These experiments will be continued and a full account published in the Acta pharmacologica et toxicologica Scandinavica.

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Résumé

Huit diurétiques mercuriels ont été étudiés selon la technique de SPERBER utilisant la circulation porte rénale de la poule. Six d'entre eux ont montrés clairement leur élimination par secrétion tubulaire. Une diurèse acqueuse peut être obtenue avec tous les diuretiques étudiés, dans la plupart des cas elle est unilatérale du côté injecté. Une diurèse Na et Cl la suit. On peut supprimer la diurèse unilatérale par la probenécide et le vert de bromocrésol. Les composés étudiés sont éliminés à des vitesses très différentes. Ceux qui présentent l'élimination la plus lente, montrent également l'activité diurétique la plus grande et de plus longue durée.

The Problem of 'Conditioning' the Action of Antiphlogistic Corticoids by the Thyroid Gland

The communications published by DOMENJOZ *et al.*[1] and STENGER *et al.*[2] report the loss of antiphlogistic activity of cortisone, ACTH and other anti-inflammatory agents after thyro-parathyroidectomy. These authors used the formalin arthritis test as indicator. SELYE could not confirm their observations. In addition to the formalin arthritis test, he also used dextran edema of the rat paw and the so-called 'granuloma pouch' as an experimental model[3]. The participation of other factors in the antiphlogistic action of corticoids seemed very interesting to us, and we tried to verify these observations using another indicator 'the cotton pellet granuloma test' modified according to MEIER *et al.*[4]. This test is frequently used in testing antiphlogistic corticoids, which decrease the quantity of newly formed granulomatous tissue around implanted cotton pellets.

Methods.—Sixty-three male Wistar rats, kept under standard conditions on Larsen diet and tap water *ad libitum*, were subdivided into 7 groups of 9 animals. The average body weight of these animals was 110–140 g. In the Group V, VI, VII thyro-parathyroidectomies were performed under ether anaesthesia. The operated animals received 100 mg/kg of calcium gluconate subcutaneously daily and 1% calcium lactate in the drinking water. After a week all animals were taken into the experiment. Cotton pellets of average weight 20 ± 1 mg were implanted subcutaneously in the interscapulary area of the back. After implantation, treatment with prednisone (1-dehydrocortisone-Ultracorten CIBA) was initiated in Groups III and VI. Each animal of these groups obtained 5 mg of prednisone *per os* daily for 7 days. In Groups IV and VII, the implanted cotton pellets were injected with a single dose of 5 mg hydrocortisone acetate on 0·2 ml of aqueous crystalline suspension (Hydrocortisate Leo). Groups I, II and V served as controls. Group I included the intact control animals, each animal of Group II received 100 mg/kg of calcium gluconate subcutaneously daily for 7 days and drank 0·1% calcium lactate to eliminate the influence of injected and ingested calcium. Finally, Group V consisted of control, thyro-parathyroidectomized animals. After 7 days, the granulomas which developed were excised in all groups and carefully dissected from the surrounding free tissue. The granulomas were dried at 54° C overnight and then weighed to estimate the dry weight. The weight of the implanted cotton pellet was then subtracted from the dry weight of the granuloma.

Results.—The principal findings are summarized in the Table. The statistical evaluation was made after FISHER[5]. The antiphlogistic corticoids given either *per os* (prednisone) or local (hydrocortisone acetate) inhibited the development of cotton pellet granuloma. Calcium gluconate alone did not influence significantly in any way the development of granuloma. Thyro-parathyroidectomized animals exhibited slightly reduced formation of granulomatous tissue. Prednisone and hydrocortisone acetate exerted a marked inhibitory effect also in thyro-parathyroidectomized animals. From these results we could not confirm the observation of DOMENJOZ and STENGER. The mechanism of antiphlogistic corticoids action is mainly direct, independent of thyroid and

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[3] P. BOIS and H. SELYE, Exper. *12*, 111 (1956).

[4] R. MEIER, W. SCHULER, and P. DESAULLES, Exper. *6*, 469 (1950).

[5] R. FISHER, *Statistical methods for research workers* (London 1934).

The effect of prednisone and hydrocortisone acetate on the formation of cotton pellet granuloma in intact and thyro-parathyroidectomized rats.

Group	Treatment	Dry weight of granuloma (mg)		
		Φ	σ	p
I	Intact control	48·3 ± 4·7	± 14·3	
II	Intact control – 100 mg/kg calcium gluconate daily	47·2 ± 3·8	± 11·4	insignificant
III	Prednisone 5 mg *per os* daily	32·8 ± 0·7	± 2·3	< 0·01
IV	Hydrocortisone acetate 5 mg local	13·9 ± 0·5	± 1·5	< 0·01
V	Thyro-parathyroidectomy control	45·0 ± 5·8	± 17·6	
VI	Thyro-parathyroidectomy – prednisone 5 mg *per os* daily	31·7 ± 0·9	± 2·6	< 0·01
VII	Thyro-parathyroidectomy – hydrocortisone acetate 5 mg local	17·0 ± 1·3	± 3·0	< 0·01

Φ statistical average; σ statistical deviation; p value of probability

other endocrine glands. The reactivity of inflammed tissue on anti-inflammatory agents is of course dependent on various factors of nervous and humoral origin. It must be taken into consideration that the course of experimentally induced inflammation is slightly reduced in the hypothyroid animals as we have observed in other unpublished experiments. The anti-inflammatory effect of corticoids was always marked in thyro-parathyroidectomized animals or in animals receiving methylthiouracil for a long time. Although it is well known that cortisone and phenylbutazone inhibit the thyroid function, it would be very difficult to find a parallel between the inhibition of thyroid gland and the antiphlogistic action of corticoids.

