ALTERED THEOPHYLLINE KINETICS DURING A VIRAL ILLNESS

by

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The effect of an acute viral infection on the distribution of drugs is largely unknown. Recent reports in the literature have suggested that theophylline kinetics may be altered during an acute viral illness. To date, no well controlled prospective studies with an adequate number of normal volunteers and asthmatics have been performed. The purpose of this preliminary study was to detect any change in theophylline clearance in healthy volunteers and asthmatics experiencing an acute viral illness to determine if a larger scale study is indicated.

Theophylline is a mainstay of therapy in patients with acute and chronic airway disease. The clearance of theophylline can be altered in many ways including a smoking habit,[1] various disease states,[2] drug interactions,[3-5] and diet.[6,7] Recently, interest has focused on the role of influenza immunizations and upper respiratory viral infections in de-

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1. Jusko W.J., et al. Enhanced biotransformation of theophylline in marijuana and tobacco smokers. Clin Pharmacol Ther 1978;4(24):406-410.

2. Powell J.R., et al. Theophylline disposition in acutely ill hospitalized patients. Am Rev Respir Dis 1978;118:229.

3. Landay R.A., et al. Effect of phenobarbital on theophylline disposition. J Allergy Clin Immunol 1978;62:37.

4. Kozak P.P., et al. Administration of erythromycin to patients on theophylline. J Allergy Clin Immunol 1977;60:149.

5. Weinburger M., et al. Troleandomycin (TAO): an inhibitor of theophylline metabolism. J Allergy Clin Immunol 1976:57:262.

6. Caldwell J.,et al. The influence of dietary methyxanthines on the pharmacokinetics of intravenously administered theophylline. Br J Clin Pharmacol 1977;4:637.

7. Welling P.G., et al. Influence of diet and fluid in bioavailability of theophylline. Clin Pharmacol Ther 1975;4(17):475-480.

creasing theophylline clearance. Renton,[8] et al have presented results suggesting that the elimination of theophylline following an influenza vaccine is significantly decreased. Their investigation involved only four healthy volunteers(two women and two men) with no ages given, and diet was controlled only for methylxanthines. In contrast, Goldstein,[9] et al studied sixteen patients with chronic airway disease who were being treated with a theophylline containing medication. Serum theophylline levels were measured 24 hours before and 24 hours after influenza vaccination with no significant alteration in blood levels to theophylline. Chang,[10] et al determined the plasma half-life of theophylline in six children with chronic asthma during and one month following a viral upper respiratory tract infection. Their results demonstrated a significantly longer theophylline half-life during serologically proven upper respiratory tract infection in five of the six asthmatic children. One subject experienced acute theophylline toxicity during a viral illness. Fleetham[11] assessed theophylline disposition on four occasions over a three month period in a single healthy 32 year old male volunteer who suffered one upper respiratory infection. He found an increase in theophylline half-life due to a decreased clearance rate. A recent study by Kraemer,[12] et al

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8. Renton K.W., et al. Decreased elimination of theophylline after influenza vaccination. Can Med Assoc J 1980;123:2-8-290.

9. Goldstein R.S., et al. Letter. Can Med Assoc J 1982;126:470.

10. Chang K.C., et al. Altered theophylline kinetics during acute respiratory infections. Lancet 1978;1(8074):1132.

11. Fleetham J.A., et al. Theophylline pharmacokinetics and respiratory infections. Lancet 1978;2(8095):898.

12. Kraemer M.J., et al. Altered theophylline clearance during an influenza B outbreak. Pediatrics 1982;69(4):476-480.

revealed that during an influenza B outbreak, eleven children whose asthma had previously been controlled with a stable theophylline dose, developed theophylline toxicity on this same dose. The toxicity appeared to be related to a decrease in theophylline clearance which returned to normal in one to three months.

One hypothesis for the observed decrease in the plasma half-life of theophylline during an acute viral infection may be due to a reduction in the capacity of the cytochrome P-450 system of the liver to metabolize theophylline.[13,14] Renton[15] demonstrated this hypothesis in animals by inducing the production of interferon which produced a decrease in hydroxylation by cytochrome P-450. Renton believes that agents that induce the formation of interferon, including viruses, bacteria, and vaccines, may alter drug biotransformation and elimination.

Theophylline is a widely used agent with a narrow therapeutic margin. The hypothesis to be tested: is there a statistically significant change in theophylline clearance between healthy subjects and asthmatics experiencing a viral infection and those same individuals once their viral infection has subsided? Due to the chance of severe side effects from theophylline, it is important to verify whether of not there is a change in the clearance of theophylline during a viral upper respiratory infection so that necessary dosage adjustments can be instituted.

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13. Renton K.W. and Mannering G. Depression of the hepatic cytochrome P-450 mono-oxygenase system by administered tilorone. Drug Metab Dispos.1976;4:223.

14. Renton K.W., et al. Journal of Microsomes and Drug Oxidation. 1977; (ed. V. Ullrich) Oxford:483.

15. Renton K.W. and Mannering G. Depression of the hepatic cytochrome P-450-dependent monooxygenase systems with administered interferon inducing agents. Biochem Biophys Res Commun. 1976;73:343.

METHODOLOGY

Three nonsmoking adult asthmatics and eight healthy nonsmoking adult volunteers participated in the study after providing informed consent. The protocol was reviewed and accepted by the investigational review board of the Center for Health Sciences. Subject selection was based on: 1) good health as confirmed by a collaborating physician, 2) no history of heart, renal, liver or gastric disease, 3) no prior or current history of theophylline or caffeine allergy, 4) no current smoking habit(cigarette or marijuana), 5) no current potentially interacting drugs, 6) no recent influenza vaccination.

Study participants were instructed not to take any other medications at the time of the study period (with the exception of oral contraceptives, inhaled bronchodilators and inhaled beclomethasone) and were instructed to abstain from coffee, tea, chocolate, and any caffeine containing soda during the study period. The study period was defined as twelve hours before the single dose of theophylline was given until the last blood sample was taken. Each subject received a solution of theophylline, 3.6mg/kg as Elixophyllin^{R} (Berlex) orally when each asthmatic or normal subject had maximum symptoms associated with an upper respiratory viral infection such as fever, sore throat, malaise, coryza and sneezing as confirmed by the collaborating physician. Each theophylline dose was given at 8:00 AM after a standardized light meal of cereal, (Special K, 5/8 oz.) a glass of milk (8 oz.) and a glass of orange juice (8 oz.). No other food was allowed until three hours after ingestion of the dose. Plasma samples (8ml) were drawn either by direct venipuncture or via an indwelling heparin well in a forearm vein at times 0, one-half, one two, four, six, eight and twelve hour(s) after the single dose of

theophylline. After the upper respiratory infection had resolved, the same procedure was repeated on all healthy volunteers after a "wash out" period of at least two weeks. Each blood sample was collected in a heparinized 10ml evacuated tube and centrifuged for ten minutes at 3000 G. The plasma was recovered and stored at -20° C until subsequent analysis.

Asthmatics performed the same procedure outlined for healthy volunteers. Asthmatics that were currently taking a long acting theophylline preparation were converted to the short acting aminophylline preparation (Searle, N.J.) at the start of their upper respiratory infection. The short acting form of aminophylline was taken for at least twenty-four hours before ingesting the assigned dose of theophylline oral solution. Asthmatics were not allowed to ingest another aminophylline dose until 8:00 PM at the conclusion of the study. Each asthmatic was allowed to use their inhalers more frequently during the study period if needed.

An FEV_1 (amount of air the lungs can forcibly expel in one second) was performed on all the study participants (healthy volunteers and asthmatics) between 1200noon-1:00 PM at the peak of their upper respiratory infection and again when each subject had recovered and repeated the study.

The concentration of theophylline in each plasma sample was determined by a high pressure liquid chromatography procedure adapted from Upton,[16,17] as described by Welling(unpublished). The extraction and

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16. Upton R.A., et al. Evaluation of the absorption from some commercial enteric-release theophylline products. J Pharmaco Biopharm 1980;8: 151-164.

17. Upton R.A., et al. Evaluation of the absorption from some commercial sustained-release theophylline products. J Pharmaco Biopharm 1980; 8:131-149.

chromatographic procedures are as follows. To 0.5 ml of plasma was added 100 microliters of a 15 microgram/ml aqueous solution of internal standard β-hydroxyethyltheophylline,[18] and 8 ml of 5% isopropanol[19] in dichloromethane.[20] For preparation of standard curves, 100 microliters of aqueous solutions of theophylline[19] were also added. After shaking for five minutes at low speed and centrifuging for five minutes at 3000 G, the upper aqueous phase was aspirated and discarded. The remaining organic phase was transferred to a clean 12 ml centrifuge tube and evaporated to dryness under nitrogen at 40° C (waterbath). The walls of each test tube were rinsed with one milliter of dichloromethane and again evaporated to dryness. The residue was reconstituted into 100 microliters of mobile phase and vortexed before injecting 20 microliters of each sample into the chromatograph.

The high pressure liquid chromatography system consisted of a solvent pump,[21] a fixed volume (20 microliter) sample injection valve,[22] a 7 cm x 2mm precolumn[23] and a 30 cm x 4 mm 10-micrometer particle size reversed phase octadecyl column[24] and a variable length wavelength UV detector[25] set at 254 nm. All chromatograms were reported at a chart speed of

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18. Purity 99%, Sigma Chemical Co., St. Louis, Mo. 63178 (lot 39C-0257).
19. MCG Reagents, Cincinnati, Ohio, Lot 3N09J.
20. HPLC Grade, Burdick and Jackson, Muskegon, MI., Lot AH544.
21. Beckman Pump, Model 110A, Arlington Heights, Illnois 60004.
22. Model 210, Altex Scientific, Berkley, California 94710.
23. CO: Pell ODS, 30-38 micrometer, Whatman Inc., Clifton, N.J. 07014
24. MCH-10 Micropak, Varian Associates, Palo Alto, Calif, 94303.
25. Model 160, Beckman, Arlington Heights, Illinois 60004

10 cm/hour.

The mobile phase was prepared by adding 5.5ml of 1M phosphoric acid and 160ml of acetonitrile[26] to 1500 ml of distilled water to produce a 9.6% aqueous solution of acetonitrile, pH 3.5-4.0. The flow rate was 2ml/min with a pump pressure of approximately 1000 psi. Retention times for theophylline and internal standard were five and six minutes respectively. The theophylline concentration of each sample was determined by the peak height ratio method, comparing the standard to the unknown concentration of theophylline. On the day of each assay, samples of standard theophylline solutions in plasma (0.125, 0.25, 0.5, 5, 10, 20, and 25 microliters/ml) were used for determination of a calibration curve.

Individual plasma levels of theophylline were examined to obtain maximum drug concentrations, C_{max}, areas under the drug plasma profiles 0 to 12 hours, and the clearance of the drug from the plasma. Individual profiles were fitted by non-linear regression to Equation 1, where C is the concentration of drug in plasma at any time t, Ka and Kel are first order rate constants. Ka is the absorption of drug into plasma. Kel is elimination of drug from plasma. The time interval, t_o, is the interval

$$C = \frac{FD}{V}\left(\frac{Ka}{Ka-Kel}\right)\left(e^{-Kel(t-t_o)} - e^{-Ka(t-t_o)}\right) \quad \text{Equation 1}$$

between drug administration and the appearance of measurable drug in plasma. Initial prameter estimates were obtained graphically (Graph 1-11) and final estimates were obtained using the non-linear program NREG on a

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26. Burdick and Jackson, Muskegon, Michigan, Lot AH504.

Univac Model 1100 digital computer. A paired Students t-test was used to evaluate the data.

RESULTS

After reaching peak levels, theophylline plasma concentrations declined exponentially with time. The elimination half-life of theophylline was 5.54 ± 2.69 hours (mean ± SD) for all eleven subjects (both asthmatics and normal volunteers) during the non-viral period. The half-life was 5.96 ± 3.50 hours during the viral infection for all eleven subjects. The three asthmatics had a half-life of 7.19 ± 3.31 hours without a viral infection while during the viral infection the half-life was 8.60 ± 4.76 hours. The eight healthy subjects had a half-life of 4.92 ± 2.38 hours without a viral infection. During a viral infection these same patients had a half-life of 4.98 ± 2.63 hours. All half-life data is listed in Table II.

Other parameters, Ka(the absorption rate constant), Ke(the elimination rate constant), FD/V(fraction of dose absorped x dose/volume of distribution), AUC(area under the curve) and clearance(amount of drug cleared from the body), were similarly evaluated. These are listed in Tables III-VII.

A paired Students t-test was used to evaluate the pharmacokinetic parameters of Ka, Ke, $t_{1/2}$, FD/V, AUC, and clearance. Each group was compared separately(normal subjects from asthmatics) and jointly. There was no statistically significant difference for any of the parameters between patients having a viral infection and the same patients without an infection for either of the groups(normals vs asthmatics). There was

also no significant difference in the FEV_1 between normal healthy subjects and asthmatics before and after a viral infection.

DISCUSSION

This study was performed in order to detect if a viral upper respiratory infection produces a significant change in theophylline pharmacokinetics. Other cases and studies previously cited have produced inconclusive evidence as to whether or not theophylline clearance is altered in adults with an upper respiratory infection.

