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of experimentally induced inflammation is slightly reduced in the hypothyroid animals as we have observed in other unpublished experiments.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.

The author is grateful to CIBA AG., for supplying prednisone (Ultracorten).

K. TRNAVSKÝ

*Research Institute for Rheumatic Diseases, Piestany (Czechoslovakia), February 19, 1957.*

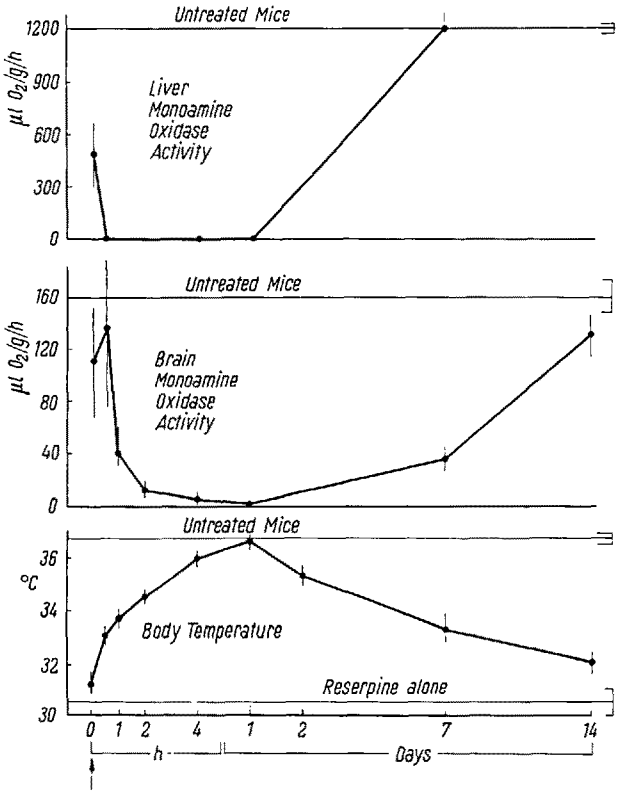
*Zusammenfassung*

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

[1] M. CHESSIN, B. DUBNICK, E. R. KRAMER, and C. C. SCOTT, Fed. Proc. *15*, 409 (1956). – B. B. BRODIE, A. PLETSCHER, and P. A. SHORE, J. Pharmacol. *116*, 9 (1956).

[2] A. PLETSCHER, P. A. SHORE, and B. B. BRODIE, J. Pharmacol. *116*, 46 (1956).

[3] P. A. SHORE, S. L. SILVER, and B. B. BRODIE, Science *122*, 284 (1955).

[4] E. R. ZELLER, J. BARSKY, and E. R. BERMAN, J. biol. Chem. *214*, 267 (1955).

[5] A. W. LESSIN and M. W. PARKES, Brit. J. Pharmacol. *12*, 245 (1957).

[6] A. N. DAVISON and M. SANDLER, Clin. chim. Acta *1*, 450 (1956).

the reserpine administration. It has been shown[7] that 20 h after treatment with iproniazid, the HT content of the brain is not greatly affected by reserpine. The demonstration that brain monoamine oxidase inhibition by iproniazid proceeds in step with reduction in reserpine hypothermia supports the view that reduced destruction of brain HT is the factor diminishing the hypothermic action of reserpine after iproniazid.

A. N. DAVISON, A. W. LESSIN, and M. W. PARKES

*Biological Research Laboratories, Roche Products Ltd., Welwyn Garden City (Herts, England), April 9, 1957.*

*Zusammenfassung*

Durch Vorbehandlung mit Iproniazid wird die hypothermische Wirkung von Reserpin bei Mäusen abgeschwächt. Dieser Effekt geht mit der Monoaminoxydase-Hemmung parallel.

[7] A. PLETSCHER, Exper. *12*, 479 (1956).

## Variations in Encephalic and Intestinal Serotonin After Electrical Shock[1]

The increasing amount of research carried out in recent years on the relations between drugs active in schizophrenic forms (Reserpine and Chlorpromazine) and serotonin (5 HT)[2] led us to undertake a series of experiments on the variations of encephalic 5 HT after electrical and cardiazolic shock.

We employed rats of an average weight of 150 g (supplied by the firm C. Erba of Milan), to which cardiazol was administered intraperitoneally at the dose of 80 mg/kg, or on which electroshock of 0·2 s, 125 V and 130 mA was carried out. At 10 min, 1 h, 2 h and 24 h after this electric treatment, or after the first appearance of convulsions in rats treated with cardiazol, the animals were killed by decapitation and their brains and large intestine removed.

