Changes in the diabetogenic effect of alloxan (250 mg/kg subcutaneously), administered to mice 10 min before, 2, 6, and 24 h after BZ-55 respectively, and 24 h following the daily administration of the same drug for 1 and 3 weeks

Alloxan administered after BZ-55	Number of animals	Average glycemia mg%	Percentage of diabetic animals *	Mortality rate in 10 days in %
−10 min	19	259±23	47·2	5·0
+2 h	20	467±56+	73·4+	65·0+
+6 h	7	510±48+	100·0+	57·0+
24 h	20	244±22	37·5	20·0
+24 h (after administration for one week)	15	231±36	35·7	20·0
+24 h (after administration for three weeks)	13	385±60+	69·2	21·4
Control—Alloxan alone	20	218±25	31·7	5·0

* glycemia above 250 mg%

\+ statistically significant difference as compared with control ($P = 0{\cdot}01 - 0{\cdot}02$)

ministration closely before alloxan injection in mice[9], glucagon in dogs[11], or adrenalin in rabbits[4], protect the β-cells from alloxan. Under these circumstances, β-cells are stimulated to increased activity.

Our experiments suggest that BZ-55 increases the diabetogenic effect of alloxan. We may thus conclude that this substance causes a state of *functional hypoactivity* of the β-cells. This may be due to the direct effect of BZ-55 or secondary to the decrease of the blood sugar or both factors. It will be necessary to make a more detailed analysis of these factors. So far we can only say that the factor of hypoglycemia could not play a role in the group of mice which were given alloxan 10 min prior the BZ-55 and 24 h after BZ-55 had been administered for three weeks. The tendency of potentiation of the diabetogenic effect of alloxan, however, exists. No signs of protection of β-cells were detected as might be expected if BZ-55 exerted a favorable effect on their metabolism and increased their functional activity.

This seems to be in disagreement with the hypothesis of some authors[2] that the hypoglycemic action of BZ-55 is due to stimulation of the β-cells. It cannot, however, be ruled out that after the administration of BZ-55 insulin is released in some unknown (more or less passive) manner. Our finding is in agreement with the views of other authors[12,13] who, as a result of histological changes of the β-cells in rabbits, assume that after the administration of BZ-55 these cells are in a quiescent stage similarly to that during fasting or after the administration of exogenous insulin.

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Institute for Human Nutrition, Physiological Department, Prague, April 9, 1959.

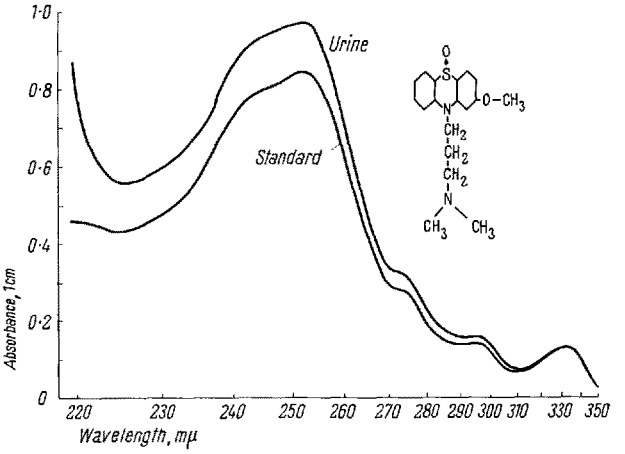
Zusammenfassung

Es wird festgestellt, dass im voraus verabreichtes BZ-55 die diabetogene Wirkung des Alloxans bei Mäusen potenziert.

[11] J. L. ARTETA and A. CARBALLIDO, J. Endocrin. *15*, 243 (1997).
[12] H. MASKE Dtsch. med. Wschr. *1956*, 899.
[13] W. CREUTZFELDT und H. FINTER, Dtsch. med. Wschr. *1956*, 892.

On the Urinary Elimination of Methoxypromazine in Man

Methoxypromazine[1] (MPZ) is a phenothiazine derivative, which has recently been introduced as a tranquillizer. Chemically it is closely related to chloropromazine (CPZ), although the 2-Cl group has been substituted for a 2-methoxy group. During a clinical trial of the drug it was thought of interest to determine the urinary output to check that the drug was taken by the patients and to get an idea of the metabolism.



