References

1. เกรียงศักดิ์ สายธนู, เกรียงศักดิ์ พูนสุข และ สมชัย ศันตระวรศิลป์ "โรคซึ่งเกิดจากการติดเชื้อ แอร์โรโมนาส ไฮโดรฟิล่า" การประชุมวิชาการสัตวแพทย์ครั้งที่ 4 (2519) คณะวิทยาศาสตร์ มหาวิทยาลัยเกษตรศาสตร์

2. เกรียงศักดิ์ สายธนู และ เกรียงศักดิ์ พูนสุข "การศึกษาเพื่อป้องกันและรักษาโรคติดเชื้อ แอร์โรโมนาส ไฮโดรฟิล่าในปลาช่อน โดยใช้ยาต้านจุลชีพ" วารสารโรคสัตว์น้ำ 7,1(2527) : 1-52

3. Watanabe, T, Aoki, T, Ogata, Y. and Egusa, S. "R-factors Related to Fish culturing" Ann. New York Acad. Sci 182(1971) : 383-410.

4. Watanabe, T., Aoki, T., Yada, C, Ogata, Y., Sagawara, K., Saito, T. and Egusa, S. "Fish culturing and R-fectors" Prop. 1 st Int Symp. Infectious Antibiotics, bacterial plasmids and antibiotics resistance, Czechoslovakia, 1972, 131-141.

5. Aoki, T. "Effect of Chemotherapeutics on bacterial Ecology in water of ponds and the Intestinal Tracts of Cultured Fish, Ayu (Plecoglossus altivelis)" Japan J. Microbiol 19(1975) : 7-12.

6. Herwig, N, Garibaldi, L and Wolke, R.E. "A Manual of Fish Pharmacology and Materia Medica" in Handbook of Drugs and Chemicals Used in the Treatment of Fish Diseases pp. 1-271. Charles C Thomas Publisher, Springfield, Illinois, USA, 1979.

7. Snieszko, S.F. "Antibiotics in Fish Diseases and Fish Nutrition" Antibiotics and Chemotherapy 1(1959) : 541-545.

8. Wolf, K. and Snieszko, S.F. "Uses of Antibiotics and Other Antimicrobials in Therapy of Diseases of Fish" Antimicrob. Agt. and Chemother. 1(1964) : 597-603.

9. Martin, A.R. "The Tetracyclines" in Textbook of Organic Medicinal and Pharmaceutical Chemistry (Doerge, R.F.), 8th ed, pp 268-278, J.B. Lippincott Company, U.S.A, 1982.

10. Sande, M.A. and Mandell, G.L. "Tetracyclines and Chloramphenicol" in The Pharmacological Basis of Therapeutics (Gilman, A.G., Goodman, L.S. and Gilman, A.) 6thed, pp. 1181-1199, Macmillan Publishing Co, INC, New York, 1980.

11. Martindale, the Extrapharmacopoeia, 21sted, pp 1216-1223, The Pharmaceutical Press, London, England, 1982.

12. Dornbush, A.C. and Abbey, A. "Microbiological Assay of Tetracyclines" in Analytical Microbiology(Kavanagh, F) pp 365-382, Academic Press, New York, 1972.

13. Faraj, B.A. and Ali, F.M. "Development and Application of a Radioimmunoassay for tetracycline" J Pharmacol. Exp. Ther. 217(1981) : 10-14.

14. Poiger, H. and Schlatter, Ch "Fluorimetric Determination of Tetracycline In Biological Materials" Analyst (1976) : 808-814.

15. Hermansson, J. "Rapid determination of tetracycline and lumecycline in Human Plasma and Urine, Using High Pressure-Performance Liquid Chromatography" Journal of Chromatography 232 (1982) : 385-393.

16. Wright, W.W. "Detection of Antibiotics in Animal tissues" Journal of the AOAC 53(1970) : 219-223.

17. Eksborg, S., Ehrsson, H. and Lonroth "Liquid Chromatographic Determination of tetracycline in plasma and Urine" Journal of Chromatography 185(1979) : 583-591.