Two methods, spectrophotometric and biological, were used for 5 HT determination. For the spectrophotometric method, the serotonin was extracted according to BOGDANSKI *et al.*[3], and assayed at 275 mμ according to UDENFRIEND *et al.*[4]; for the biological method, we employed the isolated rat colon in atropinized, calcium-free Ringer, according to the suggestions of DALGLIESH *et al.*[5].

The results obtained are shown in two tables.

Our values show that, very soon after electroshock or cardiazolic shock, there is an increase in cerebral 5 HT and a decrease in intestinal 5 HT. The variations obtained by employing the two methods of assay, are qualitatively similar but quantitatively very different. It should be remarked, however, that whereas the spectrophotometric data concerning cerebral 5 HT of control animals are in satisfactory agreement with those quoted in the literature[6], those obtained by biological method are distinctly lower.

Our data on the physiological 5 HT content of intestine agree with those in the literature.

The very marked increase of 5 HT in the brain, as shown by the biological test which we used after electro- and cardiazol-shock, might also depend upon the release of an active substance which may potentially give the serotonin effect, or from the lack of inhibition due to decreased presence of an inhibiting factor present in the normal extracts, for instance noradrenaline. It is necessary to point out, moreover, that serum adrenaline is increased and not decreased after electroshock[7].

As to the mechanism which causes the rapid increase of cerebral 5 HT and the rapid decrease of intestinal 5 HT after electrical and cardiazol shock, we can merely suggest as possible hypothesis, a variation of enzymatic activities involved in 5 HT synthesis, or breakdown or release of free 5 HT from complexes that may conceal its presence.

The decrease of 5 HT in the intestine may indicate its mobilization, which might also be significant with regard to the increase of 5 HT in the brain, bearing in mind other experiments showing increased cerebral permeability after cardiazol or electroshock[8].

[1] Paper partially communicated at the XX. Congress of Physiology, Bruxelles, July 30 – August 4, 1956.

[2] S. M. HESS *et al.*, Fed. Proc. *15*, 437 (1956). – E. COSTA, Proc. Soc. exp. Biol. Med. *91*, 39 (1956). – S. GARATTINI and L. VALZELLI, Boll. Soc. Ital. Biol. sper. *31*, 1648 (1955); *32*, 292 (1956). – P. A. SHORE and G. L. SILVER, Exper. *11*, 272 (1955). – J. H. GADDUM and N. J. GIARMAN, Brit. J. Pharmacol. *11*, 88 (1956).

[3] D. BOGDANSKI and S. UDENFRIEND, J. Pharm. *117*, 83 (1956).

[4] S. UDENFRIEND *et al.*, J. biol. Chem. *215*, 337 (1955).

[5] G. E. DALGLIESH, C. C. TOH, and T. S. WORK, J. Physiol. *120*, 298 (1953).

[6] A. PLETSCHER, Exper. *12*, 479 (1956).

[7] H. WEIL-MALHERBE, Arch. exp. Path. Pharm. *216*, 149 (1952).

[8] G. P. PANIZZARI and A. VEGETO, Boll. Soc. Ital. Biol. sper. *31*, 854 (1955). – S. GARATTINI and E. GENOVESE, Atti Soc. Lomb. Sci. Med. Biol. *8*, 17 (1953).

*Table I*

Brain 5 HT concentration (spectrophotometric method)

| Treatment | Time after treatment | Number of animals | Number of assays | Cerebral 5 HT γ/g ± S.E. | Range |
|---|---|---|---|---|---|
| – | – | 64 | 10 | 0·97 ± 0·04 | 0·75 – 1·3 |
| Electroshock . . . | 10 min | 13 | 4 | 3·48 ± 0·22 | 3·17 – 4·0 |
| Electroshock . . . | 1 h | 13 | 4 | 2·96 ± 0·21 | 2·5 – 3·5 |
| Electroshock . . . | 2 h | 13 | 4 | 1·72 ± 0·09 | 1·5 – 1·9 |
| Electroshock . . . | 24 h | 15 | 5 | 1·03 ± 0·07 | 0·85 – 1·4 |

Other assays show a decrease in intestinal 5 HT 10 min after electroshock (from the normal values of 2·5 γ/g down to values of 1·2 γ/g). These values go back to normal after only 2 h.