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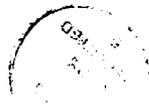
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ANTIVIRAL DRUG DEVELOPMENT: IDENTIFICATION AND  
ACQUISITION OF CHEMICALS AND DRUGS

FINAL REPORT

E. L. STEPHEN

DECEMBER 30, 1990



A-1

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND  
Fort Detrick, Frederick, Maryland 21702-5012

Contract No. DAMD17-89-C-9148

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10078 Tyler Place  
Ijamsville, Maryland 21754

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<p>During this contract period the following objectives were achieved: 1) Enhanced the database on Antiviral Drug Information System (ADIS) by the addition of critical functions including report generators and data loaders. 2) Received and registered over 2,900 compounds during the contract period. 3) Received more than 32,000 in vitro test results and incorporated them into the database. 4) A total of 4,249 samples were sent for testing. 5) Over 430 compounds were confirmed to be active in vitro.</p>			
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### *Summary of Achievements*

The Biological Research Faculty and Facility, Inc. (BRFF) was able to perform pivotal work related to antiviral drug development for the Department of Defense (DOD). The work spanned a period of eighteen months (which is reported as 6 quarters) and achieved several noteworthy objectives of the Program as follows:

- o transitioned all aspects of the project with no disruption of work;
- o enhanced the database on Antiviral Drug Information System (ADIS) by the addition of critical functions including report generators and data loaders;
- o received and registered over 2,900 compounds during the contract period; and,
- o received more than 32,000 *in vitro* test results that have been incorporated into the database.

This work helped to integrate various elements of this important drug development program including both government and contractor elements, and has proven to be quite successful. The success of the Antiviral Drug Development Program is attested to by the single most important finding that 189 confirmed *in vitro* active samples have been identified during this contract period (and a cumulative number of 432 from inception of the contract). Based on a sample volume of 2,914, this represents a success rate of 6.5%.

### *Detailed Report*

The Biological Research Faculty and Facility, Inc. (BRFF) has been able to continue expansion of elements of the antiviral drug development program centered at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). USAMRIID, a laboratory within the United States Army Medical Research and Development Command, provides the only research and development effort to discover antiviral drug candidates for use against virus-induced diseases of particular interest to DOD. This antiviral drug development program is necessary because viral infections of importance to the military represent the equivalent of orphan drug products to the U.S. pharmaceutical industry. As such, antiviral drugs would not be developed or become available. This Army-sponsored drug discovery and development effort may, however, indirectly benefit other countries where these diseases are endemic and, thus, represent an important potential contribution for consideration of transferable technology or products.

An overview of the Volume of Transactions during the BRFF contract period relating to sample receipt and shipment, data receipt, number of reports sent to suppliers, and active compounds is shown in Table 1 and Figures 1 through 5.

During the BRFF contract, 2914 new chemicals were received from different suppliers. There was a steady increase in the number of samples received as shown in Figure 1. A total of 4249 samples were sent for testing. Figure 2 shows the number of samples shipped for testing, which is increased during each quarter. The maximum number of shipment was in the 4th quarter of BRFF contract.

Figure 3 shows the number of in vitro results received during each quarter. Figure 4 shows human immunodeficiency virus (HIV) test results separated as Virology Compounds (these are compounds received by the Department of Antiviral Studies that were tested against HIV as well as other viruses of interest) and NCDDG Compounds (compounds acquired by USAMRIID's National Cooperative Drug Discovery for AIDS sponsored by the National Institute of Allergy and Infectious Diseases of the NIH). The large increase in samples received and tested during the fourth quarter of 1990 represents a single large shipment from a single supplier. Figure 5 represents the number of HIV reports sent to suppliers. The number of suppliers is also shown graphically.

### *Conclusions*

The contract to support compound acquisition, repository functions, database design, implementation and support has been remarkably successful. BRFF was able to accomplish the transition from a previous contractor with zero loss in productivity. As documented by statistics and figures contained in this report, BRFF was able to expand and enhance all aspects of this critical project.

As documented in this report, objectives of the program have been successfully achieved. Most noteworthy is the list of confirmed active compounds totaling 432 chemicals.

