Practical and Theoretical Considerations Concerning Treatment of Bacterial Pneumonia in Feedlot Cattle, With Special Reference to Antimicrobic Therapy

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When effective antimicrobic therapy can be initiated on the first day that clinical signs are evident to an experienced observer and continued for 48 hours after fever, dyspnea and toxemia have abated, and if appropriate shelter, nutrition and nursing care are provided, mortality from acute, uncomplicated bacterial pneumonia in feedlot cattle will be negligible. Mortality is increased when disease detection is inadequate, resulting in delayed treatment, when ineffective antimicrobics are utilized, or when inappropriate dosages, routes of administration or treatment intervals are selected, and when treatment is irregularly administered or prematurely terminated. Failure to promptly reinstitute treatment when relapses occur is often a factor in excessive mortality.

Sick cattle should be kept dry and provided with shelter from cold winds or hot sun. Sick cattle penned together should be of similar size and should not be overcrowded. At least 12 linear inches and preferably 24 linear inches of feed bunk space should be provided per animal.

Good quality long-stem pasture grass or grain hay should be available at all times. Legume hays are not recommended for sick cattle as their use is often associated with fatal bloat. Starting ration should be fed free-choice in addition to hay to feedlot cattle. Clean, fresh water should be available at all times. Supplementary feeding is not required for cattle on good pasture.

When treating severe or non-responsive bacterial pneumonias in valuable individual cattle, the causative bacterium should be isolated from bronchial exudate obtained by transtracheal aspiration (1). Antimicrobic therapy is then based upon the results of sensitivity tests. However, when large numbers of commercial cattle are to be treated, this is impractical. When more than 50 to 60% of an animal's lungs have become consolidated, response to treatment is nearly always unsatisfactory, regardless of the treatment chosen or the antimicrobic sensitivity of the infecting organism. In those few cases that do respond, relapses are to be expected.

Relatively unsatisfactory response rates may be observed in calves shipped long distances to western feedlots, especially out of southeastern states. Most of these calves originate in herds of fewer than 50 cows and several weeks may elapse between weaning and arrival in the feedlot, as calves are sorted for size, sex, condition and quality and assembled into large groups. These cattle may be exhausted, if not debilitated, when they finally arrive in the feedlot and often are too tired and weak to eat for several days after arrival. If sick on arrival, or if they should become sick before recovering from the effects of shipping, response to treatment may be unsatisfactory. Sickness in these cattle is frequently an exacerbation of an older pneumonia which may have been inadequately treated by stockyard personnel during assembly and shipment. Extension from the original lesions may reach 50 to 60% consolidation before a decision is made to initiate treatment at the feedlot. Mortality is high in these cases.

Bacterial pneumonia in feedlot cattle was most frequently associated with *Pasteurella hemolytica, P. multocida* and *Corynebacterium pyogenes* (2) (Table 1). Mycoplasmas were also isolated from most pneumonic lungs (Table 1), but were not considered by the author to be of etiologic significance. Attempts by the author to reproduce a pneumonia in cattle with the most frequently isolated mycoplasma *(M. agalactiae var. bovis)* were unsuccessful (3). Perhaps more significantly, antimicrobics such as sulfamethazine and penicillin G (which have no activity against mycoplasmas) were more effective in treatment of feedlot pneumonia than antimicrobics such as oxytetracycline, tylosin and erythromycin which may be active against mycoplasmas (2).

P. hemolytica and *P. multocida* were usually sensitive to sulfonamides, penicillin G, ampicillin, tetracyclines, chloramphenicol, neomycin, kanamycin, gentamicin, polymyxin B, cephalothin, and cephaloridine; were usually resistant to dihydrostreptomycin and erythromycin; and were always

resistant to tylosin (Table 3; Figures 1 and 2). *C. pyogenes* was always sensitive to penicillin G, ampicillin, cephalothin and cephaloridine; was usually sensitive to chloramphenicol, neomycin, kanamycin and gentamicin; was frequently resistant to erythromycin and tylosin; was usually resistant to oxytetracycline and dihydrostreptomycin; and was always resistant to sulfonamides and polymyxin B (Figures 3 and 4).

Table 1

Results of Microbiological Examination of Lungs From 500 Fatal Cases of Bovine Bacterial Pneumonia

Organisms isolated	No. of Isolations	Frequency of Isolation (%)
Mycoplasmas	331	86.2*
Pasteurella hemolytica	260	52.0
P. multocida	130	26.0
Escherichia coli (non-hemolytic)	70	14.0
Corynebacterium pyogenes	61	12.2
Proteus spp.	22	4.4
Pasteurella spp.	21	3.4
E. coli (hemolytic)	15	3.0
Negative (no growth)	13	2.6
Salmonella newport	10	2.0
Hemophilus oakley	7	1.4
Actinobacillus-like organisms	5	1.0
Streptococcus viridans	5	1.0
Alpha streptococci	4	0.8
Corynebacterium spp.	2	0.4
Enteric spp.	2	0.4
Alcaligenes fecalis	1	0.2
Flavobacterium spp.	1	0.2
Pseudomonas aeruginosa	1	0.2
S. dublin	1	0.2
S. typhimurium	1	0.2
Staphylococcus aureus	1	0.2
Streptococcus fecalis	1	0.2
Streptococcus fecium	1	0.2
All Pasteurellas	414	82.8

*A total of 381 lungs were examined for Mycoplasmas.

Familiarity with the following general concepts is essential for understanding the limitations of antimicrobic therapy as well as for making most effective use of antimicrobics in treatment of bacterial infections. I. Bacteriostatic or bacteriocidal antimicrobic concentrations are the same *in vivo* as *in vitro* for a given bacterial isolate (4). However, the concentration required for an inhibitory effect is also proportional to the size of the bacterial population to be inhibited (4,5). Severe infections, associated with large numbers of bacteria, require higher antimicrobic concentrations (implying higher dosages) for control than do ordinary infections. Physicians routinely seek to achieve serum antimicrobic concentrations of 8 to 10 times the minimal inhibitory concentration (MIC) for the bacterium isolated from the patient when treating life-threatening infections in man (6,7). II. Inhibitory serum concentrations should be continuously maintained when treating with bacteriostatic antimicrobics such as sulfonamides (8), tetracyclines, erythromycin, tylosin and chloramphenicol. III. Maintenance of inhibitory serum concentrations does not necessarily assure a satisfactory clinical response for the following reasons: 1) Intact host defense mechanisms are also essential for satisfactory responses: (a) Granulocytopenic patients do not respond normally to treatment (8), even when bacteriocidal drugs are utilized (9). (b) The phagocytic activity of the reticuloendothelial system may be greatly reduced in severe, chronic infections. Bacteria that are merely inhibited, rather than killed, are not disposed of (8). (c) Suppression of the inflammatory response by corticosteroids may reduce the therapeutic effectiveness of bacteriostatic drugs (7). 2. Antimicrobics may not reach important foci of bacterial activity in effective concentrations because of: (a) Failure to freely pass through the walls of abscesses (7). (b) Failure to diffuse freely into specific tissues or tissue spaces such as the central nervous system (cephalosporins, poly-

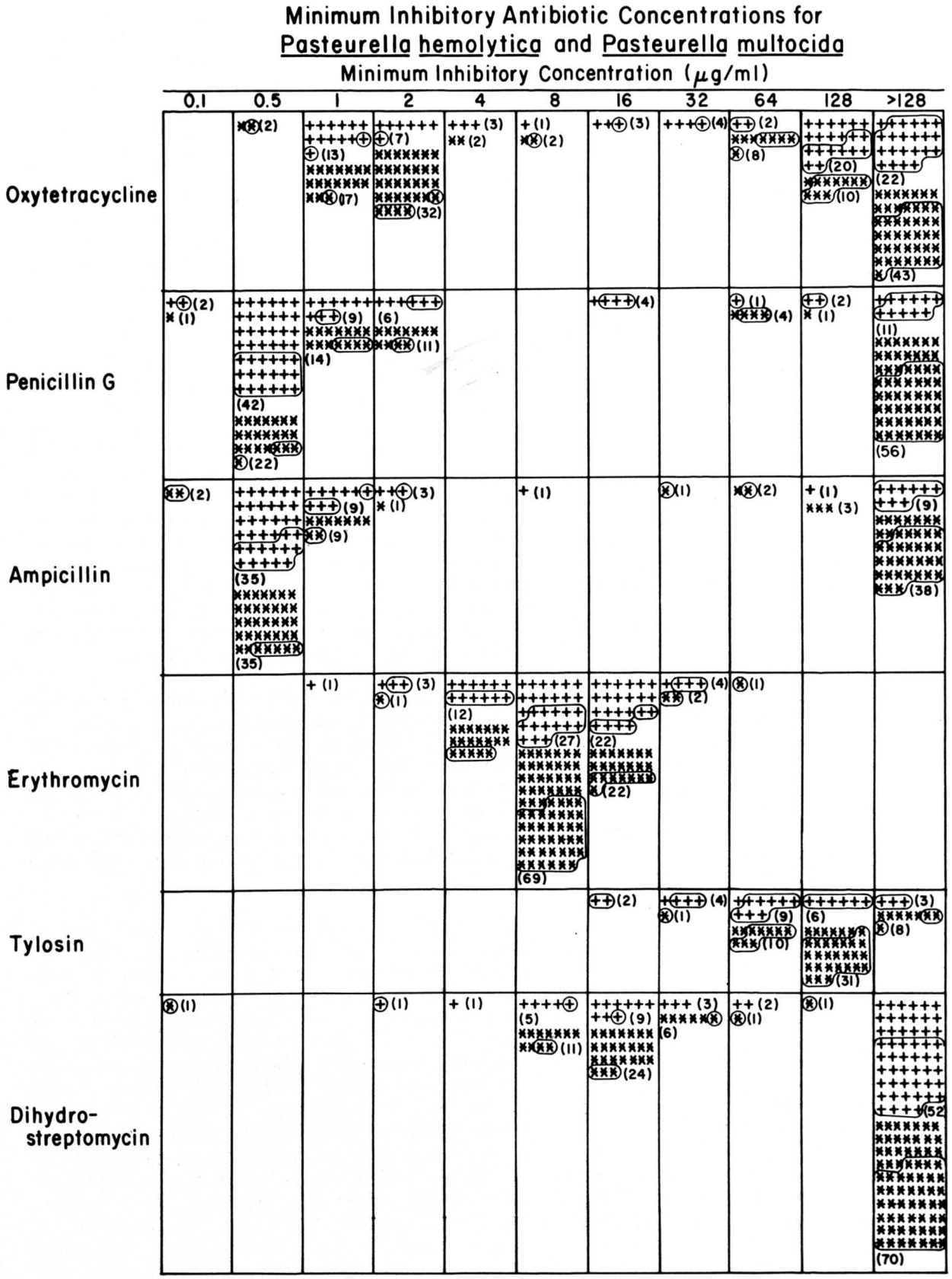
Table 2

Recommendations Concerning Dosages, Treatment Intervals and Withdrawal Periods for Sulfonamide Therapy in Cattle

Sulfonamide	Dosage		Treatment Interval	Withdrawal (Days)	
	Priming	Maintenance		Slaughter	Milk
Sulfamethazine, USP	1-1/2 Gr./lb.	3/4-1 Gr./lb.	24 hrs.	10	4
Sulfamerazine	1-1/2 Gr./lb.	1/2 Gr./lb.	12 hrs.	10	...
Sulfapyridine	1 Gr./lb.	1/2 Gr./lb.	12 hrs.	10	...
Sulfathiazole	1-1/2 Gr./lb.	1/2 Gr./lb.	6-8 hrs.	10	...
Vetisulid®	15-23 mg/lb.	15-23 mg/lb.	12 hrs.	5 (a) - 7 (b)	NA (c)
Albon® (d)	25 mg/lb.	12.5 mg/lb.	24 hrs.	5 (a) - 7 (b)	2-1/2
Albon-S.R.® (d)	62.5 mg/lb.	...	4 days	21	NA
S.E.Z.®	25 mg/lb.	25 mg/lb.	24 hrs.	16	NA
S.E.Z.C.-R®	100 mg/lb.	...	3 days	16	NA
Sulfabrom® (e)	1-1/2 Gr./lb.	1-1/2 Gr./lb.	48 hrs.	10	4
Spanbolet II®	1 bolus/150 lbs.	...	5 days	28	NA
Hava-Span® (f)	1 bolus/200 lbs.	...	3-1/2 days	16	NA
	1 bolus/100 lbs.	...	5 days	16	NA

(a) after intravenous administration; (b) after oral administration; (c) NA - not approved for use in lactating cattle; (d) blood levels reported by the manufacturer with the recommended dose are only marginally therapeutic; (e) absorption from digestive tract not always reliable (8); (f) therapeutic blood concentrations not obtained during the first 14 to 18 hours after administration.

Figure 1. Minimum inhibitory concentrations of approved antibiotics for *Pasteurella hemolytica* and *P. multocida* isolates.



myxin B and gentamicin) (6), and the pleural space (7) and joints (6) (polymyxin B). (c) Binding by phospholipids of cell membranes (polymyxin B) (7). And (d) presence of interfering substances: (1) Action of sulfonamides may be blocked by nucleic acids in pus (7). (2) Antimicrobics may be adsorbed on to exudates and necrotic debris (7). (3) The highly acid pH, which is often present in necrotic tissue (7) may destroy or reduce the activity of antimicrobics such as sulfonamides (7,8), penicillin G (7), erythromycin (10) and the aminoglycosides (7) (dihydrostreptomycin, neomycin, kanamycin and gentamicin). IV. Subacute or chronic infections may not respond well to antimicrobics such as penicillin G (11), ampicillin, cephalothin and cephaloridine, in which bacteriocidal activity (inhibition of the transpeptidation reaction in cell wall synthesis (7)) is dependent on rapid bacterial cell growth (11). Bacterial growth is most rapid during the early stages of infection (11). V. It is not always essential to maintain continuously inhibitory serum concentrations of penicillin G. Scarlet fever in man was treated as effectively when inhibitory concentrations of penicillin G were present for six hours per day as when more continuous concentrations were maintained (12,13). Similar latitude might be possible with other bacteriocidal antimicrobics such as ampicillin, dihydrostreptomycin, neomycin, kanamycin, gentamicin, polymyxin B, cephaloridine and cephalothin. Supportive data is lacking on this point.

Table 3

Antimicrobic Sensitivity of Pasteurellae Isolated From Nasal Secretions of Cattle with Feedlot Pneumonia*

	Date of Isolation			
	1972**		1974+	
Antimicrobic	No. Tested	Sensitive (%)	No. Tested	Sensitive (%)
Tetracycline	73	97.3	97	62.9
Sulfathiazole	73	78.1	53	90.6
Penicillin G	73	63.0	94	77.7
Erythromycin	23	34.8	97	21.6

*Isolated on the first day of clinical illness, prior to initial treatment.
**Isolated between 7-12-72 and 12-5-72.
+Isolated during July of 1974.

Use of Sulfonamides in Treatment of Feedlot Bacterial Pneumonias

All sulfonamides are bacteriostatic through competitive inhibition of bacterial para-aminobenzoic acid utilization for the synthesis of folic acid (8). Since bacterial cross-resistance generally occurs between all sulfonamides (8), selection of a specific one for treatment of bacterial pneumonia in cattle should be based only upon such considerations as: (1) relative risk of toxicity, (2) gastrointestinal absorption characteristics, (3) urinary excretion characteristics, (4) concentrations of free (active, unbound) drug achieved in blood serum, and (5) cost. Sodium salts of sulfamethazine, sulfamerazine, sulfapyridine, sulfathiazole, sulfadimethoxine (Albon®-Roche), and sulfachlorpyridazine (Vetisulid®-Squibb) are marketed for intravenous administration in cattle. Sulfamethazine, sulfabromomethazine (Sulfabrom®-Merck), sulfadimethoxine (Albon®-Roche), sulfachlorpyridazine (Vetisulid®-Squibb), and sulfaethoxypyridazine (S.E.Z.®-Cyanamid) are marketed in bolus form for oral administration in cattle. Oral sustained-release bolus formulations are available for sulfamethazine (Hava-Span®-Haver-Lockhart; Spanbolet II®-Norden), sulfadimethoxine (Albon-S.R.®-Roche), and sulfaethoxypyridazine (S.E.Z. C-R®-Cyanamid).

It is essential that continuously bacteriostatic blood concentrations be maintained during treatment with sulfonamides (8). A concentration of at least 8 to 15 mg per 100 ml of blood is desired, with 5 mg per 100 ml being the minimum effective concentration (8). When using sulfonamides such as sulfadimethoxine (8) or sulfaethoxypyridazine (14) in which the ratio of active drug to protein-bound drug in blood is low, even higher concentrations are probably desirable. In general, the greater the blood concentration, the better the therapeutic response (toxicity being the limiting factor) (8). Recommendations concerning dosages, treatment intervals, and withdrawal periods are summarized (Table 2).

Approximately 78 to 91% of *P. hemolytica* and *P. multocida* isolates, recovered from nasal secretions of feedlot cattle with clinical signs of respiratory disease, were sensitive to sulfonamides (Table 3). *C. pyogenes* was resistant to sulfonamides (3). In a series of acute feedlot pneumonia cases summarized by the author, 81.9% responded satisfactorily when treated with sulfamethazine U.S.P. boluses, as recommended (Table 2).

Sulfonamides are potentially toxic. Recommended dosages should not be exceeded. The treatment period should not exceed 5 to 7 days. Severely dehydrated animals should not be treated with sulfonamides. Water should be continuously available to treated animals. Acute toxicity, characterized by weakness, ataxia, and collapse may occur when sulfonamides are administered by rapid intravenous injection (8). The problem is avoided by proper technique. Renal obstruction by sulfonamide crystals is characterized by anorexia, depression, hematuria, anuria, frequent attempts to urinate, renal colic, sulfonamide crystalluria, albuminuria, and elevated blood urea nitrogen values (8). Agranulocytosis has occurred in connection with prolonged sulfonamide therapy (8). In reality, sulfonamide toxicity in cattle is a relatively rare occurrence. Most toxicity problems have involved sulfathiazole or sulfapyridine (8), which are no longer commonly used.

Figure 2. Minimum inhibitory concentrations of non-approved antibiotics for *Pasteurella hemolytica* and *P. multocida* isolates.

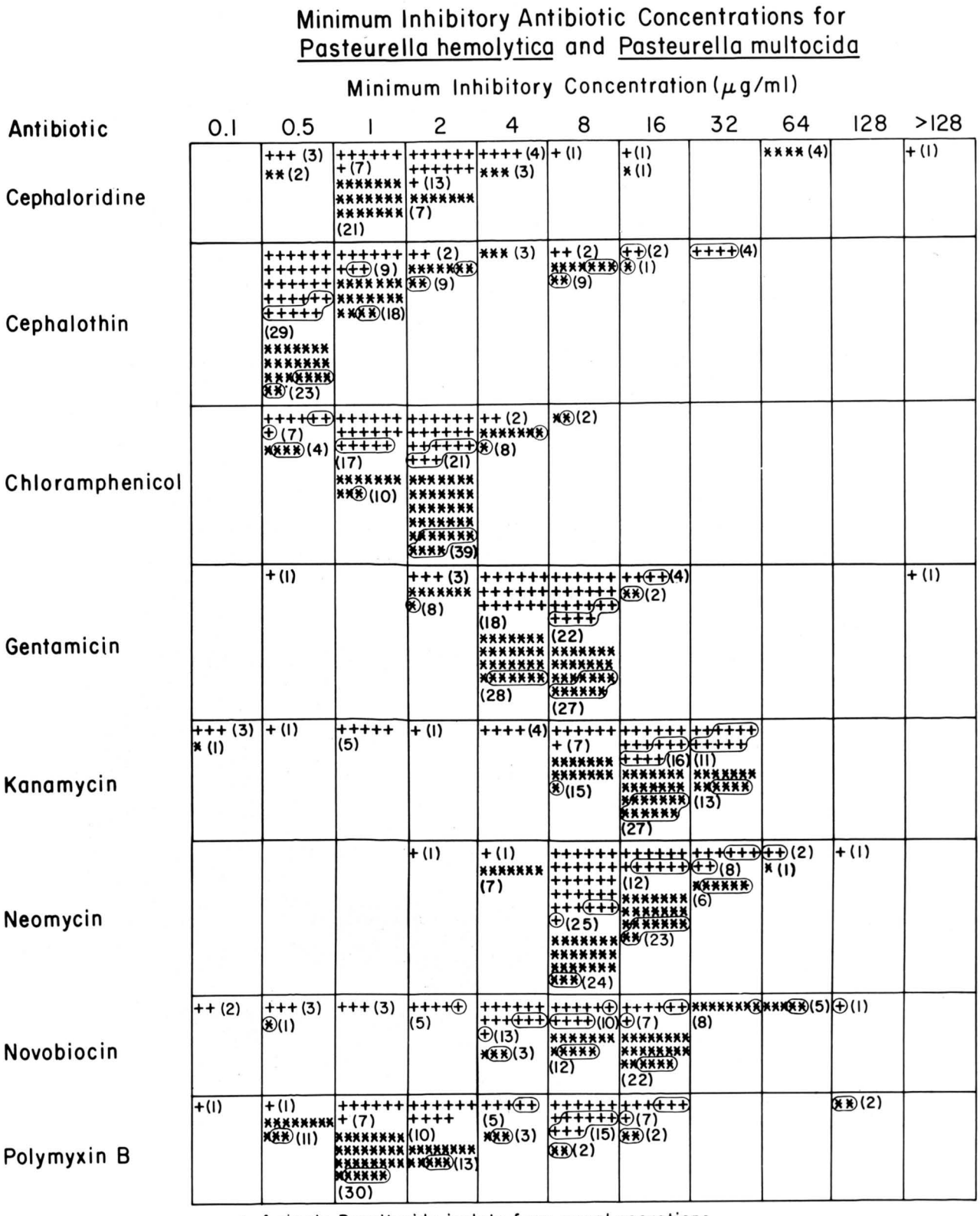


Figure 3. Minimum inhibitory concentrations of approved antibiotics for *Corynebacterium pyogenes* isolates.