This study involving eight healthy adults and three adult asthmatics, revealed the largest clearance difference in two of the healthy adults and two of the three asthmatics. These subjects experienced up to a two fold increase in clearance of theophylline after resolution of their upper respiratory infection.

Other patient differences were also noted. Six of the eight healthy subjects revealed an increase in theophylline clearance during their viral infection. One of the three asthmatics experienced an increase in theophylline clearance during the viral episode.

Half-lives did not always correlate with differences in clearance. In subjects 1 and 2, the half-life decreased as well as the clearance when neither subject had a viral infection. In subjects 3,6, and 8, the clearance of theophylline decreased during their non-viral state while their half-life increased. In the asthmatic group, subjects 10 and 11 experienced an increase in clearance while their half-life decreased during their non-viral state. Subject 9 experienced the reverse.

Half-lives did not follow a single pattern. In subjects 1, 2, 5, 7,

10, 11, the half-life decreased as Fleetham[11] studied and reproduced in the same patient two other times.
Chang[10] also observed a decrease in half-life one month after a viral illness in six children with chronic asthma. In subjects 3, 6, 8, and 9, the half-life increased after resolution of the viral infection which conflict with the findings of Fleetham and Chang.

Results of this study add to the confusion of published literature reports. The majority of investigations in this area have involved children. Kraemer[12] retrospectively studied eleven cases of asthmatic children who after having an influenza B infection experienced some form of theophylline toxicity. All eleven children had previously been in control of their asthma. Kraemer presumed this toxicity was caused by an alteration in theophylline clearance. The study by Chang[10] involved ten asthmatic children who were studied during and one month following their viral episodes. Chang revealed the theophylline half-life to be significantly longer during serologically proven upper respiratory infection in five of six asthmatic children. Fleetham[11] is the only published study involving an adult male volunteer who after suffering an upper respiratory viral infection experienced a prolongation in theophylline half-life.

This is the first published study involving more than four healthy adult volunteers and adult asthmatics which compares the clearance of theophylline in patients experiencing a viral infection and after recovery. Previous studies have been cited in children, but the literature is scarce involving adults. Although clearance differences are shown in this study, these differences fail to represent a statistical signifi-

cance. A sample size of three adult asthmatics is too small to reveal any significant results but eight healthy adult subjects was large enough to show that in adults as compared to children, interpatient variability exists. Because of this variability, generalizations regarding theophylline clearance in children should not be extrapolated to adults.

Additional research would be beneficial in solving the question of whether of not theophylline clearance changes during a viral infection in adult asthmatics and healthy adults. Patient variation found in this preliminary comparison should prohibit the modification of therapy based on previous literature reports. Since this study revealed patient variability, a larger scale study would be beneficial in determining the extent of this variability before generalizations can be extrapolated to the population as a whole.

TABLE I

STUDY POPULATION

SUBJECTS	SEX	AGE	DOSE	LEAN BODY WEIGHT	FEV_1-VIRAL	FEV_1-NONVIRAL
1	M	25	245 mg	69 Kg	3.7 L	3.7 L
2	M	35	243 mg	67 Kg	3.8 L	3.7 L
3	F	31	180 mg	50 Kg	2.7 L	2.7 L
4	F	27	200 mg	55 Kg	3.3 L	3.7 L
5	M	28	288 mg	80 Kg	4.0 L	4.6 L
6	M	24	300 mg	83 Kg	5.2 L	5.2 L
7	M	33	232 mg	68 Kg	3.9 L	4.1 L
8	F	27	230 mg	64 Kg	3.6 L	3.6 L
ASTHMATICS						
9	M	29	288 mg	80 Kg	4.2 L	4.3 L
10	F	25	190 mg	53 Kg	2.2 L	2.3 L
11	F	22	200 mg	55 Kg	2.9 L	3.0 L

TABLE II

Plasma half-lives of theophylline in normal adult volunteers with and without an upper respiratory viral infection.

SUBJECT	VIRAL INFECTION	NO INFECTION
1	5.8 hr	4.3 hr
2	5.2 hr	4.5 hr
3	5.1 hr	8.8 hr
4	1.5 hr	1.5 hr
5	9.1 hr	6.2 hr
6	3.5 hr	6.0 hr
7	7.7 hr	2.1 hr
8	2.0 hr	6.0 hr
MEAN	5.0 hr	4.9 hr
SD	2.6 hr	2.4 hr

Plasma half-lives of theophylline in three adult asthmatics with and without an upper respiratory viral infection.

9	6.0 hr	10.9 hr
10	5.7 hr	4.6 hr
11	14.1 hr	6.1 hr
MEAN	8.6 hr	7.2 hr
SD	4.8 hr	3.3 hr

For all eleven subjects the MEAN and STANDARD DEVIATION:

MEAN	6.0 hr	5.5 hr
SD	3.5 hr	2.7 hr

TABLE III

The absorption (Ka) rate constant in normal adult volunteers with and without an upper respiratory viral infection:

SUBJECT	VIRAL INFECTION	NO INFECTION
1	1.8 hr^{-1}	0.3 hr^{-1}
2	2.0 hr^{-1}	3.5 hr^{-1}
3	2.0 hr^{-1}	1.0 hr^{-1}
4	0.5 hr^{-1}	0.5 hr^{-1}
5	1.3 hr^{-1}	3.1 hr^{-1}
6	0.9 hr^{-1}	3.6 hr^{-1}
7	2.7 hr^{-1}	0.3 hr^{-1}
8	0.4 hr^{-1}	1.0 hr^{-1}
MEAN	1.4 hr^{-1}	1.7 hr^{-1}
SD	0.8 hr^{-1}	1.5 hr^{-1}

The absorption rate constant (Ka) in asthmatics with and without an upper respiratory viral infection.

9	1.7 hr^{-1}	2.6 hr^{-1}
10	5.1 hr^{-1}	3.0 hr^{-1}
11	4.2 hr^{-1}	2.0 hr^{-1}
MEAN	3.7 hr^{-1}	2.6 hr^{-1}
SD	1.8 hr^{-1}	0.5 hr^{-1}

For all eleven subjects the mean and standard deviation:

MEAN	2.0 hr^{-1}	1.9 hr^{-1}
SD	1.5 hr^{-1}	1.3 hr^{-1}

TABLE IV

The elimination rate constant, K_{el} (hr^{-1}) in normal adult volunteers with and without an upper respiratory viral infection.

SUBJECT	VIRAL INFECTION	NO INFECTION
1	0.12	0.16
2	0.13	0.15
3	0.14	0.08
4	0.47	0.47
5	0.08	0.11
6	0.20	0.12
7	0.09	0.33
8	0.35	0.12
MEAN	0.20	0.19
SD	0.14	0.14

The elimination rate constant, K_{el}(hr^{-1}) in asthmatics with and without an upper respiratory viral infection.

SUBJECT	VIRAL INFECTION	NO INFECTION
9	0.12	0.06
10	0.12	0.15
11	0.05	0.11
MEAN	0.10	0.11
SD	0.04	0.04

For all eleven subjects the mean and standard deviation are:

MEAN	0.17	0.17
SD	0.13	0.12

TABLE V

The parameter $\frac{FD}{V}$ in normal adult volunteers with and without an upper respiratory viral infection. (Units are in mg/l).

SUBJECT	VIRAL INFECTION	NO INFECTION
1	3.5	6.9
2	3.1	3.7
3	4.5	4.6
4	9.4	9.9
5	3.0	3.7
6	3.1	3.5
7	3.9	4.5
8	7.2	4.2
MEAN	4.7	5.1
SD	2.4	2.2

The parameter $\frac{FD}{V}$ in asthmatics with and without an upper respiratory viral infection.

SUBJECT	VIRAL INFECTION	NO INFECTION
9	4.4	3.9
10	10.8	6.8
11	6.5	6.5
MEAN	7.2	5.7
SD	3.3	1.6

For all eleven subjects the mean and standard deviation are:

MEAN	5.4	5.3
SD	2.7	2.0

TABLE VI

The parameter AUC (area under the curve), in normal adult volunteers with and without an upper respiratory viral infection. (Units are mg/ml/hr).

SUBJECT	VIRAL INFECTION	NO INFECTION
1	29	43
2	23	24
3	33	58
4	20	21
5	39	33
6	16	30
7	43	14
8	21	37
MEAN	28	32
SD	9.6	14

The parameter AUC, in adult asthmatics with and without an upper respiratory viral infection.

SUBJECT	VIRAL INFECTION	NO INFECTION
9	38	61
10	89	45
11	133	58
MEAN	87	55
SD	48	8.5

For all eleven subjects the mean and standard deviation are:

MEAN	44	39
SD	36	16

TABLE VII

The clearance of theophylline (ml./min.) in normal adult volunteers with and without an upper respiratory viral infection.

Subject	Viral Infection	No Infection
1	140	95
2	169	160
3	92	52
4	167	159
5	123	144
6	319	166
7	95	299
8	184	105
Mean	161	148
SD	72	73

The clearance of theophylline (ml./min.) in asthmatics with and without an upper respiratory viral infection.

Subject	Viral Infection	No Infection
9	126	78
10	36	71
11	25	58
Mean	62	69
SD	55	10

For all eleven subjects the mean and standard deviation are;

Mean	134	126
SD	80	71

TABLE VIII

Concentrations(mcg/ml) at various times after the dose.(NV=nonviral, V= viral infection)

SUBJECTS		TIME 0	0.5	1	2	4	6	8	12
1	NV	0.35	0.64	1.31	---	3.37	3.02	2.59	1.91
	V	0.43	1.93	2.79	2.85	2.34	1.83	1.52	0.83
2	NV	0.05	2.94	3.13	2.78	2.3	1.75	2.04	1.18
	V	0.00	1.67	2.63	2.33	1.94	1.41	1.08	0.76
3	NV	0.04	1.31	2.70	4.5	3.13	2.89	2.53	2.07
	V	0.53	2.57	3.45	3.42	2.92	2.18	1.53	0.94
4	NV	0.51	1.58	2.48	4.34	2.54	1.46	1.04	0.24
	V	0.65	0.85	2.89	4.05	2.52	1.36	0.89	0.14
5	NV	0.4	2.84	3.27	3.14	2.88	1.09	1.77	1.32
	V	0.72	1.25	2.10	2.57	2.23	1.75	2.04	1.18
6	NV	0.29	2.82	3.0	2.92	2.17	1.89	1.38	0.82
	V	0.36	1.33	1.54	2.04	1.89	1.13	0.75	0.43
7	NV	0.65	0.29	0.90	1.59	1.94	1.47	0.053	0.57
	V	0.37	2.93	3.08	3.16	3.61	1.68	2.42	1.19
8	NV	0.10	0.96	2.87	3.06	3.03	2.07	.91	1.36
	V	0.65	0.44	1.87	2.73	2.48	1.80	1.18	0.54
9	NV	1.12	2.80	3.33	3.51	3.39	2.48	2.26	----
	V	1.0	3.17	2.35	3,99	2.97	2,48	1.65	----

TABLE VIII (con't)

10	NV	2.67	5.3	5.29	5.67	3.79	2.68	1.85	0.98
	V	5.70	9.55	9.81	8.39	7.62	5.64	4.39	2.19
11	NV	3.65	4.06	5.20	5.33	4.75	3.12	2.51	2.02
	V	3.4	5.67	6.12	5.34	6.20	5.11	4.58	3.12

TABLE IX

STATISTICAL ANALYSIS

Analysis was done on all variables using a paired Students t-test. Each subject served as their own control. For each variable (Ka, Ke, $t_{1/2}$, FD/V, AUC, FEV_1 and clearance) the 8 healthy subjects were evaluated separately from the three asthmatics and then all eleven subjects were evaluated together.

8 Non-asthmatic subjects: df=7

	Ka	Kel	$t_{1/2}$	FD/V	AUC	clearance
$t_{calc.}$	.401	.081	.046	.698	.772	.378

None of these values is statistically significant at $p > 0.05$.

3 Asthmatic subjects: df=2

	Ka	Kel	$t_{1/2}$	FD/V	AUC	clearance
$t_{calc.}$	1.05	.414	.380	1.19	1.100	.239

None of these values is statistically significant at $p > .05$.

All 11 patients: df=10

	Ka	Kel	$t_{1/2}$	FD/V	AUC	clearance
$t_{calc.}$	.25	.03	.35	.16	.56	.306

None of these values is statistically significant at $p > .05$.

FEV_1 for 8 healthy subjects: df = 7

$t_{calc.} = 1.70$ This value is statistically significant at $.10 > p > .05$.