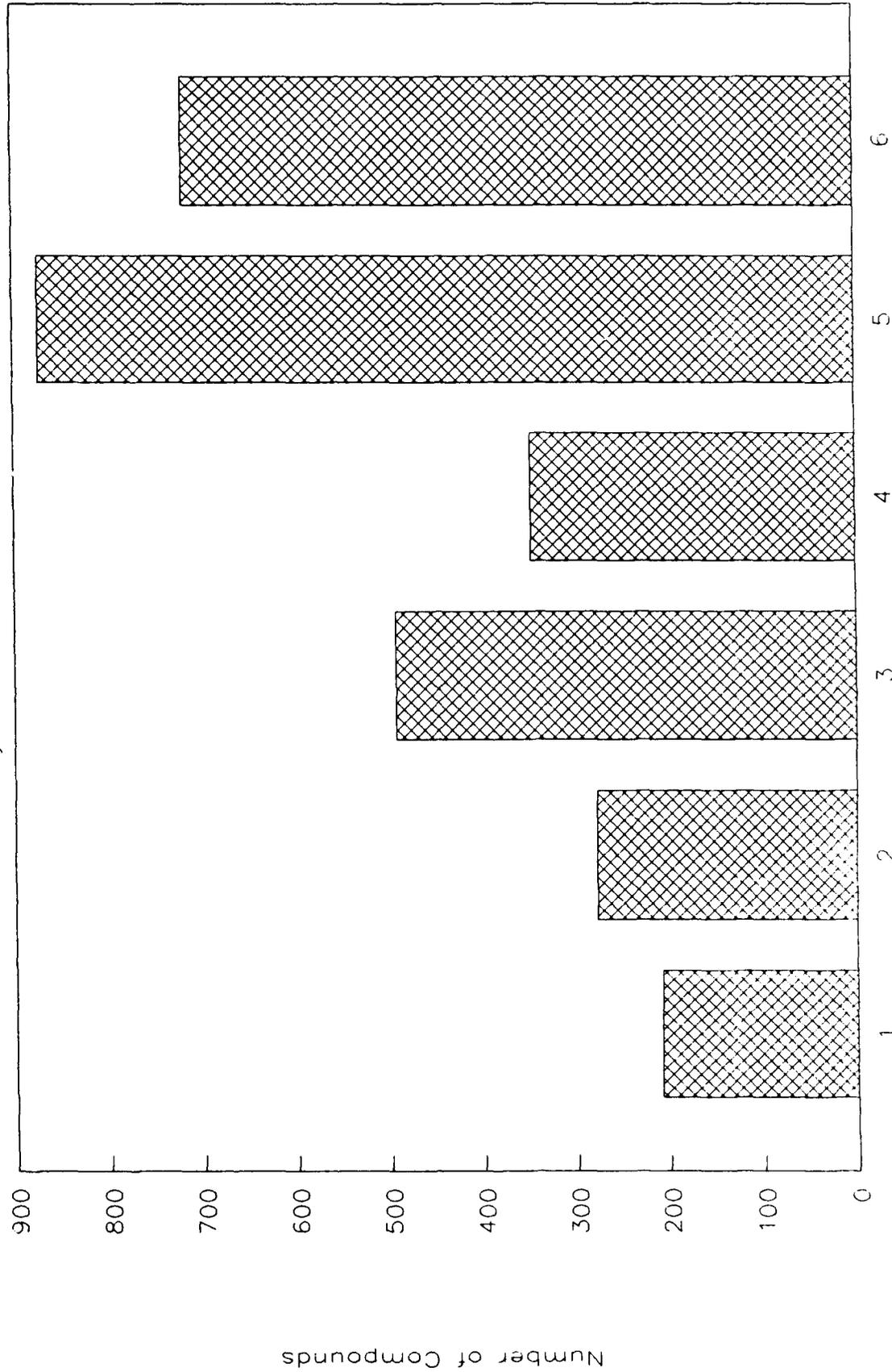
**TABLE 1. SUMMARY OF RESULTS ACHIEVED DURING THE CONTRACT PERIOD**

Tasks Performed	Reporting period in quarters						Total
	1	2	3	4	5	6	
No. of new samples registered	208	277	492	346	873	718	2914
No. samples shipped for testing	367	540	634	755	895	1058	4249 <sup>a</sup>
No. of shipments for testing	14	19	25	35	27	21	141
No. <i>In vitro</i> results received	9958	4990	3513	4318	5571	4128	32478 <sup>b</sup>
No. <i>In vivo</i> results received	0	0	0	0	0	0	0
No. of prescreen results received	705	1067	181	1890	2026	1698	7567
No. of prescreen samples tested	-	-	-	1016	846	598	2460
No. of prescreen samples indicating activity	-	149	17	53	45	22	286
HIV: USAMRIID compounds	363	823	202	377	612	140	2517
HIV: NCDDG compounds	61	46	11	5	12	518	653
No. of reports sent to suppliers	122	46	43	38	34	42	325
No. of compounds reported to suppliers	5572	907	1000	1203	1156	1928	11766
No. of samples confirmed active <i>in vitro</i> during BRF contract	0	50	5	46	9	79	189
No. of samples confirmed active <i>in vitro</i> (cumulative, from inception)	243	293	298	344	353	432	432

<sup>a</sup> BRF was able to ship a total of 4,249 samples in 141 shipments to fifteen testing facilities.