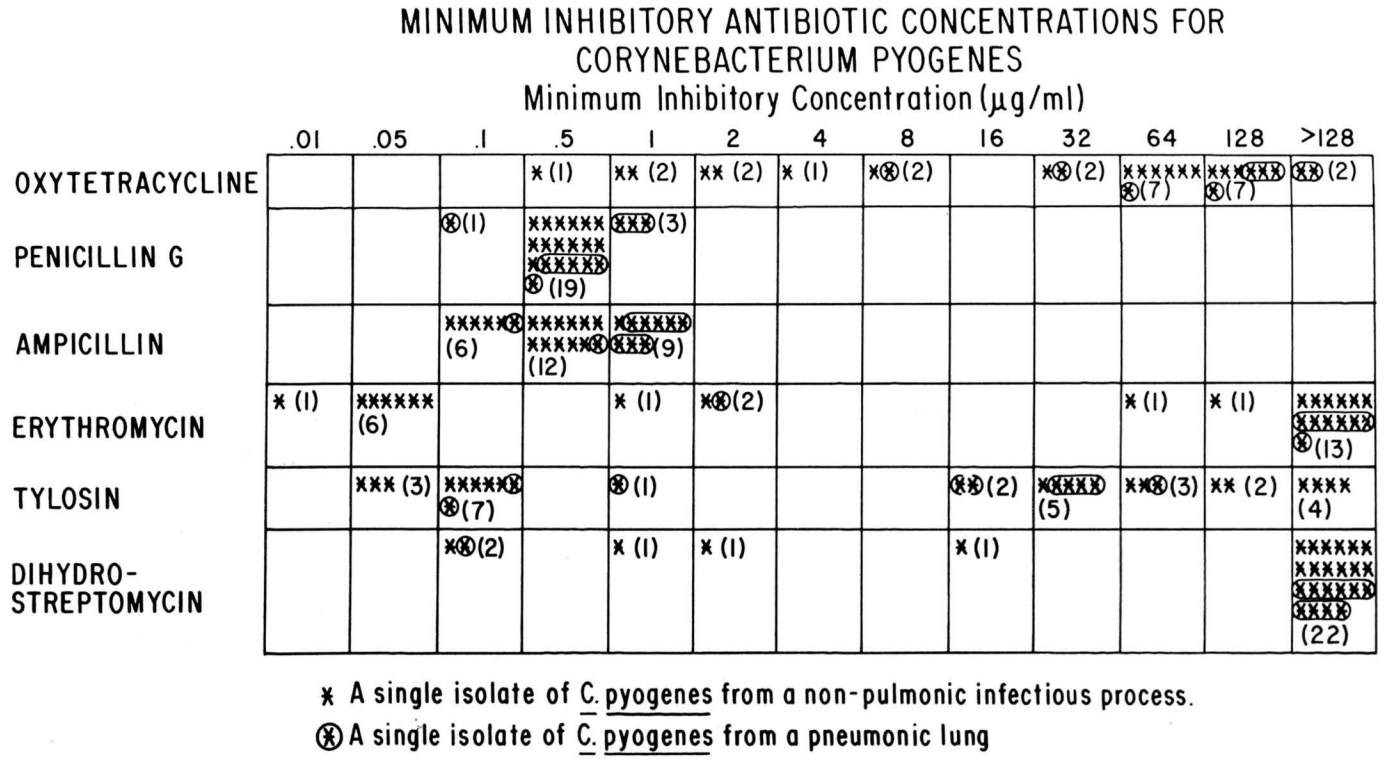
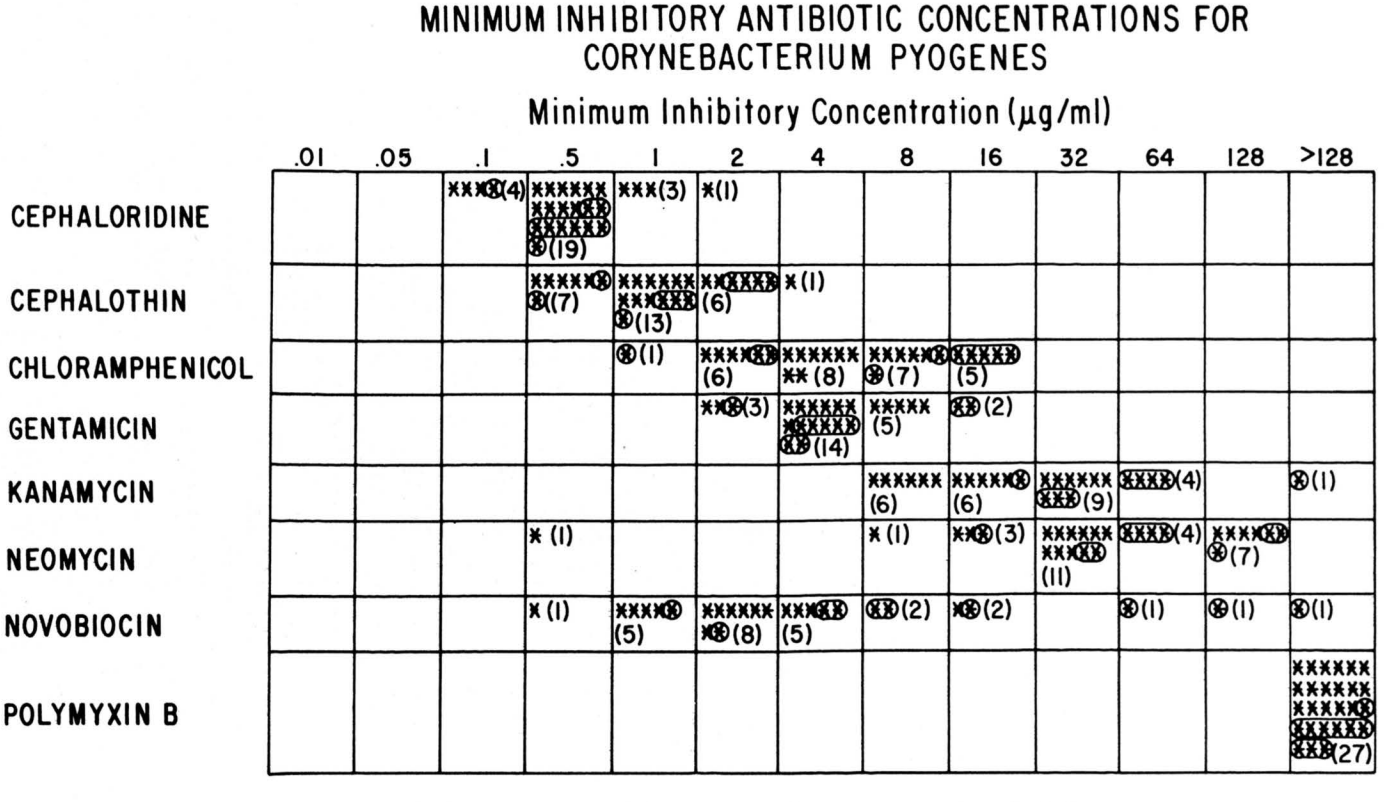


Figure 4. Minimum inhibitory concentrations of non-approved antibiotics for *Corynebacterium pyogenes* isolates.



Use of Antibiotics in Treatment of Bacterial Pneumonias in Feedlot Cattle

"Approved" drugs have been approved by the Food and Drug Administration (FDA) of the United States Department of Health, Education and Welfare for use in food-producing animals. Most, but not all, approved drugs are freely available to the livestock owner through "over-the-counter" sales, but must be used according to label instructions with regard to dose, route of administration, maximum duration of treatment, and withdrawal period before slaughter or marketing of milk from treated animals. Procaine penicillin G, aqueous suspension, benzathine penicillin G, ampicillin trihydrate, oxytetracycline hydrochloride, tetracycline hydrochloride, dihydrostreptomycin sulfate, erythromycin, and tylosin are approved by the FDA for parenteral administration in cattle.

"Prescription legend" drugs are available to livestock owners only from a licensed veterinarian, or by his prescription. Withdrawal recommendations have not been established for most prescription drugs. It is legal for a veterinarian to use and prescribe these drugs for use in food-producing animals which are directly under his or her care or supervision. However, in so doing, the veterinarian assumes legal responsibility for any drug residues which are subsequently detected in meat or milk from treated animals. A veterinarian is also legally responsible when a residue is found in an animal treated with an FDA-approved drug, if he has administered the drug without informing the owner or caretaker as to the proper withdrawal period, or when he has used or recommended the use of the drug in a dose or by a route of administration which is contrary to label recommendations. Persons found responsible for contamination of meat or milk with drug residues are subject, upon first conviction, to a fine of not more than $5,000 and not more than one year in prison. A second conviction carries a fine of not more than $10,000 and not more than five years in prison. Consequently, the use of non-approved drugs, or non-approved use of approved drugs in treatment of livestock diseases should be undertaken by the veterinarian only when he has considered all other alternatives and is satisfied that: (1) such use is truly in the best economic interest of his client, and that (2) a suitably long drug withdrawal period can be enforced. In the case of aminoglycoside antibiotics (neomycin, kanamycin, gentamicin), no period of less than four months should be considered safe. Other prescription antibiotics should not be used unless a withdrawal period of at least 100 days can be insured. Fortunately, the vast majority of feedlot bacterial pneumonia cases can be successfully managed with one or the other of three approved antimicrobics: a sulfonamide (especially sulfamethazine), procaine penicillin G, or a tetracycline (especially oxytetracycline). Non-approved antibiotics are frequently used by veterinarians primarily for the purpose of demonstrating to a client that a licensed veterinarian has a large armamentarium of new and potent drugs which are not available to the layman. In many cases, equal or better results can be obtained at lower cost using approved drugs. Of the non-approved antibiotics having potential value for treatment of feedlot bacterial pneumonia, only chloramphenicol and neomycin sulfate are sufficiently inexpensive to permit their use for treatment of commercial cattle (Table 4).

The only true medical indication for the the use of non-approved antibiotics in treatment of bacterial pneumonia in cattle is isolation of a pathogenic bacterium by bronchial wash (1) which is sensitive only to a non-approved antibiotic. Non-approved antibiotics with potential for successful management of bacterial pneumonia in cattle include chloramphenicol, neomycin sulfate, kanamycin sulfate (Kantrim®-Bristol), gentamicin sulfate (Gentocin®-Schering), polymyxin B sulfate, cephalothin (Keflin®-Lilly), cephaloridine (Loridine®-Elanco), and erythromycin lactobionate (Erythrocin Lactobionate I.V.®-Abbott).

Label recommendations concerning dosages, routes of administration, and treatment intervals have been determined empirically for all existing FDA-approved antibiotics. In no case does the label recommendation permit the most effective use with respect to the organisms most commonly associated with bacterial pneumonia in feedlot cattle. Unfortunately, the veterinarian is in the position of being forced to choose between a treatment regimen which is less than optimally effective in a substantial proportion of his cases and one which is effective in a greater number of cases, but for which reliable drug withdrawal information is lacking. The author has summarized suggested dosage, administration route and treatment interval regimens for oxytetracycline hydrochloride, procaine penicillin G, aqueous suspension, ampicillin trihydrate (Polyflex®-Bristol), erythromycin (Erythro-200®-Abbott), tylosin (Tylan-200®-Elanco), dihydrostreptomycin sulfate, chloramphenicol, neomycin sulfate, kanamycin sulfate (Kantrim®-Bristol), gentamicin sulfate (Gentocin®-Schering), polymyxin B sulfate, cephalothin (Keflin®-Lilly), cephaloridine (Loridine Injectable®-Elanco) and erythromycin lactobionate (Erythrocin Lactobionate I.V.®-Abbott) (Table 4). The suggested regimen for a given antibiotic is one which maintained blood serum concentrations which would be inhibitory for antibiotic-sensitive feedlot *P. hemolytica* and *P. multocida* isolates for at least two-thirds of the time period between treatments. Only oxytetracycline hydrochloride, procaine penicillin G, aqueous suspension, erythromycin (Erythro-200®-Abbott), and tylosin (Tylan 200®-Elanco) have actually been used by the author for treatment of clinical cases. Suggested withdrawal periods have been determined only for procaine penicillin G, erythromycin (Erythro-200®-Abbott), and tylosin (Tylan 200®-Elanco). In the case of the others, the

author can guarantee neither efficacy nor freedom from possible toxicity associated with prolonged therapy. Each suggested treatment regimen should be considered a starting point subject to future modifications based on field experiences.

Materials and Methods

The bacteria studies were isolated over a two-year period from resident cattle in a 13,000-head capacity feedlot located 25 miles north of Davis. *P. hemolytica* and *P. multocida* were recovered from the lungs of fatal pneumonia cases at necropsy and from nasal secretions of cattle with signs of respiratory disease prior to administration of antimicrobics. Most fatal cases of pneumonia had been treated with antimicrobics, but had failed to respond. *C. pyogenes* isolates were recovered from a variety of infectious processes, including pneumonic lungs. Nasal secretions were obtained by inserting a sterile swab deep into the ventral nasal meatus. Bacteria were isolated, identified, recultured in brain-heart broth (containing 10% horse serum when growing *C.*

Table 4. Summary of Antimicrobic Usage Recommendations

Antibiotic	Proprietary name	Manufacturer	Packaging	Price	Bacterial spectrum	Treatment interval	Dosage/ treatment	Route of administration	Cost for 24 hrs. for a 500-lb. calf
Oxytetracycline†	Terramycin Injectable	Pfizer	500 ml. vial, 50 mg./ml.	$3.20	Broad Spectrum	24 hrs.	5 mg./lb. b.w.	s.c.	$0.32
Sulfamethazine*	Sulmet Oblets	Cyanamid	Pkg. of 50 15 G. oblets	$8.00	Broad Spectrum	24 hrs.	1 gr./lb. b.w. (maint. dose)	Oral	$0.36
	Sulfamethazine Na, 24% sol.	Cyanamid	500 ml. vial	$3.00		24 hrs.	1 gr./lb. b.w. (maint. dose)	i.v.	$0.84
Procaine Penicillin G†	Crysticillin	Squibb	100 ml. vial, 300,000 units/ml	$1.77	Mainly Gram +	24 hrs.	30,000 u./ lb. b.w.	i.m., s.c.	$0.89
Erythromycin†	Gallimycin Injectable	Abbott	200 ml. vial, 200 mg./ml.	$5.70	Mainly Gram +	24 hrs.	20 mg./lb. b.w.	i.m.	$1.43
Dihydrostreptomycin**,†	Dihydrostreptomycin	Burns	100 ml. vial, 500 mg./ml.	$5.60	Broad Spectrum	12 hrs.	25 mg./lb. b.w.	i.m.	$2.80
Tylosin**	Tylan 200	Elanco	250 ml. vial, 200 mg./ml.	$15.75	Mainly Gram +	24 hrs.	20 mg./lb. b.w.	i.m.	$3.15
Chloramphenicol†	P/M Chloramphenicol, Oral Solution	Pittman-Moore	200 ml. vial, 100 mg./ml.	$13.00	Broad Spectrum	12 hrs.	7.5 mg./lb.	s.c.	$4.88
						24 hrs.	20 mg./lb.	s.c.	$6.50
	Chloromycetin Na Succinate	Parke Davis	1 Gm. vial	$ .90		12 hrs.	15 mg./lb. b.w.	s.c., i.m.	$13.50
Neomycin†, (a)	Biosol Liquid	Upjohn	1 pt., 140 mg./ml.	$7.35	Broad Spectrum	8 hrs.	40 mg./lb. b.w.	i.m., s.c.	$6.56
Ampicillin†	Polyflex	Bristol	10 gm. vial	$8.40	Broad Spectrum	12 hrs.	10 mg./lb. b.w.	s.c.	$8.40
Polymyxin B**,†,(b)	Polymyxin B	Pfizer	500,000 u. vials	$1.55	Broad Spectrum	12 hrs.	15,000 u./ lb. b.w.	i.m., s.c.	$46.50
Cephaloridine†	Loridine	Elanco	20 ml. vial, 100 mg./ml.	$7.95	Broad Spectrum	12 hrs.	25 mg./lb. b.w.	s.c.	$99.40
Kanamycin†	Kantrim	Bristol	50 ml. vial, 200 mg./ml.	$29.00	Broad Spectrum	8 hrs.	25 mg./lb. b.w.	s.c.	$108.75
Cephalothin†	Keflin	Lilly	50 ml. vial, 80 mg./ml.	$11.02	Broad Spectrum	6 hrs.	25 mg./lb. b.w.	i.m., s.c.	$137.75
Erythromycin lactobionate†	Erythrocin lactobionate I.V.	Abbott	1 gm. vials	$4.22	Mainly Gram +	12 hrs.	50 mg./lb. b.w.	s.c.	$211.00
Gentamicin†	Gentocin	Schering	50 ml. vials, 50 mg./ml.	$56.00	Broad Spectrum	12 hrs.	10 mg./lb. b.w.	i.m., s.c.	$224.00

sc = subcutaneous. iv = intravenous. im = intramuscular. *Approved by the FDA for use in beef cattle as indicated in the table. **Not recommended for treating *Pasteurella* infections. †Dosage, treatment interval, and route of administration adjusted so as to assure an antibiotic concentration in the serum which is equal to or greater than the minimum inhibitory concentration for sensitive *P. hemolytica* and *P. multocida* isolates for no less than 67% of the period between treatments. (a) Approved only for oral and intramammary use. (b) Approved only for intramammary use.

pyogenes), and stored at -60°C. Antimicrobic sensitivity testing was performed using a modification of the method of Kirby and Bauer (15). Minimum inhibitory concentrations (MIC) were determined using an agar plate dilution technique (16).

Serum antibiotic concentrations were determined in normal Holstein steers and bulls following administration by intramuscular, subcutaneous or intravenous injection. Calves were purchased weighing 300 to 400 lbs. and utilized until they were 700 to 800 lbs. in weight, when they were replaced. The calculated dose of antibiotic was injected into the right-dorsal cervical musculature, the right cervical subcutaneous tissues, or the right jugular vein. A maximum volume of 10 ml was injected into any single intramuscular or subcutaneous site. Serial blood samples were obtained from the left jugular vein using disposable needles and evacuated glass tubes. Blood samples were usually obtained only at 1, 2, 4, 8, 12, 18 and 24 hours post-administration. Samples were allowed to clot at room temperature for approximately 1 hour, then centrifuged, and the serum removed and stored at -60°C until assay could be performed.

Two antibiotic assay methods were utilized. When high serum concentrations were anticipated, the large plate technique was utilized (17). When low concentrations were anticipated, the penny cylinder technique was used (18). Good correlation between the two methods was observed. All samples were analyzed in triplicate and the results averaged. Assay organisms were obtained from Difco Laboratories *(Bacillus subtilis* and *B. cereus)* and the American Culture Collection *(Sarcina lutea* and *Brucella bronchiseptica)*. Statistical significance of the data was determined with student's t test.

Table 5

Serum Concentrations of Oxytetracycline in Cattle Resulting From Continuous Ad Libitum Administration in Medicated* Feeds

Dosage (mg./lb. b.w.)	Basal Diet: Alfalfa pellets** Serum oxytetracycline concentration (μg./ml.)+	Basal Diet: Oat hay (ground)** Serum oxytetracycline concentration (μg./ml.)+
1	NM	NM
5	NM	0.15
15	0.21	0.40
25	0.37	0.45
40 (a)	1.20	--

*Oxytetracycline provided as Terramycin Crumbles (2 Gm. oxytetracycline/lb.), Agricultural Div., Pfizer, Inc., New York, N.Y. 10017.

**Alfalfa pellets and oat hay contained 1.38% and 0.43% calcium, respectively.

+Mean values from two steers sampled at 48, 60, 72 and 84 hours after initiation of feed medication.

NM=concentration not measurable.

(a) Terramycin crumbles fed *ad libitum* as total ration (calcium content was 1.27%).

Tetracyclines

From 63 to 97% of *P. hemolytica* and *P. multocida* isolates recovered from nasal secretions of sick cattle and approximately 20% of *C. pyogenes* isolates were sensitive to tetracyclines (Table 3 and Figure 3). Chlortetracycline and oxytetracycline are both available in forms suitable for feed or water medication, but absorption from the digestive tract of cattle is limited (19). Doses of 40 mg. per lb. of body weight per day were required for inhibitory (1 to 2 μgm/ml) serum concentrations (Tables 5 and 6). Adverse effects on ruminal flora preclude the use of large doses of tetracyclines by the oral route for management of acute bacterial infections in cattle.

Table 6

Serum Concentrations of Chlortetracycline in Cattle Re ulting From Continuous Ad Libitum Administration in Medicated Feeds*

Dosage (mg./lb. b.w.)	Basal Diet: Alfalfa pellets** Serum oxytetracycline concentration (μg./ml.)+	Basal Diet: Oat hay (ground)** Serum oxytetracycline concentration (μg./ml.)+
1	NM	0.02
5	0.21	0.25
15	0.45	0.26
25	0.50	0.63
40 (a)	1.70	--

*Chlortetracycline provided as CTC-2 (2 gm. chlortetracycline/lb.), Diamond Shamrock Chemical Co., Newark, N.J. 07102.

**Alfalfa pellets and oat hay contained 1.38% and 0.43% calcium, respectively.

+Mean values from two steers sampled at 48, 60, 72 and 84 hours after initiation of feed medication.

NM=concentration not measurable.

(a) CTC-2 fed *ad libitum* as total ration (calcium content was 1.32%).

Tetracycline hydrochloride is available as a soluble powder and may be diluted in saline and administered intravenously for treatment of pneumonia.

Of the three major tetracyclines, only oxytetracycline hydrochloride is suitable for intramuscular or subcutaneous injection. Consequently, it is the one most frequently utilized for systemic therapy. Seven proprietary formulations are currently marketed. All contain a vehicle, such as propylene glycol or povidone, which retards absorption from local injection sites, prolonging inhibitory serum concentrations and permitting once-daily administration. A maximum dose of 5 mg per pound of body weight is approved by the FDA. Inhibitory serum concentrations are generally obtained with this dosage (Table 7 and Figure 5). Three products are approved only for intramuscular administration, three are approved for intramuscular or intravenous administration and one is approved only for intravenous administration. Withdrawal periods of 15 to 22 days are required

before slaughter, depending on the formulation. Only one (Terramycin Injectable Solution®-Pfizer) is approved for use in lactating dairy cattle. Milk must not be marketed for 96 hours and eight milkings after the last treatment.

Oxytetracycline hydrochloride (Terramycin Injectable Solution. Agricultural Div., Pfizer Inc., New York, N.Y. 10017) was administered to calves by intramuscular, subcutaneous or intravenous injection in doses of 2, 5 or 25 mg per pound of body weight (Table 7 and Figure 5). With intravenous injection, serum oxytetracycline (OTC) concentrations significantly exceeded those obtained with intramuscular and subcutaneous injection for two hours and four hours post-administration, respectively. Serum OTC concentrations were significantly greater with intramuscular injection than with subcutaneous injection for four hours post-administration. Between the eighth hour and the 24th hour post-administration, serum OTC concentrations were not significantly influenced by route of administration (Table 7 and Figure 5).

Subcutaneous administration, though not an FDA-approved procedure, is considered by the author to be the preferred method. Inhibitory serum OTC concentrations (1 to 2 μgm/ml) were obtained within one to four hours after subcutaneous injection with a dose of 5 mg per pound of body weight (Table 7 and Figure 5). With some proprietory preparations, a substantial concentration advantage over intravenous and intramuscular administration was obtained during the last 8 to 16 hours of a 24-hour treatment interval (3). The frequency of post-injection abscessation was thought to be less with subcutaneous administration than with intramuscular administration. When abscessation did occur, less damage resulted to edible tissues. OTC is usually injected into the dorsal midcervical muscles or the cervical subcutaneous tissues. In order to minimize local tissue irritation, the calculated dose is administered in multiple injection sites, using a maximum volume of 10 ml per site. Serum OTC concentrations resulting from a given dose are usually higher in sick cattle than in normal cattle (19). In a series of acute feedlot pneumonia cases summarized by the author, 70.8% responded satisfactorily when treated with OTC injected subcutaneously in a dose of 5 mg per pound of body weight.