18. Muhammud, N. and Bodnar, J.A. "Separation and Quantitation of Chlortetracycline, 4-Epitetracycline, 4-Epianhydrotetracycline and Anhydrotetracycline in Tetracycline by High-Performance Liquid Chromatography" J. Pharm. Sci. 69(1980) : 928-930.

19. Bogert, C.V.D. and Kroun, A.M. "Fluorometeric Determination of Tetracycline in Small Blood and Tissue Samples" J. Pharm. Sci. 70(1981) : 186-189.

20. Kohn, K.W. "Determination of Tetracycline by Extraction of Fluorescent complex" Anal. Chem. 33(1961): 862-866.

21. Honikel, K.O., Schmidt, U., Woltersdorf, W. and Leistner, L. "Effect of Storage and Processing on Tetracycline Residus in Meat and Bones" J. Assoc. Off. Anal. Chem. 61(1978) : 1222-1227.

22. AMA Division of Drugs "AMA Drug Evaluation" 5^{th} ed., pp. 1167-1681 American Medical Association, U.S.A. 1983.

23. Krieg, N and Holt, J.G., Bergey's Manual of Systemic Bacteriology Vol. I pp. 546-548. William & Wilkin Baltimore/London, 1984.

24. Ziv, G. and Sulman, F.G. "Analysis of Pharmacokinetic Properties of Nine Tetracycline Analogues in Dairy Cows and Ewes" Am. J. Vet. Res 35(1974) : 1197-1201.

25. Baggot, J.D., Powers, T.E., Powers, J.D., Kowalski, J.J. and Kerr, K.M. "Pharmacokinetics and Dosage of Oxytetracycline in Dogs" Res. Vet. Sci 24(1977) : 77-81.

26. Harvey, S.C., "Antimicrobial Drugs" in Remington's Pharmaceutical Sciences,pp 1087-1171, The Philadephia College of Pharmacy and Science, 1975.

27. Gilmartin, W.G., Camp, B.J. and Lewis, D.H. "Bath Treatment of Channel Catfish with Three Broad-spectrum Antibiotics" J. Wildlife Disease 12(1976) : 555-559.

28. Meyer, F.P. "Field treatment of Aeromonas liquefaciens infections in Golden Shiners (Notomigonus crysoleucas)" Prog Fish Cult 26(1964) : 33-35 cited in Gilmartin, W.G., Camp. B.J. and Lewish, D.H. "Bath Treatment of Channel Catfish with Three Broad-Spectrum Antibiotics" J Wildlife Disease 12(1976) : 555-559.

29. Nechiporenco, Yu, D., Osaachaya, E.F., Karpenko, I.M. and Mareeva, A.V. Primenic levomitsetina diyabor by Krasnokhoi Karpa Ryhboe Khor 38(1962) : 30-31. cited in Gilmartin, W.G., Camp, B.J. and Lewis, D.H. "Bath Treatment of Channel Catfish with Three Broad-Spectrum Antibiotics" J. Wildlife Disease 12(1976) : 555-559.

30. Flakas, K.G. "Sulfonamide therapy of furunculosis in Brown Trout" Amer Fish Soc 78(1948) : 117-127. cited in Gilmartin, W.G., Camp, B.J. and Lewis, D.H. "Bath Treatment of Channel Catfish with Three Broad-Spectrum Antibiotics" J. Wildlife Disease 12(1976) : 555-559.

31. Amend, D.F. and Fryer, J.L. "The Administration of Sulfonamide Drugs to Adulf Salmon" Progr Fish Cult 30(1968) : 168-172. cited in Gilmartin, W.G., Camp, B.J. and Lewis, D.H. "Bath Treatment of Channel Catfish with Three Broad-Spectrum Antibiotics" J. Wildlife Disease 12(1976) : 555-559.

32. Mccracken, A., Fidgeon, S., O'Brien, J.J. and Anderson, D. "An investigation of Antibiotics and Drug Residues in Fish" J. Appl. Bact. 10(1976) : 61-66.

