air-tight containers at 0°C. until it was analyzed. Carotene estimations were made by the official A. O. A. C. method (*3*), modified by the use of Hyflo Supercel and magnesium oxide, 3:1, as the chromatographic adsorbent.

Seed was not available for the Iowa I205 x Ohio 28 cross; hence, the carotene value for this combination is missing from the data. The range of yields of the other single cross combinations tested was from 71 to 123 bushels/acre.

The average difference between the highest and lowest of the three carotene values for the individual single crosses was of the order of 17 per cent, the values given in Table 1 being

TABLE 1

CAROTENE CONTENT OF CORN

(mg./lb.—15.5 per cent moisture basis)

	Nebraska 6	Wisconsin 8	Illinois M14	Illinois A	Indiana WF9	Ohio 28	Wisconsin 32	Ohio 51A	Wisconsin 22	Iowa I205
Nebraska 6		1.91	1.64	1.50	1.41	1.30	1.48	1.09	1.08	.67
Wisconsin 8	1.91		1.68	1.27	1.27	1.17	1.31	1.01	.88	1.07
Illinois M14	1.64	1.68		1.26	1.23	1.03	.93	1.17	.84	.70
Illinois A	1.50	1.27	1.26		.97	.95	.95	.93	.79	.66
Indiana WF9	1.41	1.27	1.23	.97		.93	.98	.79	.74	.62
Ohio 28	1.30	1.17	1.03	.95	.93		.88	.66	.72	—
Wisconsin 32	1.48	1.31	.93	.95	.98	.88		.79	.73	.58
Ohio 51A	1.09	1.01	1.17	.93	.79	.66	.79		.60	.53
Wisconsin 22	1.08	.88	.84	.79	.74	.72	.73	.60		.69
Iowa I205	.67	1.07	.70	.66	.62	—	.58	.53	.69	
Inbred line averages	1.34	1.29	1.16	1.03	.99	.96	.96	.84	.79	.69

Least significant difference between single crosses = .19 mg.

the means for three duplicate estimations. These data show that there are striking significant differences between the carotene contents of some of the inbred lines, irrespective of the lines with which they were crossed. On the average, combination of Nebraska 6 and Wisconsin 8 with other inbreds produced corn with the highest carotene content, while all crosses employing Iowa I205 were relatively low. The combination of Nebraska 6 with Wisconsin 8 produced corn with the highest carotene value of all the crosses.

The superior value of yellow corn over white corn as a source of carotene has been recognized for many years. However, little attention has been paid to the fact that different strains of yellow corn may vary greatly in carotene content among themselves. The results presented here show that the genetic constitution of corn may be responsible, in large part, for its content of carotene, and that, all other conditions being the same, different strains of yellow corn may vary widely in carotene content. The results suggest further that, in the development of new corn hybrids, attention should be given to the content of important nutritive factors, among which carotene is but one. Further work along this line is now in progress.

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Enhancement of Penicillin Blood Levels Following Oral Administration of Caronamide

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Daily dosages of 5,000,000–40,000,000 units of penicillin were required with or without enhancing agents in treatment of the last 15 patients of a consecutive series of 150 cases of subacute bacterial endocarditis infected with nonhemolytic streptococci, including the resistant *Streptococcus* s.b.e. (*6*, *9*). The penicillin was administered by continuous venoclysis for a span of at least 8 weeks, which was made possible technically by the conjoint use of heparin in the treatment program. These 15 patients, most of whom were treatment failures with penicillin per se before being admitted to our Clinic, received a total of 66,000,000–4,000,000,000 units of penicillin, the average being 630,000,000. At times streptomycin was also included in the treatment program. Of these 15 refractory patients, 3 (20 per cent) were unequivocal treatment failures despite these massive dosages, and 12 (80 per cent) were salvaged and considered cured by all clinical and laboratory criteria.

Early in our experience with this type of patient, it was found necessary to resort to agents for enhancing penicillin blood levels, primarily to obtain therapeutic values and also to conserve limited supplies of penicillin. In our studies in connection with the treatment of a case of subacute bacterial endocarditis infected with *Veillonella gazogenes* (*10*), curative levels of penicillin were obtained only by means of incorporating in the treatment program large amounts of PAH (sodium p-aminohippurate), as originally suggested by Beyer, Flippin, Verwey, and Woodward (*2*). Additional patients similarly treated were cured chiefly because of the penicillin-augmenting properties of PAH; the detailed data of these observations will be included in a forthcoming communication (7).

In conducting these studies with PAH it was soon evident that this agent, while extremely effective in augmenting penicillin levels by competing with the antibiotic for the tubular excretory apparatus, poses serious technical difficultues. It is ineffective when given by mouth and must necessarily be administered by vein in daily dosages of 200–240 grams. It has the additional disadvantages of unpleasant side-effects and a sclerosing effect on veins when given in the requisite concentration. As a result of all this, treatment cannot be continued uninterruptedly for any extended period.