Penicillin G

From 63 to 78% of *P. hemolytica* and *P. multocida*

Table 7. Serum Oxytetracycline Concentrations After Administration of Terramycin Injectable Solution* to Normal Calves

Dosage (mg./lb. b.w.)	Route of administration	No. of calves		Serum concentrations (μgm./ml.) at postadministration hours 0.08	0.5	1	2	4	8	12	18	24
2	im	2	M	NS	1.7 (e) ±0.3	2.15 (f) ±0.6	2.25 ±0.8	2.05 ±0.6	1.65 ±0.8	1.37 ±0.6	SNM	NM
			R	NS	1.5–1.9	1.7–2.6	1.7–2.8	1.6–2.5	1.1–2.2	0.94–1.8	NM–0.9	NM
	iv	2	M	17.8 ±5.3	5.8 (e) ±0.6	5.1 (f) ±0.1	3.7 ±0.0	2.6 ±0.2	1.5 ±0.1	1.0 ±0.5	NM	NM
			R	14.0–21.5	5.4–6.2	5.0–5.2	3.7	2.4–2.7	1.4–1.5	0.6–1.3	NM	NM
5	im	6	M	NS	NS	3.4 (a,g) ±1.0	3.8 (b,h) ±0.7	4.0 (c,d) ±1.0	3.3 ±0.7	2.4 ±0.7	1.7 ±0.5	0.8 ±0.3
			R	NS	NS	2.5–5.0	2.7–4.9	3.0–5.2	2.7–4.6	2.0–3.8	1.2–2.6	0.6–1.3
	sc	6	M	NS	NS	0.8 (a,i) ±0.4	1.2 (b,j) ±0.4	2.0 (c,k) ±0.7	2.5 (d) ±1.0	1.7 ±0.4	1.6 ±0.3	1.0 ±0.2
			R	NS	NS	0.5–1.3	0.5–1.7	1.0–2.8	1.6–4.2	1.4–2.4	1.2–2.0	0.8–1.4
	iv	5	M	74.0 ±16.9	19.7 ±4.4	11.9 (g,i) ±2.4	6.8 (h,j) ±1.4	4.5 (k) ±0.8	2.8 ±0.6	2.2 ±0.7	SNS	0.7 ±0.5
			R	58.0–94.0	14.5–26.0	9.0–15.0	5.9–9.0	3.7–5.6	1.7–3.2	1.3–3.0	0.8–1.5	0.3–1.4
25	iv	2	M	400.0 ±113.1	130.0 ±0.0	87.5 ±10.6	62.0 ±11.3	35.5 ±3.5	20.8 ±1.8	13.0 ±0.0	6.2 ±1.4	3.1 ±0.1
			R	320.0–480.0	130.0	80.0–95.0	54.0–70.0	33.0–38.0	19.5–22.0	13.0	5.2–7.2	3.0–3.1

*Oxytetracycline hydrochloride. Agricultural Div., Pfizer, Inc., New York, N.Y. 10017. im = intramuscular. iv = intravenous. sc = subcutaneous. M = mean ± standard deviation. R = range. NS = no samples. SNS = some calves not sampled. NM = not measurable. SNM = some samples not measurable. Values having the same superscript are significantly different (d,f, P = <0.05; e, P = <0.02; c,h, P = <0.005; a,b,g,i,j,k, P = <0.001).

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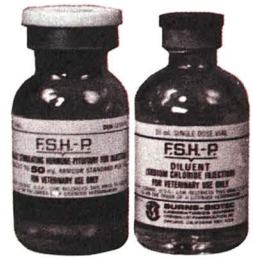

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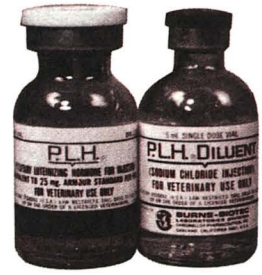

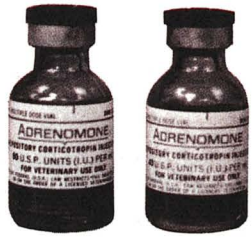

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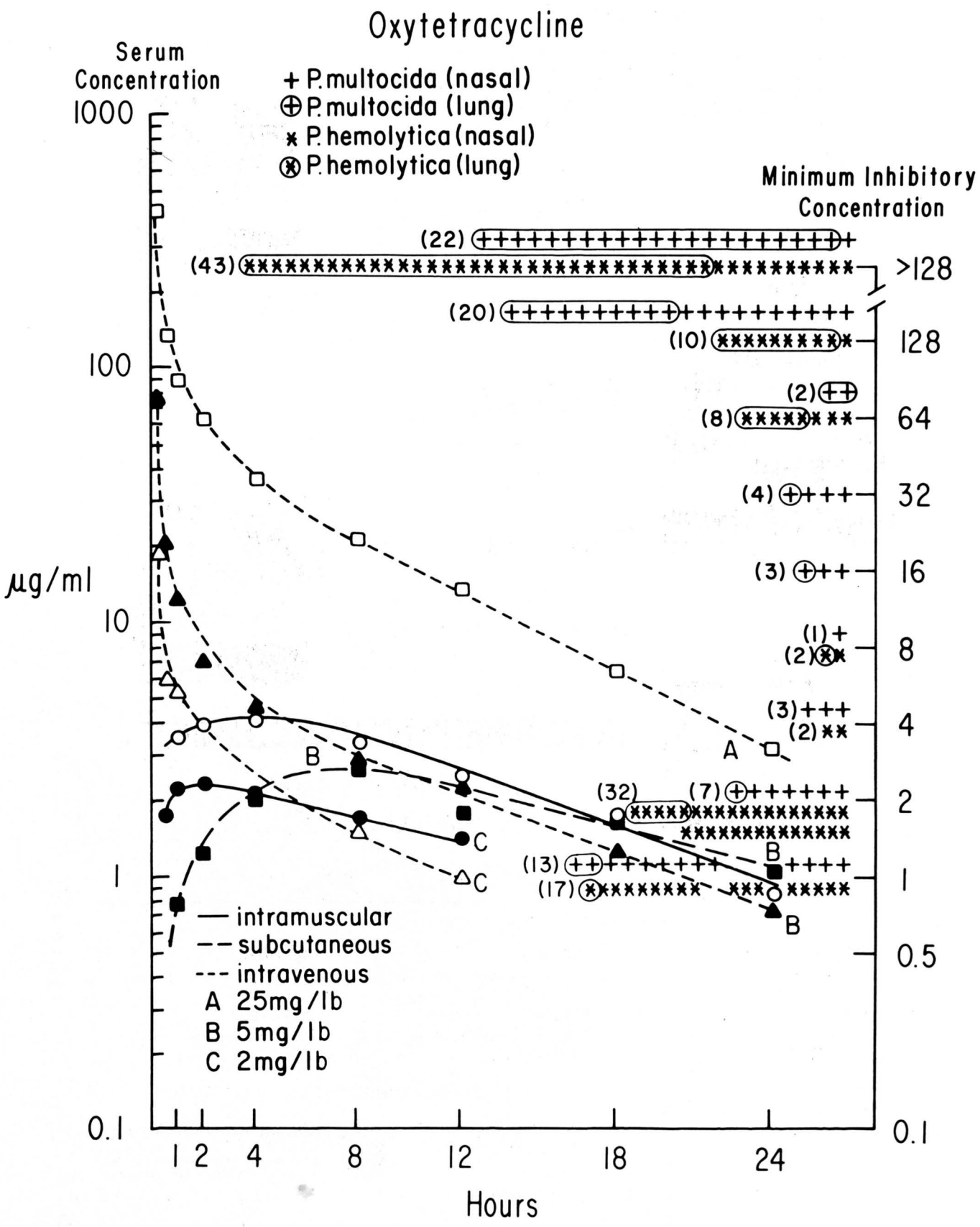
Figure 5. Serum oxytetracycline concentrations, after administration of Terramycin Injectable Solution® to normal calves, in relation to minimum inhibitory concentrations for *Pasteurella hemolytica* and *P. multocida* isolates.



isolates recovered from nasal secretions of sick cattle were sensitive to penicillin G (Table 3). All *C. pyogenes* isolates were sensitive to penicillin G (Figure 3).

Because of rapid absorption from injection sites and rapid urinary excretion, multiple daily administration is required when treating with sodium or potassium penicillin G (11).

Serum concentrations of penicillin G were inhibitory for penicillin G-sensitive *P. hemolytica* and *P. multocida* isolates (0.5 to 2 μgm/ml) for only four hours following administration of benzathine penicillin G (Bicillin Fortified [Benzathine Penicillin G and Procaine Penicillin G in Aqueous Suspension]. Wyeth Laboratories, Inc., Philadelphia, Pa. 19101) in the FDA-approved regimen of 2 ml per 150 pounds of body weight, injected subcutaneously. Even at five times the approved dose, serum penicillin G concentrations were inhibitory for only 12 hours following injection (Table 8 and Figure 6).

Table 8. Serum Penicillin G Concentrations After Administration of Bicillin Fortified* to Normal Calves

Dosage	Route of administration	No. of calves		Serum concentrations (μgm./ml.) at postadministration hours							
				0.5	1	2	4	8	12	18	24
2 ml./ 150 lb. b.w.	sc	2	M	0.51 ±0.27	0.56 ±0.11	0.55 ±0.06	0.54 ±0.18	0.30 ±0.03	0.17 ±0.01	0.14 ±0.01	SNM
			R	0.32–0.70	0.48–0.63	0.51–0.59	0.41–0.67	0.28–0.32	0.16–0.18	0.13–0.14	NM–0.13
10 ml./ 150 lb. b.w.	sc	2	M	1.75 ±0.92	2.7 ±1.7	2.8 ±0.71	3.2 ±0.57	1.6 ±0.42	0.69 ±0.13	0.41 ±0.0	0.33 ±0.04
			R	1.1–2.4	1.5–3.9	2.3–3.3	2.8–3.6	1.3–1.9	0.6–0.78	0.41	0.30–0.36

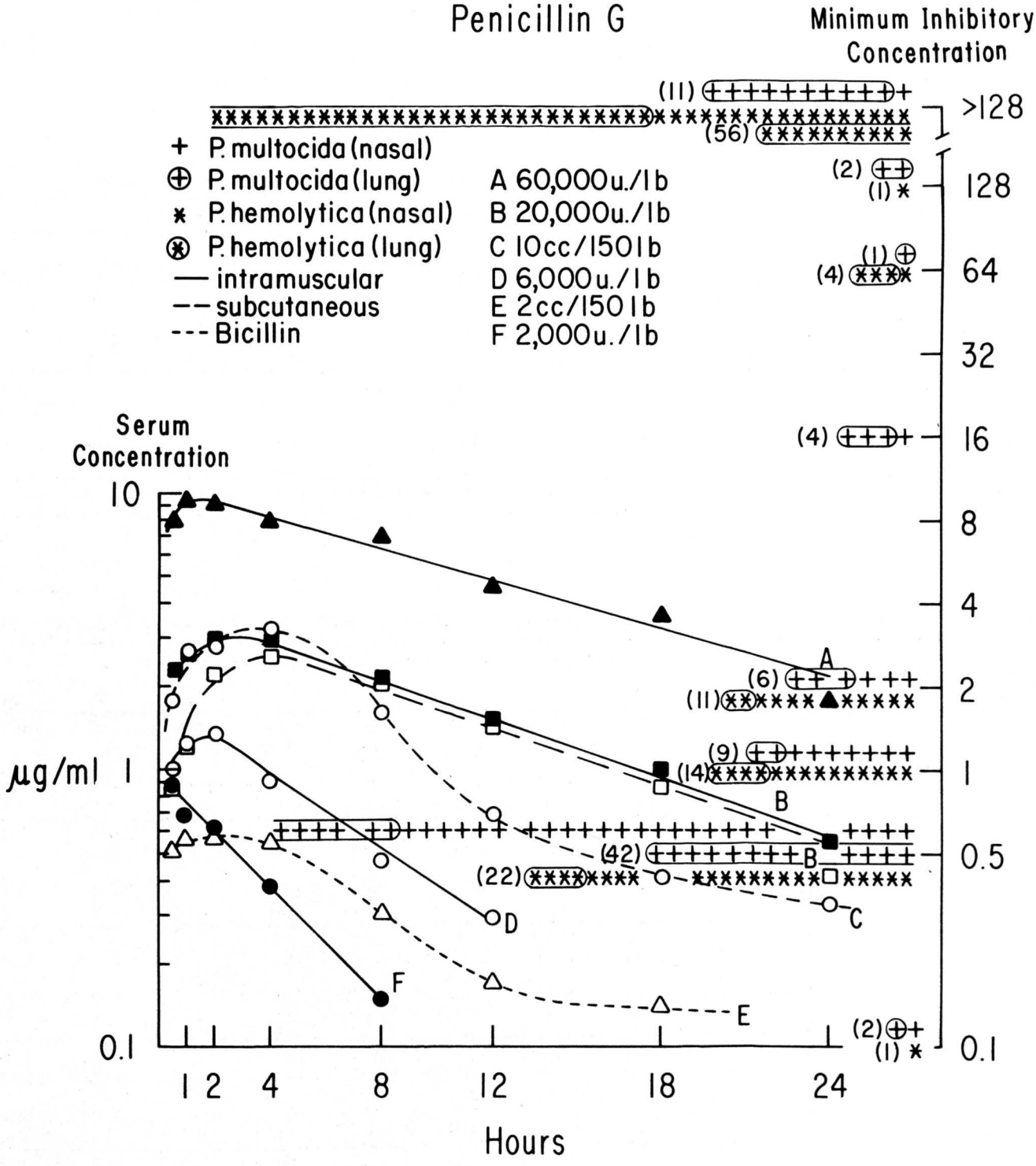
*Sterile benzathine penicillin G and procaine penicillin G in aqueous suspension. Wyeth Laboratories, Inc., Philadelphia, Pa. 19101. M = mean ± standard deviation. R = range. NM = not measurable. SNM = some samples not measurable. sc = subcutaneous.

Table 9. Serum Penicillin G Concentrations After Administration of Procaine Penicillin G, Aqueous Suspension, to Normal Calves

Dosage (units/ lb. b.w.)	Route of administration	No. of calves		Serum concentrations (μgm./ml.) at postadministration hours							
				0.5	1	2	4	8	12	18	24
2,000	im	2	M	0.87 ±0.33	0.68 ±0.11	0.61 ±0.13	0.38 ±0.12	0.15 ±0.02	SMN	NM	NM
			R	0.64–1.1	0.6–0.76	0.52–0.7	0.29–0.46	0.13–0.16	NM–0.09	NM	NM
6,000	im	2	M	0.98 ±0.17	1.24 ±0.37	1.35 ±0.07	0.90 ±0.08	0.47 ±0.1	0.29 ±0.03	0.13 ±0.06	SNM
			R	0.86–1.1	0.98–1.5	1.4–1.3	0.96–0.84	0.4–0.54	0.31–0.27	0.05–0.15	NM–0.08
20,000	im	3	M	2.3 (a) ±0.46	2.7 (b) ±0.70	3.0 ±0.67	2.9 ±0.57	2.1 ±0.35	1.5 ±0.15	1.0 ±0.41	0.65 ±0.22
			R	1.9–2.8	2.0–3.4	2.4–3.7	2.4–3.5	1.9–2.5	1.3–1.6	0.58–1.4	0.44–0.88
	sc	5	M	0.84 (a) ±0.29	1.2 (b) ±0.45	2.4 ±0.85	2.6 ±1.32	2.0 ±0.6	1.4 ±0.67	0.89 ±0.38	0.42 ±0.16
			R	0.56–1.3	0.72–1.7	1.6–3.8	1.6–4.9	1.7–1.9	0.84–2.5	0.46–1.3	0.28–0.66
60,000	im	2	M	7.9 ±1.27	9.25 ±1.06	9.25 ±1.77	7.9 ±0.99	6.8 ±0.0	4.6 ±0.14	3.6 ±0.14	1.78 ±1.03
			R	7.0–8.8	8.5–10.0	8.0–10.5	7.2–8.6	6.8	4.5–4.7	3.5–3.7	1.05–2.5

M = mean ± standard deviation. R = range. NM = not measurable. SNM = some samples not measurable. im = intramuscular. sc = subcutaneous. Values having the same superscript are significantly different (a, P = <0.005; b, P = <0.01).

Figure 6. Serum penicillin G concentrations, after administration of procaine penicillin G, aqueous suspension, and Bicillin Fortified® to normal calves, in relation to minimum inhibitory concentrations for *Pasteurella hemolytica* and *P. multocida* isolates.



Procaine penicillin G, aqueous suspension, is the form of penicillin G best suited for treatment of bacterial pneumonia in cattle. Serum penicillin G concentrations were determined in calves following administration of procaine penicillin G, aqueous suspension, by intramuscular or subcutaneous injection in doses of 2,000, 6,000, 20,000 or 60,000 units per pound of body weight (Table 9 and Figure 6). With the FDA-approved regimen of 2,000 units per pound injected intramuscularly, serum penicillin G concentrations were inhibitory for penicillin-G sensitive *P. hemolytica* and *P. multocida* isolates for only two hours after administration (Table 9 and Figure 6). This regimen was probably borrowed from human medicine where it is utilized with eight-hour treatment intervals in therapy of pneumococcal pneumonia (20). The minimum inhibitory concentration of penicillin G for penicillin G-sensitive *P. hemolytica* and *P. multocida* isolates was 0.5 to 2 μgm/ml (Figure 1) in contrast to 0.02 μgm/ml (20) for *Streptococcus pneumoniae*. Obviously, the same dosage recommendation cannot be appropriate for both kinds of infections. A minimum dosage of 20,000 to 30,000 units of procaine penicillin G, aqueous suspension, is recommended by the author for once-daily treatment of bacterial pneumonia in cattle (Table 4). Serum concentrations of penicillin G were obtained which were inhibitory for all penicillin G-sensitive *P. hemolytica* and *P. multocida* isolates for eight hours following treatment, and which were still inhibitory for 60% of sensitive isolates after 24 hours (Table 9 and Figure 6). A dose of 60,000 units per pound of body weight resulted in serum concentrations which were inhibitory for all penicillin G-sensitive isolates for 24 hours (Table 9 and Figure 6). In a series of acute feedlot pneumonia cases summarized by the author, 78.6% responded satisfactorily when treated with procaine penicillin G using a dose of 30,000 units per pound of body weight. Of those not responding, 33.3% responded when the dosage was increased to 60,000 units per pound of body weight. Serum concentrations of procaine penicillin G were not significantly affected by route of administration after the second hour post-treatment (Table 9 and Figure 6).

A withdrawal period of five days before slaughter or three days and six milkings before marketing of milk from treated animals is required with the FDA-approved treatment regimen of 2,000 units per pound of body weight, injected intramuscularly. Following subcutaneous injection of 2,000 units per pound of body weight, penicillin G was detected in urine of treated cattle for three days (Figure 7). When procaine penicillin G, aqueous suspension, was injected subcutaneously in a dose of 60,000 units per pound of body weight, penicillin G was detected in urine of treated cattle for up to 13 days (Figure 7). A tentative withdrawal period of 20 days was utilized by the author when treating with dosages of 30,000 to 60,000 units per pound of body weight. In a 3-1/2-year period, no residue violations occurred at slaughter in approximately 50,000 fat cattle, of which perhaps 3,000 to 5,000 were treated with procaine penicillin G. The tentative withdrawal period (TWP) was determined according to the following rationale:

$TWP = UP_2 + (AWP\text{-}UP_1)$, where TWP is the tentative withdrawal period for a dose of 60,000 units per pound of body weight, UP_2 is the number of days that penicillin G can be detected in urine following administration of that dose, AWP is the FDA-approved withdrawal period (for 2,000 units per pound of body weight), and UP_1 is the number of days that penicillin G can be detected in the urine following administration of that dose. The value of TWP was calculated to be 15 days. A withdrawal period of 20 days was actually utilized in order to provide a margin of safety.

Ampicillin

Sensitivity of *P. hemolytica* and *P. multocida* isolates to ampicillin closely paralleled sensitivity to penicillin G. Of 390 penicillin G-resistant isolates, 82.8% were also resistant to ampicillin (2). As with penicillin G, all *C. pyogenes* isolates were ampicillin-sensitive (Figure 3). Ampicillin is marketed as the trihydrate for use in cattle. The FDA-approved treatment regimen is 5 mg per pound of body weight, injected intramuscularly, at 24-hour intervals. The required withdrawal period is six days before slaughter or two days and four milkings before milk is marketed from lactating cattle. Serum ampicillin concentrations were determined in calves following administration of ampicillin trihydrate (Polyflex [Ampicillin Trihydrate for Suspension for Aqueous Injection]. Bristol Laboratories, Div. of Bristol-Myers Co., Syracuse, N.Y. 13201) by intramuscular or subcutaneous injection in doses of 3 or 10 mg per pound of body weight (Table 10 and Figure 8). Serum ampicillin concentrations were better maintained with subcutaneous administration than with intramuscular administration. Values were significantly greater with subcutaneous administration at the 8th and 12th hours post-treatment (Table 10 and Figure 8). The suggested treatment regimen (Table 4) of 10 mg per pound of body weight, injected subcutaneously at 12-hour intervals, provided serum ampicillin concentrations which were continuously inhibitory for 96% of ampicillin-sensitive *P. hemolytica* and *P. multocida* isolates (Table 10 and Figure 8).

Erythromycin

Erythromycin is marketed for use in cattle as Erythro-200®. Serum erythromycin concentrations were determined in calves following administration of Erythro-200 (Agricultural and Veterinary Products Div., Abbot Laboratories, North Chicago, Ill. 60064) by intravenous, intramuscular or subcutaneous injection in doses of 2, 5, 10, 15 or 25 mg per pound of body weight (Table 11 and Figure 9). With the FDA-approved treatment regimen of 2 mg per pound of body weight injected intramuscularly at 24-hour in-

Table 10. Serum Ampicillin Concentrations After Administration of Polyflex* to Normal Calves

Dosage (mg./lb. b.w.)	Route of administration	No. of calves		Serum concentrations (μgm./ml.) at postadministration hours						
				1	2	4	8	12	18	24
3	im	6	M	1.13 ±0.59	1.14 ±0.60	0.61 ±0.16	0.17 ±0.03	SNM	SNM	SNM
			R	0.38–2.1	0.39–2.2	0.54–0.8	0.14–0.21	NM–0.16	NM–0.096	NM–0.032
10	im	6	M	4.2 (a) ±1.08	4.3 ±1.07	3.9 ±0.76	0.59 (b) ±0.1	0.36 (c) ±0.07	0.19 ±0.05	0.09 ±0.05
			R	3.1–5.6	2.9–5.8	2.9–4.6	0.49–0.78	0.28–0.45	0.14–0.27	0.019–0.17
	sc	6	M	2.8 (a) ±0.78	3.6 ±1.39	3.2 ±0.92	1.9 (b) ±0.35	0.87 (c) ±0.36	0.3 ±0.21	0.11 ±0.06
			R	2.0–4.2	2.2–5.6	2.1–4.6	1.3–2.3	0.64–1.6	0.12–0.68	0.018–0.19

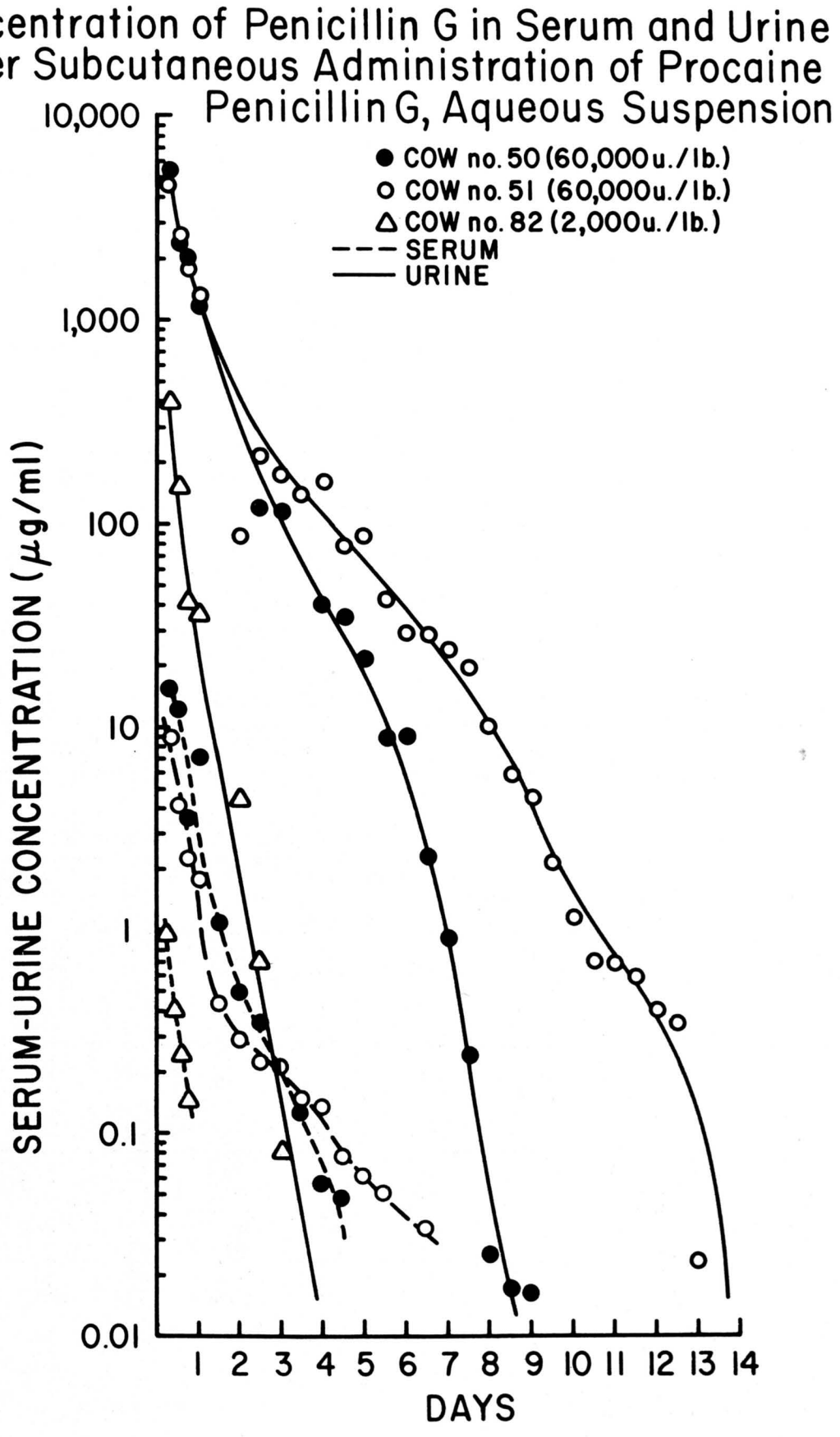
*Ampicillin trihydrate. Veterinary Products, Bristol Laboratories, Div. of Bristol Myers Co., Syracuse, N.Y. 13201. im = intramuscular. sc = subcutaneous. M = mean ± standard deviation. R = range. NM = not measurable. SNM = some samples not measurable. Values having the same superscript are significantly different (a, P = <0.05; c, P = <0.01; b, P = <0.001).

