

**Zusammenfassung.** Von den vier Cyclodekapeptiden, die als mögliche Strukturen für Polymyxin B<sub>1</sub> vorgeschlagen wurden, konnten nun auch die Ringstrukturen mit 7 Aminosäuren, nämlich 7 $\gamma$  und 7 $\alpha$  (vgl. Fig.), synthetisiert werden. Diese erwiesen sich im Gegensatz zu 8 $\gamma$  und 8 $\alpha$  als hochaktive antimikrobielle Wirkstoffe mit Wirkungsqualitäten der Polymyxine. Ob 7 $\gamma$  oder 7 $\alpha$  mit natürlichem

Polymyxin B<sub>1</sub> identisch ist, wird durch weitere Versuche abgeklärt.

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### Influence of Isoniazid and *p*-Aminosalicyc Acid on Plasma 17-Hydroxycorticosteroids in Guinea Pigs

Earlier publications reported that the antituberculous isoniazid (INH) and *p*-aminosalicyc acid (PAS) produce many effects similar to those noted following the administration of adrenocorticotrophin (ACTH). In the animal experiments, after the administration of large doses either of isoniazid or of PAS, histological changes in adrenals, depletion of adrenal ascorbic acid and cholesterol and eosinopenia occurred<sup>1-4</sup>. In the present paper we were interested to find out how the level of plasma 17-hydroxycorticosteroids (17-OHCS) in guinea pigs is influenced in the course of treatment with INH and PAS.

In experiments, male guinea pigs weighing 300–400 g were used. The compounds tested were administered *per os* in water solution. The animals were divided into groups. The first group of animals received 100 mg INH/kg per day and the second group was treated with 1 g PAS/kg per day for a period of 1–10 days. The animals were sacrificed and bled in heparinized test tubes on the first, third, fifth, tenth day, 3 h after administration. Control animals were treated identically except that they received no INH and PAS. Plasma 17-OHCS concentrations were determined by the method of SILBER and PORTER<sup>5</sup>.

Table I summarizes the data concerning the effects on plasma 17-OHCS of INH administered in the dose of 100 mg/kg. It can be seen that even one dose caused a 9% increase of plasma 17-OHCS, but this was not significant. In the course of three and five days' treatment, INH produced a highly significant elevation of plasma 17-OHCS. On the third day the mean increase was 52% and on the fifth day 127% ( $P < 0.01$ ).

Table II shows the concentration of plasma 17-OHCS in guinea pigs following the administration of 1 g PAS/kg. After one dose of PAS, no elevation in plasma 17-OHCS was found. Three days' administration resulted in 36% increase of plasma 17-OHCS ( $P < 0.05$ ). This increase was augmented further in five days' treatment to 56% and in ten days to 130% if compared with the control group ( $P < 0.01$ ).

On the third day, INH already exerted a higher effect on plasma 17-OHCS than PAS. The more evident difference between the effects of antituberculous was found on the fifth day. The mode of application seems also to be important. GOOD et al.<sup>6</sup> ascertained higher effect on plasma 17-OHCS after the intraperitoneal administration of sodium salicylate than after oral administration.

Very interesting is the question of whether the stimulatory effect of antituberculous on the adrenal cortex is mediated by anterior hypophysis. CAUWENBERGE<sup>1</sup> did not find in hypophysectomized PAS-treated rats the depletion of adrenal ascorbic acid and cholesterol. From these experiments it seems that PAS does not stimulate the adrenal cortex directly. INH, on the other hand, following the administration of higher doses, may stimulate the adrenal cortex even in hypophysectomized rats and

Tab. I. Effects of orally administered 100 mg INH/kg on plasma 17-OHCS in guinea pigs

	Number of animals	Mean $\mu\text{g}/100\text{ ml}$	Plasma 17-OHCS SE	Increase %
Control group	10	92	4.8	
INH treated				
day 1	8	100	9.9	$P < 0.2$ 9
day 3	7	140	10.2	$P < 0.01$ 52
day 5	6	209	5.5	$P < 0.01$ 127

Tab. II. Effects of orally administered 1 g PAS/kg on plasma 17-OHCS in guinea pigs

	Number of animals	Mean $\mu\text{g}/100\text{ ml}$	Plasma 17-OHCS SE	Increase %
Control group	10	92	4.8	
PAS treated				
day 1	6	92	7.4	
day 3	5	125	12.5	$P < 0.05$ 36
day 5	5	144	16.3	$P < 0.01$ 56
day 10	6	211	14.2	$P < 0.01$ 130

produce the depletion of adrenal ascorbic acid<sup>3</sup>. Although the adrenal ascorbic acid depletion may show the function of adrenal cortex, a direct measurement of plasma 17-OHCS would be preferable.

From our results it can be concluded that the treatment with high doses, either of INH or of PAS, produced a marked effect on circulating 17-OHCS. These results are in correlation with our findings<sup>7</sup> of the depletion of adrenal ascorbic acid and cholesterol in rats treated with INH or PAS for 14 days.

**Zusammenfassung.** Bei zehntägiger Verabreichung von 1 g PAS/kg oder 100 mg INH/kg peroral kommt es bei Meerschweinchen zu einer signifikanten Steigerung der 17-Hydroxy-corticosteroide. Eine ausgeprägte restimulierende Wirkung wurde im Fall von INH beobachtet. Der Unterschied fiel besonders am fünften Tag auf, wobei nach INH-Gabe die Steigerung zirkulierender Corticosteroide im Vergleich zur PAS verdoppelt war.

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<sup>5</sup> R. H. SILBER and C. C. PORTER, *J. biol. Chem.* 210, 923 (1954).

<sup>6</sup> T. A. GOOD et al., *Metabolism* 6, 346 (1957).

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