University of Nebraska Medical Center
BREAKTHROUGHS FOR LIFE

University of Nebraska Medical Center
DigitalCommons@UNMC

MD Theses

Special Collections

1955

ACTH effect of salicylates

Mary I. Larson
University of Nebraska Medical Center

This manuscript is historical in nature and may not reflect current medical research and practice. Search PubMed for current research.

Follow this and additional works at: https://digitalcommons.unmc.edu/mdtheses

Recommended Citation

Larson, Mary I., "ACTH effect of salicylates" (1955). *MD Theses*. 2088.
https://digitalcommons.unmc.edu/mdtheses/2088

This Thesis is brought to you for free and open access by the Special Collections at DigitalCommons@UNMC. It has been accepted for inclusion in MD Theses by an authorized administrator of DigitalCommons@UNMC. For more information, please contact digitalcommons@unmc.edu.

THE ACTH EFFECT OF SALICYLATES

Mary I. Larson

Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska

April 1, 1955

Omaha, Nebraska

TABLE OF CONTENTS

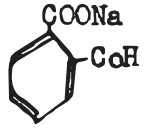
		Page
I.	Introduction	1
II.	Similarity of Uses	2
III.	Comparison of Actions	3
	(A) Increased Adrenal Cortical Activity	3
	(B) On Carbohydrate Metabolism	9
	(C) On Protein Metabolism	11
	(D) Inhibition of Hyaluronidase . . .	13
	(E) In Hypersensitivity	15
	(F) Antipyretic and Analgesic Properties	19
	Site of Action of Salicylates	21
V.	Discussion	24
VI.	Summary	26
VII.	Bibliography	27

I. Introduction

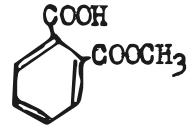
It has been said that "aspirin is the poor man's cortisone". Some authors have referred to the "ACTH effect of salicylates". It is the purpose of this paper to review the literature presented so far which may enlighten the author as to the relationship between ACTH, cortisone and salicylates.

Chemistry

All salicylates are derivatives of o-hydroxybenzoic acid. The most common salicylates are sodium salicylate and acetylsalicylic acid, although many others have been used.



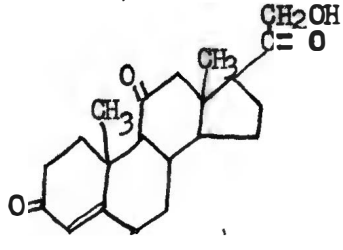
Sodium Salicylate



Acetylsalicylic Acid

ACTH is a protein with a molecular weight of about 20,000.

Cortisone has a structure similar to cholesterol.



Cortisone or

Kendall's Compound E

Thus, we see there is very little similarity in the chemical structures of these compounds.

II. Similarity of Uses

Salicylates

It is thought that Chase, in 1865, was the first to refer to the use of salicylates in treatment of inflammatory rheumatism and MacLagan in 1876 was the first to popularize the use of salicylates in rheumatic fever.(1) For centuries before this, crude preparations of salicylates had been used as analgesics. (Hippocrates, 2,400 years ago, recommended leaves of the willow tree for pain in childbirth.)

Coburn in 1943 (2) re-emphasized the importance of the use of salicylates in acute rheumatic fever and introduced the concept that a high level of plasma salicylates was necessary to prevent progression of the inflammatory process while at a lower level there was only a relief of symptons with a masking of the disease process.

Cortisone

Hench (1949) (3) noted in the presence of pregnancy, jaundice and surgical trauma or malnutrition there frequently appeared a clinical remission of rheumatoid arthritis. In the same year (4) he reported relief of symptons of rheumatoid arthritis and a reduced sedimentation rate after treatment with compound E or ACTH and that these symptons returned if treatment was discontinued. Since that time ACTH and cortisone have been used in many hypersensitive conditions.

III. Comparison of Actions of ACTH and Salicylates

(A) Increased Adrenal Cortical Activity

It has been firmly established that discharge of ACTH from the adenohypophysis is an essential link in activation of the adrenal cortex. The activity of the adrenal cortex can be measured (5) by

a. size of the adrenal gland
b. depletion of cholesterol and ascorbic acid content of the adrenal gland
c. increase in urinary and blood corticosteroids
d. decrease in circulating eosinophils (6)
e. increased ratio of urinary uric acid: urinary creatinine (6), and
f. development of signs of Cushing's syndrome.

If salicylates have an ACTH-like effect, it would be expected that with administration of salicylates there would occur an increased activity of the adrenal cortex which could be measured by these indices.

(1) There were no reports in which a change in the size of the adrenal gland was measured following salicylate therapy.

(2) Depletion of Ascorbic Acid and Cholesterol of the Adrenal Gland

Blanchard (1950) (7) stated that "a number of cinchoninic acid derivatives, salicylic acid and amino-

pyrine have been found to decrease the adrenal ascorbic acid of rats".

Robinson (1951) (8) found a depletion of cholesterol or other stainable material within thirty minutes of administration of aspirin and that the reticularis and fasiculata showed marked depletion while the glomerulosa was unaffected.

Hetzel and Hine (1951) (9) concluded that the salicylate radical depleted the ascorbic acid content of the suprarenal glands in proportion to the dose.

Cronheim, King and Hyder (1952) (10) found that the salicylic acids caused a depletion of adrenal ascorbic acid with the exceptions being p-amino-salicylic and p-hydroxysalicylic acids - which have not been successful in treatment of collagen disorders either.

Eades and King (1953) (11) detected amounts of ACTH in the blood of rats following salicylate administration by transfusing this blood into hypophysectomized rats and then measuring the adrenal ascorbic acid content before and after the transfusion.

