to muscle in the first minutes of flight is one that can be oxidized anaerobically such as glucose. Later, a fuel such as the UFA, which must be oxidized aerobically, which is of high calorific value, and which is available in relatively unlimited quantity, comes into its own when the respiratory and circulatory systems are delivering more oxygen to the tissues.

Résumé. Lorsque l'organisme est mis brusquement dans une situation exigeant de promptes réactions, une décharge sympathique cause immédiatement une importante élévation du glucose sanguin alors qu'il n'y a tout au plus qu'une légère augmentation des acides gras non-estérifiés du plasma. Une augmentation plus durable de ces acides gras non-estérifiés suit le retour à la normale du glucose sanguin.

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Inhibition of Pentobarbital and Meprobamate Metabolism by some 'Inducers' of Drug-Metabolizing Enzymes

Recently, a variety of 'prolonging agents', which enhance drug action by virtue of their ability to inhibit drug biotransformation, have been reported.

For example, SKF 535 A (2-diethylaminoethyl-diphenylpropyl-acetate) Lilly 18947, (N, N-diethyl-N-2-phenyl-4, 6-dichlorophenoxy-ethylamine) iproniazid and N-ethyl-3-piperidyldiphenylacetate, owe their prolonging action to nonspecific inhibition of some microsomal drug-metabolizing enzymes[1,2].

On the other hand, drugs, such as phenobarbital, phenaglycodol, glutethimide, chlorcyclizine, phenylbutazone, aminopyrine, zoxazolamine, meprobamate, chlorpromazine, niketamide, chloretone, if injected 12–24 h in advance, induce an increase activity of some microsomal drug-metabolizing enzymes[3–11].

The hypothesis arises that some of the above mentioned drugs inducing a late increase of activity of drug-metabolizing enzymes, have an immediate blocking action on the same enzyme systems.

Male rats of the Sprague-Dawley strain, weighing about 60 g were used.

The enzyme activities were determined by measuring the amount of metabolized drugs during an incubation of 1 h with liver microsome-containing supernatant as described previously.

Concentrations of pentobarbital and meprobamate were determined according to the methods of BRODIE et al., and HOFFMANN and LUDWIG, respectively[12,13].

In every case, the possibility of an interference in the determinations of pentobarbital and meprobamate concentrations by the inhibitors and their metabolites was excluded.

The concentrations of inhibitors which produce 50% inhibition of pentobarbital and meprobamate metabolism is shown in the Table.

Concentration of SKF 525 A[14] and Lilly 18947[14] producing 50% inhibition were also given, because they can induce the microsomal drug-metabolizing enzymes[15].

Chlorcyclizine had the most potent inhibitory action which is almost of the same potency as that of SKF 525 A and about 2 times more potent than that of Lilly 18947.

Glutethimide was potent not only in the metabolism of pentobarbital, but also in the meprobamate metabolism. These facts suggest that glutethimide inhibits pentobarbital metabolism not only by virtue of the similarity of its chemical structure to pentobarbital.

Phenobarbital which has the most potent inducing action of the microsomal drug-metabolizing enzymes, shows however, a weak inhibitory action on the me-

Inhibition of pentobarbital and meprobamate metabolism by some inducing-drugs of the microsomal drug-metabolizing enzymes

Inhibitors	Concentrations producing 50% inhibition (Mol)	
	Metabolism of pentobarbital	Metabolism of meprobamate
1 Chlorcyclizine	2.0×10^{-5}	1.4×10^{-4}
2 Glutethimide	8.3×10^{-5}	6.5×10^{-5}
3 Phenaglycodol	1.2×10^{-4}	9.3×10^{-5}
4 Phenobarbital	—	4.2×10^{-4}
5 Chlorpromazine	1.6×10^{-4}	2.3×10^{-4}
6 Zoxazolamine	1.8×10^{-4}	2.3×10^{-4}
7 Chloretone	1.9×10^{-4}	2.2×10^{-4}
8 Phenylbutazone	—	3.9×10^{-4}
9 Niketamide	5.2×10^{-4}	7.8×10^{-4}
10 Aminopyrine	9.6×10^{-4}	7.2×10^{-4}
11 SKF 525 A	1.7×10^{-5}	1.5×10^{-5}
12 Lilly 18947	4.4×10^{-5}	5.2×10^{-5}

The incubation mixture (5.0 ml) contained 2 ml of the microsome-containing supernatant (obtained by centrifugation at 8500 *g* for 15 min), 0.1 ml of 20 µmole glucose-6-phosphate, 0.4 µmole TPN 50 µmole nicotinamide and 75 µmole $MgCl_2$ and 1 *M* KCl, and more 2.3 ml of 0.1 *M* sodium phosphate buffer pH 7.4 and 0.2 ml of the substrates (final concentration were 2×10^{-4} Mol ×) and 0.1 ml of inhibitors. Phenobarbital and phenylbutazone interfered with determination of pentobarbital concentration.

