I gratefully acknowledge the help of the Hungarian Academy of Sciences, the accomodation provided by Prof. Z. CSÜRÖS and the aid of Mr. Zs. DUSZA and Dr. E. PUNGOR. A detailed account will appear in the Acta Chimica Hungarica.

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Zusammenfassung

Die Einwirkung von Schwefelsäure auf eine benzolische β-Carotinlösung und die nachträgliche Behandlung der so gebildeten blauen Umwandlungsprodukte mit Wasser führte zu gelblichen Stoffen unbekannter Konstitution. Die chromatographische Analyse dieser Verbindungen zeigte die Abwesenheit von β-Carotin. Einige Eigenschaften der neuen Stoffe werden beschrieben.

Lipaemia Clearing Effect of Chlorpromazine

In the course of our investigations concerning the metabolic effects of chlorpromazine, it was observed that the plasma of the experimental animals became unexpectedly transparent after injection of the drug[1]. This effect resembled that exerted by heparin on lipaemic plasma first described by HAHN[2] in 1943. Our observation was supported by HOLLISTER and KANTER's[3] findings gained in two cases of essential hyperlipaemia: they found that chlorpromazine treatment decreased the turbidity of the sera of their patients and "produced a marked decrease in all fractions of blood fat, including a shift in the lipoprotein classes to a more nearly normal pattern", just like heparin treatment. On the basis of these findings, the question arose as to whether chlorpromazine exerts any effect on alimentary lipaemia?

Eleven mongrel dogs of both sexes were given 10 g/kg body weight of margarine orally after a 24 h fasting period. 3 h later, blood was taken from the femoral artery and chlorpromazine was given intravenously immediately afterwards in doses of 4–11 mg/kg body weight. In the course of the following 90 min, blood was withdrawn every 10 or 15 min from the femoral artery and mixed in a ratio of 1:9 with a 3·8% solution of sodium citrate. The blood samples were immediately centrifuged and the turbidity of the plasma recorded by means of a Pulfrich-photometer (Zeiss), with a S_{66} filter, against a water blank using ½ and 1 cm cells, respectively. All the figures obtained are given as optical density values of 1 cm cell-thickness.

After administration of chlorpromazine, the turbidity of the plasma decreased in every case. The decrease expressed in terms of optical density seems to a certain extent to be related to the chlorpromazine dose applied. The clearing effect was first observed 15–20 min after administration of the drug, the maximum was reached between 20 and 35 min. Afterwards a returbification occurred (Table I, Fig. 1).

In some of the cases, the changes in the lipoprotein pattern were recorded by means of paper-electrophoresis with the result that chlorpromazine caused a similar shift as heparin does (Fig. 2).

Table I

Dose of CPZ mg/kg	Optical density of the plasma before administration of CPZ	Maximal clearing effect %
4·0	0·615	26·81
5·0	0·690	38·20
5·0	1·980	38·80
5·0	0·420	91·00
6·0	1·206	45·30
8·0	2·240	10·26
8·0	0·850	53·00
9·0	0·772	58·30
10·0	1·920	37·20
11·0	1·270	98·74
12·5	0·927	73·80

Considering that these findings are very similar to those observed after small doses of heparin, it was assumed that chlorpromazine exerts its effect through mobilizing endogenous heparin. To support this assumption, the following experiment was carried out. 5 dogs were treated as described above, but 10 min before administering chlorpromazine, protamine-sulphate was given intravenously in a dose of 3 mg/kg body weight, all experimental conditions remaining unchanged. In each of the animals, protamine-sulphate inhibited the lipaemia clearing effect of chlorpromazine (Table II, Fig. 1).

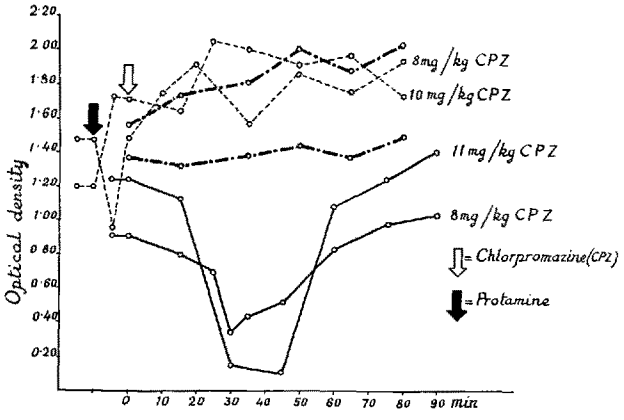

Fig. 1. —o———o———o = CPZ treatment only; o – – – – o = Protamine + CPZ treatment; o – · – · – · – o = no treatment.

HOLLISTER and KANTER suggest that the effect of chlorpromazine treatment in essential hyperlipaemia is due to the direct action of the drug on the liver; but they admit the possibility that the adrenolytic property of chlorpromazine may be responsible for the changes. Our experiments point to the fact that chlorpromazine exerts its lipaemia clearing effect via heparin, presumably by mobilizing endogenous heparin. Our hypothesis is supported by the fact that the clearing effect appears rapidly, bringing about a similar shift in the lipoprotein pattern as heparin, and that the effect is inhibited by protamine. PERLICK[4] reports that the complement-activity of the sera was decreased in patients during prolonged sleep-therapy produced by phenothiazine

[1] "Largactil", Specia, Paris.