There are no reports disputing that salicylates give depletion of ascorbic acid and cholesterol, however, it should be noted that these tests were conducted on experimental animals.

(3) Increase in Urinary and Blood Corticosteroids

Van Canwenberge and Hensghem (1951) (12) noted a very high urinary excretion of reducing steroids in patients with collagen disorders during treatment with aspirin (1 gm q 3 hours) but found variable amounts of 17-ketosteroids* excreted in the same patients.

Bertolami et al (1951) (14) found an increased urinary excretion of 17-ketosteroids on the third and fourth days of therapy with salicylates in acute asteo myelitis but after the fourth day there was a progressive decrease until the tenth day.

Roskam and Van Canwenberge (1953) (15) found salicylates to increase the excretion of glucosteroids but the excretion of 17-ketosteroids was variable in their experiments.

Smith, Gray and Lunnon (1954) (16) stated that salicylates did not cause an increased excretion of adrenocortical steroids and that a large increase was observed during subsequent administration of corticotrophin to two of these same patients.

Bayliss and Steinbeck (1954) (17) found no significant increase in the plasma level of 17-hydroxycortico-

* Liddle (1954) (13) states that urinary 17-hydroxy corticoids are most serviceable in assay of ACTH effect on adrenals and urinary 17-ketosteroids are less sensitive in this respect.

steroids in seven patients treated with acetylsalicylic acid (10 - 25 gr. q 4 h.) for a prolonged time or in four patients treated with a single large dose of sodium salicylate.

Therefore, we find contradictory results in measuring urinary and blood corticosteroids following salicylate administration. It is of interest that Bertolani reported a difference in steroid excretion as the salicylate therapy proceeded. The other authors did not record successive levels or state very carefully the time element. These factors seem to be of great import if salicylates should have an ACTH-effect - for according to Selye (18) the response of the adrenals depends on the duration and the amount of the stress applied. Other conditions must be carefully controlled. For example, barbiturate medication would invalidate the results.

(4) Decrease in Circulating Eosinophils (Thorn, 1946 (6) states this measures adrenal activity in terms of 11-oxysteroids)

Bertalami et al (1951) (14) found eosinopenia and lymphopenia in guinea-pigs treated with salicylates.

Meade and Smith (1951) (19) found no significant decrease in circulating eosinophils with salicylates at a plasma level of 38 mg/100 ml. However, they added that continued therapy may have given a different result since

Janus in a personal communication to them had noted an eosinophilia in cases of rheumatic arthritis and rheumatic fever which responded to sodium salicylate or aspirin.

Roskam and Cauwenberge (1951) (20) were in conformity with Meade and Smith in that they found no significant decrease in the number of circulating eosinophils four hours after the intake of 4-6 gm. of sodium salicylate, but from that time on there was a decrease until six hours after the dose. Also, they found a significant decrease at four hours if the administration was intravenous rather than oral. This paper seems to adequately disprove the conclusion presented by Meade and Smith.

The evidence is in favor of a decrease in eosinophils with salicylate therapy.

(5) Increased Ratio Urinary Uric Acid: Urinary Creatinine.
(Thorn 1946 (6) states this also measures adrenal activity in terms of 11-oxysteroids)

Roskam and Van Cauwenberge (1951) (20) found the urinary uric acid: creatinine ratio increased significantly by two hours after an intake of 4-6 gms of sodium salicylate orally in twelve healthy volunteers.

In a later paper (15) these same authors contend that patients showing an insufficient eosinopenia or increase in urinary uric acid: creatinine ratio in four,

six and eight hours after 6 gm. salicylate is administered orally will also fail to respond to salicylate treatment.

(6) Development of Signs of Cushing's Syndrome

Cochran, Watson and Reid (1950) (21) reported the case of a rheumatic fever patient who was treated with salicylates and developed features similar to Cushing's syndrome. For fifteen days the patient was given 5 gms. aspirin daily and developed rounding of the facial contours, acne, diminished glucose tolerance, glycosuria and an alteration of the mental state. On the fifteenth day the dosage was reduced to three gms. daily, on the nineteenth day to 2 gms. daily and on the twentyfourth day to 1 gm daily. Following this reduction, these features gradually disappeared. They noted, however, that in aspirin therapy there is a respiratory alkalosis and in cortisone therapy there is a fixed base alkalosis.

From these reports, it seems justified to conclude that there is some increased activity of the adrenal cortex upon the administration of a therapeutic dosage of salicylates, even though there was considerable disagreement as to whether there was an increase in urinary and blood corticosteroids, since all other evidence points to increased activity.

(B) On Carbohydrate Metabolism

Ingle (1950) (22) found a marked amelioration of the glycosuria in partially depancreatized rats with administration of aspirin which is the opposite effect of cortisone. When the aspirin was withdrawn, there was an exacerbation of glycosuria. On repition of this experiment in 1953 (23), the same effect was noted in rats which were adrenalectomized and rats which had intact adrenals which indicated that this inhibition of glycosuria was in no way mediated by the adrenal glands.

Smith (1952) (24) found in alloxan-diabetic rats that salicylates reduced glycosuria and blood glucose but caused no change in the liver-glycogen content. He found in the normal rats that salicylates caused no alteration in the blood glucose but a depression of the liver glycogen content. In another paper (25) he reported that salicylates reduced the glycosuria and hyperglycemia induced by cortisone in the normal rat. While cortisone alone caused deposition of liver-glycogen in the adrenalectomized rats, the concurrent administration of salicylates produced not only depletion of the existing glycogen but also prevented the deposition of new glycogen by the cortisone.

Sproull (1954) (26) observed that liver-glycogen concentrations in salicylate-treated mice were signifi-

cantly lowered and that a hyperglycemia occurred in the females but there was no significant alteration of the blood sugar concentration in the males. No explanation was offered for this observation.