33. Kaper, J.B., Lockman, H. and Colwell, R.R. "Aeromonas hydrophila : Ecology and Toxigenicity of Isolates from an Estuary" J. Appl. Bact. 50(1981) : 359-377.

34. Kaper, J., Seidler, R.J., Lockman, H. and Colwell, R.R., "Medium for the Presumptive Identification of Aeromonas hydrophila and Enterobacteriaceae" Appl. Environ. Microbiol. 38(1979) : 1023-1026.

35. Shotts, E.B. and Rimler, R. "Medium for Isolation of Aeromonas hydrophila" Appl. Microbiol. 26(1973) : 550-553.

36. Edwards, P.K. and Ewing, W.H., Identification of Enterobacteriaceae, 3rd ed., Burgess publishing Co, Minneapolis, Minn, 1972 cited in Kaper, J., Seidler, R.J., Lockman, H. and Colwell, R.R., "Medium for the Presumptive Identification of Aeromonas hydrophila and Enterobacteriaceae" Appl. Environ. Microbiol. 38(1979) : 1023-1026.

37. Rippey, S.K. and Cabelli, V.J. "Membrane filter procedure for enumeration of Aeromonas hydrophila" Appl. Environ. Microbiol. 38(1979) : 108-113.

38. Davis, W.A., Kane, J.G. and garagusi, V.F. "Human aeromonas infection" Medicine 57(1978) : 267-277.

39. ประกิตติสิน สีหนนท์, วีรวุฒิ มหามนตรี และ วนิดา โพธาราภิก "สภาวะทางธรรมชาติของเชื้อ Aeromonas hydrophila และ สภาวะแวดล้อมที่อาจมีผลโน้มนำต่อการระบาดของโรคที่เกิดจากเชื้อ A. hydrophila" วารสารชมรมโรคปลา 6,3(2526) : 165-174.

40. เกรียงศักดิ์ สายธนู, โสมทัต วงศ์สว่าง และเกรียงศักดิ์ ชูนสุข "ประสิทธิภาพของ แอร์โรโมนาส ไฮโดรฟีล่า วัคซีน 2 ชนิดในการทำให้เกิดแอนติบอดี้ในปลาดุกด้าน" วารสารโรคสัตว์น้ำ 5(2525) : 1-8.

41. เกรียงศักดิ์ สายธนู และเกรียงศักดิ์ พูนสุข "การป้องกันโรคแผลในปลาดุกด้าน โดยการฉีดวัคซีน ผลจากการศึกษาในห้องปฏิบัติการ" วารสารชมรมโรคปลา 3,3(2523) : 153-160.

42. ประกิตต์สิน สีหนนท์, วีรวุฒิ มหามนตรี และ วนิดา โพธารามิก "การศึกษานิเวศ-น์วิทยาของเชื้อ แอร์โรโมนาส ไฮโดรฟีล่า สายพันธ์ F 588" วารสารโรคสัตว์น้ำ 6,3(2526) : 115-125.

43. ประกิตต์สิน สีหนนท์, วีรวุฒิ มหามนตรี, วนิดา โพธารามิก และ สมเกียรติ ปิยะธีรธิติวรกุล "ผลของ Casamino acid และ Paraquat ต่อการติดเชื้อ แอร์โรโมนาส ไฮโดรฟีล่า เอฟ 588 ในปลาช่อน" วารสารโรคสัตว์น้ำ 6,3(2526) : 127-143.

44. Kramer, J., Carter, G.G., Arret, B., Wilner, J., Write, W.W., and Kirshbaum, A. "Antibiotic Residues In Milk Daily Products, and Animal Tissues : Methods, Reports and protocols" National Center for Antibiotic and Insulin Analysis, Food and Drug Administration, Department of Health, Education and Welfare, Washington D.C. 20204, 1974.

45. Baray, A.L. "Agar Dilution Techniques" The Antimicrobic Susceptibility test : Principle and Practices, pp 76-83, Lee & Febiger,Philadelphia, 1976.