Table 11. Serum Erythromycin Concentrations After Administration of Erythro-200* to Normal Calves

Dosage (mg./lb. b.w.)	Route of administration	No. of calves		Serum concentrations (μgm./ml.) at postadministration hours								
				0.08	0.5	1	2	4	8	12	18	24
2	im	4	M	NS	0.36 ±0.16	SNS	0.47 ±0.13	0.40 ±0.13	0.35 ±0.14	0.21 ±0.03	0.25 ±0.12	SNS
			R	NS	0.23–0.59	0.26–0.37	0.23–0.59	0.25–0.54	0.18–0.24	0.18–0.24	0.12–0.36	0.15–0.35
5	im	4	M	SNS	0.56 ±0.26	0.67 ±0.34	0.99 ±0.34	0.97 ±0.34	1.16 ±0.99	0.81 ±0.69	0.34 ±0.14	SNM
			R	0.19–1.4	0.28–0.9	0.26–1.1	0.4–1.8	0.58–1.3	0.45–2.6	0.31–1.8	0.22–0.52	NM–0.26
10	iv	2	M	29.25 ±2.47	13.25 ±1.77	9.4 ±0.85	5.55 ±0.78	3.25 ±0.07	1.1 ±0.0	0.37 ±0.06	0.16 ±0.03	NM
			R	27.5–31.0	12.0–14.5	8.8–10.0	5.0–6.1	3.2–3.3	1.1	0.32–0.41	0.14–0.18	NM
15	im	2	M	NS	2.0 (a) ±0.0	NS	3.0 (b,d) ±0.0	2.8 (c) ±0.28	2.05 ±0.07	1.58 ±0.39	0.91 ±0.07	0.43 ±0.0
			R	NS	2.0	NS	3.0	2.6–3.0	2.0–2.1	1.3–1.85	0.9–0.91	0.43
	sc	2	M	NS	0.29 (a) ±0.07	NS	0.66 (b) ±0.17	1.2 (c) ±0.14	1.5 (d) ±0.28	1.45 ±0.21	1.15 ±0.21	0.77 ±0.13
			R	NS	0.24–0.34	NS	0.54–0.78	1.1–1.3	1.3–1.7	1.3–1.6	1.0–1.3	0.67–0.86
25	im	2	M	NS	2.1 ±0.14	2.6 ±0.57	3.5 ±0.57	4.3 ±0.85	3.8 ±0.0	3.7 ±0.0	2.45 ±0.35	1.5 ±0.0
			R	NS	2.0–2.2	2.2–3.0	3.1–3.9	3.7–4.9	3.8	3.7	2.2–2.7	1.5

*Erythromycin. Agricultural and Veterinary Products Div., Abbott Laboratories, N. Chicago, Ill. 60064. im = intramuscular. sc = subcutaneous. iv = intravenous. M = mean ± standard deviation. R = range. NS = no samples. SNM = some samples not measurable. SNS = some calves not sampled. NM = not measurable. Values having the same superscript are significantly different (c,d, P = <0.005; a, P = <0.001).

Figure 7. Concentrations of penicillin G in serum and urine of normal cows after administration of procaine penicillin G by subcutaneous injection in doses of 2,000 and 60,000 units per pound of body weight.



tervals, serum erythromycin concentrations were not inhibitory for *P. hemolytica* and *P. multocida* isolates (Table 11 and Figure 9). Approximately 28% of *C. pyogenes* isolates were inhibited by similar erythromycin concentrations (Figure 3).

Administration of Erythro-200® by intramuscular injection in a dose of 25 mg per pound of body weight produced serum erythromycin concentrations which were inhibitory for 19% of *P. hemolytica* and *P. multocida* isolates (Figure 9) and 40% of *C. pyogenes* isolates (Figure 3). However, use of this dosage was sometimes associated with transient signs of toxicity in feeder-weight cattle. Signs included depression, polypnea, incoordination, mild bloat and recumbency, usually persisting for three hours or less. Similar signs were observed in adult cattle with a dose of 20 mg per pound of body weight. These effects were attributed to the vehicle rather than to the erythromycin since administration of erythromycin lactobionate in sterile water in doses up to 50 mg per pound of body weight was not associated with similar effects.

The author has evaluated Erythro-200® for treatment in a large series of feedlot pneumonia cases using a dose of 20 mg per pound of body weight, injected intramuscularly at 24-hour intervals. No signs of toxicity were observed. Response rates ranging from 28 to 43% were recorded (2). Severe local tissue reactions were associated with the use of Erythro-200® in this dosage. No more than 10 ml should be administered in any one injection site. Extreme care should be taken to avoid administering the drug into previously injected muscle masses. The first dose was divided equally between the gluteal and lateral hamstring muscles of the left rear limb. The second dose was similarly distributed in the opposite limb. The third and fourth doses were injected into the medial hamstring muscles of the left and right rear limbs, respectively. Treatment was usually limited to a maximum of four days. Relapsing cattle, previously treated with Erythro-200®, were not retreated with it. Erythro-200® should be reserved for treatment of pneumonias associated with bacteria which are resistant to sulfonamides, penicillin G and tetracyclines.

Peak serum erythromycin concentrations were achieved more rapidly and were significantly higher with intramuscular administration of Erythro-200® than with subcutaneous administration. Between 12 and 24 hours post-treatment, serum concentrations were slightly but insignificantly higher with subcutaneous administration (Table 11 and Figure 9).

The required withdrawal period before slaughter is 14 days with the FDA-approved dose of 2 mg per pound of body weight. Milk cannot be marketed for three days and six milkings after treatment of lactating cattle.

Erythromycin was detected in urine of cattle for 3 days and 16 days following administration of Erythro-200® in doses of 2 mg and 20 mg per pound of body weight, respectively (Figure 10). A tentative withdrawal period of 30 days has been successfully utilized by the author in connection with the 20 mg per pound dosage, based on the rationale discussed in the section on penicillin G.

Serum erythromycin concentrations were determined in calves following administration of erythromycin lactobionate (Erythrocin Lactobionate I.V. [Lyophilized Erythromycin Lactobionate for Injection]. Abbott Labs, North Chicago, Ill. 60064) by intramuscular or subcutaneous injection in doses of 5,

Table 12. Serum Erythromycin Concentrations After Administration of Erythrocin Lactobionate I.V.* to Normal Calves

Dosage (mg./lb. b.w.)	Route of administration	No. of calves		Serum concentrations (μgm./ml.) at postadministration hours							
				0.5	1	2	4	8	12	18	24
5	im	2	M	1.8 ±0.35	1.7 ±0.07	1.6 ±0.28	1.6 ±0.35	0.84 ±0.06	0.41 ±0.05	NM	NM
			R	1.5–2.0	1.6–1.7	1.4–1.8	1.3–1.8	0.8–0.88	0.37–0.44	NM	NM
10	im	2	M	5.6 ±0.35	5.0 ±0.57	5.1 ±0.71	4.5 ±0.42	2.4 ±0.28	1.3 ±0.28	0.53 ±0.10	SNM
			R	5.3–5.8	4.6–5.4	4.6–5.6	4.2–4.8	2.2–2.6	1.1–1.5	0.46–0.6	NM–0.41
30	im	4	M	NS	11.5 ±4.6	9.6 ±0.69	7.7 ±1.45	4.7 ±1.1	3.9 ±1.42	1.49 ±0.63	0.65 ±0.38
			R	NS	7.4–18.0	8.8–10.5	6.4–9.0	3.3–6.0	2.4–5.8	0.64–2.1	0.39–1.2
50	sc	2	M	NS	10.3 ±1.77	11.2 ±0.0	9.9 ±0.14	8.9 ±1.27	6.7 ±0.71	3.4 ±0.21	2.1 ±0.49
			R	NS	9.0–11.5	11.2	9.8–10.0	8.0–9.8	6.2–7.2	3.2–3.5	1.7–2.4

*Erythromycin lactobionate. Abbott Laboratories, N. Chicago, Ill. 60064. im = intramuscular. sc = subcutaneous. M = mean ± standard deviation. R = range. NS = no sample. NM = not measurable. SNM = some samples not measurable.

Figure 8. Serum ampicillin concentrations, after administration of Polyflex® to normal calves, in relation to minimum inhibitory concentrations for *Pasteurella hemolytica* and *P. multocida* isolates.

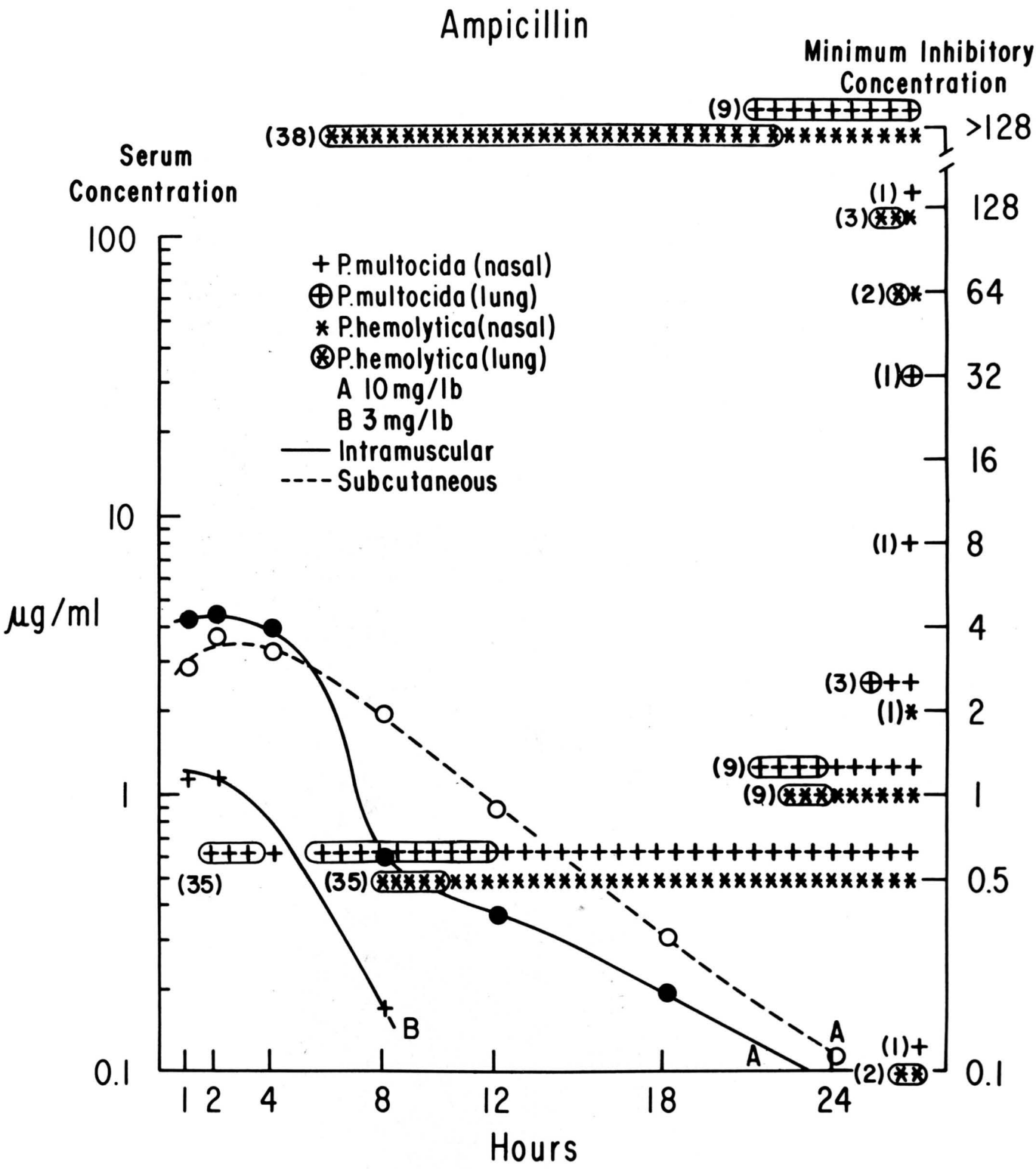
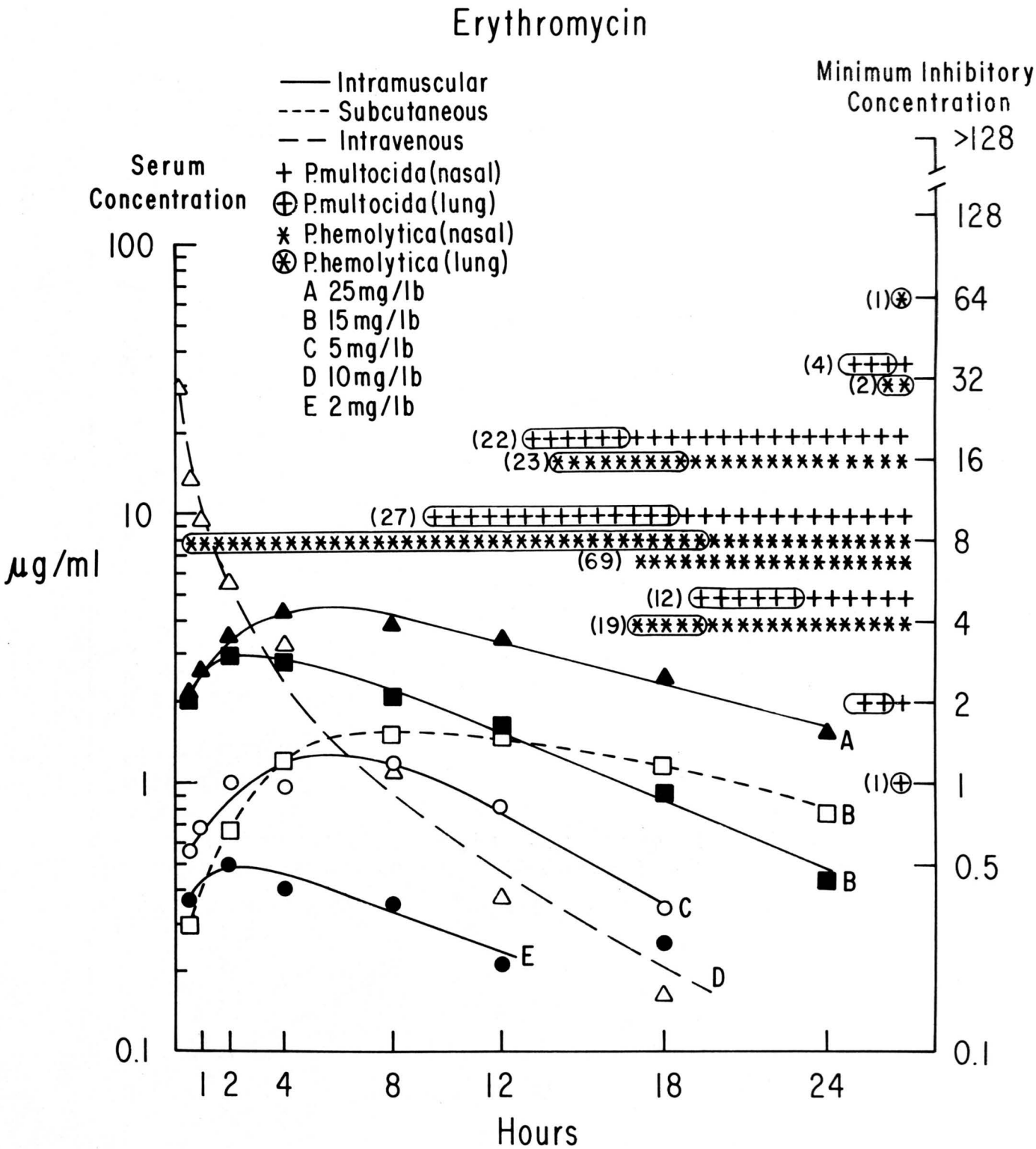


Figure 9. Serum erythromycin concentrations after administration of Erythro-200® to normal calves, in relation to minimum inhibitory concentrations for *Pasteurella hemolytica* and *P. multocida* isolates.



10, 30 or 50 mg per pound of body weight (Table 12 and Figure 11). The suggested treatment regimen of 50 mg per pound of body weight injected subcutaneously at 12-hour intervals (Table 4) was associated with serum erythromycin concentrations (6 to 11 μgm/ml) which were inhibitory for approximately 72% of *P. hemolytica* and *P. multocida* isolates (Table 12 and Figure 11), and for approximately 40% of *C. pyogenes* isolates (Figure 3).

Tylosin

Serum tylosin concentrations were determined in calves following administration of Tylan 200 (Elanco Products Co., a division of Eli Lilly and Co., Indianapolis, Ind. 46206) by intravenous, intramuscular or subcutaneous injection in doses of 2, 5 or 25 mg per pound of body weight (Table 13 and Figure 12). *P. hemolytica* and *P. multocida* isolates were not inhibited by serum concentrations of tylosin achieved with any of these regimens (Table 13 and Figure 12). Approximately 37% of the *C. pyogenes* isolates were inhibited by the serum concentrations achieved with the FDA-approved regimen of 2 mg per pound of body weight, injected intramuscularly (Table 13 and Figure 3). The author has successfully utilized tylosin, in a dose of 20 mg per pound of body weight, as an alternative to penicillin G therapy in refractory *C. pyogenes* infections (2). Sensitive *C. pyogenes* isolates were inhibited by substantially lower concentrations of tylosin than penicillin G (Figure 3). In addition, tylosin could be more active than penicillin G in the presence of exudates and/or necrotic tissues.

Intramuscular administration was preferred to subcutaneous administration, since absorption from subcutaneous sites was significantly retarded (Table 13 and Figure 12).

Use of tylosin in the treatment of bacterial pneumonia should be limited to penicillin G-refractory *C. pyogenes* infections and to infections with unusual organisms which are resistant to sulfonamides, penicillin G, and tetracyclines. In a series of acute bacterial pneumonia cases summarized by the author, 23% responded favorably to tylosin therapy. Response rates of up to 37% were obtained in chronic cases, which were more commonly associated with a *C. pyogenes* component (2).

With the FDA-approved regimen of 2 mg per pound of body weight injected intramuscularly, a withdrawal period of eight days is required before slaughter. Milk cannot be marketed for four days and eight milkings following treatment of lactating cattle. Tylosin was detected in urine for one day and for up to 11 days after administration in doses of 2 and 20 mg per pound of body weight, respectively (Figure 13). A tentative withdrawal period of 20 days has been successfully utilized by the author in connection

Table 13. Serum Tylosin Concentrations After Administration of Tylan 200* to Normal Calves

Dosage (mg./lb. b.w.)	Route of administration	No. of calves		Serum concentrations (μgm./ml.) at postadministration hours								
				0.08	0.5	1	2	4	8	12	18	24
2	im	2	M	NS	0.56 ±0.2	0.6 ±0.21	0.44 ±0.08	NM	NM	NM	NM	NM
			R	NS	0.42–0.70	0.45–0.74	0.38–0.5	NM	NM	NM	NM	NM
5	im	2	M	NS	0.55 ±0.18	0.76 ±0.34	0.81 ±0.27	0.61 ±0.04	NM	NM	NM	NM
			R	NS	0.42–0.68	0.52–1.0	0.62–1.0	0.58–0.64	NM	NM	NM	NM
	iv	2	M	18.25 ±2.47	7.4 ±4.81	3.35 ±1.63	1.49 ±0.86	SNM	NM	NM	NM	NM
			R	16.5–20.0	4.0–10.8	2.2–4.5	0.88–2.1	NM–1.05	NM	NM	NM	NM
25	im	2	M	NS	2.6 ±0.14	3.45 (a) ±0.64	3.7 (b) ±1.41	3.45 ±2.33	2.38 ±1.17	1.45 ±0.35	SNM	NM
			R	NS	2.5–2.7	3.0–3.9	2.7–4.7	1.8–5.1	1.55–3.2	1.2–1.7	0.0–0.62	NM
	sc	3	M	NS	NS	0.86 (a) ±0.22	1.1 (b) ±0.19	1.4 ±0.39	1.5 ±0.28	1.2 ±0.18	0.94 ±0.10	0.76 ±0.13
			R	NS	NS	0.66–1.1	0.84–1.2	0.94–1.5	1.25–1.8	1.05–1.4	0.86–1.05	0.62–0.88

*Tylosin. Elanco Products Co., a div. of Eli Lilly and Co., Indianapolis, Ind. 46206. im = intramuscular. sc = subcutaneous. iv = intravenous. M = mean ± standard deviation. R = range. NS = no sample. SNM = some samples not measurable. NM = not measurable. Values having the same superscript are significantly different (a, P = <0.01; b, P = <0.05).

Figure 10. Concentrations of erythromycin in serum and urine of normal cows after administration of Erythro-200® by intramuscular injection in doses of 2 mg. and 20 mg. per pound of body weight.