Smith (25) suggested four means by which the salicylates could give this effect:

1. Inhibition of gluconeogenesis
2. Increased deposition of muscular glycogen
3. Increased glucose in tissues
4. Conversion to fat of the carbohydrates.

The inhibition of xanthine oxidose, dismutation between hexose diphosphatose and pyruvate, and carboxyloses by salicylates was reported by Lutwak-Mann (1942) (27). Kaplan (1954) (28) reports inhibition of 2-keto dehydrogenose and succinic dehydrogenase by salicylates. These enzyme systems are intimately connected with the tricarboxylic acid cycle. This seems to be strong evidence that the effects of salicylates on carbohydrate metabolism is by inhibition of glyconeogenesis by these inhibitions of enzyme systems.

There may be increased glycose utilization in the tissues as suggested by Cochran's (29) finding increased oxygen consumption with salicylates.

There were no reports on muscular glycogen deposition or fat conversion in relation to salicylate administration.

Whatever the mechanism is by which salicylates decrease liver glycogen and blood sugar levels in diabetic rats, it seems certain salicylates do not have a similar role in carbohydrate metabolism as ACTH and cortisone.

(C) On Protein Metabolism

Reid (1951) (30) observed that in the first five days of salicylate therapy in accute rheumatic fever there was a relief of fever, tachycardia, joint pain and swelling and the degree of relief was related to the plasma salicylate level which was most effective when bordering toxic levels giving the "special salicylate syndrome" of hyperpnea, slowing of pulse rate, peripheral vasodilatation, nausea, vomiting, tinnitus, deafness and drowsiness.

In his patients at the same time there was a relief of joint pain and swelling there was a decrease in cellular protein, potassium and water. The erythrocyte sedimentation rate then, also, became normal when, next, there occurred a decrease of plasma protein, sodium, chloride and water. He proposed that this dehydration effect follows a reduction in cellular and plasma proteins which results from increased protein catabolism. The first change following a decreased cellular proteins is a reduction of cellular water with a temporary increase in

plasma and interstitial fluids, and is later followed by a diminution in both, as indicated by a fall in plasma volume and by the development of a diuresis.

Reid, therefore, purposes that the chief pharmacalogical action of salicylates in rheumatic fever is protein catabolism. This action is brought about by the salicylates acting directly on the tissues giving catabolism or by acting on vagal nerve endings giving hyperpnea which alters the chemical environment of the cells which causes protein catabolism.

With ACTH and cortisone therapy there is also a negative nitrogen balance (31). Kroop (1953) (32) describes a situation in rheumatic carditis patients treated with cortisone similar to Reid's findings with salicylates. Despite clinical improvement and an insignificant weight gain, all of Kroop's patients developed distended neck veins, hepatomegaly and ascites in seven to eleven days after therapy started. He suggested that this congestive failure contributed evidence that the cortisone stimulated a shift of water from cells to extra cellular space, giving an increased blood volume. Since the serum electrolytes were not much out of normal range in these patients, he proposed that there had been a shift in intra cellular electrolytes. He had not observed the plasma or cellular

proteins for a change after the cortisone therapy, but Carlisle (31) lists protein catabolism as one of the metabolic effects of cortisone.

It is of question then whether the protein catabolism is primary or secondary to the electrolyte change. Whitney and Bennett (33) found that a diet high in potassium chloride inhibited the catabolic effect of ACTH but did not inhibit the adrenals. Rupp, Paschkis and Cantarow (34) found that this inhibition of catabolism was only effective if small doses of ACTH had been used and that potassium chloride did not inhibit protein catabolism at therapeutic dosage levels of ACTH and cortisone.

In summary, there is protein catabolism in both salicylate and cortisone therapy with a similar change in electrolytes and body fluids, but the mechanisms of these changes have not been satisfactorily explained.

(D) Inhibition of Hyaluronidose

Duran Reynals (1942) (35) showed that micro-organisms produce hyaluronidose which increases their spreading through tissues by hydrolizing the hyaluronic acid.

In 1946 Guerra (36) found salicylates at 275 micrograms per c.c. inhibited the hyaluronidose and reduced the spreading effect on connective tissues. Sulfadiazine did not have this effect.

Lapin and Starkey (1949) (37) observed that one of the highest concentrations of hyaluronic acid in the mammalian body is to be found in synovial fluid and that hyaluronic acid is an important component of connective tissue gound substance. He further observed that rheumatic diseases have been shown to be primarily connective tissue diseases and that non-encapsulated groups A and C hemolytic streptococci produce hyaluronidose. Atlas, Gaberman and Eisenberg (38) found the hyaluronidose spreading reaction was inhibited in rheumatoid and normal patients treated with salicylates.

On the other hand Fulton (1948) (39) failed to get inhibition of hyaluronidose at 100 mg percent of sodium salicylate in vitro but got inhibition at 10 mg per c.c. which is beyond the therapeutic dosage. Swyer (40) also found over a three percent solution of salicylate is necessary to inhibit hyaluronidose (at 0.25 U./ml.) while a true inhibitor-heparin-is effective at a 0.0066 percent solution. He suggested the effect of salicylates in vivo was to inhibit histamine's ability to increase capillary permeability.

Pellaja (1952) (41) experimentally confirmed that in vivo salicylates inhibit the spreading reaction of indian ink in the dermis by hyaluronidose except after adrenalectomy or hypophysectomy and therefore he suggested

that the effect of salicylates on hyaluronidose is very likely related to the anatomical integrity and functional activity of the pituitary and adrenal glands.