U.V. absorption curves of methoxypromazine sulfoxide (standard) in aqueous solution (acetate buffer pH 5·6 acidified with sulfuric acid) and of the metabolite, extracted from urine according to SALZMAN and BRODIE[3], in the same solvent.

MPZ (maleate) in aqueous solution shows a characteristic ultraviolet absorption with a main maximum at 251 mμ and a low maximum at 302 mμ. This is closely analogous to that of CPZ[2,3] and other 10-aminoalkylphenothiazines[4]. The colour reaction characteristic of some phenothiazine compounds with concentrated sulfuric acid (DUBOST and PASCAL[5] and others) is also obtained. On addition of an equal volume of sulfuric acid to MPZ in aqueous solution, a red colour (absorption peak at 565 mμ) develops, which is fairly stable, but the absorbance is not very reproducible. Also this reaction is less sensitive than the U.V. absorption. Extraction of MPZ is easily performed from an alkaline aqueous solution with ether, and from ether to an acid aqueous phase, with recoveries around 90%. The acid aqueous extract is suitable for direct U.V. spectrophotometry or the sulfuric acid reaction. Absorption curves for the red colour obtained with such extracts from the urine of patients receiving 300–375 mg MPZ daily were similar to those for pure MPZ, but the U.V. absorption curves showed characteristic deviations indicating that metabolites might be present. In fact the curves were similar to those of CPZ sulfoxide[3], showing maxima at 252, 273, 296, and 332 mμ and a 'shoulder' at about 242 mμ (Fig.).

In order to establish whether the metabolite was identical with MPZ sulfoxide, this compound was synthesized

[1] Mopazine —, produced by A. B. Astra, Sweden, and Rhône-Poulenc S.A., France.
[2] N. P. SALZMAN, N. C. MORAN, and B. B. BRODIE, Nature *176*, 1122 (1955).
[3] N. P. SALZMAN and B. B. BRODIE, J. Pharmacol. exp. Therap. *118*, 46 (1956).
[4] R. DAHLBOM and T, EKSTRAND, Acta chem. scand. *5*, 102 (1951).
[5] P. M. DUBOST and S. PASCAL, Ann. pharm. franç. *11*, 615 (1953).

by the oxidation of MPZ oxalate with 30% hydrogen peroxide. The MPZ sulfoxide oxalate melted at 208–210°C under decomposition and the free base melted at 93–94°C. Infrared analysis showed strong absorption at 9·82 μ which indicates the presence of a sulfoxide group. The U.V. absorption curve of the MPZ sulfoxide base in absolute ethanol showed maxima at 242, 253·5, 277, 296·5, and 335 mμ, which seems to be characteristic for aminoalkylphenothiazine sulfoxides. The MPZ sulfoxide in aqueous solution (acetate buffer pH 5·6 acidified with sulfuric acid) showed the same maxima as given above for the metabolite (Fig.).

Urine and concentrated ethereal extracts were also analysed by paper chromatography (Whatman 1, descending in (A) butanol-acetic acid-water, 40:10:50 and (B) butanol-citric acid-water on paper treated with citrate buffer pH 3·7, according to CURRY and POWELL[6]). Spots were identified (1) by U.V. illumination[7] of the paper with a fluorescein screen as background and (2) by immersion of the paper strips rapidly in 50% sulfuric acid[3] containing 0·25% ferric chloride, which gives coloured spots with a number of phenothiazine derivatives. The sensitivity of both methods is about 1 μg MPZ per cm². MPZ showed R_f 0·83 in solvent (A) and 0·73 in solvent (B) (mean values). With urine and ethereal extracts from urine of patients treated with MPZ, a main spot with R_f 0·69 in solvent (A) and 0·45 in solvent (B) was obtained, which showed U.V. absorption and the sulfuric acid reaction. MPZ sulfoxide standard showed identical properties. After elution of the spot in solvent (A) in 0·1 *N* sulfuric acid solution, a U.V. absorption curve identical with that of the synthetic MPZ sulfoxide, was obtained.

