than an interesting speculation, to be investigated in the future.

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The Function of Vitamin C in the Adrenal Cortex[1]

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Under usual conditions the adrenal cortex produces two types of compounds. One type, which includes cortisone (17-hydroxy-11-dehydrocorticosterone), is more highly oxidized than the other type, which includes desoxycorticosterone. These compounds seem to have the opposite effect on the development of arthritic lesions in the scorbutic guinea pig (*1, 2*). The injection of cortisone tends to inhibit the development of these arthritic lesions, whereas the injection of desoxycorticosterone promotes such lesions.

Since cortisone prevents the development of severe arthritic lesions in the scorbutic guinea pig, it may be concluded that for some reason the adrenal cortex does not produce an adequate amount of this type of hormone when the guinea pig receives a diet deficient in vitamin C. On such a diet the adrenal cortex contains very little vitamin C (*3*).

One explanation for the failure of the adrenal cortex to function normally under scorbutic conditions could be that vitamin C is a necessary component of the oxidation-reduction system which produces the oxy-type of adrenal hormones. Such an explanation seems reasonable since it has been shown that vitamin C can serve as a coenzyme in a biological oxidation system (*4*) and also that desoxycorticosterone can be oxidized *in vitro* to cortisone by the adrenal cortex in the presence of vitamin C (*5*).

The adrenal cortex of scorbutic guinea pigs is capable of responding to injections of adrenalcorticotropic hormone (ACTH), since it has been shown to reduce the cholesterol content of the adrenal cortex (*6*). From earlier work (*3, 7*) it is suggested that the adrenal cortex of guinea pigs affected with scurvy is capable of producing some adrenal-cortical hormones when activated by ACTH. If this hypothesis is true, then injections of ACTH should prevent arthritic lesions in a manner similar to the results produced by the injection of cortisone (*1*).

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TABLE 1

THE EFFECT OF DAILY INJECTIONS OF ACTH, CORTISONE, AND DESOXYCORTICOSTERONE INTO SCORBUTIC GUINEA PIGS ON THE DEVELOPMENT OF ARTHRITIC LESIONS

Group	No. of pigs	Daily injections	Severity of arthritis	Days for scorbutic symptoms to occur
I	7	None	Very severe	13
II	6	5 mg cortisone acetate*	Very slight	13
III	6	5 units ACTH†	Severe	11
IV	5	5 mg desoxycorticosterone acetate‡	Very severe	8
V	6	4.3 mg vitamin C	None	

* Cortone acetate (11-dehydro-17-hydroxycorticosterone-21-acetate), Merck & Co.
† Corticotropin, Wilson.
‡ Cortate, Schering Corp.

The following experiment was conducted to determine whether ACTH has an action similar to that of cortisone in preventing arthritic lesions in scorbutic guinea pigs. Five groups of female guinea pigs weighing 300–450 g were fed a basal ration deficient in vitamin C and injected subcutaneously, as shown in Table 1. The group receiving vitamin C was given 4.3 mg each day, as this meets the requirements reported by Kuether (*8*).

With the exception of the group receiving ascorbic acid, all groups showed varied degrees of scorbutic symptoms. On the eighth day the group receiving desoxycorticosterone showed the first evidence of scurvy, and by the thirteenth day their joints were swollen and they exhibited signs of pain. After 11 days the guinea pigs receiving ACTH were less active than they had been previously, and on the thirteenth day symptoms appeared that were similar to those present in Group IV, but not as severe. One guinea pig receiving ACTH was afflicted with swollen joints, and all the animals of this group showed signs of pain. The negative control (Group I) also developed severe scorbutic symptoms by the thirteenth day, whereas the animals in Group II evidenced only slight pain and no articular enlargement during the same period.

Administration of desoxycorticosterone and ACTH apparently aggravated the arthritic condition, and, conversely, cortisone suppressed these clinical manifestations, which is in agreement with previous work (*1*). From this experiment it is evident that the injections of ACTH did not stimulate the cortex of the

adrenal gland to produce the hormones necessary to prevent arthritic symptoms in the scorbutic guinea pigs. This is in agreement with the theory that vitamin C may be essential in the production of the oxy-type of adrenal-cortical hormones.

