

Salicylates, Stress and Cortisone

Working with salicylate in rheumatic fever we could demonstrate that the effect of large salicylate doses essentially differs from that of smaller ones.

In the case of *large* doses of salicylate the non-specific defense mechanism of the organism is remarkably activated. According to our experiments performed in animals as well as in man, a large dose of salicylate mobilizes the cortisone-compound F system, whereas with the application of *small* doses such an effect could not be demonstrated. The significance of these observations relating to rheumatic fever and allied disorders is well known¹.

To prove this statement we shortly report out investigations carried out on 89 rats (including controls) and 27 men.

(A) EXPERIMENTS ON RATS

(I) *The effect of large doses*

Giving 500–600 mg salicylate subcutaneously pro kg body weight to albino rats weighing 140 to 180 grams:

(a) *The absolute count of eosinophil cells* decreases to 70 to 90 per cent of their initial number in the fourth hour (THORN-test²) (9 cases).

(b) *The histological signs of SELYE's alarm reaction* can be demonstrated in thymus, spleen, adrenals as well as the *C-vitamine depletion* of, and the *discharge of lipids* from, the adrenal cortex³ (3 cases).

(c) *The acute formaline test* described recently by SELYE⁴ gives negative (or minimal) response 5–6 hours after the salicylate was injected. The marked hyperæmia and œdema following the subaponeurotic application of 0.1 cm³ of 1 per cent formaldehyde fails to develop (7 cases). According to SELYE, ACTH, cortisone, and stresses exert similar effects.

(d) Negative responses were also gained with our *hyaluronidase limb-œdema test*⁵. After subaponeurotic administration of 1 gamma pro 1 gram body weight of hyaluronidase (Schering), neither padded œdema and hyperæmia of the foot back nor swelling of the thigh develops on animals treated with salicylate 5–6 hours before (9 cases). ACTH, and cortisone 4–4 mg pro 100 g exerted *milder* effects in this test, whilst neoantergan (Specia) acted similarly (5 cases).

(e) A few tests with 200 gammas of *histamine* using the same technic (c, d) also gave negative (or minimal) responses when pretreated with salicylate (3 cases)⁶.

(f) The eosinophilic response fails to occur, and the reactions described in paragraphs c, d, and e, are entirely *positive* in salicylate-treated rats if *bilateral adrenalectomy* was performed 2–5 days before (4 cases). It is worthy of mention that the eosinophil count markedly increased in all of the adrenalectomized rats after salicylate-stress, this increase being 1.5 to 5.5-times their initial number. ACTH cannot produce this reaction. After administering 3–3 mg to the same adrenalectomized animals the eosinophilic count remained unchanged. Several animals perished after salicylate-stress.

¹ P. S. HENCH, E. C. KENDALL, CH. H. SLOCUMB, and H. F. POLLEY, Arch. Int. Med. 85, 545 (1950).

² L. RECANT, D. M. HUME, P. H. FORSHAM, and G. W. THORN, J. Clin. Endocrinology 10, 187 (1950).

³ H. SELYE, *Textbook of Endocrinology* (Acta Endocrinol., Montréal, 1947).

⁴ H. SELYE, Brit. Med. J. 2, 1129 (1949).

⁵ E. KELEMEN, J. IVÁNYI, and M. MAJOROS, unpublished.

⁶ Experiments on guinea-pigs also showed that the large salicylate doses protect the animals by a nonspecific way.

(II) *The effect of small doses*

Doses of 200–300 mg pro kg body weight are always *insufficient* and do not produce the reactions described in a, b, c, d, and e (24 cases). The corresponding serum values are about 20 mg per cent in the group I, and about 35–55 mg per cent in the II.

(B) EXPERIMENTS IN MEN

The absolute eosinopenia appears and increases with elevation of the serum salicylate level. Small salicylate doses with serum levels of the 4th hour at 20–30 mg per cent and below (4–5 g of salicylate) did not produce any fall of the eosinophils (16 cases), while in the case of levels of 30–35 mg per cent (6 g single dose), the decrease is about 50 per cent of the original (8 cases). *Higher levels* (7–10 g within 4–5 hours) are accompanied with more pronounced diminution of the absolute eosinophil count (3 cases). Fractionation of doses is disadvantageous in this respect. According to THORN, FORSHAM *et al.*, this decrease indicates mobilization of adrenocorticotrophine and/or cortisone and compound F. There are no differences between rheumatic fever cases, rheumatoid arthritis patients, and normal persons respectively. It is to be noted that repeated doses of salicylate cannot provoke eosinopenia regularly, but it is known that cortisone too behaves in the same manner¹.

FORMAN, SEIFTER, and EHRICH² suggested already that a large salicylate dose could provoke an alarm reaction.

On the one hand our results shed a new light on COBURN's much contested report relating to therapeutic significance of a high salicylate level³, and on the other hand they again stress the important role which in the course of the last few years has been attributed to the "alarm reaction", i. e. the aspecific reaction of the organism: "the general adaptation syndrome", elaborated in details by SELYE.

"Cortisone-like effect", "antihyaluronidase-effect", "antihistamine-effect", "alarm-reaction", can all *parily* be accounted for in a similar manner. The favourable clinical effect obtained with salicylate in several diseases, which so far could hardly be interpreted satisfactorily, may also be explained in this way. However, it must be emphasized that, as concerns *prolonged treatment*, the results of these experiments can only be transferred with reserve. The quantitative estimation of cortisone etc. in urine is needed.

Details of this work will appear as supplement to the Acta Medica Scandinavica, Stockholm.

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Zusammenfassung

Die vorliegenden Tierexperimente und Versuche an Menschen stützen die Auffassung, daß «große» Salicylatdosen imstande sind, Cortison usw. in wirksamen Mengen zu mobilisieren. Kleinere Quantitäten von Salicylat geben keinen solchen Effekt. Es scheint sich um eine unspezifische Abwehrreaktion zu handeln, in der die Nebennierenrinde eine bedeutsame Rolle spielt.

¹ R. G. SPRAGUE, M. H. POWER, H. L. MASON, A. ALBERT, D. R. MATHIESON, P. S. HENCH, E. C. KENDALL, CH. H. SLOCUMB, and H. F. POLLEY, Arch. Int. Med. 85, 199 (1950).

² C. FORMAN, J. SEIFTER, and W. E. EHRICH, Amer. J. Med. Sci. 215, 714 (1948).

³ A. F. COBURN, Bull. Johns Hopkins Hosp. 73, 435 (1943).