FEV_1 for 3 asthmatics: df=2

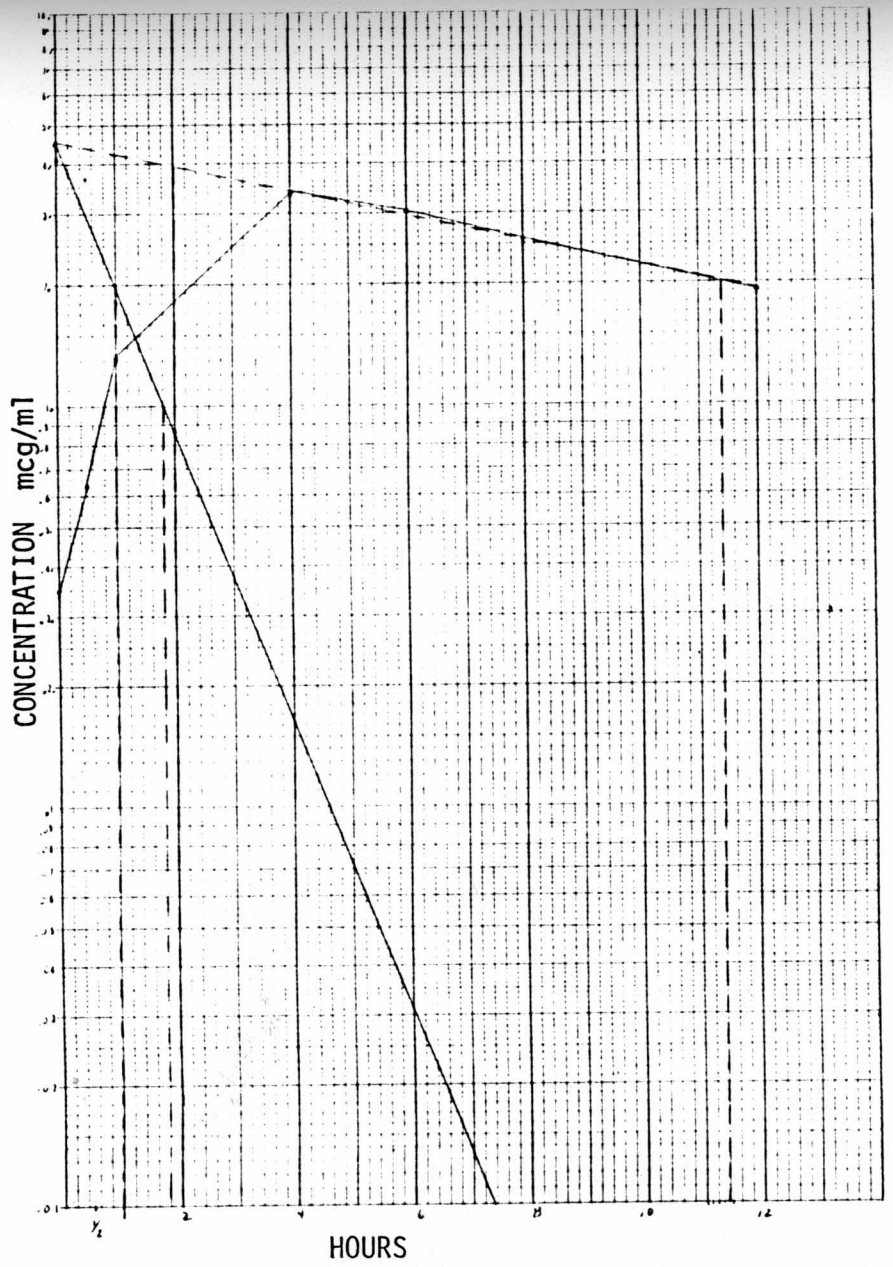
$t_{calc.} = 6.38$ This value is statistically significant at $p < .025$.

FEV_1 for 11 subjects: df=10

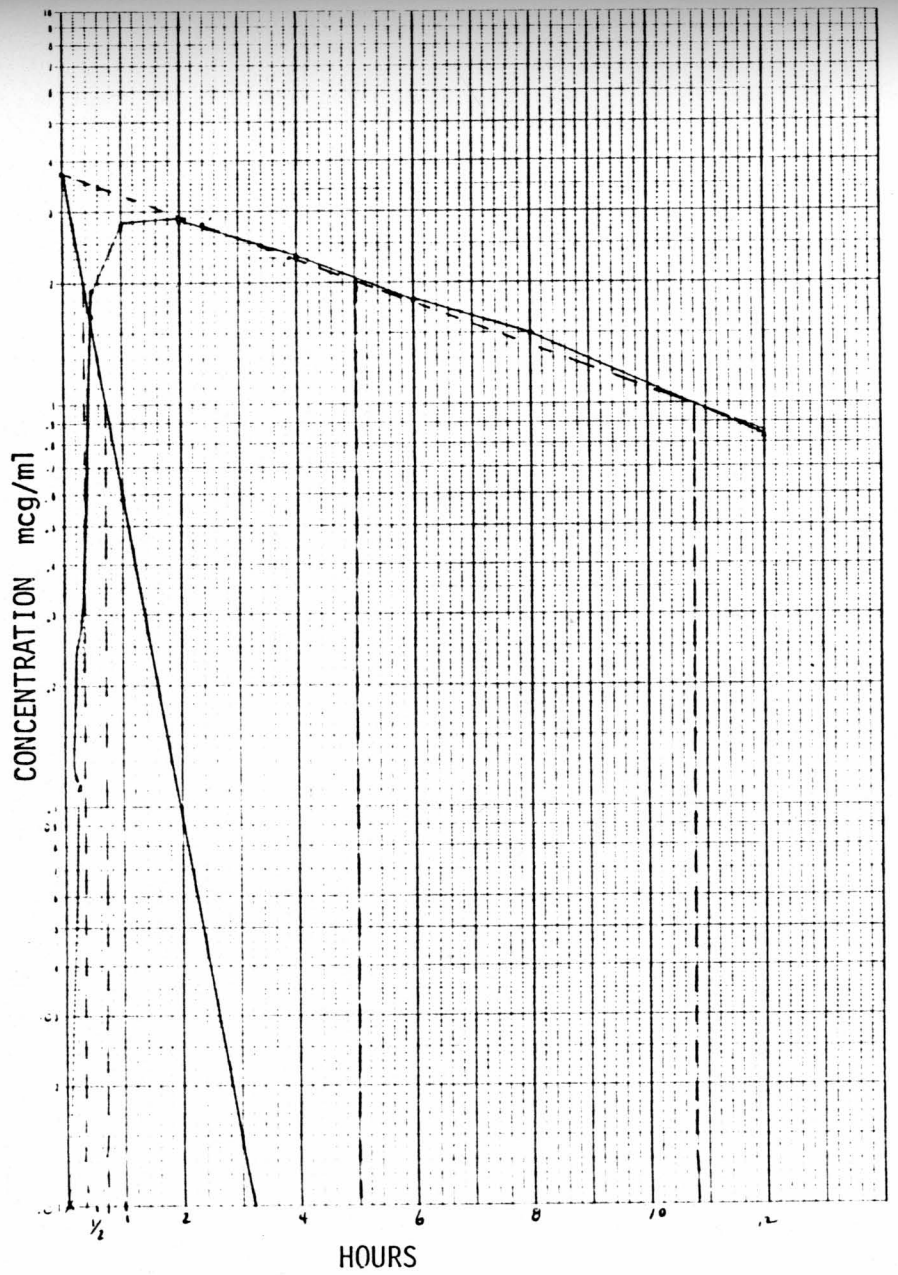
$t_{calc.} = 2.06$ This value is statistically significant at $p < .05$.

TABLE IX-cont.

The method as outlined be Daniel (Biostatistics: A Foundation For Analysis In the Health Sciences, p.182) was followed for all calculations concerning the paired Students t-test. A programmable Casio FX-520P calculator was utilized for computation of all t-values.