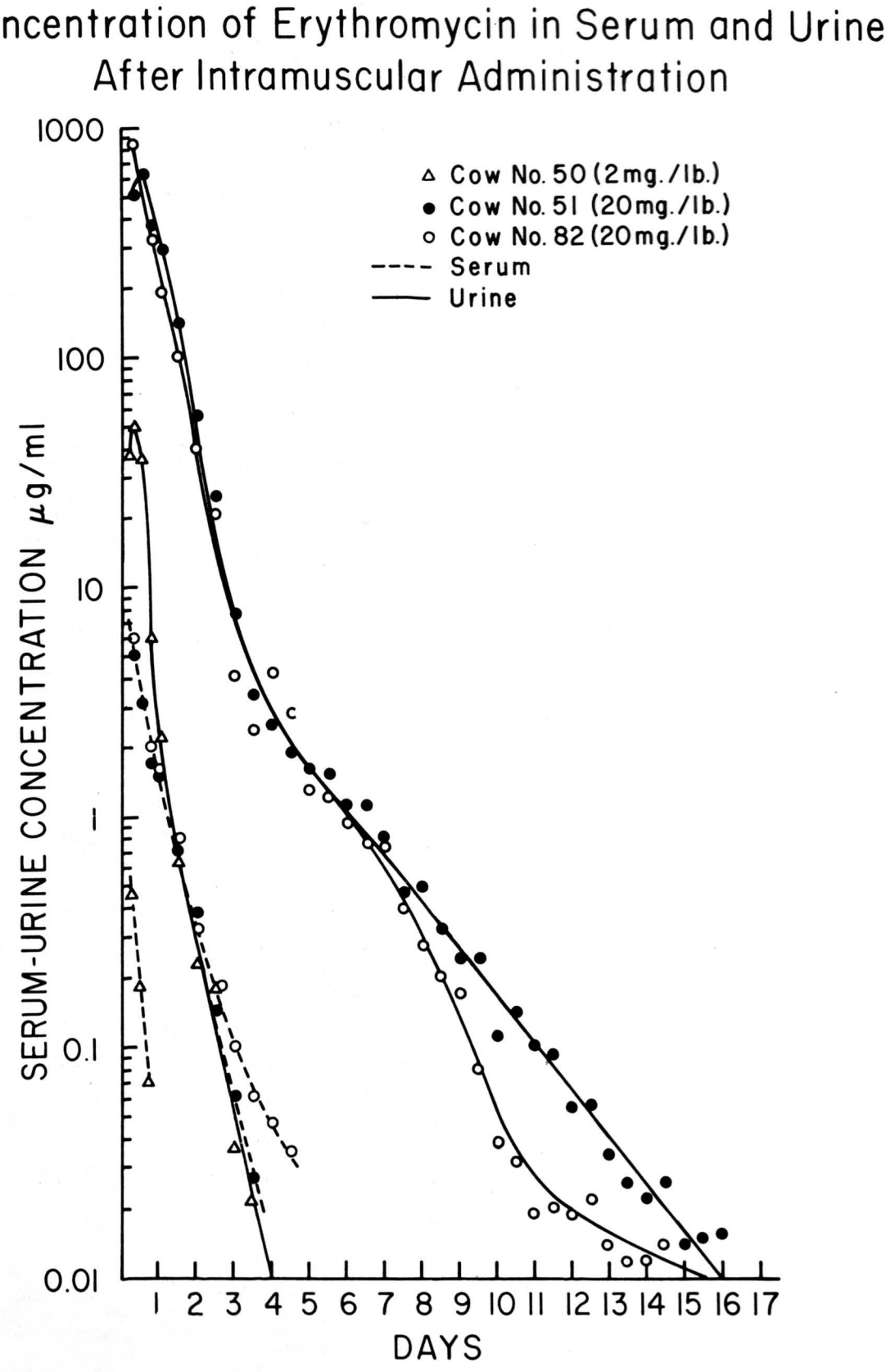
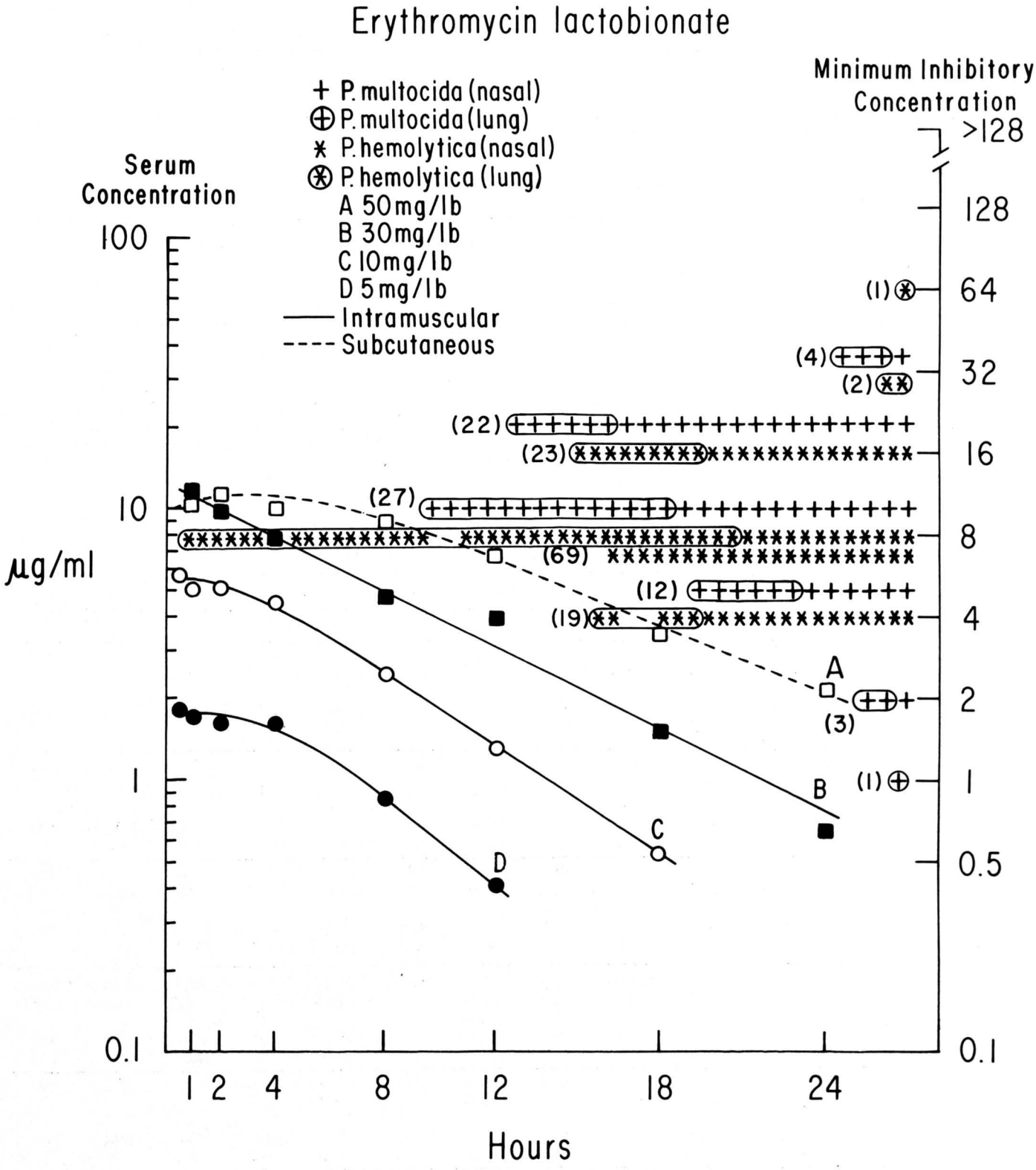


Figure 11. Serum erythromycin concentrations, after administration of Erythrocin Lactobionate I.V.® to normal calves, in relation to minimum inhibitory concentrations for *Pasteurella hemolytica* and *P. multocida* isolates.



with the 20 mg per pound dosage regimen, based on the rationale discussed in the section on penicillin G.

Dihydrostreptomycin

Dihydrostreptomycin is commercially available for use in parenteral therapy as the sulfate salt (DHS) in aqueous solution, or in combination with procaine penicillin G, aqueous suspension. Serum DHS concentrations were determined in calves following administration of DHS by intramuscular or subcutaneous injection in doses of 5 mg or 25 mg per

Table 14. Serum Dihydrostreptomycin Concentrations After Administration of Dihydrostreptomycin Sulfate to Normal Calves

Dosage (mg./lb. b.w.)	Route of administration	No. of calves		Serum concentrations (μgm./ml.) at postadministration hours							
				0.5	1	2	4	8	12	18	24
5	im	2	M	17.0 ±8.49	15.5 ±3.54	12.5 ±2.12	SNM	NM	NM	NM	NM
			R	11.0–23.0	13.0–18.0	11.0–14.0	NM–6.8	NM	NM	NM	NM
25	im	2	M	40.0 ±11.3	64.0 ±28.3	68.0 ±21.2	44.0 (a) ±2.12	19.0 ±5.66	7.0 ±2.12	SNM	NM
			R	32.0–48.0	44.0–84.0	53.0–83.0	42.0–45.0	15.0–23.0	5.4–8.4	NM–3.3	NM
	sc	2	M	NM	74.0 ±21.2	63.3 ±16.6	29.0 (a) ±1.4	10.3 ±2.33	4.1 ±1.3	NM	NM
			R	NM	59.0–89.0	51.5–75.0	28.0–30.0	8.6–11.9	3.1–5.0	NM	NM

im = intramuscular. sc = subcutaneous. M = mean ± standard deviation. R = range. SNM = some samples not measurable. NM = not measurable. Values having the same superscript are significantly different (a, P = <0.025).

Table 15. Serum Chloramphenicol Concentrations After Administration of Chloromycetin Sodium Succinate* and P/M Chloramphenicol, Oral Solution**, to Normal Calves

Dosage (mg./lb. b.w.)	Route of administration	No. of calves		Serum concentrations (μgm./ml.) at postadministration hours									
				1	2	3	4	5	6	7	8	12	18	24
20**	im	3	M	8.3 ±5.8	8.5 ±2.6	10.0 ±1.0	9.6 ±1.33	8.8 ±1.1	8.0 ±0.4	7.2 ±0.68	6.4 ±1.1	3.8 (c) ±0.25	NM	NM
			R	5.0–15.0	6.7–11.5	9.0–11.0	8.8–11.1	8.0–10.1	7.6–8.4	6.4–7.7	5.4–7.6	3.5–4.0	NM	NM
	sc	3	M	SNM	5.7 ±1.02	7.1 ±2.2	7.1 ±2.3	7.6 ±1.2	7.6 ±1.2	7.7 ±1.6	7.1 ±1.7	5.3 (c) ±0.64	SNM	NM
			R	0.0–3.5	4.5–6.4	5.6–9.6	5.6–9.8	6.9–9.0	6.8–9.0	6.8–9.6	6.0–9.0	4.8–6.0	NM–3.2	NM
75**	im	2	M	27.5 ±2.1	30.5 (a) ±0.71	37.5 (b) ±0.71	40.5 ±9.2	40.5 (d) ±7.8	39.0 ±9.9	41.0 (e) ±12.7	41.0 (f) ±7.1	29.5 ±0.71	17.8 ±0.35	8.0 ±0.0
			R	26.0–29.0	30.0–31.0	37.0–38.0	34.0–47.0	35.0–46.0	32.0–46.0	32.0–50.0	36.0–46.0	29.0–30.0	17.5–18.0	8.0
	sc	2	M	14.5 ±4.2	14.3 (a) ±5.3	23.0 (b) ±2.8	28.0 ±2.8	27.5 ±3.5	SNS	37.5 ±13.4	35.5 ±12.0	34.5 ±12.0	25.0 ±18.4	12.6 ±10.7
			R	11.5–17.5	10.5–18.0	21.0–25.0	26.0–30.0	25.0–30.0	26.0	28.0–47.0	27.0–44.0	26.0–43.0	12.0–38.0	5.0–20.1
75*	im	4	M	28.8 ±2.8	34.0 ±8.5	32.0 ±2.7	30.5 ±3.7	27.0 (d) ±3.5	25.1 ±2.5	22.0 (e) ±4.0	18.0 (f) ±1.7	SNM	NM	NM
			R	25.2–31.5	26.0–45.0	28.0–34.0	26.0–35.0	24.0–32.0	23.0–27.5	17.5–26.5	16.0–20.0	NM–14.0	NM	NM

*Chloramphenicol sodium succinate. Parke, Davis and Co., Detroit, Mich. 48232. **Pitman-Moore, Inc., Washington Crossing, N.J. 08560. im = intramuscular. sc = subcutaneous. M = mean ± standard deviation. R = range. NM = not measurable. SNM = some samples not measurable. Values having the same superscript are significantly different (a,d, P = <0.05; b,c,e, P = < 0.025; f, P = <0.001).

Figure 12. Serum tylosin concentrations, after administration of Tylan 200® to normal calves, in relation to minimum inhibitory concentrations for *Pasteurella hemolytica* and *P. multocida* isolates.

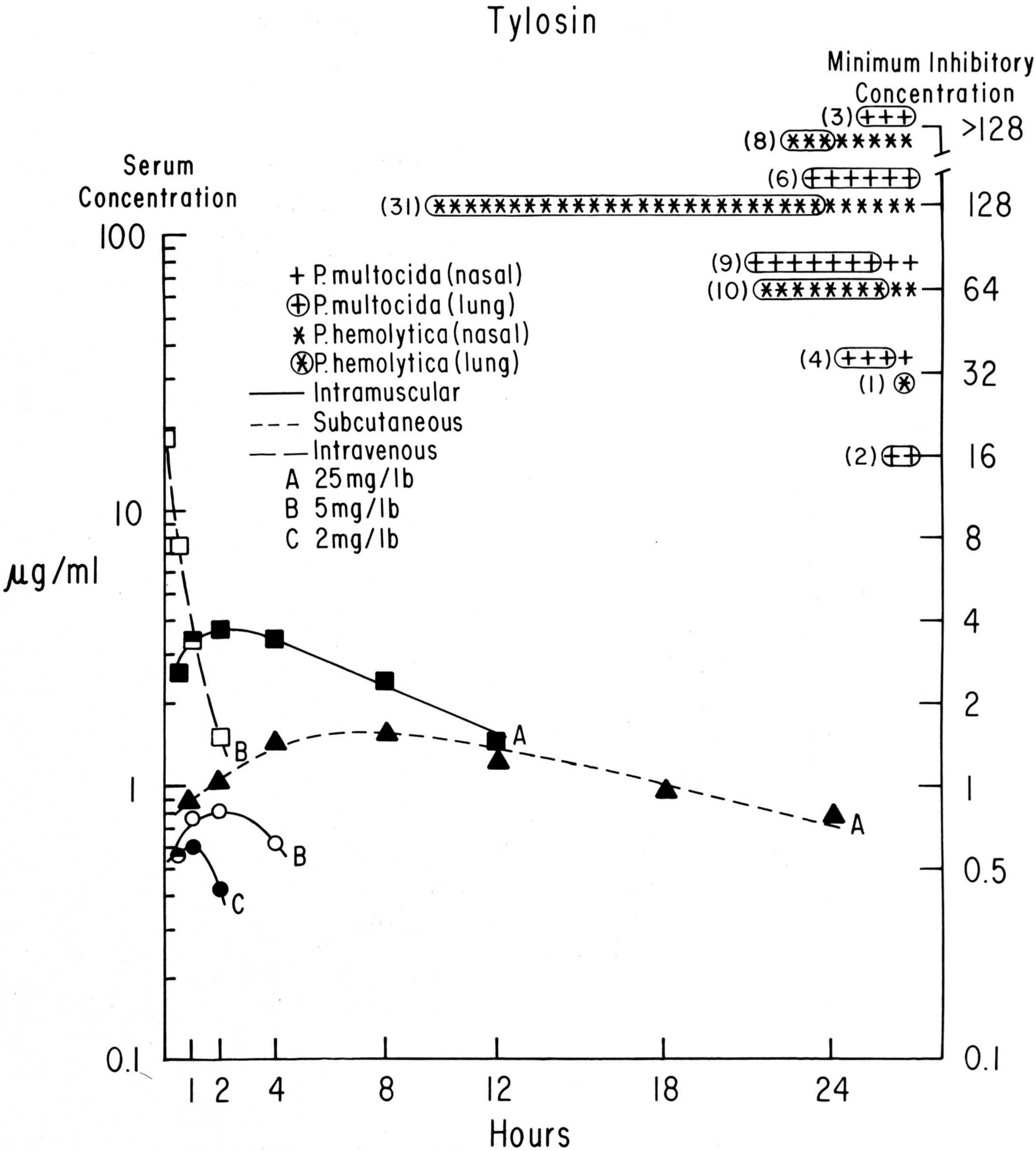


Figure 13. Concentrations of tylosin in serum and urine of normal cows after administration of Tylan 200® by intramuscular injection in doses of 2 mg. and 20 mg. per pound of body weight.

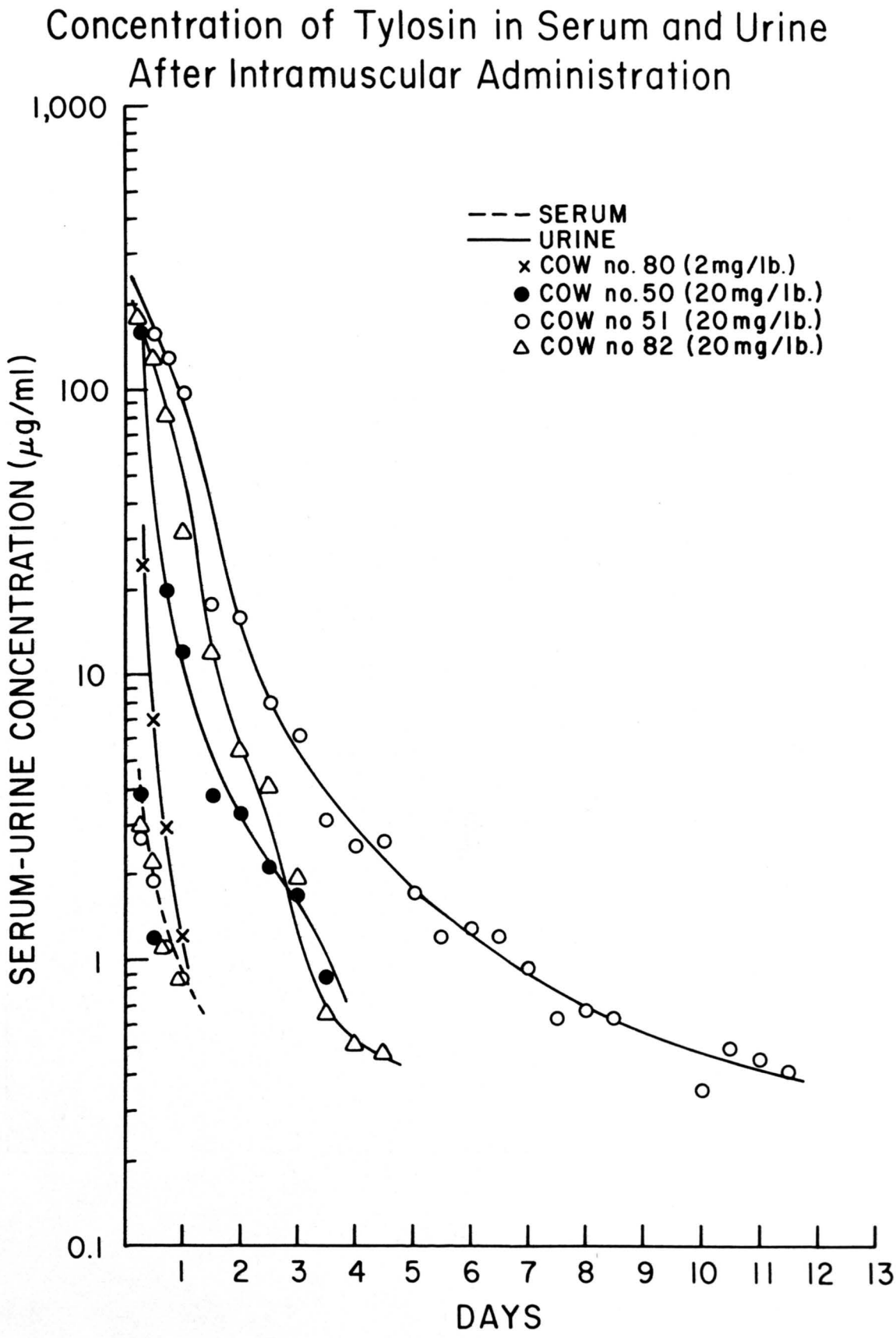
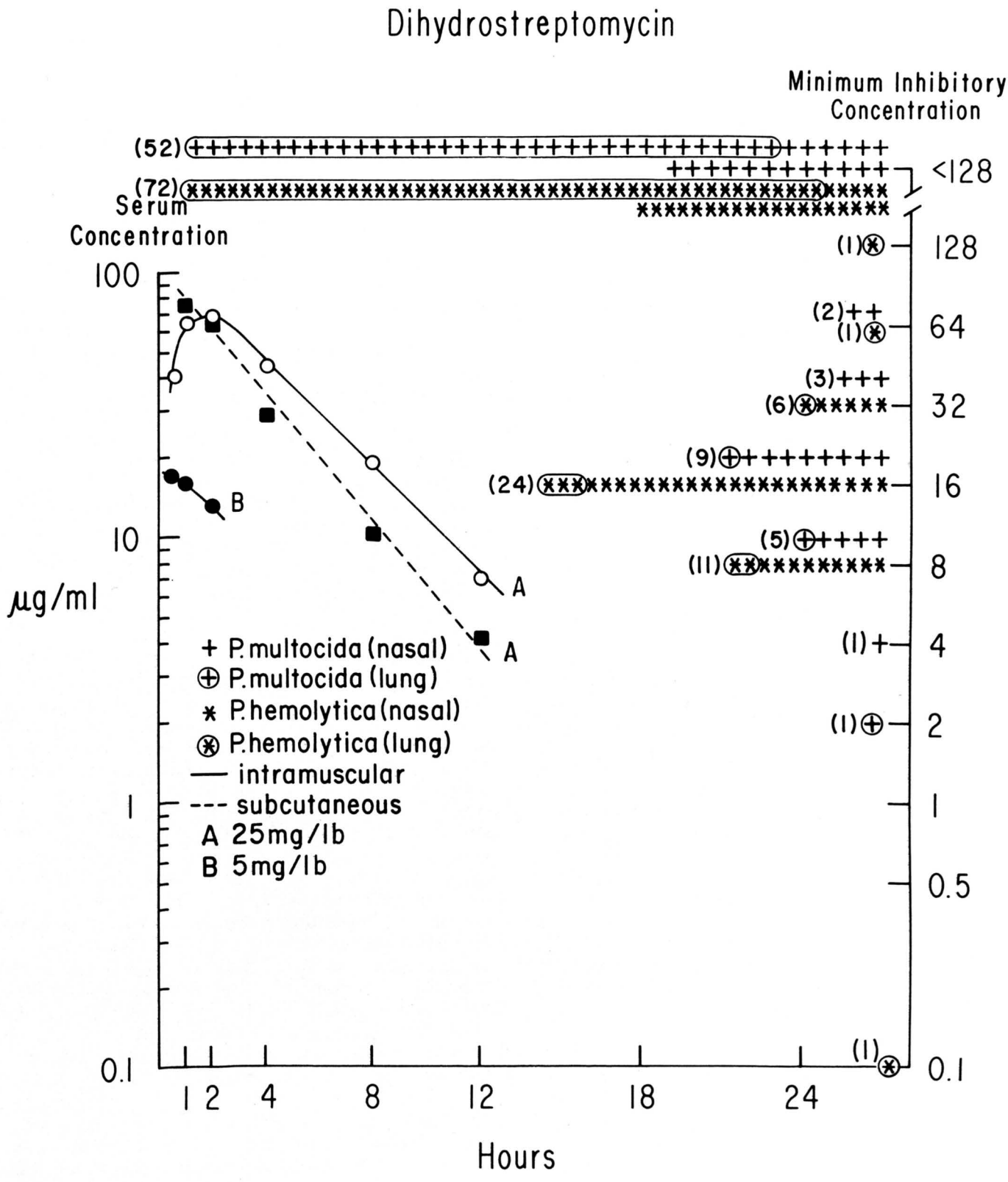


Figure 14. Serum dihydrostreptomycin concentrations, after administration of dihydrostreptomycin sulfate to normal calves, in relation to minimum inhibitory concentrations for *Pasteurella hemolytica* and *P. multocida* isolates.



pound of body weight (Table 14 and Figure 14). Approximately 72% of *P. hemolytica* and *P. multocida* isolates and approximately 81% of *C. pyogenes* isolates were *not* inhibited by the concentrations of DHS achieved in serum with the FDA-approved regimen of 5 mg per pound of body weight, injected intramuscularly (Table 14; Figures 3 and 14). With this dosage, DHS must be administered at eight hour intervals in order to maintain serum concentrations in the 8 to 18 μgm/ml range (Figure 14). A withdrawal period of 30 days is required prior to slaughter. Milk cannot be marketed for two days and four milkings following treatment of lactating cattle. With the suggested treatment regimen of 25 mg per pound of body weight, injected intramuscularly at 12-hour intervals (Table 4), serum concentrations of DHS were inhibitory for approximately 34% of *P. hemolytica* and *P. multocida* isolates (Table 14 and Figure 14). However, with this increased dosage, long withdrawal periods would be required, relatively small improvements in efficacy would be expected, and cost of treatment and risk of auditory and/or vestibular toxicity (5) would be substantially increased. Consequently, DHS is not recommended for treatment of routine cases of bovine bacterial pneumonia, but should be reserved for those cases in which the infecting organism is resistant to sulfonamides, penicillin G, tetracyclines, erythromycin and tylosin. Serum concentrations of DHS were better sustained following intramuscular injection than following subcutaneous injection, although the difference was significant only at the fourth hour post-administration (Table 14).