46. Daniel, W.W. "Simple Linear Regression and Correlation" in Biostatistics : A Foundation for Analysis in the Health Sciences 2nd ed, pp. 254-303, John Wiley & Sons Inc, New York, 1974.

47. Acar, J.F. "The Disc Susceptibility Test" in Antibiotics in Laboratory Medicine (Lorian, V.) pp. 24-54, William & Wilkins, Baltimore/London, 1980.

48. Powis, G. "A study of the interaction of tetracycline with human serum lipoproteins and albumin" J. Pharm. Pharmac. 26(1974) : 113-118.

49. Adir, J. "Enterohepatic Circulation of tetracycline in Rats" J. Pharm Sci. 64(1975) : 1847-1850.

50. Immelman, A. "Blood levels of oxytetracycline in dogs after oral administration" J. of the South African Veterinary Association 48(1977) : 183-186.

51. Silven,L, Johansson N. and Ljungberg, G. "Terramycin and sulphamerazine residues in muscle,tissue and interior organs of Rainbow Trout after Oral Drug Treatment" Bull. off. int. Epiz. 69(1968) : 1465-1474.

52. Ljungbirg,O., Silven, L., Johanson, N. "Residues of sulphamerazine and terramycin in artificially fed rainbow trout" Proc. 5 th Symp. World Ass. Vet. Hyg. (1965), 565. cited in Mccracken, A, Fidgeon, S., O'Brien, J.J. and Anderson, D. "An Investigation of Antibiotic and Drug Residues in Fish" J. appl. Bact. 10(1976) : 61-66.

53. Thrupp, L.D. "Susceptibility testing of Antibiotics in Liquid Media" in Antibiotics in Laboratory Medicine (Lorian, V), pp 73-113, William & Wilkins, Baltimore/London, 1980.

54. Aoki, T. and Egusa, S. "Drug sensitivity of Aeromonas liquefaciens isolated from freshwater fishes" Bulletin of the Japanese Society of Scientitic Fisheries 37 (1971) : 176-185.

55. Lorian, V., Koike, M., Zak, O, Zanon, U., Sabath, L.D., Grassi, G.G. and Stille, W. "Effects of subinhibitory concentrations of concentrations of antibiotics on bacteria. In Current Chemotherapy Proceedings of the Tenth International Congress of Chemotherapy, Vol I. (Siegenthaler, W., and Luthy, R., Ed.) American Society for Microbiology, Washington, D.C. pp. 72-78, 1977 cited in Sande, M.A. and Mandell, G.L. "Chemotherapy of Microbial Diseases in the Pharmacological Basis of therapeutics (Gilman, A.G, Goodman, L.S. and Gilman, A.) 6th ed, pp 1080-1105; Macmillan Publishing Co. INC, New York, 1980.

56. Lorian, V., and Atkinson, B."Abnormal Forms of Bacteria Produced by Antibiotics" American Journal of Clinical Pathology. 64(1975) : 678-688.

57. Sriubolmas, N. "Effect of Subinhibitory Concentrations of Ampicillin and Gentamicin on Staphylococcus aureus and Pseudomonas aeruginosa" M.Sc. (Pharmacy) Thesis, Chulalongkorn University, 1980.

58. Cowan, S.T. Manual for the identification of medical bacteria, University Printing House, Cambridge, England, 1974.

59. Elliott, R.P., Clark, D.S., Lewis, K.H., Lundbeck, H., Olsen, Jr. J.C. and Simmonsen, B. Microorganisms in food. I Their significance and methods of enumeration 2nd ed, University of Toronto Press, Canada, 1978.

60. Notari, R.E. (ed) in Biopharmaceutics and Clinical Pharmacokinetics : An Introduction 3rd ed, pp. 1-387, Marcel Dekker Inc, New York, 1980.

61. Charumanee, S. "Pharmacokinetics of Ampicillin and Bacampicillin in Healthy Thai Volunteers" M.Sc. (Pharmacy) Thesis, Chulalongkorn University, 1985.

