results obtained may provide leads for further and more intensive in vivo study. Whether the information gained in the study of isolated cell systems can be extrapolated to the intact animal is an area for speculation. The method does, however, offer some insight into complex processes at a cellular level which would otherwise be impossible to study in the intact animal. Also established was the difficulty to find any relationship between the structural formulas of these compounds and the concentration needed to produce toxic effects. While the lathyrogens exhibit a common effect in the animal, it is doubtful that their mechanisms of action are necessarily similar[16].

Zusammenfassung. Für 11 bekannte lathyrogenische Substanzen wurden In-vitro-Modellsysteme entwickelt. Die günstigste Dosierung entsprach der höchsten atoxischen Konzentration des Lathyrogens.

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The Effect of Imipramine and Desipramine on UDP-Glucuronyltransferase

Imipramine (N-(3-dimethylaminopropyl) imino-dibenzyl hydrochloride) and desipramine (N-(3-methylaminopropyl) iminodibenzyl hydrochloride) are iminodibenzyl derivatives used extensively as antidepressants[1]. After imipramine administration relatively high concentrations are found in the liver, brain and lungs, the distribution being similar to the phenothiazines[2]. The major pathways of imipramine metabolism involve hydroxylation[3] and N-demethylation as well as glucuronide conjugation. Desipramine is formed by the demethylation of imipramine and has been considered to be the pharmacologically active form of imipramine[4].

Jaundice has been recorded in 0.5% to 1% of patients treated with imipramine[1]. The jaundice is transient and clears promptly when administration of the drug is discontinued[5]. The jaundice is usually cholestatic in type and resembles jaundice due to phenothiazines although a fatal case of hepatic necrosis associated with combined imipramine and desipramine therapy has been described[6]. Since chlorpromazine and some related drugs inhibit UDP-glucuronyltransferase (UDP-glucuronate glucuronyltransferase (acceptor unspecific) E.C.2.4.1.17.) we have examined the effect of imipramine and desipramine on conjugation mechanisms in rat and guinea-pig liver using in vitro systems in order to determine the possible cause of the jaundice. Bilirubin conjugation was determined in rat liver slices and guinea-pig liver homogenates by the method of LATHE and WALKER[7]. *o*-Aminophenol conjugation was determined in rat liver slices by the method of LEVVY and STOREY[8] and in guinea-pig liver homogenates by the method of STEVENSON and DUTTON[9].

The addition of imipramine and desipramine lowered the rates of conjugation of *o*-aminophenol by rat liver slices. Imipramine decreased the rate of bilirubin conjugation but desipramine did not consistently decrease the rate of bilirubin conjugation by rat liver slices (Table I). The transferase stage of conjugation was examined in guinea-pig liver homogenates incubated with ample uridine diphosphate glucuronic acid. Imipramine reduced the rates of conjugation of bilirubin and *o*-aminophenol but desipramine only reduced the rate of conjugation of *o*-aminophenol (Table II).

The effect of imipramine and desipramine on rat liver slices was investigated further by determining the conjugated bilirubin in the liver slice after 2 h incubation[10]. Imipramine decreased the amount of conjugated bilirubin in the slice whereas desipramine did not (Table III). Both imipramine and desipramine increased the unconjugated bilirubin in the liver slice.

Jaundice following imipramine and desipramine therapy is usually cholestatic in type but they can also cause hepatocellular necrosis. The jaundice is similar to that seen after phenothiazine administration. Imipramine and desipramine resemble the phenothiazines since they are metabolized in liver microsomes to form hydroxylated and desmethyl metabolites which are excreted unchanged or conjugated with glucuronic acid. Imipramine and desipramine inhibit *o*-aminophenol conjugation in liver slice and homogenate preparations. Imipramine inhibits bilirubin conjugation in rat liver slices and guinea-pig homogenates but desipramine does not consistently inhibit bilirubin conjugation. This could be explained

Table I. Effect of imipramine and desipramine on conjugation in rat liver slices

Concentration (m*M*)	Rate of conjugation (nmoles/mg wet wt./h) Imipramine		Desipramine	
	Bilirubin	*o*-Aminophenol	Bilirubin	*o*-Aminophenol
0	0.055	0.36	0.041	0.36
0.01	0.047	0.34	0.023	0.28
0.1	0.030	0.27	0.017	0.23
1.0	0.016	0.07	0.023	0.07
10.0	0	0.05	0.019	0.04
	(6)	(6)	(5)	(3)

Number of experiments in parentheses.

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Table II. Effect of imipramine and desipramine on conjugation in guinea-pig liver homogenate

Concentration (mM)	Rate of conjugation (nmoles/mg wet wt./h) Imipramine		Desipramine	
	Bilirubin	*o*-Aminophenol	Bilirubin	*o*-Aminophenol
0	0.32	2.66	0.25	2.29
0.01	0.32	2.64	0.22	2.24
0.1	0.29	3.00	0.26	2.31
1.0	0.28	1.95	0.23	1.78
10.0	0.20	0	0.24	0
	(3)	(3)	(3)	(3)

Number of experiments in parentheses.

