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DEPARTMENT OF THE ARMY
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REPLY TO
ATTENTION OF:

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MEMORANDUM FOR Administrator, Defense Technical Information Center, ATTN: DTIC-OCP, Fort Belvoir, VA 22060-6218

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FOR THE COMMANDER:

ERRATA

for CORNELIUS R. FAY III
Lieutenant Colonel, MS
Deputy Chief of Staff for
Information Management

COOPERATIVE AGREEMENT: DAMD17-88-H-8004

TITLE: IMMUNOLOGICAL STUDIES OF ANTI-AIDS DRUGS IN ARC/AIDS

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13. ABSTRACT (Maximum 200 words)

The objectives of the project were to discover and characterize immunomodulatory drugs for patients with HIV-infection and AIDS using in-vitro models and utilizing the murine LP-BM5 (MAIDS) model. Drugs were supplied, coded by number and were tested using those model systems. Diethyldithiocarbamate and Imexon were found to be highly active in the in-vivo system. Imexon was synergistic with AZT. Imexon in addition to activity in LP-BM5 was also active in the prevention of the development of lymphoma in the SCID mouse given human PBMC. Imexon was also found to be active against B cell malignancies in vitro. Imexon was recommended to the NIAID for development as a drug for HIV. Other compounds were found to be active in-vitro but were not further developed because of the early termination of the project. The activity was mainly in the augmentation of mitogen responses or in the augmentation of NK activity. These included compounds 1758, 4729 and 8522. The investigator feels continued work on immunomodulation in AIDS is justified.

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FOREWORD

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GMK In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Evan McHenry MD 10/24/93

PI - Signature Date

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INTRODUCTION

The objectives of the project were to discover and characterize immunomodulatory drugs for patients with HIV-infection and AIDS using in-vitro models and utilizing the murine LP-BM5 (MAIDS) model.

Drugs studied included DTC, DTC analogues, imexon, imexon analogues, thymic hormones, and a variety of drugs identified by number only such as AVS 8522 and AVS PGG. These drugs were studied along and in combination with AZT and DDI.

DTC was shown to augment mitogen and Nk responses in vitro. It was highly active in vivo either when started 2 weeks or 10 weeks after virus inoculation. Seven analogues were studied both in vitro and in vivo. In general, none of these analogues was as active as the original compound DTC. The results on DTC were reported in several papers (1, 2, 3). Research on the analogues continues under the supervision of a graduate student even though the grant has terminated.

Imexon also showed a high level of activity against the LP-BM5 model. Again, it was active when started either 2 weeks or in excess of 10 weeks after inoculation of virus. Because imexon (and DTC) cause reduction and disappearance of polyclonal B cell activation and lymphadenopathy, we hypothesized that it would be active in AIDS-related lymphoma. Thus, we tested its effect in SCID mice inoculated with human lymphocytes. Imexon treatment markedly delayed the usual development of an AIDS-like lymphoma in these mice. Subsequently, we discovered that imexon was acting as a topoisomerase I inhibitor in B-cells of various types. Of great interest the drug was non-myelosuppressive. The results on DTC were reported in a series of papers (4,5,6).

In the LP-BM5 model imexon but not DTC had synergistic activity with AZT in terms of immunomodulation (augmentation of a depressed PHA response) and on lymphadenopathy and on survival. Synergy with DDI was not explored in detail.

Other Cyanoaziridine compounds were scheduled for study but the grant terminated before they could be evaluated.

Thymic humoral factor was studied on the LP-BM5 model. It had a minor or inconsistent effect on the progression of the disease in spite of being given over a 2 log dose range.

Over the 4 years of the grant a total of 68 compounds were evaluated, predominantly in in vitro systems of mitogen response and NK cell activity. Fifteen were found to have some immunomodulatory activity. Three of the most active were 1758, 4728 and 8522.

Since all the drugs were provided by the NIH or drug companies, there were no inventions on this project.

Experimental Methods

I. In Vitro

EXPERIMENTAL PROCEDURES FLOW CHART FOR TIER I ANALYSIS

1. TOXICITY DETERMINATION - I
   a. Purpose: to determine that concentration of drug yeilding a toxic effect.
   b. Methods:
      1. To be performed with normal cells only.
      2. 8 serial log dilutions starting from 100 ug/ml of culture or the highest solubilizable concentration if 100 ug/ml can not be achieved.
      3. PHA response only will be evaluated at day 3.

2. TOXICITY DETERMINATION - II (REFINED)
   a. Purpose: to refine the determination of the toxic concentration and define the IC^{20} and IC^{50} concentrations.
   b. Methods:
      1. To be performed with normal cells only.
      2. Re-evaluate those serial log dilutions between the first non-toxic and the last overtly toxic with the addition of 1:2 dilutions of these concentrations.
      3. PHA response only will be evaluated at day 3.

3. LBR - I (Optimal Stimulation)
   a. Purpose: To determine if the LBR of optimally stimulated cells can be augmented and/or if the culture period in which a significant response occurs can be extended.
   b. Methods:
      1. This experiment is to be performed with normal cells. If significant augmentation is detected evaluation with patient cells will be added.
      2. The following mitogens and/or antigens will be cultured for 3, 5, and 7 days.
         1. Unstimulated
         2. PHA
         3. PWM
         4. CON-A
         5. SLO
      3. Drug concentrations studied will begin with the highest non-toxic concentration and extend down a minimum of 5 log dilutions.
      4. If an active concentration is determined subsequent experiments will be performed with half log dilutions on either side of this value.

4. LBR - II (Suboptimal Stimulation)
    a. Purpose: To determine if the response of lymphocytes stimulated with suboptimal concentrations of mitogens or antigens can be augmented.
    b. Methods:
        1. This experiment is to be performed with normal cells. If significant augmentation is detected evaluation with patient cells will be added.
        2. Optimal and sub-optimal concentrations will be set on the same plate.
        3. Two sub-optimal concentrations for PHA and SLO will be used.
        4. Cultures will be evaluated at days 3 and 5.
        5. Drug concentrations to be studied as in #'s 3 & 4 for LBR-I.

5. NK Activity - I
    a. Purpose: To determine if the activity of NK cells in a 4hour ^{51}Cr test can be augmented following drug treatment for various time points.
    b. Methods:
        1. This experiment is to be performed with normal cells. If significant augmentation is detected evaluation with patient cells will be added.
        2. Drug concentrations to be studied are the highest non-toxic concentration as defined by the Toxicity - II experiment with a minimum of 5 log dilutions below that.
        3. Three drug incubation periods will be evaluated:
            a. Fresh, during the 4 hours of the assay only.
            b. 18 hours before the assay.
            c. 48 hours before the assay.
        4. Incubation with drug will take place in the assay plate
        5. A spontaneous release control with each drug concentration used is required.

6. NK Activity - II:
    a. Purpose: To refine the active concentration range and time course of exposure for any positive results seen in NK Activity - I.
    b. Methods:
        1. As above.
        2. Drug concentrations to bracket either side of any active concentration seen in half log levels.

2. In Vivo (LP-BM5) Model

C57 BL/10 mice were maintained in microisolator cages, 5 animals per cage. Each individual cage and all mice were manipulated only in a laminar air-flow hood. The animals were maintained with conventional water and food. Mice were approximately 608 weeks and weighed 20 g at the start of each experiment. In general, there were 5-8 animals per group in each of the experiments. Mice were inoculated with a virus dose chosen so there would be an approximate doubling of the serum IgM level at 2 weeks after virus inoculation.

The drug solution was prepared fresh daily. The requisite amount of drug was dissolved in special neutral diluent (because of the acid lability of the drug) and injected intraperitoneally in a volume of 0.1 and ml contained various doses depending upon the experiment. Animals were treated either once a week or 5 days per week (Monday-Friday).

Animals were examined weekly for lymphadenopathy and the number of animals with palpable lymph nodes and the approximate lymph node size were measured with calipers and recorded. The day of mortality was also recorded.

For the measurement of serum IgM, the animals were bled from the retro-orbital plexus at approximately 2-4 week intervals. Serum IgM was measured using the enzyme-linked immunosorbent assay (ELISA) method. Microtiter plates (Falcon Labware) were coated with goat anti-mouse IgM (Accurate Chemical). Mouse serum was added and the binding by IgM was detected using a peroxidase-labeled rabbit anti-mouse IgG antibody (Immuno Research Laboratories).

For the measurement of lymphocyte blastogenesis, animals were sacrificed by cervical dislocation every 2-8 weeks, their spleens removed, weighed, minced with a single cell suspension resulting. T and B cells were stimulated by the addition of phytohaemagglutin (PHA) 1 μg/ml, and lipopolysaccharide from *Escherichia coli* 0111:B4 (LPS) 50 μg/ml, respectively. Proliferation was measured by the addition of [^{3}H] thymidine on the second day of culture. Following a 4-h pulse, the plate was harvested on a cell harvester. The amount of incorporated radioactivity was measured using liquid scintillation techniques.

The measurement of lymphocyte surface markers among spleen cells, was determined by a 30 minute incubation of the spleen cells and the primary

antibody. This was followed with a 30 minute incubation with the secondary antibody, goat anti-rat IgG FITC conjugated. Immunofluorescence was detected by a Becton-Dickinson Facsan Flow Cytometer.

Results Obtained

Diethyldithiocarbamate was found to be active in the LP-BM5 model. This is covered in reference numbers 1, 3, 4, 8, 10-15, 17, 20 (see appendix for reprints).

Imexon was found to be active in the LP-BM5 model. This is covered in references 6, 7, 9, 16, 18 (see appendix for reprints). Imexon was also active in the prevention of lymphoma development in the SCID mouse inoculated with human lymphocytes. This is covered in reference 9 (see appendix for reprint) . Imexon was shown to selectively inhibit the proligeration of normal and malignant B cells. We therefore speculate that this could be an important drug in AIDS and AIDS lymphoma. The data was presented at a meeting at the NIAID attended by representatives of NIAID, USAMRIID and the drug company as well as the members of the NCDDG. No decision was taken as the future plans for drug development. Thymic humoral factor (^{T}HFα2) was studied both in vitro and in the LP-BM5 model. some very modest activity was noted but no decision was taken for further development based on the work of this project. However Adria Laboratories did initiate clinical trials of the agent which yielded equivocal results in HIV and AIDS patients. Definitive reports on those trials are pending from Adria Labs.

A large number of studies were done of various drugs supplied to the investigator by the NCDDG. These were studied only in vitro. Several appeared promising and were recommended for further study.

However, further studies were not carried out because of the termination of the employment of the PI at USAMRIID and the decision of the Army not to appoint a new PI. Therefore, all projects except Dr. Hersh's project were terminated in mid 1991 and further cooperative drug development was precluded.

Summary statements on those drugs are given below and the data generated is included in the Appendices

Results Obtained in 1988

Six drugs were supplied and studied as of 6/88. These were #1969, 2776, 3925, 3926, 3927, 3934. In the course of the studies of the solubilized drugs it was observed that DMSO was toxic to the various leukocyte functions and only a concentration of 1% by volume of DMSO, or less, in the culture systems avoided toxicity. This may somewhat limit our ability to evaluate the drugs. Drug #1968 was found to be relatively lymphocytotoxic and concentrations of greater 8 μg/ml completely abrogated the PHA and CON-A lymphocyte proliferative responses. #3934 neither augmented nor suppressed lymphocyte proliferation responses at concentrations ranging from .02 up to 208 μg/ml. drug #2776 was lympho-cytotoxic only at concentrations above 50 μg/ml. The toxicity noted with Drug #1968, on the PHA and CON-A response, was also noted at about the same concentration when the drug was incubated with our cell mediated cytotoxicity targets: daudi, K562 and H9. These three drugs had no effect on lymphocyte surface marker expression. The doses of the drugs which inhibited cell proliferation did not inhibit ADCC against K562. In fact, Drug #3934, at a very low concentration of .04-.2 μg/ml actually augmented ADCC of AIDS patients' lymphocytes against the K562 target. The other drugs had no effect. As noted above, the DMSO necessary to dissolve Drugs #3925, #3926, #3927 was itself toxic except at a concentration lower than 2.5% by volume. Studies with Drugs #3925, #3926, and #3927 in this concentration of DMSO showed that #3925 and #3926 were completely inhibitory of the PHA response of peripheral blood lymphocytes at concentrations greater than 2 μg/ml, while #3927 was completely non-toxic of great interest, ADCC of AIDS patients' lymphocytes, was significantly augmented by low concentrations of Drugs #3925, #3926, and #3927 in the range of .02-.04 μg/ml with the greatest augmentation being from 28% control to 42% drug treated specific target cell lysis.

As of October 1988 additional drugs were studied and are summarized herein. Pages 24-92 are in the Appendix.

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SYNOPSIS

Ficoll Hypaque separated leucocytes from both control and HIV infected donors are incubated with various concentrations of the candidate drugs for 1 to 8 days and then subjected to various functional assays. After determination of the IC_{10} and IC_{50} for each drug the functional assays are performed in a two tier system. Demonstrated immunomodulatory activity in the first tier (lymphocyte blastogenesis, NK cell activity, and cell surface phenotypic analysis) is indication for second tier analysis (ADCC, both non specific and to HIV infected cells, monocyte adherence, and in vitro production of both IL-2 and alpha-IFN).

Nine of the sixteen drugs received to date have completed their screening for in vitro toxicity and first tier immunomodulatory activity. Five of these nine drugs have shown some immunomodulatory activity and are now undergoing confirmatory and second tier analysis. The remaining seven drugs are still in first tier analysis.

TESTED DRUG IMMUNOMODULATORY STATUS
BY FIRST TIER ASSAY SYSTEMS

DRUG #	ASSAY SYSTEMS BLASTOGENESIS	NK ACTIVITY	PHENOTYPE
1969	NEGATIVE	NEGATIVE	MARGINAL
2776	MARGINAL	NEGATIVE	MARGINAL
3925*	POSITIVE	POSITIVE	POSITIVE
3926*	POSITIVE	POSITIVE	POSITIVE
3927	NEGATIVE	POSITIVE	POSITIVE
3931*	POSITIVE	MARGINAL	POSITIVE
3932*	POSITIVE	MARGINAL	POSITIVE
3934	NEGATIVE	NEGATIVE	MARGINAL
4594*	POSITIVE	POSITIVE	POSITIVE

* DRUGS ENTERING SECOND TIER ANALYSIS

AVS-001968

A. TOXICITY

Evaluated in a concentration range between 833 and 0.083ug/ml of culture the IC_{50} and IC_{20} in mitogen stimulated blastogenesis were determined.

MITOGEN	IC_{50}	IC_{20}
PHA	5.0	0.83
CON-A	3.0	0.50

B. BLASTOGENESIS

1. HIV⁻ donor results:
   No response in one, slight PHA enhancement in the second, and slight CON-A enhancement in the third.
2. HIV⁺ donor results:
   No response in one, slight PHA enhancement in the other.
3. Essentially no immunomodulatory activity.

C. NK ACTIVITY

1. HIV⁻ donor results:
   Enhancement at both E to T ratios seen.
2. HIV⁺ donor results:
   No enhancement seen.
3. Immunmodulatory activity is marginal.

D. PHENOTYPE ANALYSIS

1. HIV⁻ donor results:
   Positive percent change: +28% for NK(Leu7), +27% for CTL($Leu4^+/Leu19^+$) and +29% for $Leu2^+/Leu7^+$.
2. HIV⁺ donor results:
   Positive percent change: +38% for IL2r(CD25).
   Negative percent change: -23% for NK(Leu11\CD16), and a -27% for CTL($Leu4^+/Leu19^+$).
3. Immunomodulatory activity is marginal.

AVS-002776

A. TOXICITY

Evaluated in a concentration range of between 55 to 0.005 ug/ml of culture the IC_{50} and IC_{20} in mitogen stimulated blastogenesis were determined.

MITOGEN	IC_{50}	IC_{20}
PHA	39	20.5
CON-A	55	25.0

B. BLASTOGENESIS

1. HIV⁻ donor results:
   No enhancement in 3 of 3.
2. HIV⁺ donor results:
   Slight PHA enhancement in one and CON-A enhancement in the second.
3. Slight immunomodulatory activity is suggested.

C. NK ACTIVITY

1. HIV⁻ donor results:
   Enhancement seen at the 20:1 E to T ratio but not at 5:1.
2. HIV⁺ donor results:
   No enhancement seen at either E to T ratio.
3. No immunomodulatory activity present.

D. PHENOTYPE ANALYSIS

1. HIV⁻ donor results:
   Positive % changes: +36% for NK(Leu7) and +44% for $Leu2^+/Leu7^+$.
2. HIV⁺ donor results:
   Positive % changes: +29% for NK(Leu-11\CD16), +24% for NK(Leu7), +35% for IL2r(CD25) and +25% for $Leu2^+/Leu7^+$.
3. The data suggests changes in NK cell expression can be induced.

AVS-003925

A. TOXICITY

Evaluated in a concentration range of 90.9 to 0.004 ug/ml of culture the IC_{50} and IC_{20} in mitogen stimulated blastogenesis were determined.

MITOGEN	IC_{50}	IC_{20}
PHA	0.85	0.35
CON-A	0.50	0.25

B. BLASTOGENESIS

1. HIV⁻ donor results:
   No response in 2 of 2.
2. HIV⁺ donor results:
   Major enhancement in CON-A and PWM responses with maintenance of significant response levels past optimal culture times.
2. This data suggests definite immunomodulatory activity.

C. NK ACTIVITY

1. HIV⁻ donor results:
   No response in one, enhancement at the 20:1 ratio only in a second and enhancement at both the 20:1 and 5:1 ratios in the third.
2. HIV⁺ donor results:
   Enhanced responses in three, one at the 20:1 ratio only and two at the 5:1 ratio only.
3. Immunomodulatory activity is suggested.

D. PHENOTYPE ANALYSIS

1. HIV⁻ donor results:
   Positive percent changes: +32% for Suppressor T (Leu2\CD8), +50% for B(Leu12\CD19), and +26% for Inducers of Suppression ($Leu3^+/Leu8^+$).
   Negative percent changes: -38% for T cells(Leu5\CD2), -43% for NK(Leu11\CD16), -26% for NK(Leu-7), -30% for HLA-DR, -23% for IL2r(CD25) and -28% for $Leu2^+/Leu7^+$.
2. HIV⁺ donor results:
   Positive percent changes: +59% for IL2 CD25).
   Negative percent changes: -48% for Helper T (Leu3\CD4), -26% for NK(Leu19), -96% for B(Leu12\CD19), -35% for HLA-DR, -33% for Inducers of Help($Leu3^+/Leu8^-$), -52% for Inducers of Suppression($Leu3^+/Leu8^+$), and -47% for the H/S ratio.
2. The data indicates a major effect on the surface phenotypes of cells incubated with this drug.

//

AVS-003926

A. TOXICITY

Evaluated in a concentration range of between 454 to 0.021 ug/ml of culture the IC_{50} and IC_{20} in mitogen stimulated blastogenesis were determined.

MITOGEN	IC_{50}	IC_{20}
PHA	0.85	0.35
CON-A	0.45	0.40

B. BLASTOGENESIS

1. HIV⁻ donor results:
   Enhancement of response to both PHA and SLO in 1 of 2.
2. HIV⁺ donor results:
   Major enhancement of response to CON-A, PWM, and SLO with maintenance of significant response levels past optimal culture times.
3. Immunomodulatory activityi is indicated.

C. NK ACTIVITY

1. HIV⁻ donor results:
   Enhancement was seen with 2 of 3 at both E to T ratios.
2. HIV⁺ donor results:
   Enhancement was seen with 2 of 3 at both E to T ratios.
3. Immunomodulatory activity is indicated.

D. PHENOTYPE ANALYSIS

1. HIV⁻ donor results:
   Positive percent changes: +51% for CTL(Leu4⁺/Leu19⁺).
   Negative percent changes: -35% for T cells(Leu5\CD2), -39% for NK(Leu11\CD16), and -22% for IL2r(CD25).
2. HIV⁺ donor results:
   Positive percent changes: +70% for IL2r(CD25) and +32% for CTL(Leu4⁺/Leu19⁺).
   Negative percent changes: -20% for T cells(Leu5\CD2), -23% for Helper T(Leu3\CD4), -31% for NK(Leu19), -34% for HLA-DR, -46% for Inducers of Help(Leu3⁺/Leu8), and -22% for Inducers of Suppression(Leu3⁺/Leu8⁺).
3. Immunomodulatory activity is indicated.

AVS-003927

A. TOXICITY

Evaluated in a concentration range of between 9.1 and 0.033 ug/ml of culture the IC_{50} and IC_{20} in mitogen stimulated blastogenesis were determined.

MITOGEN	IC_{50}	IC_{20}
PHA	NONE	NONE
CON-A	NONE	2.0

B. BLASTOGENESIS

1. HIV^- donor results:
   One of three demonstrated a slight enhancement of the PHA response.
2. HIV^+ donor results:
   No enhancement with either of two.
3. No evidence of immunomodulatory activity.

C. NK ACTIVITY

1. HIV^- donor results:
   Enhancement was seen in both donors, but limited to the 20:1 ratio only.
2. HIV^+ donor results:
   Enhancement was seen with both donors, one at the 20:1 ratio but not the 5:1, and in the other at 5:1 but not at the 20:1 ratios.
3. Immunomodulatory activity is evident.

D. PHENOTYPE ANALYSIS

1. HIV^- donor results:
   Positive percent changes: +20% for Helpers(Leu3\CD4), +32% for NK(Leu19), and +77% for Inducers of Help($Leu3^+/Leu8^-$).
   Negative percent changes: -53% for NK(Leu11\CD16), -34% for IL2r(CD25), and -27% for Inducers of Suppression($Leu3^+/Leu8^+$).
2. HIV^+ donor results:
   Positive percent changes: +29% forNNK(Leu11\CD16).
   Negative percent changes: -32% for T cells(Leu\CD2), -30% for Helpers(Leu3\CD4),-25% for Suppressors (Leu2\CD8), -36% for HLA-DR, -45% for IL2r(CD25), -20% for Inducer of Help($Leu3^+/Leu8^-$), -33% for Inducer of Suppression($Leu3^+/Leu8^+$), -60% for CTL($Leu4^+/Leu19^+$), and -22% for ($Leu2^+/Leu7^+$).
2. Immunomodulatory activity is indicated.

AVS-003931

A. TOXICITY

Evaluated in a concentration range of between 41.7 and .00008 ug/ml of culture no toxicity was seen.

B. BLASTOGENESIS

1. HIV$^-$ donor results:
   Of three donors one had no response, the second had enhancement of the PHA response, and the third had enhancement of the PHA, CON-A, PWM, and SLO responses at optimal and post optimal days of culture.
2. HIV$^+$ donor results:
   None evaluated.
3. Immunomodulatory activity is indicated.

C. NK ACTIVITY

1. HIV$^-$ donor results:
   Of six studied one had a slight enhancement at both E to T ratios and one major enhancement at the 20:1 ratio only.
2. HIV$^+$ donor results:
   Of three studied one had a major enhancement at both E to T ratios, one marginal enhancement at the 20:1 ratio, and the third showed no enhancement.
2. Immunomodulatory activity is indicated.

C. PHENOTYPE ANALYSIS

1. HIV$^-$ donor results:
   None seen
2. HIV$^+$ donor results:
   Positive percent changes: +39% for NK(Leu11\CD16) and +33% for the H/S ratio.
   Negative percent changes: -25% for Helpers (Leu3\CD4), -27% for Suppressor(Leu2\CD8),-30% for B cells(Leu12\CD19), and -29% for Inducers of Suppression (Leu3$^+$/Leu8$^+$).
3. Immunomodulatory activity of HIV$^+$ cells is indicated.

AVS-003932

A. TOXICITY

Evaluated in a concentration range of between 41.7 and and 0.00008 ug/ml of culture no toxicity was detected.

B. BLASTOGENESIS

1. HIV⁻ donor results:
   Two of three had no enhancement while the third had major enhnacement of PHA, CON-A, PWM, and SLO at both optimal and post optimal culture times.
2. HIV⁺ donor results:
   One of one had major enhancement of PHA, CON-A, PWM, and SLO responses at both optimal and post optimal culture periods.
3. Immunomodulatory activity is indicated.

C. NK ACTIVITY

1. HIV⁻ donor results:
   Minimal enhancement at both E to T ratios was seen with one of six, moderate enhancement of the 20:1 ratio only with two others.
2. HIV⁺ donor results:
   Of three evaluated one had moderate enhancement at both E to T ratios and a second had moderate enhancement only at the 20:1 ratio.
3. Some immunomodulatory activity is indicated.

D. PHENOTYPE ANALYSIS

1. HIV⁻ donor results:
   Positive percent changes: +35% for CTL(Leu4⁺/Leu19⁺).
   Negative percent changes: none.
2. HIV⁺ donor results:
   Positive percent changes: +95% for NK(Leu11\CD16) and +37% for B cells(Leu12\CD19).
   Negative percent changes: -60% for Helpers(Leu3\CD4), -24% for Suppressors(Leu2\CD8), -65% for Inducers of Suppression (Leu3⁺/Leu8⁺), and -44% for H/S ratio.
2. Immunomodulatory activity is indicated.

AVS-003934

A. TOXICITY

Evaluated in a concentration range of 208 to 0.02 ug/ml of culture no toxicity was seen.

B. BLASTOGENESIS

1. HIV$^-$ donor results:
   No enhancement seen in 3 of 3 donors.
2. HIV$^+$ donor results:
   Slight PHA enhancement seen in 1 of 2 donors.
3. Essentially no immunomodulatory activity.

C. NK ACTIVITY

1. HIV$^-$ donor results:
   Slight enhancement at only one E:T ratio.
2. HIV$^+$ donor results:
   Slight enhancement at only one E:T ratio.
3. Essentially no immunomodulatory activity.

D. PHENOTYPE ANALYSIS

1. HIV$^-$ donor results:
   Positive percent change: +21% for NK(Leu7), and +40% for (Leu2$^+$/Leu7$^+$).
   Negative percent change: -31% for NK(Leu11\CD16) and -23% for the H/S ratio.
2. HIV$^+$ donor results:
   Positive percent change: +27% for IL2r(CD25).
3. The data suggests little if any immunomodulatory activity.

AVS-004594

A. TOXICITY

Evaluated in a concentration range of 41.7 to 0.00008 ug/ml of culture no toxicity was seen.

B. BLASTOGENESIS

1. HIV$^-$ donor results:
   Two of three had no response while the third had significant enhancements of PHA, CON-A, PWM, and SLO with maintenance of significant response levels past optimal culture times.
2. HIV$^+$ donor results:
   One of two had significant enhancements of PHA, CON A, PWM, and SLO with response maintenance past optimal culture times while the second donor had no enhancement.
3. Immunomodulatory activity is indicated.

C. NK ACTIVITY

1. HIV$^-$ donor results:
   Four of six showed no response while of the remaining two; one had enhancement at the 20:1 ratio only while the second had enhancement at both ratios.
2. HIV$^+$ donor results:
   Two of three demonstrated enhancement at both ratios while the third had no response.
3. Immunomodulatory activity is indicated.

D. PHENOTYPE ANALYSIS

1. HIV$^-$ donor results:
   Positive percent changes: none seen.
   Negative percent changes: -22% for IL2r(CD25).
2. HIV$^+$ donor results:
   Positive percent changes: +24% for Suppressors (Leu2\CD8), +35% for NK(Leu19), +36% for NK(Leu11\CD16), +22% for NK(Leu7), +54% for CTL(Leu4$^+$/Leu19$^+$), +49% for (Leu2$^+$/Leu7$^+$), and +44% for H/S ratio.
   Negative percent changes: -22% for T cells(Leu4\CD3), and -40% for B cells(Leu12\CD19).
3. Immunomodulatory activity is indicated.

Anti-viral drugs were co-cultured with normal human HIV⁻ lymphocytes in a 3 day mitogen induced blastogenesis assay. Data was expressed as the % inhibition of the untreated response relative to the drug treated responses. Two degrees of response inhibition, moderate (20% or less) and significant (50% or greater), were defined and the concentration of anti-viral drugs inducing these states was determined. Subsequent functional mononuclear cell assays were performed with drug concentrations usually not exceeding those that induced the moderate inhibition.

CONCENTRATIONS OF ANTI-VIRAL AGENTS INDUCING GROWTH INHIBITION DURING CO-CULTURE IN A 3 DAY MITOGEN INDUCED LYMPHOCYTE BLASTOGENIC RESPONSE ASSAY

AVS DRUG #	CONC. RANGE EVALUATED (UG/ML CULTURE)	CONC. INDUCING 20% INHIBITION PHA	CONC. INDUCING 20% INHIBITION CON-A	CONC. INDUCING 50% INHIBITION PHA	CONC. INDUCING 50% INHIBITION CON-A
1968	833.3 - 0.083	0.83	0.5	5.0	
3934	208.3 - 0.021	NONE	NONE	NONE*	NONE
2776	55.0 - 0.005	20.5	25.0	39.0	55.0
3925	90.9 - 0.004	0.35	0.25	0.85	0.50
3926	454.0 - 0.021	0.35	0.40	0.85	0.45
3927	9.1 - 0.033	NONE	2.0	NONE	NONE
3931	41.7 - $0.8X10^{-5}$	NONE	NE**	NONE	NE
3932	41.7 - $0.8X10^{-5}$	NONE	NE	NONE	NE
4594	41.7 - $0.8X10^{-5}$	NONE	NE	NONE	NE

* NONE = No toxicity at this level for any concentrations studied.
** NE = Not evaluated.

Lymphocyte blastogenesis response cultures were set with a variety of mitogens and antigens in the presence and absence of selected doses of anti-viral drugs. Cultures were harvested at various days after initiation and responses of the drug treated cultures were evaluated for enhancement relative to the corresponding non-treated cultures.

ENHANCEMENT OF HIV$^-$ OR HIV$^+$ LYMPHOCYTE BLASTOGENIC RESPONSES IN THE PRESENCE OF ANTI-VIRAL DRUGS

AVS DRUG NO. I.D.	INDIVIDUAL LYMPHOCYTE DONOR VIRUS STATUS	STIMULATING MITOGEN OR ANTIGEN	DAYS IN CULTURE	% MITOGEN RESPONSE ENHANCEMENT	NET CPM INCREASE (X 10^3)
1968	HIV$^-$	NR*	-	-	-
	HIV$^-$	PHA	3	10.5	7.36
	HIV$^-$	CON-A	3	7.9	7.43
	HIV$^+$	NR	-	-	-
	HIV$^+$	PHA	3	11.0	11.63
3934	HIV$^-$	NR	-	-	-
	HIV$^-$	NR	-	-	-
	HIV$^-$	NR	-	-	-
	HIV$^+$	NR	-	-	-
	HIV$^+$	PHA	3	11.6	12.32
3927	HIV$^-$	NR	-	-	-
	HIV$^-$	NR	-	-	-
	HIV$^-$	PHA	5	19.5	17.90
	HIV$^+$	NR	-	-	-
	HIV$^+$	NR	-	-	-

AVS DRUG NO. I.D.	INDIVIDUAL LYMPHOCYTE DONOR VIRUS STATUS	STIMULATING MITOGEN OR ANTIGEN	DAYS IN CULTURE	% MITOGEN RESPONSE ENHANCEMENT	NET CPM INCREASE (X 10^3)
2776	HIV⁻	NR	-	-	-
	HIV⁻	NR	-	-	-
	HIV⁻	NR	-	-	-
	HIV⁺	PHA	3	7.4	8.39
	HIV⁺	CON-A	3	16.9	13.94
3925	HIV⁻	NR	-	-	-
	HIV⁻	NR	-	-	-
	HIV⁺	CON-A	3	29.5	5.57
		"	6	10.5	4.83
		PWM	6	35.2	8.71
		"	8	44.1	9.67
3926	HIV⁻	NR	-	-	-
	HIV⁻	PHA	3	10.1	9.05
		SLO	6	33.0	7.56
	HIV⁺	CON-A	3	24.1	3.82
		"	6	35.8	4.70
		PWM	6	44.6	6.15
		"	8	66.2	14.59
		SLO	8	41.4	15.56
3931	HIV⁻	NR	-	-	-
	HIV⁻	PHA	3	14.7	6.63
	HIV⁻	PHA	3	10.1	7.68
		"	6	32.0	8.95
		"	8	21.0	1.80
		CON-A	3	20.5	15.96
		PWM	3	96.3	19.39
		"	6	43.8	20.25
		"	8	38.8	7.20
		SLO	6	32.4	3.25
		"	8	66.0	10.37

AVS DRUG NO. I.D.	INDIVIDUAL LYMPHOCYTE DONOR VIRUS STATUS	STIMULATING MITOGEN OR ANTIGEN	DAYS IN CULTURE	% MITOGEN RESPONSE ENHANCEMENT	NET CPM INCREASE ($\times 10^3$)
3932	HIV⁻	NR	-	-	-
	HIV⁻	NR	-	-	-
	HIV⁻	PHA	3	23.2	29.47
		"	6	38.0	10.47
		"	8	115.4	5.59
		CON-A	3	20.5	14.91
		PWM	3	45.5	8.81
		"	6	43.0	20.43
		"	8	87.0	14.15
		SLO	6	32.4	3.25
		"	8	66.0	10.37
	HIV⁺	PHA	3	24.8	11.58
		"	6	46.9	19.67
		"	8	52.4	6.58
		CON-A	3	22.5	8.61
		"	8	67.5	2.80
		PWM	3	72.7	6.15
		SLO	6	14.5	2.45
4594	HIV⁻	NR	-	-	-
	HIV⁻	NR	-	-	-
	HIV⁻	PHA	3	16.4	12.69
		"	6	18.1	5.60
		"	8	207.2	6.43
		CON-A	6	25.9	4.68
		PWM	6	37.9	18.78
		"	8	89.0	12.11
		SLO	6	34.7	4.36
		"	8	95.9	17.82
	HIV⁺	NR	-	-	-
	HIV⁺	PHA	3	29.0	13.14
		"	6	16.4	9.01
		"	8	65.7	6.45
		CON-A	3	31.6	12.33
		"	6	16.9	7.36
		PWM	3	50.9	4.73
		"	6	31.6	6.42
		SLO	6	32.6	5.85
		"	8	46.0	10.82

Mononuclear cells isolated from a mixed population of HIV^- and HIV^+ donors were incubated with anti-viral drugs at various concentrations for 18 hours. All cells were then washed and the standard four hour ^{51}Cr release assay to measure NK function against K562 target cells was set using effector to target cell ratios of 20:1 and 5:1. Data was evaluated for drug concentrations inducing either an increase or decrease of 20% or more over the untreated controls.

CONCENTRATIONS OF ANTI-VIRAL DRUGS INDUCING CHANGES OF 20% OR MORE IN NK CELL KILLING OF K562 TARGET CELLS IN A COMBINED HIV^-/HIV^+ POPULATION

AVS DRUG #	CONC. RANGE EVALUATED UG/ML CULTURE	MAXIMUM CONC. $\geq$ 20% INCREASE	MAXIMUM CONC. $\geq$ 50% INCREASE
1968	$8.33 - 8.33X10^{-2}$	0.83	0.83
3934	$208.30 - 4.16X10^{-2}$	208.30	0.21
2776	55.00 - 0.55	0.666	NONE*
3925	$0.91 - 0.42X10^{-3}$	$0.83X10^{-3}$	$0.83X10^{-3}$
3926	$4.50 - 0.21X10^{-1}$	$3.60X10^{-2}$	$3.60X10^{-2}$
3927	$9.10 - 0.33X10^{-1}$	$6.60X10^{-2}$	NONE
3931	4.17 - 0.417	$4.17X10^{-2}$	NONE
3932	4.17 - 0.417	$4.17X10^{-2}$	$0.42X10^{-2}$
4594	$4.2E^{-2} - 0.83X10^{-2}$	$4.17X10^{-2}$	?

* NONE = NO ACTIVITY OF THIS MAGNITUDE

PERCENT CHANGE IN SURFACE MARKER EXPRESSION ON HIV⁻ AND HIV⁺ LYMPHOCYTES FOLLOWING INCUBATION WITH ANTIVIRAL DRUGS FOR 18, 72,OR 120HOURS

SURFACE ANTIGEN			AVS-1968 HIV⁻	AVS-1968 HIV⁺	AVS-3934 HIV⁻	AVS-3934 HIV⁺
LEU-5 *	CD2 *	E-ROSE	NC*	NC	NC	NC
LEU-4 *	CD3 *	PAN T	NC	NC	NC	NC
LEU-3 *	CD4 *	HELPER	NC	NC	NC	NC
LEU-2 *	CD8 *	SUPPRE	NC	NC	NC	NC
LEU-19*	- *	NK	NC	NC	NC	NC
LEU-11*	CD16*	NK	NC	-23	-31	NC
LEU-7 *	- *	NK	+28	NC	+21	NC
LEU-12*	CD19*	B	+135	NC	NC	NC
HLA-DR*	- *		NC	NC	NC	NC
IL2r *	CD25*		NC	+38	NC	+27
L3⁺&L8⁻		IND.HELP	NC	NC	NC	NC
L3⁺&L8⁺		IND.SUPP	NC	NC	NC	NC
L4⁺&L19⁺		CTL	+27	-27	NC	NC
L2⁺&L7⁺			+29	NC	+40	NC
H/S RATIO			NC	NC	-23	NC

* NC = NO CHANGE OR LESS THAN 20% CHANGE FROM NO DRUG CONTROLS.

PBL were incubated with anti-viral drugs at non-toxic concentrations for 18, 24, 72, or 120 hours before staining with directly conjugated antibodies.

No differences of significance were seen when various incubation times were compared.

These data are averages for all time points evaluated .

PERCENT CHANGE IN SURFACE MARKER EXPRESSION ON HIV⁻ AND HIV⁺ LYMPHOCYTES FOLLOWING INCUBATION WITH ANTIVIRAL DRUGS FOR 18, 72,OR 120HOURS

SURFACE ANTIGEN			AVS-3926		AVS-3927	
			HIV⁻	HIV⁺	HIV⁻	HIV⁺
LEU-5 *	CD2 *	E-ROSE	-35	-20	NC	-32
LEU-4 *	CD3 *	PAN T	NC	NC	NC	NC
LEU-3 *	CD4 *	HELPER	NC	-23	+20	-30
LEU-2 *	CD8 *	SUPPRE	NC	NC	NC	-25
LEU-19*	- *	NK	NC	-31	+32	NC
LEU-11*	CD16*	NK	-39	NC	-53	+29
LEU-7 *	- *	NK	NC	NC	NC	NC
LEU-12*	CD19*	B	+100	NC	+196	NC
HLA-DR*	- *		NC	-34	NC	-36
IL2r *	CD25*		-22	+70	-34	-45
L3⁺&L8⁻		IND.HELP	NC	-46	+77	-20
L3⁺&L8⁺		IND.SUPP	NC	-22	-27	-33
L4⁺&L19⁺		CTL	+51	+32	..	-60
L2⁺&L7⁺			NC	NC	NC	-22
H/S RATIO			NC	NC	NC	NC

PERCENT CHANGE IN SURFACE MARKER EXPRESSION ON HIV⁻ AND HIV⁺ LYMPHOCYTES FOLLOWING INCUBATION WITH ANTIVIRAL DRUGS FOR 18, 72,OR 120HOURS

SURFACE ANTIGEN		AVS-2776		AVS-3925	
		HIV⁻	HIV⁺	HIV⁻	HIV⁺
LEU-5 * CD2 * E-ROSE		NC	NC	-38	NC
LEU-4 * CD3 * PAN T		NC	NC	NC	NC
LEU-3 * CD4 * HELPER		NC	NC	NC	-48
LEU-2 * CD8 * SUPPRE		NC	NC	+32	NC
LEU-19* - * NK		NC	NC	NC	-26
LEU-11* CD16* NK		NC	+29	-43	NC
LEU-7 * - * NK		+36	+24	-26	NC
LEU-12* CD19* B		NC	NC	+50	-96
HLA-DR* - *		NC	NC	-30	-35
IL2r * CD25*		NC	+35	-23	+59
L3⁺&L8⁻	IND.HELP	NC	NC	NC	-33
L3⁺&L8⁺	IND.SUPP	NC	NC	+25	-52
L4⁺&L19⁺	CTL	NC	NC	NC	NC
L2⁺&L7⁺		+44	+25	-28	NC
H/S RATIO		NC	NC	NC	-47

PERCENT CHANGE IN SURFACE MARKER EXPRESSION ON HIV⁻ AND HIV⁺ LYMPHOCYTES FOLLOWING INCUBATION WITH ANTIVIRAL DRUGS FOR 18, 72,OR 120HOURS

SURFACE ANTIGEN			AVS-3931		AVS-3932	
			HIV⁻	HIV⁺	HIV⁻	HIV⁺
LEU-5 *	CD2 *	E-ROSE	..	..	..	..
LEU-4 *	CD3 *	PAN T	NC	NC	NC	NC
LEU-3 *	CD4 *	HELPER	NC	-25	NC	-60
LEU-2 *	CD8 *	SUPPRE	NC	-27	NC	-24
LEU-19*	- *	NK	NC	NC	NC	NC
LEU-11*	CD16*	NK	NC	+39	NC	+95
LEU-7 *	- *	NK	NC	NC	NC	NC
LEU-12*	CD19*	B	NC	-30	NC	+37
HLA-DR*	- *		NC	NC	NC	NC
IL2r *	CD25*		NC	NC	NC	NC
L3⁺&L8⁻		IND.HELP	NC	NC	NC	NC
L3⁺&L8⁺		IND.SUPP	NC	-29	NC	-65
L4⁺&L19⁺		CTL	NC	NC	+35	NC
L2⁺&L7⁺			NC	NC	NC	NC
H/S RATIO			NC	+33	NC	-44

PERCENT CHANGE IN SURFACE MARKER EXPRESSION ON HIV⁻ AND HIV⁺ LYMPHOCYTES FOLLOWING INCUBATION WITH ANTIVIRAL DRUGS FOR 18, 72,OR 120HOURS

SURFACE ANTIGEN			AVS-4594 HIV⁻	AVS-4594 HIV⁺
LEU-5 * CD2 *		E-ROSE	..	..
LEU-4 * CD3 *		PAN T	NC	-22
LEU-3 * CD4 *		HELPER	NC	NC
LEU-2 * CD8 *		SUPPRE	NC	+24
LEU-19* - *		NK	NC	+35
LEU-11* CD16*		NK	NC	+36
LEU-7 * - *		NK	NC	+22
LEU-12* CD19*		B	NC	-40
HLA-DR* - *			NC	NC
IL2r * CD25*			-22	NC
L3⁺&L8⁻		IND.HELP	NC	NC
L3⁺&L8⁺		IND.SUPP	NC	NC
L4⁺&L19⁺		CTL	NC	+54
L2⁺&L7⁺			NC	+49
H/S RATIO			NC	+44

DRUG DILUTION/CONCENTRATION TABLE

DRUG #	DILUTION	UG/ML CULTURE
1968	F/S	833.3
	1:10	83.3
	1:100	8.33
	1:500	1.666
	1:1000	0.833
	1:5000	0.166
	1:10000	0.083
3934	F/S	208.3
	1:10	20.83
	1:100	2.083
	1:1000	0.208
	1:5000	0.041
	1:10000	0.021
2776	F/S	55.0
	1:5	11.0
	1:10	5.5
	1:50	1.1
	1:100	0.55
	1:1000	0.055
	1:10000	0.005

1989 Summary Data

The second component of our Drug Discovery program includes an in vitro analysis od drugs supplied from the Group Discovery Group. These analysis include in vitro lymphocyte mitogen and antigen stimulation responses, in vitro immunotoxicity, and in vitro effects on Nk cell activity utilizing the lymphocytes of normal subjects and HIV patients. In the period of time covered by this report, 20 drugs have been received from the Drug discovery group and 18 have undergone some degree of analysis. Of the 18 studied drugs, 9 have shown immunotoxicity at some point over the dose range, while 3 have shown immunological augmentation. These have been measured by the lymphocyte proliferative responses to phytohemagglutinin, concanavalin A, Pokeweed Mitogen, streptolysin O. Of the 18 studied drugs, 8 have shown immunological enhancement of the NK cell response. In general, effects or lack of effects seen when the drugs were applied to normal lymphocytes were paralleled when the drugs were applied to patient lymphocytes.

The drugs which showed immunological augmentation included 5018, 5026, and 5073 as measured by the lymphocyte blastogenic response. While those which showed immunological augmentation by the NK cell response included 4596, 5014, 5016, 5019, 5025, 5026, and 5074. The most active drug among these was 5025. Tables 1-8 summarize these results.

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Table 1: Listing of the drugs reported on last year and those covered in the current report.

Table 2: Status of the drugs under evaluation with regard to the procedures being used.

Table 3: A summary table derived from the first toxicity experiments showing the presence of toxicity or enhancement for each drug as + or -.

Table 4: A summary table of the LBR 1 (Optimal Mitogen/Antigen Stimulation) results. Results given as No Chance (NC), Toxicity (TX), or Enhancement (EN), with the P value by Student's T Test given for each TX or EN case.

Table 5: Identical to Table 4 above, but this is the LBR 2 (Sub-Optimal Mitogen/Antigen) stimulation results.

Table 6: Presents the % Cytotoxicity by NK cells at a 20:1 ratio following 18 hours of drug incubation.

Table 7: As in Table 6 above, but at the 5:1 ratio.

Table 8: A summary of the data in Tables 6 and 7 above indicating the presence of enhanced NK activity as + or -.

TABLE 1

REPORT STATUS OF DRUGS RECEIVED
FOR IN VITRO EVALUATIONS

PREVIOUS REPORT 1988	CURRENT REPORT 1989	NOT YET EVALUATED
1968	1792	1767
2776	2777	4595
3925	2778	
3926	2880	
3927	4596	
3931	5014	
3932	5015	
3934	5016	
4594	5017	
	5018	
	5019	
	5020	
	5025	
	5026	
	5027	
	5028	
	5073	
	5074	

Identified by the last four digits of their AVS code number.