[1] B. B. BRODIE, J. Pharm. Pharmacol. *8*, 1 (1956).
[2] J. M. FUJIMOTO, K. B. PEARCE, and G. L. PLAA, J. Pharm. exp. Therap. *129*, 139 (1960).
[3] H. REMMER, Arch. exp. Path. Pharmak. *237*, 296 (1959).
[4] R. KATO, Atti Soc. Lombarda Sci. Med. Biol. *14*, 777 (1959).
[5] R. KATO, Med. Exp. *3*, 95 (1960).
[6] R. KATO, E. CHIESARA, and P. VASSANELLI, Atti Accad. Med. Lombarda *15*, 443 (1960).
[7] R. KATO, E. CHIESARA, and G. FRONTINO, Jap. J. Pharmacol. *11*, 31 (1960).
[8] R. KATO and E. CHIESARA, Brit. J. Pharmacol. *18*, 29 (1962).
[9] R. KATO, P. VASSANELLI, and E. CHIESARA, Biochem. Pharmacol. *11*, 211 (1962).
[10] A. H. CONNEY, C. DAVISON, R. GASTEL, and J. J. BURNS, J. Pharm. exp. Therap. *131*, 1 (1960).
[11] A. H. CONNEY, I. A. MICHAELSON, and J. J. BURNS, J. Pharm. exp. Therap. *132*, 202 (1961).
[12] B. B. BRODIE, J. J. BURNS, L. C. MARK, P. A. LIEF, E. BERNSTEIN, and E. M. PAPPER, J. Pharm. exp. Therap. *109*, 26 (1953).
[13] A. J. HOFFMANN and B. J. LUDWIG, J. Amer. pharm. Assoc. *68*, 740 (1959).
[14] SKF 525 A and Lilly 18947 were kindly supplied by Dr. H. E. DUELL (Smith Kleine and French Lab., USA) and Dr. J. A. LEIGHTY (The Lilly Research Lab., USA). Also zoxazolamine was kindly supplied by Dr. E. L. NOWICKI (McNeil Lab., USA).
[15] R. KATO, E. CHIESARA, and P. VASSANELLI, Med. Exp., *6*, 254 (1962).

probamate metabolism. On the other hand, SKF 525 A and Lilly 18947 have a weak inducing action as recently reported by us, though they have a potent inhibitory action[15].

These results suggest that most of the inducing drugs have an inhibitory action on the drug metabolism, but that there is no direct relation between the level of the immediate inhibition and that of the late induction of increased activity of the drug-metabolizing enzymes.

These results also suggest that the inducing and inhibitory drugs have some similar affinities to the liver microsomes and this inhibitory action of the inducing drugs might be the factor responsible for producing an increase of *de novo* biosynthesis of the microsomal drug-metabolizing enzymes. But further studies on the relationship between the inducing action and inhibitory action of numerous compounds are necessary to clear up the mechanism of the induction.

These results are also of practical importance in the case of an evaluation of combined effects of two drugs. For example, chlorcyclizine, glutethimide, and phenaglycocol et al. prolong pentobarbital action not only due to synergisms by their action, but also by *in vivo* inhibition of pentobarbital metabolism[16].

Riassunto. Gli autori hanno dimostrato che alcuni farmaci (p.e. la clorciclizina, la glutetimide, il fenaglicodolo, il fenobarbital, la clorpromazina, il cloretone ed altri), che posseggono una tardiva attività «inducente» di stimolo su enzimi microsomici epatici, attivi nel metabolismo di svariati farmaci, determinano invece una inibizione degli enzimi stessi quando vengano fatti agire direttamente.

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[16] R. KATO, E. CHIESARA, and P. VASSANELLI, in preparation.

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Zur Pathogenese des Urämiesyndroms[1]. Brenztraubensäure, Acetoin und 2,3-Butylenglykol in Blut von Patienten mit Nieren- und Leberkrankheiten[2]

Blut-Brenztraubensäurewerte werden bei hepatischen Bewusstseinsstörungen häufig, bei urämischen Bewusstseinsstörungen gelegentlich erhöht gefunden[3,4]. Vermutlich besteht bei diesen Patienten eine Störung des oxydativen Brenztraubensäureabbaus zu aktiver Essigsäure. Es interessierte uns deshalb, ob Brenztraubensäure (BTS) bei Patienten mit urämischen und hepatischen Bewusstseinsstörungen vermehrt in Acetoin (Acetylmethylcarbinol: AMC) und 2,3-Butylenglykol (Butandiol-(2,3): BD) umgewandelt wird. Beide Substanzen wirken am Tier narkotisch. Es wäre deshalb möglich, dass AMC und BD in der Pathogenese urämischer und hepatischer Bewusstseinsstörungen eine Rolle spielen.

