potassium content were reduced. 2. The results indicate that the response of normal rabbits to cortisone acetate varies with the size of the dose and with the length of the period of administration. The results suggest that the earliest change to occur following the administration of a small dose daily was a retention of water in the extracellular fluid compartment; with continued administration of this dose, water was redistributed into the intracellular phase. The administration of a larger dose of cortisone daily resulted in depletion of the body's store of potassium.

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Effect of Salicylic Acid on Adrenal-Pituitary System.* II. Influence of Aminoacids and Other Compounds. (20037)

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The influence of salicylic acid (SAL) on the adrenal pituitary system of normal rats, as evidenced by a reduction of adrenal ascorbic acid, has been established by several investigators(1-5). This effect is quite specific for many substituted aromatic ortho-hydroxy carboxylic acids(5) and several other types of compounds(1,5). Since the metabolism of SAL involves conjugation with glycine and glucuronic acid, oxidation to gentisic acid and possibly other reactions, and since SAL bloodlevels can be influenced by administration of other substances, (PABA, ascorbic acid)(6-8), the effect of such combinations on the adrenal pituitary system was investigated. The main purpose was to determine whether it might be possible to augment the specific activity of SAL.

Methods. All experiments were made in female Wistar rats in the manner described previously(5). All compounds were administered as the sodium salts (except calcium pantothenate.) The pH of the solutions was not adjusted. The results for the treated animals are expressed in per cent of those for saline controls, since it had been shown that thereby the variations from day to day and from group to group are eliminated.

Results. The substances combined with SAL may be divided into 3 groups: carbohydrate metabolites, aminoacids and miscellaneous compounds. (Table I) None of these 21 acids, at a dose of 150 mg/kg, had any influence upon the ascorbic acid depletion produced by the simultaneous administration of 150 mg/kg of SAL. Particular attention was given to glucuronic and p-aminobenzoic acid because the former conjugates with SAL and both have been suggested for the treatment of rheumatoid arthritis and collagen diseases(9-12). PABA has also been shown to produce higher SAL bloodlevels by interference with renal clearance.

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TABLE I. Compounds Which in a Dose of 150 mg/kg Did Not Change the Effect of 150 mg/kg of Salicylic Acid on Adrenal Ascorbic Acid of Normal Rats. ( ) No. of animals.

Carbohydrate metabolites (acid)		Aminoacids		Miscellaneous compounds (acid)	
Acetic	(4)	d,l-α-Alanine	(4)	Adipic	(4)
Citric	(20)	β-Alanine	(8)	p-Aminobenzoic	(11)
Fumaric	(4)	l-Asparagine	(8)	Ascorbic	(4)
Lactic	(7)	l-Cystine	(8)	Gluconic	(8)
Pyruvic	(4)	l(-)-Leucine	(8)	Glucuronic	(28)
Succinic	(8)	d,l-Methionine	(8)	Pantothenic	(24)
		N-Phenylglycine	(8)		
		l-Tryptophane	(8)		
		l-Tyrosine	(8)		
		Hippuric acid	(4)		

TABLE II. Effect of Glycine upon Adrenal Ascorbic Acid Depletion Produced by Salicylic Acid. ( ) No. of animals.

	Dose in mg/kg			
	75	150	300	600
	Adrenal ascorbic acid in % of saline controls			
Salicylic acid	92(8)	78 (10)	61(12)	
Glycine			101 (4)	96(11)
Salicylic acid — glycine (equal parts)	86(7)	63*(20)		

* This value is significantly different from the corresponding SAL value. ($p = .01$.)

The only compound which has been found to augment the SAL action on adrenal ascorbic acid was glycine. (Table II). While this aminoacid alone, up to 600 mg/kg, had no effect, an amount of 150 mg/kg given together with an equal dose of SAL significantly increased the action of the latter on adrenal ascorbic acid. Even with smaller doses of both SAL and glycine, the results point in the same direction, but due to the small size of the absolute decrease in ascorbic acid concentration, the experimental variations are too great to make the difference statistically significant. Blood-level determinations of SAL did not show any change produced by glycine.