TABLE 2
PROCEDURES STATUS
OF AVS DRUGS IN EVALUATION

AVS #	TOX 1 FULL	TOX 2 PART	LBR 1 OPTIMAL	LBR 2 SUB-OPT	NK1 FULL	NK2 PART
1792	X	0	X	X	X	0
2777	X	0	-	-	X	0
2778	X	0	X	X	X	0
2880	X	0	-	-	-	-
4596	X	0	X	X	X	-
5014	X	-	X	X	X	-
5015	X	0	X	X	X	0
5016	X	0	X	X	X	-
5017	X	0	X	X	X	0
5018	X	0	X	X	X	0
5019	X	X	-	-	X	-
5020	X	-	X	X	X	0
5025	X	X	-	-	X	-
5026	X	X	X	X	X	-
5027	X	X	-	-	X	-
5028	X	X	-	-	X	0
5073	X	-	X	X	X	0
5074	X	-	X	X	X	-

X = COMPLETE
- = PENDING
0 = NOT REQUIRED

SUMMARY TABLE 3

INITIAL DOSE RESPONSE● STUDIES DETERMINING TOXICITY OR ENHANCEMENT OF THE LBR

AVS #	TOXICITY	ENHANCEMENT
1792	-•	-
2777	-	-
2778	-	-
2880	+••	-
4596	-	-
5014	-	-
5015	-	-
5016	+/-	-
5017	-	-
5018	-	+/-
5019	+	-
5020	+	-
5025	+/-	-
5026	+/-	+
5028	+	-
5073	+/-	+/-
5074	+/-	-

● 0.01 TO 100UG PER ML OF CULTURE
• NOT PRESENT
•• PRESENT
P VALUES OF DRUG VS NO DRUG CONTROL $\leq .010$

SUMMARY TABLE 4

BLASTOGENIC RESPONSES OF LYMPHOCYTES STIMULATED WITH OPTIMAL CONCENTRATIONS OF MITOGENS OR ANTIGEN IN THE PRESENCE OF AVS - DRUGS

DRUG #	MITOGEN ANTIGEN	UG DRUG PER ML CULTURE 1	10	100
1792	PHA	NC*	NC	NC
	CON-A	NC	EN (.025)**	NC
	PWM	NC	NC	TX (.010)***
	SLO	NC	NC	TX (.010)
2778	PHA	NC	EN (.025)	NC
	CON-A	TX (.001)	EN (.025)	TX (.025)
	PWM	TX (.001)	EN (.001)	NC
	SLO	NC	NC	EN (.001)
4596	PHA	NC	EN (.025)	NC
	CON-A	NC	EN (.010)	TX (.010)
	PWM	EN (.025)	EN (.001)	EN (.001)
	SLO	NC	NC	TX (.010)
5014	PHA	NC	NC	NC
	CON-A	NC	NC	NC
	PWM	NC	NC	NC
	SLO	NC	NC	TX (.025)
5015	PHA	NC	NC	NC
	CON-A	NC	TX (.025)	TX (.025)
	PWM	NC	NC	NC
	SLO	NC	EN (.025)	EN (.025)
5016	PHA	NC	NC	NC
	CON-A	NC	TX (.010)	TX (.010)
	PWM	NC	TX (.010)	TX (.010)
	SLO	TX (.010)	NC	NC
5017	PHA	NC	NC	NC
	CON-A	NC	NC	NC
	PWM	NC	NC	NC
	SLO	NC	NC	NC
5018	PHA	NC	TX (.010)	NC
	CON-A	NC	NC	NC
	PWM	NC	NC	NC
	SLO	NC	NC	NC

SUMMARY TABLE 4 CONTINUED

BLASTOGENIC RESPONSES OF LYMPHOCYTES STIMULATED
WITH OPTIMAL CONCENTRATIONS OF MITOGENS OR ANTIGEN
IN THE PRESENCE OF AVS - DRUGS

DRUG #	MITOGEN ANTIGEN	UG DRUG PER ML CULTURE 1	10	100
5020	PHA	NC	NC	NC
	CON-A	NC	NC	NC
	PWM	NC	NC	NC
	SLO	NC	NC	NC
5026	PHA	NC	TX (.025)	NC
	CON-A	NC	NC	NC
	PWM	NC	NC	NC
	SLO	NC	NC	NC
5073	PHA	NC	NC	EN (.010)
	CON-A	NC	NC	NC
	PWM	NC	NC	NC
	SLO	NC	NC	NC
5074	PHA	NC	NC	NC
	CON-A	NC	NC	EN (.025)
	PWM	NC	NC	NC
	SLO	NC	NC	NC

* NC = NO CHANGE COMPARED TO NO DRUG CONTROL
** TX = TOXICITY " " " " "
*** EN = ENHANCEMENT " " " " "
( ) = P VALUE " " " " " BY STUDENT'S T

SUMMARY TABLE 5

BLASTOGENIC RESPONSES OF LYMPHOCYTES STIMULATED WITH SUB-OPTIMAL CONCENTRATIONS OF MITOGENS OR ANTIGEN IN THE PRESENCE OF AVS - DRUGS

DRUG #	MITOGEN ANTIGEN	UG DRUG PER ML CULTURE 1	10	100
1792	PHA	TX (.025)	NC	NC
	CON-A	NC	NC	TX (.025)
	PWM	NC	EN (.025)	TX (.001)
	SLO	NC	NC	TX (.025)
2778	PHA	TX (.010)	EN(.001)	NC
	CON-A	NC	NC	TX (.010)
	PWM	TX (.010)	EN (.010)	NC
	SLO	EN (.025)	NC	NC
4596	PHA	TX (.025)	NC	TX (.001)
	CON-A	NC	TX (.001)	TX (.001)
	PWM	EN (.025)	EN (.001)	NC
	SLO	TX (.010)	NC	NC
5014	PHA	TX (.025)	NC	NC
	CON-A	NC	NC	NC
	PWM	NC	NC	NC
	SLO	NC	NC	TX (.025)
5015	PHA	NC	NC	NC
	CON-A	NC	NC	NC
	PWM	NC	NC	NC
	SLO	NC	EN (.025)	EN (.010)
5016	PHA	NC	NC	NC
	CON-A	NC	NC	NC
	PWM	NC	NC	NC
	SLO	TX (.025)	NC	NC
5017	PHA	NC	NC	NC
	CON-A	NC	NC	N
	PWM	NC	NC	EN (.010)
	SLO	NC	NC	EN (.010)
5018	PHA	NC	TX (.025)	NC
	CON-A	NC	NC	EN (.001)
	PWM	NC	TX (.025)	NC
	SLO	NC	NC	EN (.010)

SUMMARY TABLE 5 CONTINUED

BLASTOGENIC RESPONSES OF LYMPHOCYTES STIMULATED
WITH SUB-OPTIMAL CONCENTRATIONS OF MITOGENS OR ANTIGEN
IN THE PRESENCE OF AVS - DRUGS

DRUG #	MITOGEN ANTIGEN	UG DRUG PER ML CULTURE 1	10	100
5020	PHA	NC	NC	NC
	CON-A	NC	NC	TX (.025)
	PWM	NC	NC	NC
	SLO	NC	NC	NC
5026	PHA	NC	EN (.010)	EN (.010
	CON-A	NC	NC	NC
	PWM	NC	EN (.010)	EN (.001)
	SLO	NC	NC	NC
5073	PHA	NC	EN (.025)	NC
	CON-A	NC	NC	NC
	PWM	NC	NC	NC
	SLO	NC	NC	NC
5074	PHA	NC	NC	NC
	CON-A	NC	EN (.010)	NC
	PWM	NC	NC	NC
	SLO	NC	NC	NC

* NC = NO CHANGE COMPARED TO NO DRUG CONTROL
** TX = TOXICITY
*** EN = ENHANCEMENT
( ) = P VALUE BY STUDENT'S T

TABLE 6
% CYTOTOXICITY BY NK CELLS
FOLLOWING 18 HOURS PREINCUBATION WITH AVS DRUGS
(EFFECTOR TO TARGET RATIO = 20:1)

DRUG #	UG DRUG PER ML CULTURE 0	.001	.01	.1	1	5	10	25	50	100
1792	18	19	20	19	19	-	17	-	-	17
	40	-	-	-	13	20	14	15	15	20
	53	-	-	-	52	-	56	-	-	43
2777	33	-	-	-	18	14	17	25	22	14
2778	19	-	-	-	12	15	9	11	10	9
4596	20	18	14	17	17	-	17	-	-	14
	35	-	-	-	9	25	26	22	25	17
5014	22	16	18	20	19	-	17	-	-	18
	39	-	-	-	30	30	27	17	26	27
	45	-	-	-	44	-	66	-	-	72
5015	39	-	-	-	33	32	28	25	29	30
5016	17	21	20	17	18	-	20	-	-	16
	19	-	-	-	22	26	29	21	27	27
	59	-	-	-	56	-	65	-	-	47
5017	34	-	-	-	36	33	39	39	41	37
5018	24	-	-	-	29	18	17	16	15	14
5019	14	-	-	-	15	17	25	16	20	20
	72	-	-	-	74	-	81	-	-	51
5020	12	-	-	-	13	10	12	6	18	12
	58	-	-	-	60	-	58	-	-	49
5025	13	-	-	-	11	15	11	12	12	21
	53	-	-	-	67	-	74	-	-	55
5026	12	20	17	16	19	-	18	-	-	17
	22	-	-	-	21	18	15	17	16	20
5028	17	-	-	-	15	15	13	17	6	1
	64	-	-	-	61	-	62	-	-	4
5073	16	22	18	19	18	-	20	-	-	19
	22	-	-	-	18	13	17	21	21	22
	64	-	-	-	63	-	61	-	-	67
5074	18	-	-	-	7	11	10	16	16	18
	49	-	-	-	46	-	52	-	-	39

TABLE 7
% CYTOTOXICITY BY NK CELLS
FOLLOWING 18 HOURS PREINCUBATION WITH AVS DRUGS
(EFFECTOR TO TARGET RATIO = 5:1)

DRUG #	UG DRUG PER ML CULTURE 0	.001	.01	.1	1	5	10	25	50	100
1792	3	1	5	3	3		2	-	-	3
	23	-	-	-	10	20	18	30	30	24
	33	-	-	-	34	-	38	-	-	24
2777	9	-	-	-	14	12	16	12	14	7
2778	17	-	-	-	12	14	8	9	9	7
4596	2	4	3	2	4	-	3	-	-	2
	18	-	-	-	3	29	25	25	27	15
5014	1	1	4	4	3	-	5	-	-	4
	32	-	-	-	29	34	29	25	32	30
	43	-	-	-	46	-	53	-	-	45
5015	23	-	-	-	21	23	30	21	23	24
5016	1	5	4	1	3	-	3	-	-	3
	21	-	-	-	22	24	29	20	29	25
	30	-	-	-	38	-	36	-	-	28
5017	19	-	-	-	27	27	26	26	20	20
5018	16	-	-	-	20	17	16	14	11	18
5019	17	-	-	-	13	17	21	21	22	15
	40	-	-	-	42	-	45	-	-	29
5020	14	-	-	-	16	7	12	10	14	19
	38	-	-	-	41	-	37	-	-	27
5025	14	-	-	-	13	16	13	12	15	17
	32	-	-	-	37	-	46	-	-	28
5026	1	3	3	3	2	-	3	-	-	2
	16	-	-	-	24	28	21	19	23	22
5028	11	-	-	-	16	17	15	13	7	0
	41	-	-	-	42	-	39	-	-	2
5073	2	4	4	3	3	-	4	-	-	2
	15	-	-	-	18	15	13	17	15	18
	41	-	-	-	45	-	34	-	-	25
5074	13	-	-	-	13	15	10	15	17	20
	30	-	-	-	32	-	44	-	-	32

SUMMARY TABLE 8

ENHANCEMENT OF NK ACTIVITY FOLLOWING 18 HOURS DRUG EXPOSURE

AVS #	EFFECTOR TO TARGET RATIOS 20:1	5:1
1792	-	-
2777	-	-
2778	-	-
4596	-	+/-
5014	+/-	-
5015	-	-
5016	+/-	-
5017	-	-
5018	-	-
5019	+/-	-
5020	-	-
5025	+	+
5026	-	+
5028	-	-
5073	-	-
5074	-	+

- = NO ENHANCEMENT SEEN
+ = $\geq$ 10% ENHANCEMENT
+/- = VARIABLE BY EFFECTOR CELL DONOR

1990 Summary Data

a. In vivo Studies

Three experiments have been conducted in vivo in the LP-BM5 model with AVS-5027 (Imexon). These experiments indicate that AVS-5027 should be a very active agent in AIDS. Doses of 12.5, 25, 50, 100 and 150 mg/kg were used in these experiments. Treatment was started from either the day of virus inoculation, 2 weeks after virus inoculation or 11 weeks after inoculation. The dose of 150 mg/m^2 was toxic. All dose levels had some biologic activity. The optimal dose was 50-100 mg/kg. AVS-5027 was active at all doses and at all starting times. Activities included reduction in hypergammaglobulinemia, restoration of the lymphocyte response to PHA and LPS reduction in splenomegaly and adenopathy and prolongation of survival. For example in one experiment survival was 9% in the virus infected animal compared to 100% at 50 and 100 mg/kg measured at 22 weeks after virus inoculation.

One experiment was done combining AZT at 0.05, 0.10 and 0.20 mg/ml in the drinking water with AVS-5027. No additive or synergistic effect was seen. Two further experiments have been done with diethyldithiocarbamate (DTC). AZT at 0.05, 0.10 and 0.20 mg/ml in the drinking water was combined with a suboptimal dose of DTC (200 mg/kg). Evidence for additive or synergistic interaction between these drugs resulting in further prolongation of survival was noted.

Other drugs understudy in the in vivo model include AS101, thymic humoral factor, analogues of DTC and N-acetyl Cysteine.

b. In vitro Studies, Results and Recommendations

In the current grant year 67 compounds have been received for evaluation. Twenty-none have been evaluated over a dose range, usually of 0.075 - 500 ug/ml. Toxicity index on lymphocyte blastogenesis, toxicity index on NK cell activity and potential enhancement or augmentation of these functions by the drugs were studied. Five of the drugs showed fairly broad augmentation of PHA, ConA PWM, and SLP proliferative responses usually at 7 days in the suboptimally stimulated cultures. These were AVS-1757, 1758, 1767, 4732 and 5579. These drugs will be further pursued and if appropriate will be tested in the vivo model. Most of the drugs tested for inhibition, were induced inhibitory but usually only at concentrations of .25 ug/ml. None were not inhibitory at all. Only 4 were inhibitory at concentrations under 25 ug/ml. Correlation of this data with their antiviral activity will be needed.

Drugs 1755 and 1756 (MVE-4) was not pursued because they are macrophage activators, only very limited amounts are available and Hercules/Adria do not intend to produce more.

Drug 1758 (Bru-Pel) is active in cancer immunotherapy and has been given to man. Since it may be an IFN inducer in part, it may not have much advantage over IFN. A brief study was proposed to be worthwhile.

Drug 1761 (Poly ICLC) is very toxic and was not proposed to be studied.

Drug 1799 (Azimexon) is another cyanoaziridine. We actually did a study of it in HIV patients at M.D. Anderson. As a relative of Imexon, it is of great interest. We recommended it for study.

Our in vitro data suggested a high priority for 8522 and PGG.

In summary, we need 1) To know the identity of certain drug, 2) To obtain pharmacology and company data on the selected drugs, and 3) To obtain adequate supplies for completion of in vitro evaluation and animal model studies.

ENHANCEMENT OF MITOGEN RESPONSE
- 1755 MVE-3
- 1756 MVE-4
- 1788 LEVAMISOLE
- 4593 P188
- 4596 LCP-100
- 4729 Lithium polyacrylate

ENHANCEMENT OF NK ACTIVITY
- 1758 BRU-PEL
- 1761 POLY ICLC
- 1799 AZIMEXON
- 3926 ?
- 3928 TP-3
- 4728 Glycyrrhizin monolithium
- 4731 Lithium butyrate
- 4733 Lithium polyacrylate germanate (IV)
- 5013 EL200 adult syrup
- 5022 D-ELS4
- 5025 MA-CDA
- 5411 ACT
- 8522 ?
- 8528 ?
- AGG ?

LISTING OF ALL DRUGS EVALUATED
1987-1991

AVS NUMBER	NK	LBR	DRUG NAME
1755		*	Pyran copolymer MVE-3
1756		*	Pyran copolymer MVE-4
1757	*	*	Isoprinosine
1758	*	*	Bru-Pel
1759		*	Pyran copolymer MVE-1
1761	*	*	POLY ICLC
1763		*	Pyran copolymer MVE-5
1765	*	*	Cimetidine
1766	*	*	ATF-1011
1767	*	*	AM-3
1768	*	*	Imidazole
1772	*	*	Azimexon
1776	*	*	Levamisole hydrochloride
1788	*	*	Levamisole hydrochloride
1792	*	*	Pyran copolymer MVE-2
1797	*	*	Azimexon
1799	*	*	Azimexon
1968	*	*	
2704	*	*	N-Acetyl carnitina
2776	*	*	
2777	*	*	
2778	*	*	
3925	*	*	
3926	*	*	
3927	*	*	
3928	*	*	TP-3
3931	*	*	TP-3
3932	*	*	TP-4
3934	*	*	
3960	*	*	N,N-Dimethylglycine
4282	*	*	AM-5
4287	*	*	P117
4593	*	*	P188
4594	*	*	Imexon
4596	*	*	LCP-100
4597	*	*	Madecassol pills
4728	*	*	Glycyrrhizin monolithium
4729	*	*	Lithium polyacrylate
4730		*	Polyacrylic acid
4731	*	*	Lithium butyrate
4732	*	*	Ascorbate germanate (IV)
4733	*	*	Lithium polyacrylate germanate (IV)
4734	*	*	Ethylene diamine phosphonoacetic acid
5010	*	*	Leucotrofina-100
5011	*	*	Leucotrofina syrup
5013	*	*	EL200 adult syrup
5014	*	*	ELS3
5015	*	*	ELS4
5016	*	*	ELS5
5017	*	*	ELS6
5018	*	*	ELS7
5019	*	*	Thymolymphotropine

LISTING OF ALL DRUGS EVALUATED (Cont.)

5020	*	*	Thymomodulin
5021	*	*	D-ELS3
5022	*	*	D-ELS4
5023	*	*	D-ELS5
5025	*	*	MA-CDA
5026	*	*	MA-MP
5028	*	*	Madecassol (liquid)
5073	*	*	ELS1
5074	*	*	ELS2
5218		*	
5411	*	*	AZT
5564	*		Leucotrofina syrup
5579	*	*	AM-5A
6284		*	Polymer-1
6286		*	Pharmaservice-2
8522	*	*	
8523	*	*	
8524	*	*	
8525	*		
8526	*	*	
8527			
PGG	*	*	
	65	71	

71 AVS drugs were evaluated for Lymphocyte Blastogenic Response (LBR) enhancing activity. Those drugs with activity are indicated on the LBR data summary sheet with a *. This activity was evaluated separately for each mitogen, mitogen concentration and incubation period. The * designation was given if the p value of the experimental points, relative to the no drug mitogen controls, was 0.05 or less.

LYMPHOCYTE BLASTOGENIC RESPONSE ENCHANCING ACTIVITY

AVS #	MITOGENS ENHANCED PHA	PWM	CON-A	SLO
1755	*	*	*	.
1756	*	*	*	.
1757	.	.	.	*
1758	*	.	*	.
1759	*	.	*	.
1763	.	*	.	.
1765	*	.	*	*
1767	.	.	*	*
1776	.	*	.	*
1788	*	*	*	*
2778	*	.	*	.
3931	.	*	.	.
3932	*	*		

. LYMPHOCYTE BLASTOGENIC RESPONSE ENCHANCING ACTIVITY (Cont.)

4593	*	*	*	*
4596	*	*	*	.
4729	*	*	*	.
4731	*	.	.	.
4732	*	.	*	*
4733	*	.	*	*
5010	*	.	.	*
5011	*	.	.	*
5411	*	.	*	.
5579	.	.	.	*
8524	.	*	*	.
8526	*	.	.	.

* = activity present
. = no activity

65 AVS drugs were evaluated for NK enhancing activity. The potential for NK enhancement was determined with 4, 18 or 48 hours of effector cell pre-incubation with the drugs and was evaluated over a range of three E to T ratios; 20:1, 10:1, and 5:1. The drugs with NK cell augmenting activity are listed below.

SELECTED DRUGS WITH NK ENHANCING ACTIVITY

AVS #	DRUG NAME
1758	Bru Pel
1761	Poly ICLC
1799	Azimexon
3926	
3928	TP-3
4728	Glycyrrhizin monolithium
4731	Lithium butyrate
4733	Lithium polyacrylate germanate IV
5013	EL200 adult syrup
5022	D-ELS4
5025	MA-CDA
5411	AZT
8522	
8525	
PGG	

... of the more active immunomodulators to which we ... to give high priority are listed below in the order in which they were studied:

1	AVS	3925
2	AVS	3926
3	AVS	4594
4	AVS	5018
5	AVS	5026
6	AVS	5027
7	AVS	5073
8	AVS	1757
9	AVS	1758
10	AVS	1767
11	AVS	4732
12	AVS	5579
13	AVS	8522
14	AVS	PGG
15	AVS	4728

Additional agents showed some activity but usually of either low level or only one parameter. The in vitro activity of AVS 4728 and AVS 1758 are illustrated in the figures 11 a-d and 12 a-d. We believe each of these agents has shown sufficient in vitro activity that the literature on them should be thoroughly searched and that those which seem most promising after that evaluation should be studied in the LP-BM5 model. Those which are active alone in the model should be tested in combination with AZT and DDI. However, evaluations of all 15 promising agents would go beyond our current capability and support level.

DISCUSSION OF RESULTS

The work done under this NCDDG revealed several compounds of interest and preliminary data worthy of follow up. The most promising agents are the 2-Cyanoaziridine derivates of which we studied one and proposed several others. In this regard, Imexon not only is an immune modulator but also is active against B cell proliferation.

CONCLUSIONS

Diethyldithiocarbamate (DTC) is active in the LP-BM5 model and based on that should be further investigated in human AIDS. However, while several clinical trials of DTC were positive in AIDS and HIV patients others were negative. Therefore, the company (Merieux Institute) has withdrawn the drug from clinical trials.

Imexon is active in several murine AIDS-related models. it is also a potent inhibitor of benign and malignant B cell proliferation. Therefore, we feel it should be further developed in HIV infection and may be particularly suitable to AIDS-lymphoma.

Other agents studied in vitro showed promise and should be studied in vivo in relevant murine models.

Personnel Receiving Pay from Agreement Support:

Evan M. Hersh, M.D. - Principal Investigator
Charles Gschwind - Research Scientist
Carole Funk - Research Assistant II
Jacque Brailey - Research Assistant II
Joan (Coxhead) Prince - Research Assistant I
Rebecca Curtis - Research Assistant I

Graduate Student

Virginia Guptil - Ph.D degree still in progress..

REFERENCES
Journal Articles

1. Brewton GW, **Hersh EM**, Rioa A, Mansell PWA, Hollinger B and Reuben JM: A pilot study of diethyldithiocarbamate in patients with acquired immune deficiency syndrome (AIDS) and the AIDS -related complex. Life Sciences, 45(26) :2509-2520, 1989.

2. Halpern MD, **Hersh EM** and Yocum DE: Diethyldithiocarbamate, a novel immunomodulator, prolongs survival in autoimmune MRL-*lpr/lpr* mice: Clin Immuno and Immunopath, 55:242-254, 1990.

3. **Hersh EM**, Funk CY, Petersen, Mosier DE and the Ditiocarb Study Group: Biological activity of diethyldithiocarbamate (Ditiocarb, Imuthiol®)in an animal model of retrovirus-induced immunodeficiency disease and in clinical trials in patients with HIV infection. Develop. Biol Standard, 72:333-363, 1990.

4. **Hersh EM**, Funk CY, Ryschon KL, Petersen EA and Mosier DE: Effective therapy of the LP-BM5 murine retrovirus-induced lymphoproliferative immunodeficiency disease with diethyldithiocarbamate. .AIDS Res and Human Retroviruses, 7(6):553-561, 1991.

5. **Hersh EM**, Brewton G, Abrams D, Bartlett J, Galpin J, Gill P, Gorter R, Gottlieb M, Jonikas JJ, Landesman S, Levine A, Marcel A, Petersen EA, Whiteside M, Zahradnik J, Negron C, Boutitie F, Caraux, J, Dupuy JM, Salmi LR: Ditiocarb sodium (diethyldithiocarbamate) therapy in patients with symptomatic HIV infection and AIDS: A randomized, double-blind, placebo-controlled, multicenter Sstudy. JAMA 265:1538-1544, 1991.

6. Funk CY, Eisman J, **Hersh EM**: Treatment of the Murine, Retrovirus-Induced Lymphoproliferative Immunodeficiency Disease (LP-BM5) in C57Bl0 Mice with the Immunomodula r Imexon. AIDS Res and Human Retroviruses 8(5):633-638, 1992.

7. **Hersh EM**, Gschwind CR, Taylor CW, Dorr RT, Taetle R, Salmon SE: Antiproliferative and antitumor activity of the 2-Cyanoaziridine compound Imexon on tumor cell lines and fresh tumor cells in vitro. J. NCI, 84(16):1238-1244, 1992.

8. **Hersh EM**, Funk CY, Petersen EA, Rvschon KL and Mosier DE: Dose response and timing effects in the therapy of the LP-BM5 murine retrovirus-induced lymphoproliferative immunodeficiency disease with diethyldithiocarbamate. Int. J. Immunopharmac., 15:137-143, 1993.

9. **Hersh EM**, Grogan TM, Funk CY and Taylor CW: Suppression of human lymphoma development in the severe combined immune-deficient mouse by imexon therapy. J. of Immunotherapy 13:77-83, 1993

Book Chapter

10. **Hersh EM**, Caraux J and Hessel L: Effectiveness of Diethyldithiocarbamate (DTC, Imuthiol) in reducing the incidence of opportunistic infections in patients with AIDS and ARC. A randomized placebo controlled multicenter study. IN: Immunotherapeutic Prospects of Infectious Diseases. Masihi, KN and Lange W (eds), Berlin, Springer-Verlag 1990, pp. 141-142.

Abstracts

11. **Hersh EM**, Petersen E, Yocum DE, Gorman RS and Darragh JM: Dose response study of Diethyldithiocarbamate (DTC or Imuthiol) in patients with ARC and AIDS. Proc. ASCO, Atlanta, GA, May 17-19, 6:2, (#5), 1987.

12. **Hersh EM**, Mosier D, Funk C and Petersen EA: Effective therapy of the murine AIDS model (LP-BM5) retrovirus infection of C57BL6 mice) with diethyldithiocarbamate (DTC). IV International Conference on AIDS, Stockholm, Sweden, June 13-16, 1:228 (#3035), 1988.

13. Petersen EA, **Hersh EM**, Yocum DE, Gorman RS and Darragh JM: Dose response study of diethyldithiocarbamate (DTC) in patients with ARC/AIDS. IV International Conference on AIDS, Stockholm, Sweden, June 13-16, 1:230 (#3041), 1988.

14. Funk C, Mosier D, Petersen E and **Hersh EM**: Therapy of MAIDS (LP-BM5 infection of C57BL-6 mice) with diethyldithiocarbamate (DTC). V International Conference on AIDS, Montreal, Canada, June 4-9, Section C-595 (W.C.P.19), 1989.

15. Petersen EA, Hersh EM, Fish D, Kaplan C, Gorman R and Darragh M: Dose response study of daily diehyldithiocarbamate (DTC) in patients with ARC/AIDS. V International Conference on AIDS, Montreal, Canada, June 4-9, Section B:399 (w.b.p.267), 1989.

16. **Hersh EM**, Funk C, Gschwind C, Petersen EA, and Mosier D: Imexon alters the course of the murine LP-BM5 retrovirus-induced lymphoproliferative immunodeficiency disease. Proc. AACR, Washington, D.C.. May 23-26, 31:302 (#1791), 1990.

17. **Hersh EM**, Brewton G, Abrams D, Bartlett G, Gottlieb M, Landesman S, Levine A, Whiteside M, Petersen E, Zahradnik J, Negron C, Dupuy J, Salmi R and Carauz J: A randomized, double-blind, placebo-controlled trial of diethyldithiocarbamate (Ditiocarb, Imuthiol®) in patients with ARC and AIDS. VI International Conference on AIDS, San Francisco, California, June 20-24, 3:208 (S.B.489), 1990.

18. Dorr RT, Liddil JD, Dalton WS, Galler L and **Hersh EM**: The cyanoaziridine imexon (1) produces protein-linked DNA single strand breaks (SSB) possibly by topoisomerase I inhibition. Proc. AACR, Orlando, FL, May 19-22 , 34:328 (#1951), 1993.

19. Salmon SE, Fanta P, Kottman A and **Hersh E**: Imexon exhibits selective in vitro antitumor activity against human multiple myeloma. Proc. AACR, Orlando, FL, May 19-22, 34:378 (#2252), 1993

20. Berlyn KA and **Hersh EM**: Effects of diethyldithiocarbamate (DTC) on immune function during the course of murine AIDS. AAI-CIS, CO, May 21-25, 1993, 150:159A (#906), 1993.

APPENDIX (See following attachments)

APPENDIX: 1988 Study Data

COOPERATIVE AGREEMENT NO: DAMD17-88-H-8004

TITLE: IMMUNOLOGICAL STUDIES OF ANTI-AIDS DRUGS IN ARC/AIDS

Evan M. Hersh, M.D.
Principal Investigator

APPENDIX: 1988 Study Data

NATIONAL COOPERATIVE DRUG DISCOVERY GROUP FOR THE TREATMENT OF ACQUIRED IMMUNE DEFICIENCY SYNDROME

PROGRESS REPORT

PREPARED
OCTOBER, 1988

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TOXICITY FOR 1968, 3934, 2776

DRUG	DIL.	CONT	PHA	CON-A
1968	0	445	130306	73521
	1:10000	470	126631	64292
	1:1000	164	26305	6273
	1:100	249	171	400
	1:10	125	257	183
	F/S	159	238	261
3934	0	346	143107	69082
	1:10000	328	136204	63850
	1:1000	1555	138639	60049
	1:100	1504	148936	66700
	1:10	597	128268	61290
	F/S	423	134027	62226
2776	0	443	139063	70100
	1:10000	314	137526	64449
	1:1000	414	133988	58741
	1:100	408	143695	52083
	1:10	566	138509	52805
	F/S	190	16081	3165

GROSS CPM
MEANS OF TRIPLICATE POINTS

LYMPHOCYTE MITOGEN INDUCED BLASTOGENESIS
IN THE PRESENCE OF AVS-1968,3934,2776
HIV$^+$ AND HIV$^-$ CELLS

DRUG	DOSE	HIV$^+$			HIV$^-$		
		CONT	PHA	CON-A	CONT	PHA	CON-A
1968	NO RX	260	64566	77741	527	69438	95075
	1:100	435	485	378	130	44951	1665
	1:500	401	55434	66125	499	65542	95347
	1:1000	283	55025	71236	502	57161	89112
	1:5000	299	60913	60441	626	60319	90503
	1:10000	281	64260	72321	737	59463	102718
3934	NO RX	328	61166	75413	612	63115	101767
	F/S	400	60607	53767	710	56340	93328
	1:10	224	60949	57254	1617	54495	97191
	1:100	304	64708	65467	1282	60891	87053
	1:1000	327	59145	74935	810	66331	101151
	1:5000	336	64531	58359	515	66202	92893
2776	NO RX	327	68955	82535	586	77288	108508
	F/S	358	64219	80847	442	51005	77354
	1:5	353	66202	83173	517	61061	85941
	1:10	362	65431	82359	564	57754	94622
	1:50	376	62797	83829	778	63311	91024
	1:100	320	70196	96446	869	63933	107429

GROSS CPM : MEANS OF TRIPLICATE VALUES.

EFFECTS OF AVS-3925, 3926, AND 3927
ON MITOGEN INDUCED LYMPHOCYTE BLASTOGENESIS
(HIV* DONOR)

Experiment #12-HIV-1988 indicated that even at the DMSO tolerable volume level all of the above drugs were still profoundly toxic to or inhibitory of lymphocyte blastogenesis. This experiment was set in an identical manner but with much lower drug doses and DMSO levels per culture.

DMSO LEVEL CONTROL PLATE:

DOSE	CONTROL	PHA	CON-A
100 ul*	209	100,750	46,896
75 ul	157	91,227	46,810
50 ul	404	116,934	51,048
25 ul	117	112,217	52,650
10 ul	274	-	-
0 ul	317	131,013	81,877

* volume of a 1% DMSO solution.

AVS-3925

DOSE	CONTROL	PHA	CON-A
90.9*	447	862	761
68.2	319	347	396
45.4	565	627	1,321
22.7	582	1,480	1,513
9.1	509	175	382
0.0	363	123,876	74,791

* ug of AVS-3925 per ml of culture.

AVS-3926

DOSE	CONTROL	PHA	CON-A
45.4*	425	404	648
34.1	297	364	337
22.7	378	317	306
11.4	415	363	367
4.5	287	342	614
0.0	355	126,815	74,452

* ug of AVS-3926 per ml of culture.

AVS-3927

DOSE	CONTROL	PHA	CON-A
9.1*	198	130,398	33,717
6.8	424	107,323	46,227
4.5	635	107,650	48,087
2.3	686	114,883	62,627
0.9	279	122,249	48,224
0.0	297	128,792	77,351

* ug of AVS-3927 per ml of culture.

USARIID DRUG BLASTOGENESIS STUDY
DOSE RESPONSE STUDY AND POSSIBLE RESPONSE ENHANCEMENT
OF HIV⁺ DONOR LYMPHOCYTES WITH OPTIMAL AND SUB-OPTIMAL
CONCENTRATIONS OF PHA

The design of this experiment required the use of five separate culture plates, each plate contained its own set of untreated controls. Table 1 presents that data as the average of triplicate wells for each plate with the overall average and S.D.

TABLE 1
NO DRUG TREATMENT CONTROLS

PLATE	CONT	PHA 1:10	PHA 1:50
1	240	107,838	66,367
2	519	103,006	88,690
3	349	78,400	67,553
4	416	102,003	64,927
5	340	86,662	68,387
MEAN	373	95,381	71,961
S.D.	92	11,190	8,830

All drugs were added at initiation of the cultures, so this data is representative of a three day exposure to drug concurrent with the three day PHA stimulation period. In additon to the standard PHA concentration used for drug toxicity evaluation a sub-optimal PHA concentration was used to determine if any response enhancement could be produced.

NORMAL LYMPHOCYTE MITOGEN INDUCED BLASTOGENESIS
IN THE PRESENCE OF AVS-3925, 3926 & 3927

	PHA				CON-A			
	DMSO	3925	3926	3927	DMSO	3925	3926	3927
NONE	102.5*				72.8			
20 ul	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0
10 ul	0.1	0.0	0.0	0.6	0.1	0.0	0.0	0.0
5 ul	0.0	0.7	0.1	0.3	0.1	0.0	0.1	0.7
2.5ul	90.2	0.6	0.3	0.2	40.4	0.0	0.0	0.3
1 ul	99.9	0.0	0.0	0.0	45.0	0.2	0.1	0.2
0.5ul	112.8	0.0	0.1	0.0	64.7	0.0	0.0	0.1

* net CPM x 10^3 (mean of triplicates)

ANALYSIS:

1. The three drugs used in this experiment are soluble only in DMSO.
2. At all but the lowest volume of DMSO in the culture system the drug data is not interpretable because of the DMSO toxicity.
3. All three drugs are toxic to lymphocytes in 0.5ul volumes of DMSO. At this volume of DMSO the concentration of the drugs on a mg per ml of culture basis is:
   AVS-3925 0.454 mg/ml
   AVS-3926 0.227 mg/ml
   AVS-34927 0.045 mg/ml

FUTURE PLAN:

1. Dilute the drugs one log lower in DMSO.
2. Attempt to place this lower dilution in an aqueous media.
3. Repeat the experiment at lower drug and DMSO concentrations.

TABLE 2
LYMPHOCYTE BLASTOGENIC RESPONSES
TO OPTIMAL AND SUB-OPTIMAL CONCENTRATIONS OF PHA
IN THE PRESENCE OF DRUGS

DRUG/CONC.*	UNSTIM.	PHA 1:10	PHA 1:50
1968 / 0.3336	355	118,092	89,122
0.1668	441	111,190	84,243
0.0834	474	99,996	74,961
3934 / 208.5	307	109,169	89,352
/ 20.85	323	111,198	87,527
/ 2.085	337	118,090	79,718
/ 0.2085	394	118,819	80,024
2776 / 11.09	424	114,919	100,803
/ 5.546	365	112,300	97,029
/ 0.5546	572	105,226	92,569
3925 / 9.1	431	384	341
/ 6.82	358	489	549
/ 4.54	354	464	416
/ 2.27	365	24,339	8,969
/ 0.91	335	77,051	66,197
3926 / 4.54	262	387	532
/ 3.41	404	621	561
/ 2.27	197	13,925	5,978
/ 1.14	266	78,283	46,544
/ 0.45	195	100,647	64,330
3927 / 9.09	224	97,867	77,734
/ 6.82	340	103,234	75,806
/ 4.54	462	113,329	75,270
/ 2.27	354	99,201	74,926
/ 0.91	348	105,259	77,041

* micrograms of drug per ml of culture.

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
3 AND 5 DAY INCUBATIONS WITH
3925

UG/ML CULT.	3 DAY CONT	3 DAY PHA	3 DAY CON-A	5 DAY CONT	5 DAY PHA	5 DAY CON-A
0	0.39	77.23	30.79	0.80	99.64	33.93
9.1	0.46	0.28	0.61	0.13	1.87	0.95
6.8	0.33	0.59	0.30	0.49	0.48	0.81
4.5	0.35	0.92	0.52	0.20	0.47	0.56
2.3	0.42	0.18	0.26	0.35	0.19	0.33
0.91	0.29	2.13	0.96	0.35	33.06	1.62

GROSS CPM X 10^3
MEANS OF TRIPLICATE CULTURES

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
3 AND 5 DAY INCUBATIONS WITH
3926

UG/ML CULT.	3 DAY CONT	3 DAY PHA	3 DAY CON-A	5 DAY CONT	5 DAY PHA	5 DAY CON-A
0	0.41	92.45	40.18	0.63	98.55	28.21
9.1	0.23	0.35	0.56	0.34	0.87	0.68
6.8	0.38	0.46	0.89	0.46	0.36	0.53
4.5	0.19	0.37	1.21	0.56	0.45	0.81
2.3	0.32	3.26	0.37	0.45	24.99	0.54
0.91	0.39	56.78	16.59	0.36	121.44	42 56

GROSS CPM X 10^3
MEANS OF TRIPLICATE CULTURES

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
3 AND 5 DAY INCUBATIONS WITH
3927

UG/ML CULT.	3 DAY CONT	3 DAY PHA	3 DAY CON-A	5 DAY CONT	5 DAY PHA	5 DAY CON-A
0	0.30	85.69	35.57	0.76	92.37	31.37
9.1	0.31	55.00	25.34	0.64	110.15	22.18
6.8	0.25	56.63	20.16	1.04	103.12	25.20
4.5	0.42	55.90	15.07	0.74	96.17	29.38
2.3	0.60	55.92	24.31	0.91	90.21	28.32
0.91	0.48	76.74	12.41	0.72	98.34	36.88

GROSS CPM X 10^3
MEANS OF TRIPLICATE CULTURES

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
3 DAY STIMULATION BY
OPTIMAL AND SUBOPTIMAL CONCENTRATIONS OF PHA
IN THE PRESENCE OF 1968

UG/ML CULT.	CONT.	PHA CONCENTRATIONS 1:10	1:50	1:100
0	582	70,599	40,069	29,952
0.833	507	77,884	42,039	30,925
0.499	465	73,929	41,770	31,356
0.166	521	72,946	41,326	32,902
0.033	488	71,813	39,573	30,951

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
3 DAY STIMULATION BY
OPTIMAL AND SUBOPTIMAL CONCENTRATIONS OF PHA
IN THE PRESENCE OF 2776

UG/ML CULT.	CONT.	PHA CONCENTRATIONS 1:10	1:50	1:100
0	538	72,682	36,428	29,587
11.0	569	77,305	39,993	23,231
5.50	545	73,599	36,301	23,292
1.10	641	73,546	37,568	24,726
0.55	497	64,038	36,202	22,439

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
3 DAY STIMULATION BY
OPTIMAL AND SUBOPTIMAL CONCENTRATIONS OF PHA
IN THE PRESENCE OF 3934

UG/ML CULT.	CONT.	PHA CONCENTRATIONS 1:10	1:50	1:100
0	526	72,027	41,174	32,399
208.3	425	73,747	41,503	26,303
20.83	400	70,643	38,953	21,455
2.083	439	77,827	37,652	18,520
0.208	447	60,656	33,861	20,867

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
3 DAY STIMULATION BY
OPTIMAL AND SUBOPTIMAL CONCENTRATIONS OF PHA
IN THE PRESENCE OF 3925

UG/ML CULT.	CONT.	PHA CONCENTRATIONS 1:10	1:50	1:100
0	628	64,300	52,175	33,818
0.0004	716	63,408	48,369	30,377
0.0006	694	49,564	39,803	30,277
0.0008	724	60,436	37,861	28,951

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
3 DAY STIMULATION BY
OPTIMAL AND SUBOPTIMAL CONCENTRATIONS OF PHA
IN THE PRESENCE OF 3926

UG/ML CULT.	CONT.	PHA CONCENTRATIONS 1:10	1:50	1:100
0	692	68,019	53,758	32,426
0.021	609	70,354	55,303	36,690
0.030	601	65,511	47,628	35,211
0.036	681	65,245	51,738	32,473

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
3 DAY STIMULATION BY
OPTIMAL AND SUBOPTIMAL CONCENTRATIONS OF PHA
IN THE PRESENCE OF 3927

UG/ML CULT.	CONT.	PHA CONCENTRATIONS 1:10	1:50	1:100
0	778	66,609	41,882	30,106
0.033	747	62,544	48,181	32,510
0.050	744	60,179	48,275	29,794
0.066	703	68,303	52,367	35,544

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
3 DAY STIMULATION BY
OPTIMAL AND SUBOPTIMAL CONCENTRATIONS OF PHA
IN THE PRESENCE OF 3931

UG/ML CULT.	CONT.	PHA CONCENTRATIONS 1:10	1:50
0	536	45,706	6,988
* 0	723	74,892	15,278
* 41.7	761	63,591	12,021
* 4.17	603	78,190	19,582
* 0.417	482	77,816	4,901
0.0834	646	50,120	12,339
* 0.0417	627	72,733	6,190
0.00834	359	47,004	13,820
* 0.00417	858	68,840	13,820
0.000834	569	52,366	5,013
0.000417	421	48,173	3,778
0.000083	611	45,202	5,119

GROSS CPM
MEANS OF TRIPLICATE CULTURES
* DIFFERENTIATES DATA FROM TWO COMBINED EXPERIMENTS

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
3 DAY STIMULATION BY
OPTIMAL AND SUBOPTIMAL CONCENTRATIONS OF PHA
IN THE PRESENCE OF 3932

UG/ML CULT.	CONT.	PHA CONCENTRATIONS 1:10	1:50
0	536	45,706	6,988
* 0	723	74,892	15,278
* 41.7	583	76,306	14,206
* 4.17	559	67,675	12,288
* 0.417	521	77,700	13,747
0.0834	698	47,537	6,838
* 0.0417	568	74,463	12,025
0.00834	449	45,409	7,294
* 0.00417	666	75,834	13,876
0.000834	476	48,061	5,979
0.000417	598	47,559	5,674
0.000083	696	44,538	6,511

GROSS CPM
MEANS OF TRIPLICATE CULTURES
* DIFFERENTIATES DATA FROM TWO COMBINED EXPERIMENTS

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
3 DAY STIMULATION BY
OPTIMAL AND SUBOPTIMAL CONCENTRATIONS OF PHA
IN THE PRESENCE OF 4594

UG/ML CULT.	CONT.	PHA CONCENTRATIONS 1:10	1:50
0	536	45,706	6,988
* 0	723	74,892	15,278
* 41.7	702	719	762
* 4.17	384	10,981	2,387
* 0.417	675	68,522	13,502
0.0834	472	47,077	6,293
* 0.0417	619	88,023	15,360
0.00834	477	45,717	6,354
* 0.00417	617	78,884	18,894
0.000834	572	32,617	4,691
0.000417	525	38,726	7,006
0.000083	596	46,929	6,340

GROSS CPM
MEANS OF TRIPLICATE CULTURES
* DIFFERENTIATES DATA FROM TWO COMBINED EXPERIMENTS

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
FOR 3, 6, OR 8 DAYS
WITH 3925

CULTURE TIME	MITOGEN USED	DRUG CONC. UG/ML CULTURE 0	0.04	0.02
3-D	CONT	560	662	635
	PHA	76,786	79,880	80,853
	CON-A	65,518	66,066	67,923
	PWM	18,831	21,330	18,975
	SLO	2,986	3,110	3,980
6-D	CONT	3,811	4,785	4,746
	PHA	12,378	15,510	14,282
	CON-A	3,360	3,467	3,105
	PWM	27,804	24,396	25,630
	SLO	39,401	37,878	32,434
8-D	CONT	2,394	4,122	6,312
	PHA	5,411	4,623	4,334
	CON-A	2,162	2,033	2,415
	PWM	14,130	15,090	13,133
	SLO	21,209	20,857	21,790

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
FOR 3, 6, OR 8 DAYS
WITH 3926

CULTURE TIME	MITOGEN USED	DRUG CONC. UG/ML CULTURE 0	0.08	0.04
3-D	CONT	601	1,108	1,460
	PHA	90,128	99,689	93,692
	CON-A	63,671	67,728	65,831
	PWM	18,468	19,980	19,083
	SLO	2,616	2,952	3,664
6-D	CONT	4,654	4,283	7,063
	PHA	15,338	17,908	17,698
	CON-A	2,356	2,734	2,950
	PWM	26,029	27,244	26,733
	SLO	27,540	28,719	37,506
8-D	CONT	4,350	8,075	7,739
	PHA	5,175	6,006	5,436
	CON-A	2,319	2,624	2,870
	PWM	18,780	16,730	11,928
	SLO	29,092	26,727	24,597

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
FOR 3, 6, OR 8 DAYS
WITH 3927

CULTURE TIME	MITOGEN USED	DRUG CONC. UG/ML CULTURE 0	0.45	0.23
3-D	CONT	678	861	779
	PHA	94,140	93,583	92,592
	CON-A	68,767	66,770	66,266
	PWM	19,533	28,881	20,235
	SLO	2,579	2,465	3,335
6-D	CONT	3,830	4,238	5,347
	PHA	15,899	13,807	11,740
	CON-A	2,101	3,052	3,636
	PWM	31,495	29,712	29,430
	SLO	36,260	33,680	37,975
8-D	CONT	3,516	8,431	9,543
	PHA	5,190	4,731	5,094
	CON-A	2,114	2,470	2,705
	PWM	16,956	17,416	16,714
	SLO	27,682	20,819	20,504