Opsahl (1949) (42) and Shuman and Finestone (1950) (43) observed hyaluronidose inhibition *in vivo* by cortisone.

Benditt (1950) (44) found that a minimum of 24-48 hours of pretreatment with ACTH or cortisone acetate were required to inhibit hyaluronidose spreading effect and suggested an intermediate step between cortisone therapy and its action on the connective tissue. Pellaja (41) had also noted that ACTH and cortisone did not have this inhibitory effect *in vitro* and theorized that this effect was due to various factors such as increased water content of the skin.

However, Barer (1954) (45) states that spreading in the skin with and without hyaluronidose was not significantly altered by preadministration of cortisone or salicylates.

This leaves rather inconclusive evidence but suggests both salicylates and cortisone may inhibit hyaluronidose with nonspecific conditions rather than specifically since neither are effective *in vitro*.

(E) In Hypersensitivity

In 1922, Swift (46) found that rabbits receiving

intravenous injections of Streptococci virridous did not develop as high a titer of agglutinins and hemolysins if they received sodium salicylate daily by mouth while those without salicylate therapy did develop high titers. At that time, this effect was thought to be a direct action on the antigen. Derick, Hitchcock and Swift (47) later in 1928 suggested that salicylates keep the circulating antibodies at a low level by suppressing antibody formation.

Coburn (1943) (48) reported that sodium salicylate modifies the precipitation of normal rabbit serum protein by tungstate and partially inhibits the precipitation of horse serum englobulin by rabbit antiserum. Sodium salicylate added to a system containing crystalline egg albumin and its antibody partly prevented the formation of a precipitate, the degree of inhibition being related to the concentration of salicylate administered. Precipitation in the equivalence zone was more readily prevented by salicylates than precipitation in the region of antibody excess. Also, formed precipitates were partly dissolved following resuspension in the presence of salicylate. He proposed this action of salicylate was due to inactivation of antibody.

Dammin and Bukanty (1949) (49) did not feel the action of salicylates therapeutically was due to this inactivation of the antibody since the concentration required was thirty

times a therapeutic level. Scherer (1948) (50) found no depressing effect on the production of Rh antibodies in rabbits treated with salicylates.

Jager and Nickerson (1947) (51) noticed a suppression of antibody formation in human subjects maintained on salicylates at 300 microgram/c.c. plasma concentration for three weeks in response to typhoid vaccine.

Campbell (1948) (52) found acetyl salicylic acid premedication protected rabbits from anaphylactic shock but was ineffective in histamine shock. Roberts, Crockett and Lapply (1949) (53) were in agreement with this finding in similar experiments.

MacGregor and Wood (1950) (54) found a reduced incidence of vascular and valvular lesions of hearts of rabbits sensitized to horse serum when treated with sodium salicylate.

Lepper, Caldwell and Smith (1950) (55) decreased the death incidence from anaphylactic shock in rabbits with salicylates. Both MacGregor and Lepper thought the action of salicylates was by interference with antibody-antigen combination.

Smull, Wissler and Watson (1948) (56) observed a moderate depression in the concentration of circulating antibodies to horse serum in rabbits treated with salicylates as compared to untreated animals. This occurred

eighteen to twenty-two days after the first serum injection while earlier the antibody titers were not significantly different in the treated animals. Also, in 1948, Sullivan, Parker and Hibbet (57) found that the administration of sodium salicylate to rabbits well in advance of the initial contact with horse serum antigen prevents the development of arterial lesions. He claimed the arterial lesions failed to develop even though circulating antibodies are present in a moderate quantity. He believed that the lesions failed to develop because there was no antigen-antibody reaction, and that this reaction could not take place because the salicylates had prevented the antigen from uniting with tissue cells (i.e. salicylates blocked antigen fixation in the tissues by inhibiting hyaluronidase activity.)

Cortisone and ACTH inhibited anaphylactoid reactions in rats sensitized to egg white according to Selye (1949) (58). Nelson, Fox and Freeman (59), Dworetzky, Code and Higgins (60), and Rich, Berthrong and Bennett (61) also, found cortisone and ACTH inhibited anaphylactoid reactions in mice, guinea-pigs and rabbits, respectively. On the other hand, Leger et. al. (62) and Landau, Nelson and Gay (63) did not find this inhibition in guinea-pigs with cortisone.

Bradley et. al. (64) and Germuth (65) found cortisone

and ACTH effective in suppressing local hypersensitive reactions.

Sayers (5) suggests that ACTH and cortisone inhibited hypersensitive reactions by

(1) interference with release or toxic action of the anaphylactogenic substance of the antigen-antibody reaction

(2) alteration in cell permeability through action on hyaluronidase, or

(3) suppression of mesenchymal tissue, in particular inhibition of the development of granulation tissue.

Seifter et. al. (66) stressed the anti hyaluronidase action of ACTH and cortisone in suppressing hypersensitive reactions.

Most of the evidence indicates that both salicylates and cortisone do suppress hypersensitivity. This does not seem to be a direction on antigens or histamine. There is probably a decrease in antibody production and tissue reaction, but there also may be an action suppressing antigen-antibody combination and products of that combination.

(F) Antipyretic and Analgesic Properties

Salicylates, of course, are well-known for their antipyretic effect in conditions of elevated temperature.

Recant, Ott and Fischel (1950) (67) claimed cortisone to have an antipyretic effect in rabbits given pneumococcal vaccine. He suggests this may be a peripheral action on the tissues since cortisone inhibits inflammatory reactions and fever is thought to occur from the products of inflammatory exudate, or as in salicylates, a central action on the hypothalamic thermo regulator in that cortisone changes the E.E.G. pattern and has psychic effects.

