each other only in having respectively a —$CH_3$ and a —CHO group on C-10, are of identical potency. This is in fair agreement with cat assay results if allowance is made for experimental error.

(2) A daily oral dose in man of 1.3 to 3.7 mg has been suggested for thevetin[11] as compared with 0.1 to 0.2 mg for digitoxin[12] or an average molar ratio of about 1/15. In the isolated heart thevetin is 1/25 as potent as digitoxin, which is in much better agreement than is the cat assay for which the ratio is about 1/2. The genins corresponding to these 2 drugs are stereo-isomeric and different triosides are attached at C-3. The influence of the stereochemical arrangement may be judged if it is assumed that this difference in the sugars is of minor significance.

(3) Ouabain is one-eighth as active as digitoxin. In man, ouabain is considered an unreliable drug by the oral route but it has never been determined with certainty whether this is due to poor absorption, rapid dissipation or failure to "cumulate." Ouabain is twice as potent as digitoxin in the cat.

(4) Amphorous gitalin from the water-soluble fraction of Digitalis purpurea has about half the potency of digitoxin by either method. Stroud and coworkers[13] found the daily oral dose of gitalin to be approximately 0.27 mg, which gives a molar ratio to digitoxin of about 0.49.

(5) The 2 angelica lactones show an activity 1/800 to 1/500 that of digitoxin. Furthermore, their effect on the heart is qualitatively different from the glycosides in that ventricular arrest frequently appears before and instead of atrioventricular block. This contributes further evidence that the lactone ring is only part of the structural configuration necessary for the typical effects of the cardiac glycosides. These compounds are not considered to have digitalis-like action in the cat.

(6) Cerberin is a crystalline glycoside of uncertain structure, which, like gitalin, has about the same ratio to digitoxin by either method.

*Summary.* The potency of a number of glycosides and related compounds for the embryonic chick heart has been reported and various implications suggested. As a means of studying the relationship of chemical constitution and physiologic action, the embryonic heart method appears to offer definite advantages over methods employing intravenous administration to intact animals.

11 Middleton, W. S., and Chen, K. K., *Am. Heart J.*, 1936, **11**, 75.

12 Gold, H., Kwit, N., and Cattell, McK., *J. Pharmacol.*, 1940, **69**, 177.

13 Stroud, W. D., Livingston, A. E., Bromer, A. W., Vander Veer, J. B., and Griffith, G. C., *Ann. Int. Med.*, 1934, **8**, 710.

## 15605

## Failure of Tyrothricin in the Treatment of Experimental Syphilis of Rabbits.

JOHN A. KOLMER AND ANNA M. RULE.

*From the Research Institute of Cutaneous Medicine, Philadelphia, Pa.*

From the standpoint of antibiotic therapy the possible therapeutic effectiveness of tyrothricin in the treatment of experimental syphilis of rabbits is not without interest. Owing to its toxicity by intravenous injection, however, largely due to hemolytic activity, the compound has not been generally employed in the treatment of experimental infections of the lower animals by this route of administration.

In these experiments a 2% alcoholic solution of tyrothricin (Parke-Davis Co.) was employed, suspensions being freshly prepared by diluting 1 cc with 99 cc of sterile distilled

TABLE I.
Toxicity of Tyrothricin for Rabbits by Intravenous Injection.

| No. | Dose per kg g | Survival: days 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.0002 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 2 | 0.0002 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 3 | 0.0004 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 4 | 0.0004 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 5 | 0.0006 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 6 | 0.0006 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 7 | 0.0008 | — | — | — | — | — | — | D | | | | | | | |
| 8 | 0.0008 | — | — | — | — | — | — | — | — | — | D | | | | |
| 9 | 0.001 | — | — | — | D | | | | | | | | | | |
| 10 | 0.001 | — | — | — | — | D | | | | | | | | | |

water (0.0002 g per cc). Normal adult rabbits were given varying amounts by intravenous injection as shown in Table I; with the tyrothricin employed the maximum tolerated dose was about 0.0006 g per kg of weight.

Sixteen 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. Four rabbits were kept as untreated controls while the remaining 12 were given daily intravenous injections of 0.5 cc of 1:100 suspensions of tyrothricin per kg of weight over a period of 15 days. This dose corresponded to 0.0001 g per kg, being equivalent to about one-sixth of the maximum single tolerated dose. Clinical records and darkfield examinations for *T. pallidum* were made at daily intervals.

All animals survived with apparently no clinical evidences of toxicity. During and at the end of the period of treatment none showed any clinical evidences of healing of the testicular lesions as compared with the untreated controls and all 16 animals showed persistently positive darkfield examinations. Under the circumstances lymph node transfers were regarded unnecessary.

*Summary.* The maximum single tolerated dose of tyrothricin for adult rabbits by intravenous injection was about 0.0006 g per kg. Fifteen intravenous injections of 0.0001 g per kg, at daily intervals (totalling 0.0015 g per kg) were completely ineffective in the treatment of acute testicular syphilis of rabbits.

## 15606

## Failure of Penicillin and Streptomycin in the Prophylaxis and Treatment of Experimental Vaccinia of Rabbits.

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Andrews and his colleagues[1] have reported that penicillin is ineffective in the treatment of vaccinia and Parker and Diefendorf[2] have found that the compound was without effect on the multiplication of the virus in the Rivers-Li culture medium and in the intact chick embryo. The activity of streptomycin on the virus has not been reported upon but the results of experiments herein briefly summarized, employing both compounds in the

[1] Andrews, C. H., *et al., J. Path. and Bact.*, 1943, **55**, 173.

[2] Parker, R. F., and Diefendorf, H. W., PROC. SOC. EXP. BIOL. AND MED., 1944, **57**, 351.