In addition, a spot corresponding to MPZ was obtained in the two solvents although the intensity varied in the different cases. In general it was less intense than the sulfoxide spot.

Quantitative analyses by extraction[3] and U.V. spectrophotometry have shown that up to one third of the MPZ dose given is eliminated in the urine, mainly as the sulfoxide.

Additional spots, showing U.V. absorption and the sulfuric acid reaction, were obtained with urine in some cases. R_f values were below 0·3.

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Zusammenfassung

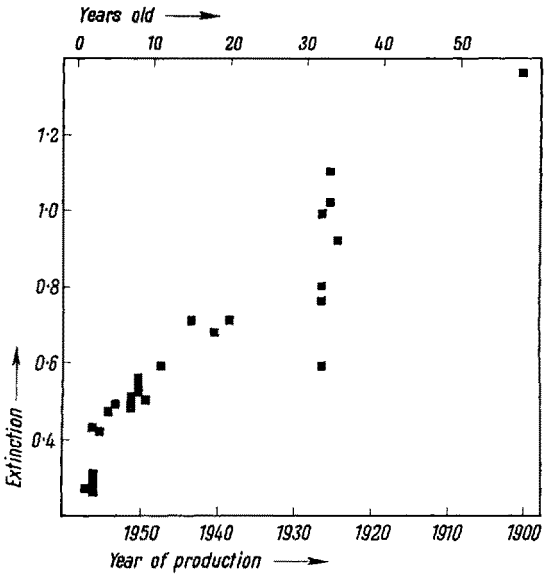
Die Ausscheidung eines neuen neuroleptisch wirksamen Phenothiazinderivates – Mopazin – im Harn wurde spektrophotometrisch und papierchromatographisch untersucht. Als wichtigstes Abbauprodukt wurde Methoxypromazin-sulfoxyd gefunden. Daneben waren unverändertes Methoxypromazin und 1–3 nicht identifizierte Abbauprodukte nachzuweisen. Bei den letzteren handelt es sich möglicherweise um Konjugate.

[6] A. S. CURRY and H. POWELL, Nature *173*, 1143 (1954).
[7] L.-G. ALLGÉN, Scand. J. clin. Lab. Invest. *9*, 71 (1957).

On the Possibilities of Estimating the Approximate Age of Macedonian Opium by Means of a Simple Colour Reading

In the course of the work on the direct spectrophotometric determination of opium origin performed in this laboratory[1], it has been observed that the yellow colour of the buffered water extracts of various types of opium was relatively intense in old samples, whereas recent samples generally exhibited only slightly coloured extracts. For this reason, an attempt was made to examine in detail the relationship between the yellow colour of the extracts and the year of production of samples belonging to a certain opium type. The determination of the approximate year of production of seized opium may be of great importance in a successful campaign against the illicit traffic of narcotics.

The present report concerns the results obtained by examining 41 samples of Macedonian opium (39 Yugoslavian and 2 Bulgarian) which were from 1 to 58 years old.



Relationship of the extinction values at 440 mμ and the age of the samples examined

(Samples having the same values on both the ordinates, as well as those showing nearly the same extinction values, overlap each other and therefore cannot be separately distinguished.)

The following procedure was used: 25 mg of air-dried pulverized opium were rubbed thoroughly for 1 min in a mortar with 1 drop (0·05 ml) of sodium acetate-HCl buffer by Walpole (pH 3·9). Thereafter, 4·95 ml of the same buffer were added, stirring being continued for 3 min and the mixture filtered. The extinction of the filtrate was measured at 440 mμ wavelength, against the pure buffer, on a Jobin-Yvon 'Maroc' spectrophotometer, in 1 cm cells.

In the Figure the extinction readings obtained have been plotted against the year of production. From this diagram, a certain relationship between the extinction measured and the age of opium may be observed. Accord-

[1] LJ. GRLIĆ and J. PETRIČIĆ, Farm. Glas. *12*, 487 (1956); United Nations document ST/SOA/SER. K/48 (1957). – LJ. GRLIĆ, Acta pharm. jugosl. *7*, 199 (1957); United Nations documents ST/SOA/SER. K/54 (1957) and ST/SOA/SER. K/75 (1958).