There are differences of opinion as to whether salicylates are true analgesics. Goodman and Gilman (68) state that only certain types of pain are given relief by salicylates - those being headache, myalgia, arthralgia and other pain from integumental structures rather than visceral pain.

Bonnycastle (69) found mixed doses of codeine and aspirin give an analgesic effect equivalent to a simple sumnation of doses, but Birren (70) found no significant effect of salicylates upon pain sensitivity on the surface of the forehead.

Lee and Pfeiffer (71) found no alteration of tooth or wrist pain threshold with cortisone. They believed both cortisone and antipyretic analgesics produced pain relief only in selected clinical disorders. Sonnenschein and Ivy (72) suggest that cortisone and aspirin produce

pain relief by altering pathophysiologic states, i.e. decrease joint swelling, decrease fever and skin rashes, decrease ocular inflammation and decrease edema in nephritis.

This evidence suggests that salicylates and cortisone may have a similar role in antipyresis and analgesia.

IV. Site of Action of Salicylates

Directly on Adrenals

Cochran, Watson and Reid (21) in 1950 noted the clinical and metaballic effects of aspirin in the treatment of aacute rheumatic fever resemble those attributed to cortisone. Schwartzman (1950) (73) increased the evidence supporting the theory that adrenals were the site of salicylate action by demonstrating that pantothenic acid* (a deficiency of which gave adrenocortical damage) enhanced the effects of salicylates in hypersensitive diseases while pantothenic acid alone had no effect upon the disease. Robinson (8) in 1951, using repeated doses of aspirin on rats found the adrenal cortex passed through Selye's stages, histochemically, and concluded this was due to direct stimulation of the adrenal cortex.

* According to Winters (1952) pantothenic acid is involved in the synthesis of cholesterol.

Through Anterior Pituitary Gland

Blanchard (1950) (7) suggested salicylates act through the anterior pituitary gland.

Chronheim, King and Hyder (1952) (10) found that hypophysectomy prevented the effect of salicylic acid on the adrenals. This disproves the site as being directly on the adrenals. Eades (1953) (11), Hetzel and Hine (1951) (9) and Van Conwenberge (1951) (75) all found the hypophysis to be necessary in this effect and concluded it was the site of action.

Hypothalamus

Van Conwenberge and Betz (1952) (76) found there was no ACTH effect of salicylates if dial onesthesia was used. Fulton (1949) (77) states that dial (barbiturate) anesthetics suppress the hypothalamic nuclei. Since Van Conwenberge and Betz found the usual adrenal response occurred if ACTH were used with dial onesthesia, they proposed salicylates stimulated the hypothalamus which stimulates the anterior pituitary to secrete ACTH.

Cronheim and Hyder (1954) (78) found the depletion of adrenal ascorbic acid following a single injection (300 mg./kg.) of salicylic acid lasted more than sixteen hours, at which time still appreciable blood levels of salicylic acid were present. Repeated injections of salicylic acid did not impair the response of the adrenals.

Pretreatment with cortisone reduced but did not abolish the effect of salicylic acid. Complete anesthesia with pentobarbitol blocked the effect of the salicylic acid. They interpreted that salicylic acid was effective on the hypothalamus with a subsequent stimulation of the pituitary.

It is interesting that Harris (1951) (79) stated that evidence derived from studies of pituitary transplants and grafts shows that the basic steady output of ACTH by the anterior pituitary gland is largely dependent on this gland's anatomic relationship with the hypothalamus. (He speaks of a dual regulation of ACTH releaset - (1) humoral in response to systemic stress stimuli and (2) neuro-humeral medicated by the hypothalamo - hypophyseal neuro-vascular pathway - coming into play under the influence of nervous or emotional stimuli and in optimum conditions the blood level of adrenal hormones exerting a fine control through the hypothalamus.)

Rothboller (80) noted changes in the rat hypophysi following unpleasant stimuli (needle-prick). In one-two minutes, there was vasodilatation and mobilization of the neurosecretory material toward the lumen of the blood vessel. In four-six minutes, there was pronounced vaso-dilatation with loss of the material. In one hour, restor-ation began and was complete in three hours. Mirsky, Stein

and Paulisch (1954) (81) propose that this material from the hypophysis (vasopressin and oxytocin) serves as the hypothalamic "neurohormone" responsible for action of the adenophypophysis in response to noxious stimuli.

McCann and Brobeck (1954) (82) observed that hypothalamic lesions which block ACTH secretion, as judged by adrenal ascorbic acid depletion, adrenal weight or blood ACTH concentration, uniformly destroy a significant fraction of the supraopticohypophyseal tract as evidenced by their location and the presence of diabetes insipidus. ACTH secretion appeared to be produced in animals with these lesions by large doses of pitressin. They suggested that the supraopticohypophyseal tract played a role in the regulation of ACTH secretion by release of antidiuretic hormone into the hypophyseal portal vessels.

It may be proposed then that salicylates stimulate the hypothalamus to secrete neurohormones, probably vasopitressin and oxytocin, into the hypophyseal portal vessels which carry them at a high concentration directly to the pituitary where they stimulate the secretion of ACTH.

V. Discussion

Keleman (1952) (83) did not believe the therapeutic effect of salicylates resulted from mobilization of adrenal hormones alone, although they seemed to act in the presence

of adrenals. He stated that the amount of adrenal hormones mobilized by salicylates fail to reach or approximate the amount of cortisone to produce a cortisone-remission. This is based, however, on inadequate studies of plasma and urinary corticosteroids following salicylate therapy which needs further investigation with the more recent knowledge on the formation and degradation of corticosteroid hormones.

There is also the possibility that massive doses of salicylates, as proposed since Coburn (2) in 1943, where at least 30 mg/100 ml. plasma levels have been attempted, that this, in itself, may produce a stress situation by toxicity and stimulate ACTH secretion.

