TABLE II.
Effect of Ascorbic Acid on Parasitemia of Ascorbic Acid Deficient Monkeys (Produced by Dietary Deficiency).

Days after parasite inoculation	Total parasite count: Control animal (normal diet)	Ascorbic acid deficient animals (Vitamin C deficient diet): No. 120	No. 119	No. 117
0	—	—‡	—	—
3	0.3%	0.3%‡	350/mm³	50/mm³
4	2.0 "	2.7 "‡	270/ "‡	120/ "
5	10.0 "	8.0 "‡	0.2 %‡	30/ "
6	12.6 "	14.9 "‡	0.15 "‡	150/ "
7	31.3 "*	31.0 "*	0.8 "‡	100/ "
8			3.2 "‡	300/ "
9			26.0 "	580/ "
10			144.7 "*†	2000/ "
11				0.5%
12				1.2 "
13				0.9 "
14				5.5 "‡
15				8.8 "*‡

† 84% of the red cells contained parasites with many double and triple infections per cell.
* Animal died within 18 hours following this parasite count.
‡ 80-100 mg Merck's crystalline ascorbic acid intramuscularly.

24-hour cultures have so far been inconclusive, although in the absence of the vitamin the usual protoplasmic mass is not achieved. This growth deficiency and the degenerate appearance of the parasites are also very striking in the vitamin-deficient host. These studies on the effect of ascorbic acid and of ascorbic acid analogs are being continued with simian and human plasmodia.

Conclusions and Summary. 1. Plasma and whole blood ascorbic acid levels were significantly lower in parasitized monkeys than in normal animals.

2. There was an abnormal course of parasitemia in 7 of our monkeys which showed spontaneous ascorbic acid deficiency and in 2 other animals which were made ascorbic acid deficient by removing the vitamin from their diet.

3. Following the administration of the pure ascorbic acid, there was a normal course of parasitemia in one of the monkeys spontaneously ascorbic acid deficient and in those made ascorbic acid deficient by dietary means.

Withholding ascorbic acid therapy for more than 7 days appeared to give the spontaneously deficient monkeys time to produce an immunity and to control the infections. If ascorbic acid treatment was withheld from the animals made vitamin C deficient there was a prolongation of the course of infection but eventually the parasitemia overwhelmed the animal.

15585

Toxicity and Therapeutic Activity of Tyrothricin by Oral Administration.

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Since penicillin by oral administration has been found effective in the prophylaxis and treatment of certain infections, the matter of the toxicity and possible therapeutic effectiveness of tyrothricin by this route of administration is not without interest in relation to antibiotic therapy.

In these experiments a 2% alcoholic solu-

TABLE I.
Toxicity of Tyrothricin for Mice by Oral Administration.

No.	Dose per mouse* (g)	Survival: days									
		1	2	3	4	5	6	7	8	9	10
1	0.0004	—	—	—	—	—	—	—	—	—	—
2	0.0004	—	—	—	—	—	—	—	—	—	—
3	0.0006	—	—	—	—	—	—	—	—	—	—
4	0.0006	—	—	—	—	—	—	—	—	—	—
5	0.0008	—	—	—	—	—	—	—	D		
6	0.0008	—	—	—	—	—	—	—	—	D	
7	0.001	—	—	—	—	—	—	—	—	—	—
8	0.001	—	—	—	D						
9	0.0012	—	—	D							
10	0.0012	—	—	—	D						

* Administered orally 3 times a day.

TABLE II.
Therapeutic Activity of Tyrothrycin by Oral Administration to Mice.

Infections	Dose per mouse* (g)	No. mice	Survivals: days									
			1	2	3	4	5	6	7	8	9	10
Strept. hemolyt.	0.0004	10	10	10	9	5	3	2	2	0	0	0
,, ,,	controls	10	10	7	4	2	0	0	0	0	0	0
Pneu. (type I)	0.0004	12	12	10	8	8	6	4	4	4	4	4
,, ,, ,,	controls	12	12	7	2	0	0	0	0	0	0	0
,, ,, II)	0.0004	10	10	9	6	4	3	2	2	2	2	2
,, ,, ,,	controls	10	10	4	2	1	0	0	0	0	0	0
,, ,, III)	0.0004	10	10	4	2	2	0	0	0	0	0	0
,, ,, ,,	controls	10	10	3	0	0	0	0	0	0	0	0

* At 10 A.M., 1 P.M., and 4 P.M. daily.

tion of tyrothricin (Parke-Davis Co.) was employed, freshly prepared suspensions being prepared with sterile distilled water.

For toxicity tests 1:10 suspensions were administered containing 0.002 g per cc. Adult white mice were given 3 doses per day at 10 a.m., 1 p.m. and 4 p.m. by stomach tube in varying amounts, shown in Table I, for 10 days in succession. It will be observed that the maximum tolerated dose of the tyrothricin employed was about 0.0008 g per mouse.