In der vorliegenden Arbeit wird über die Bestimmung von BTS, AMC und BD im Blut von Gesunden und von Nieren- bzw. Leberpatienten mit und ohne Bewusstseinsstörung berichtet. Die Untersuchungen wurden an 65 gesunden Kontrollen, 90 Nieren- und 39 Leberkranken durchgeführt. BTS wurde 218mal, AMC 297mal und BD 287mal bestimmt. Ausserdem wurden bei 28 Patienten mit Nieren-, Leber- und andern Affektionen BTS, AMC und BD gleichzeitig in Blut und Liquor gemessen und miteinander verglichen. BTS wurde nach FRIEDEMANN und HAUGEN, AMC und BD nach einer Modifikation der Methoden von WESTERFELD und von HAPPOLD und SPENCER bestimmt. Der Bewusstseinszustand der Patienten wurde

[1] Mit Unterstützung des «Schweizerischen Nationalfonds» und der Firma F. Hoffmann-La Roche & Co., AG, Basel.

[2] 5. Mitteilung. – 1. Mitt.: H. THÖLEN, F. BIGLER und H. STAUB, Path. Microbiol. *24*, 262 (1961). – 2. Mitt.: F. BIGLER, H. THÖLEN und H. STAUB, Helv. physiol. Acta *19*, C11 (1961). – 3. Mitt.: H. THÖLEN, F. BIGLER und H. STAUB, Exper. *17*, 359 (1961). – 4. Mitt.: F. BIGLER, H. THÖLEN und H. STAUB, Schweiz. med. Wschr. *91*, 1259 (1961).

[3] D. S. AMATUZIO und S. NESBITT, J. clin. Invest. *29*, 1486 (1950).

[4] G. BISERTE und B. DASSONVILLE, Clin. chim. Acta *1*, 49 (1956).

Tab. I. Brenztraubensäure, Acetoin und 2,3-Butylenglykol im Blut von Gesunden; Nieren- und Leberpatienten mit und ohne Bewusstseinsstörungen. (N): Anzahl der Bestimmungen. R1–R4, H1–H4: Stadium des Bewusstseins

	Brenztraubensäure mg% Mittelwert	(N)	Signifikanz C	Signifikanz R1	Acetoin γ% Mittelwert	(N)	Signifikanz C	Signifikanz R1	2,3-Butylenglykol γ% Mittelwert	(N)	Signifikanz C	Signifikanz R1
Gesunde Kontrollen (C)	1,11	(51)			10	(75)			117	(73)		
Nierenpatienten (R)		(117)				(156)				(151)		
R1	1,01	(76)	$p<0{,}10$	—	12	(92)	$p<0{,}05$	—	228	(89)	$p<0{,}001$	—
R2	1,18	(32)	$p<0{,}50$	$p<0{,}05$	16	(47)	$p<0{,}001$	$p<0{,}005$	394	(46)	$p<0{,}001$	$p<0{,}001$
R3	1,09	(3)	$p<0{,}95$	$p<0{,}70$	31	(11)	$p<0{,}001$	$p<0{,}001$	335	(10)	$p<0{,}001$	$p<0{,}05$
R4	1,94	(6)	—	$p<0{,}001$	22	(6)	—		351	(6)	—	—
			Signifikanz C	Signifikanz H1			Signifikanz C	Signifikanz H1			Signifikanz C	Signifikanz H1
Leberpatienten (H)		(50)				(66)				(63)		
H1	1,25	(29)	$p<0{,}10$	—	17	(37)	$p<0{,}01$	—	300	(36)	$p<0{,}001$	—
H2	2,06	(8)	$p<0{,}001$	$p<0{,}005$	21	(8)	$p<0{,}001$	$p<0{,}60$	266	(8)	$p<0{,}001$	$p<0{,}80$
H3	2,64	(10)	$p<0{,}001$	$p<0{,}001$	130	(11)	$p<0{,}001$	$p<0{,}01$	2500	(11)	$p<0{,}001$	$p<0{,}001$
H4	2,49	(3)	—	—	140	(10)	—	—	3240	(8)	—	—