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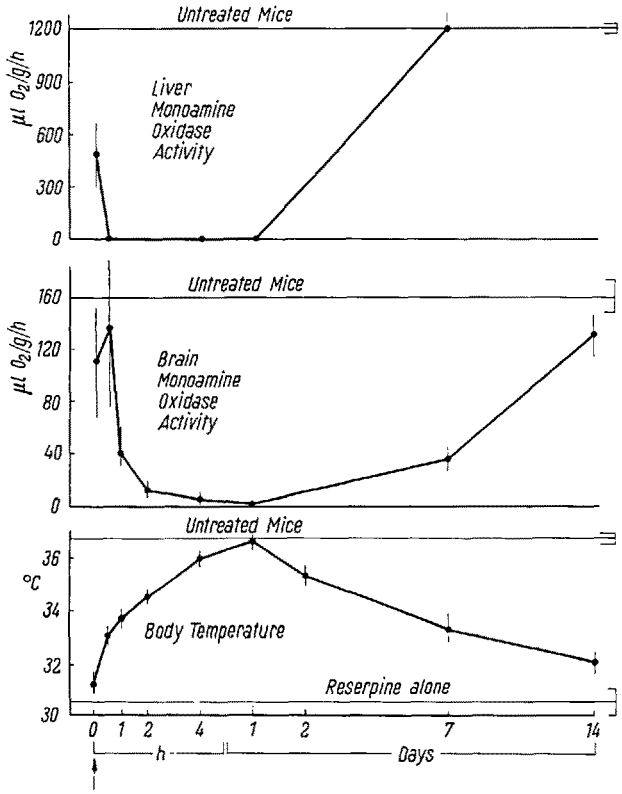
Zusammenfassung

Experimentell wurde die Wirkung von Prednison und Hydrocortisonacetat auf die Entwicklung des Fremdkörpergranuloms an intakten und an thyreoid- und parathyreoidektomierten Tieren untersucht. Nach beidseitiger Thyreoidektomie konnte keine Unterdrückung der entwicklungshemmenden Effekte der Corticoide festgestellt werden.

The Antagonism of Reserpine Hypothermia by Iproniazid

The sedative action of reserpine may be antagonized by previous administration of iproniazid[1]. It has also been shown that after the administration of reserpine, there is a fall in the level of 5-hydroxytryptamine (HT) in the brain[2] and an increase in excretion of 5-hydroxyindoleacetic acid[3]. Since iproniazid is a powerful inhibitor of monoamine oxidase[4], an enzyme likely to be responsible for the disappearance of HT from the brain following reserpine, the relationship between monoamine oxidase inhibition and reserpine antagonism by iproniazid was examined. The action of reserpine studied was the production of hypothermia in the mouse, which has been shown to be closely related to the sedative action of this drug[5].

Monoamine oxidase activity was determined in the brain and liver of groups of mice injected with 100 mg/kg iproniazid intraperitoneally. The mice were killed and the activity of homogenized brain or liver determined manometrically by a method previously described[6]. The first group was killed immediately after injection and further groups after intervals from 30 min to 14 days. Using the same intervals, corresponding groups of 10 or more iproniazid-treated mice were injected with 2 mg/kg reserpine intraperitoneally and the mean rectal temperature of each group determined 4 h later. This temperature was used as an index of the sedative activity of reserpine; the dose used in these experiments reduced the body temperature of mice to 30·5°C ± 0·5°C in 4 h at a room temperature of 22°C.



Upper two tracings—liver and brain monoamine oxidase activities: mean values for groups of mice killed at various intervals after injection of 100 mg/kg iproniazid intraperitoneally. Lower tracing—mean rectal temperatures of groups of mice, measured 4 h after injection of 2 mg/kg reserpine intraperitoneally, plotted against the interval between administration of 100 mg/kg iproniazid intraperitoneally and injection of reserpine. Vertical lines represent standard errors of mean values.

As shown in the Figure, the hypothermic action of reserpine was reduced by iproniazid, being completely abolished when the interval between the two drugs was 24 h.

Further, there was a close parallel between brain monoamine oxidase activity and the hypothermic effect of reserpine. Inhibition of the enzyme and reduction in effectiveness of reserpine by iproniazid developed together. Both commenced after ½–1 h and reached a minimum in 4–24 h. Recovery began about 2 days later and was barely complete after 14 days.

On the other hand, liver monoamine oxidase was completely inhibited within ½ h after iproniazid injection, that is, while inhibition of the brain enzyme was far from complete. Furthermore, liver monoamine oxidase activity had returned to normal by 7 days, while the enzyme activity of the brain was still considerably inhibited.

A relationship thus exists between the degree of hypothermia produced by reserpine and the level of monoamine oxidase activity in the brain at the time of

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