EFFECT OF SALICYLATES ON THE CIRCULATING EOSINOPHILS AND URINARY 17-KETOSTEROIDS IN MAN

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The anti-inflammatory and analgesic effects of salicylates have been observed for centuries, but their mode of action remains obscure. Their recommendation as the cheapest and often the safest medicament in rheumatoid arthritis (Ragan, 1949) and in rheumatic fever (McEwen, 1954; Coburn, 1943) has led to renewed efforts to discover how they work.

Salicylates and cortisone may act similarly in stimulating the pituitary to produce adrenocorticotropin, and subsequently in stimulating the adrenal cortex to increase its production of cortisone. Salicylates act like cortisone in some respects, but are totally unlike it in many effects (Hailman, 1952). The evidence for and against stimulation of the hypothalamus or the anterior pituitary by salicylate to produce an ACTH-like effect is conflicting and fragmentary (Smith, Gray, and Lunnon, 1954a, b; Bayliss and Steinbeck, 1953, 1954a, b; Meade and Smith, 1951; Shuman and Finestone, 1950; Feeney, Carló, and Smith, 1955; Done and Kelley, 1956; Marson, 1953; Cronheim, King, and Hyder, 1952, 1953; Cronheim and Hyder, 1954; Roskam and van Cauwenberge, 1951; Hetzel and Hine, 1951). The earlier studies suggested a salicylate effect *via* the pituitary-adrenal axis, but later reports discount this idea, since salicylates are able to exert their effect in the adrenalectomized animal (Ingle, 1941).

Two tests according evidence of anterior pituitary and, subsequently, adrenal cortex activation are in common use. Adrenocorticotrophic hormone in adequate doses indirectly and cortisone directly decrease the circulating eosinophils of the peripheral blood, while increasing the urinary excretion of ketosteroids. Most authorities approve of eosinopenia (the Thorn test) as a criterion of adrenal cortical stimulation (Thorn, Forsham, Prunty, and Hills, 1948; Shands and Bartter, 1952; Best, Kark, and Muehrcke, 1953).

Effect on Eosinophils.—A minimal depression of the circulating eosinophils (50-60 per cent.) is usually held to be necessary to establish a positive Thorn test. A distinction between the reaction of rheumatic and non-rheumatic individuals as regards eosinophil response and corticosteroid excretion has not been reported or, at least, the idea has not been accepted.

The published reports lack unanimity in describing the effect of salicylate upon the circulating eosinophils. Early studies indicated an eosinopenia following salicylate administration (Shuman and Finestone, 1950; Roskam and van Cauwenberge, 1951; Bertolani, Lorenzini, and Bonati, 1951), but recent workers have not confirmed this reported depression of the eosinophil count (McEwen, 1954; Meade and Smith, 1951; Marson, 1953; O'Connell, Roy, and Massell, 1955). It is suggested that the earlier results were due to the use of too large (*i.e.* toxic) doses of salicylate, so inducing a stress reaction (McEwen, 1954). According to Roskam and van Cauwenberge (1951), salicylates caused the eosinophils to decrease by 50 per cent. in 6 hours in rats. O'Connell and others (1955) found a salicylate potentiation of the eosinopenic effect of ACTH in humans; this was not interpreted as an effect upon the pituitary gland, but rather as a possible increase in peripheral utilization of the ACTH which was being given at the same time. Meade and Smith (1951) found that therapeutic doses produced no significant eosinopenia in 4 hours in humans. Lichtwitz (1944) again emphasized the distinction between the effects of therapeutic and toxic doses of salicylate in animal experiments.

Withdrawal Phenomena.—After withdrawal of steroids, the continuation by salicylate of the effects produced by doses of cortisone and adrenocorticotropin suggested that these drugs acted in a similar

manner. On the other hand, the marked relapses and disturbances which followed the withdrawal of steroids did not follow the withdrawal of salicylate. Salicylates were also synergistic in reinforcing the beneficial action of corticosteroids and ACTH in rheumatic fever (McEwen, 1954; Fischel, Frank, and McEwen, 1955; Fischel, Frank, and Ragan, 1952).