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV* DONOR LYMPHOCYTE BLASTOGENESIS
FOR 3, 6, OR 8 DAYS
WITH 3925

CULTURE TIME	MITOGEN USED	DRUG CONC. JG/ML CULTURE 0	0.04	0.02
3-D	CONT	644	761	607
	PHA	44,485	46,442	48,205
	CON-A	19,549	25,238	24,597
	PWM	4,976	5,337	5,283
	SLO	1,127	1,210	1,287
6-D	CONT	2,546	2,768	2,234
	PHA	36,292	37,738	37,225
	CON-A	48,632	53,685	47,631
	PWM	27,248	36,177	29,634
	SLO	24,097	26,970	25,861
8-D	CONT	6,818	6,408	8,943
	PHA	9,093	10,982	12,708
	CON-A	6,742	4,801	-
	PWM	28,740	37,999	27,920
	SLO	52,580	50,394	52,952

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV+ DONOR LYMPHOCYTE BLASTOGENESIS
FOR 3, 6, OR 8 DAYS
WITH 3926

CULTURE TIME	MITOGEN USED	DRUG CONC. UG/ML CULTURE 0	0.08	0.04
3-D	CONT	540	735	1,065
	PHA	47,601	50,698	51,070
	CON-A	16,368	19,101	20,717
	PWM	3,508	4,162	5,130
	SLO	1,428	1,551	1,508
6-D	CONT	3,395	3,630	2,686
	PHA	2,771	2,440	-
	CON-A	16,512	21,443	18,392
	PWM	18,349	24,732	22,606
	SLO	3,267	2,788	3,273
8-D	CONT	9,568	8,828	10,400
	PHA	9,449	10,290	10,142
	CON-A	11,728	10,206	10,521
	PWM	31,593	45,446	30,673
	SLO	47,142	61,961	60,050

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
FOR 3, 6, OR 8 DAYS
WITH 3931

CULTURE TIME	MITOGEN USED	DRUG CONC. UG/ML CULTURE 0	4.17	0.417
3-D	CONT	594	654	902
	PHA	91,317	81,944	85,647
	CON-A	65,138	67,037	66,214
	PWM	18,987	19,857	22,812
	SLO	2,843	2,653	3,343
6-D	CONT	3,064	2,781	2,683
	PHA	28,536	30,717	29,620
	CON-A	11,190	12,452	10,948
	PWM	32,305	31,684	34,114
	SLO	36,764	35,516	32,569
8-D	CONT	6,380	7,322	6,983
	PHA	7,874	9,980	10,263
	CON-A	2,044	2,008	3,239
	PWM	18,893	19,704	18,388
	SLO	21,200	21,320	23,716

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
FOR 3, 6, OR 8 DAYS
WITH 3932

CULTURE TIME	MITOGEN USED	DRUG CONC. UG/ML CULTURE 0	4.17	0.417
3-D	CONT	710	888	1,254
	PHA	86,023	84,177	81,141
	CON-A	65,003	68,770	69,561
	PWM	22,060	22,000	19,293
	SLO	2,809	2,830	6,246
6-D	CONT	3,847	3,446	4,116
	PHA	26,749	34,734	30,640
	CON-A	11,557	11,627	8,691
	PWM	34,909	32,832	31,062
	SLO	29,148	27,486	33,759
8-D	CONT	4,225	4,713	6,695
	PHA	9,703	12,353	10,219
	CON-A	1,934	1,655	1,857
	PWM	25,879	24,594	23,541
	SLO	32,076	27,332	24,231

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
FOR 3, 6, OR 8 DAYS
WITH 4594

CULTURE TIME	MITOGEN USED	DRUG CONC. UG/ML CULTURE 0	0.0417	0.00834
3-D	CONT	822	766	928
	PHA	86,465	86,555	83,077
	CON-A	70,277	69,402	70,125
	PWM	21,200	22,816	21,894
	SLO	2,560	2,676	2,376
6-D	CONT	3,455	2,736	3,385
	PHA	32,194	32,016	31,905
	CON-A	16,625	11,556	12,571
	PWM	36,538	34,798	33,267
	SLO	31,045	32,007	29,730
8-D	CONT	3,441	4,589	5,615
	PHA	13,029	12,045	12,697
	CON-A	2,401	2,449	2,698
	PWM	27,416	18,577	25,094
	SLO	26,738	29,734	28,237

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV+ DONOR LYMPHOCYTE BLASTOGENESIS
FOR 3, 6, OR 8 DAYS
WITH 4594

CULTURE TIME	MITOGEN USED	DRUG CONC. UG/ML CULTURE 0	0.0417	0.00834
3-D	CONT	368	350	390
	PHA	70,823	67,923	59,025
	CON-A	34,184	31,725	32,112
	PWM	4,198	4,156	4,670
	SLO	313	325	325
6-D	CONT	980	1,149	1,485
	PHA	15,399	17,402	15,605
	CON-A	24,236	26,453	21,759
	PWM	8,878	7,943	8,252
	SLO	1,899	2,046	1,949
8-D	CONT	1,539	1,454	1,579
	PHA	3,211	3,245	4,495
	CON-A	4,387	3,736	4,308
	PWM	4,378	2,691	3,010
	SLO	4,834	1,107	1,148

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS FOR 3, 6, OR 8 DAYS WITH 3931

CULTURE TIME	MITOGEN USED	DRUG CONC. UG/ML CULTURE 0	4.17	0.417
3-D	CONT	870	760	1,001
	PHA	76,557	79,505	84,366
	CON-A	78,753	88,096	94,841
	PWM	21,005	28,461	40,525
	SLO	1,160	1,342	1,975
6-D	CONT	2,372	748	3,616
	PHA	30,365	39,681	40,652
	CON-A	23,401	26,247	25,206
	PWM	48,544	67,166	66,132
	SLO	12,375	14,003	16,865
8-D	CONT	1,033	774	2,104
	PHA	9,606	11,542	12,480
	CON-A	2,770	2,634	2,940
	PWM	22,172	30,013	31,443
	SLO	16,752	20,352	28,198

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
FOR 3, 6, OR 8 DAYS
WITH 3932

CULTURE TIME	MITOGEN USED	DRUG CONC. UG/ML CULTURE 0	4.17	0.417
3-D	CONT	538	984	1,044
	PHA	88,917	92,690	109,896
	CON-A	73,179	83,596	88,591
	PWM	19,475	26,809	28,794
	SLO	1,006	1,752	3,209
6-D	CONT	1,558	2,432	1,919
	PHA	29,110	40,454	36,985
	CON-A	22,168	23,856	25,695
	PWM	46,942	65,239	67,729
	SLO	15,104	16,156	20,954
8-D	CONT	5,052	5,506	5,516
	PHA	9,896	14,338	15,952
	CON-A	3,338	3,498	3,427
	PWM	21,260	35,869	31,137
	SLO	19,351	24,336	22,349

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV⁻ DONOR LYMPHOCYTE BLASTOGENESIS
FOR 3, 6, OR 8 DAYS
WITH 4594

CULTURE TIME	MITOGEN USED	DRUG CONC. UG/ML CULTURE 0	0.0417	0.00834
3-D	CONT	801	1,157	1,280
	PHA	78,051	82,228	91,217
	CON-A	-	-	-
	PWM	-	-	-
	SLO	-	-	-
6-D	CONT	2,226	895	1,676
	PHA	33,321	37,590	36,315
	CON-A	20,280	22,656	24,406
	PWM	51,817	69,269	67,655
	SLO	14,759	16,423	18,565
8-D	CONT	3,993	1,901	3,445
	PHA	7,097	10,614	12,980
	CON-A	2,690	2,339	2,867
	PWM	17,596	27,615	26,339
	SLO	22,583	30,229	39,856

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV+ DONOR LYMPHOCYTE BLASTOGENESIS
FOR 3, 6, OR 8 DAYS
WITH 3932

CULTURE TIME	MITOGEN USED	DRUG CONC. UG/ML CULTURE 0	4.17	0.417
3-D	CONT	598	707	1,010
	PHA	47,355	58,278	59,347
	CON-A	38,892	47,615	42,472
	PWM	8,989	15,203	14,056
	SLO	3,015	3,206	4,607
6-D	CONT	1,214	968	1,247
	PHA	43,783	55,765	63,788
	CON-A	42,385	40,624	46,476
	PWM	34,808	27,295	30,489
	SLO	18,097	18,406	20,578
8-D	CONT	1,396	1,085	1,572
	PHA	13,963	18,143	20,721
	CON-A	5,546	7,580	8,525
	PWM	6,411	6,235	6,010
	SLO	27,789	24,737	29,631

GROSS CPM
MEANS OF TRIPLICATE CULTURES

HIV* DONOR LYMPHOCYTE BLASTOGENESIS
FOR 3, 6, OR 8 DAYS
WITH 4594

CULTURE TIME	MITOGEN USED	DRUG CONC. UG/ML CULTURE 0	0.0417	0.00834
3-D	CONT	645	628	659
	PHA	45,968	55,461	59,122
	CON-A	39,620	48,118	51,966
	PWM	9,934	14,188	14,681
	SLO	2,463	3,172	3,130
6-D	CONT	1,135	817	852
	PHA	56,022	55,862	64,746
	CON-A	40,012	47,054	44,463
	PWM	21,460	27,205	27,593
	SLO	19,064	22,174	24,632
8-D	CONT	3,002	3,107	2,593
	PHA	12,812	18,228	18,849
	CON-A	7,871	8,313	7,912
	PWM	-	8,146	9,582
	SLO	26,250	31,203	36,935

GROSS CPM
MEANS OF TRIPLICATE CULTURES

NK ACTIVITY OF HIV⁻ AND HIV⁺ EFFECTOR CELLS IN A 4 HOUR ^{51}Cr RELEASE ASSAY FOLLOWING AN 18 HOUR PRE-INCUBATION WITH AVS-3926

EXP #	DRUG CONC#	HIV⁻ 20:1	HIV⁻ 5:1	HIV⁺ 20:1	HIV⁺ 5:1
1	0	28*	10	27	13
	$4.5X10^{-2}$	23 (-18)**	8 (-20)	28 (4)	15 (15)
	$2.5X10^{-2}$	29 (3)	10 (NC)	35 (30)	10 (23)
	$0.5X10^{-2}$	27 (-3)	9 (-10)	29 (7)	11(-15)
2	0	64	5	24	17
	$3.6X10^{-2}$	72 (12)	7 (40)	27 (12)	25 (47)
	$3.1X10^{-2}$	73 (14)	4 (-20)	19 (-21)	22 (29)
	$2.1X10^{-2}$	72 (12)	4 (-20)	23 (-4)	21 (23)
3	0	9	4	34	14
	$3.6X10^{-2}$	30 (233)	11 (175)	37 (9)	13 (-7)
	$3.1X10^{-2}$	16 (78)	5 (25)	37 (9)	13 (-7)
	$2.1X10^{-2}$	14 (55)	9 (125)	18 (-47)	7 (-50)

UG/ML OF CULTURE
* % KILL, MEAN OF TRIPLICATES, ROUNDED TO NEAREST WHOLE NUMBER
** % CHANGE RELATIVE TO 0 DRUG, ROUNDED TO NEAREST WHOLE NUMBER

NK ACTIVITY OF HIV⁻ AND HIV⁺ EFFECTOR CELLS IN A 4 HOUR ^{51}Cr RELEASE ASSAY FOLLOWING AN 18 HOUR PRE-INCUBATION WITH AVS-3925

EXP #	DRUG CONC#	HIV⁻ 20:1	HIV⁻ 5:1	HIV⁺ 20:1	HIV⁺ 5:1
1	0	28*	10	27	13
	$9.1X10^{-3}$	20 (-28)**	6 (-40)	27 (NC)	9 (-30)
	$4.5X10^{-3}$	24 (-14)	9 (-10)	32 (18)	11 (-15)
	$0.9X10^{-3}$	27 (-3)	8 (-20)	33 (22)	13 (NC)
2	0	64	5	24	17
	$0.8X10^{-3}$	78 (22)	5 (NC)	23 (-4)	25 (53)
	$0.6X10^{-3}$	66 (3)	4 (-20)	22 (-8)	26 (53)
	$0.4X10^{-3}$	62 (-3)	5 (NC)	26 (8)	17 (NC)
3	0	9	4	34	14
	$0.8X10^{-3}$	37 (311)	27 (575)	35 (3)	14 (NC)
	$0.6X10^{-3}$	33 (267)	23 (475)	34 (NC)	19 (36)
	$0.4X10^{-3}$	33 (267)	23 (474)	35 (3)	14 (NC)

UG/ML OF CULTURE
* % KILL, MEAN OF TRIPLICATES, ROUNDED TO NEAREST WHOLE NUMBER
** % CHANGE RELATIVE TO 0 DRUG, ROUNDED TO NEAREST WHOLE NUMBER

NK ACTIVITY OF HIV⁻ AND HIV⁺ EFFECTOR CELLS IN A 4 HOUR ^{51}Cr RELEASE ASSAY FOLLOWING AN 18 HOUR PRE-INCUBATION WITH AVS-3927

EXP #	DRUG CONC#	HIV⁻ 20:1	HIV⁻ 5:1	HIV⁺ 20:1	HIV⁺ 5:1
1	0	28*	10	27	13
	$9.1X10^{-2}$	30 (7)**	9 (-10)	36 (33)	11 (-15)
	$4.5X10^{-2}$	31 (11)	11 (10)	41 (52)	16 (23)
	$0.9X10^{-2}$	27 (-3)	7 (-30)	27 (NC)	11 (-15)
2	0	64	5	24	17
	$6.5X10^{-2}$	74 (16)	4 (-20)	23 (-4)	23 (35)
	$5.0X10^{-2}$	73 (14)	2 (-60)	23 (-4)	23 (35)
	$3.3X10^{-2}$	72 (12)	7 (40)	21 (-12)	24 (41)

UG/ML OF CULTURE
* % KILL, MEAN OF TRIPLICATES, ROUNDED TO NEAREST WHOLE NUMBER
** % CHANGE RELATIVE TO 0 DRUG, ROUNDED TO NEAREST WHOLE NUMBER

NK ACTIVITY OF HIV⁻ AND HIV⁺ EFFECTOR CELLS IN A 4 HOUR ^{51}Cr RELEASE ASSAY FOLLOWING AN 18 HOUR PRE-INCUBATION WITH AVS-4594

EXP #	DRUG CONC#	HIV⁻ 20:1	HIV⁻ 5:1	HIV⁺ 20:1	HIV⁺ 5:1
1	0	26*	11	27	9
	$4.17X10^{-2}$	31 (19)**	11 (NC)	31 (15)	11 (22)
	$0.83X10^{-2}$	30 (15)	11 (NC)	29 (7)	10 (11)
2	0	8	3	-	-
	$4.17X10^{-2}$	8 (NC)	2 (-33)	-	-
	$0.83X10^{-2}$	-	-	-	-
3	0	28	9	-	-
	$4.17X10^{-2}$	25 (-11)	8 (-11)	-	-
	$0.83X10^{-2}$	26 (-7)	9 (NC)	-	-
4	0	17	5	-	-
	$4.17X10^{-2}$	16 (-6)	5 (NC)	-	-
	$0.83X10^{-2}$	-	-	-	-
5	0	12	3	48	19
	$4.17X10^{-2}$	17 (42)	7 (133)	40 (-17)	15 (-21)
	$0.83X10^{-2}$	10 (-17)	4 (33)	40 (-17)	16 (-16)
6	0	17	5	14	6
	$4.17X10^{-2}$	15 (-12)	5 (NC)	17 (21)	7 (17)
	$0.83X10^{-2}$	14 (-18)	5 (NC)	19 (36)	7 (17)

UG/ML OF CULTURE
* % KILL, MEAN OF TRIPLICATES, ROUNDED TO NEAREST WHOLE NUMBER
** % CHANGE RELATIVE TO 0 DRUG, ROUNDED TO NEAREST WHOLE NUMBER

NK ACTIVITY OF HIV⁻ AND HIV⁺ EFFECTOR CELLS IN A 4 HOUR ^{51}Cr RELEASE ASSAY FOLLOWING AN 18 HOUR PRE-INCUBATION WITH AVS-3932

EXP #	DRUG CONC#	HIV⁻ 20:1	HIV⁻ 5:1	HIV⁺ 20:1	HIV⁺ 5:1
1	0	26*	11	27	9
	$4.17X10^{-2}$	31 (19)**	9 (NC)	31 (15)	11 (22)
	$0.42X10^{-2}$	32 (23)	10 (-9)	31 (15)	14 (55)
2	0	8	3	-	-
	$4.17X10^{-2}$	10 (25)	2 (-33)	-	-
	$0.42X10^{-2}$	9 (12)	2 (-33)	-	-
3	0	28	9	-	-
	$4.17X10^{-2}$	30 (7)	10 (11)	-	-
	$0.42X10^{-2}$	30 (7)	10 (11)	-	-
4	0	17	5	-	-
	$4.17X10^{-2}$	17 (NC)	5 (NC)	-	-
	$0.42X10^{-2}$	16 (-6)	5 (NC)	-	-
5	0	12	3	48	19
	$4.17X10^{-2}$	11 (-8)	3 (NC)	39 (-19)	16 (-16)
	$0.42X10^{-2}$	14 (17)	7 (133)	48 (NC)	18 (-5)
6	0	17	5	14	6
	$4.17X10^{-2}$	12 (-29)	5 (NC)	17 (21)	6 (NC)
	$0.83X10^{-2}$	11 (-35)	3 (-40)	19 (36)	6 (NC)

UG/ML OF CULTURE
* % KILL, MEAN OF TRIPLICATES, ROUNDED TO NEAREST WHOLE NUMBER
** % CHANGE RELATIVE TO 0 DRUG, ROUNDED TO NEAREST WHOLE NUMBER

NK ACTIVITY OF HIV⁻ AND HIV⁺ EFFECTOR CELLS IN A 4 HOUR ^{51}Cr RELEASE ASSAY FOLLOWING AN 18 HOUR PRE-INCUBATION WITH AVS-3931

EXP #	DRUG CONC#	HIV⁻ 20:1	HIV⁻ 5:1	HIV⁺ 20:1	HIV⁺ 5:1
1	0	26*	11	27	9
	$4.17X10^{-2}$	27 (4)**	12 (9)	32 (23)	11 (22)
	$0.42X10^{-2}$	29 (11)	8 (-27)	35 (35)	11 (22)
2	0	8	3	-	-
	$4.17X10^{-2}$	11 (37)	2 (-33)	-	-
	$0.42X10^{-2}$	10 (25)	3 (NC)	-	-
3	0	28	9	-	-
	$4.17X10^{-2}$	27 (-3)	9 (NC)	-	-
	$0.42X10^{-2}$	30 (7)	10 (11)	-	-
4	0	17	5	-	-
	$4.17X10^{-2}$	17 (NC)	5 (NC)	-	-
	$0.42X10^{-2}$	15 (-12)	4 (-20)	-	-
5	0	12	3	48	19
	$4.17X10^{-2}$	12 (NC)	3 (NC)	49 (2)	18 (-5)
	$0.42X10^{-2}$	14 (17)	6 (100)	49 (2)	20 (5)
6	0	17	5	14	6
	$4.17X10^{-2}$	12 (-29)	4 (-20)	11 (-21)	4 (-33)
	$0.42X10^{-2}$	13 (-23)	5 (NC)	14 (NC)	5 (-17)

UG/ML OF CULTURE
* % KILL, MEAN OF TRIPLICATES, ROUNDED TO NEAREST WHOLE NUMBER
** % CHANGE RELATIVE TO 0 DRUG, ROUNDED TO NEAREST WHOLE NUMBER

NK ACTIVITY OF HIV⁻ AND HIV⁺ EFFECTOR CELLS IN A 4 HOUR ^{51}Cr RELEASE ASSAY FOLLOWING AN 18 HOUR PRE-INCUBATION WITH AVS-1968

EXP #	DRUG CONC#	HIV⁻ 20:1	HIV⁻ 5:1	HIV⁺ 20:1	HIV⁺ 5:1
1	0	40*	31	40	14
	8.33	- **	-	32 (-20)	12 (-14)
	1.66	-	-	35 (-12)	13 (-7)
	0.83	48 (20)	59 (90)	8 (-80)	4 (-71)
	0.17	20 (-50)	24 (-22)	23 (-42)	9 (-36)
	0.08	-	-	34 (-15)	12 (-14)

UG/ML OF CULTURE
* % KILL, MEAN OF TRIPLICATES, ROUNDED TO NEAREST WHOLE NUMBER
** % CHANGE RELATIVE TO 0 DRUG, ROUNDED TO NEAREST WHOLE NUMBER

NK ACTIVITY OF HIV⁻ AND HIV⁺ EFFECTOR CELLS IN A 4 HOUR ^{51}Cr RELEASE ASSAY FOLLOWING AN 18 HOUR PRE-INCUBATION WITH AVS-3934

EXP #	DRUG CONC#	HIV⁻		HIV⁺	
		20:1	5:1	20:1	5:1
1	0	40*	31	40	14
	208.3	48 (20)**	25 (13)	24 (-40)	10 (-28)
	20.8	-	-	28 (-30)	15 (7)
	2.08	47 (17)	26 (-16)	27 (-32)	13 (-7)
	0.21	-	-	28 (-30)	21 (50)
	0.04	-	-	36 (-10)	29 (107)

UG/ML OF CULTURE
* % KILL, MEAN OF TRIPLICATES, ROUNDED TO NEAREST WHOLE NUMBER
** % CHANGE RELATIVE TO 0 DRUG, ROUNDED TO NEAREST WHOLE NUMBER

NK ACTIVITY OF HIV⁻ AND HIV⁺ EFFECTOR CELLS IN A 4 HOUR ^{51}Cr RELEASE ASSAY FOLLOWING AN 18 HOUR PRE-INCUBATION WITH AVS-2776

EXP #	DRUG CONC#	HIV⁻ 20:1	HIV⁻ 5:1	HIV⁺ 20:1	HIV⁺ 5:1
1	0	40*	31	40	14
	0.665	51 (27)**	27 (-13)	32 (-20)	12 (-7)
	0.133	-	-	33 (-17)	14 (NC)
	0.066	55 (37)	27 (-13)	31 (-22)	9 (-36)
	0.013	-	-	31 (-22)	10 (-28)
	0.006	-	-	38 (-5)	15 (7)

UG/ML OF CULTURE
* % KILL, MEAN OF TRIPLICATES, ROUNDED TO NEAREST WHOLE NUMBER
** % CHANGE RELATIVE TO 0 DRUG, ROUNDED TO NEAREST WHOLE NUMBER

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 18 HOURS OF INCUBATION
WITH AVS 3931

SURFACE ANTIGEN	DRUG CONC. (UG/ML CULTURE) 0	4.17	0.417
LEU-5 * CD2 * E-ROSE	-	-	-
LEU-4 * CD3 * PAN T	85.3	65.9	86.0
LEU-3 * CD4 * HELPER	42.0	37.2	37.3
LEU-2 * CD8 * SUPPRE	49.2	47.4	48.2
LEU-19* - * NK	8.3	7.9	6.9
LEU-11* CD16* NK	11.6	11.1	9.7
LEU-7 * - * NK	16.8	16.7	16.1
LEU-12* CD19* B	1.3	1.7	1.1
HLA-DR* - *	29.1	28.5	27.3
IL2r * CD25*	6.9	5.8	4.7
$L3^+\&L8^-$ IND.HELP	TE	7.5	6.7
$L3^+\&L8^+$ IND.SUPP	TE	29.7	30.6
$L4^+\&L19^+$ CTL	1.6	1.6	1.7
$L2^+\&L7^+$	11.9	11.1	10.5
H/S RATIO	0.85	0.78	0.77

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 18 HOURS OF INCUBATION
WITH AVS 3932

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	4.17	0.417
LEU-5 * CD2 * E-ROSE		-	-	-
LEU-4 * CD3 * PAN T		85.3	86.2	85.0
LEU-3 * CD4 * HELPER		42.0	37.4	36.9
LEU-2 * CD8 * SUPPRE		49.2	49.5	47.8
LEU-19* - * NK		8.3	7.9	8.8
LEU-11* CD16* NK		11.6	10.5	10.7
LEU-7 * - * NK		16.8	16.3	15.9
LEU-12* CD19* B		1.3	1.4	1.2
HLA-DR* - *		29.1	25.7	27.8
IL2r * CD25*		6.9	5.1	5.2
L3⁺&L8⁻	IND.HELP	TE	6.5	5.9
L3⁺&L8⁺	IND.SUPP	TE	30.9	33.7
L4⁺&L19⁺	CTL	1.6	2.0	2.0
L2⁺&L7⁺		11.9	11.6	10.9
H/S RATIO		0.85	0.75	0.77

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 18 HOURS OF INCUBATION
WITH AVS 4594

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	.0417	.0083
LEU-5 * CD2 * E-ROSE		-	-	-
LEU-4 * CD3 * PAN T		85.3	84.6	85.0
LEU-3 * CD4 * HELPER		42.0	38.8	38.5
LEU-2 * CD8 * SUPPRE		49.2	49.4	49.2
LEU-19* - * NK		8.3	7.3	8.3
LEU-11* CD16* NK		11.6	9.7	11.6
LEU-7 * - * NK		16.8	18.7	16.8
LEU-12* CD19* B		1.3	1.4	1.3
HLA-DR* - *		29.1	29.5	27.6
IL2r * CD25*		6.9	5.2	5.5
$L3^+\&L8^-$	IND.HELP	TE	7.0	5.6
$L3^+\&L8^+$	IND.SUPP	TE	31.8	32.9
$L4^+\&L19^+$	CTL	1.6	1.5	1.6
$L2^+\&L7^+$		11.9	13.4	11.9
H/S RATIO		0.85	0.78	0.78

HIV⁺ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 18 HOURS OF INCUBATION
WITH AVS 3931

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	4.17	0.417
LEU-5 * CD2 * E-ROSE		-	-	-
LEU-4 * CD3 * PAN T		38.3	32.5	33.2
LEU-3 * CD4 * HELPER		2.0	1.5	1.9
LEU-2 * CD8 * SUPPRE		21.6	18.6	15.7
LEU-19* - * NK		7.6	8.5	7.6
LEU-11* CD16* NK		4.1	5.3	5.7
LEU-7 * - * NK		10.7	8.9	8.8
LEU-12* CD19* B		8.7	6.1	5.5
HLA-DR* - *		46.5	45.6	50.4
IL2r * CD25*		7.1	7.9	7.1
L3⁺&L8⁻	IND.HELP	0.3	0.3	0.2
L3⁺&L8⁺	IND.SUPP	1.7	1.2	1.7
L4⁺&L19⁺	CTL	2.4	2.2	2.0
L2⁺&L7⁺		7.2	6.7	5.9
H/S RATIO		0.09	0.08	0.12

HIV* DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 18 HOURS OF INCUBATION
WITH AVS 3932

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	4.17	0.417
LEU-5 * CD2 * E-ROSE		-	-	-
LEU-4 * CD3 * PAN T		38.3	33.3	35.1
LEU-3 * CD4 * HELPER		2.0	1.6	0.8
LEU-2 * CD8 * SUPPRE		21.6	18.4	16.4
LEU-19* - * NK		7.6	8.2	7.5
LEU-11* CD16* NK		4.1	5.6	8.0
LEU-7 * - * NK		10.7	11.3	9.3
LEU-12* CD19* B		8.7	5.5	5.5
HLA-DR* - *		46.5	45.5	45.0
IL2r * CD25*		7.1	8.4	7.7
L3*&L8-	IND.HELP	0.3	0.3	0.2
L3*&L8*	IND.SUPP	1.7	1.3	0.6
L4*&L19*	CTL	2.4	2.0	1.7
L2*&L7*		7.2	7.8	6.6
H/S RATIO		0.09	0.09	0.05

HIV+ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 18 HOURS OF INCUBATION
WITH AVS 4594

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	.0417	.0083
LEU-5 * CD2 * E-ROSE		-	-	-
LEU-4 * CD3 * PAN T		38.3	29.7	36.4
LEU-3 * CD4 * HELPER		2.0	2.1	2.2
LEU-2 * CD8 * SUPPRE		21.6	26.8	17.4
LEU-19* - * NK		7.6	10.3	10.3
LEU-11* CD16* NK		4.1	4.9	5.6
LEU-7 * - * NK		10.7	13.1	9.8
LEU-12* CD19* B		8.7	5.9	5.2
HLA-DR* - *		46.5	50.2	45.0
IL2r * CD25*		7.1	8.1	7.3
$L3^+\&L8^-$	IND.HELP	0.3	0.4	0.4
$L3^+\&L8^+$	IND.SUPP	1.7	1.7	1.9
$L4^+\&L19^+$	CTL	2.4	3.2	3.7
$L2^+\&L7^+$		7.2	10.7	6.7
H/S RATIO		0.09	0.08	0.13

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS FOLLOWING 72 HOURS OF INCUBATION WITH AVS 3931

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	4.17	0.417
LEU-5 * CD2 * E-ROSE		-	-	-
LEU-4 * CD3 * PAN T		86.1	86.3	85.7
LEU-3 * CD4 * HELPER		47.8	46.4	43.2
LEU-2 * CD8 * SUPPRE		29.5	31.1	25.5
LEU-19* - * NK		5.6	5.9	5.5
LEU-11* CD16* NK		5.1	4.0	4.7
LEU-7 * - * NK		6.1	6.9	6.4
LEU-12* CD19* B		2.1	2.4	2.7
HLA-DR* - *		25.9	23.9	25.9
IL2r * CD25*		9.0	8.4	8.4
$L3^+\&L8^-$	IND.HELP	7.9	7.4	7.0
$L3^+\&L8^+$	IND.SUPP	39.8	39.0	36.2
$L4^+\&L19^+$	CTL	1.1	1.3	1.1
$L2^+\&L7^+$		3.9	4.8	3.8
H/S RATIO		1.62	1.49	1.63

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 72 HOURS OF INCUBATION
WITH AVS 3932

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	4.17	0.417
LEU-5 * CD2 * E-ROSE		-	-	-
LEU-4 * CD3 * PAN T		86.1	85.2	26.7
LEU-3 * CD4 * HELPER		47.8	46.6	45.6
LEU-2 * CD8 * SUPPRE		29.5	28.9	28.9
LEU-19* - * NK		5.6	6.7	5.8
LEU-11* CD16* NK		5.1	5.1	5.3
LEU-7 * - * NK		6.1	6.8	6.6
LEU-12* CD19* B		2.1	2.5	1.9
HLA-DR* - *		26.9	25.6	24.7
IL2r * CD25*		9.0	8.5	8.3
L3⁺&L8⁻	IND.HELP	7.9	7.8	8.1
L3⁺&L8⁺	IND.SUPP	38.8	38.7	37.5
L4⁺&L19⁺	CTL	1.1	1.5	1.6
L2⁺&L7⁺		3.9	4.4	4.3
H/S RATIO		1.62	1.61	1.58

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 72 HOURS OF INCUBATION
WITH AVS 4594

SURFACE ANTIGEN	DRUG CONC. (UG/ML CULTURE) 0	.0417	.0083
LEU-5 + CD2 + E-ROSE	-	-	-
LEU-4 + CD3 + PAN T	86.1	82.9	87.6
LEU-3 + CD4 + HELPER	47.8	42.4	47.8
LEU-2 + CD8 + SUPPRE	29.5	25.4	30.7
LEU-19+ - + NK	5.6	6.9	6.4
LEU-11+ CD16+ NK	5.1	4.4	4.8
LEU-7 + - + NK	6.1	6.6	7.5
LEU-12+ CD19+ B	2.1	2.4	2.1
HLA-DR+ - +	25.9	28.5	25.4
IL2r + CD25+	9.0	7.9	7.2
L3+&L8- IND.HELP	7.9	8.2	7.7
L3+&L8+ IND.SUP?	39.8	34.1	40.1
L4+&L19+ CTL	1.1	1.3	1.4
L2+&L7+	3.9	4.1	5.4
H/S RATIO	1.62	1.67	1.35

HIV+ DONOR LYMPHOCYTE SURFACE ANALYSIS FOLLOWING 24 HOURS OF INCUBATION WITH AVS 3925

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	.0091	.0045	.0009
LEU-5 + CD2 +	E-ROSE	79.8	72.9	82.6	65.1
LEU-4 + CD3 +	PAN T	73.2	73.6	76.0	77.7
LEU-3 + CD4 +	HELPER	19.0	13.9	9.9	12.8
LEU-2 + CD8 +	SUPPRE	53.3	52.5	50.1	51.6
LEU-19+ - +	NK	9.3	6.9	7.1	9.9
LEU-11+ CD16+	NK	4.1	4.2	4.9	4.9
LEU-7 + - +	NK	22.1	24.0	20.4	22.3
LEU-12+ CD19+	B	28.1	1.1	1.3	13.1
HLA-DR+ - +		43.9	29.7	31.3	32.0
IL2r + CD25+		6.6	5.8	5.7	10.5
L3+&L8-	IND.HELP	3.9	2.8	2.6	2.9
L3+&L8+	IND.SUPP	15.1	11.0	7.3	9.9
L4+&L19+	CTL	3.5	1.9	1.8	4.9
L2+&L7+		20.6	22.0	18.4	20.2
H/S RATIO		0.36	0.26	0.19	0.25

HIV+ DONOR LYMPHOCYTE SURFACE ANALYSIS FOLLOWING 24 HOURS OF INCUBATION WITH AVS 3926

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	.045	.025	.005
LEU-5 * CD2 * E-ROSE		79.8	69.7	73.5	64.1
LEU-4 * CD3 * PAN T		73.2	74.4	71.3	73.2
LEU-3 * CD4 * HELPER		19.0	15.4	16.6	14.7
LEU-2 * CD8 * SUPPRE		53.3	47.9	51.3	47.6
LEU-19* - * NK		9.3	8.1	6.4	10.5
LEU-11* CD16* NK		4.1	5.7	4.7	5.0
LEU-7 * - * NK		22.1	21.9	24.8	23.1
LEU-12* CD19* B		28.1	2.1	20.9	3.3
HLA-DR* - *		43.9	29.0	39.4	36.7
IL2r * CD25*		6.6	6.5	11.2	8.0
L3+&L8-	IND.HELP	3.9	3.8	2.5	2.1
L3+&L8+	IND.SUPP	15.1	11.7	14.1	12.6
L4+&L19+	CTL	3.5	2.4	4.4	5.7
L2+&L7+		20.6	20.0	22.5	20.5
H/S RATIO		0.36	0.32	0.32	0.31

HIV+ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 24 HOURS OF INCUBATION
WITH AVS 3927

SURFACE ANTIGEN			DRUG CONC. (UG/ML CULTURE) 0	.091	.045	.009
LEU-5 +	CD2 +	E-ROSE	79.8	74.5	75.5	53.8
LEU-4 +	CD3 +	PAN T	73.2	64.5	65.3	62.8
LEU-3 +	CD4 +	HELPER	19.0	13.2	13.6	14.3
LEU-2 +	CD8 +	SUPPRE	53.3	45.8	47.7	39.8
LEU-19+	- +	NK	9.3	8.3	7.5	9.5
LEU-11+	CD16+	NK	4.1	3.6	3.3	5.3
LEU-7 +	- +	NK	22.1	18.1	21.0	18.6
LEU-12+	CD19+	B	28.1	1.6	1.4	1.7
HLA-DR+	- +		43.9	33.0	28.0	38.9
IL2r +	CD25+		6.6	4.4	3.6	5.8
L3+&L8-		IND.HELP	3.9	3.1	3.5	3.3
L3+&L8+		IND.SUPP	15.1	10.1	10.2	11.0
L4+&L19+		CTL	3.5	1.5	1.4	1.9
L2+&L7+			20.6	16.0	19.5	16.2
H/S RATIO			0.36	0.29	0.28	0.36

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 24 HOURS OF INCUBATION
WITH AVS 3925

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	.0091	.0045	.0009
LEU-5 * CD2 * E-ROSE		54.9	12.2	45.2	15.2
LEU-4 * CD3 * PAN T		78.0	78.9	78.9	75.8
LEU-3 * CD4 * HELPER		33.8	39.2	34.9	33.7
LEU-2 * CD8 * SUPPRE		31.0	28.4	26.4	28.5
LEU-19* - * NK		7.5	8.2	8.8	9.3
LEU-11* CD16* NK		8.4	1.4	3.0	1.1
LEU-7 * - * NK		8.5	8.3	6.7	6.2
LEU-12* CD19* B		0.3	0.6	0.4	0.4
HLA-DR* - *		9.5	9.6	7.1	7.7
IL2r * CD25*		1.1	0.7	0.6	0.6
$L3^+\&L8^-$	IND.HELP	27.9	30.1	27.1	25.4
$L3^+\&L8^+$	IND.SUPP	6.0	9.1	7.9	8.2
$L4^+\&L19^+$	CTL	0.4	0.5	0.6	0.4
$L2^+\&L7^+$		4.8	5.2	3.9	3.7
H/S RATIO		1.09	1.38	1.32	1.18

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 24 HOURS OF INCUBATION
WITH AVS 3926

SURFACE ANTIGEN			DRUG CONC. (UG/ML CULTURE) 0	.045	.025	.005
LEU-5 * CD2 * E-ROSE			54.9	17.8	41.6	21.7
LEU-4 * CD3 * PAN T			78.0	79.0	78.3	55.9
LEU-3 * CD4 * HELPER			33.8	36.7	32.3	32.5
LEU-2 * CD8 * SUPPRE			31.0	27.8	30.7	26.5
LEU-19* - * NK			7.5	6.8	9.5	9.0
LEU-11* CD16* NK			8.4	1.9	3.6	1.8
LEU-7 * - * NK			8.5	7.1	6.6	7.5
LEU-12* CD19* B			0.3	0.8	0.9	0.6
HLA-DR* - *			9.6	7.4	6.3	10.2
IL2r * CD25*			1.1	0.6	0.7	0.7
L3⁺&L8⁻	IND.HELP		27.9	30.3	26.0	25.8
L3⁺&L8⁺	IND.SUPP		6.0	6.4	6.3	6.7
L4⁺&L19⁺	CTL		0.4	0.5	0.5	0.6
L2⁺&L7⁺			4.8	4.3	4.1	4.3
H/S RATIO			1.09	1.32	1.05	1.22

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 24 HOURS OF INCUBATION
WITH AVS 3927

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	.091	.045	.009
LEU-5 * CD2 * E-ROSE		54.9	22.4	30.6	50.7
LEU-4 * CD3 * PAN T		78.0	79.0	79.6	79.2
LEU-3 * CD4 * HELPER		33.8	28.8	34.6	39.4
LEU-2 * CD8 * SUPPRE		31.0	29.3	31.5	29.4
LEU-19* - * NK		7.5	9.3	7.9	7.6
LEU-11* CD16* NK		8.4	2.6	5.4	6.1
LEU-7 * - * NK		8.5	8.1	7.6	7.0
LEU-12* CD19* B		0.3	1.6	0.3	0.8
HLA-DR* - *		9.6	10.7	10.2	12.0
IL2r * CD25*		1.1	1.5	1.5	1.4
$L3^+\&L8^-$	IND.HELP	27.9	24.3	32.3	38.4
$L3^+\&L8^+$	IND.SUPP	6.0	4.4	2.4	1.0
$L4^+\&L19^+$	CTL	0.4	0.4	0.3	0.5
$L2^+\&L7^+$		4.8	5.2	4.6	4.3
H/S RATIO		1.09	0.98	1.09	1.34

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 18 HOURS OF INCUBATION
WITH AVS 3925

SURFACE ANTIGEN			DRUG CONC. (UG/ML CULTURE) 0	.00083	.00062	.00042
LEU-5 *	CD2 *	E-ROSE	84.5	82.2	80.6	80.8
LEU-4 *	CD3 *	PAN T	61.3	59.0	57.7	60.3
LEU-3 *	CD4 *	HELPER	36.8	31.2	30.8	32.8
LEU-2 *	CD8 *	SUPPRE	48.2	77.6	78.9	45.7
LEU-19*	- *	NK	38.6	39.4	40.6	37.8
LEU-11*	CD16*	NK	33.2	32.2	36.9	32.1
LEU-7 *	- *	NK	10.6	7.8	10.1	9.2
LEU-12*	CD19*	B	1.4	1.3	-	1.5
HLA-DR*	- *		22.5	14.5	-	20.6
IL2r *	CD25*		4.4	3.7	4.0	4.4
$L3^+\&L8^-$		IND.HELP.	4.0	4.3	3.4	3.9
$L3^+\&L8^+$		IND.SUPP	32.9	26.9	27.4	28.9
$L4^+\&L19^+$		CTL	4.1	3.3	3.4	3.1
$L2^+\&L7^+$			8.4	5.5	7.4	6.6
H/S RATIO			0.76	0.40	0.39	0.72

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 18 HOURS OF INCUBATION
WITH AVS 3926

SURFACE ANTIGEN	DRUG CONC. (UG/ML CULTURE) 0	.036	.031	.024
LEU-5 * CD2 * E-ROSE	84.5	79.6	81.7	81.1
LEU-4 * CD3 * PAN T	61.3	59.1	57.6	57.8
LEU-3 * CD4 * HELPER	36.8	30.8	29.7	32.5
LEU-2 * CD8 * SUPPRE	48.2	45.6	45.8	46.3
LEU-19* - * NK	38.6	38.8	43.7	40.1
LEU-11* CD16* NK	33.2	27.7	26.7	33.9
LEU-7 * - * NK	10.5	13.8	12.0	9.1
LEU-12* CD19* B	1.4	14.8	2.2	1.2
HLA-DR* - *	22.5	22.9	19.5	19.5
IL2r * CD25*	4.4	4.5	4.6	3.9
$L3^+\&L8^-$ IND.HELP	4.0	3.9	3.3	4.6
$L3^+\&L8^+$ IND.SUPP	32.9	26.9	26.4	27.9
$L4^+\&L19^+$ CTL	4.1	3.2	7.4	3.2
$L2^+\&L7^+$	8.4	11.6	9.1	6.4
H/S RATIO	0.76	0.68	0.64	0.70

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 18 HOURS OF INCUBATION
WITH AVS 3927

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	.066	.050	.033
LEU-5 * CD2 * E-ROSE		84.5	83.6	89.4	78.8
LEU-4 * CD3 * PAN T		61.3	58.3	77.9	58.8
LEU-3 * CD4 * HELPER		36.8	35.3	59.0	36.6
LEU-2 * CD8 * SUPPRE		46.2	47.0	52.3	49.9
LEU-19* - * NK		38.6	42.3	74.6	62.7
LEU-11* CD16* NK		33.2	31.0	17.3	31.6
LEU-7 * - * NK		10.6	11.6	9.6	10.4
LEU-12* CD19* B		1.4	1.2	?	1.1
HLA-DR* - *		22.5	19.8	?	17.4
IL2r * CD25*		4.4	7.8	3.3	2.6
L3⁺&L8⁻	IND.HELP	4.0	4.1	14.1	4.5
L3⁺&L8⁺	IND.SUPP	32.9	31.2	44.9	32.1
L4⁺&L19⁺	CTL	4.1	4.7	?	24.0
L2⁺&L7⁺		8.4	9.0	7.6	7.9
H/S RATIO		0.76	0.75	1.13	0.73

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 18 HOURS OF INCUBATION
WITH AVS 3927

SURFACE ANTIGEN	DRUG CONC. (UG/ML CULTURE) 0	9.1	4.5
LEU-5 * CD2 * E-ROSE	94.2	91.8	93.6
LEU-4 * CD3 * PAN T	85.6	86.5	85.2
LEU-3 * CD4 * HELPER	44.6	38.7	40.5
LEU-2 * CD8 * SUPPRE	45.0	51.1	45.7
LEU-19* - * NK	18.5	16.8	14.4
LEU-11* CD16* NK	7.0	7.4	4.1
LEU-7 * - * NK	12.6	7.6	8.0
LEU-12* CD19* B	0.7	0.7	1.8
HLA-DR* - *	17.6	8.9	7.1
IL2r * CD25*	10.7	4.1	5.0
L3⁺&L8⁻ IND.HELP	11.2	5.3	4.7
L3⁺&L8⁺ IND.SUPP	33.4	33.4	35.8
L4⁺&L19⁺ CTL	8.0	7.6	5.7
L2⁺&L7⁺	11.4	6.7	7.2
H/S RATIO	0.99	0.76	0.88

HIV+ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 120 HOURS OF INCUBATION
WITH AVS 1968

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	.0167	.083
LEU-5 * CD2 * E-ROSE		96.0	97.0	96.6
LEU-4 * CD3 * PAN T		92.0	93.0	92.7
LEU-3 * CD4 * HELPER		41.2	42.7	41.4
LEU-2 * CD8 * SUPPRE		54.4	53.2	51.5
LEU-19* - * NK		9.8	10.5	11.0
LEU-11* CD16* NK		9.0	9.2	9.9
LEU-7 * - * NK		27.6	26.8	26.8
LEU-12* CD19* B		2.5	2.4	3.3
HLA-DR* - *		35.2	36.2	36.8
IL2r * CD25*		2.6	2.6	3.3
L3+&4B4+	IND.HELP	17.3	18.9	17.8
L3+&L18+	IND.SUPP	23.9	23.8	23.5
L4+&L19+	CTL	6.0	6.0	6.6
L2+&L7+		23.2	24.5	23.1
H/S RATIO		0.76	0.80	0.80

HIV+ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 120 HOURS OF INCUBATION
WITH AVS 3934

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	208.3	.208
LEU-5 * CD2 * E-ROSE		96.0	96.9	95.8
LEU-4 * CD3 * PAN T		92.0	94.0	93.5
LEU-3 * CD4 * HELPER		41.2	40.3	39.9
LEU-2 * CD8 * SUPPRE		54.4	56.4	54.4
LEU-19* - * NK		9.8	10.3	8.7
LEU-11* CD16* NK		9.0	6.9	8.5
LEU-7 * - * NK		27.6	31.2	29.7
LEU-12* CD19* B		2.5	2.4	2.3
HLA-DR* - *		35.2	32.7	32.7
IL2r * CD25*		2.6	2.7	3.6
L3+&4B4+	IND.HELP	17.3	17.8	17.6
L3+&L18+	IND.SUPP	23.9	22.5	22.3
L4+&L19+	CTL	6.0	6.4	4.4
L2+&L7+		23.2	26.7	25.7
H/S RATIO		0.76	0.71	0.73

HIV+ DONOR LYMPHOCYTE SURFACE ANALYSIS FOLLOWING 120 HOURS OF INCUBATION WITH AVS 2776

SURFACE ANTIGEN	DRUG CONC. (UG/ML CULTURE) 0	11.0	1.1
LEU-5 + CD2 + E-ROSE	96.0	96.8	95.5
LEU-4 + CD3 + PAN T	92.0	93.1	93.7
LEU-3 + CD4 + HELPER	41.2	40.8	41.6
LEU-2 + CD8 + SUPPRE	54.4	55.2	56.0
LEU-19+ - + NK	9.8	10.2	10.4
LEU-11+ CD16+ NK	9.0	10.4	11.6
LEU-7 + - + NK	27.6	32.2	33.4
LEU-12+ CD19+ B	2.5	2.3	2.4
HLA-DR+ - +	35.2	36.0	35.1
IL2r + CD25+	2.6	3.2	3.5
L3+&4B4+ IND.HELP	17.3	17.5	17.7
L3+&L18+ IND.SUPP	23.9	23.3	23.9
L4+&L19+ CTL	6.0	6.1	6.2
L2+&L7+	23.2	27.3	29.0
H/S RATIO	0.76	0.74	0.74