Appendix I

1. Preparation of Media

1.1 Antibiotic Medium 1 (Difco Laboratories)

Ingredients per liter

Bacto-Beef Extract	1.5	gm
Bacto-Yeast Extract	3	gm
Bacto-Casitone	4	gm
Bacto-Peptone	6	gm
Bacto-Dextrose	1	gm
Bacto-Agar	15	gm

To rehydrate the medium, suspend 30.5 gm in 1,000 ml cold distilled water and heat to boiling to dissolve the medium completely. Sterilize in the autoclave for 15 minutes at 15 pounds pressure (121^{o}C) The final pH would be obtained to 6.6 ± 0.1.

1.2 Antibiotic Medium 2 (Difco Laboratories)

Ingredients per liter

Bacto-Beef Extract	1.5	gm
Bacto-Yeast Extract	3	gm
Bacto-Peptone	6	gm
Bacto-Agar	15	gm

To rehydrate the medium, suspend 25.5 gm in 1,000 ml cold distilled water and heat to boiling to dissolve the medium completely.

Adjust the pH to 6.0 ± 0.1. Sterilize in the autoclave for 15 minutes at 15 pounds pressure (121°C).

1.3 <u>Mueller Hinton Medium</u> (Difco Laboratories)

Ingredients per liter

Beef, Infusion from	300 gm
Bacto-Casamino Acids, Technical	17.5 gm
Starch	1.5 gm
Bacto-Agar	17 gm

To rehydrate the medium, suspend 38 gm in 1 liter distilled or deionized water and heat to boiling to dissolve completely. Adjust the pH to 7.3 ± 0.1. Sterilize in the autoclave for 15 minutes at 15 pounds pressure (121°C).

1.4 <u>Nutrient broth</u> (58)

Ingredients per liter

Beef extract	10 gm
Peptone	10 gm
Sodium chloride	5 gm
Distilled Water qs.	1,000 ml

Mix the ingredients in the distilled water and heat to boiling to dissolve the ingredients completely. Adjust the pH to 7.3 ± 0.1. Sterilize in the autoclave for 15 minutes at 15 pounds pressure (121°C)

1.5 Nutrient agar[58]

Ingredients per liter

Peptone	5 gm
Beef extract	3 gm
Sodium chloride	5 gm
Agar	20 gm

Mix all ingredients in 1 liter distilled or deionized water and heat to boiling to dissolve completely. Adjust the pH to 7.3 ± 1. Sterilize in the autoclave for 15 minutes at 15 pounds pressure (121°C).

1.6 Blood agar[58]

Mix the 190 ml sterile nutrient agar (1.5) with 10 ml sheep blood.

1.7 Plate Count agar[59]

Ingredient per liter

Tryptone	5 gm
Glucose	1 gm
Yeast Extract	3 gm
Agar	15 gm

Mix all ingredients in 1 liter distilled or deionized water and heat to boiling to dissolve completely. Adjust the pH to 7.0 ± 0.1. Sterilize in the autoclave for 15 minutes at 15 pounds pressure (121°C).

2. Preparation of solutions

2.1 Normal saline solution

Dissolve 9 gm sodium chloride with 1000 ml distilled water. Sterilize in the autoclave for 15 minutes at 15 pounds pressure (121^{o}C).

2.2 0.1 M phosphate buffer pH 4.5

Dissolve 13.6 gm monobasic potassium phosphate in distilled water and dilute to 1 liter with distilled water. Sterilize in the autoclave for 15 minutes at 15 pounds pressure (121^{o}C).

2.3 Solution for intraperitoneal and intramuscular administration (1 mg/ml)

Dissolve 100 mg tetracycline HCl with normal saline solution and adjust to 100 ml with the solvent. Filter the solution through millipore filter. Discard the first 10 ml filtrate.

2.4 Solution for oral administration (20 mg/ml)

Dissolve 2.0 gm tetracycline HCl with normal saline solution and adjust to 100 ml with the solvent.