Chloramphenicol

Serum concentrations of chloramphenicol were determined in calves following administration of chloramphenicol sodium succinate (Chloromycetin Sodium Succinate, Parke, Davis and Co., Detroit, Mich. 48232) in sterile saline and following administration of chloramphenicol in a propylene glycol vehicle (P/M Chloramphenicol, Oral Solution. Pitman-Moore, Inc., Washington Crossing, N.J. 08560) (Table 15 and Figure 15). Because of insensitivity of the bioassay method within the concentration range inhibitory for *P. hemolytica* and *P. multocida* (0.5 to 4 μgm/ml), dosage recommendations (Table 4) were determined indirectly. For example: Since the mean serum chloramphenicol concentration was 5.3 μgm/ml at the 12th hour following subcutaneous injection of P/M Chloramphenicol in a dose of 20 mg per pound of body weight, a dose of 7.5 mg per pound of body weight

$$\left(\frac{2\ \mu gm/ml \times 20\ mg/lb.\ b.w.}{5.3\ \mu gm/ml}\right)$$

similarly administered, would be expected to provide the desired mean serum concentration of 2 μgm/ml at the 12th hour. Virtually all *P. hemolytica* and *P. multocida* isolates should be inhibited by the serum concentrations resulting from the treatment regimens suggested (Table 4). Approximately 56% of the *C. pyogenes* isolates should be inhibited by these same regimens (Figure 4).

Serum chloramphenicol concentrations rose less rapidly and persisted longer with subcutaneous injection of P/M Chloramphenicol® than with intramuscular injection (Table 15 and Figure 15). Serum chloramphenicol concentrations were significantly lower from two to three hours post-treatment and significantly higher at 12 hours post-treatment (Table 15).

Neomycin

Serum neomycin concentrations were determined in calves following administration of neomycin sulfate (Biosol Liquid, Upjohn Veterinary Products, Kalamazoo, Michigan 49001) by intramuscular or subcutaneous injection in doses of 2, 10, 40 or 80 mg per pound of body weight (Table 16 and Figure 16). With the suggested treatment regimen of 40 mg per pound of body weight (Table 4), serum neomycin concentrations were inhibitory for virtually all *P. hemolytica* and *P. multocida* isolates (Table 16 and Figure 16) and for approximately 74% of *C. pyogenes* isolates (Table 16 and Figure 4). Retreatment at eight-hour intervals was required to maintain serum concentrations in the inhibitory range of 0.5 to 64 μgm/ml (Figures 4 and 16). Serum neomycin concentrations were not significantly influenced by route of administration (Table 16 and Figure 16). It is recommended that the blood urea nitrogen (BUN) concentration be monitored during treatment in order to detect the possible onset of nephrotoxicity. Irreversible auditory toxicity may also result, particularly if therapy is prolonged (10).

Kanamycin

Kanamycin sulfate (Kantrim Veterinary Injection. Veterinary Products, Bristol Labs, Div. of Bristol-Myers Co., Syracuse, N.Y. 13201) was administered to calves by subcutaneous injection in doses of 5 or 25 mg per pound of body weight (Table 17 and Figure 17). With the suggested dosage of 25 mg per pound of body weight (Table 4), serum kanamycin concentrations were inhibitory for virtually all *P. hemolytica* and *P. multocida* isolates (Table 17 and Figure 17) and for approximately 81% of *C. pyogenes* isolates (Table 17 and Figure 4). Retreatment at eight-hour intervals was required to maintain serum concentrations in the inhibitory range of 0.1 to 64 μgm/ml (Figures 4 and 17). As with neomycin, nephrotoxicity and auditory toxicity may be associated with kanamycin therapy (7). Bacterial cross-resistance between neomycin and kanamycin is frequent (7). In choosing between the two antibiotics, the greater economy of neomycin must be balanced against the reduced risk of toxicity provided by kanamycin.

Gentamicin

Serum gentamicin concentrations were determined in calves following administration of gentamicin sul-

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Triangle-4 protects against 2 virus diseases: IBR (infectious bovine rhinotracheitis), a big cause of abortions in cow herds, and its "look-alike", PI-3 (parainfluenza-3), frequently isolated in respiratory cases. Triangle-4 also stimulates protection against 2 important secondary bacterial invaders: *Pasteurella multocida* and *Pasteurella haemolytica,* which so often cause complications of bronchitis and pneumonia.

Now you can protect the whole herd against 4 respiratory trouble-makers at one time, any time. There's "no waiting". Convenient, practical—Triangle-4 can help cut field time, even-out your peak seasons.

Fort Dodge Laboratories,
Fort Dodge, Iowa

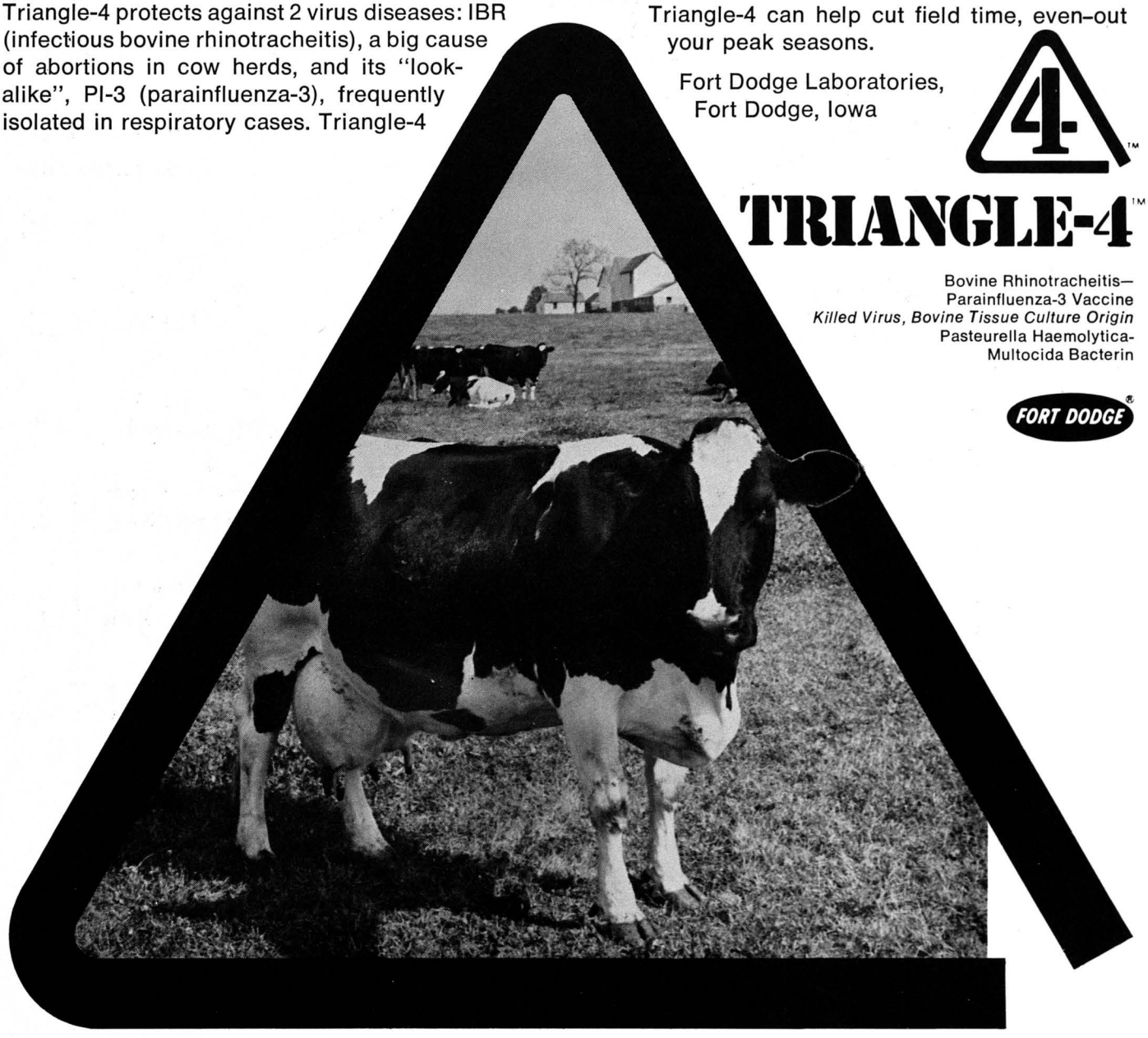

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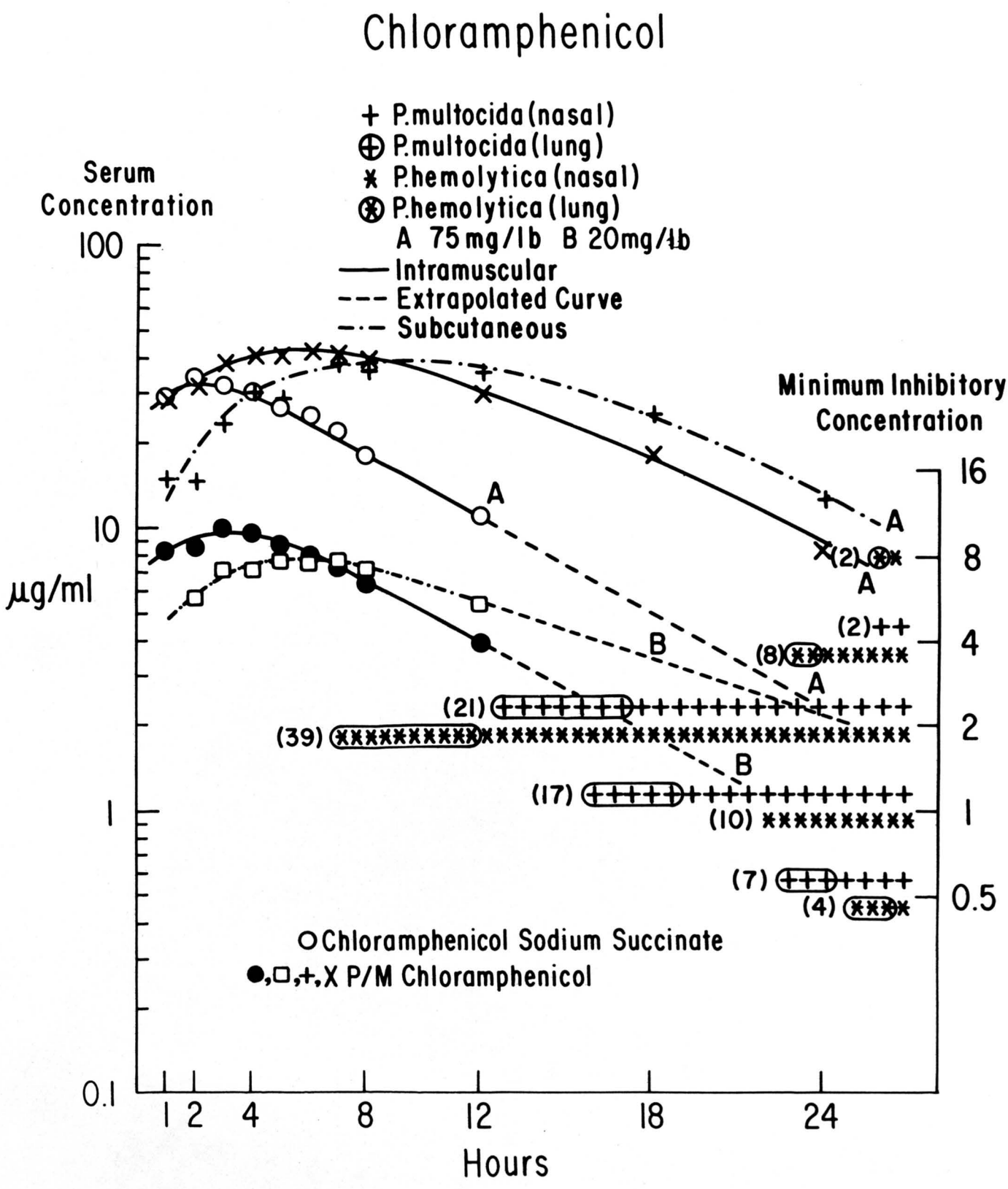
Figure 15. Serum chloramphenicol concentrations, after administration of Chloromycetin Sodium Succinate® and P/M Chloramphenicol, Oral Solution®, to normal calves, in relation to minimum inhibitory concentrations for *Pasteurella hemolytica* and *P. multocida* isolates.



fate (Gentocin Solution Veterinary. Schering Corp., Bloomfield, N.J. 07003) by intramuscular or subcutaneous injection in doses of 2 or 10 mg per pound of body weight (Table 18 and Figure 18). With the suggested regimen of 10 mg per pound of body weight (Table 4), serum gentamicin concentrations were achieved which were inhibitory for virtually all *P. hemolytica, P. multocida* (Table 18 and Figure 18) and *C. pyogenes* isolates (Table 18 and Figure 4). Retreatment at 12-hour intervals was required to maintain serum concentrations in the inhibitory range of 0.5 to 16 μgm/ml (Figures 4 and 18). Serum concentrations were not significantly influenced by route of administration (Table 18 and Figure 18). As with neomycin and kanamycin, nephrotoxicity may be associated with gentamicin therapy (6,7). Vestibular toxicity may also be a problem (6). Treatment with gentamicin should be discontinued at the first sign of renal or vestibular dysfunction.

Polymyxin B

Serum polymyxin B concentrations were determined in calves following administration of polymyxin B sulfate (Polymyxin B Sulfate Sterile. Pfizer Labs

Table 16. Serum Neomycin Concentrations After Administration of Biosol Liquid* to Normal Calves

Dosage (mg./lb. b.w.)	Route of administration	No. of calves		Serum concentrations (μgm./ml.) at postadministration hours						
				1	2	4	8	12	18	24
2	im	2	M	8.2 ±1.13	5.2 ±1.7	2.0 ±0.92	0.79 ±030	SNM	NM	NM
			R	7.4–9.0	4.0–6.4	1.3–2.6	0.58–1.0	NM–0.62	NM	NM
10	im	2	M	36.5 (a) ±2.12	25.5 ±6.36	12.0 ±4.24	4.4 ±1.77	1.7 ±0.64	0.72 ±0.06	0.47 ±0.03
			R	35.0–38.0	21.0–30.0	9.0–15.0	3.1–5.6	1.2–2.1	0.68–0.76	0.45–0.49
	sc	2	M	21.0 (a) ±2.83	14.2 ±2.55	11.2 ±0.78	3.7 ±0.07	2.3 ±0.92	0.71 ±0.04	SNS
			R	19.0–23.0	12.4–16.0	10.6–11.7	3.6–11.7	1.6–2.9	0.68–0.74	0.42
40	im	3	M	106.0 ±12.5	104 ±3.46	52.7 ±6.64	20.3 ±4.39	10.1 ±0.64	4.0 ±0.72	2.5 ±0.61
			R	96.0–120.0	102.0–108.0	45.0–56.5	15.2–23.0	9.4–10.5	3.5–4.8	1.8–3.0
80	im	3	M	321.0 ±41.51	189.3 ±1.2	102.7 ±20.6	40.3 ±8.6	20.5 ±8.9	11.6 ±5.06	6.0 ±2.8
			R	280.0–363.0	188.0–190.0	81.0–122.0	31.0–48.0	14.0–30.6	6.4–16.5	3.6–9.0

*Neomycin sulfate. Upjohn Veterinary Products, Kalamazoo, Mich. 49001. im = intramuscular. sc = subcutaneous. M = mean ± standard deviation. R = range. NM = not measurable. SNS = some calves not sampled. SNM = some samples not measurable. Values having the same superscript are significantly different (a, P = <0.025).

Table 17. Serum Kanamycin Concentrations After Administration of Kantrim* to Normal Calves

Dosage (mg./lb. b.w.)	Route of administration	No. of calves		Serum concentrations (μgm./ml.) at postadministration hours						
				1	2	4	8	12	18	24
5	sc	2	M	14.5 ±4.24	13.8 ±3.11	5.2 ±1.7	NM	NM	NM	NM
			R	11.5–17.5	11.6–16.0	4.0–6.4	NM	NM	NM	NM
25	sc	2	M	72.0 ±14.14	68.0 ±14.14	27.0 ±2.83	8.2 ±0.28	2.7 ±0.14	NM	NM
			R	62.0–82.0	58.0–78.0	25.0–29.0	8.0–8.4	2.6–2.8	NM	NM

*Kanamycin sulfate. Veterinary Products, Bristol Laboratories, Div. of Bristol-Myers Co., Syracuse, N.Y. 13201. sc = subcutaneous. M = mean ± standard deviation. R = range. NM = not measurable.

Figure 16. Serum neomycin concentrations, after administration of Biosol Liquid® to normal calves, in relation to minimum inhibitory concentrations for *Pasteurella hemolytica* and *P. multocida* isolates.

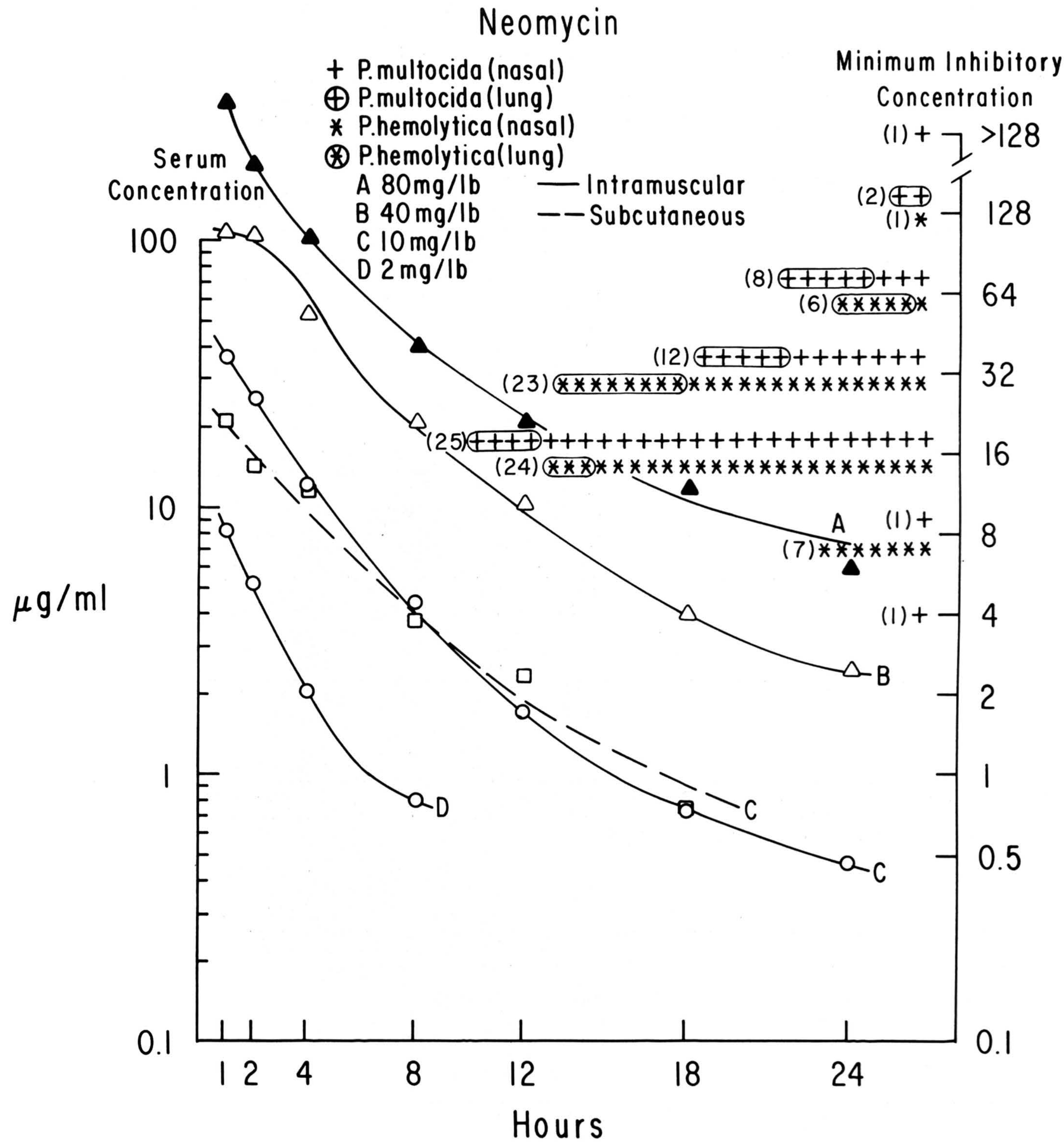


Figure 17. Serum kanamycin concentrations, after administration of Kantrim® to normal calves, in relation to minimum inhibitory concentrations for *Pasteurella hemolytica* and *P. multocida* isolates.