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 120 HOURS OF INCUBATION
WITH AVS 2776

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	11.0	1.1
LEU-5 * CD2 *	E-ROSE	93.3	93.5	92.1
LEU-4 * CD3 *	PAN T	89.1	88.8	86.9
LEU-3 * CD4 *	HELPER	64.3	61.2	63.1
LEU-2 * CD8 *	SUPPRE	32.6	33.6	34.2
LEU-19* - *	NK	8.2	8.4	10.1
LEU-11* CD16*	NK	6.4	7.8	8.4
LEU-7 * - *	NK	3.8	4.8	5.8
LEU-12* CD19*	B	2.7	3.4	2.8
HLA-DR* - *		13.0	13.9	18.1
IL2r * CD25*		7.0	6.8	7.0
L3⁺&4B4⁺	IND.HELP	55.6	57.3	56.5
L3⁺&L18⁺	IND.SUPP	39.4	35.1	36.6
L4⁺&L19⁺	CTL	2.4	3.0	2.8
L2⁺&L7⁺		3.4	4.3	5.3
H/S RATIO		1.95	1.81	1.79

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 120 HOURS OF INCUBATION
WITH AVS 1968

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	.1666	.083
LEU-5 * CD2 * E-ROSE		93.3	91.7	93.1
LEU-4 * CD3 * PAN T		89.1	86.8	87.4
LEU-3 * CD4 * HELPER		64.3	62.0	61.8
LEU-2 * CD8 * SUPPRE		32.6	32.8	35.3
LEU-19* - * NK		8.2	9.0	8.8
LEU-11* CD16* NK		6.4	5.1	6.8
LEU-7 * - * NK		3.8	3.3	5.4
LEU-12* CD19* B		2.7	2.9	2.9
HLA-DR* - *		13.0	15.2	16.6
IL2r * CD25*		7.0	5.7	6.2
L3⁺&4B4⁺	IND.HELP	55.6	52.2	56.0
L3⁺&L18⁺	IND.SUPP	39.4	36.2	37.0
L4⁺&L19⁺	CTL	2.4	2.4	2.4
L2⁺&L7⁺		3.4	2.9	5.0
H/S RATIO		1.95	1.89	1.03

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 120 HOURS OF INCUBATION
WITH AVS 3934

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	208.3	.208
LEU-5 * CD2 * E-ROSE		93.3	92.7	92.4
LEU-4 * CD3 * PAN T		89.1	90.6	87.5
LEU-3 * CD4 * HELPER		64.3	61.6	62.3
LEU-2 * CD8 * SUPPRE		32.6	31.9	32.7
LEU-19* - * NK		8.2	6.5	8.3
LEU-11* CD16* NK		6.4	6.8	6.6
LEU-7 * - * NK		3.8	4.7	5.0
LEU-12* CD19* B		2.7	7.9	3.5
HLA-DR* - *		13.0	14.4	12.8
IL2r * CD25*		7.0	7.9	6.9
L3*&4B4*	IND.HELP	55.6	55.3	56.6
L3*&L18*	IND.SUPP	39.4	34.8	36.7
L4*&L19*	CTL	2.4	2.0	1.8
L2*&L7*		3.4	4.2	4.4
H/S RATIO		1.95	1.92	1.88

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 72 HOURS OF INCUBATION
WITH AVS 1968

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	.83	.167	.083
LEU-5 * CD2 * E-ROSE		82.0	83.0	82.0	80.0
LEU-4 * CD3 * PAN T		72.0	73.0	71.0	73.0
LEU-3 * CD4 * HELPER		31.0	31.0	31.0	29.0
LEU-2 * CD8 * SUPPRE		31.0	29.0	28.0	31.0
LEU-19* - * NK		16.0	16.0	17.0	15.0
LEU-11* CD16* N..		21.0	15.0	16.0	12.0
LEU-7 * - * NK		5.0	6.0	5.0	5.0
LEU-12* CD19* B		1.0	1.0	1.0	1.0
HLA-DR* - *		17.0	16.0	16.0	15.0
IL2r * CD25*		7.0	5.0	5.0	6.0
L3⁺&4B4⁺	IND.HELP	29.0	26.0	29.0	29.0
L3⁺&L18⁺	IND.SUPP	15.0	14.0	14.0	15.0
L4⁺&L19⁺	CTL	2.0	2.0	2.0	2.0
L2⁺&L7⁺		3.0	4.0	3.0	3.0
H/S RATIO		1.00	1.07	1.11	0.93

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 72 HOURS OF INCUBATION
WITH AVS 2776

SURFACE ANTIGEN		DRUG CONC. (UG/ML CULTURE) 0	55	5.5	.55
LEU-5 * CD2 * E-ROSE		82.0	83.0	83.0	83.0
LEU-4 * CD3 * PAN T		72.0	73.0	73.0	75.0
LEU-3 * CD4 * HELPER		31.0	29.0	28.0	29.0
LEU-2 * CD8 * SUPPRE		31.0	29.0	34.0	31.0
LEU-19* - * NK		16.0	17.0	17.0	15.0
LEU-11* CD16* NK		21.0	18.0	17.0	17.0
LEU-7 * - * NK		5.0	5.0	6.0	6.0
LEU-12* CD19* B		1.0	1.0	1.0	1.0
HLA-DR* - *		17.0	12.0	16.0	14.0
IL2r * CD25*		7.0	6.0	6.0	6.0
L3⁺&4B4⁺	IND.HELP	29.0	23.0	26.0	26.0
L3⁺&L18⁺	IND.SUPP	15.0	13.0	13.0	14.0
L4⁺&L19⁺	CTL	2.0	2.0	2.0	2.0
L2⁺&L7⁺		3.0	3.0	4.0	4.0
H/S RATIO		1.00	1.00	0.82	0.93

HIV⁻ DONOR LYMPHOCYTE SURFACE ANALYSIS
FOLLOWING 72 HOURS OF INCUBATION
WITH AVS 3934

SURFACE ANTIGEN			DRUG CONC. (UG/ML CULTURE) 0	208.3	2.08
LEU-5 *	CD2 *	E-ROSE	75.8	76.7	75.7
LEU-4 *	CD3 *	PAN T	69.1	64.5	66.8
LEU-3 *	CD4 *	HELPER	36.2	33.6	40.9
LEU-2 *	CD8 *	SUPPRE	25.8	26.3	24.5
LEU-19*	- *	NK	16.7	21.0	17.8
LEU-11*	CD16*	NK	14.1	15.3	11.4
LEU-7 *	- *	NK	4.0	5.0	3.4
LEU-12*	CD19*	B	0.6	0.9	0.8
HLA-DR*	- *		25.6	25.5	27.7
IL2r *	CD25*		5.2	5.7	4.6
$L3^+\&L8^-$		IND.HELP	-	-	-
$L3^+\&L8^+$		IND.SUPP	-	-	-
$L4^+\&L19^+$		CTL	3.0	3.3	3.9
$L2^+\&L7^+$			2.9	3.4	2.5
H/S RATIO			1.40	1.30	1.70

APPENDIX: 1989 Study Data

COOPERATIVE AGREEMENT NO: DAMD17-88-H-8004

TITLE: IMMUNOLOGICAL STUDIES OF ANTI-AIDS DRUGS IN ARC/AIDS

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EXPERIMENTAL PROCEDURES FLOW CHART
FOR EVALUATION OF
AVS-DRUGS

FIRST TIER	SECOND TIER
* Toxicity levels	* ADCC - non specific
* Lymphocyte blastogenesis	HIV specific
* NK cell activity	* Monocyte adherence
* Phenotype	* IL2 production
	* Alpha IFN production

CURRENT PROCEDURAL STATUS OF DRUGS
UNDERGOING EVALUATION

FIRST TIER	SECOND TIER
1792	3925
1968*	3926
2776*	3931
2777	3932
2778	4594
2880	
3927*	
3934*	
4596	
5014	
5015	
5016	
5017	
5018	
5019	
5020	
5025	
5026	
5027	
5028	
5073	
5074	

* Drugs without activity in first tier, not entering second tier evaluation.

DRUG CONCENTRATIONS AT WHICH 50% OR GREATER
INHIBITION OF BLASTOGENESIS OCCURS

DRUG AVS #	PHA UG/ML of CULT.	CON-A
1792	-	-
1968	5.0	3.0
2776	39.0	55.0
2777	-	-
2778	-	-
2880	-	-
3925	0.85	0.50
3926	0.85	0.45
3927	-	-
3931	-	NE
3932	-	NE
3934	-	NE
4594	-	NE
4596	-	-
5014	-	-
5015	-	-
5016	-	-
5017	-	-
5018	-	-
5019		84.5
5020	-	-
5025		82.7
5026	-	-
5027	10.0	10.0
5028	100.0	100.0
5073	-	-
5074	-	-

1. Concentration range = 0.01 to 100 ug/ml culture.
2. (-) = < 50% inhibition at highest concentration tested.
3. NE = not evaluated

ASSESSMENT OF MODULATING CAPACITY OF DRUGS TESTED TO DATE IN THREE ASSAY SYSTEMS

DRUG AVS-#	ASSAY SYSTEMS		
	BLASTOGENESIS	NK ACTIVITY	PHENOTYPE
1792	-*	-	NE**
1968	-	-	-
2776	-	-	-
2777	-	PRESENT	NE
2778	-	-	NE
2880	PRESENT	NE	NE
3925	-	PRESENT	PRESENT
3926	PRESENT	PRESENT	PRESENT
3927	-	PRESENT	PRESENT
3931	PRESENT	-	PRESENT
3932	PRESENT	-	PRESENT
3934	-	-	-
4594	PRESENT	PRESENT	-
4596	-	PRESENT	-
5014	-	-	NE
5015	PRESENT	-	NE
5016	-	-	NE
5017	-	-	NE
5018	-	-	NE
5019	-	-	NE
5020	-	-	NE
5025	-	-	NE
5026	PRESENT	PRESENT	NE
5027	-	-	NE
5028	-	PRESENT	NE
5073	-	-	NE
5074	PRESENT	PRESENT	NE

*(-) = No activity
**NE = Not evaluated

Criteria for Presence of Modulation:

Blastogenesis: $\geq$ +50% change or increase of $\geq$ 10,000 net CPM.
NK Activity : $\geq$ +50% change
Phenotype : $\geq$ 50% change in any manner or any change in the H/S Ratio.

PHENOTYPE MODULATIONS OF HIV$^+$ LYMPHOCYTES
SEEN AFTER INCUBATION WITH AVS-DRUGS

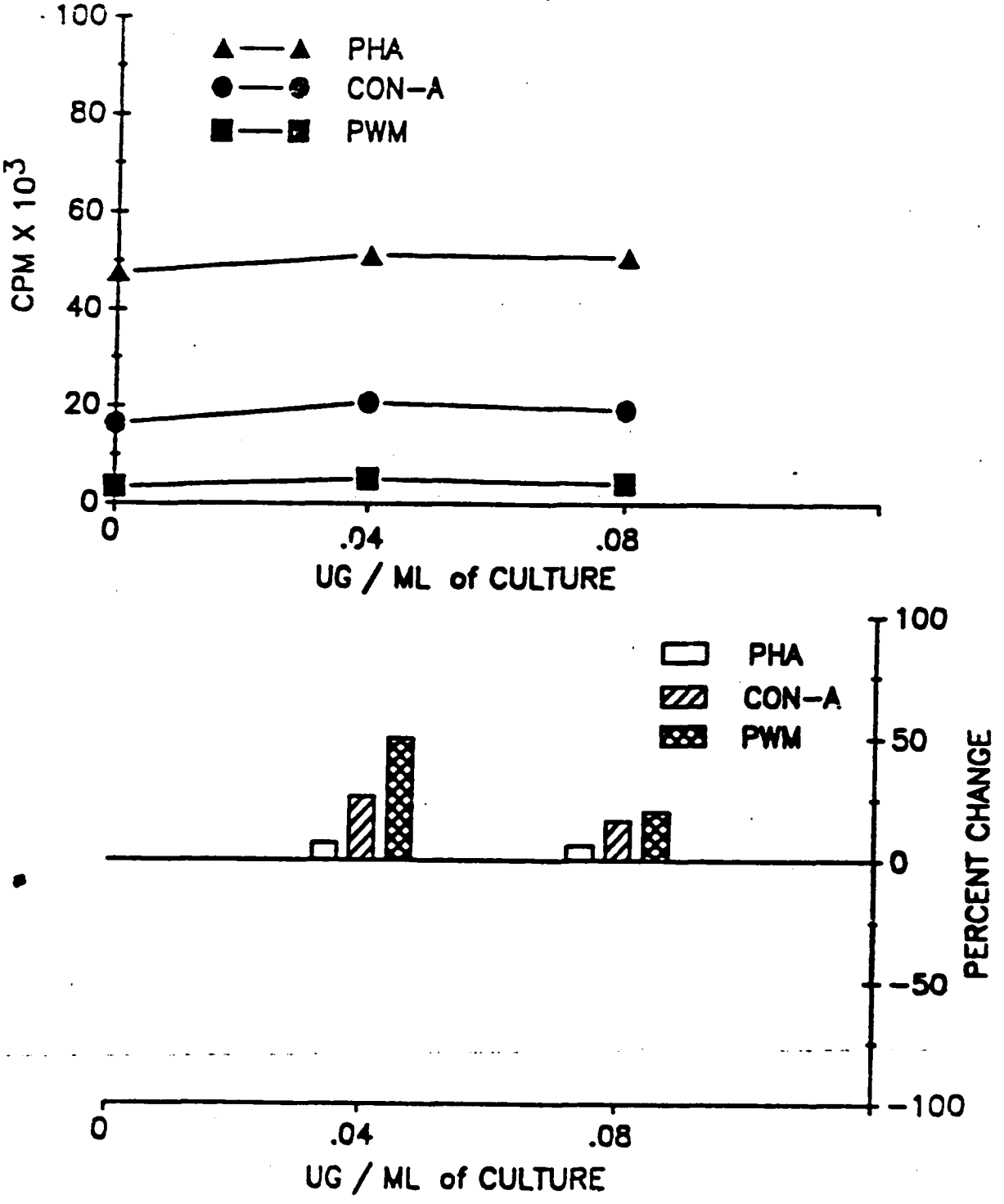
SURFACE ANTIGEN	AVS #'S				
	3925	3926	3927	3931	3932
CD2 : E-ROSE	.	-20	-32	ne	ne
CD3 : PAN-T	.	.	.	.	.
: CTL[1]	.	+32	-60	.	.
CD4 : T-HELP	-48	-23	-30	-25	-60
:IND.HELP[2]	-33	-46	-20	.	.
:IND.SUPR[3]	-52	-22	-33	-29	-65
CD8 : T-SUPR	.	.	-25	-27	-24
CD25 : IL2r	+59	+70	-45	.	.
CD19 : B	-96	.	.	-30	+37
LEU19 : NK	-26	-31	.	.	.
CD16 : NK	.	.	+29	+39	+95
LEU7 : NK	.	.	.	.	.
HLA-DR	-35	-34	-36	.	.
H/S RATIO	-47	.	.	+33	-44

[1] Cytotoxic T lymphocyte (CD3$^+$ and Leu19$^+$)
[2] (CD4$^+$ and Leu8$^-$)
[3] (CD4$^+$ and Leu8$^+$)

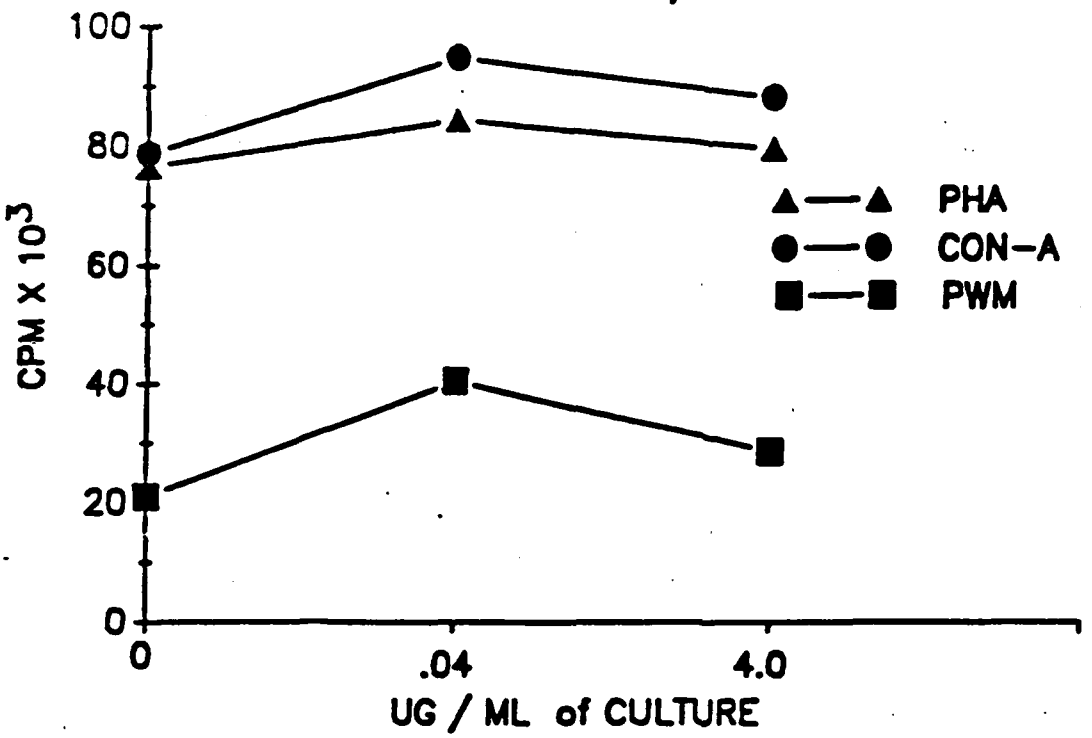
Number values are percent change relative to a no drug incubated control. (.) represent no change.

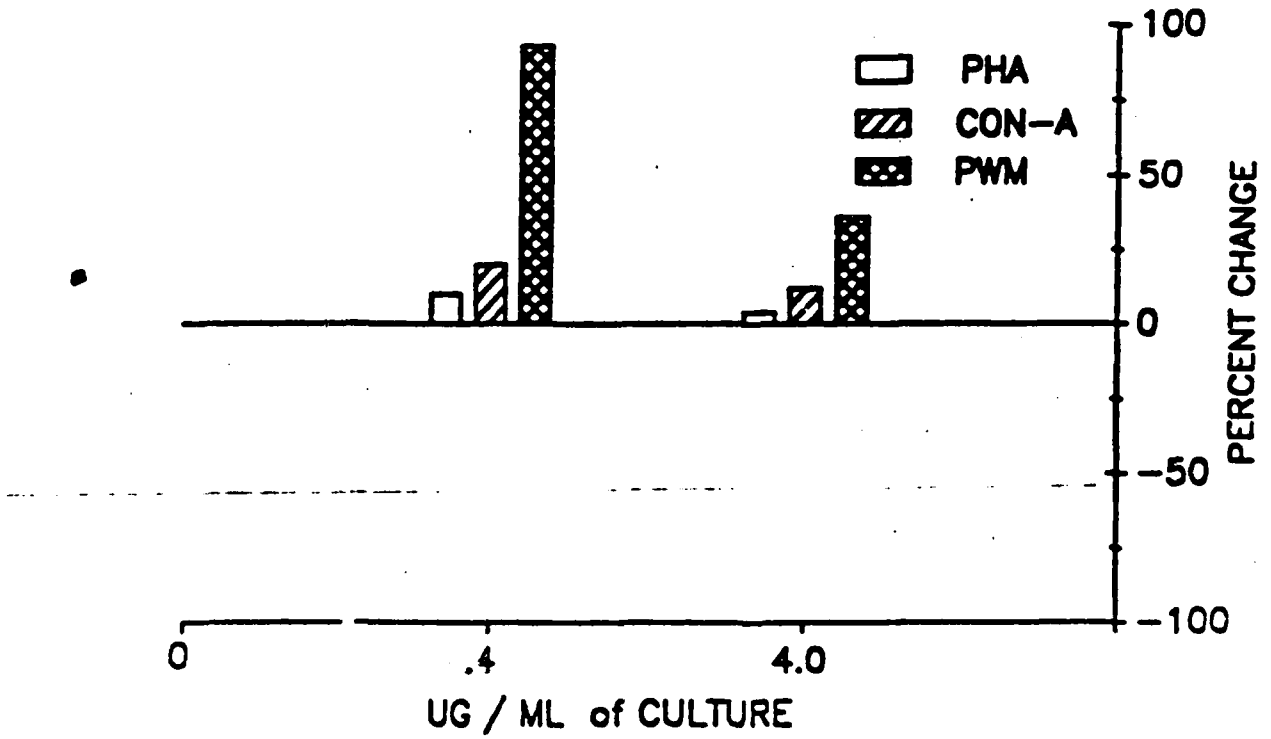
Incubation periods = 18 hours for 3931,3932
= 24 hours for 3925,3926,3927

