Technical Papers

Terramycin, a New Antibiotic

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A new actinomycete, *Streptomyces rimosus,* has been isolated from a soil sample and so named because of the cracked appearance of the growth on the surface of an agar medium. When the organism was grown on plates containing nutrient agar and when a variety of bacteria including certain of the Gram-negative enteric organisms, aerobic spore-formers and Gram-positive cocci were streaked across these plates, growth of the test organisms was inhibited in the vicinity of the colony of the actinomycete. When *Streptomyces rimosus* was grown under submerged aerobic conditions, the broth exhibited similar inhibitory powers, as demonstrated in serial dilution assays. From broth cultures of this organism, a crystalline antibiotic was isolated; the name Terramycin has been assigned to this compound.

Terramycin is amphoteric and forms the crystalline hydrochloride and sodium salt. Crystalline Terramycin has the following properties: mp approximately 185° C with decomposition; $[\alpha]_D^{25} - 196°$ (1.0% in 0.1 *N* HCl). It is soluble in methanol, ethanol, acetone and propylene glycol, in water to the extent of 0.25 mg per ml at 25° C; insoluble in ether and petroleum ether. Terramycin is stable over long periods in aqueous solutions at about pH 2.0–5.0, at room temperature. A sample of crystalline Terramycin analyzed: C, 53.05; H, 5.91; N, 5.64; O (by difference), 35.4.[1]

Terramycin crystallizes in several forms, depending upon the procedure used. One of these forms consists of thick hexagonal plates, the refractive indices of which are $\alpha = 1.636 \pm .004$, $\beta = 1.644 \pm .004$, $\gamma > 1.700$.

In 0.1 M phosphate buffer (pH 4.5), Terramycin shows ultraviolet absorption maxima at approximately 247, 275, and 353 mμ. It also shows characteristic absorption in the infrared region.

The activity *in vitro* of crystalline Terramycin Hydrochloride against a variety of microorganisms is shown in Table 1. The activity was determined by dissolving varying amounts of the antibiotic in nutrient agar and streaking with the organisms under test. Further observations on the sensitivity of these and other organisms will be reported in detail elsewhere.

Terramycin shows a low degree of toxicity in animals. The intravenous LD_0 for Terramycin Hydrochloride is equivalent to 103 mg of the crystalline amphoteric compound per kg of body weight in mice; the LD_{50} is equivalent to 192 mg per kg.

[1] These determinations were made by Dr. John A. Means of Chas. Pfizer & Co., Inc., Brooklyn, New York.

TABLE 1

ACTIVITY *in Vitro* OF CRYSTALLINE TERRAMYCIN HYDROCHLORIDE*

Species	μg/ml	Inhibition
Aerobacter aerogenes	1.0	100%
Klebsiella pneumoniae	3.0	"
Escherichia coli	5.0	"
Salmonella typhosa	3.0	"
S. paratyphi	1.0	"
S. schottmuelleri	1.0	"
S. pullorum	10.0	"
Shigella paradysenteriae	1.0	"
Bacillus subtilis (FDA 219)	3.0	"
Staphylococcus albus	1.0	"
S. aureus	1.0	"
Proteus sp.	> 1000	"
Pseudomonas aeruginosa	100	"
Brucella bronchisepticae	3.0	"

* Activity is expressed in terms of the equivalent weight (μg) of crystalline Terramycin necessary to inhibit growth.

As is the case with aureomycin and chloramphenicol, Terramycin is active *in vivo* as well as *in vitro* and displays marked chemotherapeutic activity against experimental infections in mice due to *Streptococcus hemolyticus, Diplococcus pneumoniae, Klebsiella pneumoniae, Salmonella typhosa,* and other organisms. It is effective by both the oral and parenteral routes of administration. Preliminary studies suggest that Terramycin has definite antirickettsial activity in the chick embryo.[2] In high concentrations it appears to inhibit the infection of the chick embryo with the PR8 strain of Influenza A virus.

[2] Data on the antirickettsial activity of Terramycin will be reported elsewhere by Dr. John C. Snyder, Harvard School of Public Health.

The Oxygenation of Blood by Gas Dispersion

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In the attempts to relieve anoxia of the tissue by means other than those of artificial respiration or inhalation of gas mixtures high in oxygen, widely varying means of extrapulmonary oxygen administration have been employed. Oxygen has been injected subcutaneously, intraperitoneally, and intravenously, as well as directly into the intestines, the joints, the renal pelvis, and the urinary bladder. Oxygen has even been applied locally in attempts to increase the absorption through the skin. All