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Prevention by Sodium Salicylate of Arteritis in the Experimental Allergic State.*

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(Introduced by Ralph A. Kinsella.)
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It has been established that arteritis can be produced in the experimental animal following the injection of foreign protein.[1-6] We have attempted to produce experimental arteritis in one group of rabbits and to prevent its expected production in a similar group, with the purpose of clarifying the mechanism of its pathogenesis. Several extensive reviews of the problem have appeared, among which is that of Logue and Mullins.[7] The pathology has been described, and circulating antibody has been studied.[1,4,6,8,9,10,11] The process which precedes antigen-antibody reaction in the fixed tissues has in part been indirectly demonstrated[12-15] by the recovery of humoral antibody against homologous kidney from animals injected with hemolytic streptococci; this suggests initial union of the streptococcus antigen with a kidney tissue hapten fraction. A histologic correlation with the immunological process in experimental arteritis[6] has shown that one of the earliest manifestations of the lesion is collection of lymphocytes and monocytes around the artery at which time circulating antibody is absent. These observers[6] present these findings as evidence of fixation of antigen in the arterial wall, and of antibody migration within the lymphocytes to the site of fixed antigen.

Sodium salicylate suppresses circulating antibody in the experimental animal[1,16,17] and in clinical serum sickness.[9] Given intravenously[1] it did not prevent the occurrence of experimental arterial lesions. Suppression of circulating antibody was reconciled with hastening of recovery by postulating that the same mechanism which rendered an infectious agent less antigenic might also render it less pathogenic.[16] Sodium salicylate *in vitro* exerts some inhibitory effect on immune reactions.[18,19] Some investigators have found

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in vitro and *in vivo* inhibition of hyaluronidase activity by salicylates[20,21] and believe this is due to inhibition of the enzyme reaction involved in liberation of N-acetyl-glucosamine. The toxic effects of salicylates have been studied[22,23,24] and are proportional to size of dosage.

Anti-histaminic drugs protect against anaphylaxis[25] but there is no correlation between anaphylactic reactions and the occurrence of vascular lesions.[4] However, the anti-histaminic drugs greatly minimize the vascular lesions in experimental arteritis[5] and do have an anti-hyaluronidase action.[26] Hyaluronidase greatly intensifies the size of epidermal allergic reactions.[26]

Para-aminobenzoic acid is apparently concerned with metabolic stimulation of host cells.[27]

Method. Twenty albino rabbits were given intravenous injections of sterile horse serum on 3 occasions. The first dose was 10 cc per kilo; the second dose, given 16 days later, was one cc per animal; the third dose, given 6 days later, was 10 cc per kilo. Seven days after the third injection all surviving rabbits were sacrificed by air emboli and were immediately autopsied. The organs were fixed in formalin, sectioned, stained, and the heart and kidneys carefully studied for the presence of arteritis.

The animals were divided into 4 groups.

Group A, 3 rabbits, was given para-aminobenzoic acid starting 31 days prior to the first injection of horse serum and continuing throughout the course of the experiment. The PABA was dissolved in their drinking water, each cc containing 0.0026 g of PABA.

Group B, 12 animals, was given sodium salicylate daily, starting 8 days prior to the first injection of horse serum and continuing throughout the course of the experiment. A 5% aqueous solution was employed and the injections were given subcutaneously once each day. The daily dose was 0.2 g per kilo of body weight.

Group C, 2 animals, was treated exactly the same as Group B with the exception that each injection of sodium salicylate was given intravenously prior to the first injection of horse serum. After that all sodium salicylate injections were given subcutaneously.

Group D, 3 animals, received nothing other than horse serum.

The animals in all groups were bled on one or several occasions and the serum was tested for the presence of precipitin against horse serum.

Results. The results are shown in Table I. The 3 animals in Group B that failed to survive died during the night in the last week of the experiment. In the presence of post-mortem changes no conclusions can be drawn from the appearance of their tissues. However all 3 showed the same findings, consisting of gangrene of the caecum, peritonitis, and lymphocytic and monocytic infiltration around the arteries of the kidneys. Group C animals both showed, in addition to periarterial round cell infiltration, diffuse and localized collections of lymphocytes throughout the parenchyma of the kidney, thickening of some glomerular membranes, and infiltrations of mononuclear cells around the afferent arteriole.