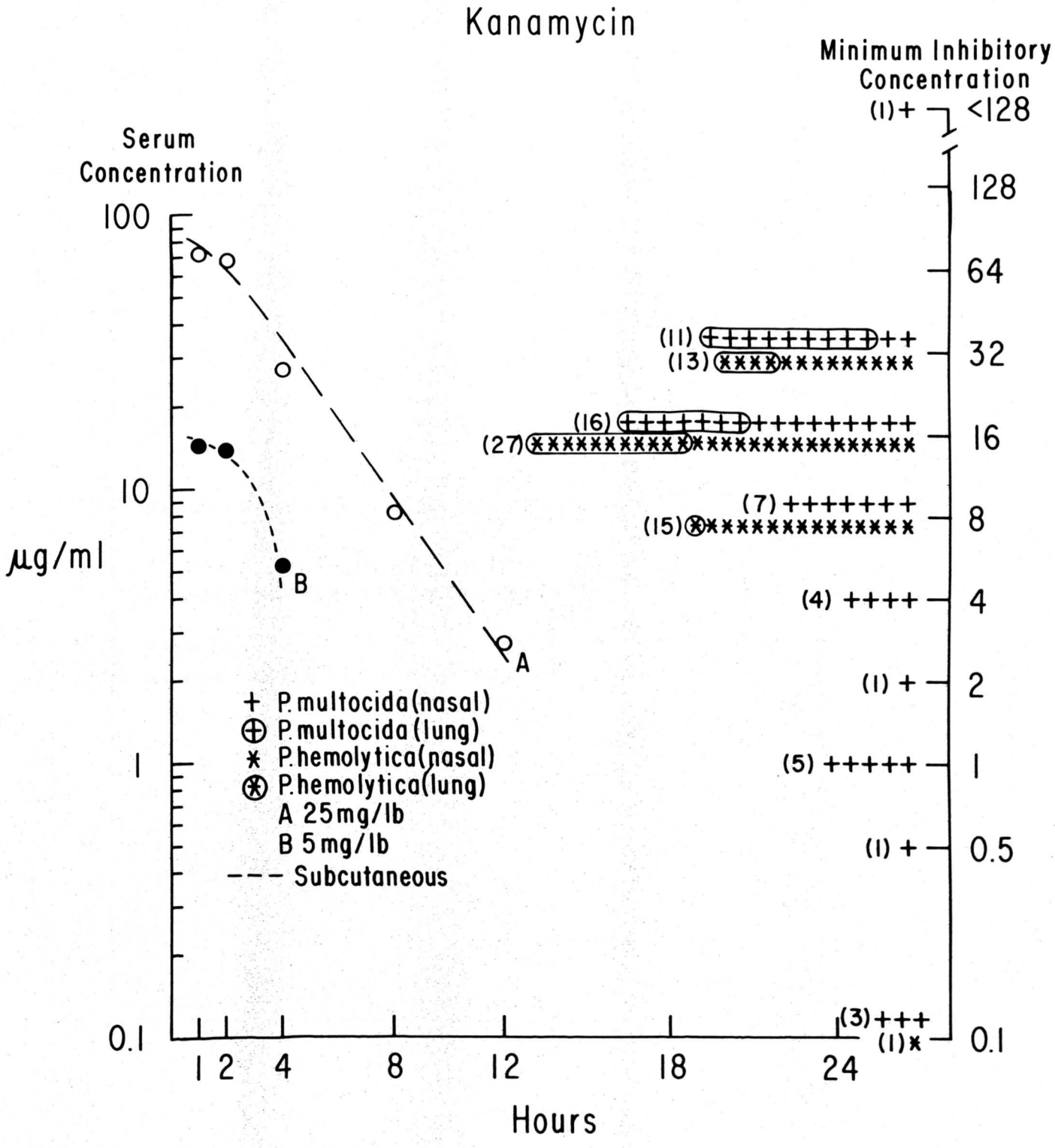
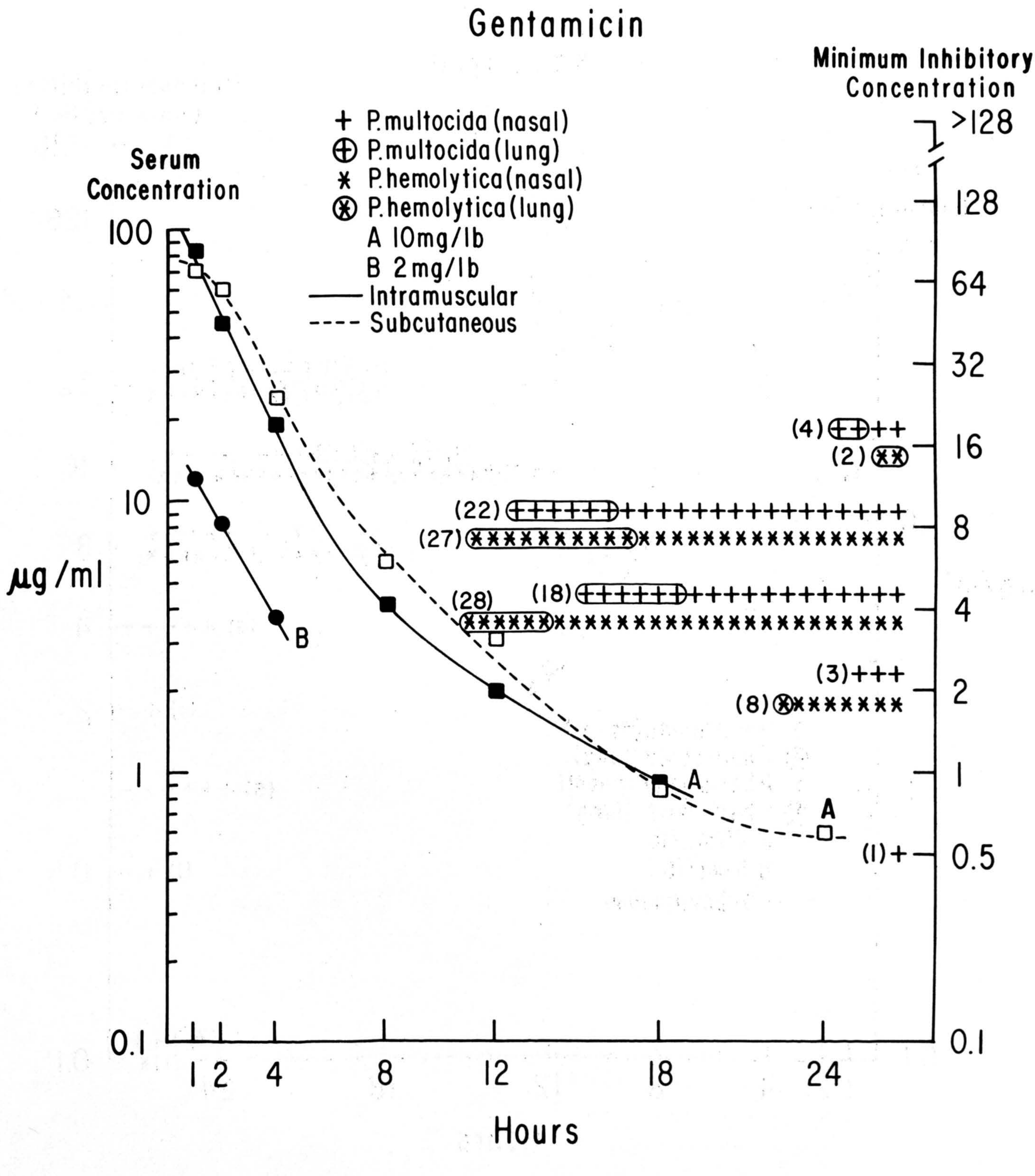


Figure 18. Serum gentamicin concentrations, after administration of Gentocin Solution Veterinary® to normal calves, in relation to minimum inhibitory concentrations for *Pasteurella hemolytica* and *P. multocida* isolates.



Div., Pfizer, Inc., New York, N.Y. 10017), in a dose of 15,000 units per pound of body weight, by intramuscular or subcutaneous injection (Table 19 and Figure 19). Serum polymyxin B concentrations were inhibitory for approximately 67% of *P. hemolytica* and *P. multocida* isolates (Table 19 and Figure 19). *C. pyogenes* isolates were resistant (Table 19 and Figure 4). Retreatment at 12-hour intervals was required to maintain serum concentrations in the inhibitory range of 0.1 to 4 μgm/ml (Figures 4 and 19). Serum concentrations were not significantly influenced by route of administration (Table 19 and Figure 19). Tissue fluid polymyxin B concentrations are expected to be considerably lower than serum concentrations, since the drug is strongly bound to the phospholipids of cell membranes (7). Polymyxin B diffuses poorly into joints (6), the cerebrospinal fluid (6,7) and the pleural space (7) even when inflammation is present. Polymyxin B may also be associated with either nephrotoxicity or neurotoxicity, the latter being characterized by weakness, ataxia, depression and occasionally by respiratory paralysis (6,7,10). Consequently, polymyxin B cannot be recommended for treatment of routine bacterial pneumonia cases. Systemic use of the drug is contraindicated, except in those instances where the infecting organism is resistant to alternative antimicrobics.

Cephalothin

Serum cephalothin concentrations were determined following administration of sodium cephalothin (Keflin [Sterile Sodium Cephalothin, U.S.P.]. Eli Lilly and Co., Indianapolis, Ind. 46206) to calves by intramuscular or subcutaneous injection in doses of 10 or 25 mg per pound of body weight (Table 20 and Figure 20). With the suggested regimen of 25 mg per pound of body weight injected subcutaneously (Table 4), serum concentrations of cephalothin were achieved which were inhibitory for approximately 94% of *P. hemolytica* and *P. multocida* isolates (Table 20 and Figure 20) and for all *C. pyogenes* isolates (Table 20 and Figure 4). Retreat-

Table 18. Serum Gentamycin Concentrations After Administration of Gentocin Solution Veterinary* to Normal Calves

Dosage (mg./lb. b.w.)	Route of administration	No. of calves		Serum concentrations (μgm./ml.) at postadministration hours						
				1	2	4	8	12	18	24
2	im	2	M	12.1 ±1.2	8.3 ±0.42	3.7 ±0.07	SNM	NM	NM	NM
			R	11.2–12.9	8.0–8.6	3.6–3.7	NM–1.3	NM	NM	NM
10	im	2	M	84.0 ±5.66	45.0 ±0.0	19.0 ±1.41	4.0 ±0.35	2.0 ±0.35	0.93 ±0.05	NM
			R	80.0–88.0	45.0	18.0–20.0	3.7–4.2	1.7–2.2	0.89–0.96	NM
	sc	2	M	71.5 ±3.54	60.0 ±10.6	24.0 ±2.83	5.9 ±0.99	3.0 ±0.71	0.86 ±0.34	0.58 ±0.03
			R	69.0–74.0	52.5–67.5	22.0–26.0	5.2–6.6	2.5–3.5	0.62–1.1	0.56–0.60

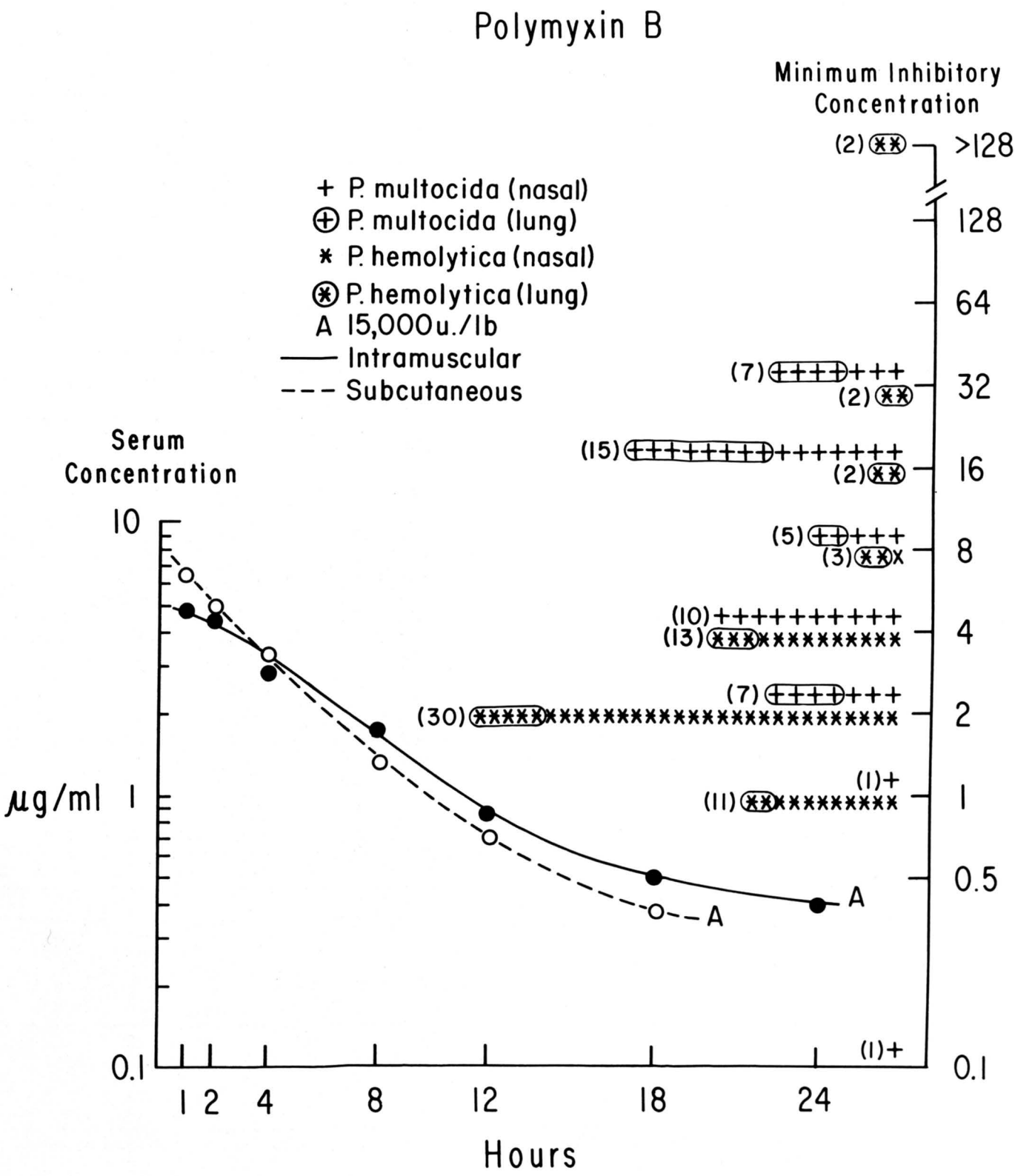
*Gentamicin sulfate. Schering Corp., Bloomfield, N.J. 07003. im = intramuscular. sc = subcutaneous. M = mean ± standard deviation. R = range. NM = not measurable. SNM = some samples not measurable.

Table 19. Serum Polymyxin B Concentrations After Administration of Polymyxin B Sulfate* to Normal Calves

Dosage (units/lb. b.w.)	Route of administration	No. of calves		Serum concentrations (μgm./ml.) at postadministration hours						
				1	2	4	8	12	18	24
15,000	im	2	M	4.7 ±0.14	4.3 ±0.71	2.8 ±0.78	1.7 ±0.35	0.84 ±0.23	0.50 ±0.11	0.4 ±0.1
			R	4.6–4.8	3.8–4.8	2.2–3.3	1.4–1.9	0.68–1.0	0.42–0.58	0.35–0.47
	sc	2	M	6.5 ±1.56	4.9 ±0.42	3.3 ±0.78	1.3 ±0.54	0.69 ±0.35	0.37 ±0.15	SNS
			R	5.4–7.6	4.6–5.2	2.7–3.8	0.94–1.7	0.44–0.94	0.26–0.47	0.26

*Pfizer Laboratories Div., Pfizer, Inc., New York, N.Y. 10017. im = intramuscular. sc = subcutaneous. M = mean ± standard deviation. R = range. SNS = some calves not sampled.

Figure 19. Serum polymyxin B concentrations, after administration of polymyxin B sulfate to normal calves, in relation to minimum inhibitory concentrations for *Pasteurella hemolytica* and *P. multocida* isolates.



ment at six-hour intervals was required to maintain serum concentrations in the inhibitory range of 0.5 to 8 μgm/ml (Figures 4 and 20). Serum concentrations were not significantly influenced by route of administration (Table 20 and Figure 20).

Cephaloridine

Serum cephaloridine concentrations were determined following administration of cephaloridine in an ethyl oleate-sesame oil vehicle (Loridine Injectable. Elanco Products Co., a division of Eli Lilly and Co., Indianapolis, Ind. 46206) by intramuscular or subcutaneous injection in doses of 5 or 25 mg per pound of body weight (Table 21 and Figure 21). With the suggested treatment regimen of 25 mg per pound of body weight, injected subcutaneously (Table 4), serum cephaloridine concentrations were inhibitory for approximately 93% of *P. hemolytica* and *P. multocida* isolates (Table 21 and Figure 21) and all *C. pyogenes* isolates (Table 21 and Figure 4). Retreatment at 12-hour intervals was required to maintain serum concentrations in the inhibitory range of 0.1 to 16 μgm/ml (Table 21; Figures 2, 4 and 21).

Serum cephaloridine concentrations rose less rapidly and persisted longer with subcutaneous administration than with intramuscular administration (Table 21 and Figure 21). Serum cephaloridine concentrations were significantly less at one hour post-treatment and significantly greater at four hours post-treatment with subcutaneous administration

Table 20. Serum Cephalothin Concentrations After Administration of Keflin* to Normal Calves

Dosage (mg./lb. b.w.)	Route of administration	No. of calves		Serum concentrations (μgm./ml.) at postadministration hours						
				1	2	4	8	12	18	24
10	im	2	M	2.7 ±0.71	0.69 ±0.18	SNM	NM	NM	NM	NM
			R	2.2–3.2	0.56–0.82	NM–0.15	NM	NM	NM	NM
25	im	2	M	6.5 ±0.42	1.8 ±0.49	0.23 ±0.11	NM	NM	NM	NM
			R	6.2–6.8	1.4–2.1	0.15–0.31	NM	NM	NM	NM
	sc	2	M	8.0 ±0.85	2.7 ±0.07	0.29 ±0.08	NM	NM	NM	NM
			R	7.4–8.6	2.6–2.7	0.23–0.35	NM	NM	NM	NM

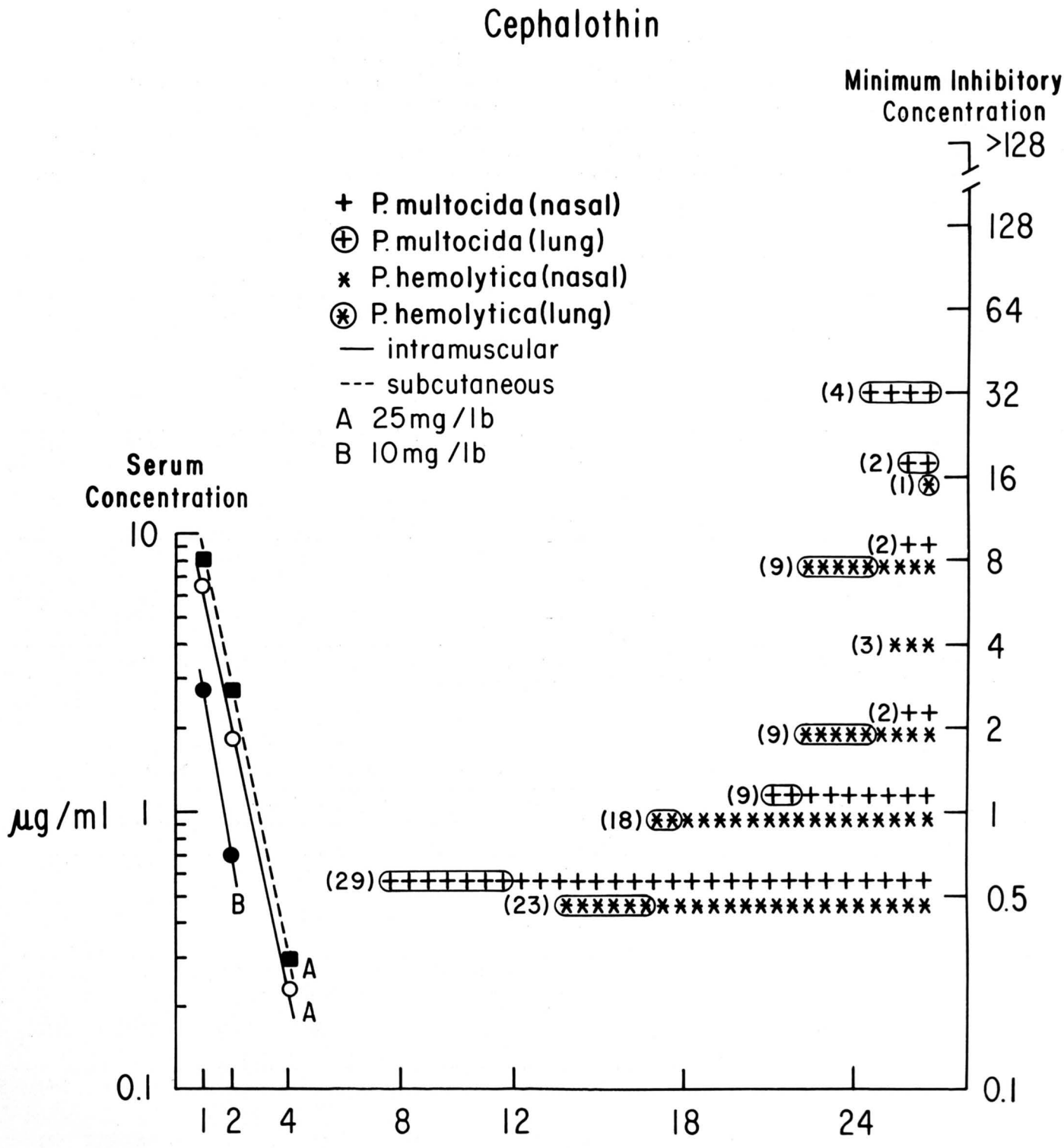
*Sodium Cephalothin, U.S.P. Eli Lilly and Co., Indianapolis, Ind. 46206. im = intramuscular. sc = subcutaneous. M = mean ± standard deviation. R = range. NM = not measurable. SNM = some samples not measurable.

Table 21. Serum Cephaloridine Concentrations After Administration of Loridine Injectable* to Normal Calves

Dosage (mg./lb. b.w.)	Route of administration	No. of calves		Serum concentrations (μgm./ml.) at postadministration hours						
				1	2	4	8	12	18	24
5	im	2	M	SNS	9.8 ±3.11	1.6 ±0.64	NM	NM	NM	NM
			R	33.0	7.6–12.0	1.1–2.0	NM	NM	NM	NM
25	im	2	M	83.8 (a) ±1.77	SNS	6.5 (b) ±1.63	1.0 ±0.11	NM	NM	NM
			R	82.5–85.0	6.2–	5.3–7.6	0.94–1.1	NM	NM	NM
	sc	2	M	30.0 (a) ±0.0	21.5 ±0.71	19.3 (b) ±1.06	4.7 ±1.56	1.3 ±1.06	SNM	NM
			R	30.0	21.0–22.0	18.5–20.0	3.6–5.8	0.5–2.0	NM–0.49	NM

*Cephaloridine. Elanco Products Co., a div. of Eli Lilly and Co., Indianapolis, Ind. 46206. im = intramuscular. sc = subcutaneous. M = mean ± standard deviation. R = range. NM = not measurable. SNM = some samples not measurable. Values having the same superscript are significantly different (a, P = <0.001; b, P = <0.025).

Figure 20. Serum cephalothin concentrations, after administration of Keflin® to normal calves, in relation to minimum inhibitory concentrations for *Pasteurella hemolytica* and *P. multocida* isolates.



(Table 21). Because complete bacterial cross resistance occurs between cephalothin and cephaloridine, infections with organisms susceptible to cephalothin should be treated with cephaloridine, since higher and more persistant serum concentrations were achieved with the latter drug.