Appendix II

1. <u>Determination of the biological half-life</u> ($t\frac{1}{2}$)[60,61]

The biological half life was calculated from the following equation.[60,61]

$$t\tfrac{1}{2} = \frac{\ln 2}{\beta} = \frac{0.693}{\beta}$$

In the present study, it could be observed that after 24 h, the drug levels in serum and muscle after the three routes of administration were decreased slowly. The linear equation[46] was established from 24 h to the terminal observed time. β is the slope of the linear line.

The tetracycline levels in muscle after the intraperitoneal administration was selected for the example of the determination of the biological half-life (see Table 6 and Figure 4). The detail was shown in Figure 16.

2. <u>Determination of under the concentration-time curve</u> (AUC_{o}^{α})[60,61]

The area under the concentration-time curve was calculated by using the trapezoidal rule and the estimation of the rest area from the terminal sampling time to infinity was calculated by using the following equation.

$$AUC^{t}{}_{x\to\alpha} = \frac{C_x}{\beta}$$

where, C_x is the drug level at the terminal sampling time.

The tetracycline levels in muscle after the intraperitoneal administration was selected for the example of the determination of the AUC_o^{α}. The detail was shown in Figure 17 and Table 13.

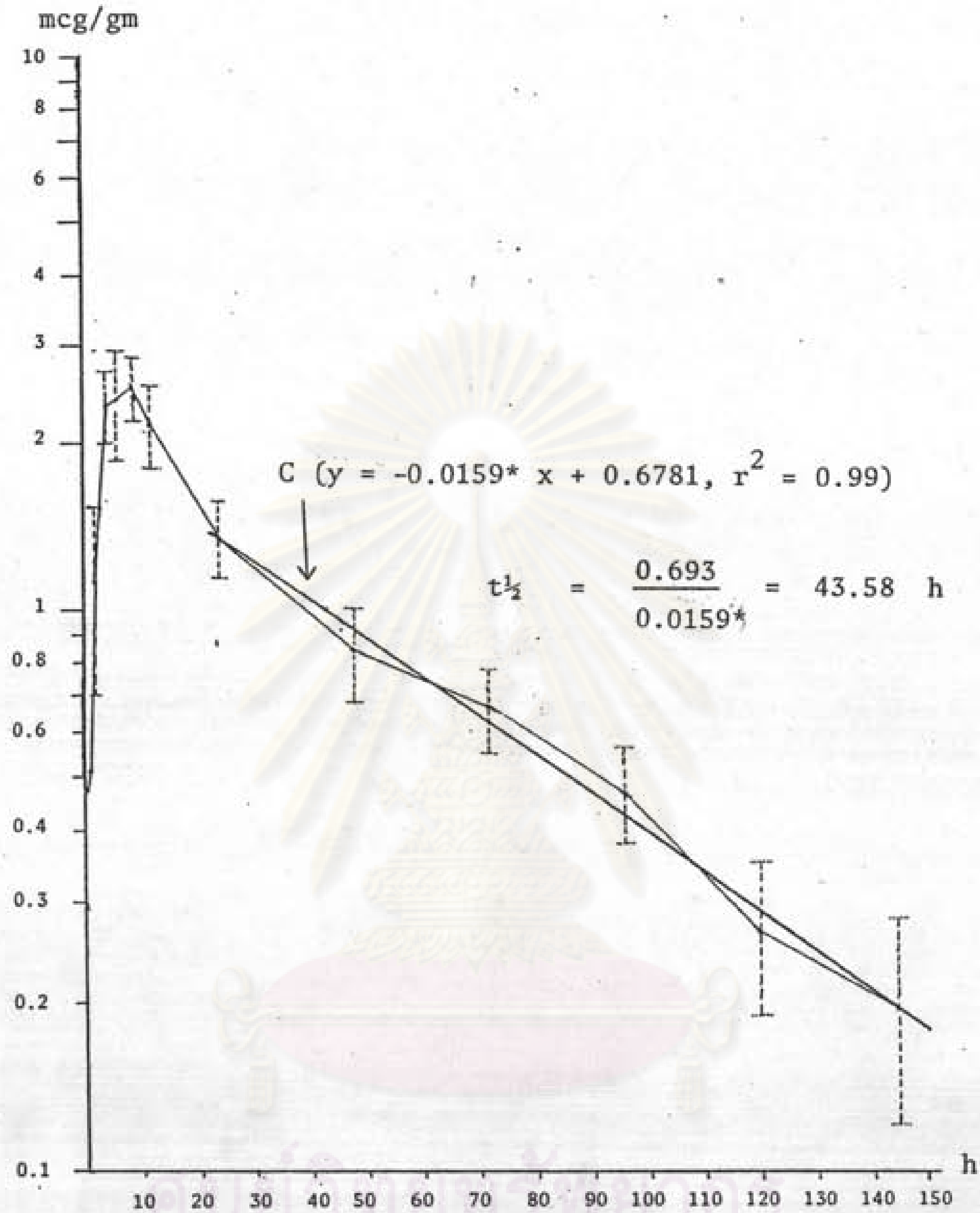

Figure 16 The tetracycline levels in muscle after the intraperitoneal administration and the established linear regression line (C) (from 24 h to 144 h)

y = ln(tetracycline levels in muscle)