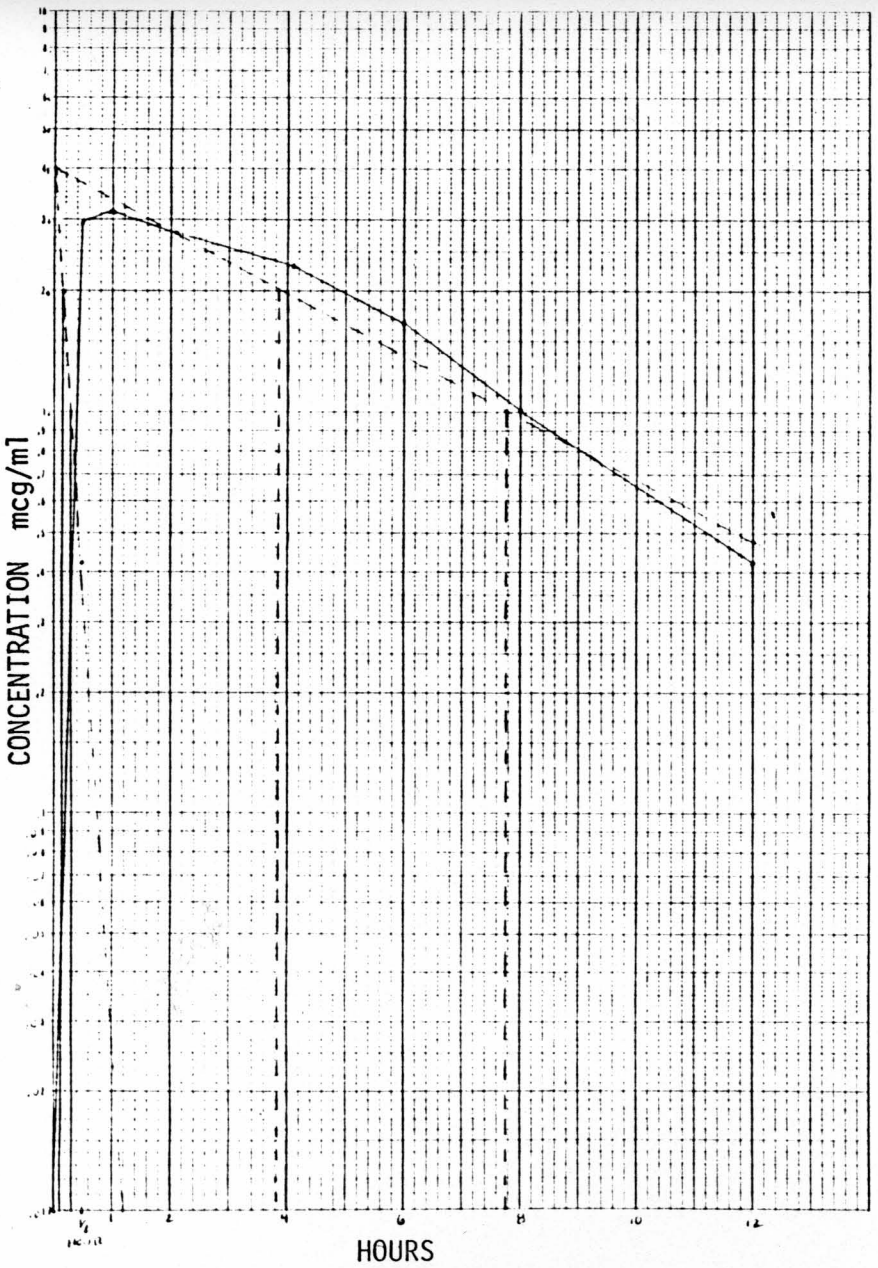


NONVIRAL INFECTION

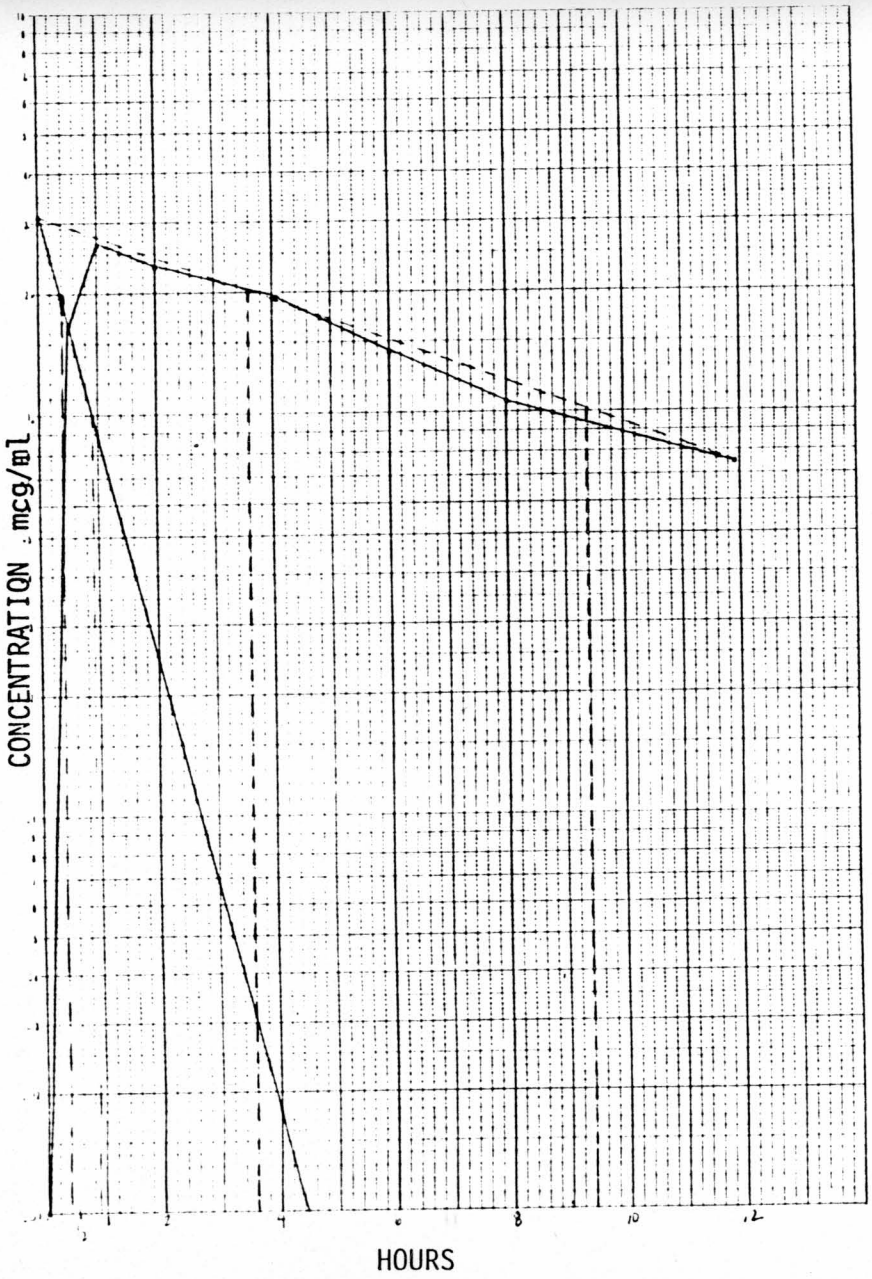


VIRAL INFECTION

SUBJECT 1

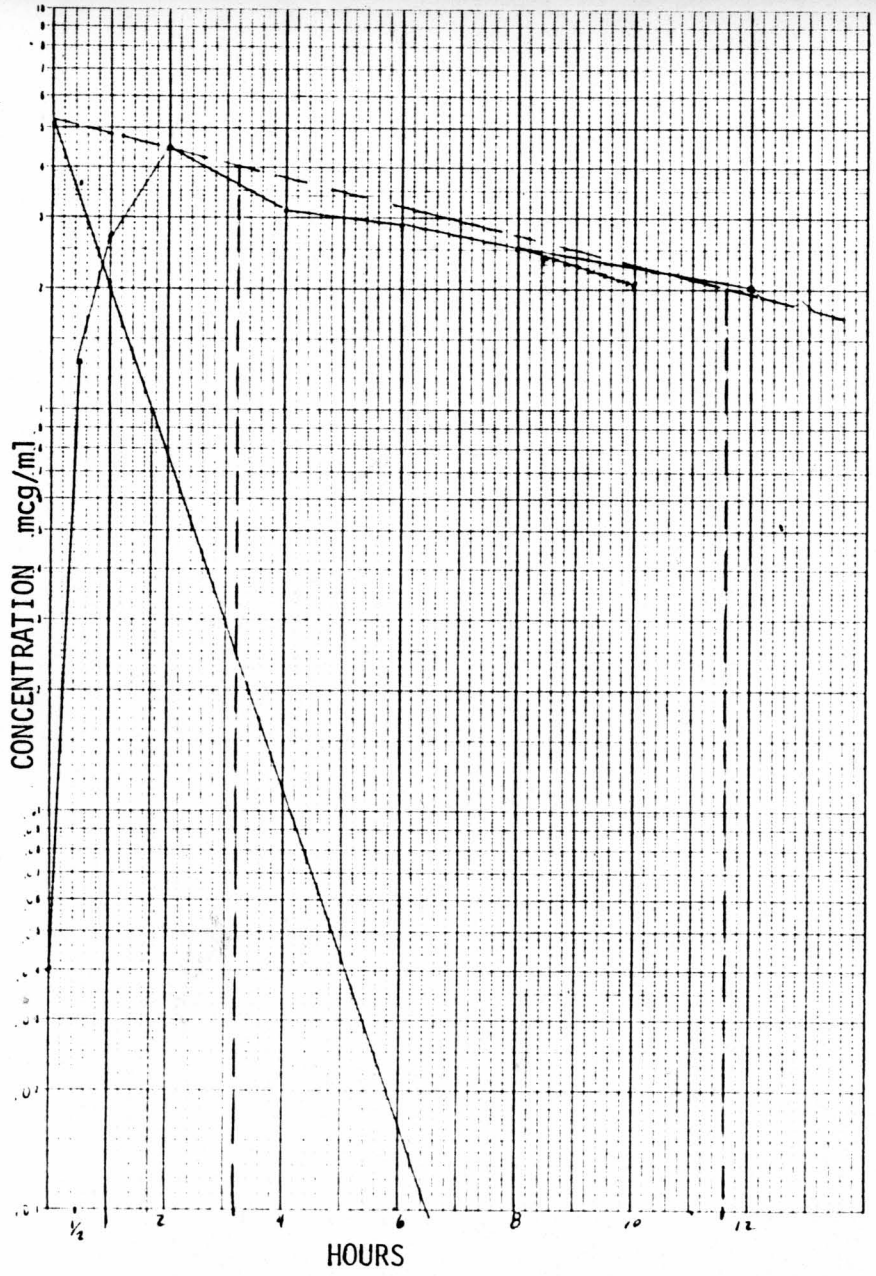


NONVIRAL INFECTION



VIRAL INFECTION

SUBJECT 2



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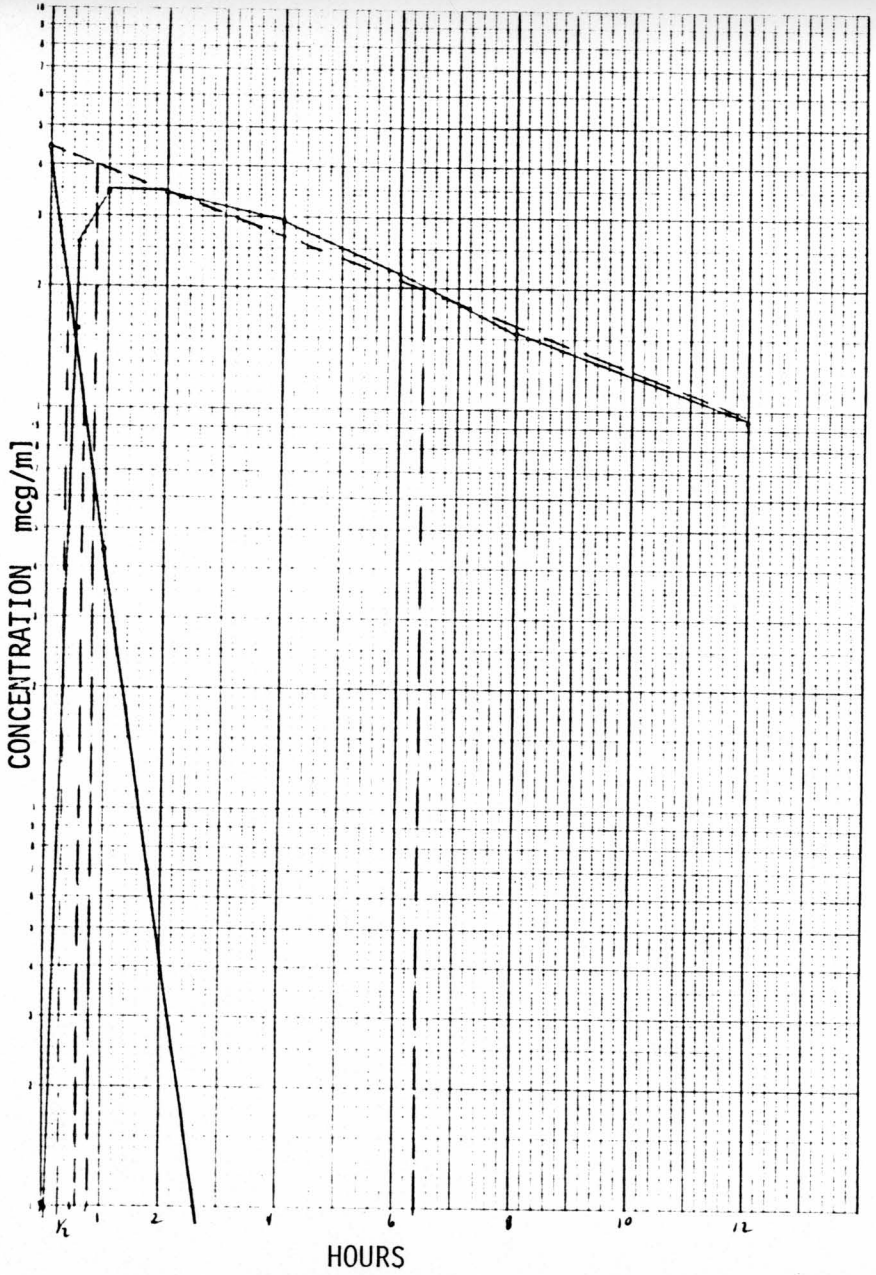

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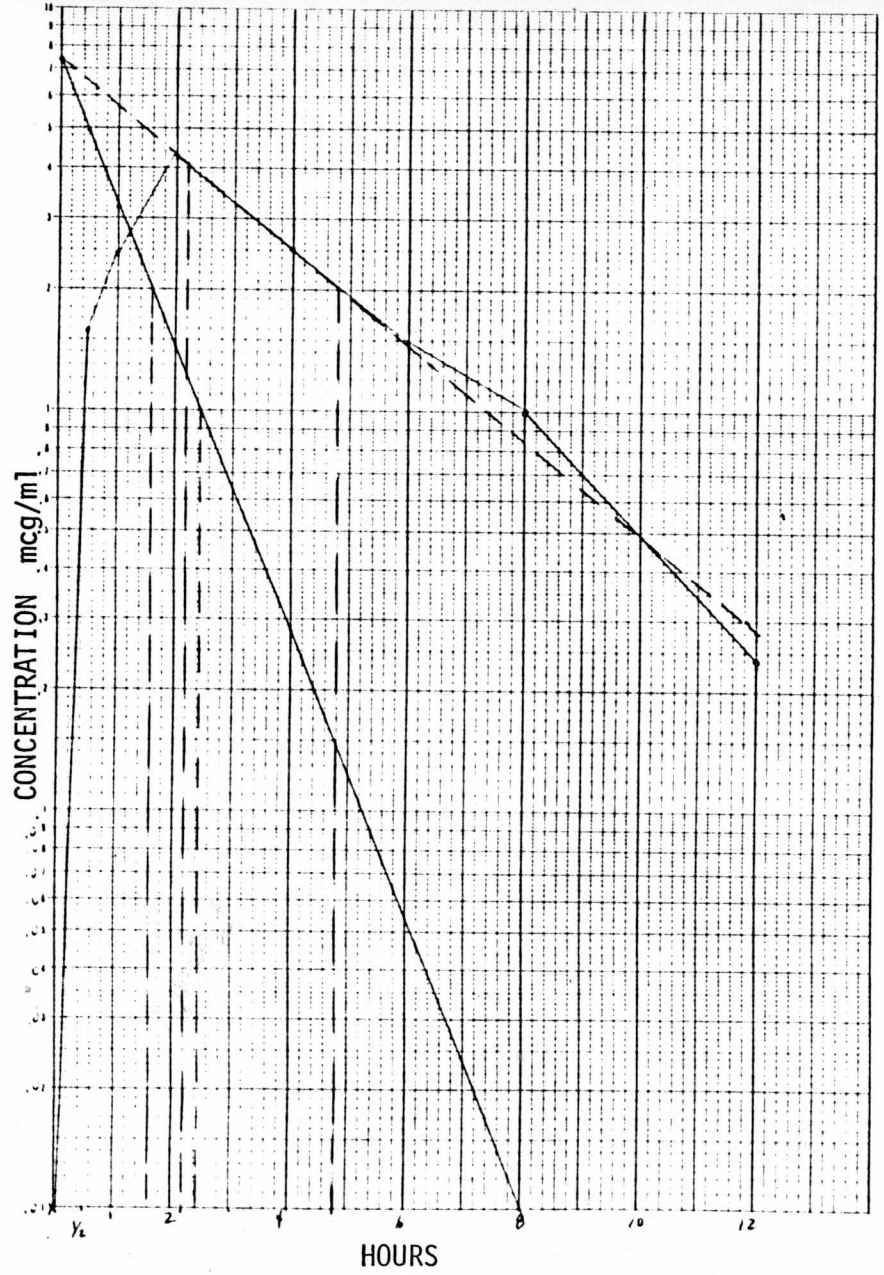