BLASTOGENESIS / AVS −3926

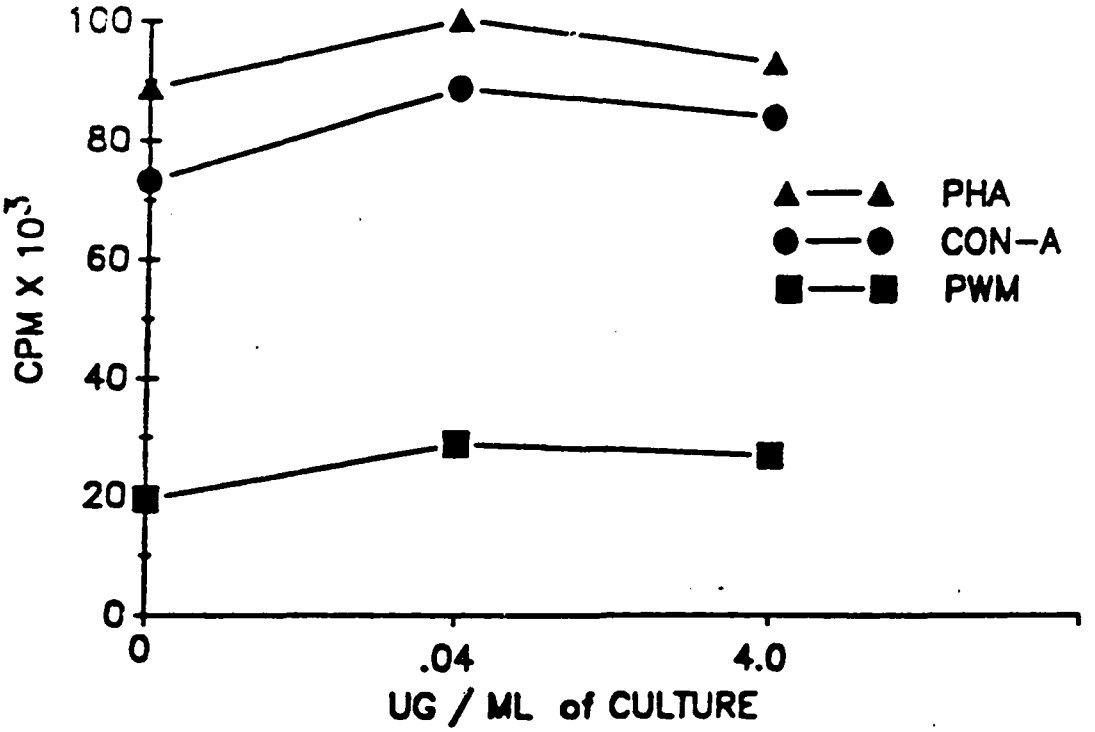


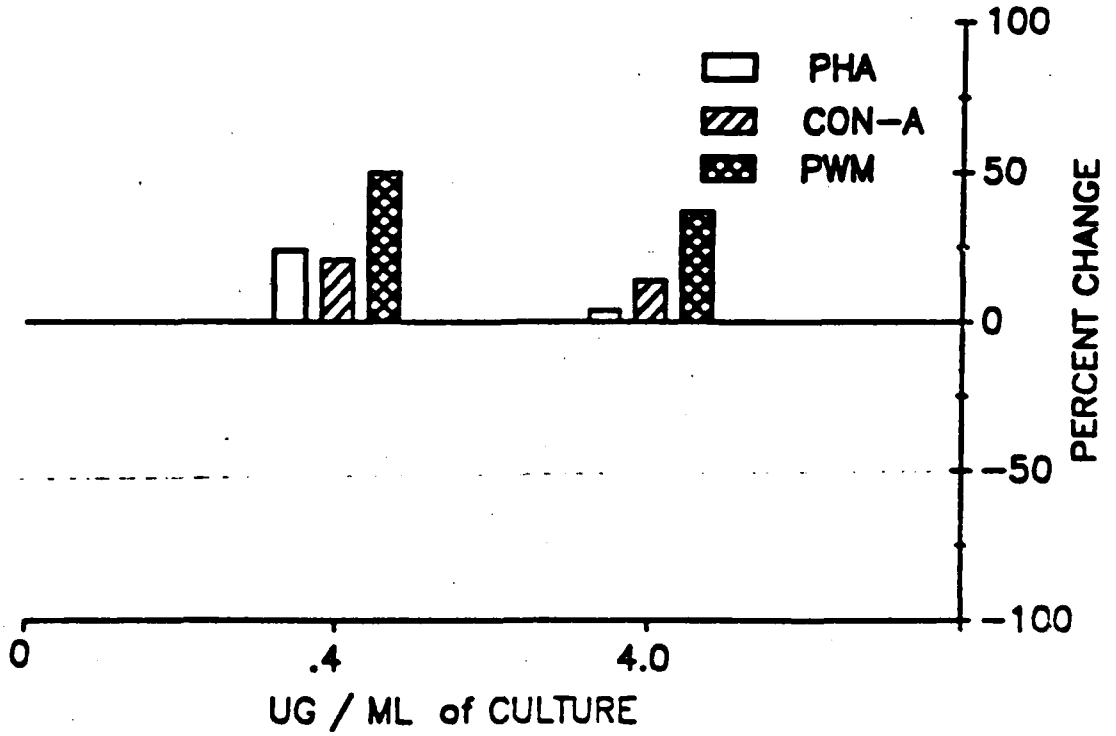
BLASTOGENESIS / AVS -3931



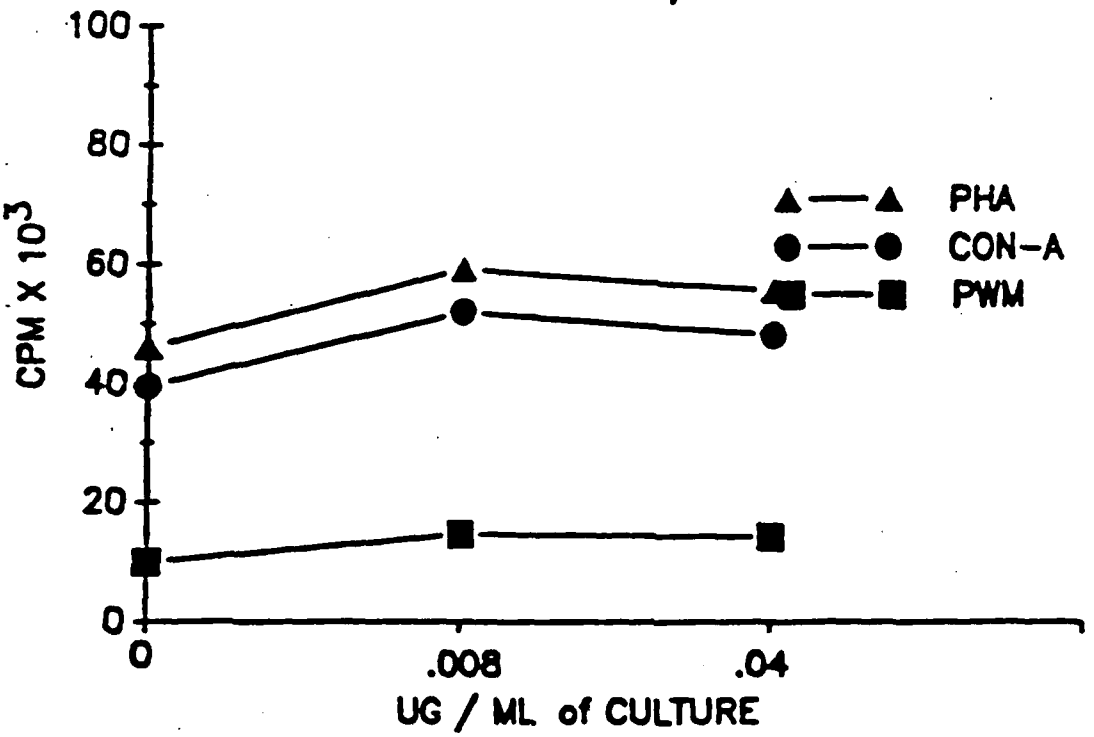


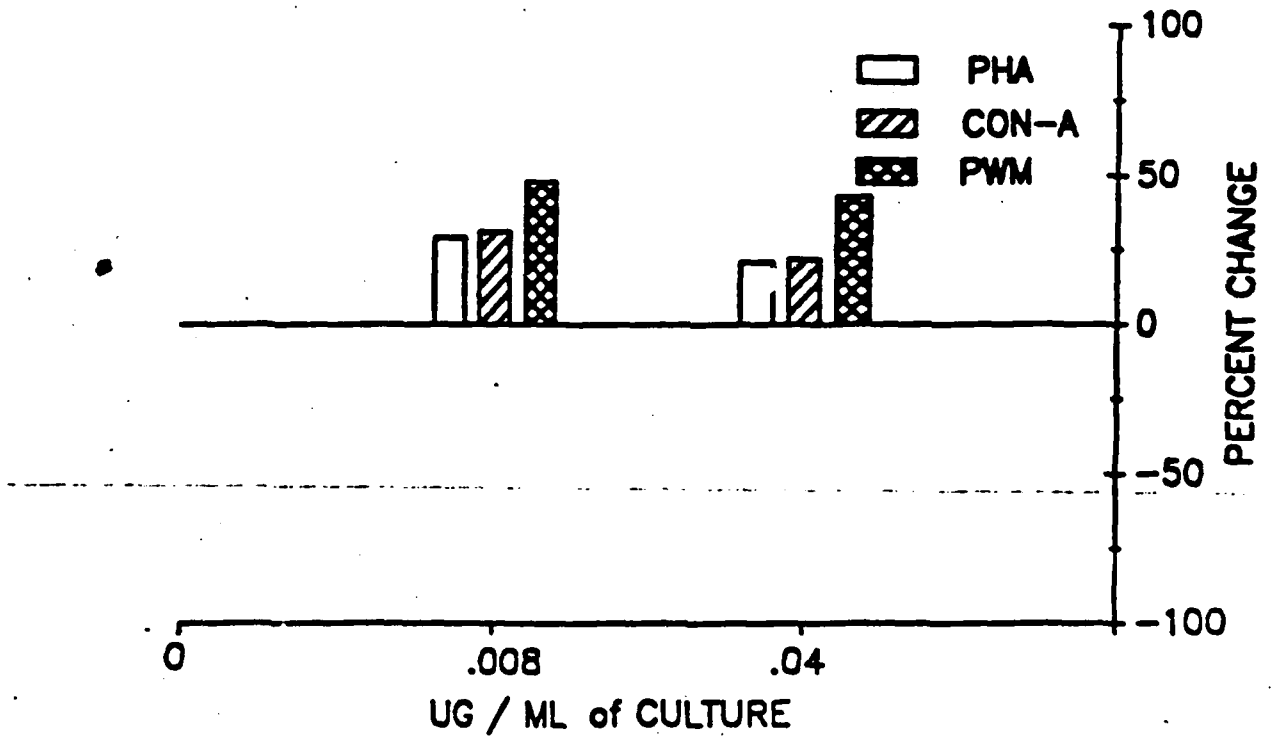
BLASTOGENESIS / AVS -3932



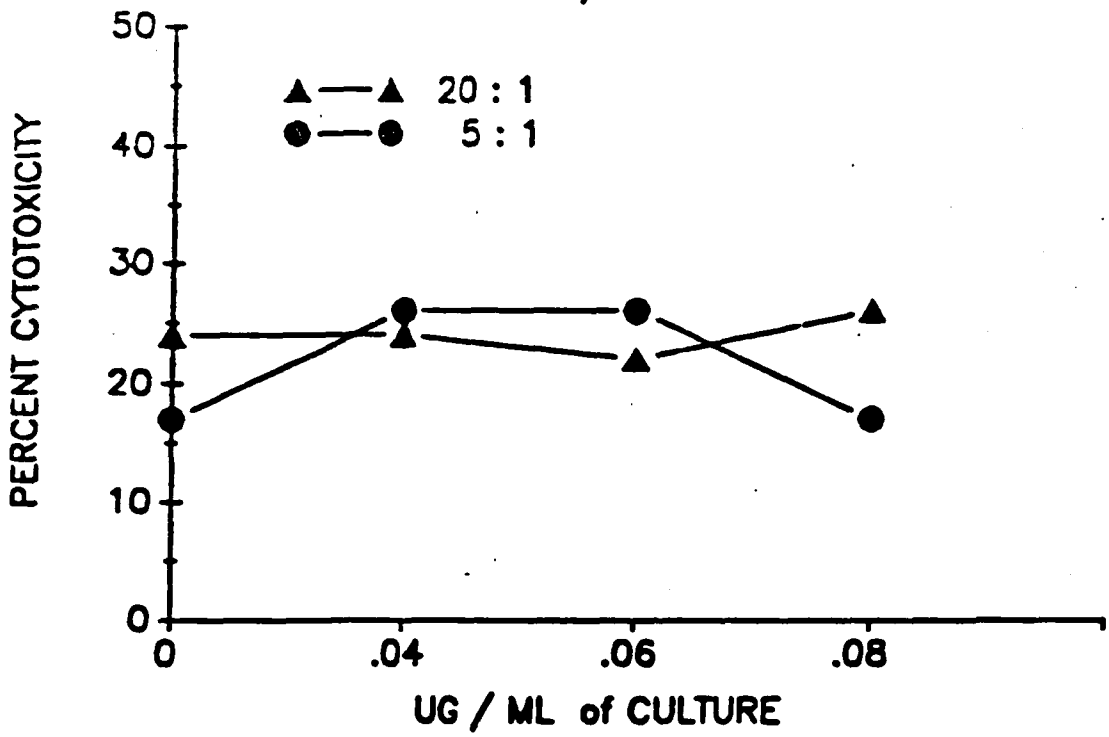


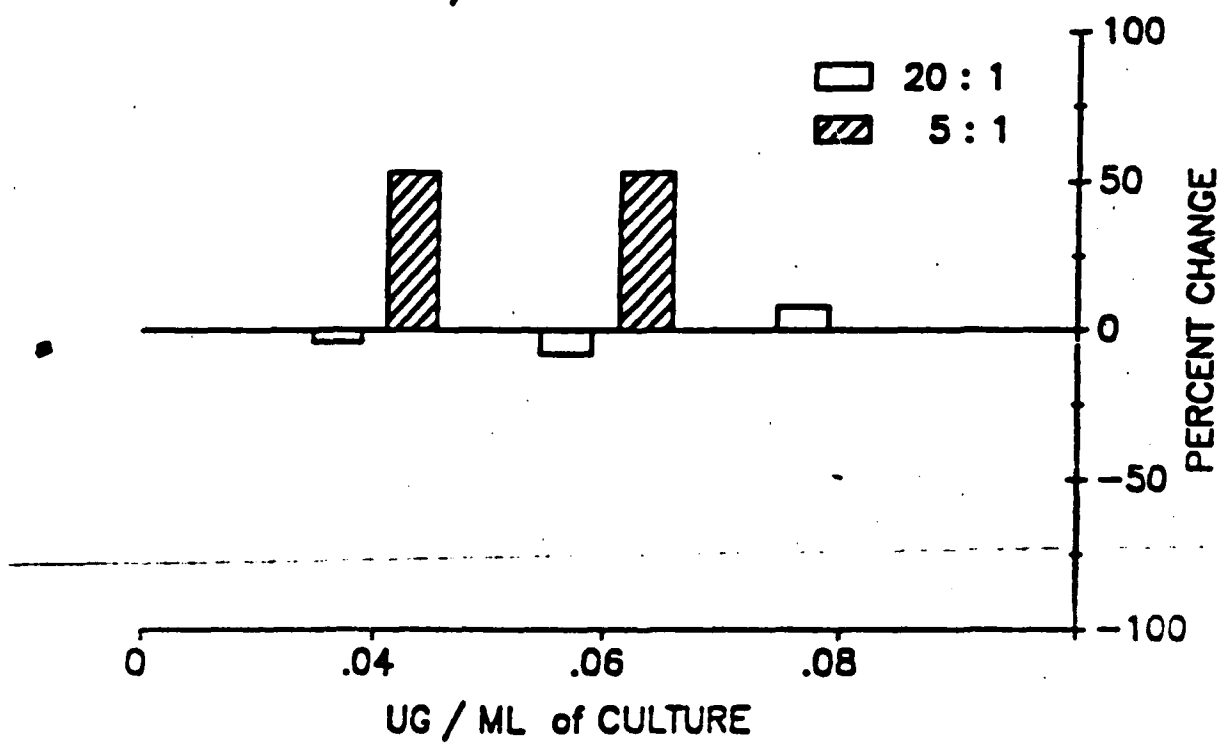
BLASTOGENESIS / AVS −4594



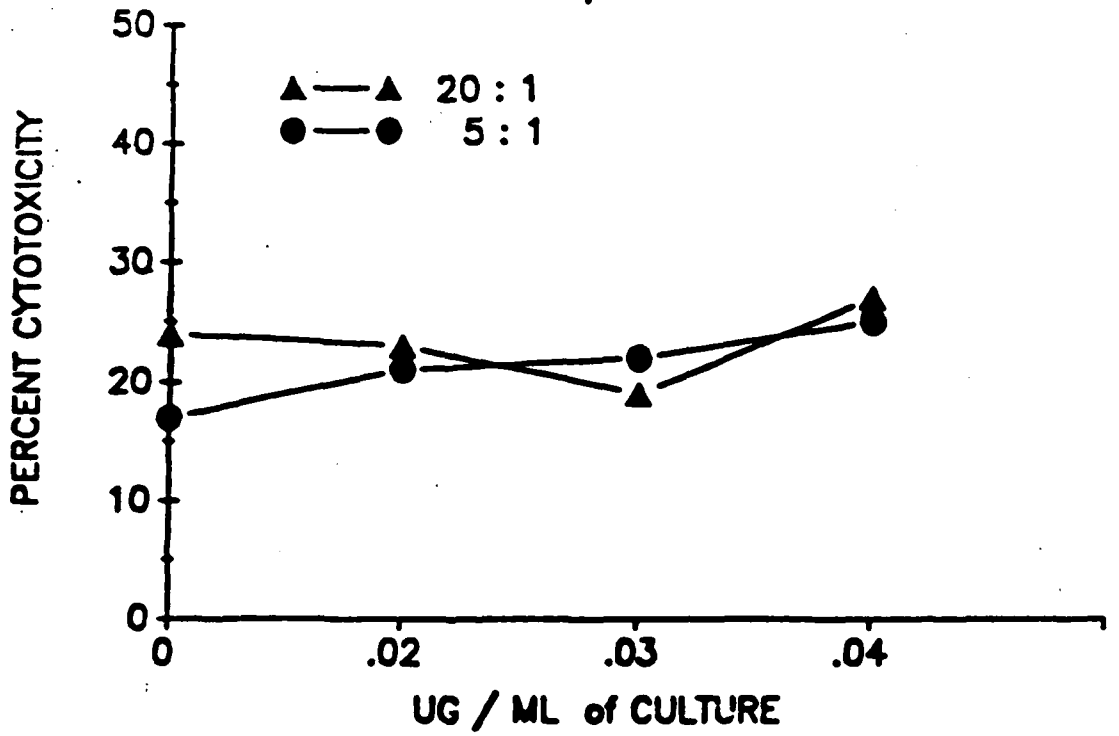


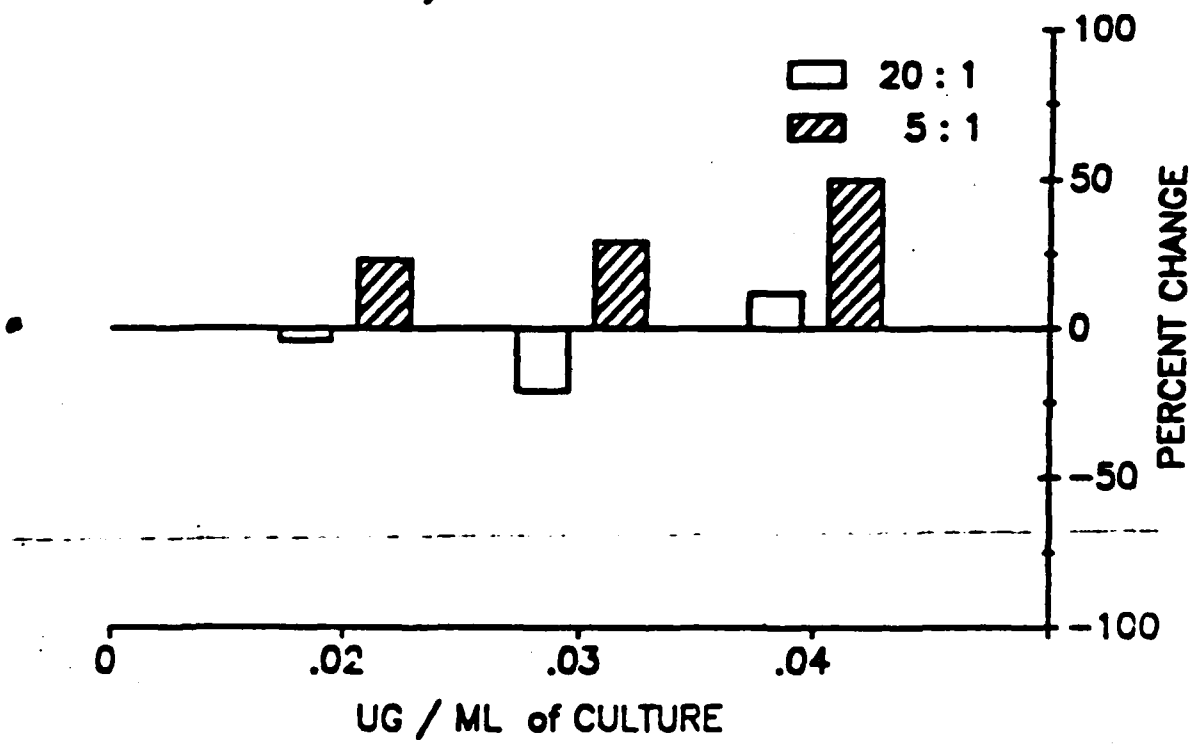
NK ACTIVITY / AVS – 3925

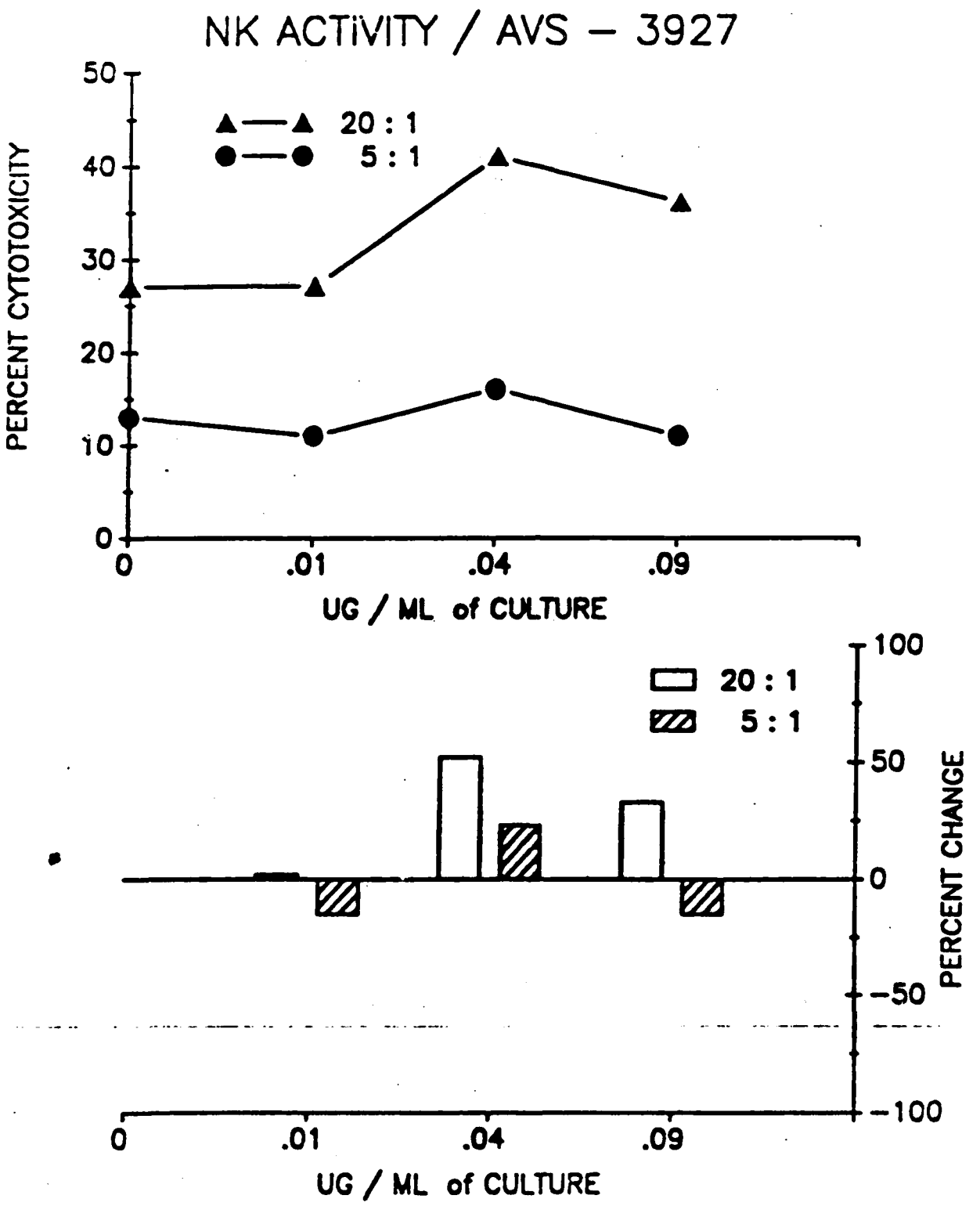




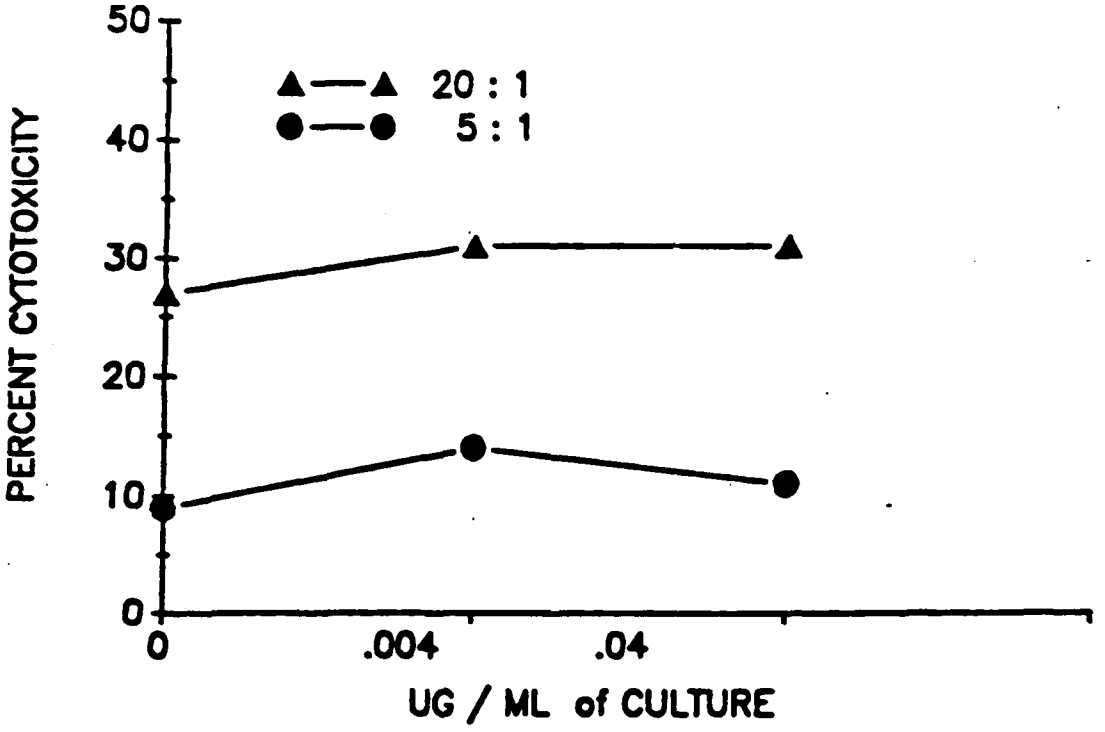
NK ACTIVITY / AVS – 3926

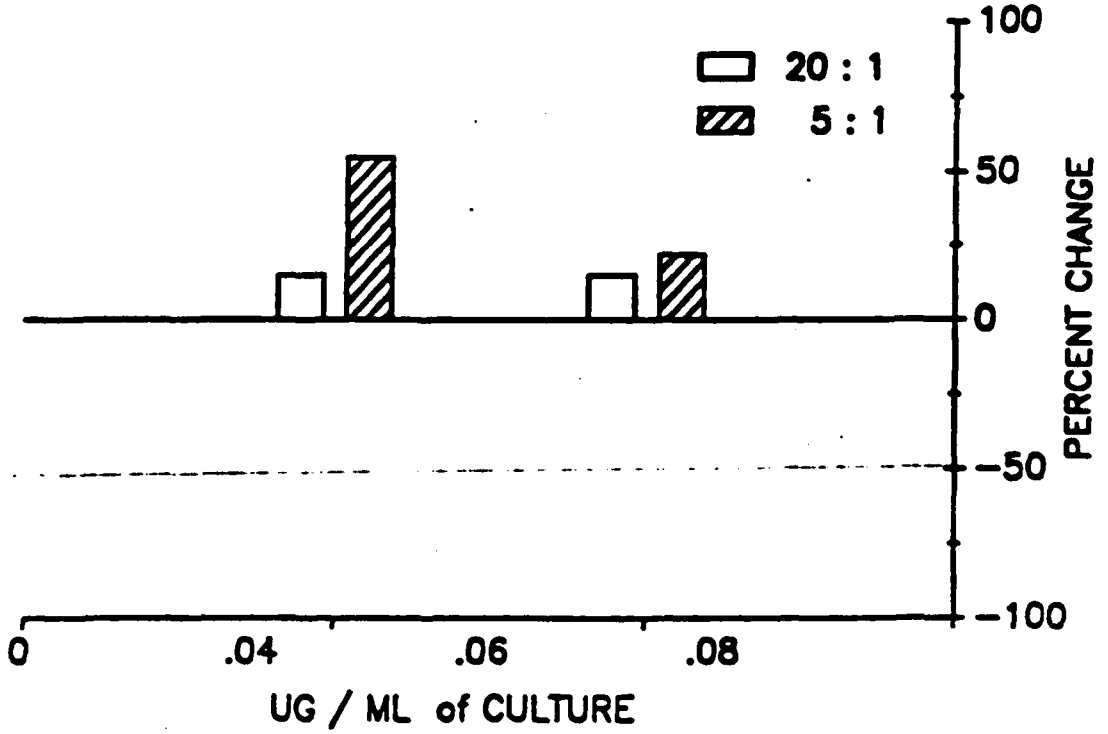




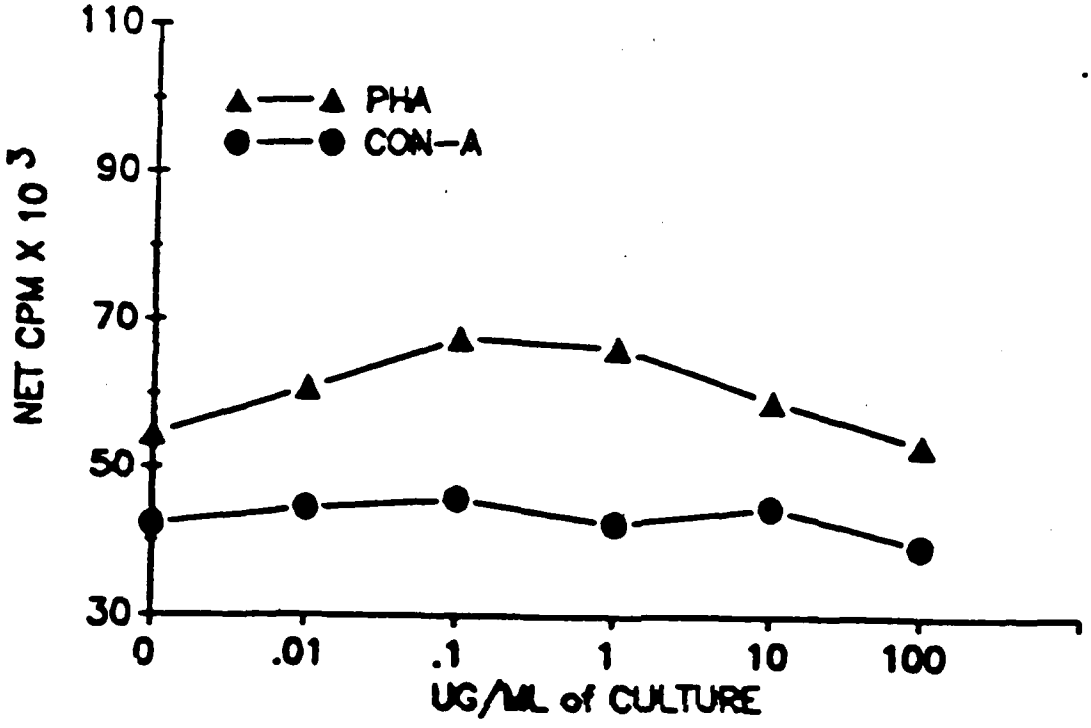

NK ACTIVITY / AVS – 3927
PERCENT CYTOTOXICITY
50
40
30
20
10
0
20 : 1
5 : 1
0
.01
.04
.09
UG / ML of CULTURE
100
50
0
−50
−100
PERCENT CHANGE
20 : 1
5 : 1
0
.01
.04
.09
UG / ML of CULTURE

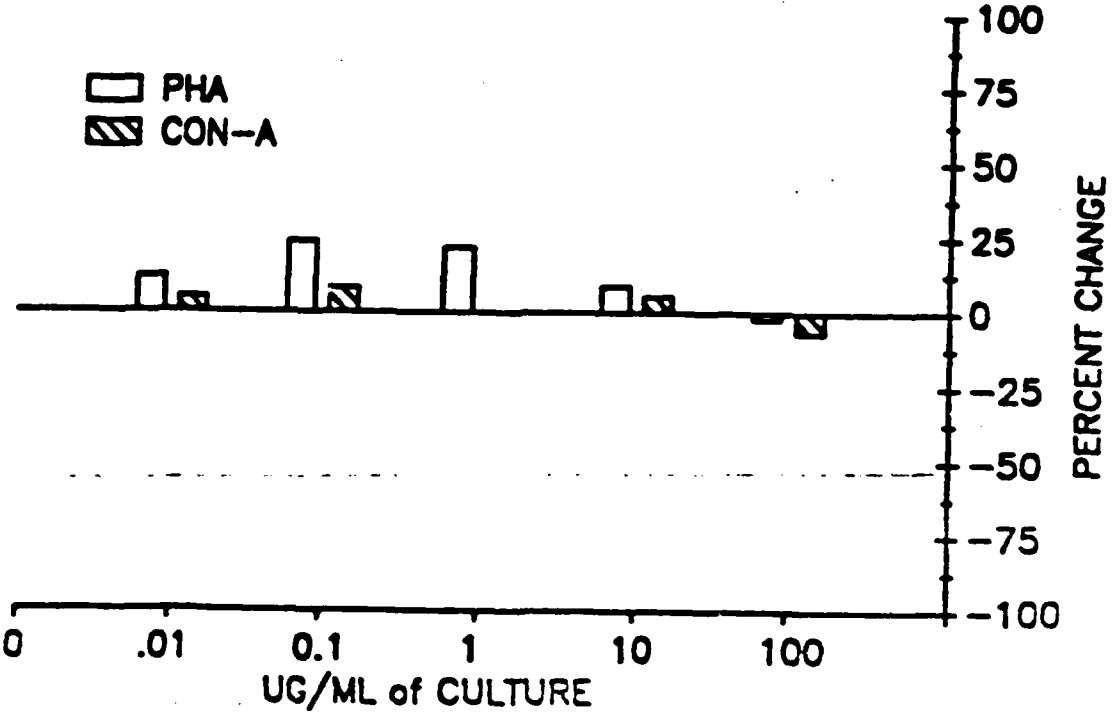
NK ACTIVITY / AVS – 3932



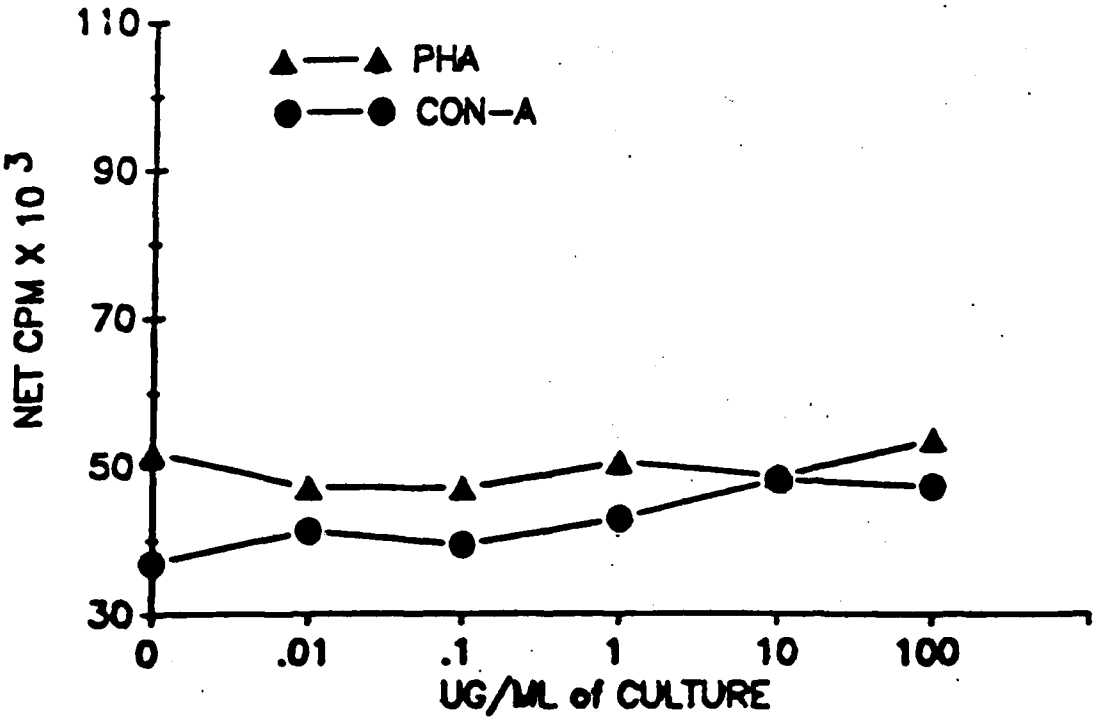


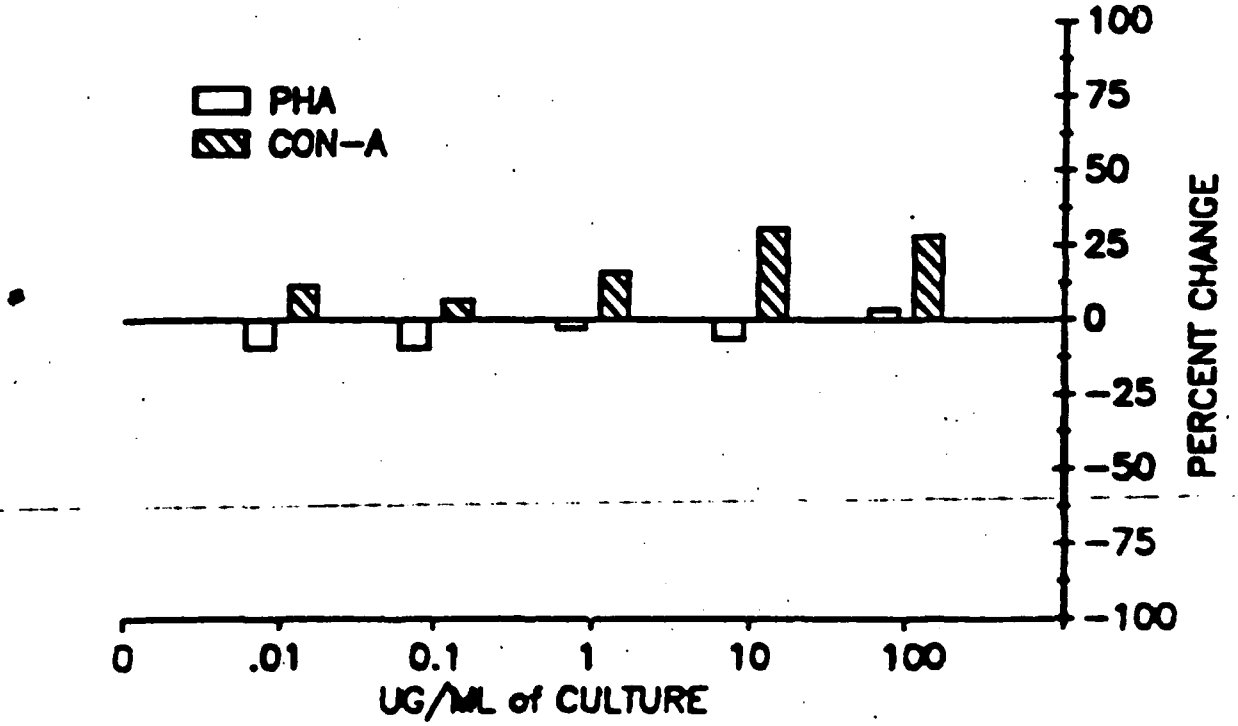
BLASTOGENESIS / AVS – 2880



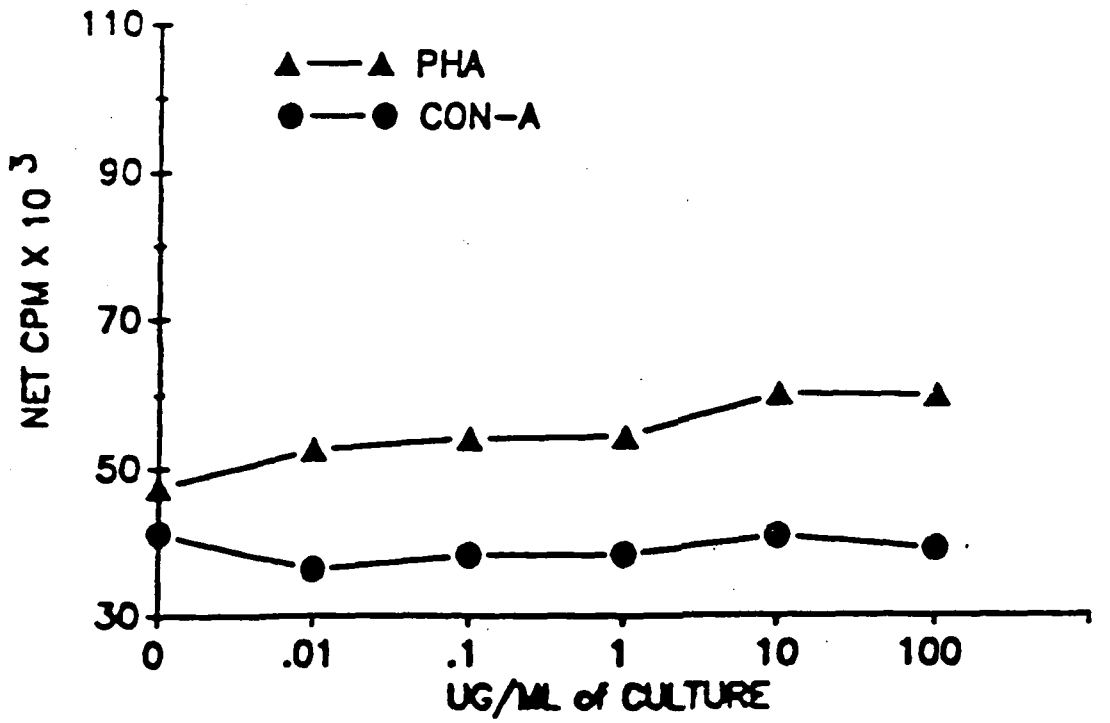


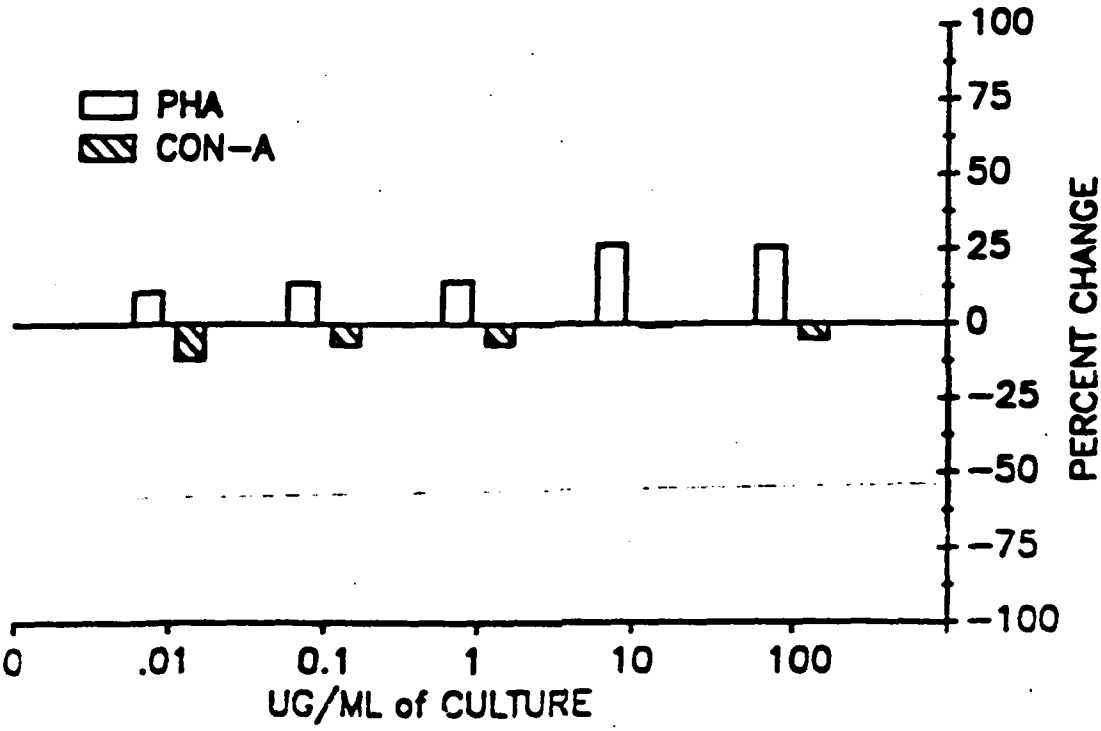
BLASTOGENESIS / AVS – 5015

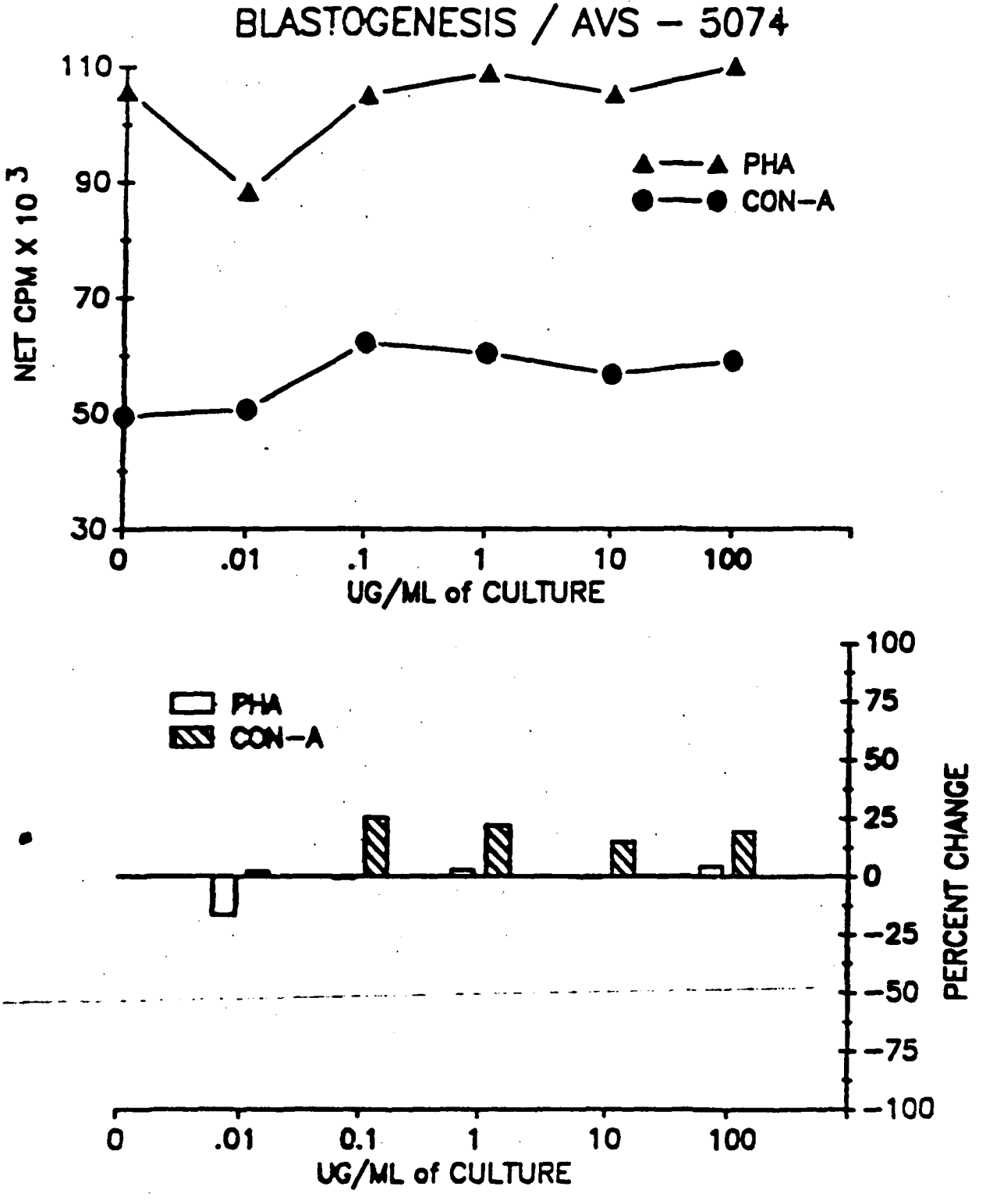




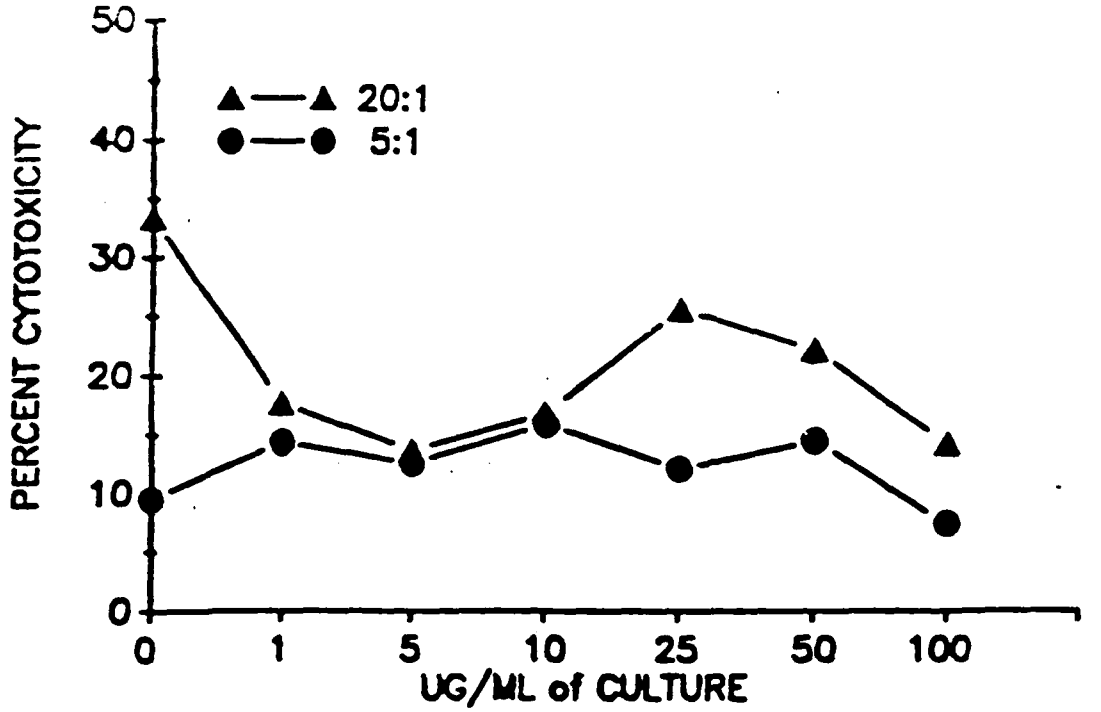
BLASTOGENESIS / AVS – 5026

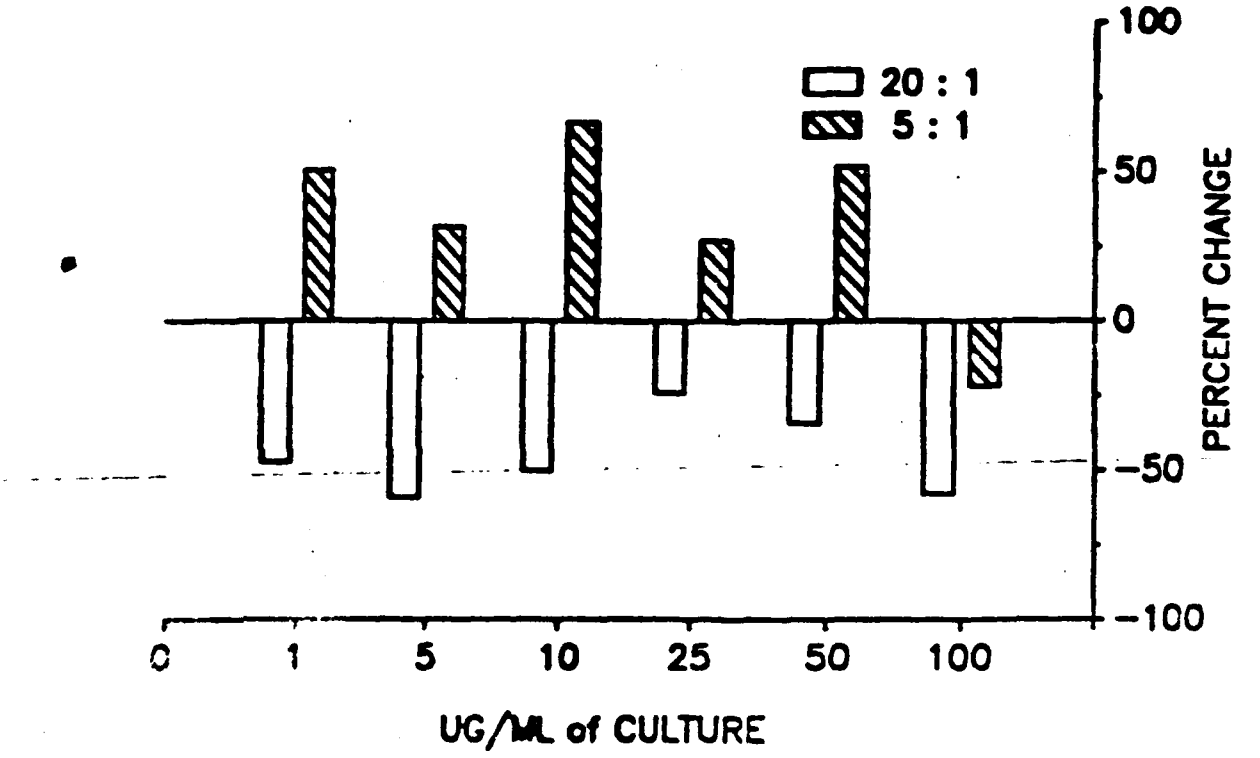




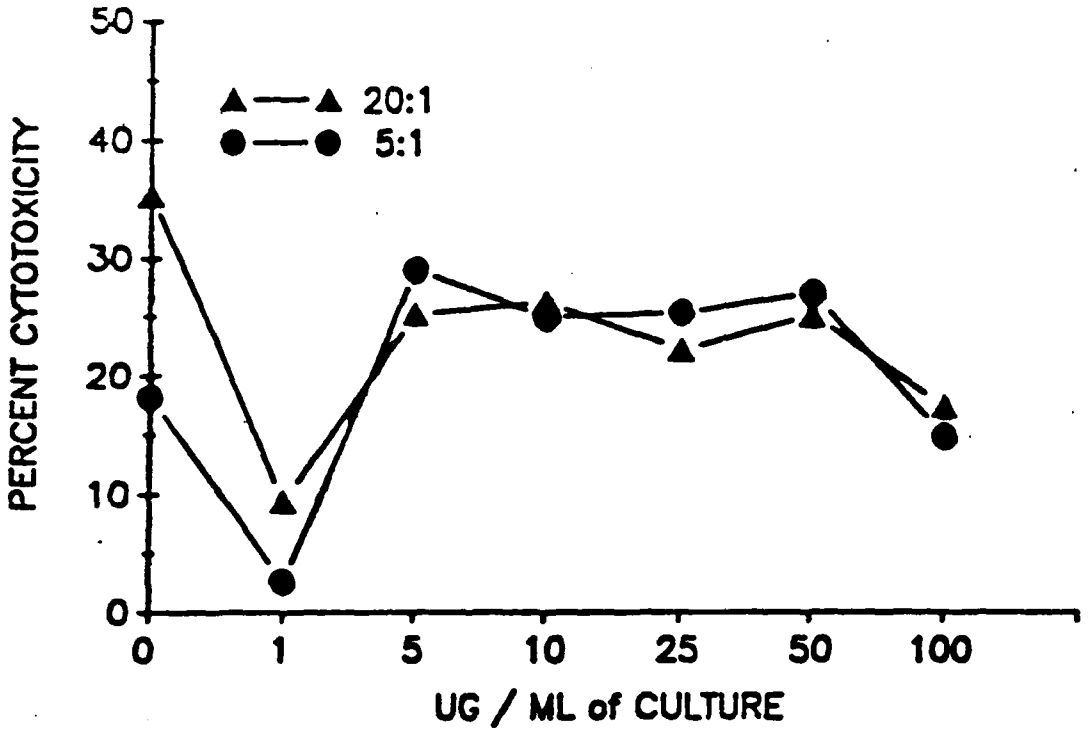

BLASTOGENESIS / AVS – 5074
NET CPM X 10 3
110
90
70
50
30
PHA
CON-A
0
.01
.1
1
10
100
UG/ML of CULTURE
PHA
CON-A
100
75
50
25
0
-25
-50
-75
-100
PERCENT CHANGE
0
.01
0.1
1
10
100
UG/ML of CULTURE