Therapeutic tests were conducted with mice inoculated intraabdominally with 100 minimal lethal doses of 18-hour hormone broth cultures of *Streptococcus hemolyticus* (group A) and pneumococci of types I, II and III. Tyrothricin was administered by stomach tube in dose of 0.2 cc of 1:10 suspension (0.0004 g per mouse) 2 hours later with a second dose, 3 hours thereafter. Subsequent doses were administered at 10 a.m., 1 p.m. and 4 p.m. daily for 9 days in succession, covering a treatment period of 10 days. Untreated controls were included inoculated with the 4 cultures respectively. Heart blood cultures were made of the majority of succumbing mice and all were positive.

As shown in Table II, all of 10 mice infected with *Streptococcus hemolyticus* and treated with tyrothricin succumbed although 5 survived 1 to 3 days longer than the 10 untreated controls. Of 12 mice infected with type I pneumococcus and treated with tyrothricin 4 survived whereas all of 12 untreated controls succumbed within 4 days. Of 10 mice infected with type II pneumococcus and treated with tyrothricin 2 survived whereas all of 10 untreated controls succumbed within 5 days. All of 10 mice infected with type III pneumococcus and treated with tyrothricin succumbed although 2 survived for 2 days longer than 10 untreated controls.

In addition, 8 adult rabbits were inoculated intratesticularly with the Nichols-Hough

strain of *T. pallidum*. In from 4 to 6 weeks all developed acute syphilomas with positive darkfield examinations. Two rabbits were kept as untreated controls while the remaining 6 were treated with tyrothricin administered by stomach tube once a day for 15 days in succession. Freshly prepared 1:100 suspensions of the compound in sterile distilled water were employed. The daily doses were 1 cc (0.0002 g), 5 cc (0.001 g) and 10 cc (0.002 g) per kg for each of 2 rabbits receiving the 3 different amounts. One of the 2 rabbits receiving 10 cc (0.002 g) died on the 8th day of treatment, apparently from the toxic effects of the compound. Clinical records and darkfield examinations were made at daily intervals. During and at the end of the period of treatment none of the animals showed any clinical evidences of healing of the testicular lesions as compared with the untreated controls and all showed persistently positive darkfield examinations. Under the circumstances lymph node transfers were regarded unnecessary.

Summary. The maximum tolerated dose of tyrothricin for adult white mice, administered by stomach tube 3 times a day for 10 days in succession, was about 0.0008 g per mouse. By this route of administration 3 doses of tyrothricin daily in dose of 0.0004 g per mouse were very slightly effective in the treatment of mice inoculated with virulent *Streptococcus hemolyticus* (group A) and type III pneumococcus, while definitely more effective in the treatment of mice inoculated with virulent types I and II pneumococci and especially type I. Tyrothricin in daily doses of 0.0002, 0.001 and 0.002 g per kg, administered by stomach tube for 15 days in succession, was completely ineffective in the treatment of acute testicular syphilis of rabbits.

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Inhibition of Bacterial Growth by Auxins.

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We have observed that a number of synthetic unsaturated ring-containing acids endowed with auxin (plant hormone) activity can exert a bacteriostatic effect on the growth of certain bacterial species. The following substances were selected as representatives of different chemical types of auxins: indole-3-acetic acid, β-(indole-3)-propionic acid, -(indole-3)-n-butyric acid, α-naphthaleneacetic acid, β-naphthoxyacetic acid, 2,4-dichlorophenoxyacetic acid, 2,3,5-triiodobenzoic acid.[1]

The order of activity of these different substances on a few bacterial species is illustrated in Table I in which are given the concentrations of auxins required to cause a 50% inhibition of growth in a medium containing by weight 0.1% enzymatic hydrolysate of casein and 0.02% yeast extract. It should be emphasized that the inhibitory concentrations recorded in Table I have only a relative value since, as will be indicated later, tryptophane and peptone can antagonize the bacteriostatic action of auxins. It is also worth recording that the antibacterial activity of 2 of these substances had been recognized before anything was known of their plant hormone activity. Thus, it was known that indole acids (indole acrylic acid in particular) inhibit the growth of certain Gram-negative bacilli in synthetic media, and that this bacteriostatic effect can be reversed by tryptophane;[2] the growth of mycobacteria in synthetic Long's medium has been shown to be inhibited by 2,3,5-triiodobenzoic acid although the same substance stimulates oxygen uptake of these organisms

[1] Zimmerman, P. W., *Indus. and Eng. Chem.*, 1943, **35**, 596.

[2] Fildes, P., *Brit. J. Exp. Path.*, 1941, **22**, 20.