Acknowledging the limitations imposed by intravenous administration and the necessity for large dosages of PAH, a new approach was sought by Beyer (*1*) which resulted in the development of the compound, caronamide (4′-carboxyphenylmethanesulfonanilide). Beyer found that the excretion of penicillin by a renal tubular transport mechanism could be physiologically inhibited reversibly. The basis for this effect is thought to be one of substrate competition between penicillin, which is excreted by the tubular, and caronamide, which is essentially refractory to excretion by that transport mechanism.

The purpose of this report is to present data indicating the capacity of orally administered caronamide to effectively en-

hance penicillin blood levels in a group of patients where excessively high levels are essential for cure. In these patients, infected with relatively insensitive organisms, enhancing agents are virtually indispensable for obtaining necessary amounts of the antibiotic in body fluids. A comparative study regarding the merits of various enhancing agents has been completed and will be the subject of a subsequent report (*8*).

Caronamide[1] was administered for 2–19 days to 9 patients (Table 1) with subacute bacterial endocarditis who were receiving conjoint intravenous penicillin-heparin therapy manner with heparin to facilitate free, uninterrupted flow of the antibiotic.[3] All the blood-level testing was done on blood samples drawn during rigidly controlled runs to insure the designated test dosage.

Enhancement of penicillin blood levels was obtained in every instance where 3 grams was used every 4 hours. Eight of our patients had a mild degree of renal disturbance, which may or may not have had some bearing on the results obtained. In no instance did caronamide aggravate the pre-existing renal disorder. Accepting the dosage of 3 grams every 4 hours as

TABLE 1

PENICILLIN BLOOD LEVELS FOLLOWING COADMINISTRATION OF PENICILLIN AND CARONAMIDE IN 9 CASES OF SUBACUTE BACTERIAL ENDOCARDITIS

Case No.	Infecting organism	Daily dosage of penicillin i.v. (Oxford units times 1,000)	Oral caronamide		Penicillin blood levels (avg. Oxford units/ml.)			Urinary findings	Side-effects of caronamide
			Dosage (grams every 4 hrs.)	Total days administered	Control	After caronamide	Times enhanced		
(1) S. N.	*Streptococcus viridans*	5,000	2	2	3.75	4.00	0	Trace of albumen; occasional rbc and wbc.	
(2) E. S.	" s.b.e.	5,000	2	2	1.5	1.5	0	Occasional rbc and wbc.	Nausea
(3) A. H.	" s.b.e.	1,000	2	2	0.05	0.05	0	Trace of albumen and occasional rbc and wbc; reducing substance.	
		2,500	2	2	0.15	0.75	5		
		20,000	2	12	2.6	2.6	0		
		20,000	3	3	2.6	12.3	4+		
(4) H. K.	" *viridans*	5,000	2	2	13.75	60.0	4+	Trace to 3 plus albumen; wbc.	
		5,000	3	2	13.75	65.0	4+		
(5) I. B.	" s.b.e.	10,000	2	2	6.0	7.5	0	Reducing substance.	
		10,000	3	2	6.0	20.0	3+		
(6) H. B.	" s.b.e.	2,000	2	2	0.5	0.45	0	Trace of albumen; occasional rbc and wbc; reducing substance.	
		2,000	3	2	0.5	1.18	2+		
		5,000	3	2	4.12	30.0	7+		
		10,000	3	2	4.17	30.0	7+		
(7) A. L.	" s.b.e.	20,000	2	2	22.5	14.1	0	Occasional rbc and wbc; reducing substance.	
		20,000	3	5	22.5	66.5	3		
(8) A. B.		10,000	2	2	40.3	37.5	0	Trace of albumen; rbc; reducing substance.	
		10,000	3	5	40.3	86.9	2+		
(9) F. L.	" *viridans*	10,000	3	8	18.0	90.5	5	Trace of albumen; occasional rbc and wbc; reducing substance.	Nausea

(*5*, *11*). The caronamide was given orally in 2- or 3-gram dosages every 4 hours, day and night. To allow for adequate equilibration, the drug was administered at least 12 hours before blood samples were drawn for penicillin assay.[2] Following the coadministration of caronamide and penicillin, blood-level testing was done at various stages of the treatment period. For the most part, blood samples for penicillin assay were drawn an hour after the intake of a given dose of caronamide, when the influence of the compound is supposedly at its peak. The penicillin was given intravenously in the usual standard, the minimum increase over control levels was two-fold, and the maximum increase was seven fold. The total daily intravenous dose of penicillin, which ranged from 1,000,000 to 20,000,000 Oxford units, apparently had no influence on the degree of augmentation following caronamide administration.

The side-effects observed in these 9 patients were transitory and insignificant. Beyer and his group have reported 3 instances of the occurrence of a rash following the administration of caronamide (*3*). No cutaneous manifestations were encountered in our patients.

A reducing substance was discovered in the urine in practically every patient receiving 3 grams of caronamide every 4 hours. This disappeared from the urine shortly after the drug was discontinued and is presumably a metabolite product of caronamide (*3*).