Urinary 17-Ketosteroids.—Evidence for increased 17-corticosteroid excretion following the administration of salicylate has been similarly conflicting. Steroids do bring about an increase in 17-ketosteroid excretion. Van Cauwenberge and Heusghem (1951) found that salicylate therapy regularly caused a rise in urinary adrenal corticosteroids, and said that it was apparent that each increase in the excretion of the reducing steroids corresponded with clinical improvement; temperature, erythrocyte sedimentation rate, and subjective symptoms all improved simultaneously. This suggests a similarity between the results of salicylate and cortisone therapy. At least three other groups of investigators, however, found that salicylate had no influence on the urinary excretion of adrenocortical steroids (Smith and others, 1954a; Bayliss and Steinbeck, 1954; Done and Kelley, 1956), and correspondingly, Norymberski, Stubbs, and West (1953) found no increase in the urinary ketosteroids. The explanation for the discrepancy in the findings has been the same: therapeutic doses do not raise the level of the 17-corticosteroids in the blood or urine, and toxic (too large) doses induce a non-specific stress effect.

Cushing's Syndrome.—Considering the frequency of Cushing's syndrome in patients treated with cortisone, Cochran, Watson, and Reid (1950) reported the development of a Cushing syndrome in a rheumatic fever patient treated with aspirin.

Adrenal Ascorbic Acid and Cholesterol.—Reduction of the content of ascorbic acid and cholesterol of the adrenal cortex is generally assumed to denote adrenal cortical activity mediated by ACTH (Feeney and others, 1955; Sayers, Sayers, Fry, White, and Long, 1944; Cronheim, King, and Hyder, 1952, 1953; Sayers, Sayers, Lewis, and Long, 1944; Rich, Berthrong, and Bennett, 1950). ACTH, as well as salicylates, has been found to deplete the ascorbic acid and cholesterol content of the adrenal glands in rats (Feeney and others, 1955). Hypophysectomy was found to prevent salicylates from reducing the ascorbic acid and cholesterol content of animal adrenals (Feeney and others, 1955; Sayers, Sayers, Lewis, and Long, 1944). On the other hand, however, some workers do not regard the reduction of ascorbic acid or cholesterol in the adrenal cortex

as specifically indicating adrenocorticoid stimulation.

Feeney and others (1955) proved that depletion of adrenal ascorbic acid and cholesterol are not criteria for the anti-rheumatic properties of a drug. The ascorbic acid depletion of the adrenal cortex has been attributed to the "stress" effect on the adrenal cortex (too large) doses of salicylates, rather than to a specific adrenocorticotrophic action (Smith and others, 1954; Norymberski and others, 1953; Sayers and others, 1944; Vogt, 1950; Roskam, van Cauwenberge, Vivario, and Vliers, 1955).

Carbohydrate Metabolism.—Several investigators have reported conflicting effects of salicylates upon carbohydrate metabolism, most agreeing that they increased blood sugar and glycosuria. Cortisone causes an increase in liver glycogen (Feeney and others, 1955; Ingle, 1950), while salicylates cause a fall in liver glycogen and reduce glycosuria in diabetic rats (Ingle, 1950).

Peripheral Blood.—In contrast with salicylates, cortisone tends to increase the erythrocytes and haemoglobin of the peripheral blood. Both cortisone and salicylates protect arteries against damage in experimental arteritis (Rich and others, 1950).

Uricosuria, Hyaluronidase, and Erythrocyte Sedimentation Rate.—Steroids and salicylates both increase uricosuria, lower the erythrocyte sedimentation rate, and have an anti-hyaluronidase effect. The metabolic changes following the administration of ACTH have been well summarized by Thorn, Prunty, and Forsham (1947), and the comparison of the metabolic effects of ACTH with those of salicylates have been summarized by Hailman (1952). The effects of steroids and salicylates are compared and contrasted in Table I.