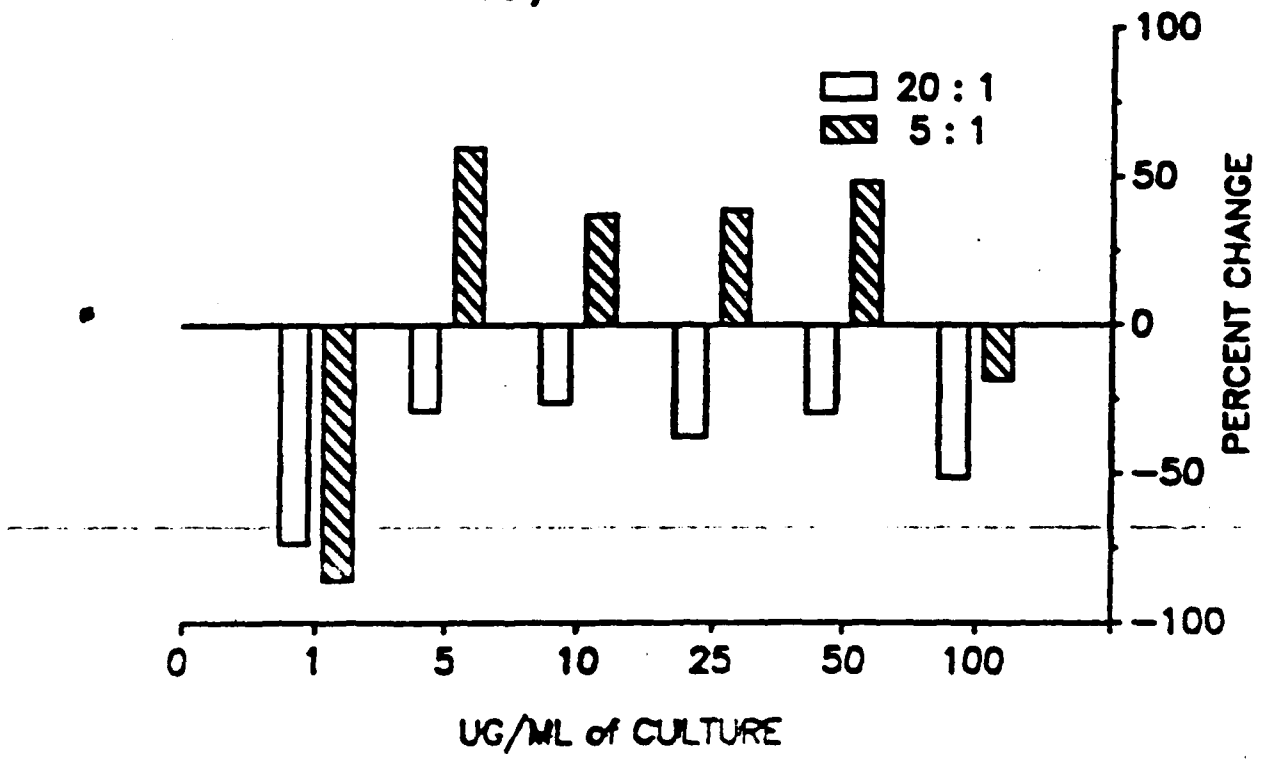
NK ACTIVITY / AVS – 2777



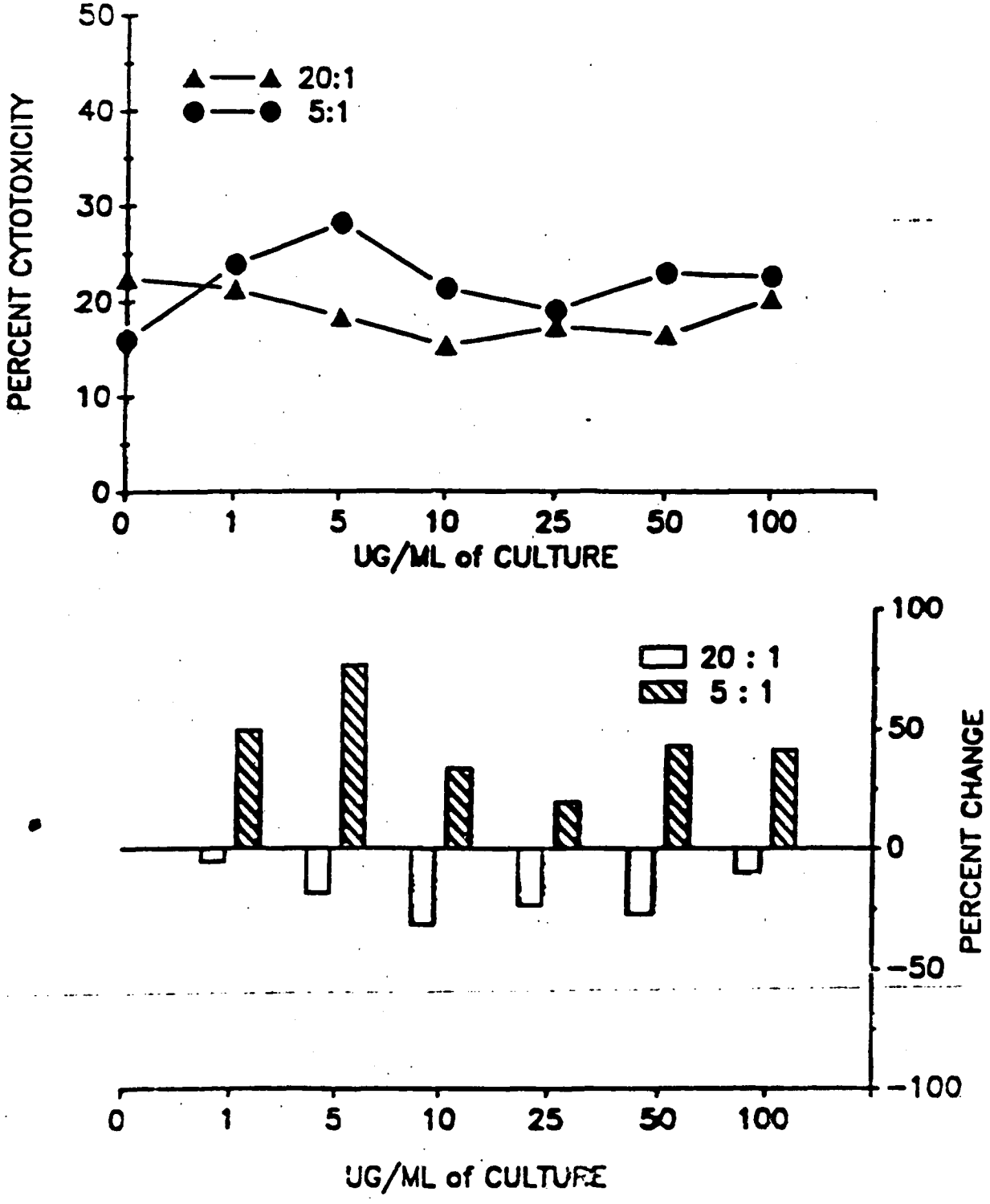


NK ACTIVITY / AVS – 4596

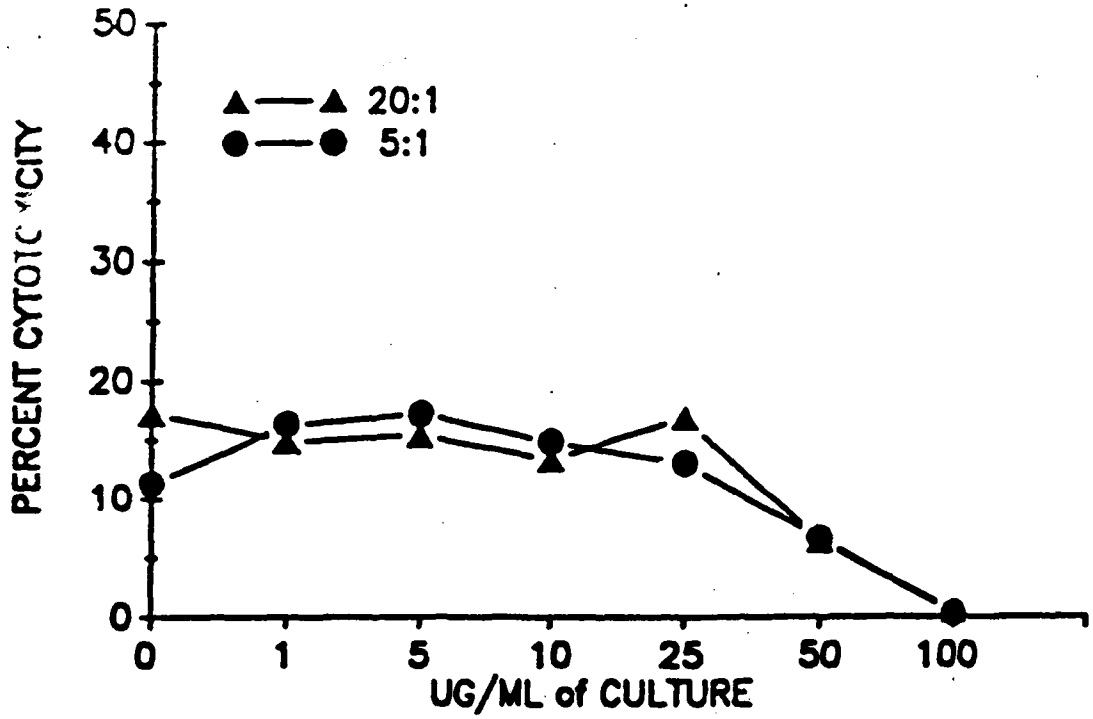


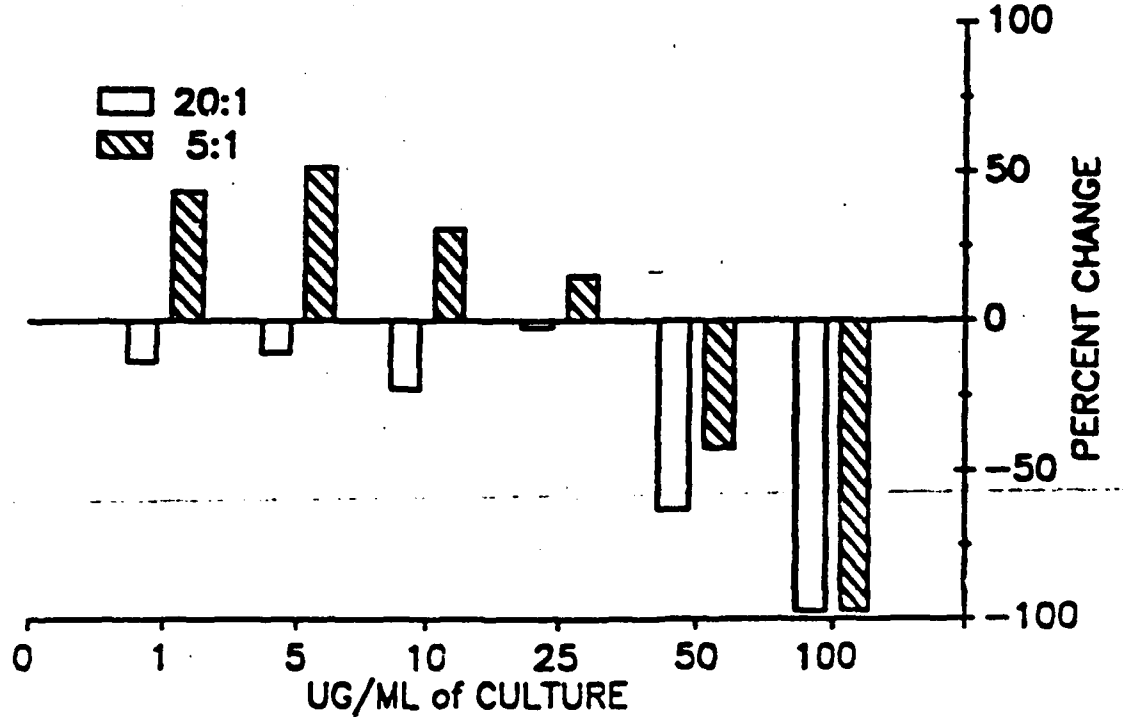


NK ACTIVITY / AVS – 5026

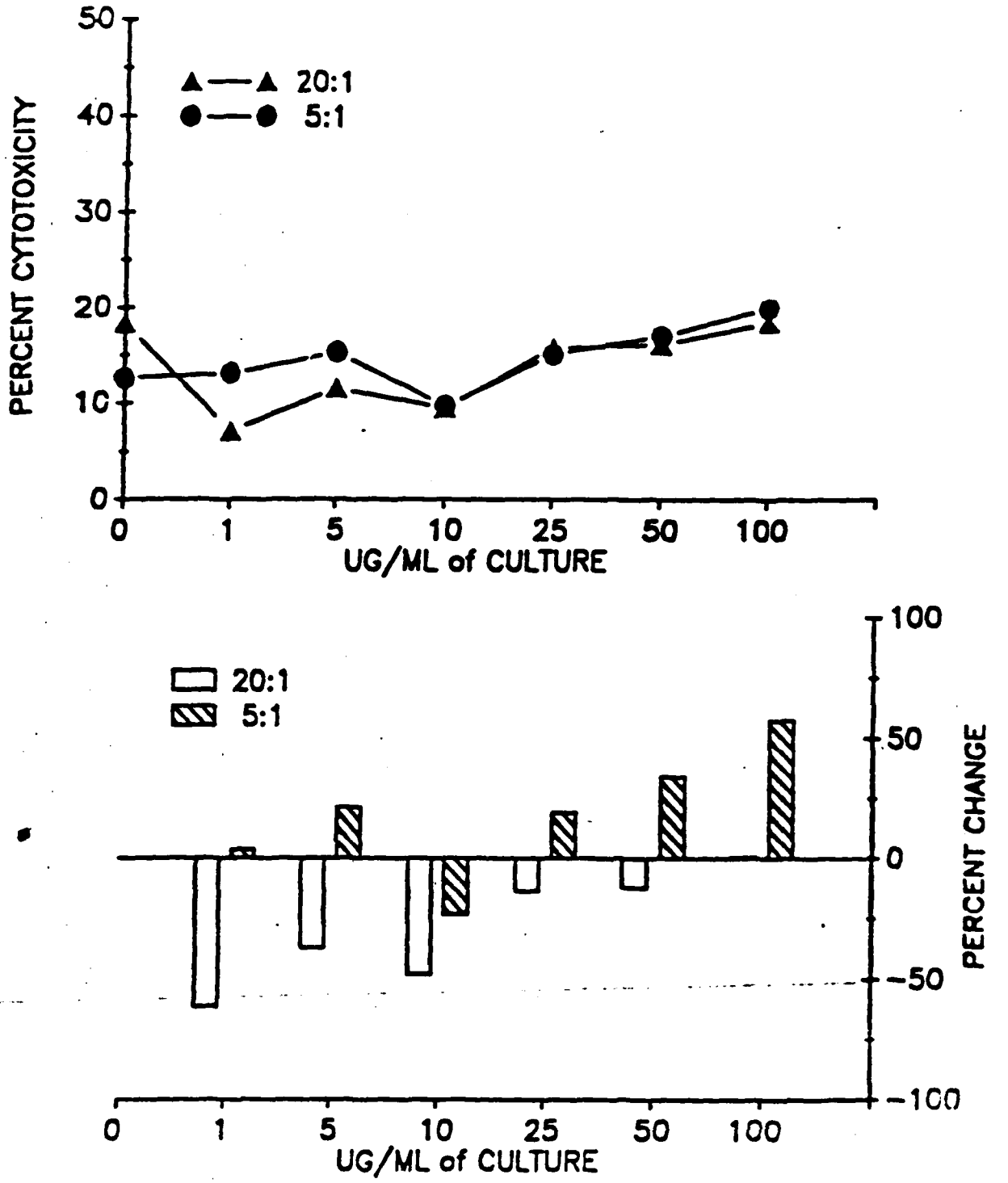


NK ACTIVITY / AVS – 5028



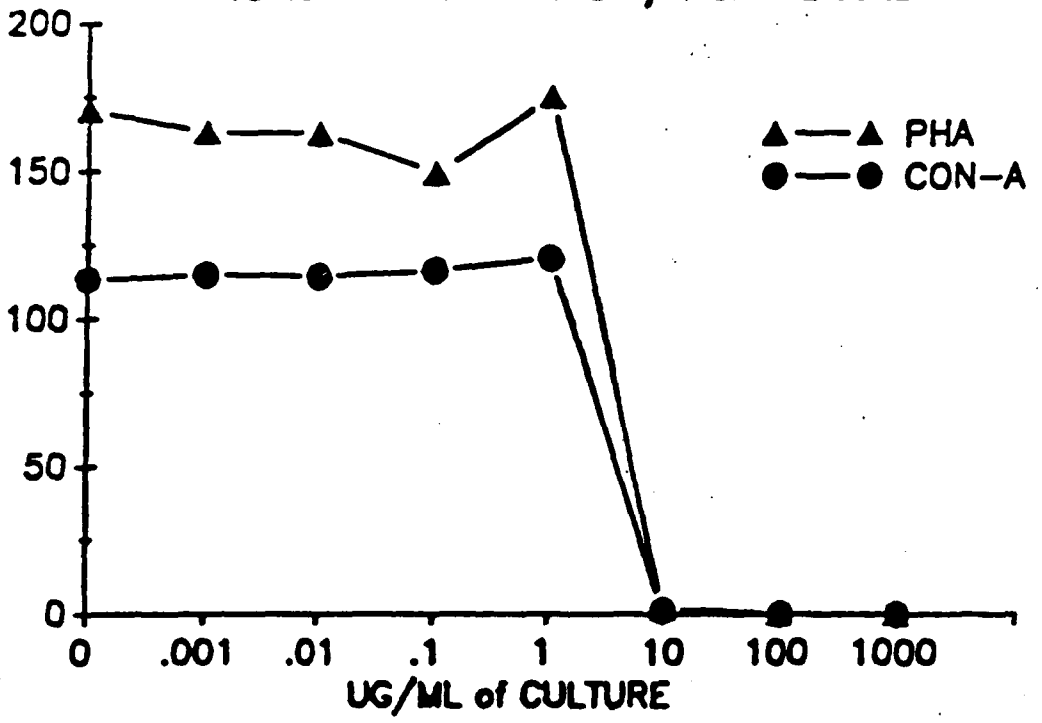


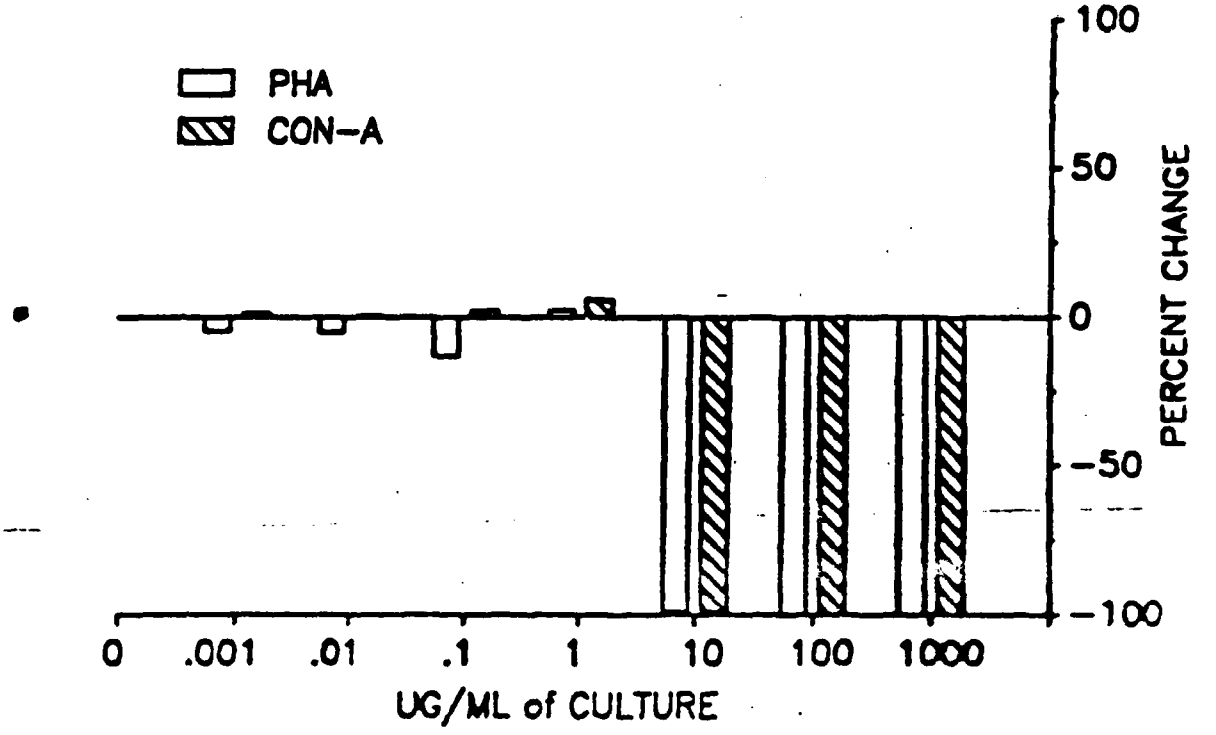
NK ACTIVITY / AVS – 5074



BLASTOGENESIS / AVS – 502?

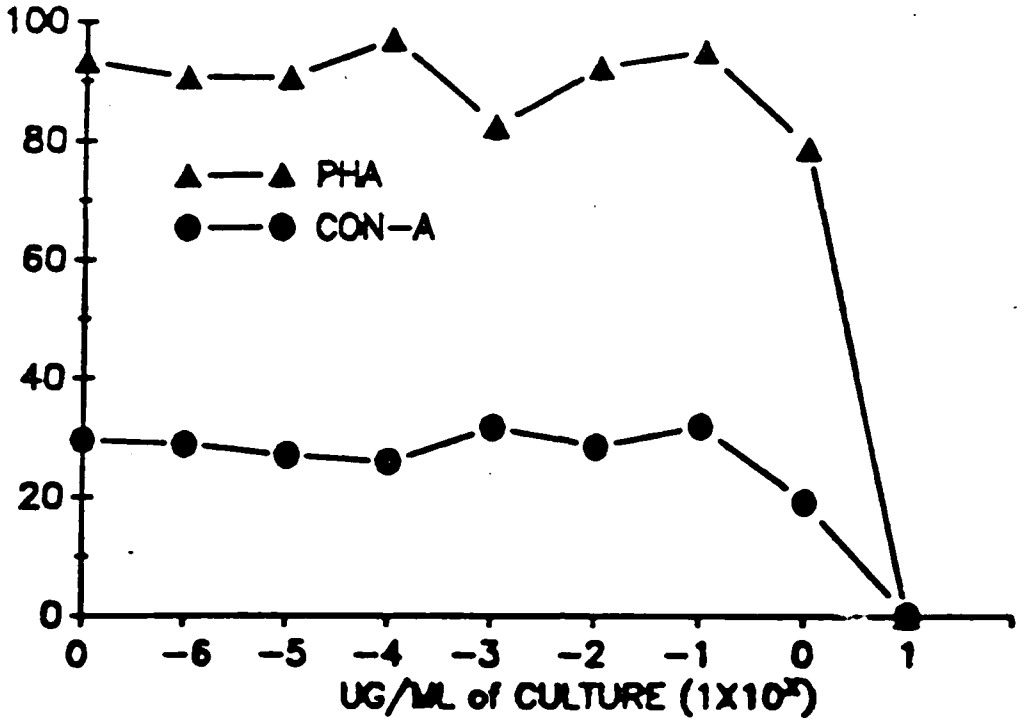
TOXICITY DETERMINATION / NORMAL CELLS

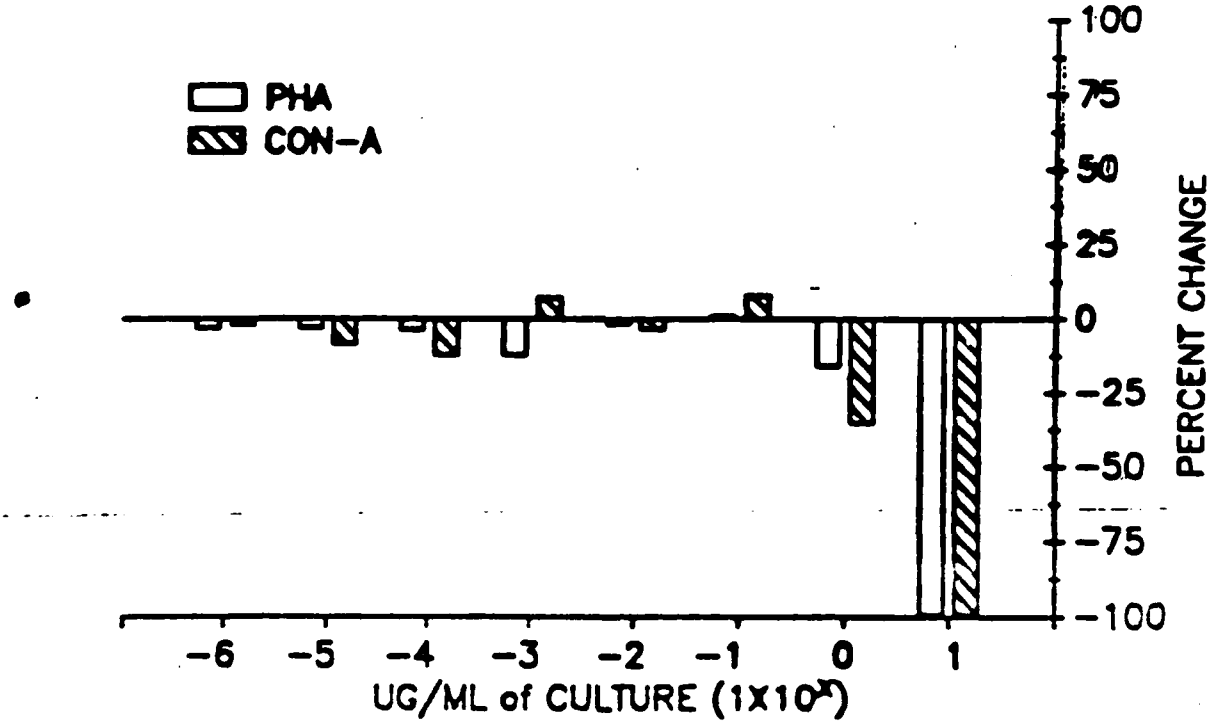


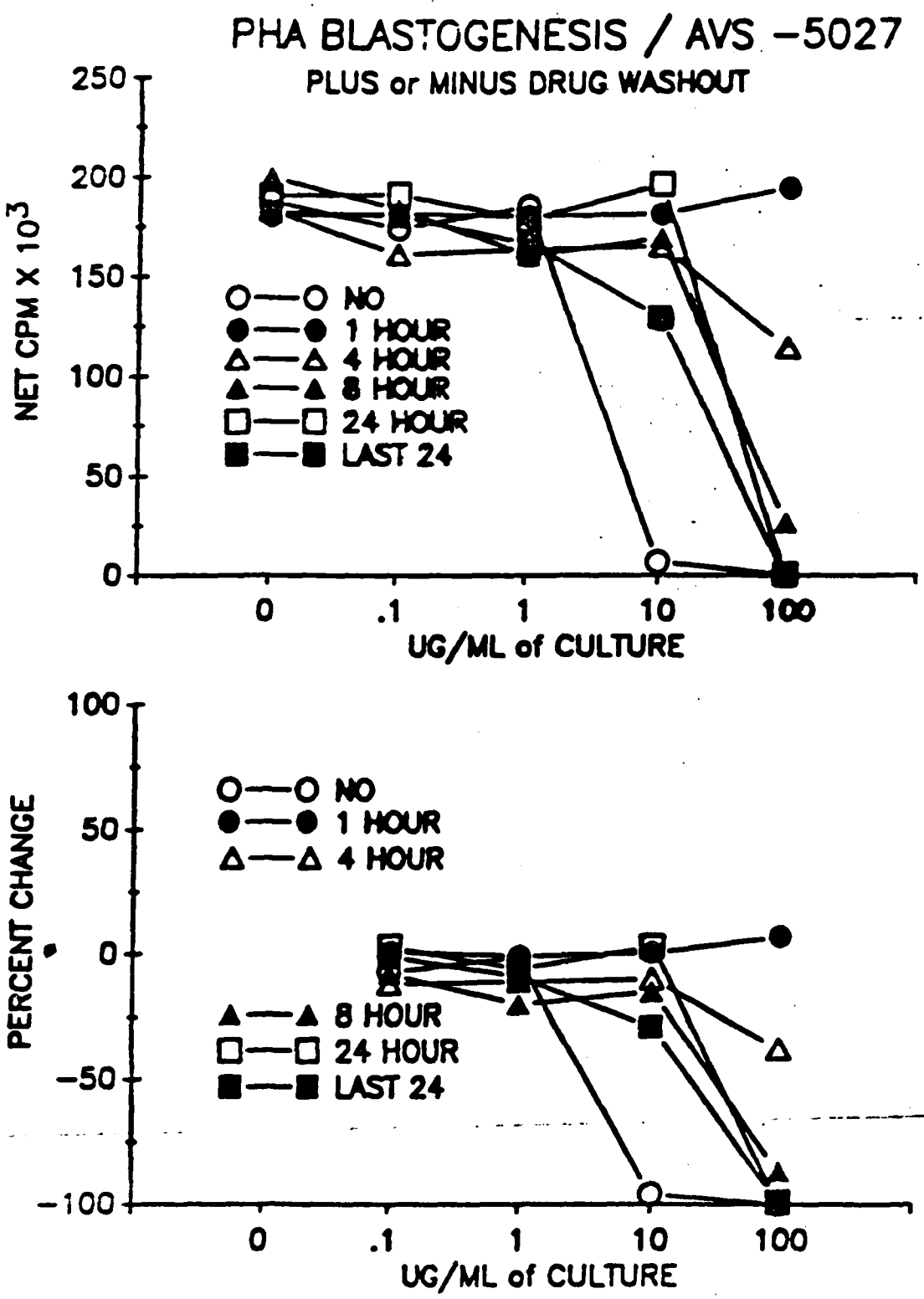


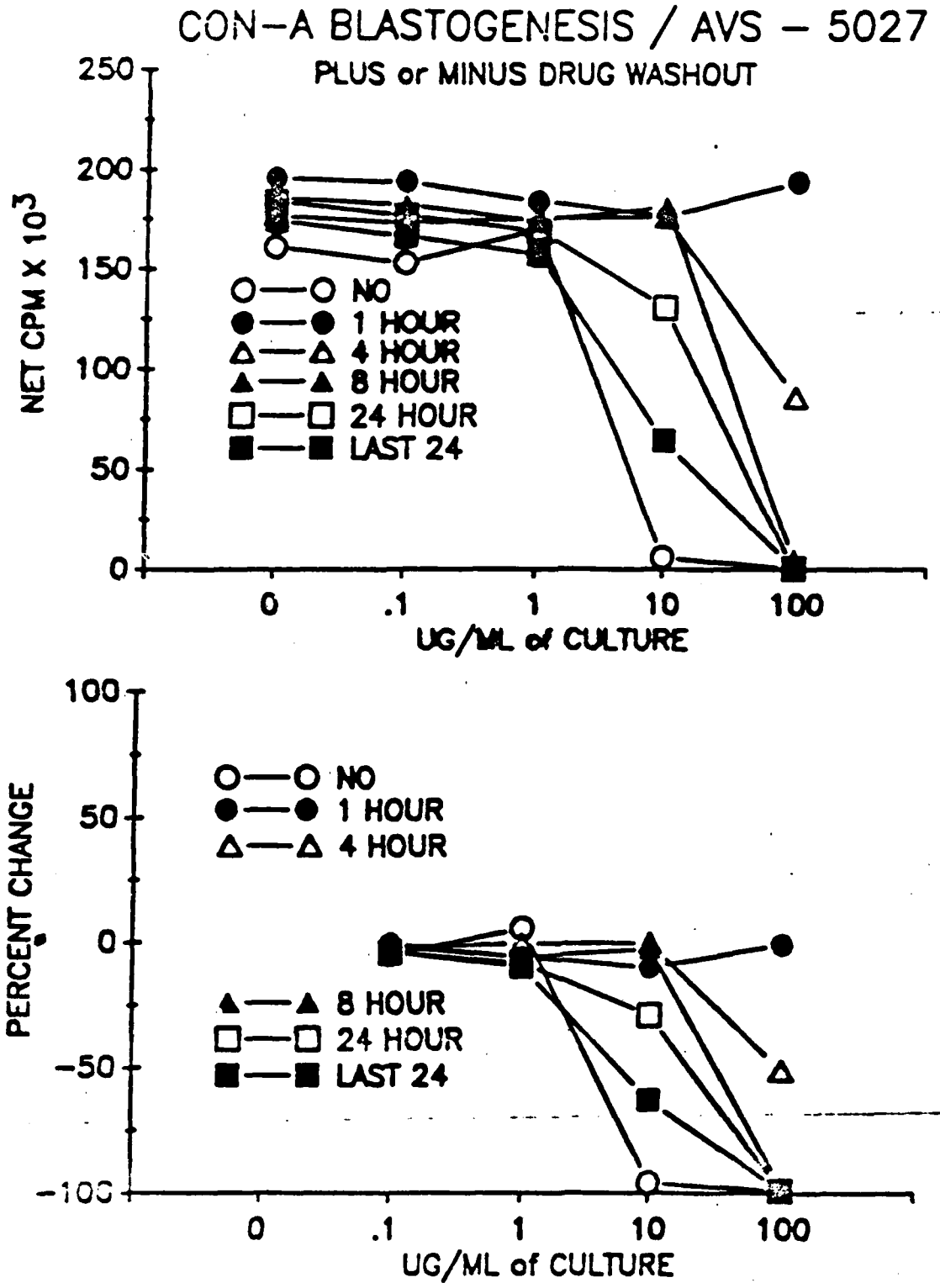
BLASTOGENESIS / AVS – 5027

PATIENT CELLS



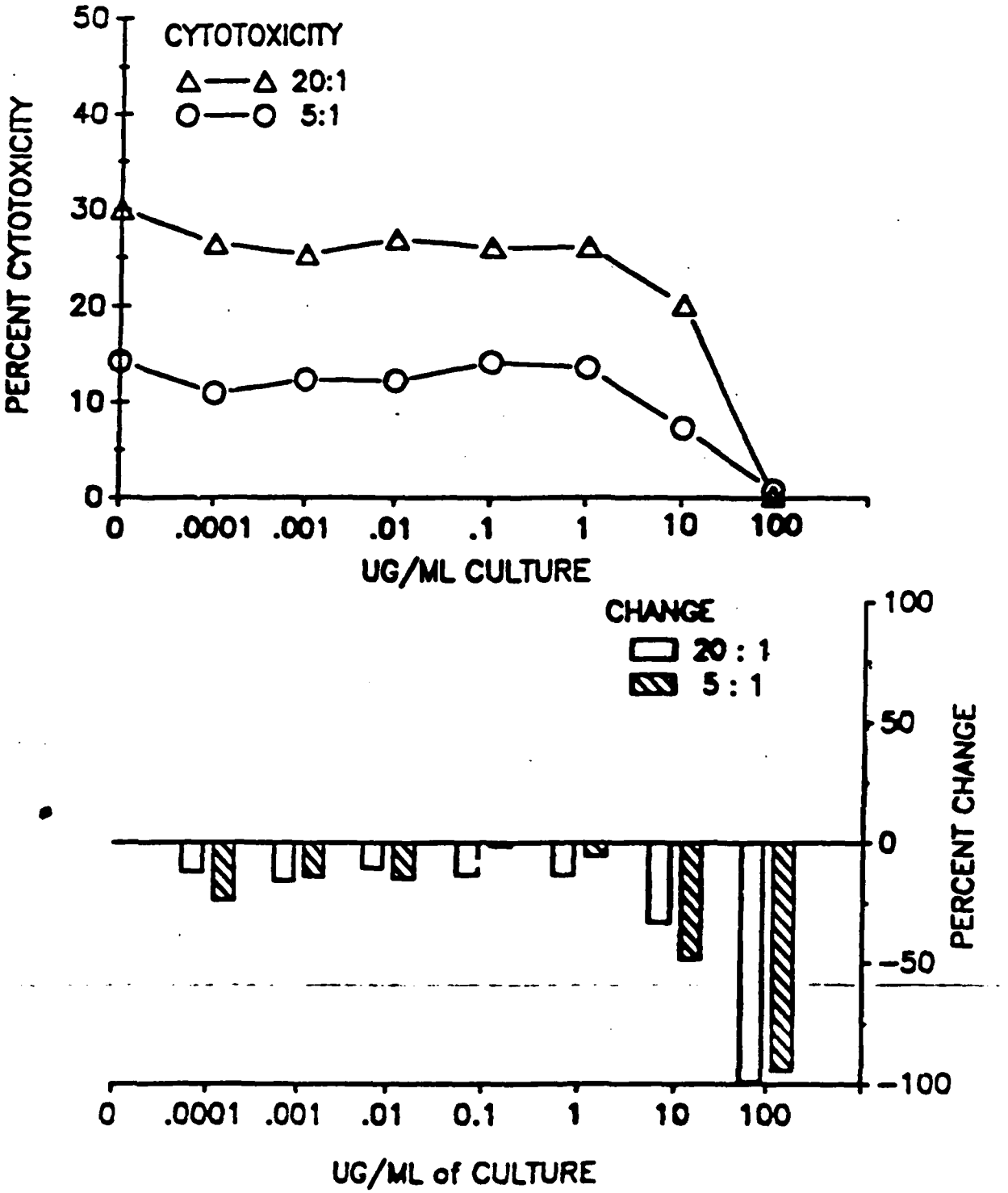



PHA BLASTOGENESIS / AVS -5027
PLUS or MINUS DRUG WASHOUT
NET CPM X 10^3
250
200
150
100
50
0
NO
1 HOUR
4 HOUR
8 HOUR
24 HOUR
LAST 24
0
.1
1
10
100
UG/ML of CULTURE
PERCENT CHANGE
100
50
0
-50
-100
NO
1 HOUR
4 HOUR
8 HOUR
24 HOUR
LAST 24
0
.1
1
10
100
UG/ML of CULTURE


CON-A BLASTOGENESIS / AVS – 5027
PLUS or MINUS DRUG WASHOUT
NET CPM X 10^3
250
200
150
100
50
0
NO
1 HOUR
4 HOUR
8 HOUR
24 HOUR
LAST 24
0
.1
1
10
100
UG/ML of CULTURE
PERCENT CHANGE
100
50
0
-50
-100
NO
1 HOUR
4 HOUR
8 HOUR
24 HOUR
LAST 24
0
.1
1
10
100
UG/ML of CULTURE

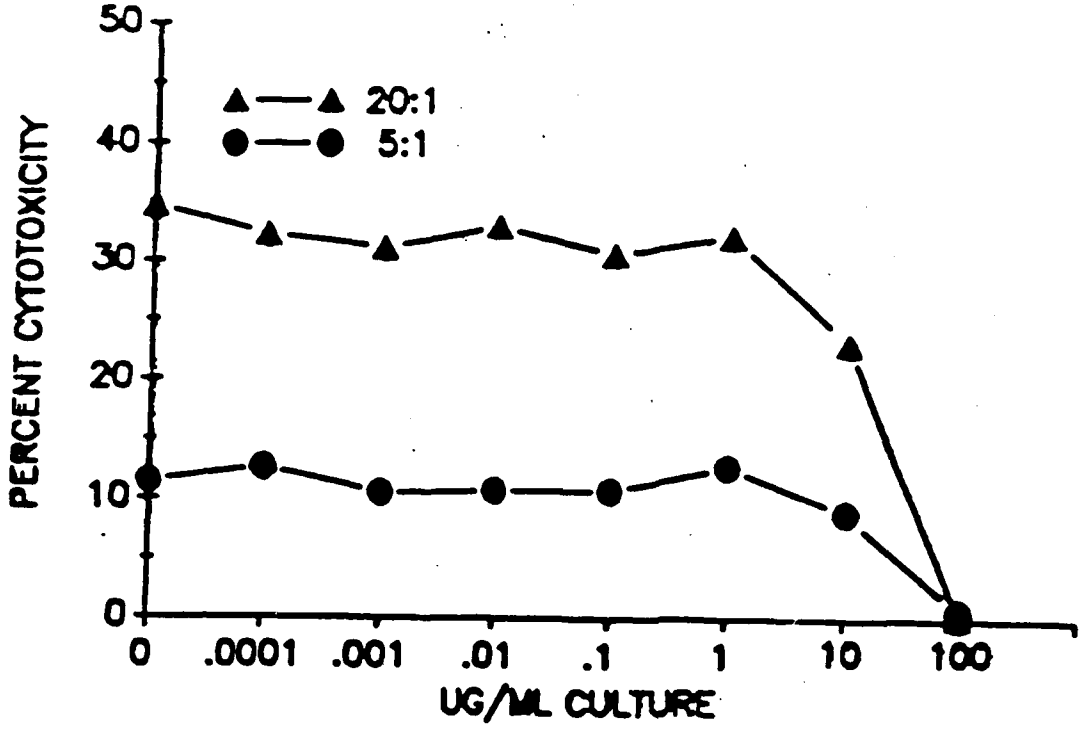
NK ACTIVITY / AVS – 5027

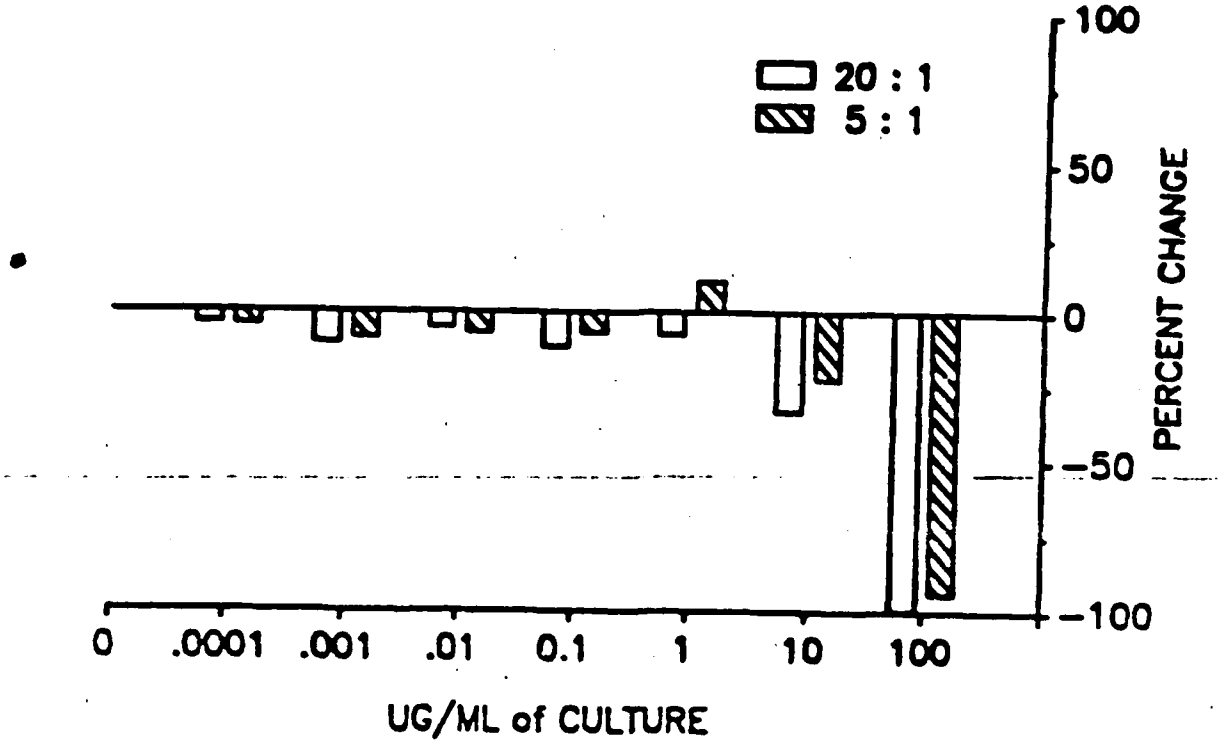
NORMAL CELLS



NK ACTIVITY / AIDS - 5027

PATIENT CELLS





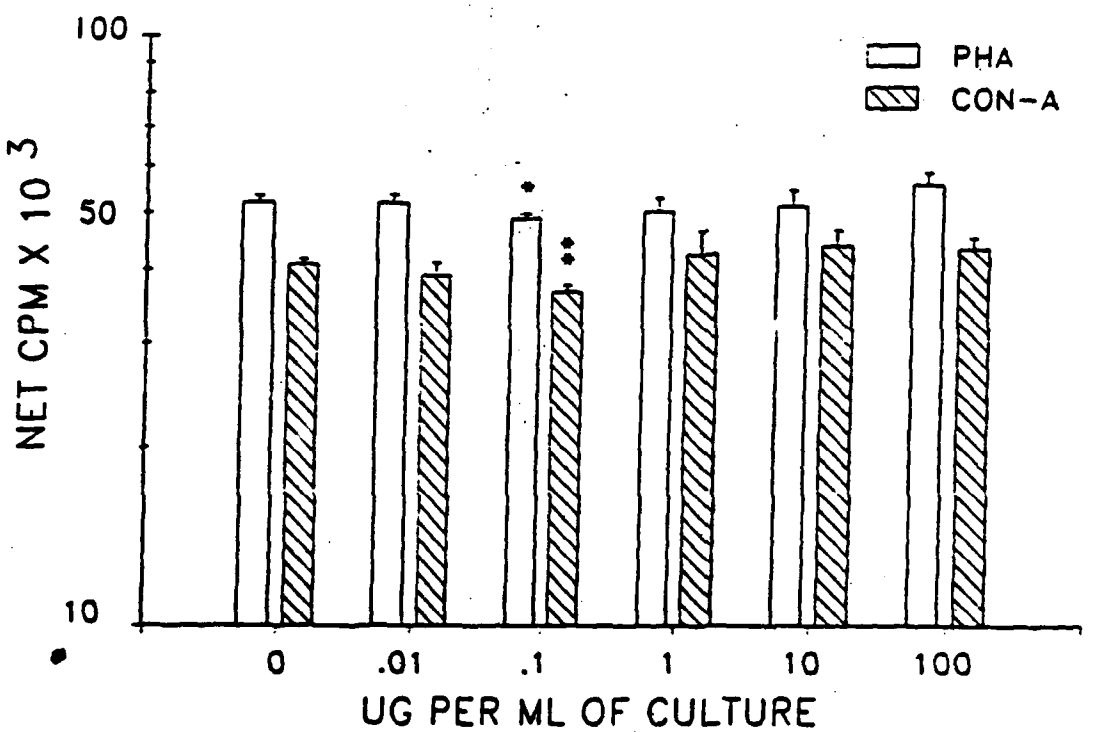
APPENDIX: 1989-90 Study Data

COOPERATIVE AGREEMENT NO: DAMD17-88-H-8004

TITLE: IMMUNOLOGICAL STUDIES OF ANTI-AIDS DRUGS IN ARC/AIDS

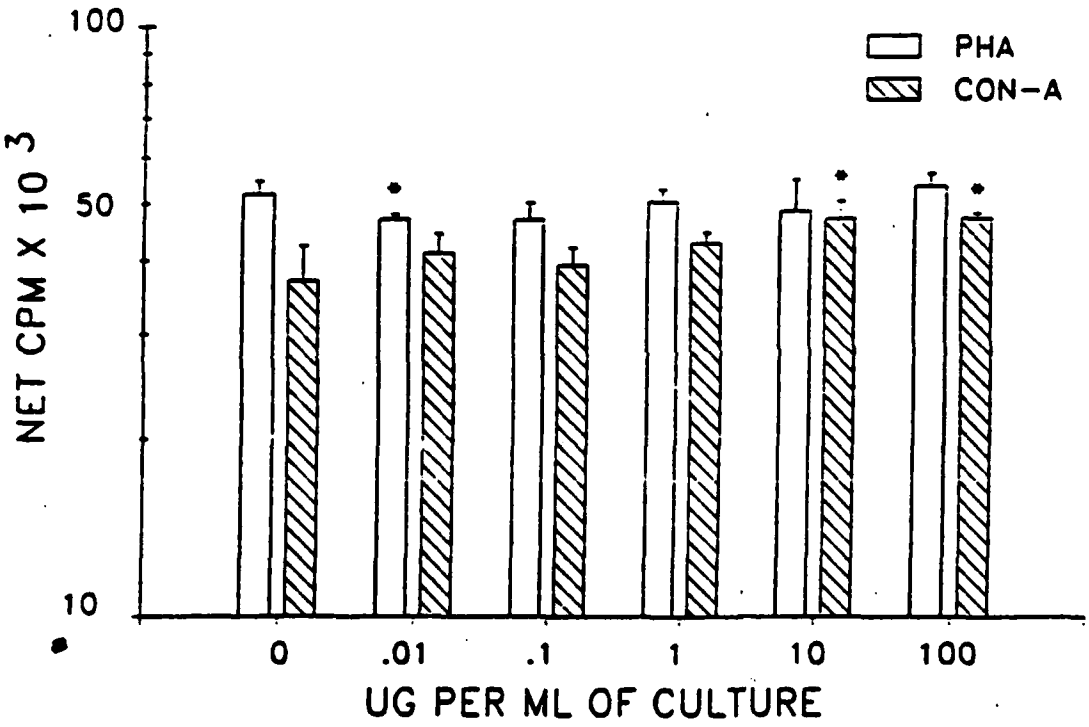
Evan M. Hersh, M.D.
Principal Investigator

TOXICITY DETERMINATIONS
AVS-5014



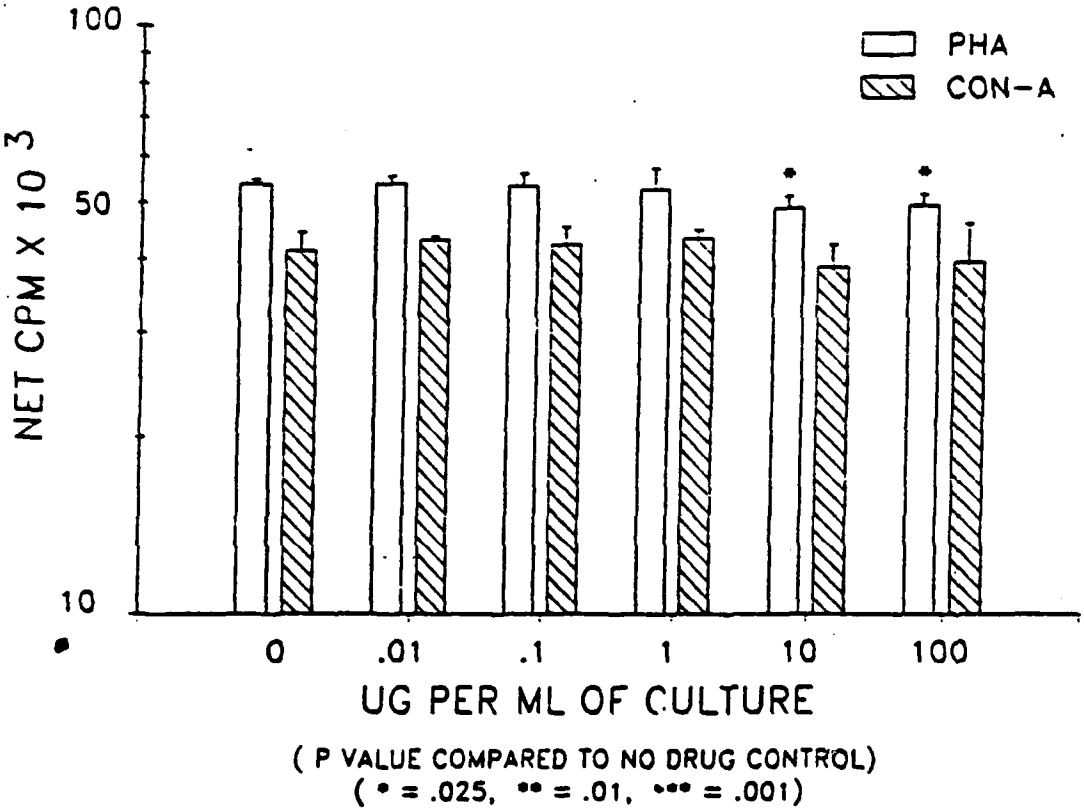
(P VALUE COMPARED TO NO DRUG CONTROL)
(* = .025, ** = .01, *** = .001)

TOXICITY DETERMINATIONS
AVS-5015



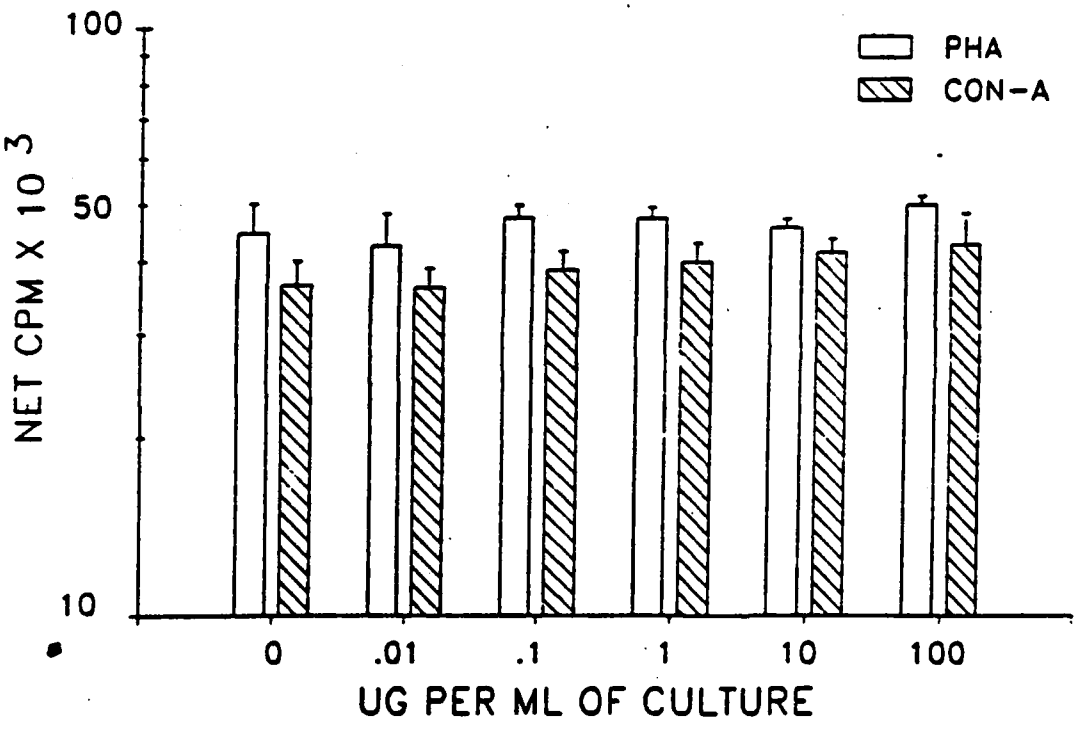
(P VALUE COMPARED TO NO DRUG CONTROL)
(* = .025, ** = .01, *** = .001)

TOXICITY DETERMINATIONS
AVS-5016



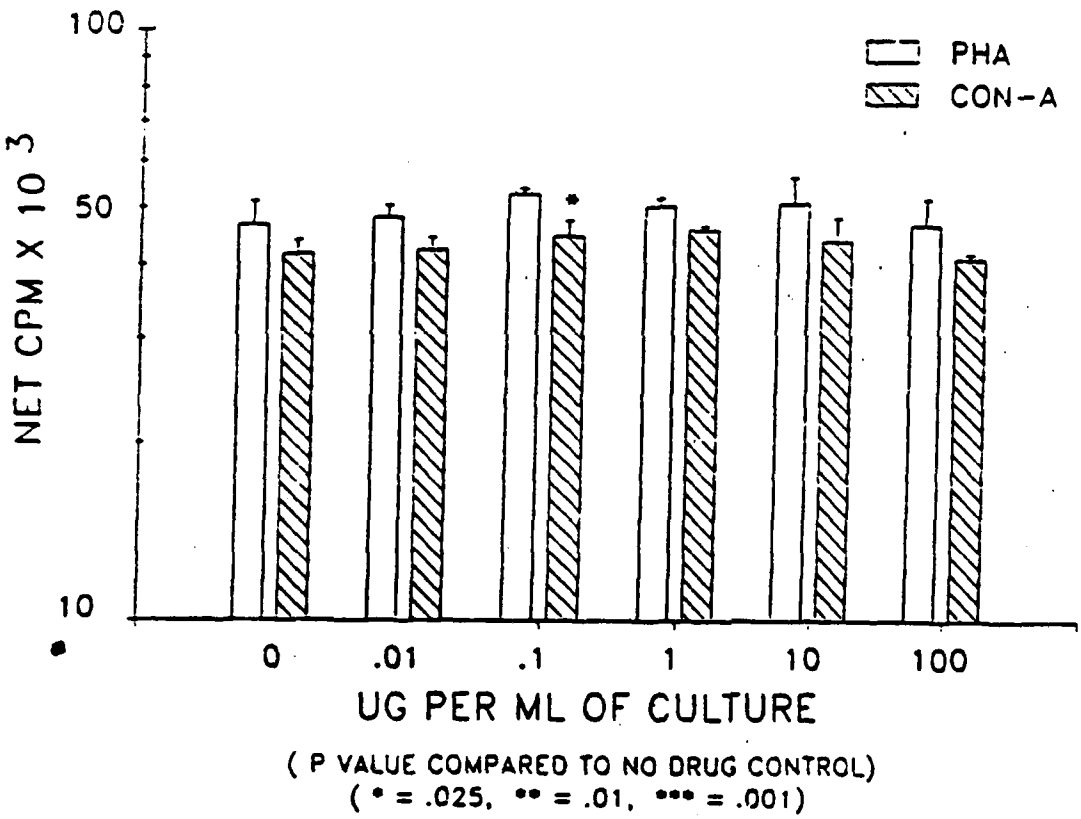
(P VALUE COMPARED TO NO DRUG CONTROL)
(* = .025, ** = .01, *** = .001)