[1] The authors are indebted to the Medical Research Division, Sharp & Dohme, Inc., for the generous supplies of caronamide used in these studies.

[2] The penicillin assay method used was that of Rosenblatt, *et al.* (*15*), which employs *Str. pyogenes* C203 as test organism. In a comparative study this system was found by Dolkart, Dey, and Schwemlein (*4*) to yield generally and, at times, appreciably lower values than the F.D.A. assay procedure described by Randall, Price, and Welch (*13*), which uses *Bacillus subtilis* NRRL B-558 as the test organism.

[3] Supplied by Chas. Pfizer & Co., Inc.

It may be stated that there is now available an oral preparation which in suitable dosage consistently augments penicillin levels. The compound helps to conserve the consumption of penicillin where massive daily dosages are required, the economic implications of which are obvious. More important, some patients have difficulty in maintaining adequate blood levels despite intensive penicillin dosage. Ordinarily, following the administration of intravenous penicillin, it is not unreasonable to expect and obtain 0.1 Oxford unit/ml. of blood for every 100,000 units of penicillin administered (*12, 14*). It is not always possible to maintain this ratio in a given patient. With the conjoint use of enhancing agents such as caronamide, not only can the expected blood values for a given intravenous dose of penicillin be obtained, but multiples of these anticipated values can, in point of fact, be achieved (Table 1, Case No. 6). This can mean the difference between success and failure in the treatment of the refractory case of subacute bacterial endocarditis.

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Experimental Determination of the Gyrofrequency

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The basic magneto-ionic theory of wave propagation in the ionosphere in the presence of the earth's magnetic field, as developed by Appleton (*1*) and by Appleton and Builder (*2*), was confirmed to an approximation in the lower latitudes some years ago. More recently extensive ionospheric observations in high latitudes have become available for the first time. Pronounced peculiarities in character of radio wave components returned at vertical incidence from the ionosphere in high latitudes have stimulated testing of the basic theory in terms of this new experimental information. For example, Scott and Davies (*4*) have described multiple magneto-ionic refraction of the wave energy into three or more components in a high geographic latitude. The three major components described by them indicate that both the longitudinal and transverse modes of wave propagation predicted by the theory occur simultaneously in certain high geomagnetic latitudes.

Through the courtesy of the College Geophysical Observatory, University of Alaska, some 800 selected ionospheric records from that station have been studied. In each record chosen it has been possible to determine independently the penetration frequency of wave components corresponding to: (a) the longitudinal ordinary ray, (b) the transverse ordinary ray, and (c) the extraordinary rays for both longitudinal and transverse modes of propagation. In addition, height of maximum electron density for the ionospheric layer under study has been determined.

The purpose of this note is to describe the experimental evidence, to review appropriate aspects of the magneto-ionic theory, and to discuss peculiarities disclosed in an attempt to reconcile theory and experiment.

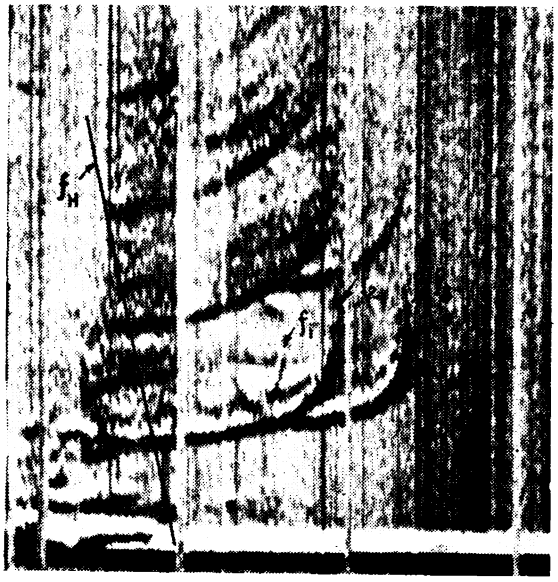

Fig. 1. Typical illustration of longitudinal and transverse modes of propagation occurring at the same time.

Consider Fig. 1, which is a typical ionospheric record taken at the University of Alaska. Ordinates are virtual height, increasing upward. Abscissas are wave frequency, increasing to the right. Penetration frequencies as noted in the figure are as follows: f_1, the longitudinal ordinary ray; f_2, the transverse ordinary ray; f_3, the extraordinary rays; and f_H, the calculated gyrofrequency for electrons in the earth's magnetic field. Experimentally, numerical values of f_1, f_2, and f_3 were determined from each record, as well as the height of maximum electron density, after the technique of Booker and Seaton (*3*).

The magneto ionic theory predicts, to a first approximation, that the relationship between wave components returned at vertical incidence from the ionosphere is as follows:

(a) For transverse mode of propagation—

$$(f_3 - f_2) = \frac{f_3 f_H}{(f_3 + f_2)} \qquad (1)$$

(b) For longitudinal mode of propagation—

$$(f_3 - f_1) = f_H \qquad (2)$$

The experimentally determined values were first examined in