TABLE I
SIMILARITIES AND DISSIMILARITIES BETWEEN THE
EFFECTS OF STEROIDS AND SALICYLATES

Results	Effects on	Steroids	Salicylates
Similar	Adrenal ascorbic acid	Decreased	Decreased
	Adrenal cholesterol	Decreased	Decreased
	Total lymphocytes	Decreased	Decreased
	Erythrocyte sedimentation rate	Decreased	Decreased
	Uricosuria	Increased	Increased
	Total eosinophils	Decreased	Decreased or unaffected
Dissimilar	Withdrawal phenomena	Present	Absent
	Haemoglobin	Increased	Unaffected
	Erythrocytes	Increased	Unaffected
	Urinary 17-ketosteroids	Increased	Reports conflict
	Liver glycogen	Increased	Decreased
	Hyaluronidase	Inhibited	Usually unaffected
	Cushing's syndrome	Induced	Usually absent

Present Investigation

We have attempted to determine whether therapeutic doses of salicylates increase the production of adrenocorticotropin, directly stimulate the adrenal cortex, or have a cortisone-like action.

Preliminary Study.—This project has grown from a previous (unpublished) study carried out by Traut, Cech, and Stoker in 1946 of eight patients with severe (Grade III) rheumatoid arthritis in the West Suburban Hospital of Oak Park, in the Cook County Hospital, and in the Oak Forest Infirmary, Cook County, Illinois. In this study the eosinophils were counted before administering salicylates 1 or 2 g. daily orally or 4 to 8 g. daily intravenously, immediately after, 4 hours after, and daily for 7 days after salicylates were started. The peripheral eosinophils were also counted by the same group of workers in patients who had taken salicylates regularly for years. It appeared that salicylates, even in doses sufficiently large to produce tinnitus and nausea, did not depress the level of the circulating eosinophils in the majority of cases. The results are shown in Table II.

TABLE II
EFFECT OF SODIUM SALICYLATE ON CIRCULATING EOSINOPHILS IN EIGHT PATIENTS WITH RHEUMATOID ARTHRITIS

UNPUBLISHED PRELIMINARY STUDY CARRIED OUT BY TRAUT, AND STOKER IN 1948

Case No.	Salicylates		Circulating Eosinophils	
	Dose (g./day)	Route	Before Treatment	After Seventh Day
1	3	Oral	62	76
2	2	Intravenous	300	481
3	2	Oral	219	306
4	4	Oral	119	112
	1	Intravenous	136	162
5	4	Oral	131	125
6	4	Oral	100	88
7	4	Oral	125	125
8	8	Oral	100	106

Tests Employed.—In the present investigation we have employed Thorn's test (depression of the circulating eosinophils: Thorn and others, 1948) and have also measured the urinary 17-corticosteroids after single and repeated doses of salicylates. The eosinophils were counted by the method of Pilot (1950), and the urinary ketosteroids were measured by the method of Archibald (1954).

Material.—We studied 43 female patients in the Cook County Hospital of Chicago. Fifteen of these patients had rheumatic disease, and 28 were non-rheumatic chosen at random.

Method.—The circulating eosinophils were counted before the study began, and 25 units of adrenocorticotrophic hormone were administered to determine the ability of these patients to react normally in producing corticosteroids with an oxygen atom on the 11 and 17 carbon positions (the so-called 11-oxysteroids and 17-oxysteroids). Acetyl-salicylic acid was then given orally to establish a therapeutic level. On the fourth day the circulating eosinophils were again measured, and the plasma salicylate level was determined in sixteen of the patients by the method of Brodie, Udenfriend, and Coburn (1944). On the eighth day of salicylate administration, the plasma salicylate level was measured in seventeen patients and the number of circulating eosinophils was determined in all the patients. The results in the 43 patients are shown in Table III (opposite).

Results.—In only four patients (7 per cent.) of the 43 tested (Nos. 11, 30, 33, 35 in Table III) did the circulating eosinophils decrease by 50 per cent. or more; one of these patients (No. 33 in Table III) had eosinophilia (amounting to 34 per cent. in the differential count) accompanying lymphogranuloma. In five patients (12 per cent.) the circulating eosinophils decreased by about 30 per cent. In 23 patients (54 per cent.) they decreased by less than 30 per cent. In eleven patients they were unaffected. These last plateau curves were obtained only in patients with rheumatoid arthritis (Table III).

In forty patients there was either an initial increase or a decrease after the third day of salicylates, the tendency being for the count on the eighth day to approximate to the initial count.

In eight patients (Nos. 36-43 to Table III), the enumeration of the circulating eosinophils was supplemented by a 24-hr determination of the urinary 17-ketosteroids before and after the administration of salicylates. The ketosteroid excretion increased by a negligible amount after the administration of salicylates for eight days. This increased excretion was not significant.