Discussion. The experimental data furnish additional evidence that the action of SAL on the adrenal pituitary system must be considered as a specific effect, quite different and distinguished from a general, nonspecific stress reaction. The mechanism by which glycine potentiates the SAL effect is not known. It is obvious from the experimental data that glycine has no direct influence, but acts only in a supporting role. A conjugation of SAL with glycine can also be excluded since salicyluric acid has been shown(5) to be much less effective than SAL in its influence on adrenal ascorbic acid. Friedman(13) had reported that the uricosuric action of SAL is also augmented by glycine. Both the depletion of adrenal ascorbic acid and urinary excretion of uric acid are assumed to be the result of an increased amount of circulating ACTH. Thus, the hypothesis is suggested for future investigations, that glycine either acts as a precursor or as a protector for ACTH, or that it inactivates through conjugation an ACTH neutralizing substance (cortisone?).

The observation that addition of p-aminobenzoic acid did not have any effect on the SAL action is due to the fact that the present experiments lasted only 2 hours. During this time, p-aminobenzoic acid has no appreciable influence on Sal bloodlevels. Analyses showed an average of 29.4 mg % of SAL as compared to 27.5 mg % when no PABA was given.

Summary. 1. The influence of aminoacids, carbohydrate metabolites and several other compounds on the adrenal ascorbic acid depletion produced by salicylic acid has been investigated. 2. Glycine is the only compound so far found which potentiated the action of salicylic acid. 3. This observation is an additional evidence in favor of a specific effect of salicylic acid on the adrenal-pituitary system.

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Morphologic Changes in the Dog's Adrenal Gland Following Anoxia.* (20038)

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Recently Selye(1) in his book on Stress summarized the literature on the adrenal gland. Apparently many observations have been made on the histochemical changes in the adrenal gland following periods of anoxia; however, few studies on morphology have been made. Rats exposed to chronic anoxia show hypertrophy of the cortex and a depletion of lipids in the zona fasciculata and zona reticularis(2-5). Since prolonged anoxia causes severe damage to the brain(6), it was of interest to ascertain whether the adrenal cortex also was damaged by anoxia. Because the adrenal gland has the greatest blood flow of any organ in the body, 5-8 ml/g/min.(7), it seemed likely that this reflected a high metabolism and that the gland therefore might be as susceptible as the cerebrum to anoxia. The present experiment gives the data obtained in this study, supplementing a previous preliminary report(8).

Experimental methods. The dogs were obtained from the pound and used soon thereafter. From their physical appearance their health was classified as excellent, good or poor. The method of producing anoxia and of resuscitating dogs has been described(9). Pure nitrogen was given unanesthetized animals to breathe by means of a special head mask. In this type of fulminating anoxia, the breathing failed within one to 2 minutes and the pulse pressure disappeared after 2 to 4 minutes. The dogs were resuscitated by two measures: periodic insufflation of the lungs with oxygen, using a special resuscitating valve for the head mask, and extrathoracic cardiac massage. This latter procedure was carried out with the dogs lying on their sides. The chest was compressed sharply between thumbs and fingers of both hands at a rate of approximately one hundred times per minute. This massage was stopped briefly every half-minute or so to ascertain whether the circulation had recovered. Soon after the blood pressure started to rise, respiration returned and quickly increased to normal pulmonary ventilation. During the first 24 hours following the induction of anoxia, episodes of decerebrate rigidity, running movements and ululation were common. The animals frequently flung themselves around the cage in apparent frenzy, with fits of "sham rage" often apparent. All grades of delirium and stupor occurred. The dogs then progressed into coma, and death occurred within two to three days. The few dogs that recovered did so slowly, showing ataxic attempts to stand and slow return of vision and hearing; after 4 or 5 days they appeared

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