Discussion. Whereas the horse serum control animals and 2 of the PABA treated animals developed arterial lesions and circulating antibody at the end of the experiment, the findings were different in the sodium salicylate treated animals. Moreover, the route of administration of the sodium salicylate apparently influenced the effect. When it was given subcutaneously the surviving animals showed no evidence of arteritis but did produce circulating antibody in moderate or attenuated quantity, late in the course of the experiment.

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TABLE I.

Effect of PABA and of Sodium Salicylate and Its Route of Administration on Humoral Antibody and Periarterial Lesions in Rabbits Injected with Horse Serum.

Rabbit No.	PABA, oral	Sodium salicylate, subcut.	Sodium salicylate, I.V. and subcut.	Precipitin reaction: 12 days after first Horse serum	Precipitin reaction: Day of second Horse serum	Precipitin reaction: Day of third Horse serum	Precipitin reaction: Last day of exper.	Died during exper.	Periarterial lesions
1.	Yes						1:1280		Negative
2.	,,						1:1280		Positive
3.	,,						1:1280		,,
4.		Yes		Neg.	Neg.	Neg.	1:140		Negative
5.		,,		,,	,,	,,	1:160		,,
6.		,,		,,	,,	,,	1:200		,,
7.		,,			,,	,,		Yes	?
8.		,,			,,	,,	1:120		Negative
9.		,,			,,	,,	1:200		,,
10.		,,			,,	,,		,,	?
11.		,,			,,	,,	Neg.		Negative
12.		,,			,,	,,		,,	?
13.		,,			,,	,,	1:120		Negative
14.		,,			,,	,,	1:80		,,
15.		,,			1:180	,,	1:160		,,
16.			Yes	,,	Neg.	,,	1:6		Positive
17.			,,	,,	,,	,,	1:16		,,
18.							1:1280		,,
19.							1:640		,,
20.							1:640		,,

When it was given intravenously first and subcutaneously later the animals did develop arteritis and glomerular changes, but produced circulating antibody in scarcely detectable quantity, late in the course of the experiment.

The following theory is offered as a possible explanation of the reactions here observed. When sodium salicylate is administered subcutaneously sufficiently in advance of the first injection of antigen, it blocks the fixation of antigen in the tissue cells. This precludes any need of antibody in the tissues and there is, therefore, no lymphocytic or monocytic migration to the tissues. In this absence of tissue antigen-antibody union the chain of events leading to production of lesions is never started. The intravenously injected antigen circulates for a prolonged period, and in its passage through the lymph nodes and other reticulo-endothelial structures gives rise to production of antibody. Union of this circulating antibody with its antigen is prevented by reason of the inability of antigen to become fixed to tissue cells. The presence of this circulating antibody thus becomes an indifferent matter to the well being of the host, at least insofar as this type of allergic reaction is concerned. The observations of others concerning the potentiating effect of hyaluronidase in a certain type of allergic reaction[26] and the anti-hyaluronidase activity of sodium salicylate,[20,21] suggest that sodium salicylate blocks antigen fixation in the tissues by inhibiting hyaluronidase activity.

No conclusions can be drawn concerning the effect produced when sodium salicylate is given intravenously prior to the first injection of the antigen and subcutaneously thereafter, since only 2 animals were treated in this manner. However, the identical findings in both suggest a lowering of the protective action against antigen-tissue fixation, and a heightening of the depressant effect on the reticulo-endothelial system. This problem is at present under further investigation.

Conclusions. 1. The subcutaneous administration of large doses of sodium salicylate to rabbits well in advance of the initial contact with horse serum antigen prevents the development of arterial lesions.

2. The arterial lesions fail to develop even though circulating antibody is present in moderate quantity.

3. It is believed that the lesions fail to develop because there is no antigen-antibody reaction, and that this reaction can not take place because salicylate has prevented antigen from uniting with tissue cells.

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Specificity of the Response of Various Assay Organisms to Nicotinic Acid.*

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It has recently been shown with *Neurospora* mutants that tryptophan can be converted to nicotinic acid and that kynurenine and hydroxyanthranilic acid are intermediates in the conversion.[1,2] This conversion, which also appears to be carried out by the intestinal flora of animals,[3,4] and possibly by animal tis-

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