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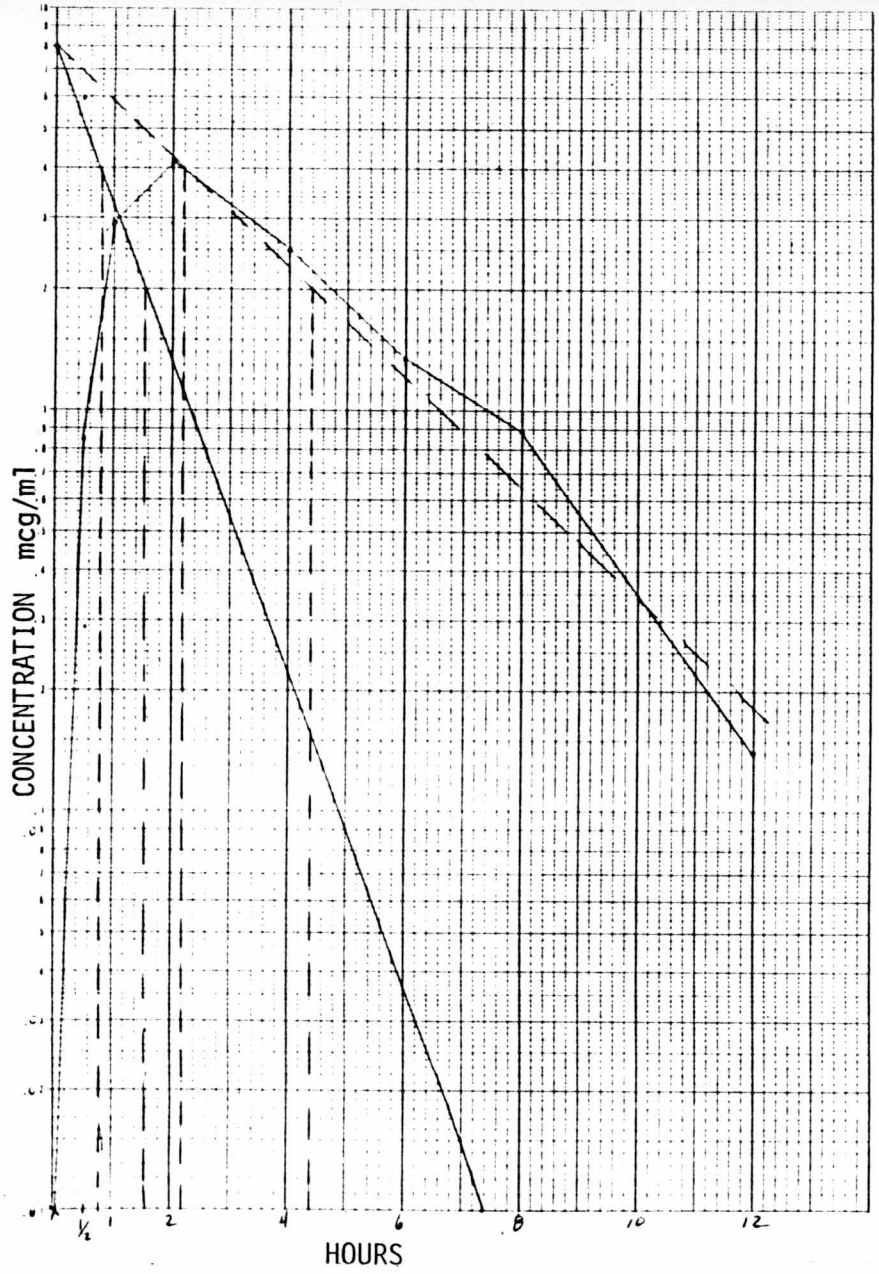

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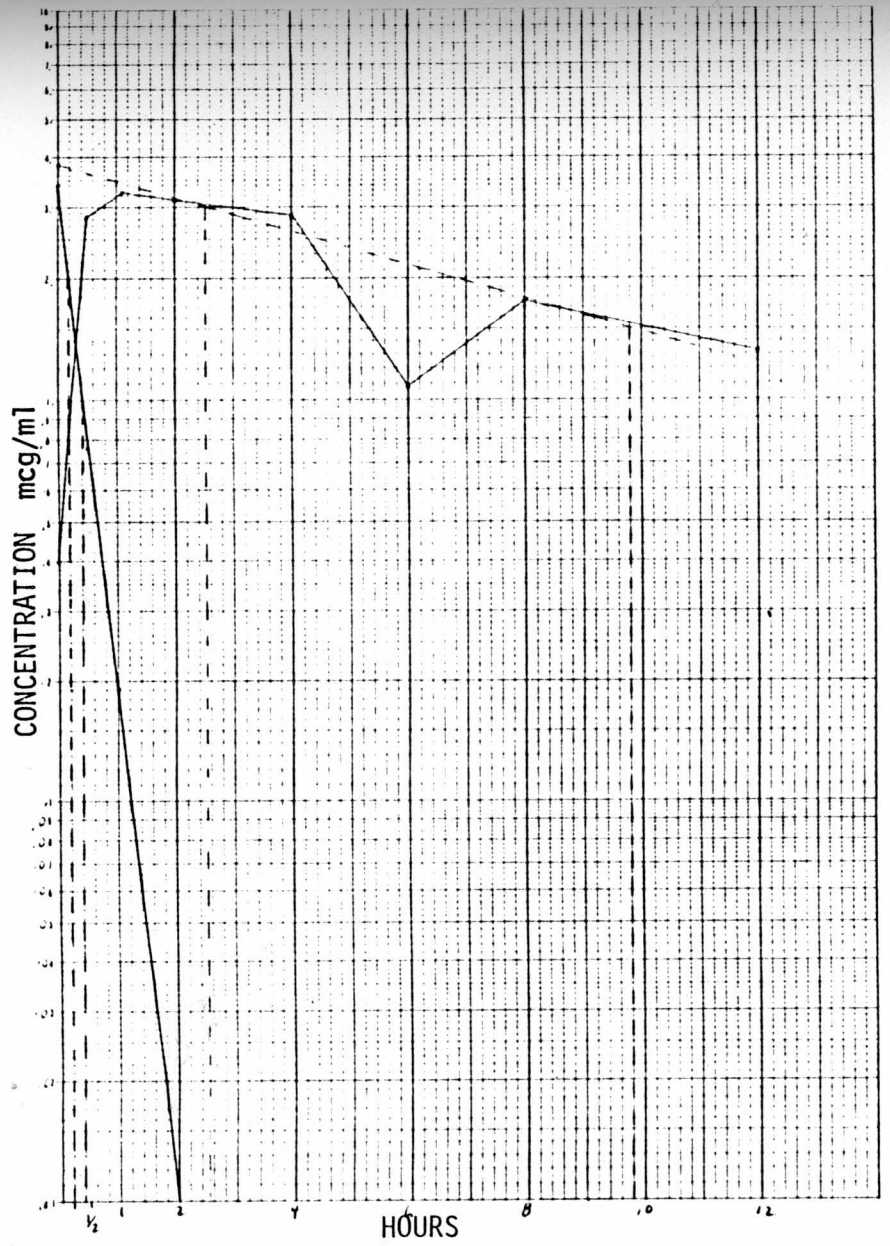

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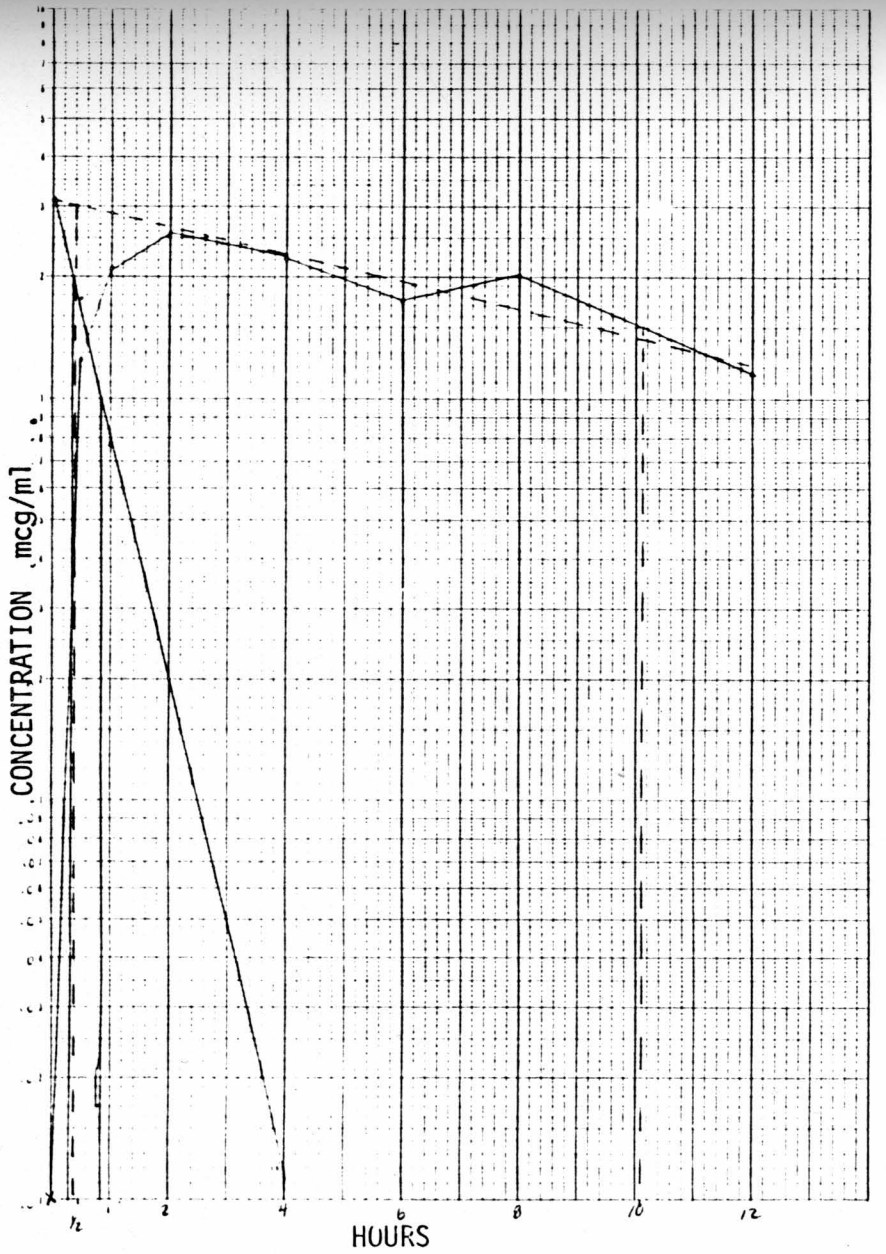

VIRAL INFECTION

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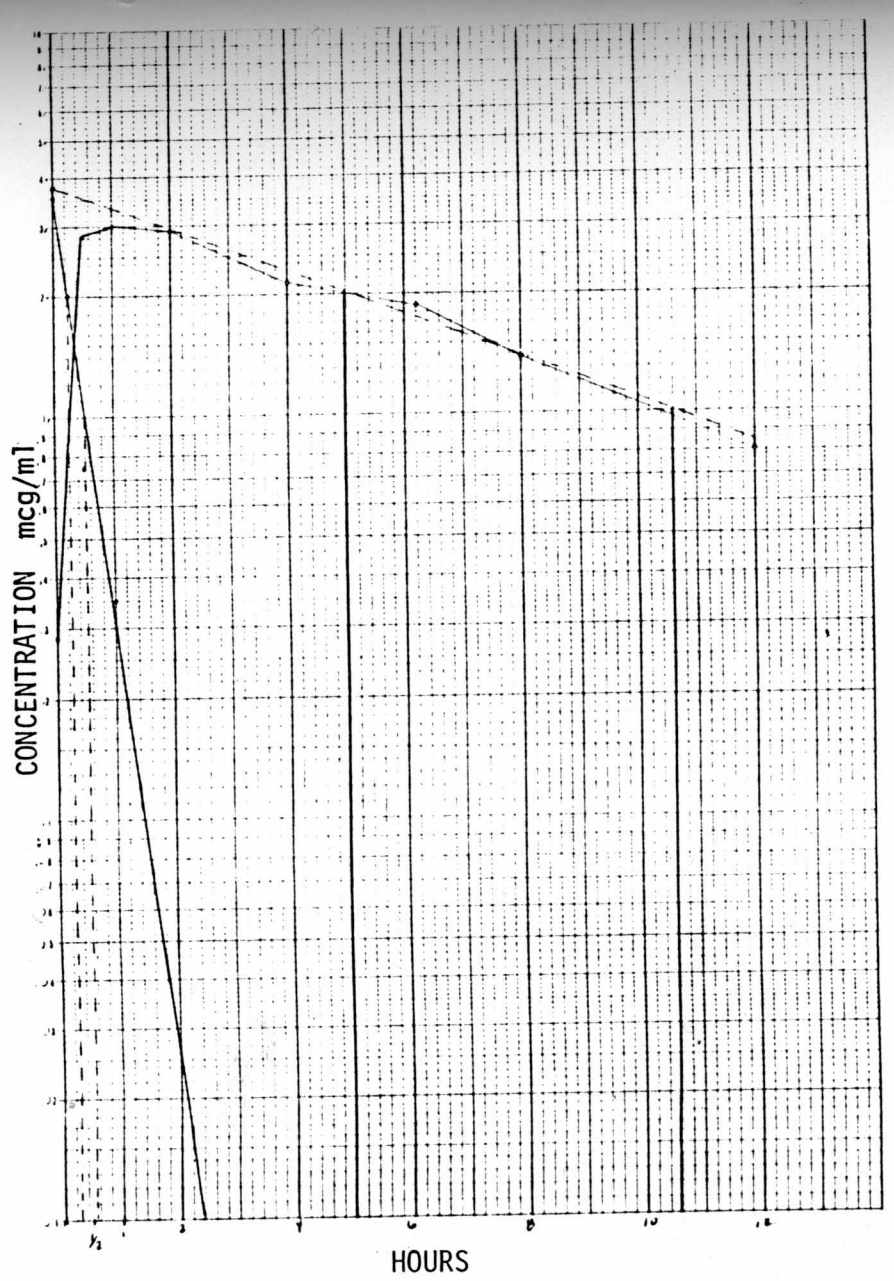