Thus, the number of circulating eosinophils fluctuated unevenly, but did not predominantly decrease. Neither did the urinary 17-ketosteroid excretion change in a manner characteristic of stimulation of the adrenal cortex.

Summary

The number of circulating eosinophils was not usually significantly decreased (*i.e.*, by as much as 50 or 60 per cent.) by giving salicylates in therapeutic doses, and in some cases it actually increased. Nor did salicylates in full therapeutic doses increase the urinary excretion of 17-ketosteroids.

The initial increase or decrease in the eosinophils was followed by a return to the original count at the end of 8 days. In three exceptional patients

TABLE III

EFFECT OF SALICYLATE ON CIRCULATING EOSINOPHILS IN 43 PATIENTS, ON PLASMA SALICYLATE LEVELS IN 28 PATIENTS, AND ON URINARY EXCRETION OF 17-KETOSTEROIDS IN EIGHT PATIENTS

Case No.	Diagnosis	Oral Salicylates (g./day)	Circulating Eosinophils			Plasma Salicylate Level (Brodie)		Urinary 17-Ketosteroids* (mg./100 ml.)	
			Before Treatment	After 4th Day	After 8th Day	After 48 hrs	After 96 hrs	Before Treatment	After 8 Days
1		4	170	120	180	—	—	—	—
2		6	110	160	100	—	—	—	—
3		5	190	110	180	—	—	—	—
4		5	175	190	265	—	—	—	—
5		5	190	230	300	—	—	—	—
6		5	200	120	180	—	—	—	—
7		5	360	320	280	—	—	—	—
8	Rheumatic Fever	5	330	350	300	—	—	—	—
9	Rheumatic Fever	5	300	225	200	—	—	—	—
10		5.5	130	410	220	—	—	—	—
11		5.5	220	100	190	—	—	—	—
12		6	120	210	120	—	—	—	—
13	Rheumatic Fever	6	120	190	130	—	—	—	—
14	Rheumatic Fever	6	200	110	195	—	—	—	—
15		6	75	185	160	—	—	—	—
16	Lupus Erythematosus with Rheumatoid Arthritis	6	150	170	120	28.0	—	—	—
17		6	230	180	150	28.5	—	—	—
18		5	180	135	275	11.0	—	—	—
19		5	210	175	150	—	41.5	—	—
20	Salicylism	5	40	100	100	—	10.0	—	—
21		5	130	140	280	—	30.5	—	—
22		5	130	142	150	—	20.5	—	—
23		8	410	350	400	25.0	51.0	—	—
24	Degenerative Arthritis	6	230	150	160	17.5	40.0	—	—
25	Rheumatoid Arthritis	6	80	90	80	25.0	32.0	—	—
26		4	270	300	230	7.0	20.0	—	—
27	Pulmonary Fibrosis	5	650	760	220	8.0	25.5	—	—
28	Allergy, Obesity and Hypertension	5	640	440	410	14.0	16.0	—	—
29	Chronic Rheumatic Fever	5	250	200	130	6.0	13.0	—	—
30	Rheumatic Fever	6	260	130	200	21.5	44.0	—	—
31	Rheumatic Fever	6	200	110	100	21.5	30.0	—	—
32	Rheumatic Fever	6	410	500	400	26.0	30.0	—	—
33	Lymphogranuloma	6	1,730	800	660	27.0	30.5	—	—
34	Rheumatoid Arthritis	6	150	190	150	8.0	33.5	—	—
35	Suicide attempted with Aspirin	54 (toxic)	62	180	121	41.5	1.0	—	—
36		5.3	105	160	100	18.0	20.0	10.7	1.0