The very different effect of salicylates on carbohydrate metabolism from that of cortisone is no hazard to the acceptance of ACTH-effects of salicylates, for drugs can certainly have more than one site of action in the body. In fact, this property may be a very good attribute to salicylates. It seems theoretically sound that in cases of hypersensitive diseases in diabetics it would aid in the therapy to administer cortisone and salicylates concurrently, since the salicylates would increase bodily production of "cortisone" and at the same time inhibit the diabetogenic activity of the cortisone.

VI. Summary

A review of the literature presents evidence that salicylates appear to have an ACTH effect. There is increased adrenal cortical activity shown by a depletion of ascorbic acid and cholesteral content of the adrenal gland, a significant decrease in circulating eosinophils, an increased urinary uric acid: creatinine ratio and the development of features of Cushing's syndrome following salicylate therapy. There was, however, contradictory evidence whether urinary and plasma corticosteroids increased significantly or not following salicylate administration.

There appears to be a similarity of action of salicylates and cortisone on protein metabolism, electrolyte and fluid balance, hyaluronidase and in hypersensitive reactions.

There is a dissimilarity of action on carbohydrate metabolism. This may be due to a side effect of salicylates by their inhibition of certain enzyme systems.

The most acceptable explanation of the ACTH effect of salicylates is by stimulation of the hypothalamus to secrete neurohormones, which are carried by the hypophyseal portal vessels in a high concentration and stimulate the anterior pituitary to secrete ACTH.

VII. Bibliography.

1. Gross, Martin and Greenberg, Leon H. The Salicylates, a critical bibliography. New Haven, Hillhouse Pr. 1948.

2. Coburn, A. F. Salicylate Therapy in Rheumatic Fever. Bull. Johns Hopkins 73:435 (1943)

3. Hench, P. S. The Potential Reversibility of Rheumatoid Arthritis. Ann. Rheum. Dist. 8:90 (1949)

4. Hench, P.S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. The Effect of a Hormone of the Adrenal Cortex (17-Hydroxy 11-dehydrocorticosterone; compound E) and of pituitary ACTH on rheumatoid arthritis: preliminary report. Proc. Staff Meeting Mayo Cl. 24:181 (1949)

5. Sayers, G. Adrenal Cortex and Homeostosis. Physiol. Rev. 30:241 (1950)

6. Thorn, G. W. A Test for Adrenal Cortex Insufficiency J.A.M.A. 137:1005 (1948); Trans. A. Am. Physicians 60:143 (1946)

7. Blanchard, K. C., Dearborn, E. H., Maren, T. H., and Marshall, E. K. Stimulation of the Anterior Pituitary by Certain Cinchoninic Acid Derivatives. Bull. Johns Hopkins 86:83 (1950)

8. Robinson, F. B. Aspirin and the Adrenal Cortex. Brit. Med. J. 1:300 (1951)

9. Hetzel, B. S. and Hine, D. C. The Effect of Salicylates on the Pituitary and Suprarenal Glands. Lancet 2:94 (1951)

10. Cronheim. G., King, J. S., and Hyder, N. The Effect of Salicylic Acid and Similar Compounds on the Adrenal-Pituitary System. Proc. Soc. Exper. Bio. and Med. 80:51 (1952)

11. Eades, C. H. and King, J. S. Detectable Amounts of ACTH in Blood Following Salicylate Administration Endocr. 52:592 (1953)

12. Van Conwenberge, H. and Heusghem, C. Acetylsalicylic Acid and Urinary Excretion of Adrenocortical Steroids. Lancet i. 771 (1951)

13. Liddle, G. E., et. al. A Clinically Significant Steroidogenic Assay of ACTH Administration Extravascularly to Human Subjects and to Guinea-Pigs. Endocr. 55:575 (1954)

14. Bertolani, et. al. Salicylates in Acute Osteomyelitis. Lancet 1:54 (1951)

15. Roskam, J. and Van Conwenberge, H. Excerpta Medica. Sect. 6 Int. Med. 7.6 1953 #5262 P.1079

16. Smith, M. J. H., Gray, C. H. and Lunnon, J. B. Urinary Excretion of Adrenocortical Steroids by Patients Receiving Salicylates. Lancet May 15,1954 p. 1008

17. Bayliss, R. I. S. and Steinbeck, A. W. Salicylates and the Plasma Level of Adrenal Steroids. Lancet May 15, 1954 p. 1010

18. Selye, Hans. The Story of the Adaptation Syndrome, told in the form of informal illustrated lectures. Montreal, Acta (1952)

19. Meade, B. W. and Smith, M. J. H. Salicylate, Gentisate and Circulating Eosinophils. Lancet 1:773 (1951)

20. Roskam, J. and Van Conwenberge, H. Effect of Sodium Salicylates on Circulating Eosinophils and Urinary Uric-Acid: Creatinine Ratio in Healthy Volunteers. Lancet 2:375 (1951)

21. Cochran, J. B., Watson, R. D., and Reid, J. Mild Cushing's Syndrome Due to Aspirin. British Med. J. ii 1411 (1950)

22. Ingle, D. J. Effect of Aspirin Upon Glycosuria of the Partially Deponcreatized Rat. Proc. Soc. Exper. Biol. and Med. 75:673 (1950)

23. Ingle, D. J., Beary, D. F., and Purmales, A. The Effect of Aspirin Upon the Glycosuria of Partially Depancreatized Rats in the Presence and Absence of the Adrenal Glands. Endocr. 52:403 (1953)

24. Smith, M. J. H., Meade, B. W., and Bernstein, J. The Effect of Salicylates on Glycosuria, Blood Glucose and Liver Glycogen of the Alloxan-Diabetic Rat. Biochem. J. 51:18 (1952)