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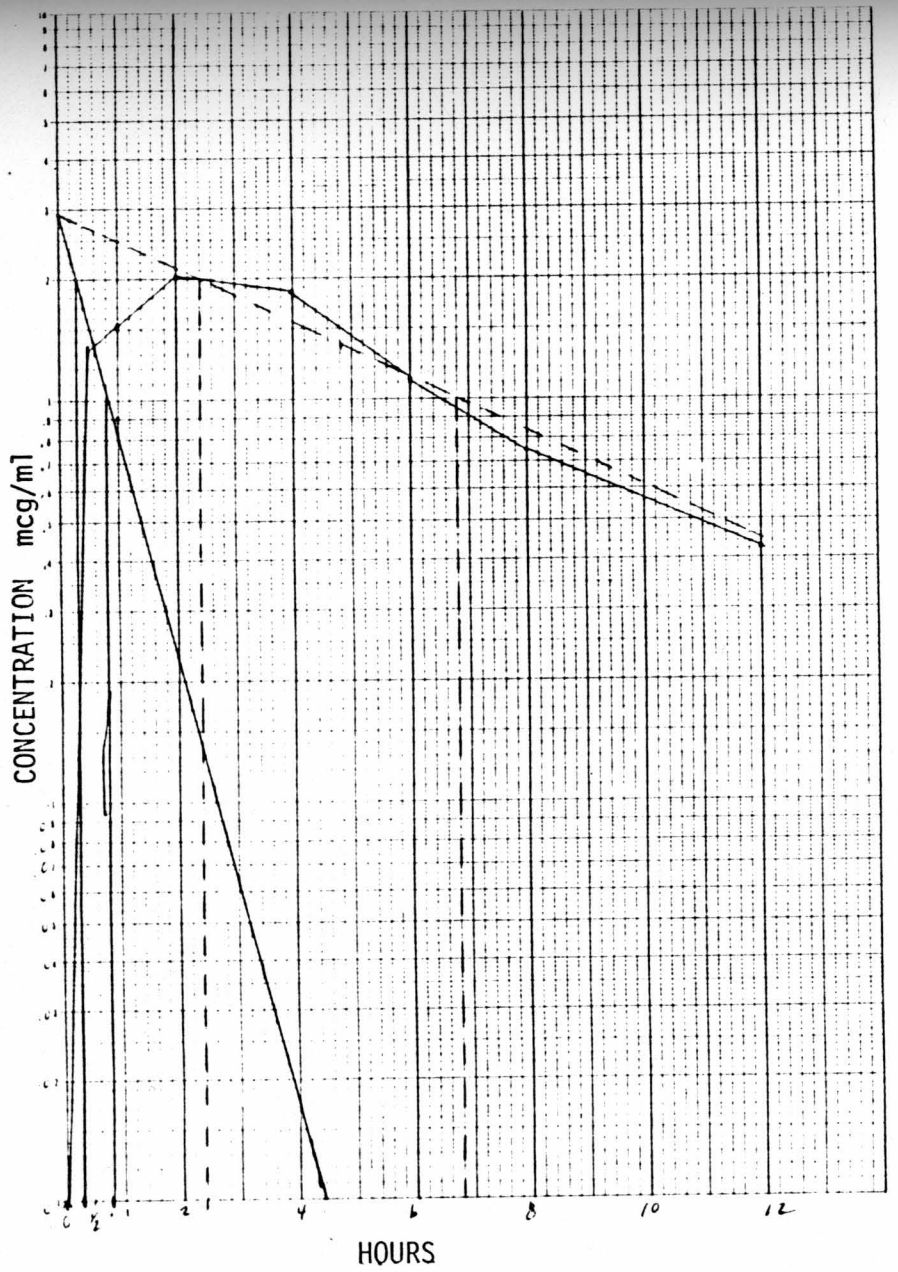

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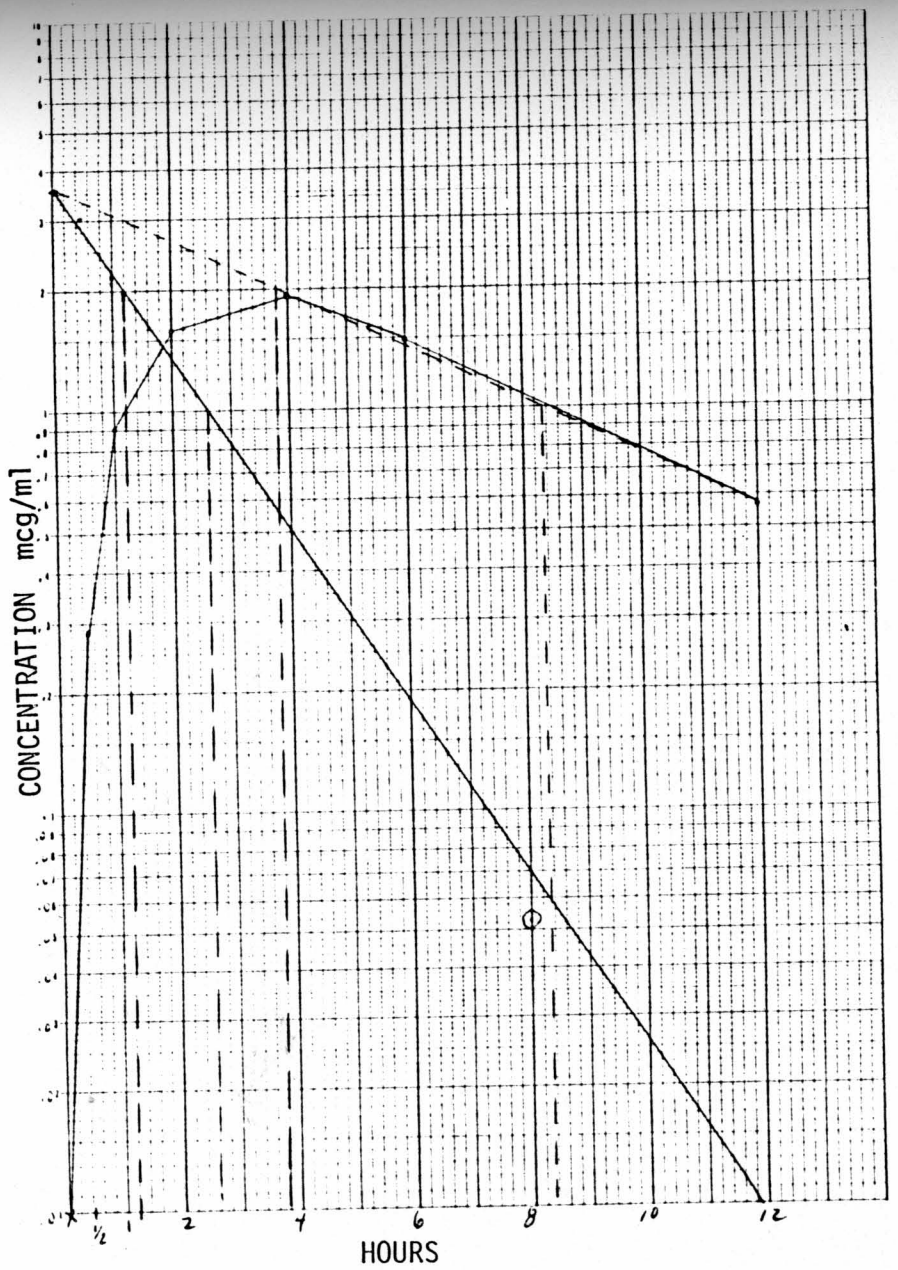

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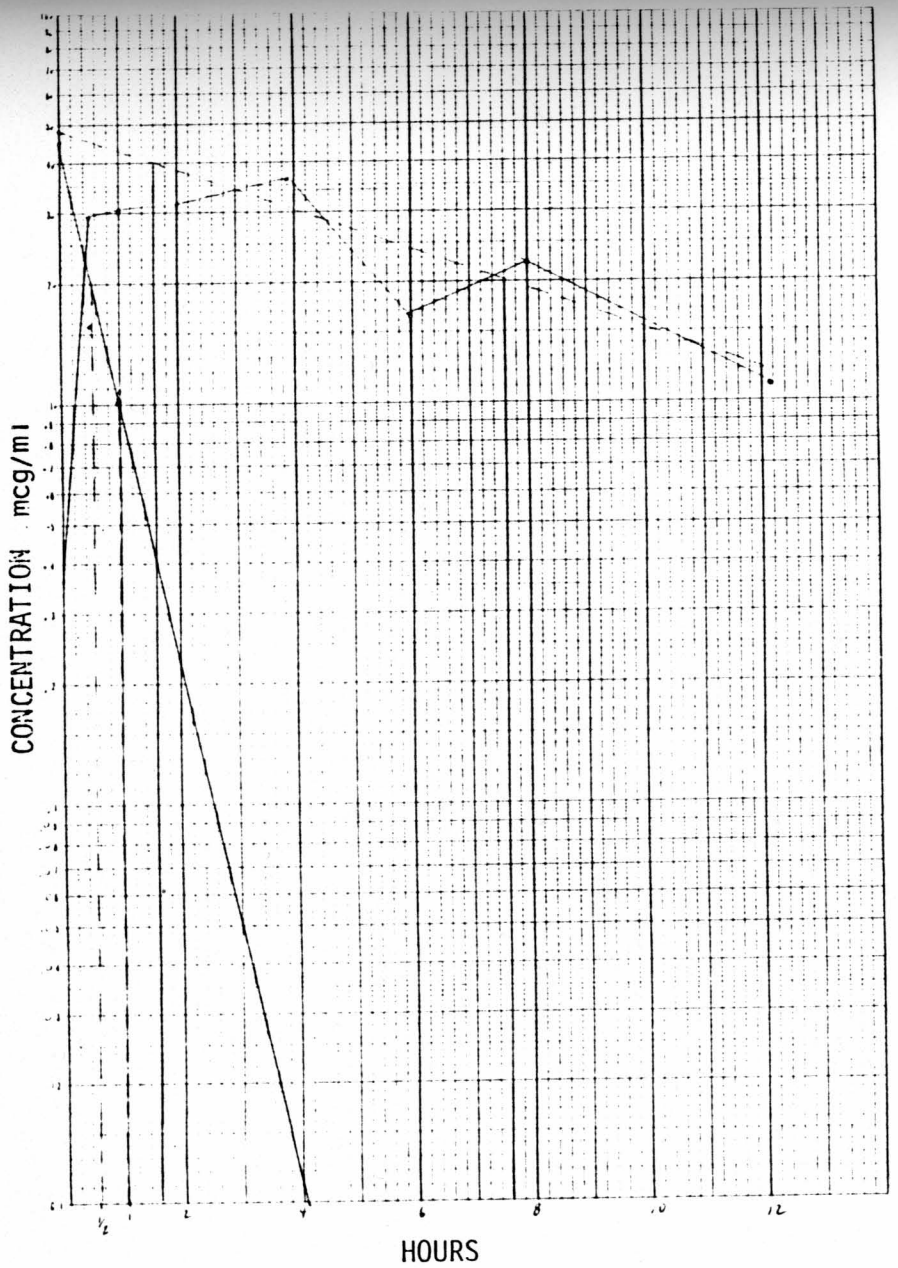

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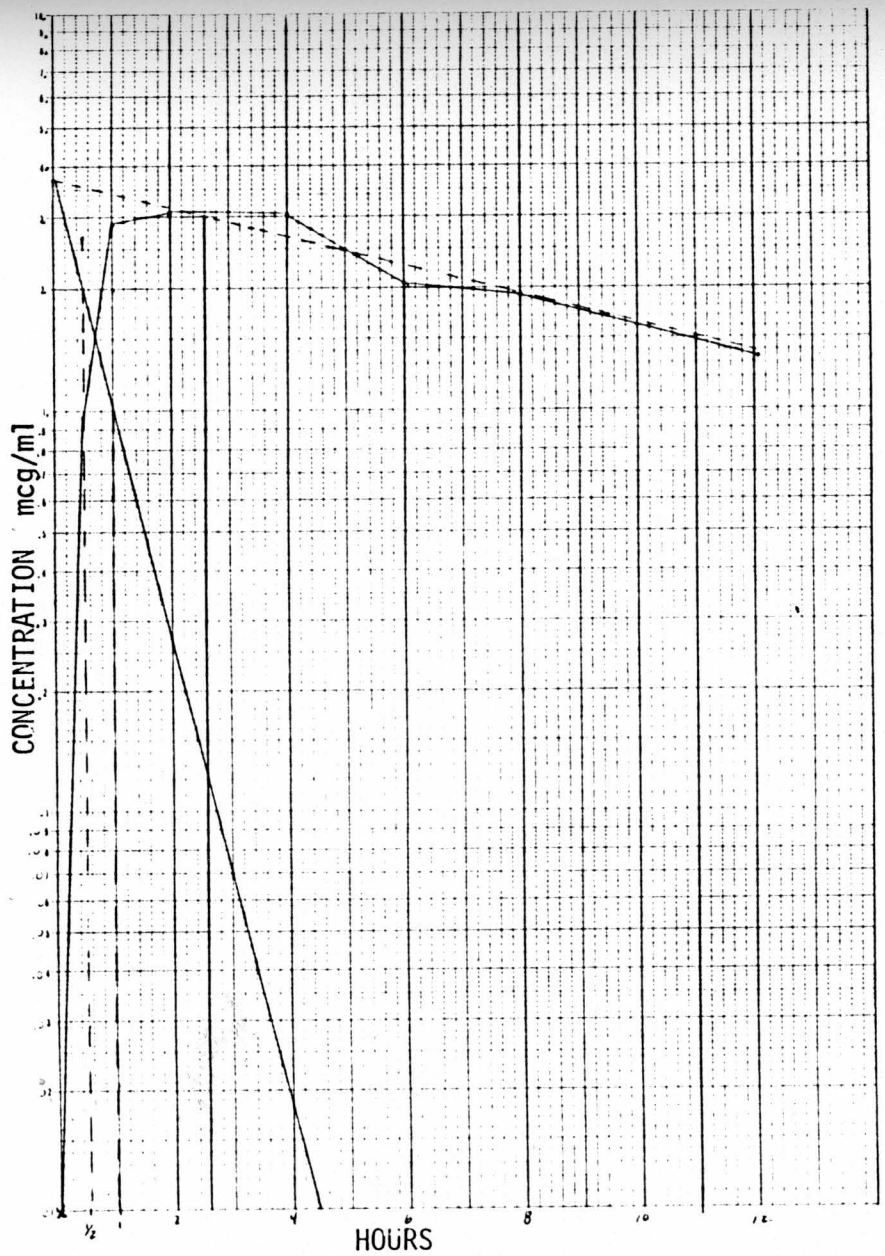