TABLE III—continued

Case No.	Diagnosis	Oral Salicylates (g./day)	Circulating Eosinophils			Plasma Salicylate Level (Brodie)		Urinary 17-Ketosteroids* (mg./100 ml.)	
			Before Treatment	After 4th Day	After 8th Day	After 48 hrs	After 96 hrs	Before Treatment	After 8 Days
37	Lupus Erythematosus	6.0	75	80	60	20.0	23.0	5.4	9.7
38		5.3	175	475	330	20.5	26.0	1.6	14.6
39	Rheumatoid Arthritis	6.6	80	120	270	17.0	21.5	3.0	4.3
40		8.0	110	140	110	17.0	32.5	10.7	8.8
41	Degenerative Arthritis	6.0	70	85	75	25.0	41.5	9.5	3.8
42		6.0	135	110	155	10.0	15.5	2.9	6.6
43		8.0	310	330	365	2.5	12.5	3.7	3.3

* Normal value for urinary 17-ketosteroids in women is 4.6 to 13.4 mg./100 ml.

with an initial eosinophilia, the eosinophils decreased more than 50 per cent., but in the majority the response of the adrenal cortex to salicylates was slight.

One patient (Case 20 in Table III) showed symptoms of salicylism upon attaining a level of 10 mg. salicylate per 100 ml. plasma, and the eosinophil count in this patient actually rose during this episode.

In a programme of maximum salicylate administration, blood salicylate levels should be estimated frequently (Coburn, 1943). Mental disturbance, incontinence, tinnitus, headache, nausea, and vomiting should be given due importance.

The presumption of salicylate benefits mediated by the pituitary gland or adrenal cortex is not therefore acceptable in the light of our findings.

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L'effet des salicylates sur les éosinophiles sanguins et les 17-cétostéroïdes urinaires chez l'homme

RÉSUMÉ

Des salicylates, en doses thérapeutiques, ne provoquaient pas généralement de chute appréciable (c'est-à-dire en dessous de 50 ou 60 pour cent) des éosinophiles sanguins et même, quelquefois, leur chiffre se trouvait augmenté. En fortes doses thérapeutiques, les salicylates n'ont pas, non plus, fait augmenter l'excrétion urinaire des 17-cétostéroïdes.

L'augmentation ou la diminution du chiffre des éosinophiles ne durait que 8 jours. Chez trois malades exceptionnels avec une éosinophilie initiale, le chiffre des éosinophiles baissa en dessous de 50%, mais dans la plupart des cas l'écorce surrénale ne réagissait que faiblement aux salicylates.

Un malade (No. 20 dans la Table III) acusa des symptômes de salicylisme au moment d'atteindre le taux de 10 mg. de salicylate par 100 c.c. de plasma; au cours de cet épisode le chiffre d'éosinophiles augmenta.

Quand on administre des doses maxima de salicylates, il faut déterminer souvent leur taux sanguin (Coburn, 1943), et considérer l'importance des désordres mentaux incontinence, tintement d'oreilles, céphalée, nausée et vomissement.

A la lumière de nos résultats on ne peut donc pas accepter l'hypothèse selon laquelle les effets favorables des salicylates seraient transmis par l'hypophyse ou l'écorce surrénale.

El efecto de los salicilatos sobre los eosinófilos circulantes y los 17-cetoesteroides urinarios en el hombre

SUMARIO

Los salicilatos, en dosis terapéuticas, no provocaban generalmente bajas significativas (es decir debajo de un 50 o 60 por ciento) de eosinófilos circulantes y hasta,

a veces, sus cifras se veían aumentadas. Con fuertes dosis terapéuticas los salicilatos tampoco hacían aumentar la excreción urinaria de los 17-cetoesteroides.

El aumento o la disminución de la tasa de eosinófilos no duraba más de 8 días. En tres enfermos excepcionales con una eosinofilia inicial, la cifra de los eosinófilos cayó debajo del 50%, pero en la mayoría de los casos la respuesta de la corteza suprarrenal a los salicilatos fué débil.

Un enfermo (No. 20 en el Cuadro III) acusó síntomas de salicilismo al alcanzar la tasa de 10 mg. de salicilato por 100 c.c. de plasma; durante este episodio su eosinofilia se vió aumentada.

Al administrar dosis maximas de salicilatos, hay que determinar su tasa sanguínea a menudo (Coburn, 1943) y atribuir importancia debida a desórdenes mentales, incontinencia, tintineo, cefalalgia, náusea y vómitos.

A la luz de nuestros resultados no se puede aceptar la hipótesis según la cual los efectos favorables de los salicilatos se transmiten por medio de la glándula pituitaria o la corteza suprarrenal.