Table III. Effect of imipramine and desipramine on bilirubin uptake in rat liver slices

Concentration (mM)	Bilirubin content µg/g wet wt. Imipramine		Desipramine	
	Conjugated	Unconjugated	Conjugated	Unconjugated
0	73.0	8.3	33.3	37.2
0.01	67.6	7.3	32.0	22.4
0.1	63.4	29.9	34.1	35.8
1.0	37.6	64.6	29.8	71.4
10.0	22.4	199.6	27.4	177.6
	(6)	(6)	(5)	(5)

Number of experiments in parentheses.

by the existence of separate systems conjugating bilirubin and *o*-aminophenol. Imipramine reduces the conjugated bilirubin content of slices which is consistent with the reduction of conjugated bilirubin in the medium containing the liver slice measured by the rate of conjugation. Desipramine does not decrease the amount of conjugated pigment in the slice. Like the phenothiazines[11] both drugs strikingly increase the amount of unconjugated bilirubin in the slice. This may be a surfactant property of the iminodibenzyl molecule and is to be expected because of the amphipathic structure of the molecule.

Imipramine inhibits bilirubin and *o*-aminophenol conjugation but desipramine only inhibits *o*-aminophenol conjugation. Since imipramine and desipramine jaundice is cholestatic or hepatocellular in type it is doubtful whether it can be explained by inhibition of UDP-glucuronyltransferase alone but enzyme inhibition may be one of the factors involved. The most striking feature of the effect of these drugs in vitro is their ability to increase bilirubin uptake by rat liver slices, a property which they share with phenothiazine derivatives[11] but with no other drugs tested[12,13].

Zusammenfassung. Der Einfluss von Imipramin und Desipramin auf die Umwandlung von Bilirubin und *o*-Aminophenol in deren jeweilige Glukuronide wurde in vitro in der Leber untersucht. Imipramin blockiert die Umwandlung von Bilirubin und von *o*-Aminophenol, während Desipramin nur diejenige von *o*-Aminophenol blockiert.

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Über die Wirkung von rac-endo-2-Bornanamin und von verwandten Verbindungen gegen Influenza-A_2-Virus Asia

Bei der routinemässigen Prüfung einer grösseren Reihe verschiedenartiger Verbindungen zeigte sich, dass rac-endo-2-Bornanamin-hydrochlorid (**1**) an der Maus gegen Influenza-A_2-Virus Asia wirksam ist. Diese Beobachtung veranlasste uns, Derivate von **1** und verwandte Verbindungen herzustellen und auf ihre Wirkung gegen Influenzaviren zu prüfen (Tabellen I und II).

Resultate. In den Tabellen I und II sind die Prüfungsergebnisse zusammengestellt. Es ist festzustellen, dass keine der Verbindungen **2** bis **42** wirksamer ist als rac-endo-2-Bornanamin (**1**). Der (+)-Antipode (**30**) des endo-2-Bornanamins schneidet nicht besser ab als das Racemat **1**. Das Racemat (**31**) und der (−)-Antipode (**32**) des exo-2-Bornanamins sind den besten Verbindungen der endo-Reihe unterlegen. Einzig die N-Methylverbindung **2** und die N-(*p*-Fluorobenzyl)-Verbindung **7** erreichen nahezu die Wirkung von **1**. Die systematische Abwandlung der Substitution des N-Benzylrestes führte nicht zu wirksameren Präparaten (Verbindungen **5** bis **20**). Das gleiche gilt für den Übergang aus der N-Benzylreihe in die N-Phenäthyl-Reihe (Präparat **21**) und in die N-(Phenylpropyl)-Reihe (Präparat **23**). Schliesslich ist zu erwähnen, dass alle Verbindungen, in welchen das N-Atom des Bornanamins infolge der Substitution nicht basisch ist, unwirksam oder höchstens schwach wirksam sind (Tabelle II).

Unter denselben Versuchsbedingungen wie für die Prüfung auf Wirkung gegen Influenza-A_2-Virus Asia entfaltete das rac-endo-2-Bornanamin (**1**) gegen die Influenzaviren A (PR_8), A_1 (Melbourne, FM_1 und $E_{1/53}$) keine Wirkung. Die Verbindung war jedoch schwach wirksam gegen Infektionen mit Influenza-B-Viren (Lee, Johannesburg, Stockholm) und Parainfluenza-Virus 1 (Sendai).

Prüfung auf Wirkung gegen Influenza-A_2-Virus Asia. Gruppen von je 10 Füllinsdorfer Albinomäusen aus geschlossener randomisierter Auszucht im Gewicht von 14–15 g werden unter leichter Äthernarkose je mit 0,05 ml einer Influenza-A_2-Virus-Asia-Suspension intranasal infiziert. Zur Herstellung des Inoculums werden Lungen von infizierten Tieren unter sterilen Kautelen im Mörser mit