x = the time (h) after the intraperitoneal administration

r^2 = the coefficient of determination

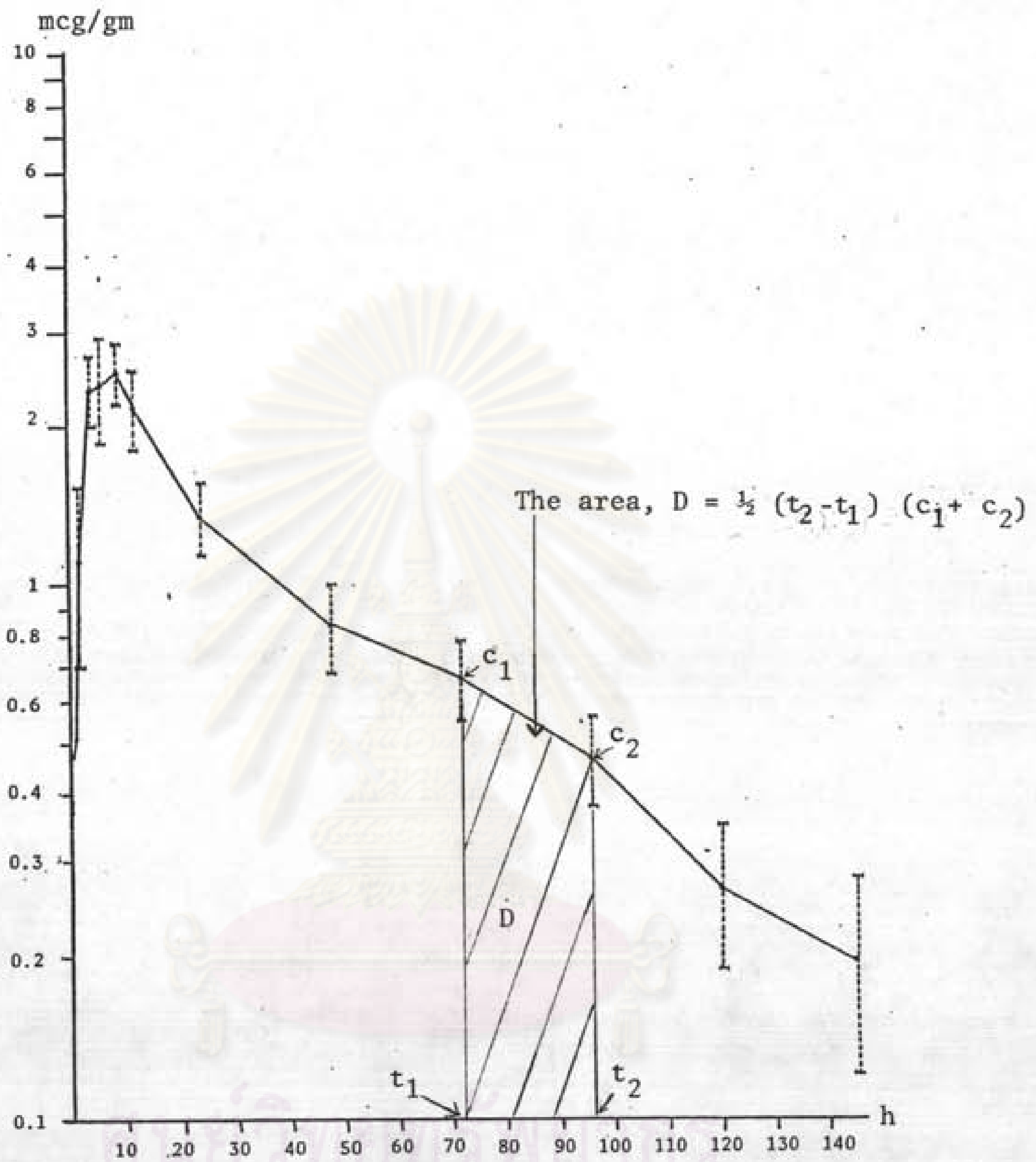

Figure 17 The determination of the area, D of tetracycline levels in muscle after the intraperitoneal administration (c_1 and c_2 are the tetracycline levels in muscle at the sampling time, t_1 and t_2, respectively.)

Table 13 The determination of the AUC_o^{α} of tetracycline in muscle (mcg.h/gm) after the intraperitoneal administration (see Table 7, Figure 16 and Figure 17)

time (n)	AUC_o^{α} of tetracycline in muscle (mcg.h/gm.)	
0 - 0.5	$\frac{1}{2}$ (0.5 - 0) (0 + 0.47)	= 0.118
0.5 - 1	$\frac{1}{2}$ (1 - 0.5) (0.47 + 0.51)	= 0.245
1 - 2	$\frac{1}{2}$ (2 - 1) (0.51 + 1.12)	= 0.815
2 - 4	$\frac{1}{2}$ (4 - 2) (1.12 + 2.31)	= 3.430
4 - 6	$\frac{1}{2}$ (6 - 4) (2.31 + 2.39)	= 4.700
6 - 9	$\frac{1}{2}$ (9 - 6) (2.39 + 2.52)	= 7.365
9 - 12	$\frac{1}{2}$ (12 - 9) (2.52 + 2.17)	= 7.035