TOXICITY DETERMINATIONS
AVS–5017



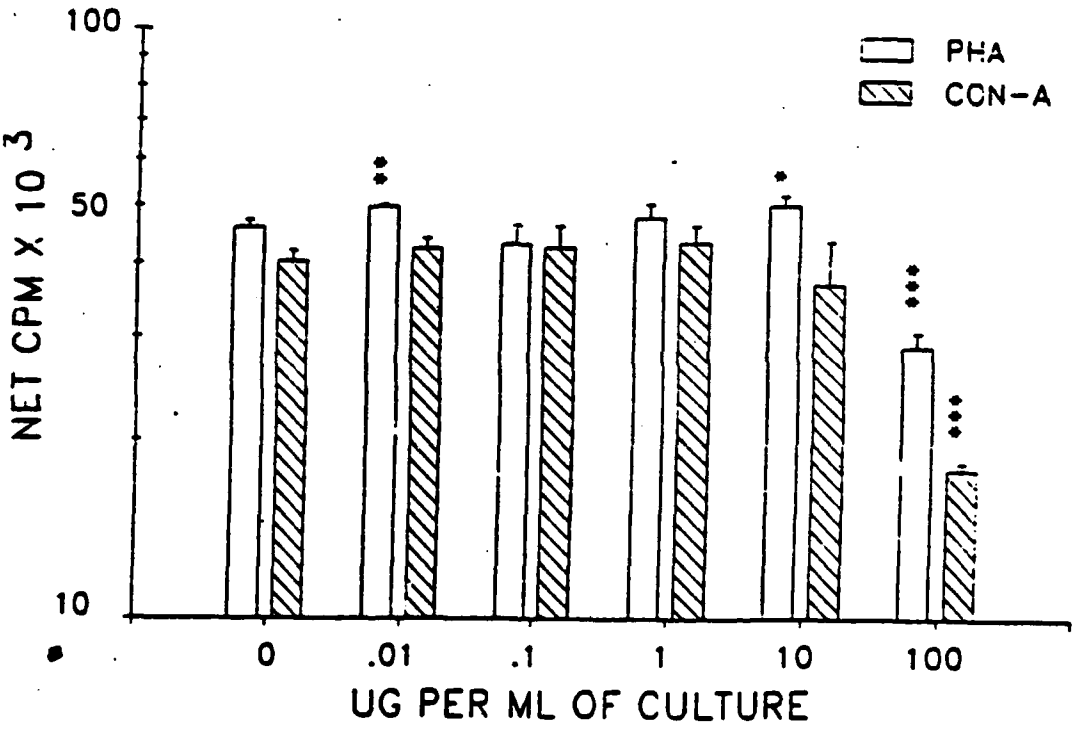
(P VALUE COMPARED TO NO DRUG CONTROL)
(* = .025, ** = .01, *** = .001)

TOXICITY DETERMINATIONS
AVS-5018



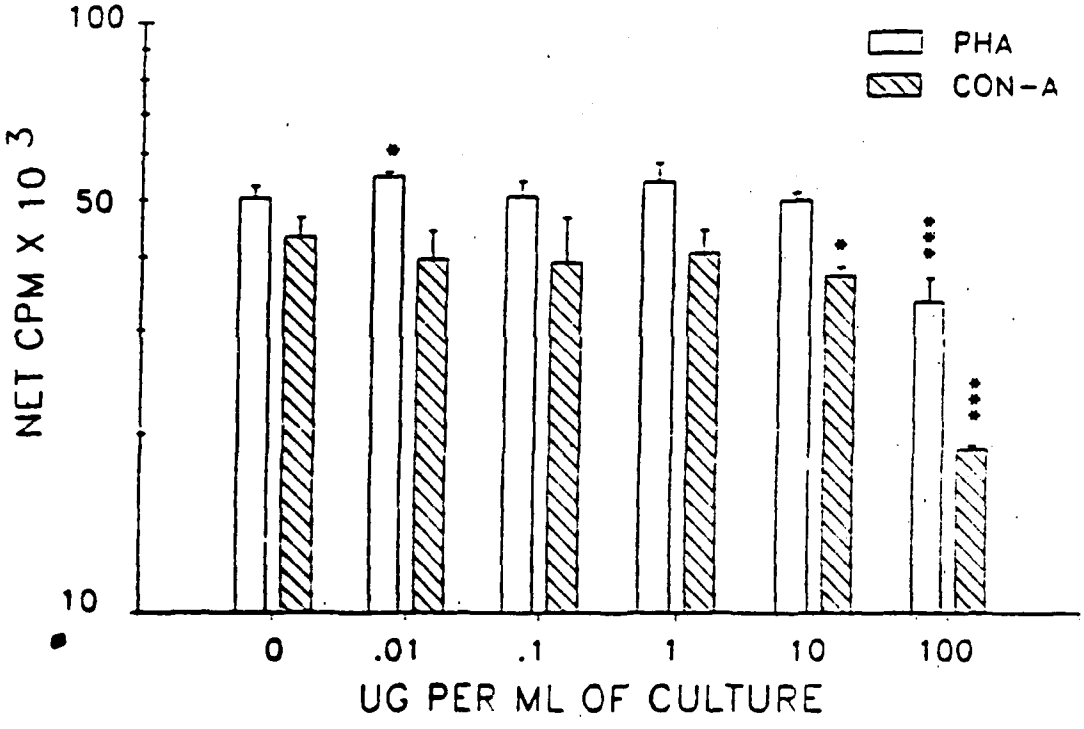
(P VALUE COMPARED TO NO DRUG CONTROL)
(* = .025, ** = .01, *** = .001)

TOXICITY DETERMINATIONS
AVS-5019



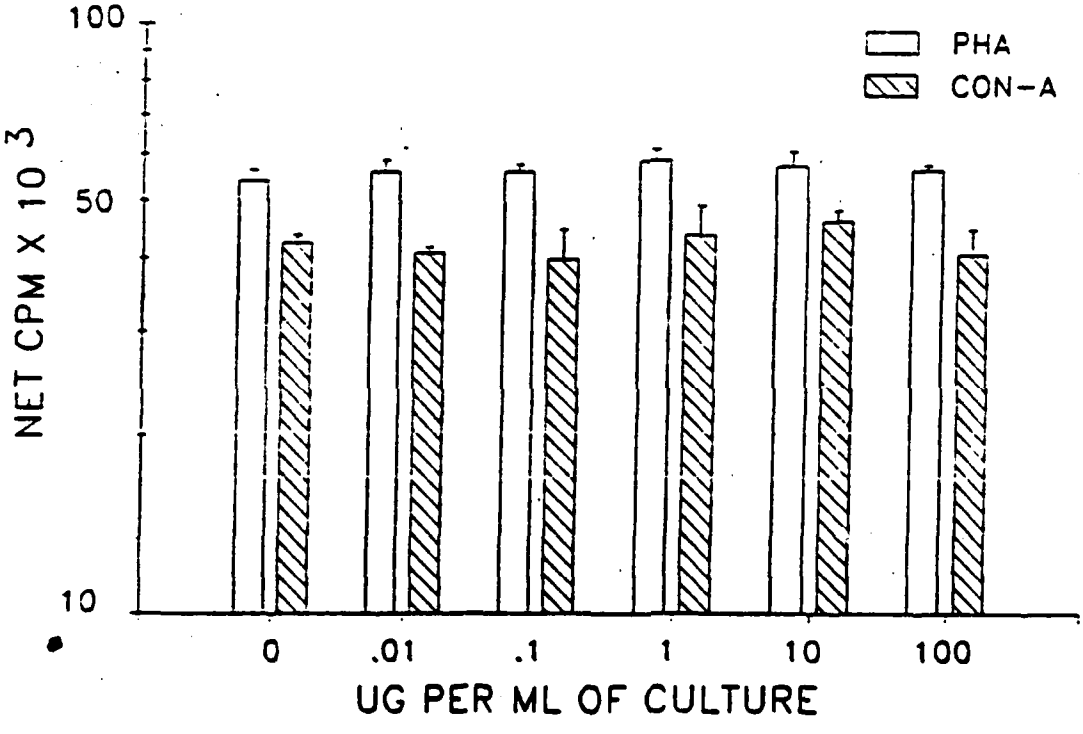
(P VALUE COMPARED TO NO DRUG CONTROL)
(* = .025, ** = .01, *** = .001)

TOXICITY DETERMINATIONS
AVS-5020



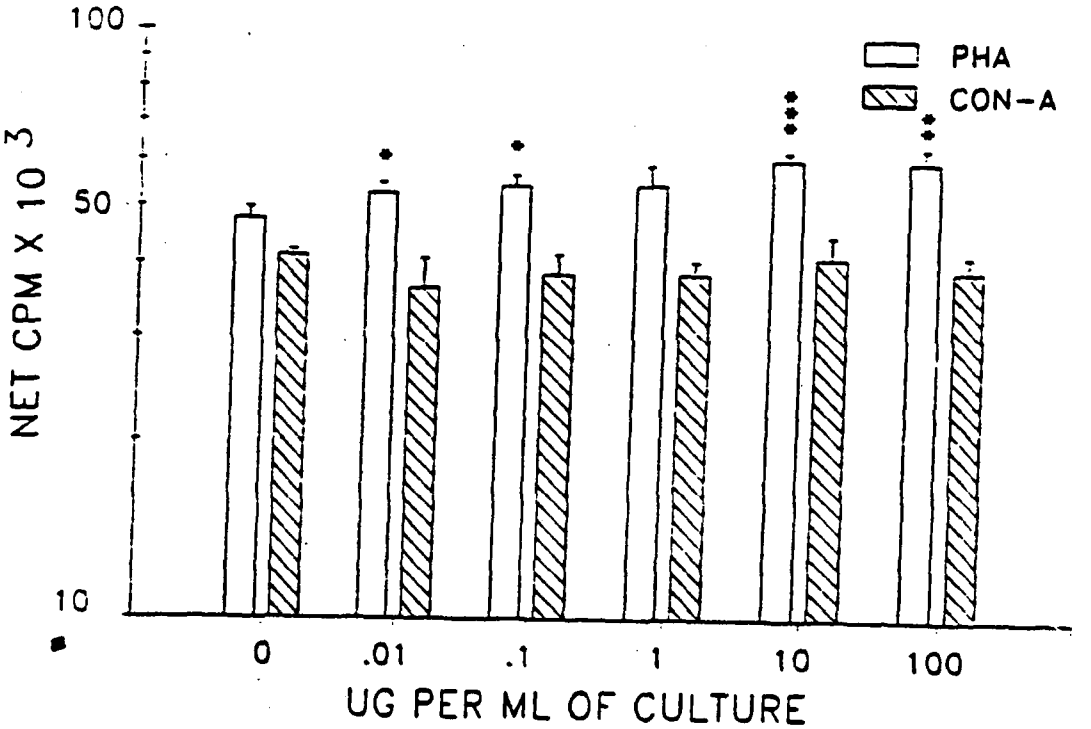
(P VALUE COMPARED TO NO DRUG CONTROL)
(* = .025, ** = .01, *** = .001)

TOXICITY DETERMINATIONS
AVS-5025



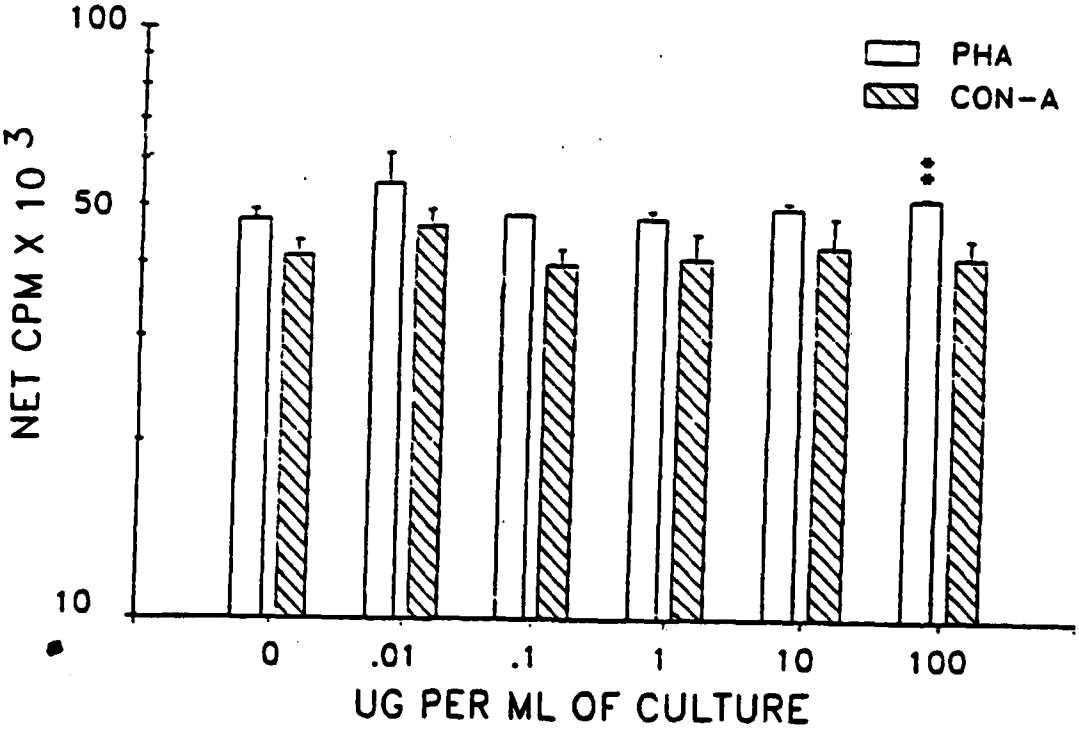
(P VALUE COMPARED TO NO DRUG CONTROL)
(* = .025, ** = .01, *** = .001)

TOXICITY DETERMINATIONS
AVS–5026



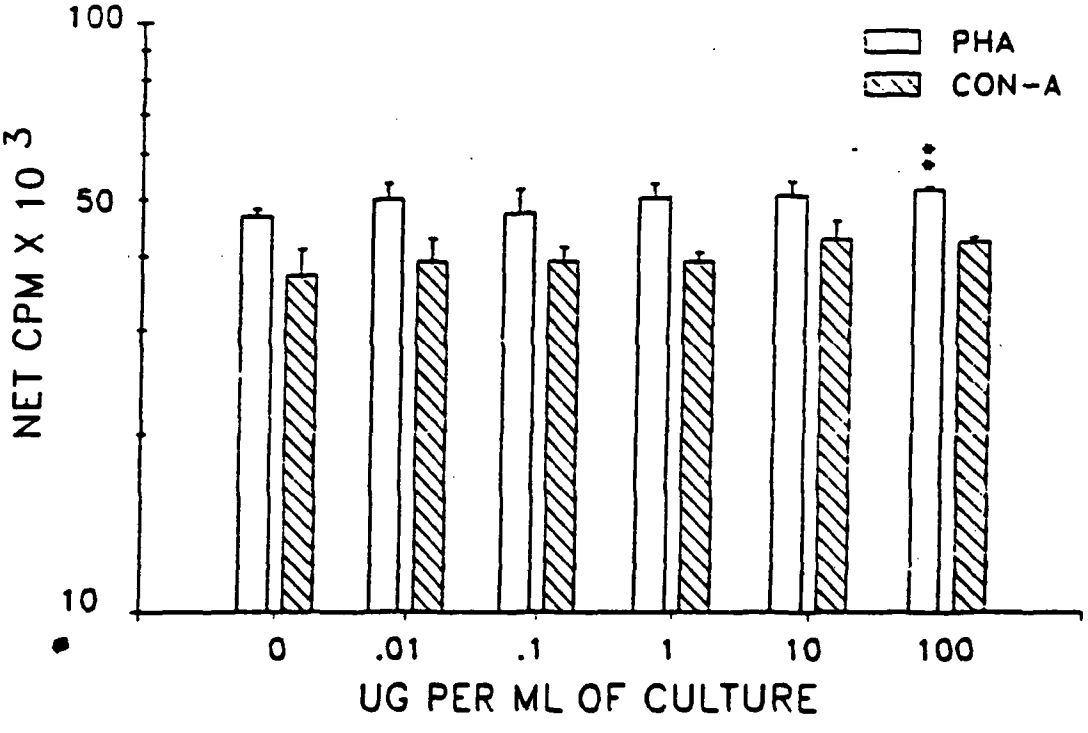
(P VALUE COMPARED TO NO DRUG CONTROL)
(* = .025, ** = .01, *** = .001)

TOXICITY DETERMINATIONS
AVS-5073



(P VALUE COMPARED TO NO DRUG CONTROL)
(* = .025, ** = .01, *** = .001)

TOXICITY DETERMINATIONS
AVS-5074

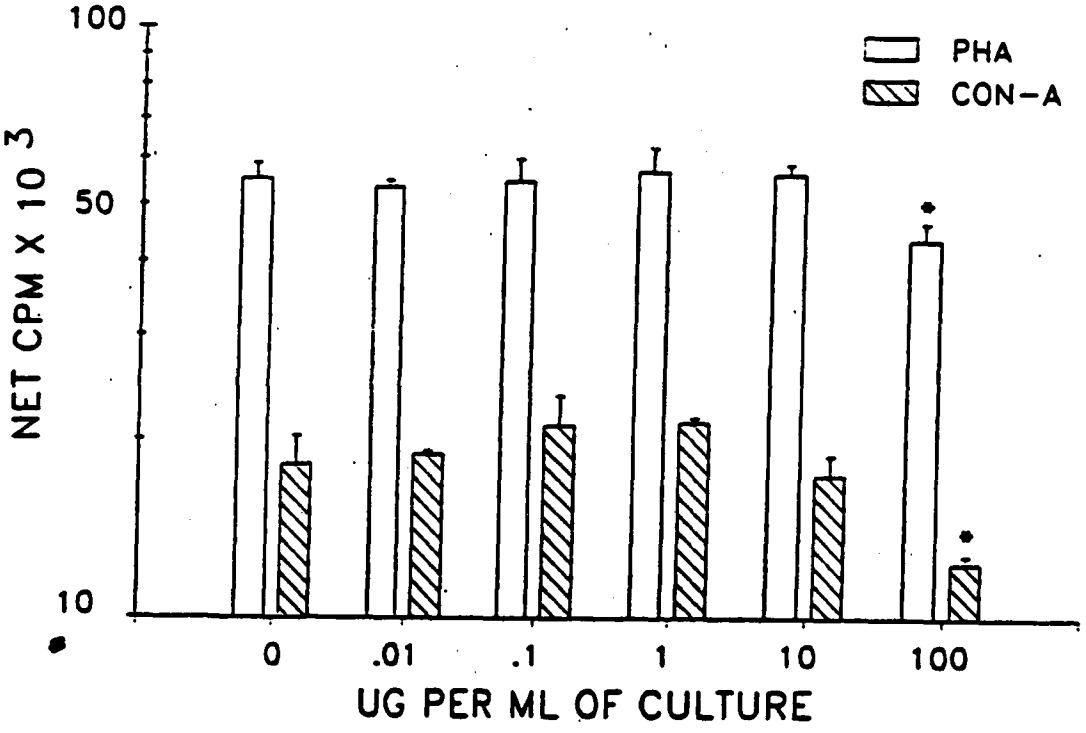


(P VALUE COMPARED TO NO DRUG CONTROL)
(* = .025, ** = .01, *** = .001)

LYMPHOCYTE BLASTOGENIC RESPONSE

HIV^{+} DONOR CELLS CO-CULTURED WITH

AVS-5020



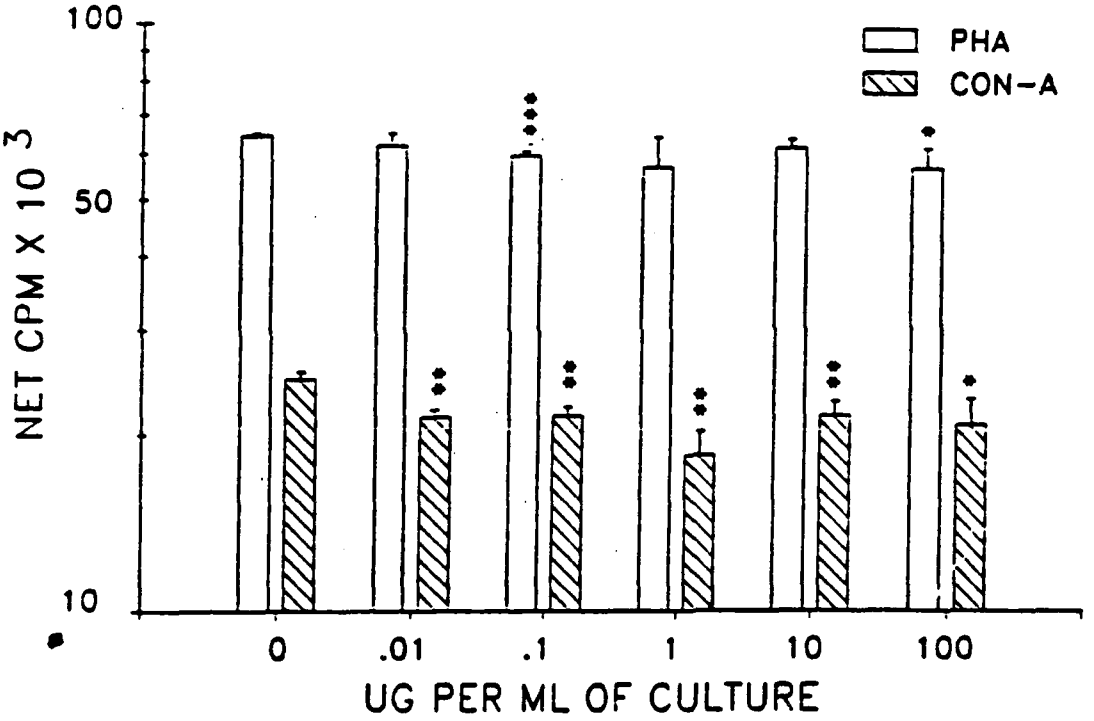
(P VALUE COMPARED TO NO DRUG CONTROL)

(• = .025, •• = .01, ••• = .001)

LYMPHOCYTE BLASTOGENIC RESPONSE

HIV$^+$ DONOR CELLS CO-CULTURED WITH

AVS-5073



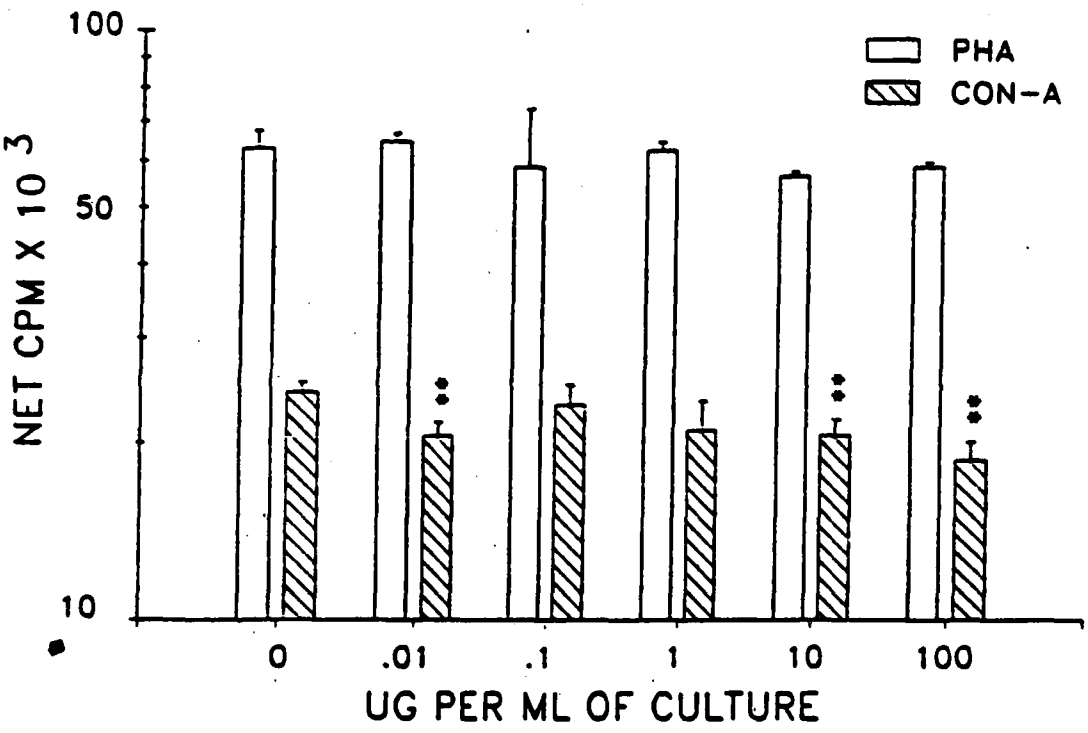
(P VALUE COMPARED TO NO DRUG CONTROL)

(* = .025, ** = .01, *** = .001)

LYMPHOCYTE BLASTOGENIC RESPONSE

HIV$^+$ DONOR CELLS CO--CULTURED WITH

AVS–5074



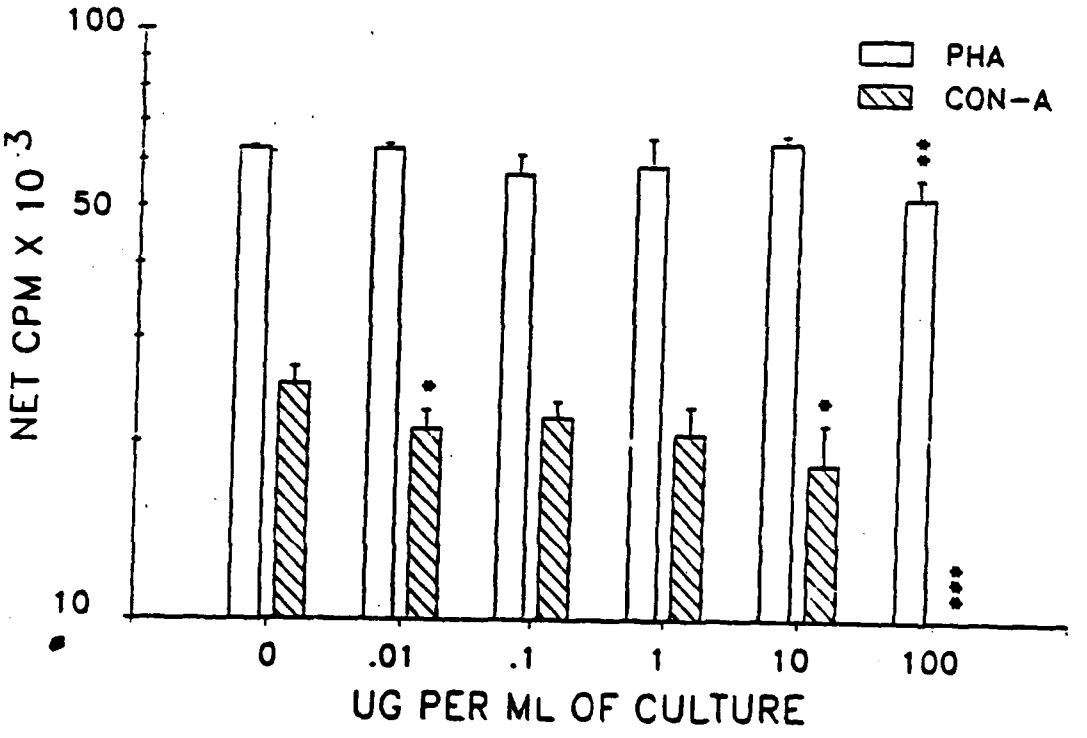
(P VALUE COMPARED TO NO DRUG CONTROL)

(* = .025, ** = .01, *** = .001)

LYMPHOCYTE BLASTOGENIC RESPONSE

HIV$^+$ DONOR CELLS CO-CULTURED WITH

AVS-5019

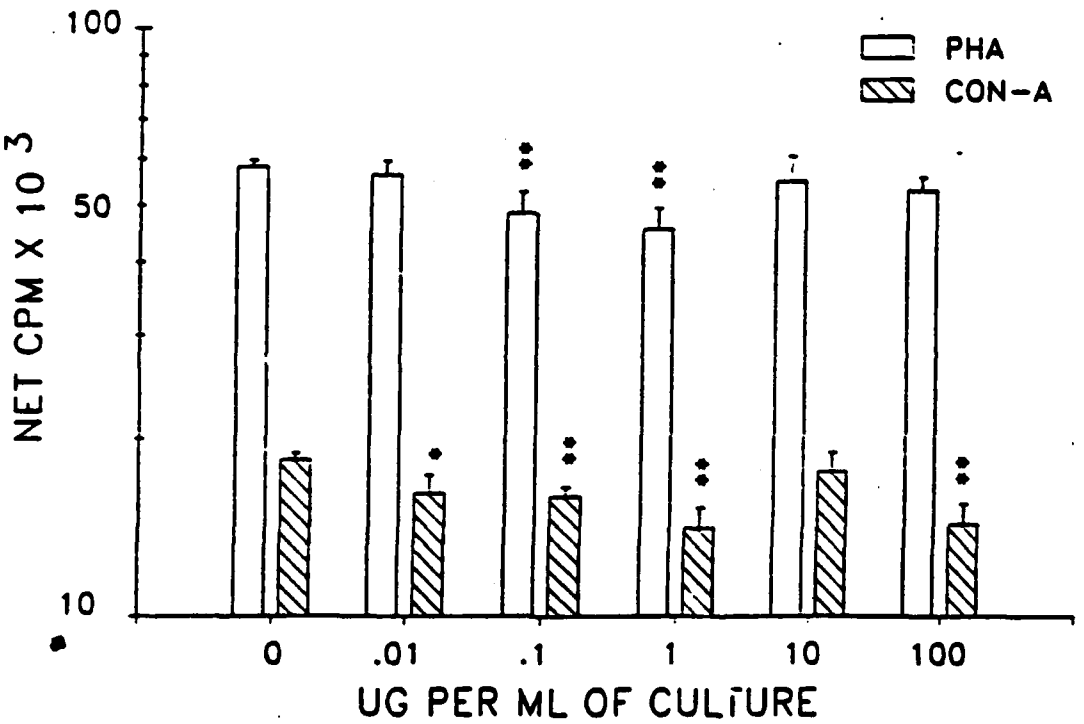


(P VALUE COMPARED TO NO DRUG CONTROL)
(* = .025, ** = .01, *** = .001)

LYMPHOCYTE BLASTOGENIC RESPONSE

HIV$^+$ DONOR CELLS CO-CULTURED WITH

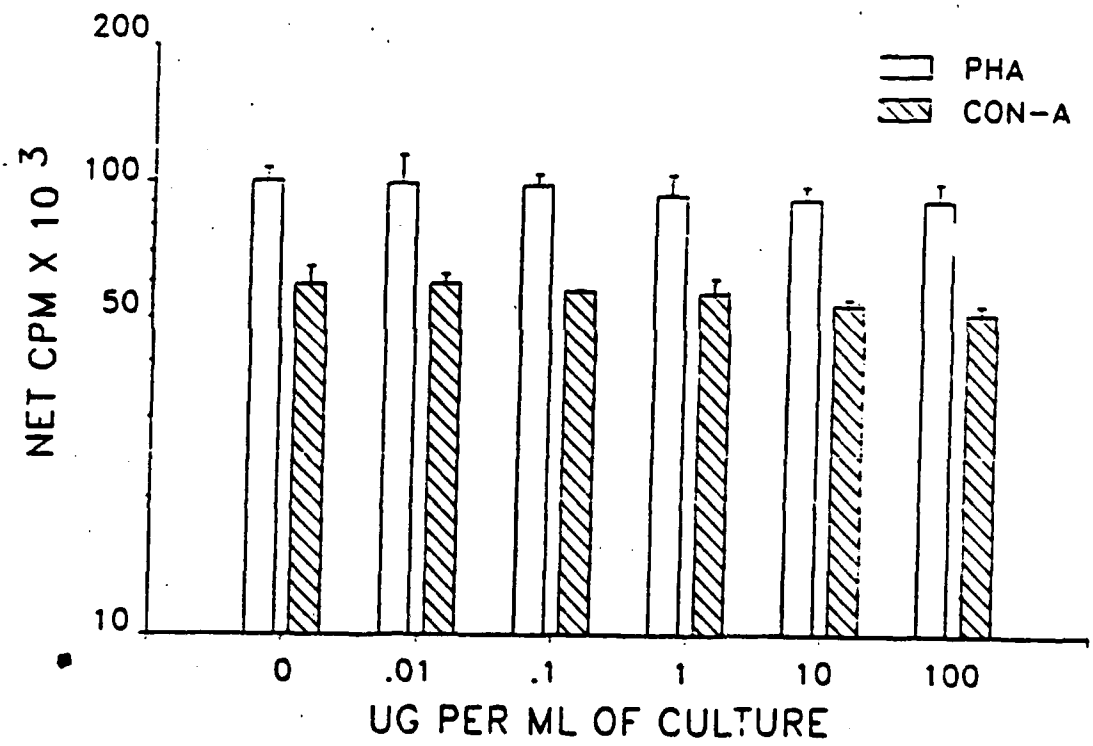
AVS-1792



(P VALUE COMPARED TO NO DRUG CONTROL)

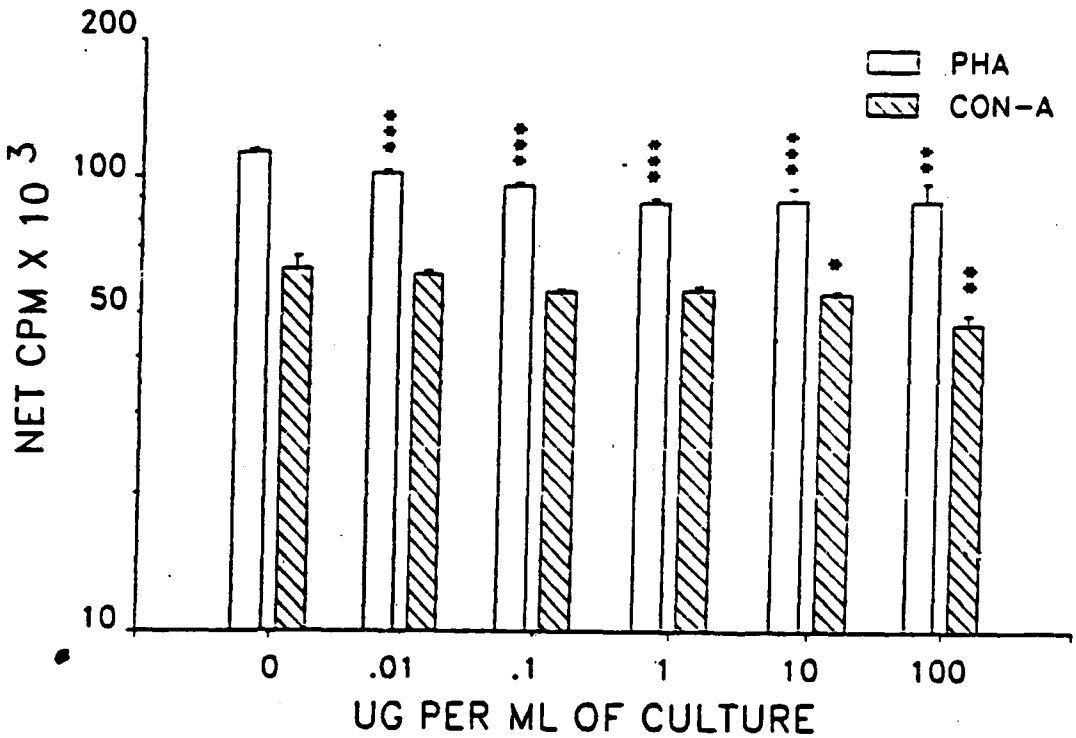
(* = .025, ** = .01, *** = .001)

TOXICITY DETERMINATIONS
AVS-5018



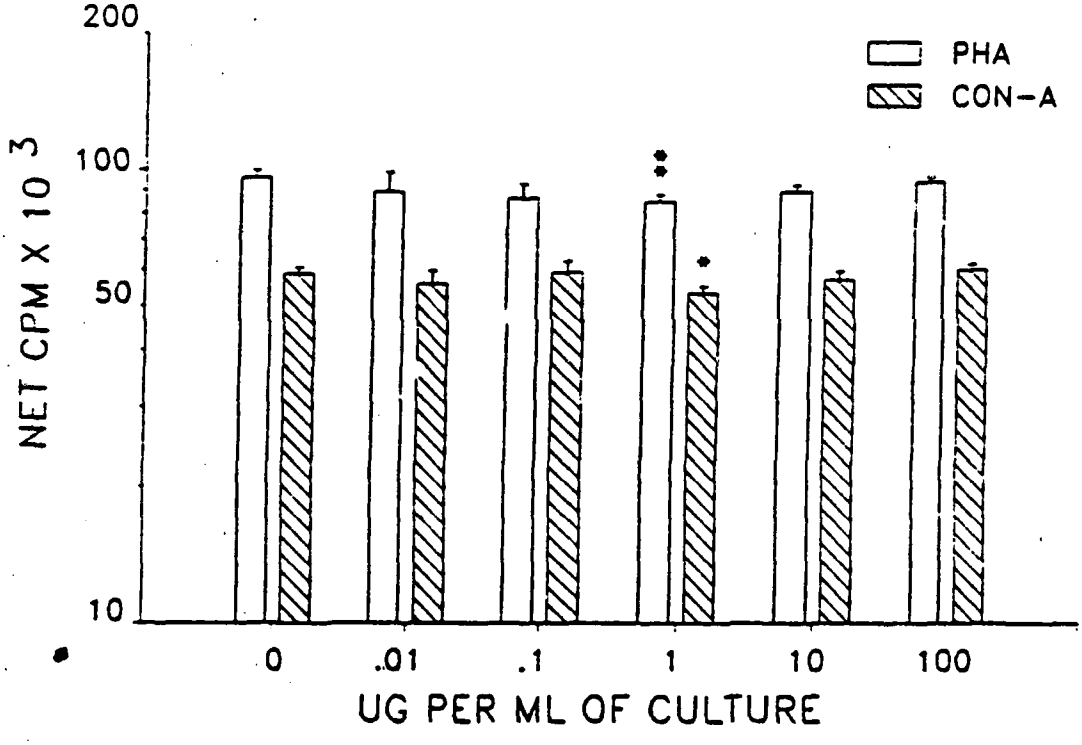
(P VALUE COMPARED TO NO DRUG CONTROL)
(* = .025, ** = .01, *** = .001)

TOXICITY DETERMINATIONS
AVS-5020



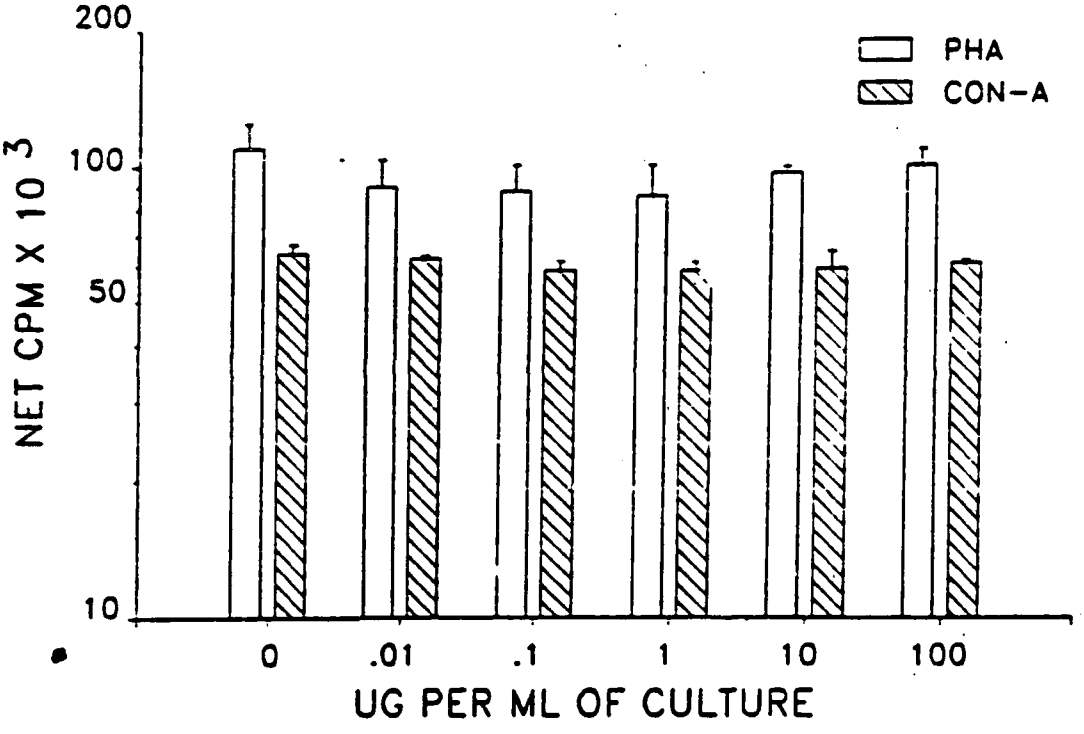
(P VALUE COMPARED TO NO DRUG CONTROL)
(* = .025, ** = .01, *** = .001)

TOXICITY DETERMINATIONS
AVS-5073



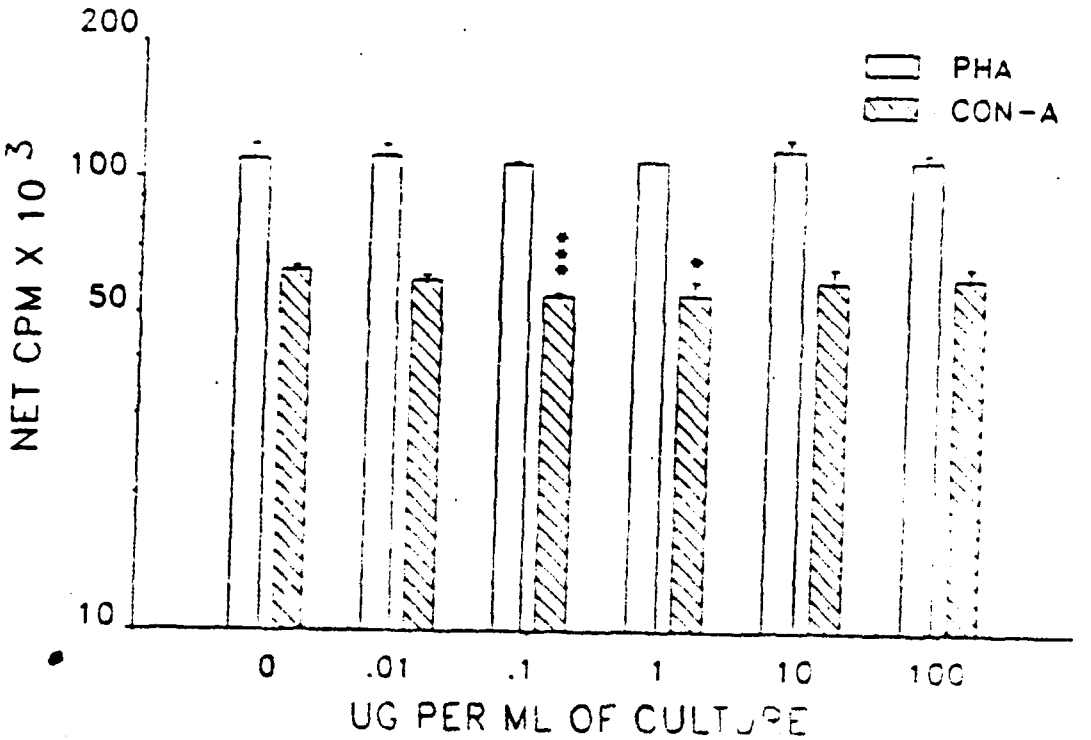
(P VALUE COMPARED TO NO DRUG CONTROL)
(* = .025, ** = .01, *** = .001)

TOXICITY DETERMINATIONS
AVS–5016



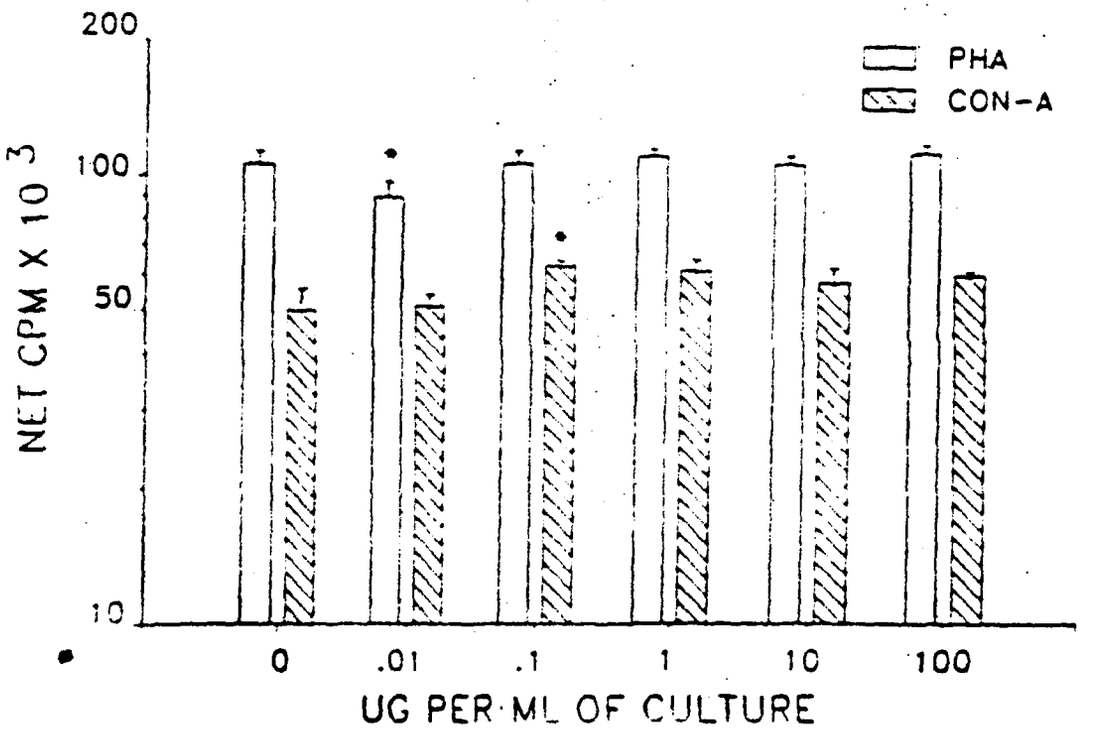
(P VALUE COMPARED TO NO DRUG CONTROL)
(* = .025, ** = .01, *** = .001)

TOXICITY DETERMINATIONS
AVS-5025



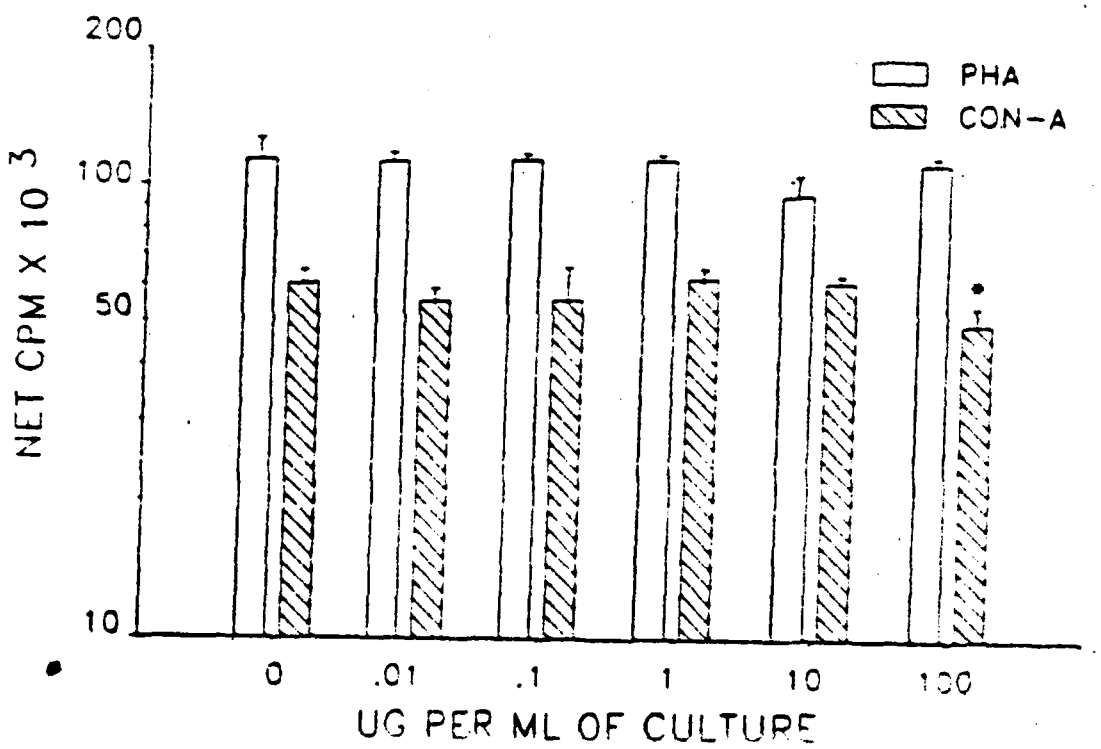
(P VALUE COMPARED TO NO DRUG CONTROL)
(• = .025, •• = .01, ••• = .001)