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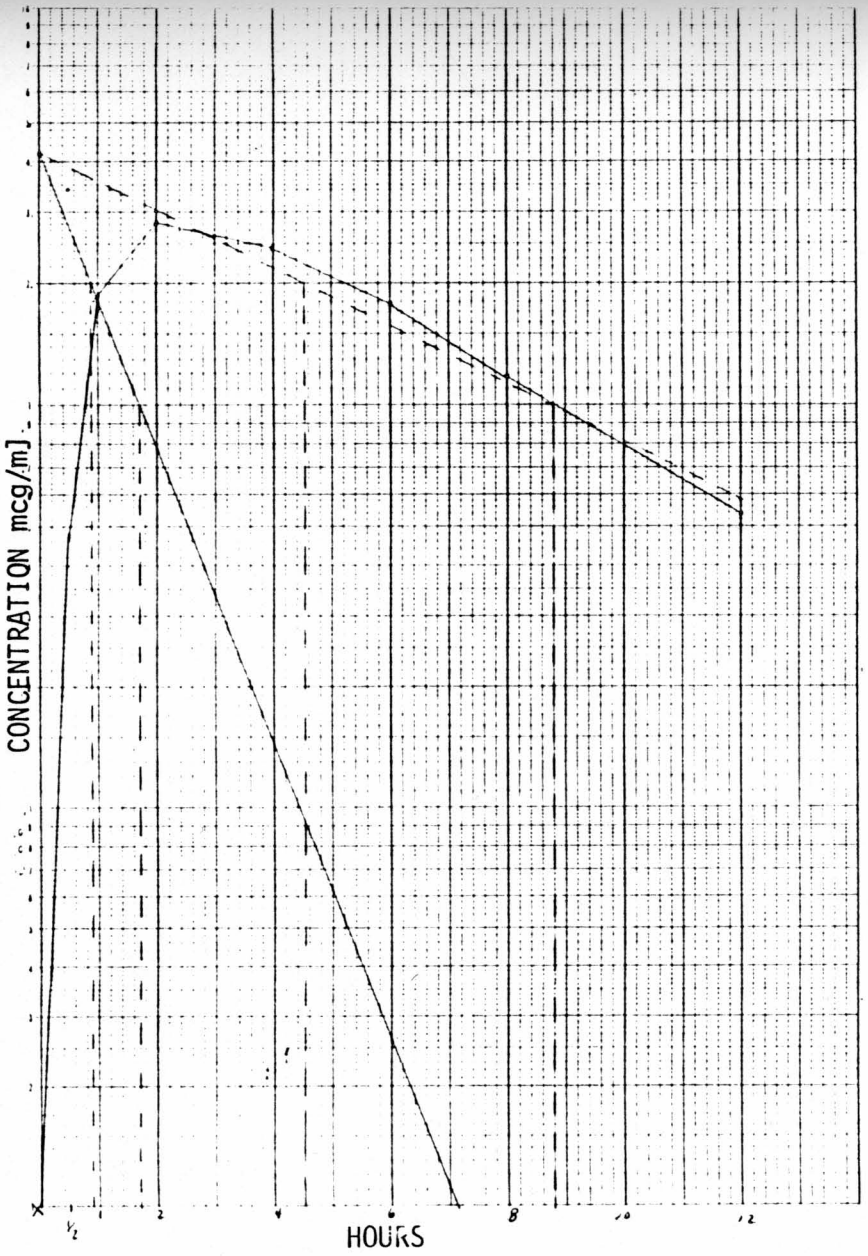

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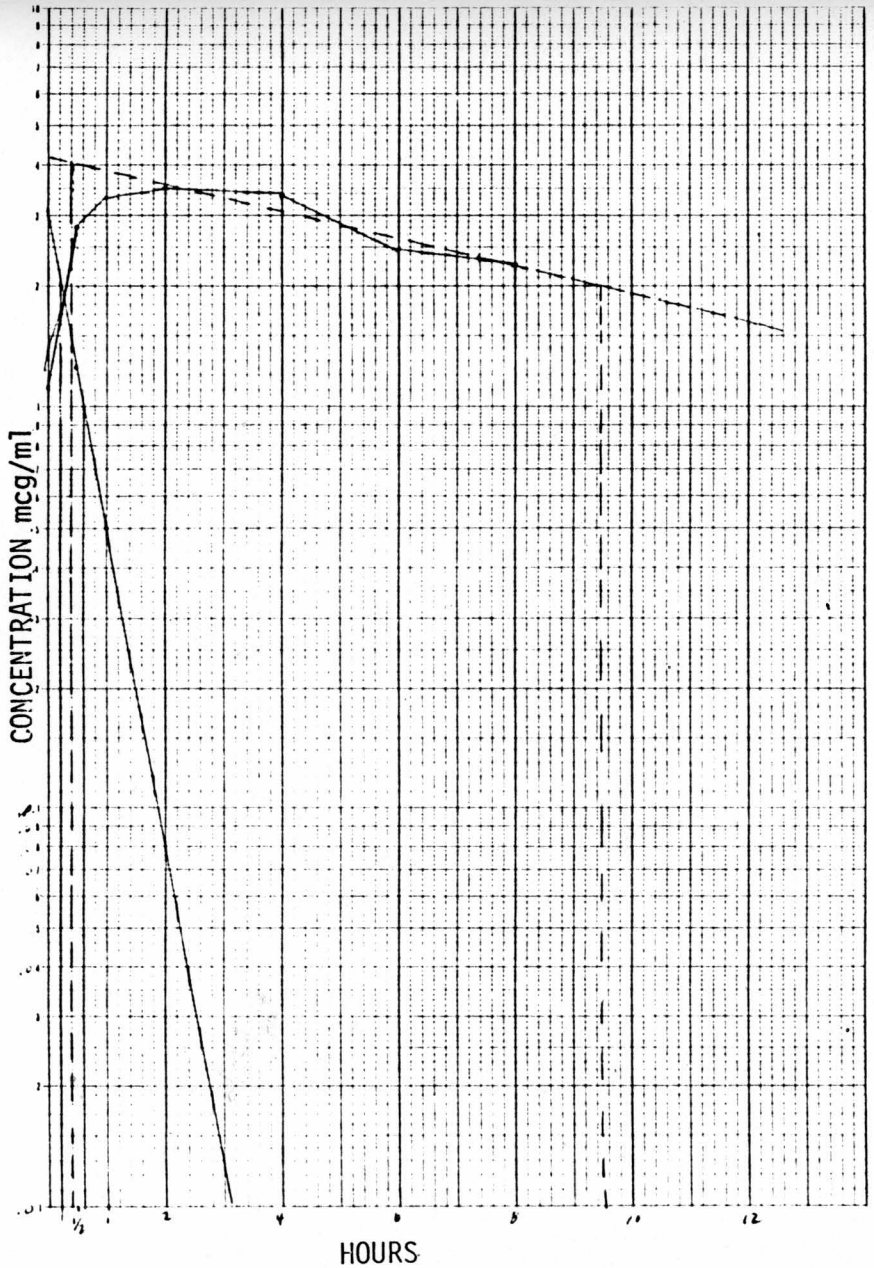

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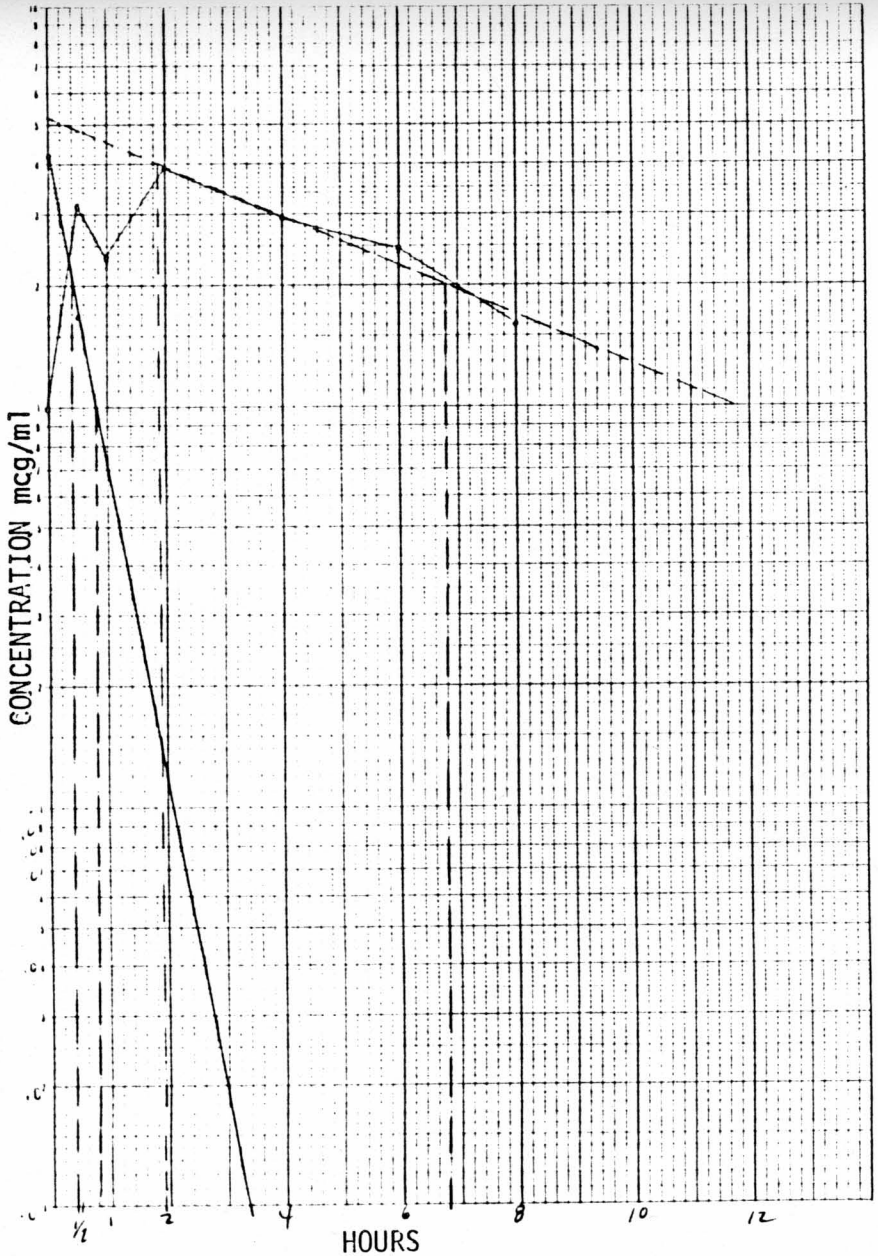

