

**Zeitschrift:** Bulletin der Schweizerischen Akademie der Medizinischen Wissenschaften = Bulletin de l'Académie suisse des sciences médicales = Bollettino dell' Accademia svizzera delle scienze mediche

**Herausgeber:** Schweizerische Akademie der Medizinischen Wissenschaften

**Band:** 8 (1952)

**Heft:** 1-2: Symposium über die Beeinflussung des reaktiven Geschehens durch Hypophyse und Nebennierenrinde = Symposium on the influence of the hypophysis and the adrenal cortex on biological reactions = Symposium sur l'influence de l'hypophyse et de la corticossurrénale dans les réactions biologiques

**Artikel:** Pituitary-adrenal mediation in the mechanism of action of salicylates

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**DOI:** <https://doi.org/10.5169/seals-307064>

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## **Pituitary-adrenal Mediation in the Mechanism of Action of Salicylates**

By **M. Pelloja** (Siena)

The discovery of ACTH and cortisone therapeutic efficacy in rheumatic diseases, and the study of their physiological effects on the organism, have helped to throw some light on the mechanism of action of salicylates. In fact, clinical observations and experimental investigations have demonstrated a marked parallelism of biological reactions after administration of ACTH or cortisone and after administration of salicylates.

It is known that ACTH produces eosinopenia (14, 20) and increased excretion of urinary 17-ketosteroids (14, 23, 22, 20), and that it produces a decrease of adrenal cortex ascorbic acid and cholesterol (30, 31). This fact is now so well established that some methods of determining adrenocorticotrophic hormone dosage are based on the evaluation of the changes of these two substances in the adrenals.

Similarly it is known that salicylates, when administered in therapeutic doses, decrease the ascorbic acid and cholesterol level of adrenal cortex (19, 18), cause a reduction of circulating eosinophils (19, 8) and an increase in urinary excretion of 17-ketosteroids (3) and of reduced steroids (38).

Another case in which salicylates and ACTH (but also cortisone) act with very close similarity is the hyaluronidase inhibition. It has been known for a long time that salicylates create *in vivo* a marked anti-hyaluronidase effect (16, 25, 9, 11, 37, 21, 35); recently, it has been discovered that also ACTH and cortisone (27, 32, 33, 34, 28, 2, 36, 40, 1, 10), as well as adrenal cortical extracts (24, 32, 33, 34, 28, 40, 1, 26), possess the same property.

On the clinical side, the observation of *Cochran, Watson and Reid* (5) is of interest, concerning the development of a mild Cushing's syndrome (rounding of the face, mild hirsutism, acne, glycosuria and diminished glucose tolerance, alterations of psyche) following administration of 5 g/day of aspirin to a girl aged 13, suffering from acute rheumatic fever. Closely corresponding symptoms have been observed following prolonged administration of cortisone (17).

Histological studies of *Champy* and *Demay* (4) further confirm the parallelism of action of salicylates and ACTH. Salicylates have been shown to produce in the adrenals hypertrophy of the zone between the glomerular and fasciculate parts, with presence of small cells, always in mitosis and with an intense staining of the cytoplasm. Following prolonged treatment, the fasciculate zone itself hypertrophies, with a loss of cholesterol in the cells and the glomerular grows thinner and appears to be in need of lipidic granulations. Salicylates also alter the spleen (severe reduction of white pulp and of Malpighian corpuscles; swelling of reticulus cells and appearance of megacaryocytes), as does cortisone. ACTH produces corresponding changes both in the adrenals and in the spleen.

Lastly, it should be kept in mind that *Wiesel* and co-workers (39) have affirmed that salicylates enhance the action of cortisone.

Although these studies demonstrate that salicylates act in a manner closely corresponding to that of ACTH (and, in part, of cortisone), they are not sufficient to explain their mechanism of action. The investigations of *Hetzel* and *Hine* (18), and those of *Pelloja* (29), agree in specifying some aspects of such a mechanism. In fact, they prove that hypophysectomy inhibits the loss of the ascorbic acid of the adrenal cortex (*Hetzel* and *Hine*, 1951) and the hyaluronidase inhibition (*Pelloja*, 1951) by salicylates. Also adrenalectomy presents the anti-hyaluronidase effect of salicylates (*Pelloja*, 1951). From this it is a logical inference, that these effects of the salicylates are only possible at the condition of functional integrity of pituitary and adrenals.

The importance of hyaluronidase and collagen on the pathogenesis of rheumatic diseases already suggested, and recent discovery of ACTH and cortisone efficacy in these diseases, suggest that also the anti-rheumatic effect of salicylates may work through an activation of the «anterior pituitary-adrenal cortex» system.

Such a mode of action of salicylates would correspond to the mechanism of stress, in the alarm reaction; and in this sense one could explain the inhibition of spreading phenomenon following a surgical operation (13, 15, 6, 7) or traumatic shock (12). At the same time it would be possible to understand why the serum of stressed animals is able to inhibit hyaluronidase (33), just as occurs in animals which have received ACTH or cortisone.

Admitting this pathogenic analogy with stress, one could also explain, on the hormonal base, the mechanism of action of certain anti-rheumatic practices, some empirical and now in disuse (as uerotherapy, for instance),

others still in use and accepted by medical science (mud-baths and thermal bath therapy). It seems very likely that in all these cases part of the favourable effects comes from an activation of the pituitary-adrenal system.

### Summary

Recent studies have demonstrated a very marked parallelism between the biological, clinical and histological reactions following ACTH or cortisone administration and following salicylates administration. Moreover, hypophysectomy has been shown to counteract the ascorbic acid decrease in adrenals caused by therapeutic doses of salicylates (*Hetzel and Hine, 1951*) and to prevent the hyaluronidase inhibition *in vivo* by salicylates (*Pelloja, 1951*). Also adrenalectomy abolishes the anti-hyaluronidase action of these drugs (*Pelloja, 1951*).

The suggestion is therefore made that salicylates act via the anterior pituitary and adrenal cortex.

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