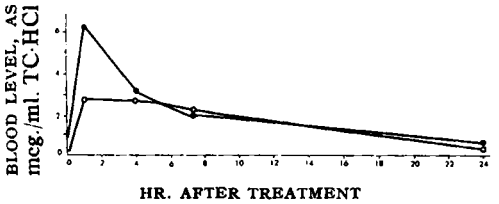

Fig. 4.—Average blood levels of three dogs per group following intramuscular administration of OTC and DMCTC-Al-Ca-gluconate. Key: O, OTC at 2.5 mg. OTC neutral/lb., AUC = 38.6 mcg./hours/ml. (formulation pH 8.5). ●, DMCTC-Al-Ca-gluconate (1:4:5:12) at 0.3 mg. DMCTC·HCl/lb., AUC = 45.3 mcg./hours/ml. (formulation pH 4.5).

Figure 4 shows the blood levels obtained with DMCTC-aluminum-calcium-gluconate (molar ratio 1:4:5:12) and a commercially available preconstituted oxytetracycline intramuscular formulation in 75% propylene glycol (Pfizer) for human administration. The DMCTC complex was administered intramuscularly to dogs at 0.3 mg. DMCTC·HCl per pound of body weight and the oxytetracycline (OTC) at a level of 2.5 mg. OTC base per pound of body weight. On an antibiotic-weight basis, approximately one-eighth as much antibiotic was administered as the complex. However, the blood levels produced nearly equal AUC's in terms of tetracycline·HCl equivalents (Fig. 4). Some of the blood level enhancement observed in this experiment results from the fact that DMCTC is more active microbiologically on a weight basis than OTC when assayed against a tetracycline·HCl standard. To date, many blood-level studies have been made in dogs, rabbits, and rats with complexes containing various tetracycline antibiotics orally, intramuscularly, and intravenously. The degree of blood level enhancement, which has been demonstrated repeatedly, is dependent on the route of administration and the constituents in the complex.

The mechanism by which blood-level enhancement occurs is not completely understood. One hypothesis is that blood-level enhancement results from limited tissue penetration of the antibiotic complex from the blood stream.

Blood Level Experiments in Humans.—Katz (7) and Katz and Fedorko (8) reported the results of a clinical trial in humans using DMCTC-aluminum-calcium-gluconate (molar ratio 1:4:5:12). They found that intramuscular administration of this complex in single doses equivalent to 25 and 50 mg. of DMCTC·HCl produced significantly higher serum levels than would have been expected from considerably larger doses of tetracycline. These doses were in a range normally expected to be therapeutic. However, several patients with tetracycline-antibiotic-susceptible infections did not respond satisfactorily at a dose of 50 mg. per day. The response was improved by increasing the dose to 100 mg. per day.

SUMMARY

Chemical and biological evaluation of metal-acid complexes with members of the tetracycline family indicate that these preparations exhibited properties that were not displayed by the uncomplexed antibiotic. The most interesting properties which are characteristic of selected complexes include enhanced solubility and alkaline stability, reduced acute toxicity and tissue irritation, and enhanced blood levels.

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ERRATUM

In the paper titled "Preparation of a Phase Diagram for Coacervation" (1), Eq. 6 on page 519 should read:

$$n = \frac{(\Delta \text{ sp. gr.})(D) - (\Delta \text{ R. I.})(\Delta \text{ sp. gr. } + B)}{(AD - BC) - (\Delta \text{ sp. gr.})(C - D)} \qquad \text{(Eq. 6)}$$

(1) Phares, R. E., Jr., and Sperandio, G. J., This Journal, **53**, 518(1964).