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Table II

Dose of CPZ mg/kg	Optical density of the plasma				
	before admin.	10 min after of protamine	15 min	25 min	35 min
			after administration of CPZ		
7·0	0·833	0·497	1·041	1·033	0·892
7·5	1·440	1·473	1·723	1·926	1·577
7·5	2·886	2·858	2·862	3·312	3·102
10·0	1·383	1·193	2·033	1·850	1·440
10·0	1·200	1·630	1·657	2·070	2·017

derivatives, and he also suggests that these drugs increase the heparin content of the blood. According to COURVOISIER[5], the coagulation time of blood is prolonged by administration of chlorpromazine.

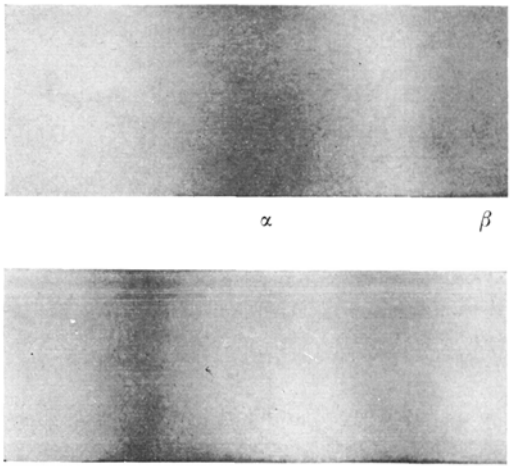

Fig. 2. – Changes in lipoprotein pattern caused by 10 mg/kg chlorpromazine shown by paper electrophoresis. *1:* before, *2:* 25 min after chlorpromazine administration (180 V, 10 mA, 20 h, Sudan Black stain).

Since the phenothiazine derivatives are widely used in therapy, several observations suggested that thromboembolic complications frequently occur[6] following the use of these drugs. Our clinical observations also support these findings. On the basis of our experiments, it may be assumed that owing to the increased release of heparin during phenothiazine-treatment the heparin-stores throughout the body become diminished; thus the interruption of continuous administration may be followed by a decrease of the heparin blood-level. The possibility that such a mechanism may be involved in post-phenothiazine thromboembolic conditions might also be taken into consideration.

B. M. KOVÁCS, G. S. KOVÁCS, and G. PETRI.

Institute of Experimental and Operative Surgery, University Medical School, Szeged, Hungary, June 19, 1956.

[5] S. COURVOISIER, J. FOURNEL, E. DUCROT, M. KOLSKY, and P. KOETSCHET, Arch. int. Pharmacodyn. *92*, 305 (1953).

[6] H. LABORIT and P. HUGUENARD, *Pratique de l'hibernothérapie en chirurgie et en médecine* (Masson et Cie, Paris 1954). – R. S. LAMBIE, L. G. JOSEPH, and G. WILSON, Brit. med. J. *1*, 840 (1956). – W. OSTEN, Ärztl. Wschr. *11*, 152 (1956).

Zusammenfassung

Bei Hunden ergibt Chlorpromazin *in vivo* eine Klärung des lipämischen Plasmas. Dieser Effekt des Präparates wird durch vorausgehende, intravenöse Protaminsulfatinjektionen aufgehoben. Es darf angenommen werden, dass diese Wirkung durch Mobilisierung von endogenem Heparin vermittelt wird. Möglicherweise ist dieser Mechanismus an den thromboembolischen Komplikationen nach Chlorpromazinbehandlung beteiligt.

The Oxidation of Cystamine and Other Sulfur-Diamines by Diamine-Oxidase Preparations

Although it is known that cystamine is oxidized by the rat *in vivo* to taurine[1], hypotaurine[2] and sulfate[3], enzymatic systems capable of carrying oxidative reaction on cystamine *in vitro* are at present unknown. Only recently, SALVADOR and BRADY[4] have reported the oxidation of cysteamine to cystamine disulfoxide by a pigeon liver preparation. No experimental data are however reported in their paper.

The incubation of cystamine with a rat liver homogenate in a Warburg system results in a slight increase of the O_2 uptake over the endogenous respiration only in the first period of incubation, followed by a depression in the second part (unpublished experiments). This result may possibly be interpreted by a partial oxidation of cystamine by the diamine-oxidase, which is contained only in small amounts in the rat liver[5], to compounds which are toxic to the liver enzymes.

In order to test the ability of diamine-oxidase to catalyze the oxidation of cystamine, and to gain evidence on the possible role of diamine-oxidase in the biological degradation of cystamine and other sulfur-diamines, a comparative study has been carried out by incubating cadaverine and sulfur-containing diamines with diamine-oxidase preparations extracted from traditional sources.

Pig-kidney diamine-oxidase.–The enzyme system was prepared in a crude form according to ZELLER[6], with minor modifications. As it is shown in Figure 1, cystamine is an excellent substrate for this enzyme, the rate of oxidation being comparable to that of cadaverine. Using cadaverine as substrate, the final O_2 uptake is close to the theory of 0·5 *M* per mole substrate; using cystamine we invariably found a higher O_2 consumption which was more than double the theoretical amount.

The higher O_2 uptake in the case of cystamine is not caused by the accumulation of H_2O_2 in the incubation mixture. This has been ruled out by tipping a solution of catalase at the end of one of these reactions: no evolution of O_2 was noticed after the catalase addition. Furthermore the higher O_2 consumption is also not attributable to the presence in the enzymatic preparation of a system capable of oxidizing the disulfide group contained in the initial substrate. This possibility has been eliminated by using N-diacetylcystamine, which was left unoxidized by the same preparation.

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