Literature Review and Discussion

The results of antimicrobic sensitivity testing of pasteurella bacteria, presented in Table 3, are similar to those previously reported from Canada (21), except that resistance to erythromycin was much less commonly encountered by the Canadian workers. Erythromycin resistance was much more frequent, penicillin G resistance was slightly more frequent, and sulfonamide resistance was less frequent than reported by a Minnesota worker (22).

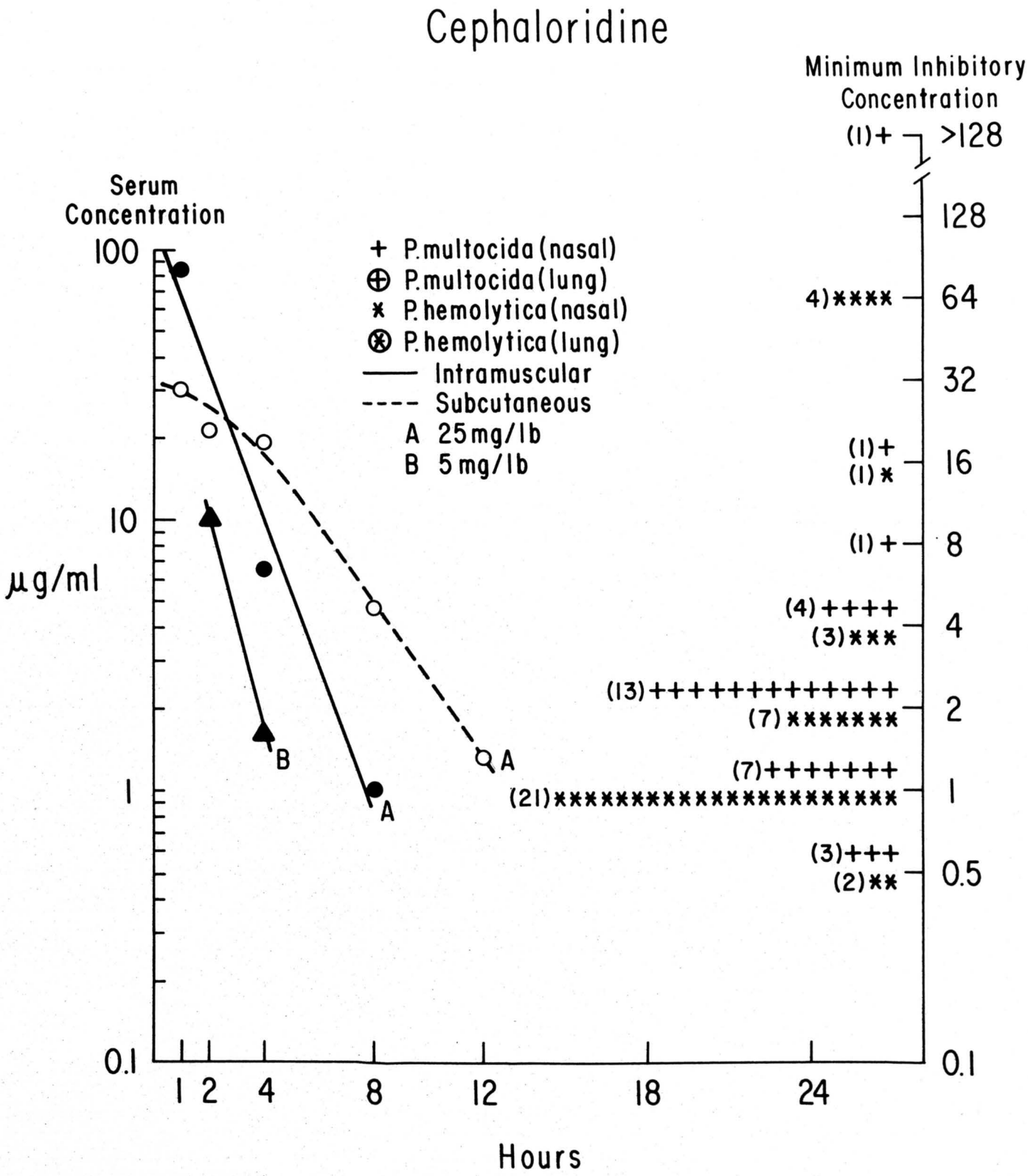
Minimum inhibitory antimicrobic concentrations have been reported for a total of 18 bovine pasteurella isolates (Table 22) using OTC (23,24) penicillin G (23,24,25), erythromycin (24,26), chloramphenicol (23,24), neomycin (24) and polymyxin B (22,24). These results are not necessarily directly comparable to those presented in Figures 1 and 2, as the inoculum size was not specified (25,26) or was larger (23,24) or smaller (23) than that used in the present study. Minimum inhibitory concentrations have been estimated in 50 bovine pasteurella isolates for OTC, penicillin G, erythromycin, chloramphenicol, neomycin and kanamycin, using a semi-quantitative method (27). In this study, general agreement with previously reported values was observed in the case of penicillin G (23,24,27), chloramphenicol (23,24,27) and neomycin (24,27). Values obtained with OTC were slightly higher than in previous studies (23,24,27). Values obtained with erythromycin were much higher than previously reported using quantitative techniques (24,26), but were in agreement with those obtained using a semi-quantitative method (27). Values obtained for kanamycin (27) and polymyxin B (23,24) were considerably lower than previously reported.

Table 22. Summary of Available Information Concerning Inhibitory Concentrations of Selected Antibiotics for *Pasteurella multocida, P. hemolytica* and *Corynebacterium pyogenes*

Bacteria	Source	No. isolates tested & ref. nos.	Minimum inhibitory concentration range (μgm./ml.)						
			Oxy-tetra-cycline	Peni-cillin G	Eryth-romycin	Tylosin	Chlor-amphenicol	Neomycin	Poly-myxin B
P. multocida	Bovine	1[25]	–	0.2	–	–	–	–	–
		1[23]	1	1	–	–	1	–	5
		12[24]	0.4-0.8	0.1-0.4	0.8-3.1	–	0.4-0.8	6.2-25	3.1-50
		1[26]	–	–	1.25	–	–	–	–
		21[42]	–	–	–	35.4±9.4*	–	–	–
	Ovine	1[25]	–	0.2	–	–	–	–	–
		2[23]	1-3	1	–	–	1	–	3
		2[26]	–	–	0.6	–	–	–	–
		1[43]	–	–	–	–	2.5	–	–
	Avian	1[25]	–	0.1	–	–	–	–	–
		1[23]	1	3	–	–	1	–	1
		1[26]	–	–	0.6	–	–	–	–
		3[43]	–	–	–	–	0.25-0.5	–	–
		1[44]	–	0.08	–	–	–	–	–
	Canine	1[23]	1	1	–	–	1	–	3
		1[26]	–	–	0.6	–	–	–	–
	Feline	1[25]	–	0.1	–	–	–	–	–
	Buffalo	1[43]	–	–	–	–	0.5	–	–
	Rabbit	1[25]	–	0.3	–	–	–	–	–
	Rat	14[25]	–	0.1-0.2	–	–	–	–	–
	Human	2[23]	1	1-10	–	–	1-10	–	10
	Unspecified	5[45]	1-4	–	–	–	–	–	–
		4[46]	–	1.6-12.5	–	–	–	–	–
		8[47]	–	–	–	–	–	0.3-25	–
		1[23]	1	1	–	–	1	–	3
		1[26]	–	–	0.3	–	–	–	–
		7[48]	–	–	–	–	–	–	2-64
P. hemolytica	Bovine	3[24]	0.4-0.8	0.2	0.4-0.8	–	0.8	12.5	–
		32[42]	–	–	–	24.1±3.7**	–	–	–
C. pyogenes	Bovine	1[43]	–	–	–	–	2.5	–	–
	Unspecified	11[45]	2-6	–	–	–	–	–	–

*Mean ± standard deviation in 3 bovine, 2 ovine, 4 canine, 5 feline and 6 unspecified isolates. **Mean ± standard deviation in 11 bovine, 18 ovine, and 3 unspecified isolates.

Figure 21. Serum cephaloridine concentrations, after administration of Loridine Injectable® to normal calves, in relation to minimum inhibitory concentrations for *Pasteurella hemolytica* and *P. multocida* isolates.



Available information from the literature concerning minimum inhibitory concentrations of antibiotics included in this study for non-bovine as well as bovine *P. multocida* and *P. hemolytica* isolates and for *C. pyogenes* is summarized in Table 22. Minimum inhibitory concentrations of ampicillin, dihydrostreptomycin, kanamycin, gentamicin, cephalothin, cephaloridine and novobiocin for *P. multocida* and *P. hemolytica* have not previously been reported. Minimum inhibitory concentrations of penicillin G, ampicillin, erythromycin, tylosin, dihydrostreptomycin, neomycin, kanamycin, gentamicin, polymyxin B, cephalothin, cephaloridine and novobiocin for *C. pyogenes* have not previously been reported.

Serum OTC concentrations, following administration of Terramycin Injectable Solution® in a dose of 5 mg per pound of body weight by the intravenous, intramuscular or subcutaneous route (Table 7), were compared to those reported by Clark, et al. (19), in normal feedlot calves. The mean concentration at any point in time after administration was nearly always less than reported by Clark, et al. (19), by an average of 9, 18 and 43% with intravenous, intramuscular and subcutaneous administration, respectively. Some of these differences may be explainable in terms of differences in body hydration and in the proportion of the dose equilibrating with digestive tract contents. The calves used by the authors were Holsteins and had been conditioned to continuous stanchioning and blood sample collection procedures. Feed and water were available throughout the period of sample collection and were consumed in normal quantities. Feed and water consumption were likely reduced in the beef calves utilized by Clark, et al. (19), as a result of the anxiety and stress associated with frequent blood sample collection from unconditioned cattle in a squeeze chute. Mean serum OTC concentrations following administration by the intravenous and intramuscular routes (Table 7) were somewhat higher than reported by others (28,29). The significantly greater serum OTC concentrations observed between 12 and 24 hours post-administration by Clark, et al. (19), with intramuscular or subcutaneous administration over intravenous administration were not confirmed by this study. Similar relationships were observed (Table 7 and Figure 5), but the differences were nonsignificant, probably because fewer animals were utilized.

The concentrations of penicillin G in serum, following subcutaneous administration of Bicillin Fortified® in a dose of 2 ml per 150 pounds of body weight, were similar to those previously reported (30,31), except that peak concentrations were higher (30) or lower (31) and declined less rapidly.

Concentrations of penicillin G in serum following intramuscular administration of procaine penicillin G, aqueous suspension, were of similar magnitude to those previously reported (32,33,34) with minor differences. Peak serum concentrations were twice as great as reported by some (32,33), although two-thirds less than reported by another (34). Following the peak, serum concentrations declined more (32,33) or less (34) rapidly than previously reported, so that, by 8 to 12 hours post-administration, serum concentrations were equal to (32,34) or greater than (33) values previously reported.

Concentrations of tylosin in serum, following administration by intramuscular injection in a dose of 2 mg per pound of body weight, were similar to those reported (35), except that peak concentrations were achieved sooner (one to two hours post-administration rather than four hours) and declined more rapidly. The shape of the plasma disappearance curve following intravenous administration closely conformed to that reported previously (35).

Serum DHS concentrations, following administration by intramuscular injection, were similar to those

Figure 22. Sample cattle medication record.

Lot No. 1 Diagnosis Tag No. 101

Date	Temp.	Degree of illness	Terra	Sulfa sol	Sulfa bolus	Pen	Gall	Tylan	Meth-agon	Other Treatment
6-15	106.2	2			3.5					
6-16	105.0	2			2.5					
6-17	105.5	2				50				
6-18	106.4	2				50				
6-19	105.0	2	50							
6-20	105.5	2	50							
6-21	103.8	2				100				
6-22	102.4	1				100				
6-23	102.6	1				100				
6-24	102.5					100				

reported by some workers (31,34), but much lower than reported by another (36).

Serum chloramphenicol concentrations, following administration of P/M Chloramphenicol Oral Solution® by intramuscular injection in a dose of 20 mg per pound of body weight, differed in some respects from those reported in mature cows, using a similar chloramphenicol formulation and a microbiological assay method (37). Peak concentrations occurred at the third hour post-administration in both studies, but were twofold higher in the present study. Following the peak, this concentration differential was gradually reduced until the 12th hour post-administration, when values were identical.

It was previously reported that peak serum chloramphenicol concentrations, resulting from intramuscular injection of chloramphenicol sodium succinate, were six times higher than those achieved with chloramphenicol in propylene glycol (37). In the present study, peak serum concentrations were similar following intramuscular administration of chloramphenicol sodium succinate or P/M Chloramphenicol Oral Solution®, which contains a propylene glycol vehicle. Following the peak, a significantly more rapid decline in serum concentrations was observed with chloramphenicol sodium succinate (Table 15 and Figure 15), as previously reported (37). Additional studies of serum chloramphenicol concentrations in cattle have utilized colorimetric analytical procedures which are more sensitive than microbiological assay methods (38-41). However, the results of these studies cannot be directly compared to the author's, since colorimetric methods measure inactive nitro-containing metabolites of chloramphenicol and protein-bound drugs as well as the unbound, active chloramphenicol assayed by microbiologic methods.

Studies of blood serum antibiotic concentrations following administration of ampicillin trihydrate, erythromycin, neomycin, kanamycin, gentamicin, polymyxin B, cephalothin or cephaloridine to cattle have not previously been reported.

Supportive Therapy

Although all are not expected to agree, in the opinion of the author, supportive treatment (other than good husbandry as previously discussed) has little application in the treatment of uncomplicated bacterial pneumonia in commercial cattle. Any benefits are usually symptomatic and are unlikely to influence final mortality or culling rates. Use of corticosteroids in uncomplicated cases should be discouraged since efficacy of bacteriostatic antimicrobics may be reduced (7). In addition, the remission of fever and toxemia resulting from their use is frequently associated with premature termination of antimicrobic therapy and subsequent exacerbations.

Treating Large Numbers of Bacterial Pneumonia Cases in Industrial Situations

A system for treating bacterial pneumonia is outlined which has been used by the author (with several modifications) (2) in a 13,000-head capacity commercial feedlot over a 3-1/2-year period with excellent results. During this time more than 15,000 cattle were treated, mostly for pneumonia. The mortality rate from bacterial pneumonias was reduced from 0.39% to 0.14% in yearling cattle, mainly as a result of this treatment system. Diagnosis and treatment were performed by feedlot personnel, according to the protocol which follows, under the close supervision of the author. Approximately 300 animals can be treated in an eight-hour day by a well-trained three-man crew. Approximately half of the deaths from bacterial pneumonias in this feedlot are presently attributed to antimicrobic-resistant bacteria. The treatment system was designed to deal more effectively with this important problem.

Treatment Protocol for Bacterial Pneumonia in Feedlot Cattle

Treatment is initiated using the drug which is most likely to aid recovery. However, if definitive evidence of improvement is lacking after 48 hours of treatment, a second drug is substituted and its effectiveness evaluated over the subsequent 48-hour period. This process continues until an effective drug is identified. Treatment with that drug is then continued until the animal is judged to have recovered.

1. As each animal is treated for the first time, a prenumbered Lone Star® tag is placed in the ear. This number is written on an individual cattle medication record card (Figure 22) along with the lot number, the date, the rectal temperature, the degree of sickness, and the medication used.
2. Under "degree of illness," the animal is assigned a number which designates a degree of severity: 3 - severely ill (weak; very depressed; labored breathing); 2 - moderately ill (moderately depressed; gaunt); 1 - slightly ill to almost normal.
3. Twenty-four hours later, the rectal temperature and the "degree of illness" are again determined, recorded on the animal's card, and the initial treatment repeated.
4. Forty-eight hours after initial treatment, the rectal temperature and "degree of illness" are again determined and recorded. The 24-hour and 48-hour findings are then compared with the initial rectal temperature and "degree of illness" in order to determine if a favorable response has occurred. If the animal is definitely better, the original antimicrobic is readministered daily (as long as improvement continues) until fever, depression, weakness, heavy breathing and inappetence are absent on two consecutive examinations. In most cases, absence of fever will mean a rectal temperature of 103.0°F or less. The following criteria are indicative of a favorable response to treatment and will ordinarily dictate continued

treatment with a given antimicrobic:

1) If the initial rectal temperature was greater than 104.0°F, a reduction to 103.5°F or less by the 48th hour is indicative of a favorable response.

2. If the initial rectal temperature was between 103.0°F and 104.0°F, progressive reduction toward 103.0°F is indicative of a favorable response. However, if the rectal temperature remains above 103.1°F on three consecutive days, with no tendency to decline toward 103.0°F, the treatment should be changed.

3) If during treatment with a given antimicrobic the rectal temperature should fall to 103.0°F or less, that antimicrobic should always be administered again on the following day, even though the rectal temperature may rebound. On the day following the rebound, the treatment should be changed unless there has been a reduction in the fever to 103.5°F or less.

4) If the initial rectal temperature was less than 103.0°F, a reduction in the degree of illness rating is indicative of a favorable response.

5) If evidence of a favorable response (as previously defined) is lacking after the mandatory number of treatments with a particular antimicrobic, the treatment should be changed.

6) When treating cases: a) which have relapsed two or more times, or b) in which response to treatment does not occur within the first three days after treatment is started, treatment should be continued until fever, depression, weakness, heavy breathing and inappetence are absent on three to five (or more) consecutive examinations, depending on the general health and past history of the individual.

5. At the time of the initial treatment, the animal should be assigned to either the 1) moderately sick, or 2) very sick categories and treated accordingly:

1) Moderately sick cattle: a) start treatment with *sulfamethazine* boluses, administered orally. The dose on the first day is 1-1/2 Gr. per pound of body weight. Thereafter, it is reduced to 1 Gr. per pound of body weight per day. b) If the animal does not respond within two days, change the treatment to procaine penicillin G in a dose of 30,000 μ. per pound of body weight, injected subcutaneously. c) If the animal fails to respond after two days of penicillin therapy, change the treatment to *oxytetracycline,* injected subcutaneously in a dose of 5 mg per pound of body weight. d) If there is no response within two days, change back to procaine penicillin G and increase the dosage to 60,000 μ. per pound of body weight, injected subcutaneously. e) If non-responsive after two days of treatment at this increased dosage, change the treatment to erythromycin (Erythro-200), injected intramuscularly in a dose of 20 mg per pound of body weight. f) If the animal fails to respond to two days of erythromycin treatment, change to tylosin *(Tylan 200),* injected intramuscularly in a dose of 20 mg per pound of body weight. g) If the animal also fails to respond after two days of treatment with tylosin, proceed as follows: (1) If time permits, continue with the daily observations of temperature and degree of illness. Treat for three days with *sulfamethazine.* If no response is obtained, treat for three more days with *procaine penicillin G.* If there is still no response, treat for three days with *oxytetracycline.* Subsequent treatments, if required, should consist of three-day cycles of *sulfamethazine* or *procaine penicillin G.* (2) If time is a factor, discontinue the daily observations of temperature and degree of illness. Place non-responsive cattle in a common pen and treat sequentially with *sulfamethazine, procaine penicillin G* or *oxytetracycline* in three-day treatment cycles. Sort the cattle on the third day of each treatment cycle and send normal-appearing cattle to a convalescent pen.

2) Very sick cattle: a) Start treatment with subcutaneous injection of *procaine penicillin G* and with an intravenous infusion of *sulfamethazine* (or with oral sulfamethazine boluses). b) If the animal fails to respond after two days, change the treatment to *oxytetracycline* injected subcutaneously, and proceed as described in the preceding section.

6. Cattle that relapse within 30 days after a previous illness should be started out on the treatment to which they previously responded. If more than 30 days have elapsed since previous illness, start out treating in the usual way.

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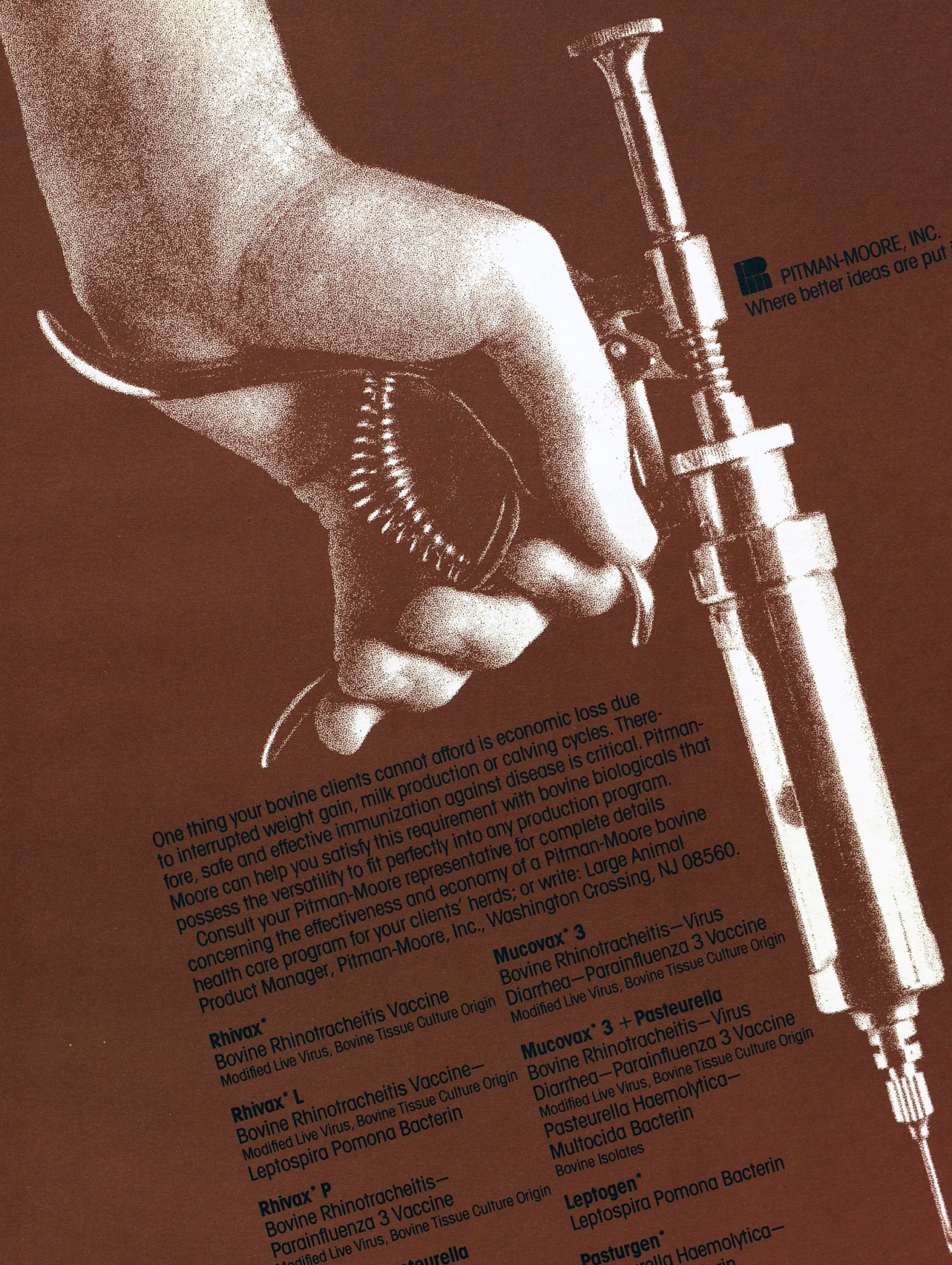

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