VIRAL INFECTION

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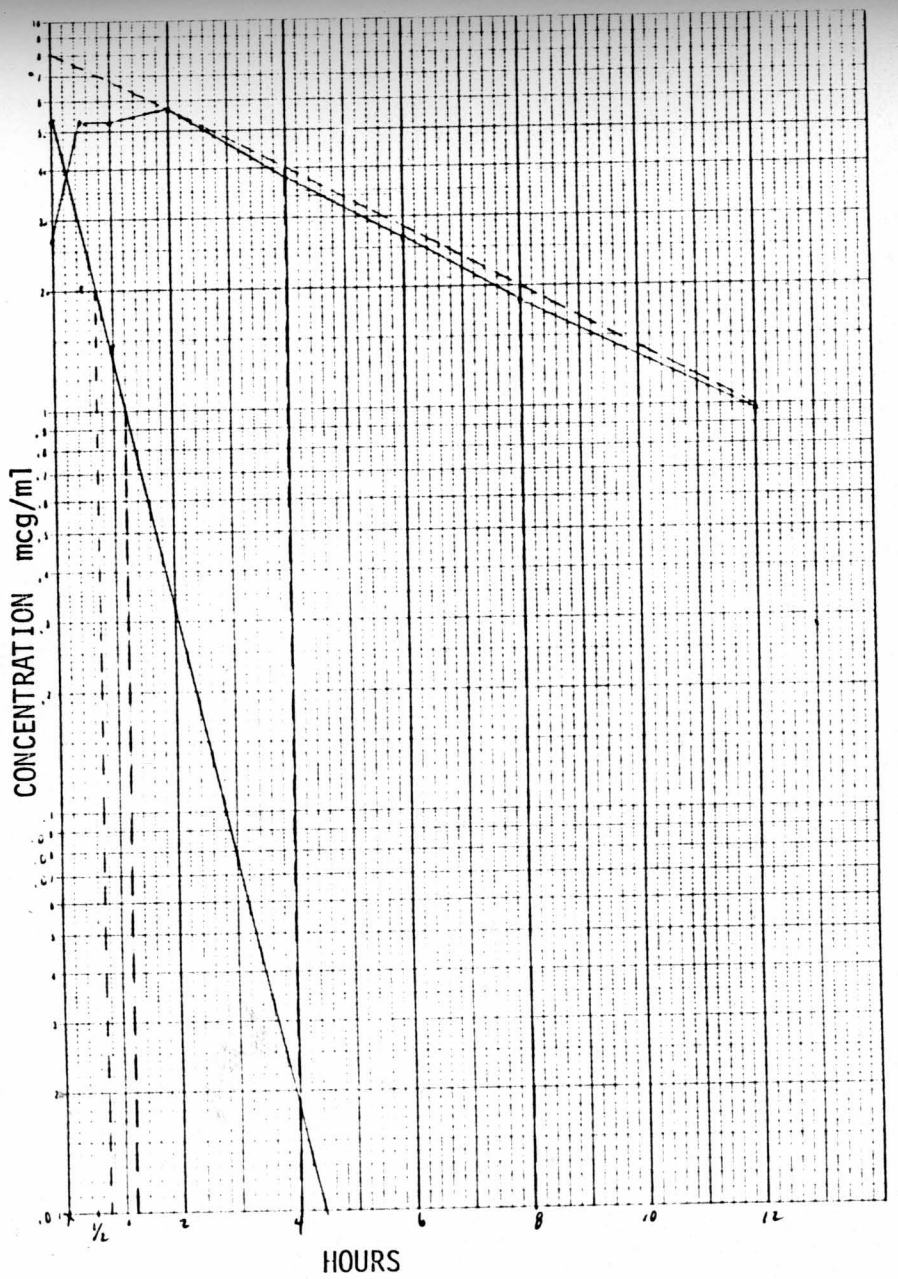

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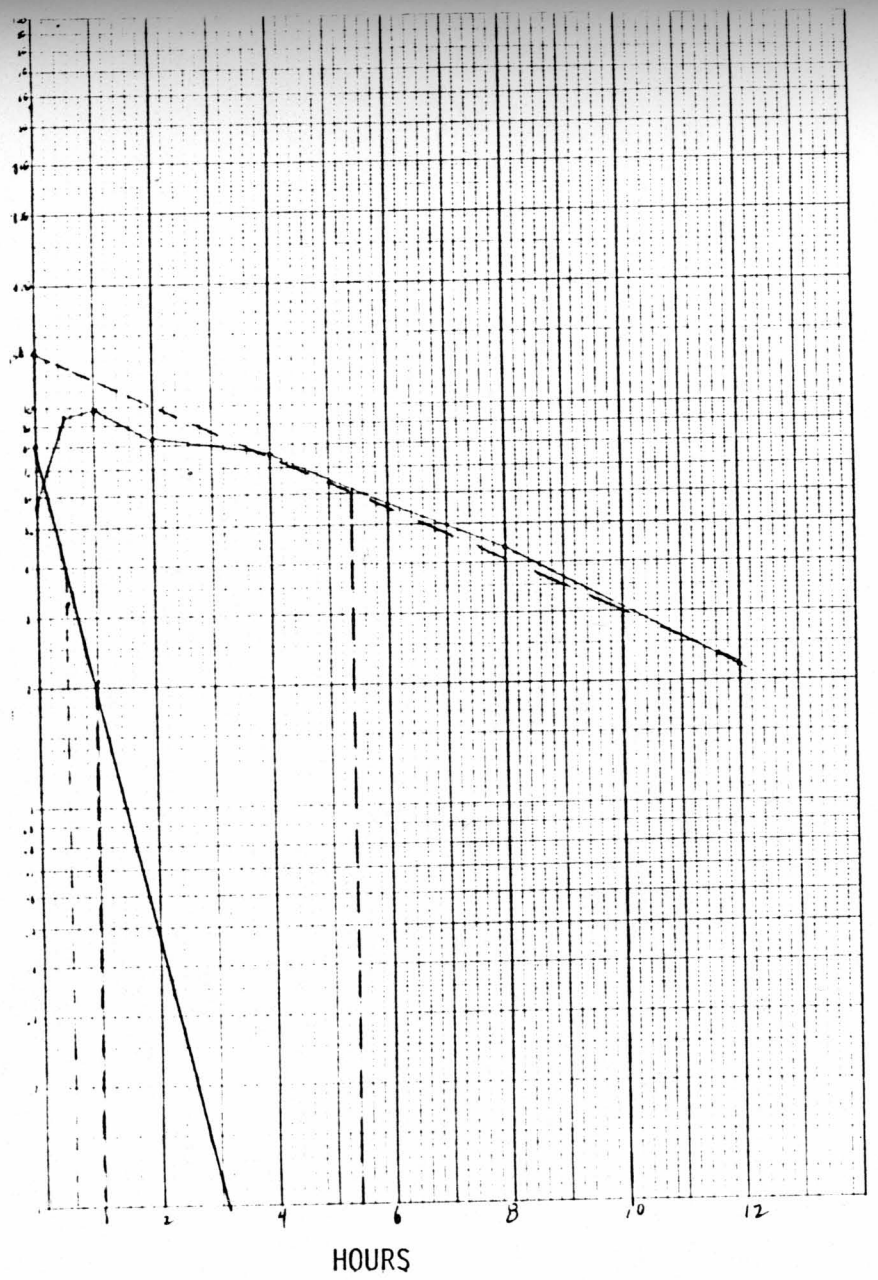

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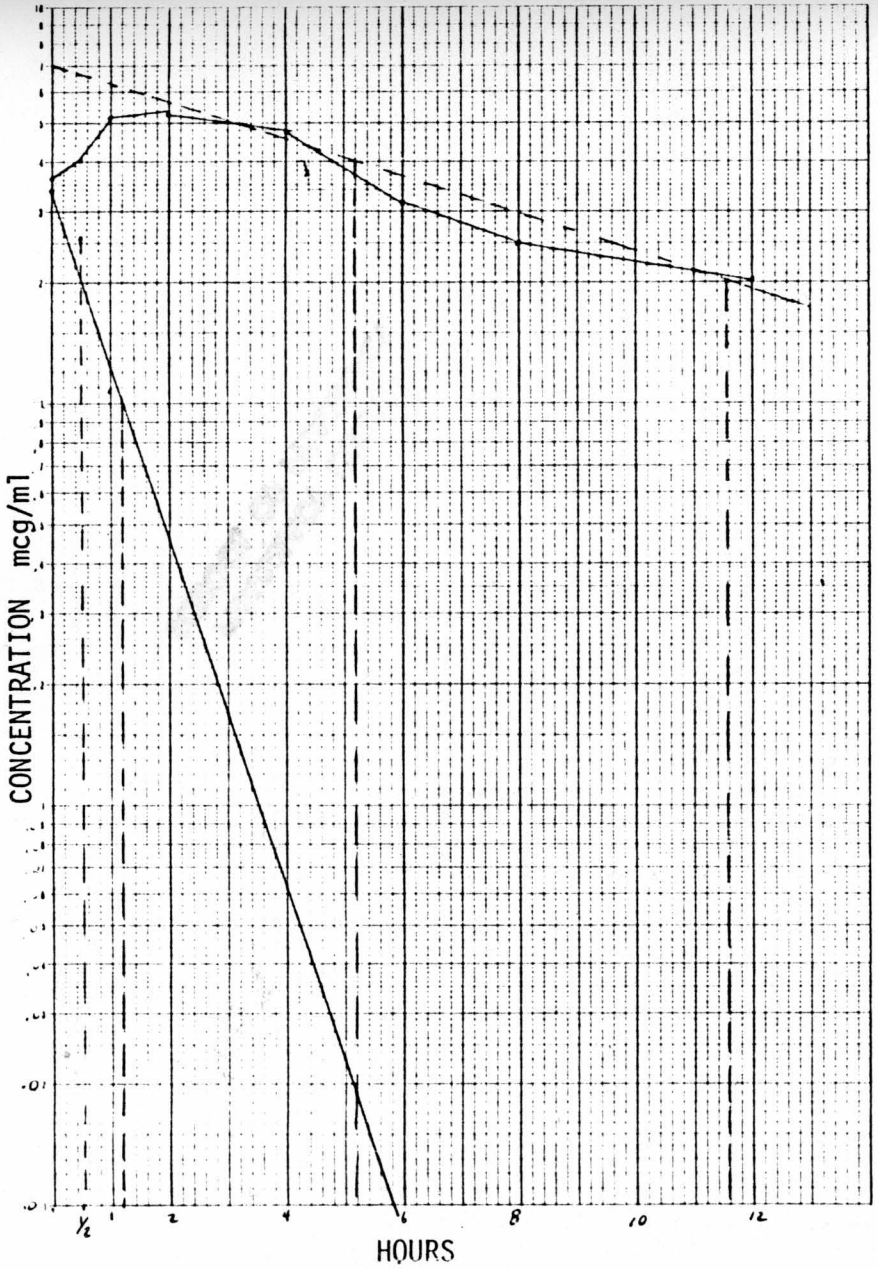
SUBJECT 10



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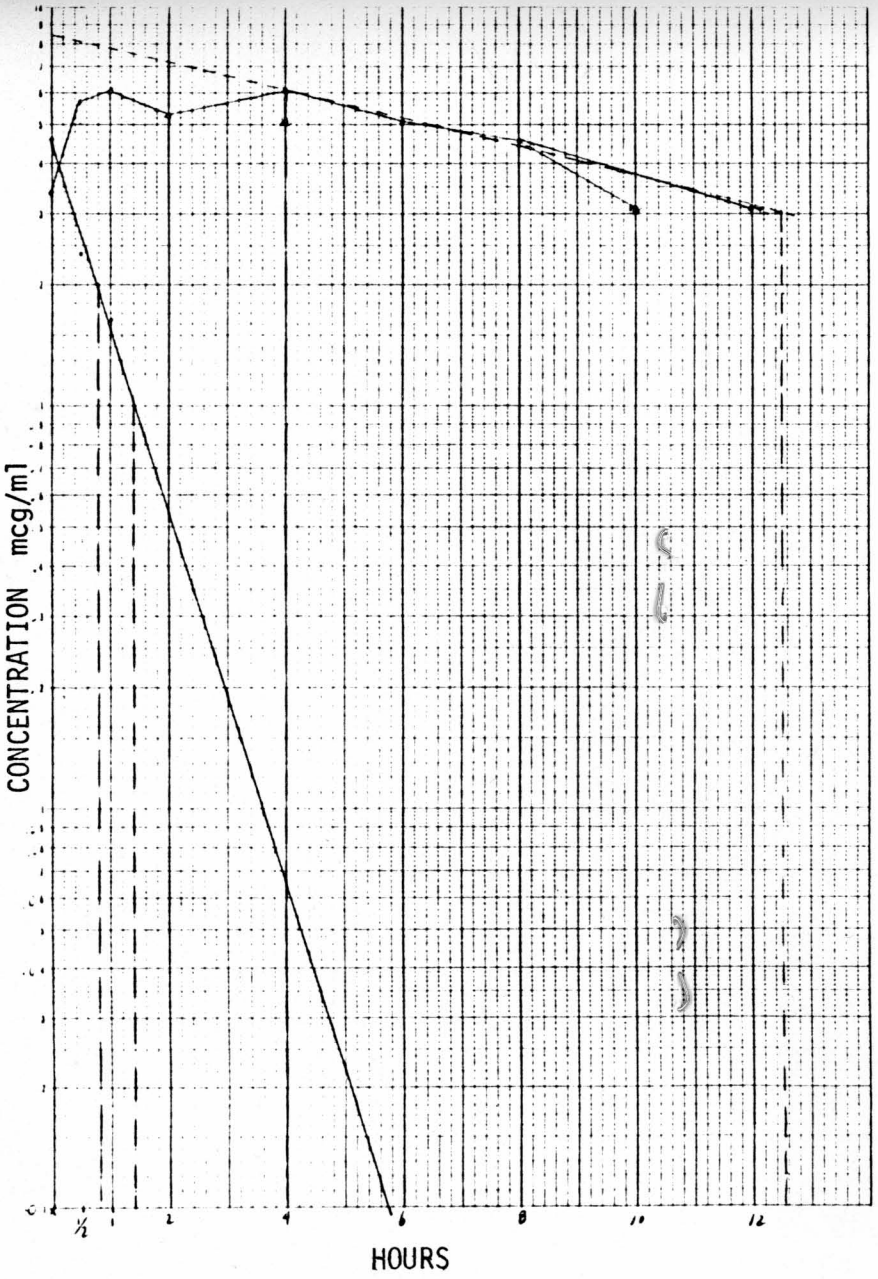

VIRAL INFECTION