TOXICITY DETERMINATIONS
AVS-5074



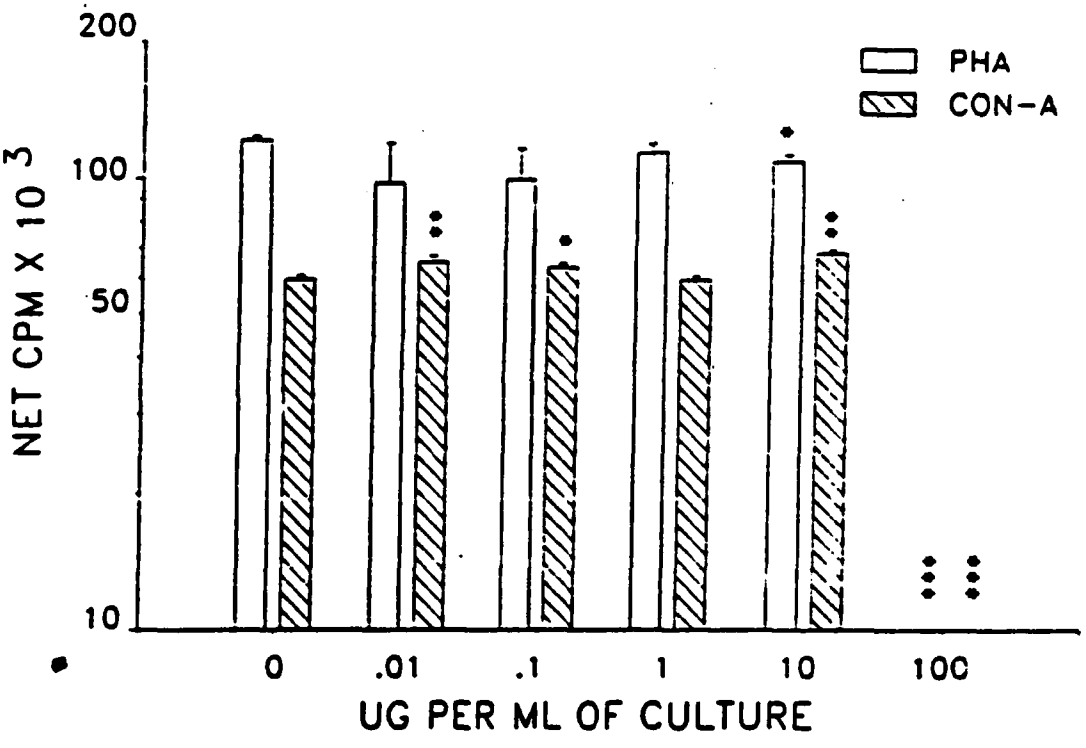
(P VALUE COMPARED TO NO DRUG CONTROL)
(* = .025, ** = .01, *** = .001)

TOXICITY DETERMINATIONS
AVS-5019



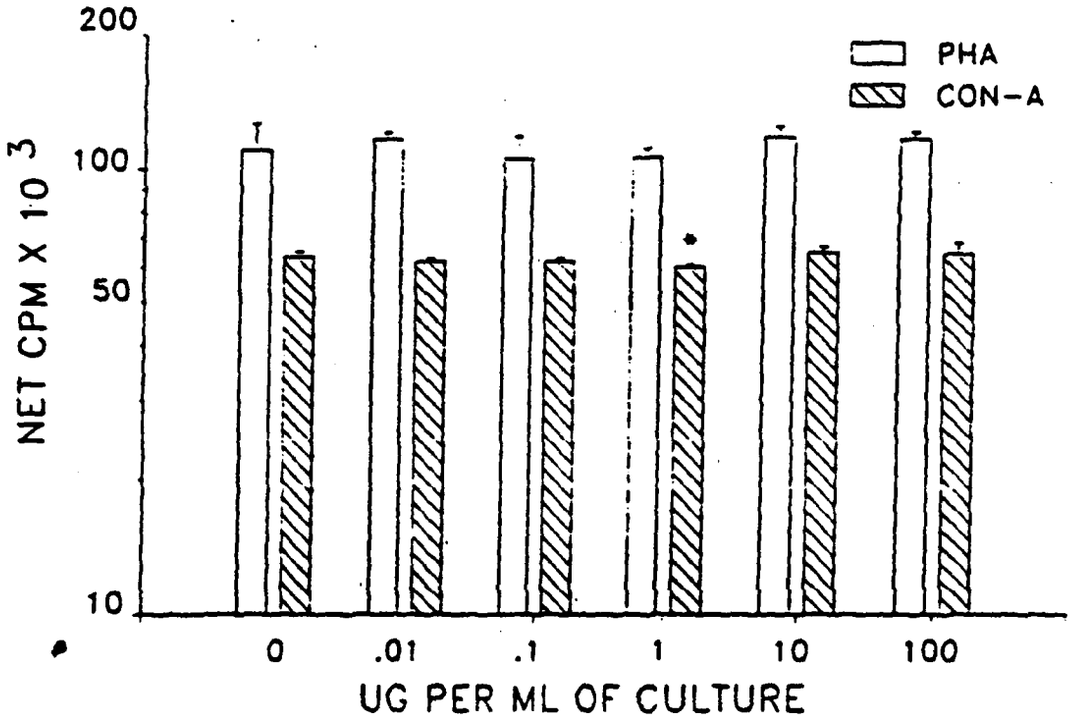
(P VALUE COMPARED TO NO DRUG CONTROL)
(• = .025, •• = .01, ••• = .001)

TOXICITY DETERMINATIONS
AVS–5028



(P VALUE COMPARED TO NO DRUG CONTROL)
(• = .025, •• = .01, ••• = .001)

TOXICITY DETERMINATIONS
AVS-1792



(P VALUE COMPARED TO NO DRUG CONTROL)
(* = .025, ** = .01, *** = .001)

APPENDIX: 1991 Study Data

COOPERATIVE AGREEMENT NO: DAMD17-88-H-8004

TITLE: IMMUNOLOGICAL STUDIES OF ANTI-AIDS DRUGS IN ARC/AIDS

Evan M. Hersh, M.D.
Principal Investigator

Figure 8

SURVIVAL OF MICE WITH LP-BM5 INFECTION TREATED WITH THFα2

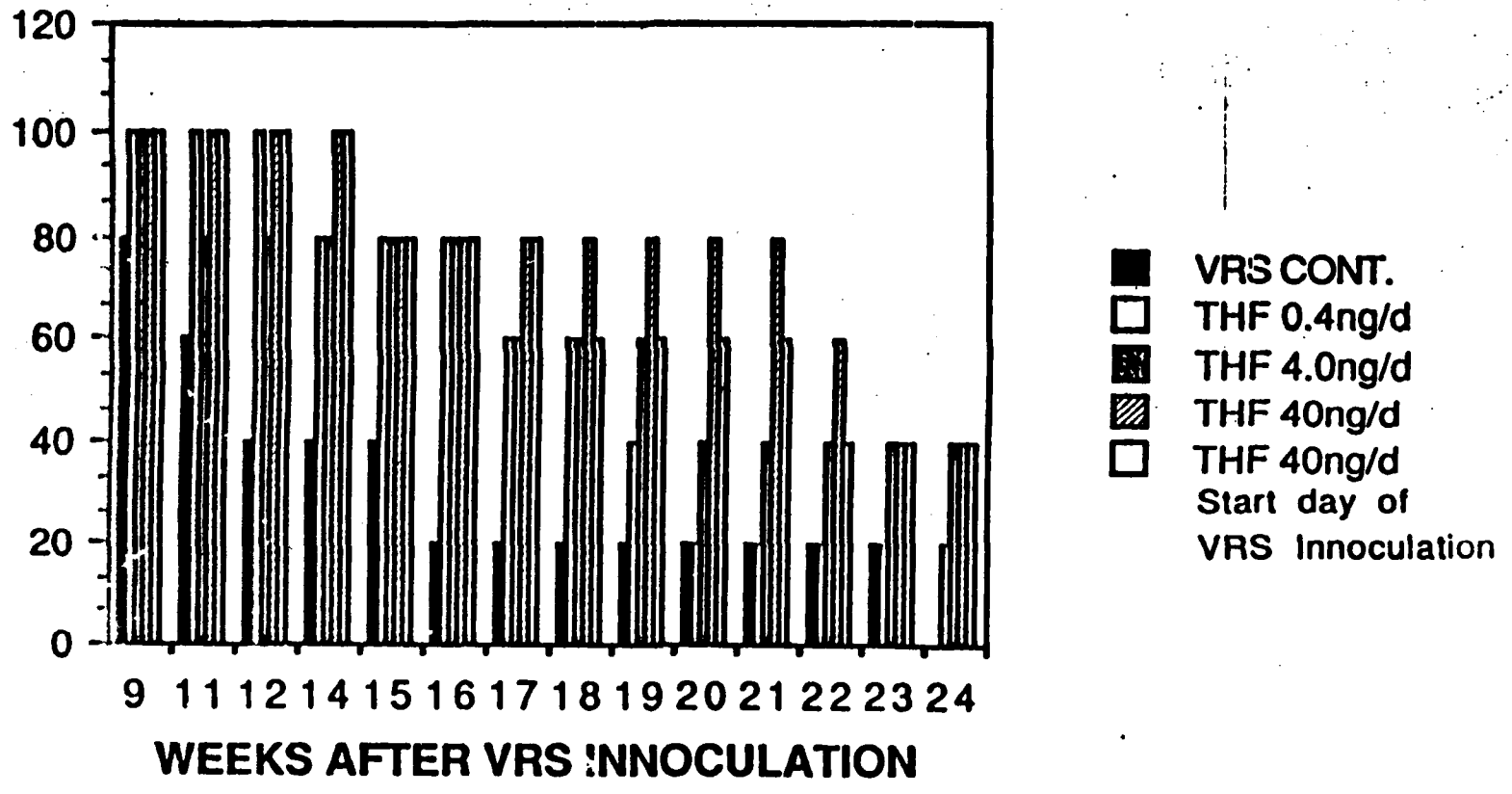


Figure 9

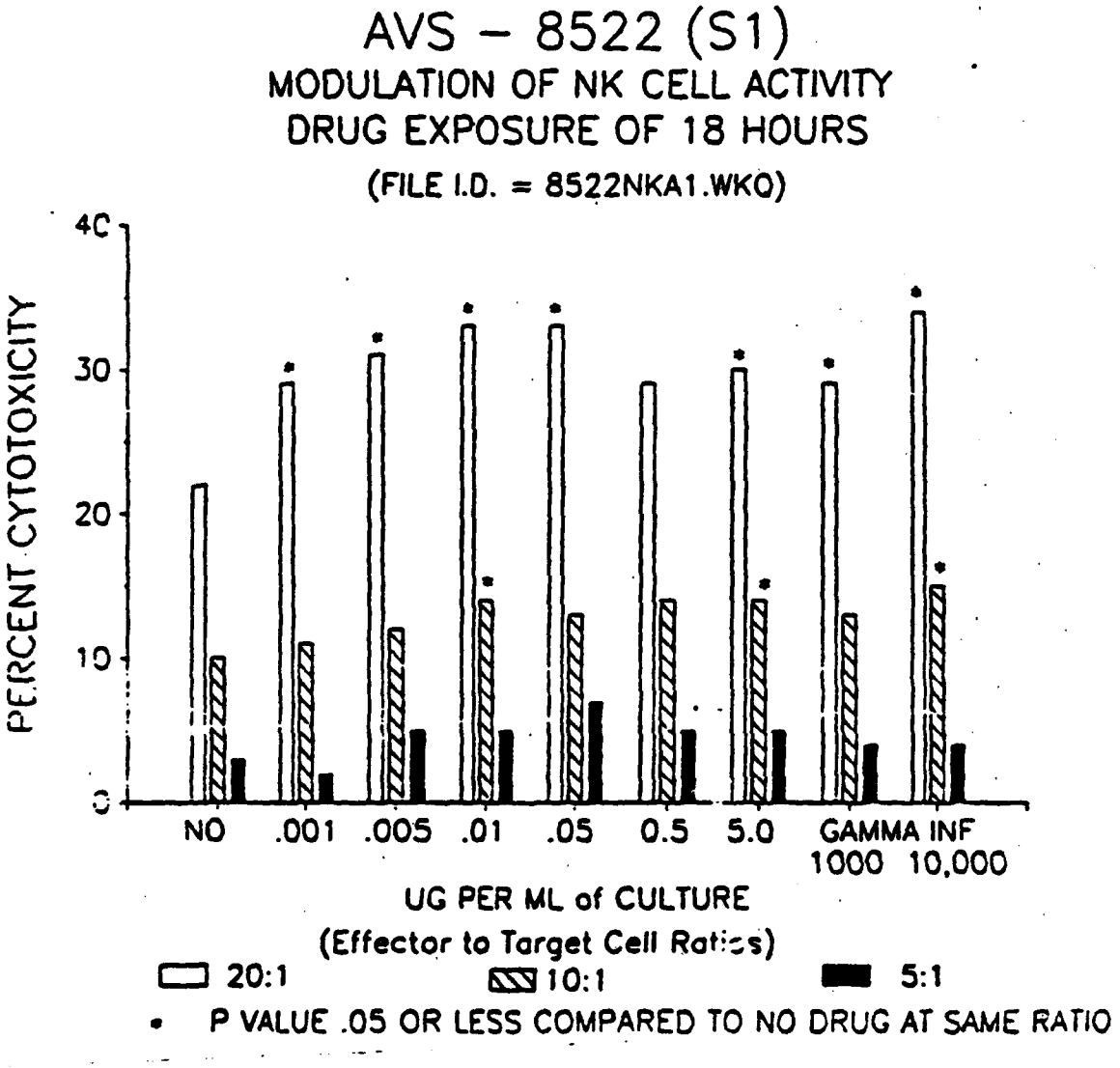

AVS – 8522 (S1)
MODULATION OF NK CELL ACTIVITY
DRUG EXPOSURE OF 18 HOURS
(FILE I.D. = 8522NKA1.WKO)
PERCENT CYTOTOXICITY
40
30
20
10
0
NO
.001
.005
.01
.05
0.5
5.0
GAMMA INF
1000
10,000
UG PER ML of CULTURE
(Effector to Target Cell Ratios)
20:1
10:1
5:1
• P VALUE .05 OR LESS COMPARED TO NO DRUG AT SAME RATIO

Figure 10

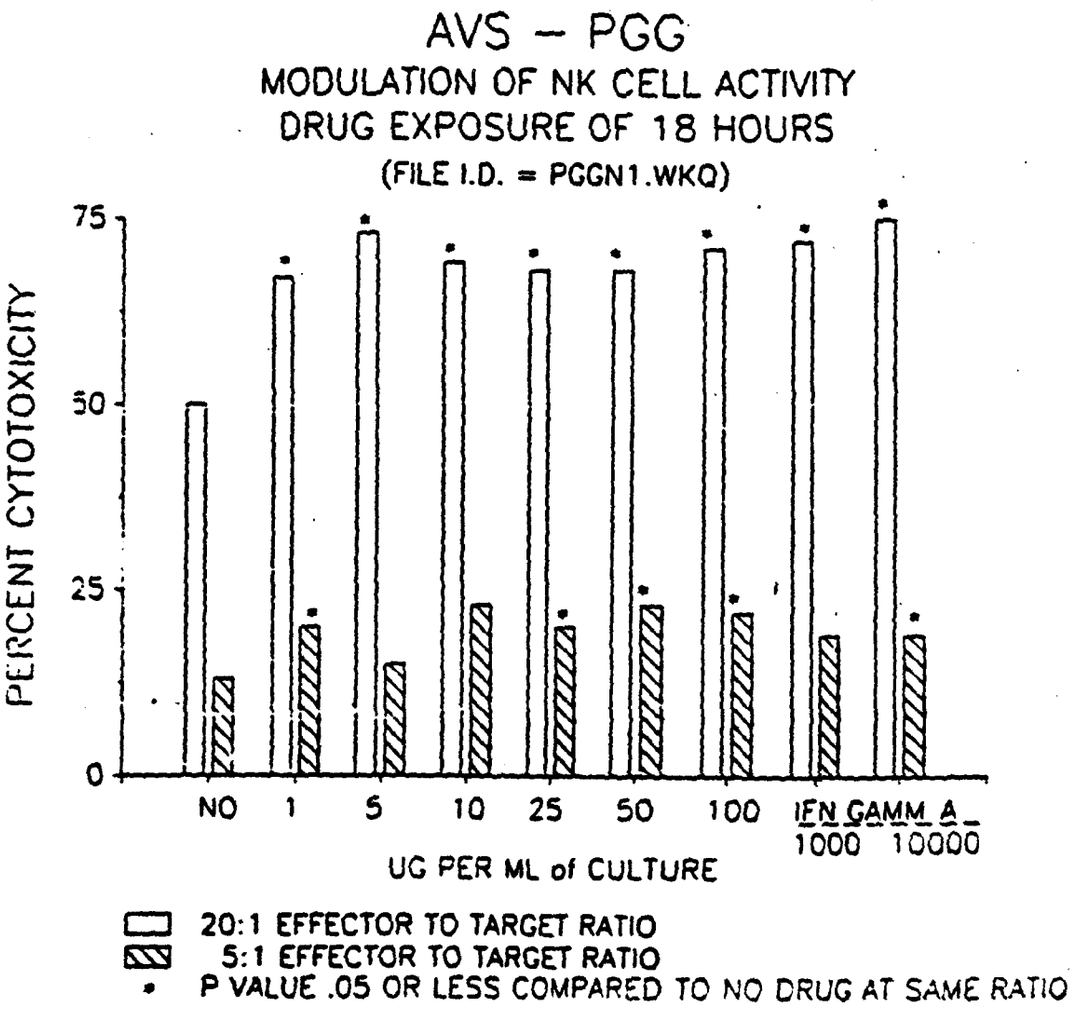

AVS – PGG
MODULATION OF NK CELL ACTIVITY
DRUG EXPOSURE OF 18 HOURS
(FILE I.D. = PGGN1.WKQ)
PERCENT CYTOTOXICITY
75
50
25
0
NO
1
5
10
25
50
100
IFN GAMM A
1000
10000
UG PER ML of CULTURE
20:1 EFFECTOR TO TARGET RATIO
5:1 EFFECTOR TO TARGET RATIO
P VALUE .05 OR LESS COMPARED TO NO DRUG AT SAME RATIO

Figure 11a

AVS – 4728

DRUG TOXICITY

INHIBITION OF PHA INDUCED LYMPHOCYTE BLASTOGENESIS

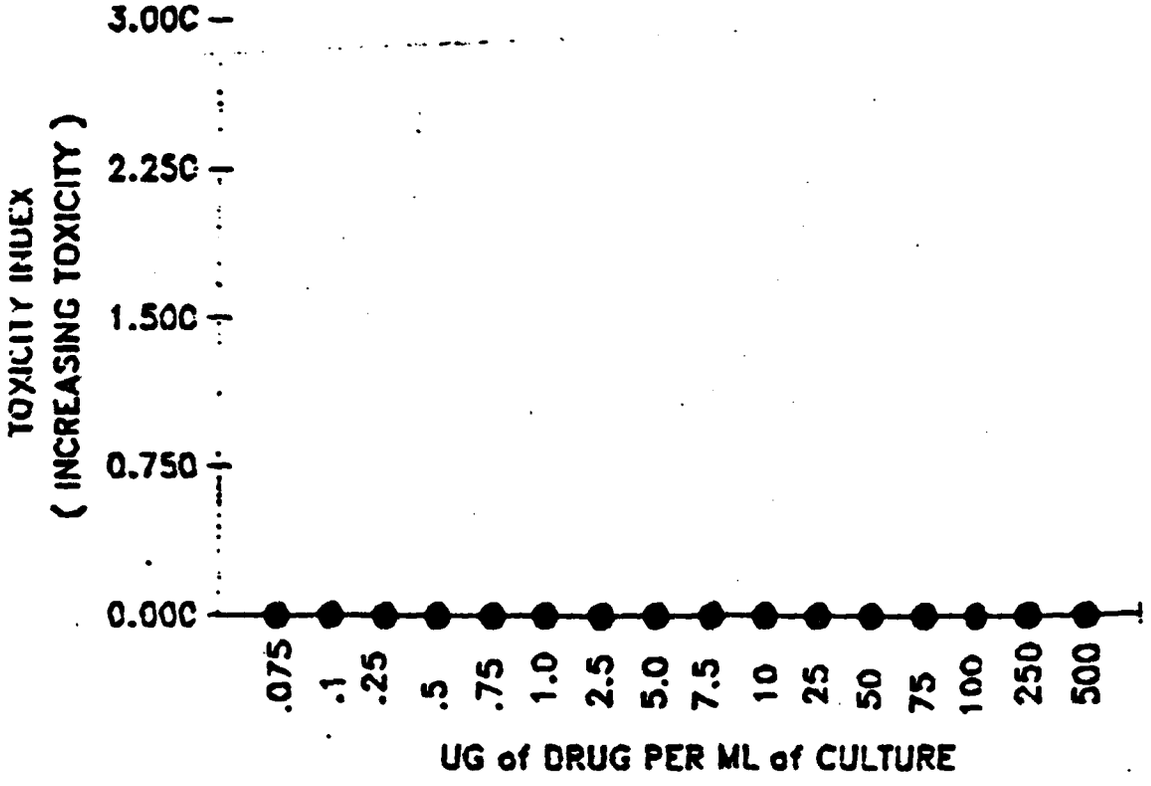


Figure 11b

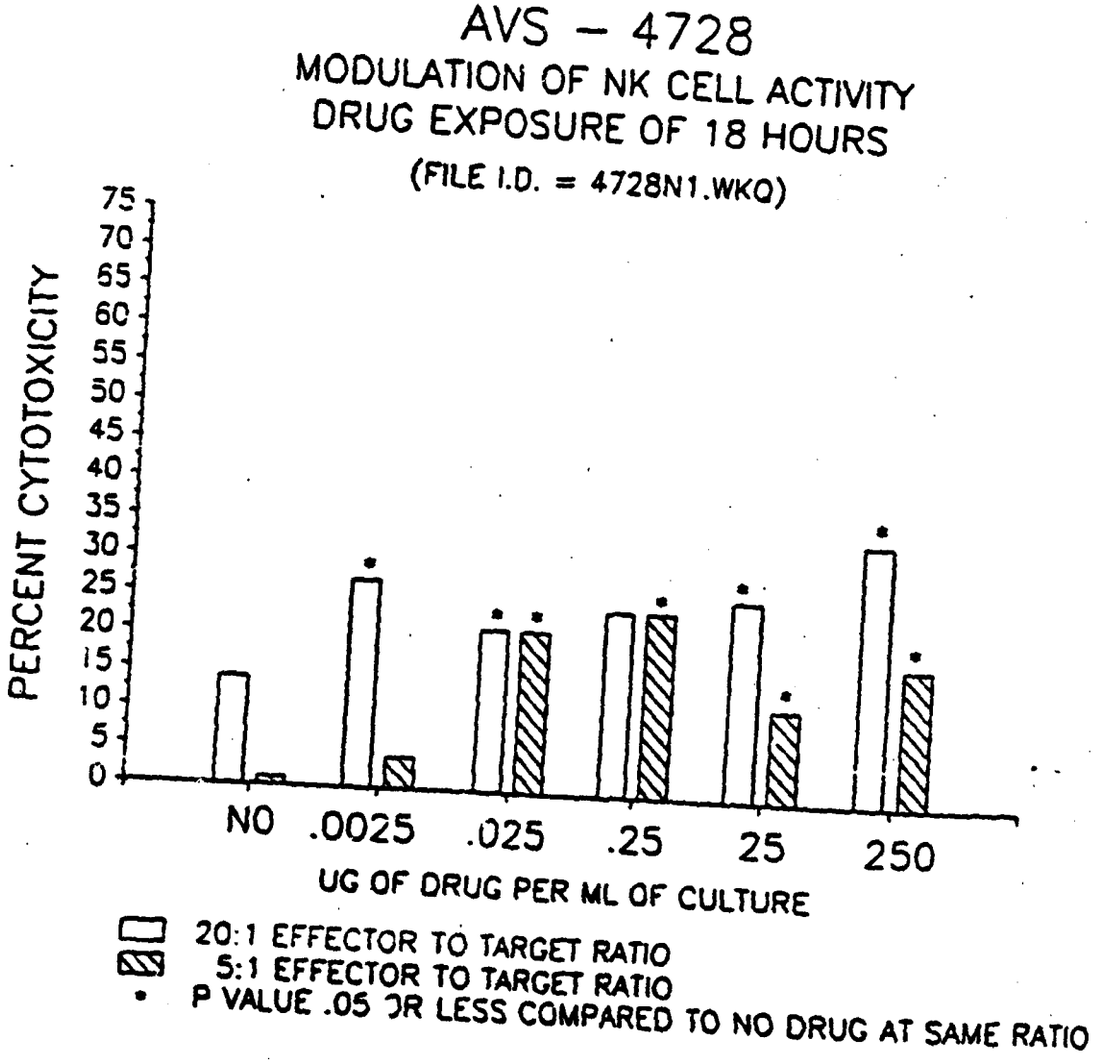

AVS – 4728
MODULATION OF NK CELL ACTIVITY
DRUG EXPOSURE OF 18 HOURS
(FILE I.D. = 4728N1.WKQ)
PERCENT CYTOTOXICITY
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
NO
.0025
.025
.25
25
250
UG OF DRUG PER ML OF CULTURE
20:1 EFFECTOR TO TARGET RATIO
5:1 EFFECTOR TO TARGET RATIO
P VALUE .05 OR LESS COMPARED TO NO DRUG AT SAME RATIO

Figure 11c

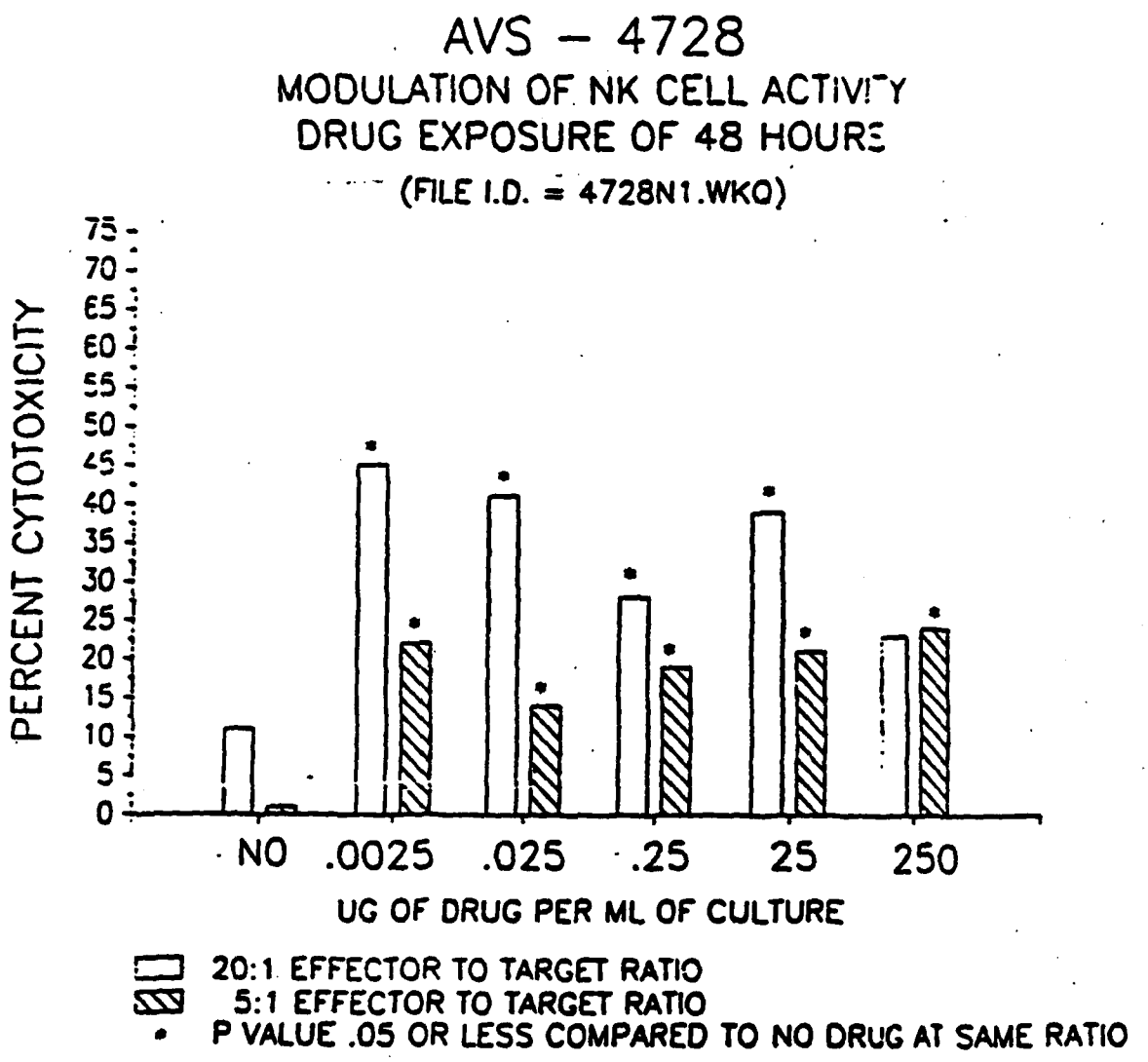

AVS – 4728
MODULATION OF NK CELL ACTIVITY
DRUG EXPOSURE OF 48 HOURS
(FILE I.D. = 4728N1.WKQ)
PERCENT CYTOTOXICITY
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
NO
.0025
.025
.25
25
250
UG OF DRUG PER ML OF CULTURE
20:1 EFFECTOR TO TARGET RATIO
5:1 EFFECTOR TO TARGET RATIO
P VALUE .05 OR LESS COMPARED TO NO DRUG AT SAME RATIO

Figure 11d

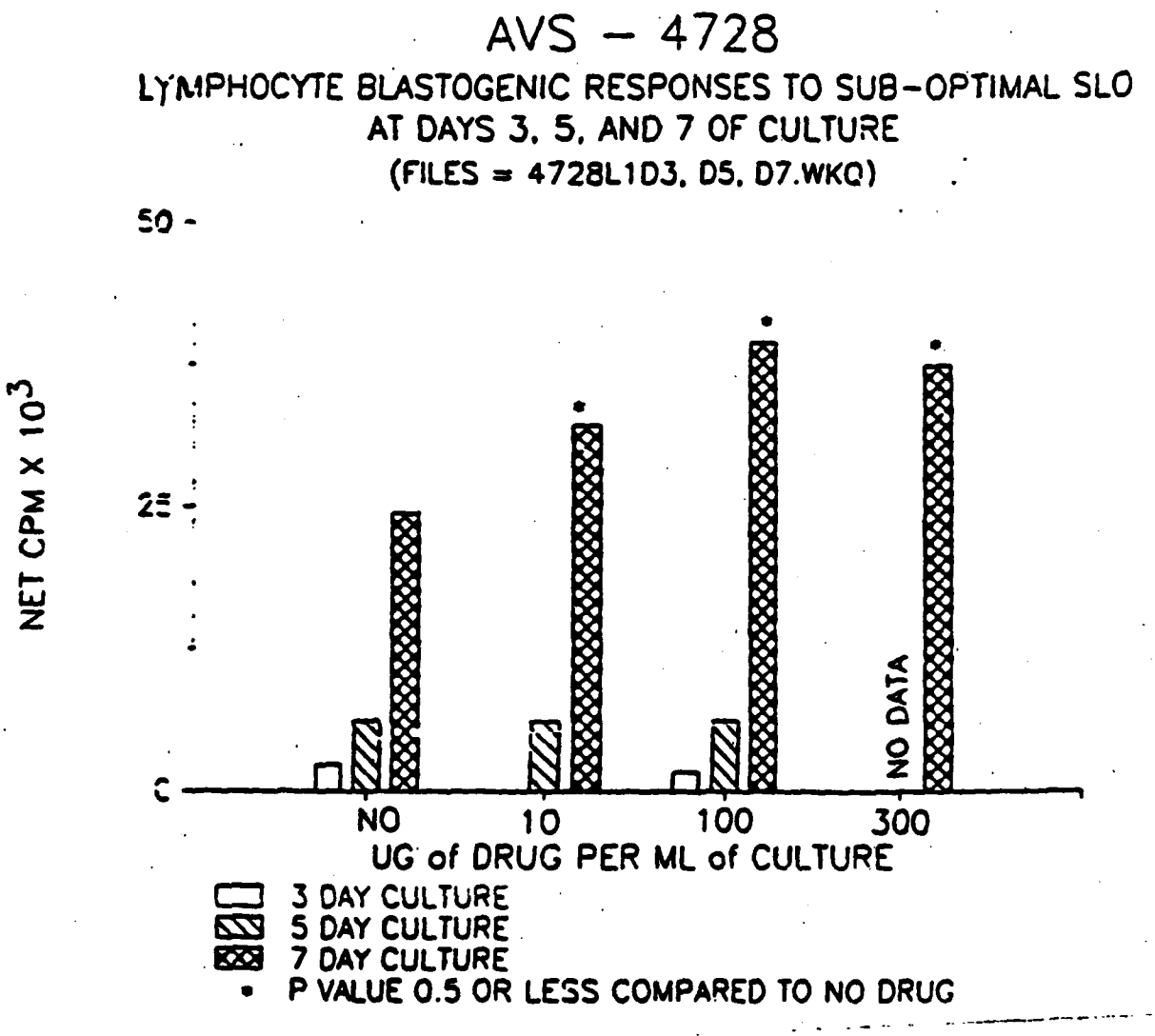

AVS – 4728
LYMPHOCYTE BLASTOGENIC RESPONSES TO SUB-OPTIMAL SLO
AT DAYS 3, 5, AND 7 OF CULTURE
(FILES = 4728L1D3, D5, D7.WKQ)
50
25
0
NET CPM X 10^3
NO DATA
NO
10
100
300
UG of DRUG PER ML of CULTURE
3 DAY CULTURE
5 DAY CULTURE
7 DAY CULTURE
P VALUE 0.5 OR LESS COMPARED TO NO DRUG

Figure 12a

AVS – 1758

DRUG TOXICITY

INHIBITION OF PHA INDUCED LYMPHOCYTE BLASTOGENESIS

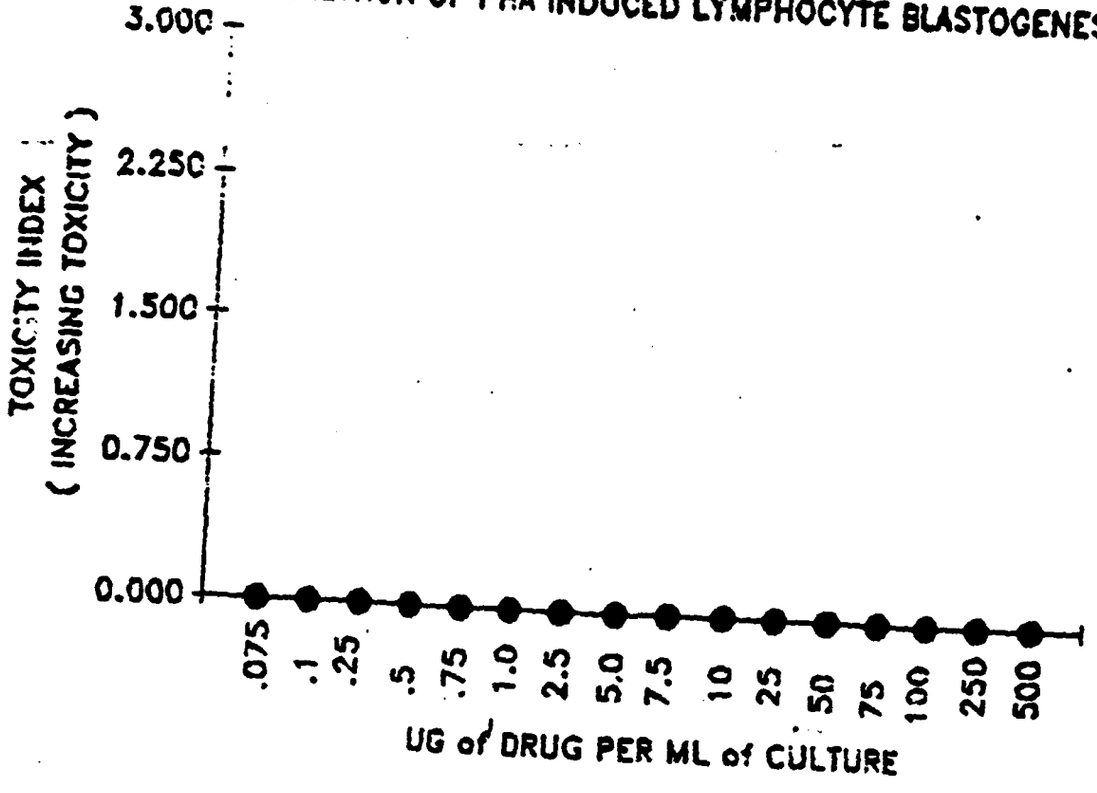


Figure 12b

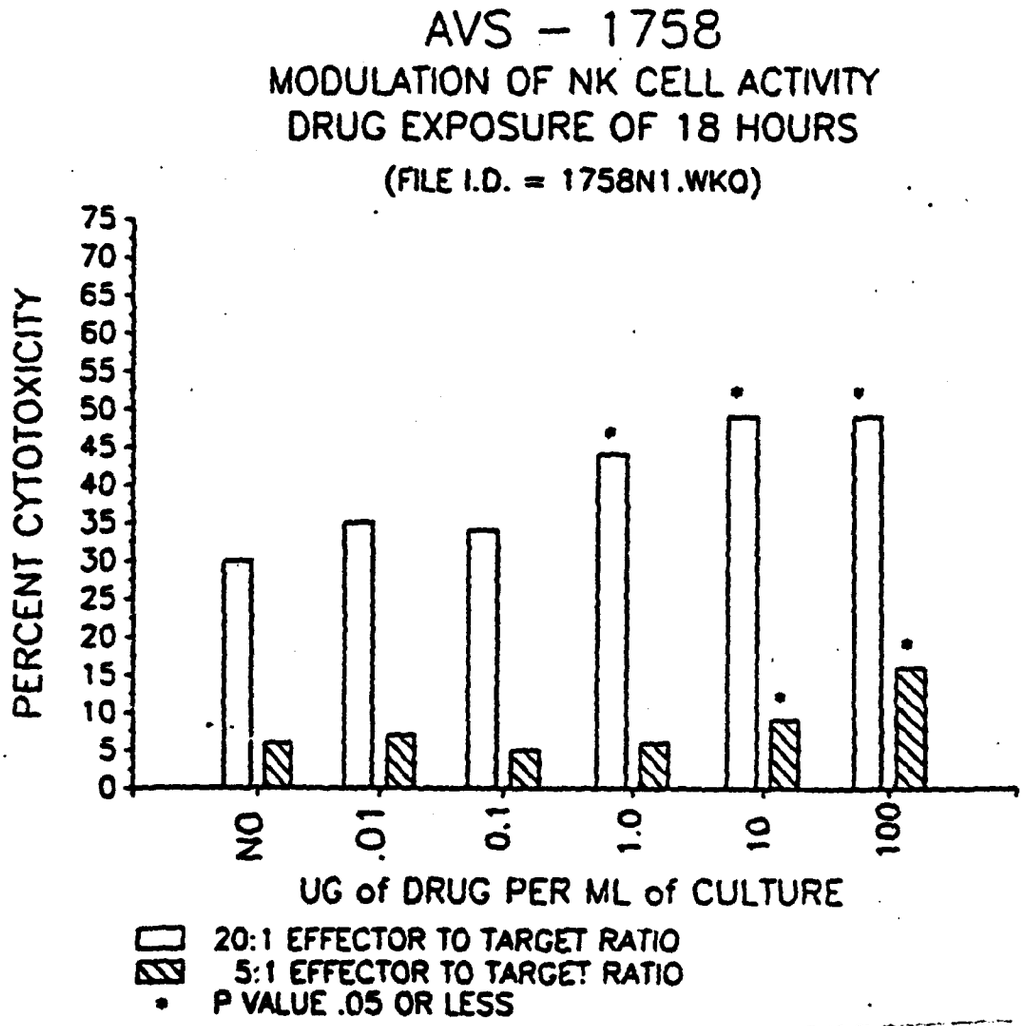

AVS – 1758
MODULATION OF NK CELL ACTIVITY
DRUG EXPOSURE OF 18 HOURS
(FILE I.D. = 1758N1.WKO)
PERCENT CYTOTOXICITY
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
NO
.01
0.1
1.0
10
100
UG of DRUG PER ML of CULTURE
20:1 EFFECTOR TO TARGET RATIO
5:1 EFFECTOR TO TARGET RATIO
P VALUE .05 OR LESS

Figure 12c

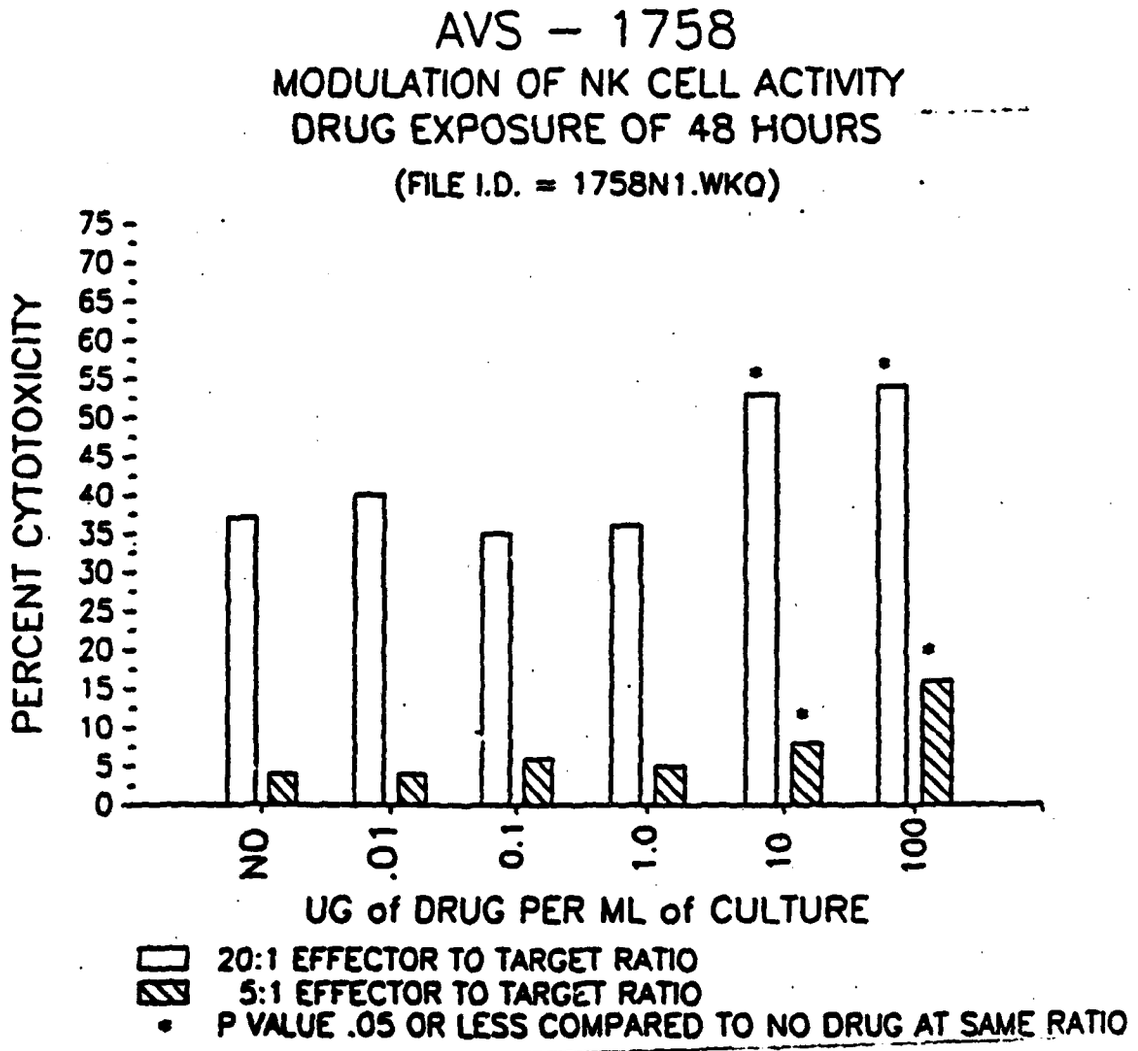

AVS – 1758
MODULATION OF NK CELL ACTIVITY
DRUG EXPOSURE OF 48 HOURS
(FILE I.D. = 1758N1.WKQ)
PERCENT CYTOTOXICITY
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
NO
.01
0.1
1.0
10
100
UG of DRUG PER ML of CULTURE
20:1 EFFECTOR TO TARGET RATIO
5:1 EFFECTOR TO TARGET RATIO
P VALUE .05 OR LESS COMPARED TO NO DRUG AT SAME RATIO

Figure 12d

AVS – 1758

LYMPHOCYTE BLASTOGENIC RESPONSES TO OPTIMAL CON-A
AT DAYS 3, 5, AND 7 OF CULTURE
(FILES = 1758L1D3, D5, D7.WKQ)