12 - 24	$\frac{1}{2}$ (24 - 12) (2.17 + 1.35)	= 21.120
24 - 48	$\frac{1}{2}$ (48 - 24) (1.35 + 0.85)	= 26.400
48 - 72	$\frac{1}{2}$ (72 - 48) (0.85 + 0.67)	= 18.240
72 - 96	$\frac{1}{2}$ (96 - 72) (0.67 + 0.47)	= 13.680
96 - 120	$\frac{1}{2}$ (120 - 96) (0.47 + 0.27)	= 8.880
120 - 144	$\frac{1}{2}$ (144 - 120) (0.27 + 0.20)	= 5.640
144 - α	$\frac{0.20}{0.0159}$	= 12.579
0 - α		=130.247

Vita

Name	Mr. Prairung Mektrairat
Education	Bachelor of Pharmacy, on March, 1981, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand.
Experience	Pharmacist of COERR Hospital (August, 1981-June, 1982), Panat Nikhom Refugees Camp, Chonburi, Thailand. Pharmacist of the Bukalo Pharmacy (July, 1982-July, 1983), Bangkok, Thailand.
Position	Full-time Pharmacist of the S.Co. Pharma LTD. (since December, 1984), Bangkok, Thailand. Part-time Pharmacist of the Samrong General Hospital (since November, 1984), Samuthprakarn, Thailand.