25. Smith, J. J. H. The Effect of Salicylates on the Glycosuria and Hyperglycemia Induced by Cortisone in the Normal Rat. Biochem. J. 52:649 (1952)

26. Sproull, D. H. The Glycogenalytic Action of Sodium Salicylate. Brit. J. Pharmacol. 9:121 (1954)

27. Lutwak-Mann, C. The Effect of Salicylates and Cinchophen on Enzymes and Metabolic Processes. Biochem. J. 36:706 (1942)

28. Kaplan, E. H., Kennedy, Jenn., and Davis, J. Effects of Salicylates and Other Benzoates on Oxidotive Enzymes of Tricarboxglic Acid Cycle in Rat Tissue Hormogenates. Arch. of Biochem. and Biophys. 51:1 July (1954) p. 47-61.

29. Cochran, J. B. Further Observations on the Metabolic Stimulating Effect of Salicylate. Brit. Med. J. March 27, 1954

30. Reid, J. The Mode of Action of Salicylates in Acute Rheumatic Fever. Quart. J. Med. 19:1 (1951)

31. Carlisle, J. M. Cortisone (Compound E) Summary of its Clinical Uses. Brit. Med. J. 2:590 (1950)

32. Kroop, I. G. and Slater, S. R. Endogenous Water Shift Producing Congestive Failure in Cortisone Treated Rheumatic Carditis. Cl. Research Proc. 1:54 (1953)

33. Whitney, J. E. and Bennett, L. L. Inhibition of the Catabolic Effect of ACTH in Rats by a Diet High in Potassium Chloride. Endocr. 50:657 (1952)

34. Rupp, J. V., Posckis, K. E. and Cantarow, A. Role of Potassium in the Protein Catabolic Effect of Cortisone and ACTH. Endocr. 55:21 (1954)

35. Duran Reynals. Tissue Permeability and the Spreading Factors in Infections. Bact. Rev. 6:197 (1942)

36. Guerra, F. Hyaluronidase Inhibition by Sodium Salicylate in Rheumatic Fever. Science 103: 686 (1946). The Action of Sodium Salicylate and Sulfadiagine on Hyaluronidase. J. Pharmacol. 87:193 (1946)

37. Lapin, L. and Starkey, H. A Review of the Pathological and Etiological Factors in Rheumatic Diseases. Canad. Med. Ass. J. 60:371 (1949)

37. Atlas, D. H., Gaberman, P. and Eisenberg, H. Hyaluronidase Spread and the Effect of Salicylates in Rheumatic Fever. Annals of Rheum. Dis. 10:418 (1951)

39. Colesnick, B. and Beutner, R. Inhibition of Hyaluronidase by Aromatic Compounds. Proc. Soc. Exp. Biol. and Med. 72:629 (1949)

40. Swyer, G. I. M. Failure of in Vitro Inhibition of Hyaluronidase with Salicylates. Biochem. J. 42:32 (1948)

41. Pellaja, M. Role of the Pituitary and Adrenal Glands in the Inhibition of Hyaluronidase by Salicylates in Vivo. Lancet 1:233 (1952)

42. Opsahl, J. C. The Role of Certain Steroids in the Adrenal-Hyaluronidase Relationship. Yale J. Biol. and Med. 22:115 (1949)

43. Shuman, C. R. and Finestone, R. J. Inhibition of Hyaluronidase in vivo by Adrenal Cortical Activation. Proc. Soc. Exp. Biol. and Med. 73:248 (1950)

44. Benditt. E. P. Influence of ACTH and Cortisone upon Alteration in Capillary Permability Induced by Hyaluronidase in Rats. Proc. Soc. Exp. Biol. and Med. 75:782 (1950)

45. Barer, G. R. Quantitative Measurements on Spreading Phenomenon in the Skin. Brit. J. Pharm. 9:346 (1954)

46. Swift, H. F. The Action of Sodium Salicylate Upon the Formation of Immune Bodies. J. Exp. Med. 36:735-760 (1922)

47. Derick, C. L., Hitchcock, C. H. and Swift, H. F. The Effect of Antirheumatic Drugs on the Arthritis and Immune Body Production in Serum Disease. J. Clin. Invest. 5:427 (1928)

48. Coburn, A. F. and Kapp. Salicylate Effect on Immune Precipitates. J. Exp. Med. 77:173 (1943)

49. Dammin, G. J. and Bukantz, S. C. Modification of Biological Response in Experimental Hypersensitivity. J.A.M.A. 139-358 (1949)

50. Scherer, W. F. Attempts to Inhibit Rh Antibody Production in Rabbits: Use of Ethylene DiSulphonate, Sodium Salicylate, Pyribenzamine and A and B Specific Substances. Am. J. Med. Sc. 215:33 (1948)

51. Jager, B. V. and Nickerson, M. The Altered Response of Human Beings to the Intromuscular Administration of Typhoid Vaccine During Massive Salicylate Therapy. Am. J. Med. 3:408 (1947)

52. Campbell, J. M. Inhibition of Anaphylactic Shock by Acetylsalicylic Acid. Science 108:478 (1948)

53. Roberts, R. C., Crockett, K. A. and Lapply, T. C. Effects of Salicylate and Benadryl on Experimental Anaphylaxis, Hypersensitive Vascular and Cardiac Lesions. Arch. Int. Med. 83:48 (1949)

54. MacGregor, A. G. and Wood, D. R. The Protective Effect of Sodium Salicylate on Serum Induced Myocarditis in Rabbits. Brit. J. Pharm. 5:9 (1950)

