or minimal in the others.

As can be seen in Table II, the concentration of dopamine and HVA in the extrapyramidal brain regions of parkinsonian patients was significantly decreased compared with corresponding values of control subjects. But amantadine treatment did not induce any significant changes in the concentrations of dopamine, HVA or noradrenaline in the brain of the patient on amantadine therapy.

Experiments carried out on rats showed (Table III) that amantadine treatment for 9 days did not significantly alter the contents of dopamine, HVA or noradrenaline in the brain.

Discussion. Studies concerning the mode of action of amantadine have shown that it has essentially no anticholinergic activity[10]. But there is recent evidence that the adrenergic system might be involved. Experimental studies have shown that amantadine is able to release catecholamines from neuronal stores in the peripheral nervous system[10], and also induce release of dopamine

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Table II. Concentration of dopamine and homovanillic acid in brain regions of a patient with Parkinson's disease treated with amantadine (200 mg daily for 2 months). [a] Number of patients im parentheses.

Group	Dopamine (μg/g)			Homovanillic acid (μg/g)		
	Controls	Parkinson patients		Controls	Parkinson patients	
		Without amantadine	With amantadine		Without amantadine	With amantadine
1. Caudate nucleus	1.20 ± 0.16 (10)[a]	0.24 ± 0.03 (4)	0.23	2.53 ± 0.42 (17)	0.54 ± 0.33 (4)	0.66
2. Putamen	2.05 ± 0.23 (9)	0.18 ± 0.07 (4)	0.01	5.00 ± 0.56 (17)	0.72 ± 0.21 (4)	0.71
3. Pallidum	0.98 ± 0.14 (10)	0.10 ± 0.05 (4)	0.01	3.26 ± 0.50 (16)	0.82 ± 0.31 (4)	0.47
4. Substantia nigra	0.63 ± 0.10 (8)	0.09 ± 0.03 (3)	0.14	1.81 ± 0.13 (16)	0.60 ± 0.27 (4)	0.17
5. Thalamus	0.35 ± 0.10 (9)	0.26 ± 0.09 (4)	0.32	0.33 ± 0.09 (8)	0.18 ± 0.33 (3)	0.04
6. Hypothalamus	0.41 ± 0.10 (7)	0.16 ± 0.08 (4)	0.15	0.64 ± 0.18 (8)	0.31 ± 0.38 (3)	0.04
7. Cerebral cortex	0.19 ± 0.05 (10)	0.13 ± 0.11 (4)	0.01	0.09 ± 0.07 (8)	0.01 ± 0.07 (3)	0
8. Cerebellar cortex	0.26 ± 0.06 (10)	0.08 ± 0.02 (4)	0.10	0.02 ± 0.03 (8)	0.04 ± 0.17 (3)	0

Corresponding analyses were also carried out on non-parkinsonian control patients and patients with Parkinson's disease without amantadine treatment. Mean ± S.E.M.

Table III. Effect of amantadine on the concentration (μg/g ± S.D.) of dopamine, homovanillic acid and noradrenaline in rat brain

Group	Dopamine	Homovanillic acid	Noradrenaline
Control	0.18 ± 0.13 (4)[a]	0.03 ± 0.02 (9)	0.26 ± 0.08 (6)
Amantadine (25 mg/kg i.p., daily for 9 days)	0.20 ± 0.09 (4)	0.03 ± 0.01 (13)	0.23 ± 0.06 (12)

[a] Number of rat brains.

within the brain[11,12]. On the other hand, large amounts of amantadine inhibits the uptake of dopamine and noradrenaline by rat brain homogenates[13] and that of dopamine by blood platelets[13]; this, however, seemed to be rather unspecific and obviously without any physiological significance. The results of the present investigation did not demonstrate any significant changes in the concentrations of HVA and 5-HIAA in the CSF, which might reflect the metabolism of dopamine and 5-hydroxytryptamine in the brain[15]. The unchanged content of amines analyzed in the brain of a parkinsonian patient on amantadine therapy further supported this point. Correspondingly, amantadine did not alter the endogenous concentration of dopamine, noradrenaline or HVA in the brain of the rat. However, it must be taken into consideration that amantadine might have certain effects on the turnover of these amines in the brain without altering their endogenous concentration. Further studies will be necessary to elucidate whether a suggested amphetamine-like mechanism on monoamines[12] might account for the clinical efficacy of this drug against Parkinson's disease.

Zusammenfassung. Nachweis des stark herabgesetzten Säuregehalts der Homovanillinsäure und der 5-Hydroxyindolessigsäure im Liquor cerebrospinalis von Parkinsonkranken im Vergleich mit normalen Versuchspersonen. Die Amantadin-Therapie hingegen ergab keine bedeutenden Veränderungen und der Gehalt von Dopamin, Noradrenalin und Homovanillinsäure im Gehirn der behandelten Parkinsonpatienten entsprach auch den Werten der übrigen Parkinsonkranken. Ausserdem hatte Amantadin keinen Einfluss auf den endogenen Gehalt dieser Amine im Rattengehirn.

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Paradoxical Inhibition of the Effects of Bradykinin by some Sulfhydryl Reagents

Phenylbutazone and similar antiinflammatory drugs inhibit bradykinin induced bronchoconstriction in the guinea-pig[1], and the second phase of the hypotension evoked in rabbits and guinea-pigs[2,3]. The same drugs interfere with the action of SRS-A[4], arachidonic acid[5], and SRS-C[6,7], in guinea-pigs, rabbits and dogs. These and other results led to the suggestion that all agonists whose in vivo pharmacological effects are inhibited by analgesic antiinflammatory drugs released a common mediator, in a process where those antagonists interfere. A new principle, called 'rabbit aorta contracting substance' (RCS), released from guinea-pig lungs by bradykinin, SRS-A and anaphylaxis, has been proposed as such a mediator, as its release is blocked by aspirin and indomethacin[8,9]. We have recently shown that injection of SRS-C and arachidonic acid is followed by a release of RCS from isolated guinea-pig lungs and that this release is similarly blocked by aspirin and phenylbutazone[10].

The present results show that certain sulfhydryl agents, known to potentiate the vascular effects of bradykinin[11,12] and the non-sulfhydryl reagents pyrogallol and hydroquinone, also inhibit the in vivo bronchoconstriction due to bradykinin in the guinea-pig. Moreover some of those antagonists at convenient doses curtail the effects of bradykinin in the rabbit, as does phenylbutazone. Finally those drugs suppress the release of RCS from isolated guinea-pig lungs injected with bradykinin. New evidence is thus provided for the common mediator hypothesis and it is suggested that in the system responsible for the release of RCS an oxidative step is involved, which is blocked by antioxidants and by acidic antiinflammatory drugs.

Materials and methods. The blood pressure of rabbits and guinea-pigs anaesthetized with sodium pentobarbitone was recorded; guinea-pig pulmonary resistance to inflation was also measured by appropriate transducers on a pen recorder. Guinea-pigs were pretreated with propranolol to prevent antagonism of bronchoconstriction due to release of adrenaline[13]. All injections were given intravenously.

Release of RCS from isolated guinea-pig lungs was investigated as described by Piper and Vane[9] with simultaneous record of pulmonary resistance[10]. Isolated strips of rabbit aorta and pulmonary artery and of rat

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