The results of the chemical and histopathological studies of the tissues of these experimental animals will be published later.

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Antitubercular Diazine Carboxamides

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The effectiveness of nicotinamide in suppression of experimental tuberculosis was discovered by Chorine (*1*) in 1945. Several years later McKenzie *et al.* (*2*) independently reported the same result. In that report and in an associated paper by Kushner (*3*) tests were described on 27 related compounds. Of these only five monosubstituted amides of nicotinic acid possessed a fraction of the activity of the parent amide. We have been engaged in examination of other nicotinamide relatives and nicotinamide isosteres. As a recent account (*4*) of the antituberculosis activity of pyrazinoic acid amide ("Aldinamide") anticipates a similar report from this laboratory (*5, 6*), we are prompted to publish a summary of our results.

In a standardized mouse assay under suitable test conditions, pyrazinoic acid amide, administered in diet, was found to be approximately three times as potent as *p*-aminosalicylic acid (*6*); it is also about three times as effective as nicotinamide. The following pyrazine derivatives, administered either orally in diet or by parenteral injection at maximum tolerated levels, had no significant activity: pyrazinoic acid, sodium pyrazinoyl hydroxamate, sodium N,N′-dipyrazinoyl hydrazine, pyrazine-2,3-dicarboxylic acid and the corresponding diamide, pyrazine-2,5-dicarboxylic acid and diamide, 2-hydroxypyrazine-3-carboxamide, 2-aminopyrazine-3-carboxamide, 2,5-dimethylpyrazine, and sodium pyrazine sulfonate.

Carboxamides of other heterocyclic ring systems were tested. The pyrimidine, imidazole, thiazole, thiophene, and quinoxaline compounds listed in Table 1 were found ineffective. Pyridazine-3-carboxamide is definitely antitubercular, at least as effective as nicotinamide on parenteral administration, whereas the isomeric 4-carboxamide is inactive. Benzamide and *m*-nitrobenzamide are also inert.

A number of nicotinamide relatives have been examined: nicotinamide methochloride, N-methyl-2-pyridone-5-carboxylic acid and amide, N-methyl-2-pyridone-3-carboxylic acid and amide, thio-nicotinamide, N,N′-dinicotinoyl methylenediamine, 3-amidinopyridine hydrochloride, 3-cyanopyridine, 3-hy-

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TABLE 1

	Antitubercular activity	pKa†	Reduction potential (polarigraphic half-wave) (in 0.1 *N* NaOH, 25°)		Nucleotidase inhibition‡	
			$E_{1/2}$ (volts)	I_d/C (μ amp/mg/ml)	Conc	Inhibition (%)
Nicotinamide	+	3.1 ± 0.2	−1.768	56.4	10^{-2}	100
					10^{-3} *M*	50, 47
Pyrazinoic acid amide	+++	−0.5 ± 0.3	−1.195	56.4	10^{-2}	1
Pyrimidine-5-carboxamide	0		−1.597	106		
Pyridazine-3-carboxamide*	+	1.0 ± 0.2	−1.301	50.6	10^{-2}	16
Pyridazine-4-carboxamide*	0	1.0 ± 0.2	−1.077	32.4	10^{-2}	0
			−1.359	32.7		
			(Two-step reduction)			
Imidazole-4-carboxamide	0	3.7 ± 0.2 and 11.8 ± 0.2	Not reducible		10^{-2}	13
Thiazole-5-carboxamide	0	0.6 ± 0.3	−1.765	31.3		
Quinoxaline-2-carboxamide	0	−0.4 ± 0.3	−0.970	48.1		

* The preparation of pyridazine-3-carboxamide (mp, 186°) and the 4-carboxamide (mp, 192°) will be described elsewhere.
† Values determined by ultraviolet absorption.
‡ A preparation of nucleotidase from guinea pig lung was employed. Coenzyme-I was determined spectrophotometrically.