55. Lepper, M. H., Caldwell, E. R. and Smith, T. K. Effects on Anaphylactic Shock of Salicylates, Aminopyrine and Other Chemically and Pharmacalogically Related Compounds. Proc. Soc. Exper. Biol. and Med. 74:254 (1950)

56. Smull, K., Wissler, R. W. and Watson, J. M., The Effect of Sodium Salicylate upon Serum Disease in Rabbits. J. Lab. and Cl. Med. 33:936 (1948)

57. Sullivan, C. J., Parker, T. W. and Hibbet, R. W. Prevention by Sodium Salicylate of Arteritis in the

Experimental Allergic State. Proc. Soc. Exper. Biol. and Med. 67:508 (1948)

58. Selye, Hans. Effect of ACTH and Cortisone upon an "Anaphylactoid Reaction". Canad. M. A. J. 61: 553 (1949)

59. Nelson, C. T., Fox, C. L., and Freeman, E. B. Inhibitory Effect of Cortisone on Anaphyloxis in the Mouse. Proc. Soc. Exper. Biol. and Med. 75:181 (1950)

60. Dworetzky, M., Code, E. F. and Higgins, G. M. Effect of Cortisone and ACTH on Eosinophils and Anaphylactic Shock in Guinea-Pigs. Proc. Soc. Exper. Biol. and Med. 75:201 (1950)

61. Rich, A. R., Berthrong, M., and Bennett, I. L. The Effect of Cortisone upon the Experimental Cardiovascular and Renal Lesions Produced by Anaphylastic Hypersensivitity. Bull. Johns Hopkins 87:549 (1950)

62. Leger, J. et. al. Effect of ACTH on Anaphylaxis in the Guinea-Pig. Proc. Soc. Exper. Biol. and Med. 69:465 (1948)

63. Landou, S. W., Nelson, W. T. and Gay, L. N. The Effect of ACTH and Cortisone on Histamine Reactions and Anaphylactic Reaction in Guinea-Pigs. Bull. Johns Hopkins 88:395 (1951)

64. Bradley, et. al. The Ability of ACTH and Cortisone to Alter Delayed Type Bacterial Hypersensitivity. Bull. Johns Hopkins 87:186 (1950)

65. Bermuth. Anatomical and Histological Changes in Rabbits with Experimental Hypersensitivity Treated with Compound E and ACTH. Proc. Soc. Exper. Biol. and Med. 76:177 (1951)

66. Seifter, J., Ehrlich, W. E. Begany, A. J. and Warren, G. H. Effects of Cortisone, Hyaluronidase, Desoxycorticosterone and Artisone on Experimental Serum Disease in Rabbits. Proc. Soc. Exper. Biol. and Med. 75:337 (1950)

67. Recant, L., Ott, W. H., and Fischel, E. E. The Anti-Pyretic Effect of Cortisone. Proc. Soc. Exper. Biol. and Med. 75:264 (1950)

68. Goodman, L. S. and Gilman, Alfred. The Pharmacological Basis of Therapeutics. New York. MacMillian Co. 1941 p. 234

69. Bonnycastle, D. D. An Examination of the Synergism in the Actions of Codeine and Acetylsalicylic Acid. Actapharmacol. et Toxical. 6:354 (1950)

70. Birren, J. E., Shapiro, H. B. and Miller, J. H. Salicylates and Pain Sensitivity. J. Pharmacal. & Exper. Ther. 100:67 (1950)

71. Lee, R. E. and Pfeiffer, C. C. Effects of Cortisone and 11-Desoxycortisone on Pain Thresholds in Man. Proc. Soc. Exper. Biol. and Med. 77:753 (1951)

72. Sonnenschein, R. R. and Ivy, A. C. J. Pharmacal. and Exper. Ther. 93:308 (1949)

73. Schwartzman, G., Schneierson, S. S. and Soffer, L. J. Suppression of the Phenomenon of Local Tissue Reactivity by ACTH. Proc. Soc. Exper. Biol. and Med. 75:175 (1950)

74. Boc, J. and Stoa, K. F. The ACTH-like Effect of Acetylsalicylic Acid. Acta Endocr. 12:201 (1953)

75. Van Conwenberge, H. Relation of Salicylate Action to Pituitary Gland; observations in rats. Lancet 2:375 (1951)

76. Van Conwenberge, H. and Betz, H. Salicylates and Neuroendocrine Stimulation. Lancet i, 1083

77. Fulton, J. F. Textbook of Physiology. 16th ed. Philadelphia and London (1949) p. 239

78. Cronheim, G. and Hyder, Nelta. Effect of Salicylic Acid on Adreno-pituitary System III Studies on Mechanism of this Effect. Proc. Soc. Exp. Biol. and Med. 86(3):409 July 1954.

79. Harris, G. W. Neural Control of the Pituitary Gland II The Adenohyphophysis with Special Reference to the Secretion of ACTH. Brit. Med. J. 2:627 (1951)

80. Rothboller, A. B. Changes in the Rat Hypophysis Induced by Painful Stimuli with Particular Reference to Neurosecretory Material. Anat. Rec. 115:21 (1953)

81. Mirsky, I. A., Stein, N. and Paulisch, G. The Secretion of an Antidiuretic Substance into the Circulation of Adrenalectomized and Hypophysectomized Rats Exposed to Noxious Stimuli. Endocr. 55:28 (1954)

82. McCann, S. M. and Brobeck, J. R. Evidence for a Role of the Supraoptico-hypophyseal System in Regulation of ACTH Secretion. Proc. Soc. Exper. Biol. and Med. 87:318 Nov. 1954.

83. Keleman, E. Cortisone Vs. Salicylates. J. Cl. Endocr. and Metab. 12:1249 (1952)