<sup>b</sup> A total of 32,478 *in vitro* test results were received from Southern Research Institute, USAMRIID and Utah State University (representing 98.2%, 1.76% and 0.02%, respectively for each of the three testing laboratories).

# CHEMICAL SAMPLES ACQUIRED by Calendar Quarter



Quarters during 1989 - 1990

**FIGURE 1**

# Chemical Samples Shipped by Reporting Period

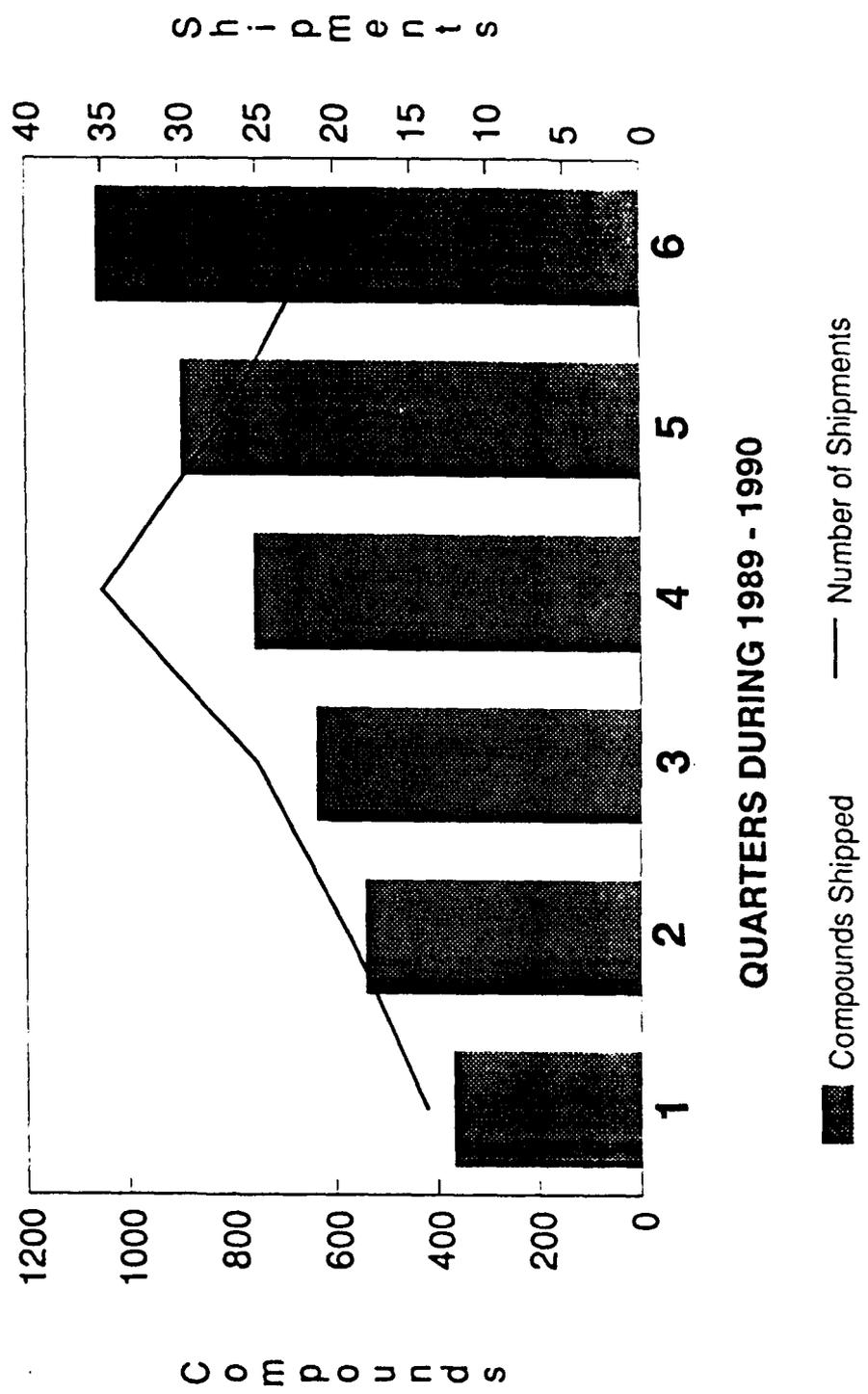


Figure 2

# In Vitro Testing Recorded by Reporting Period

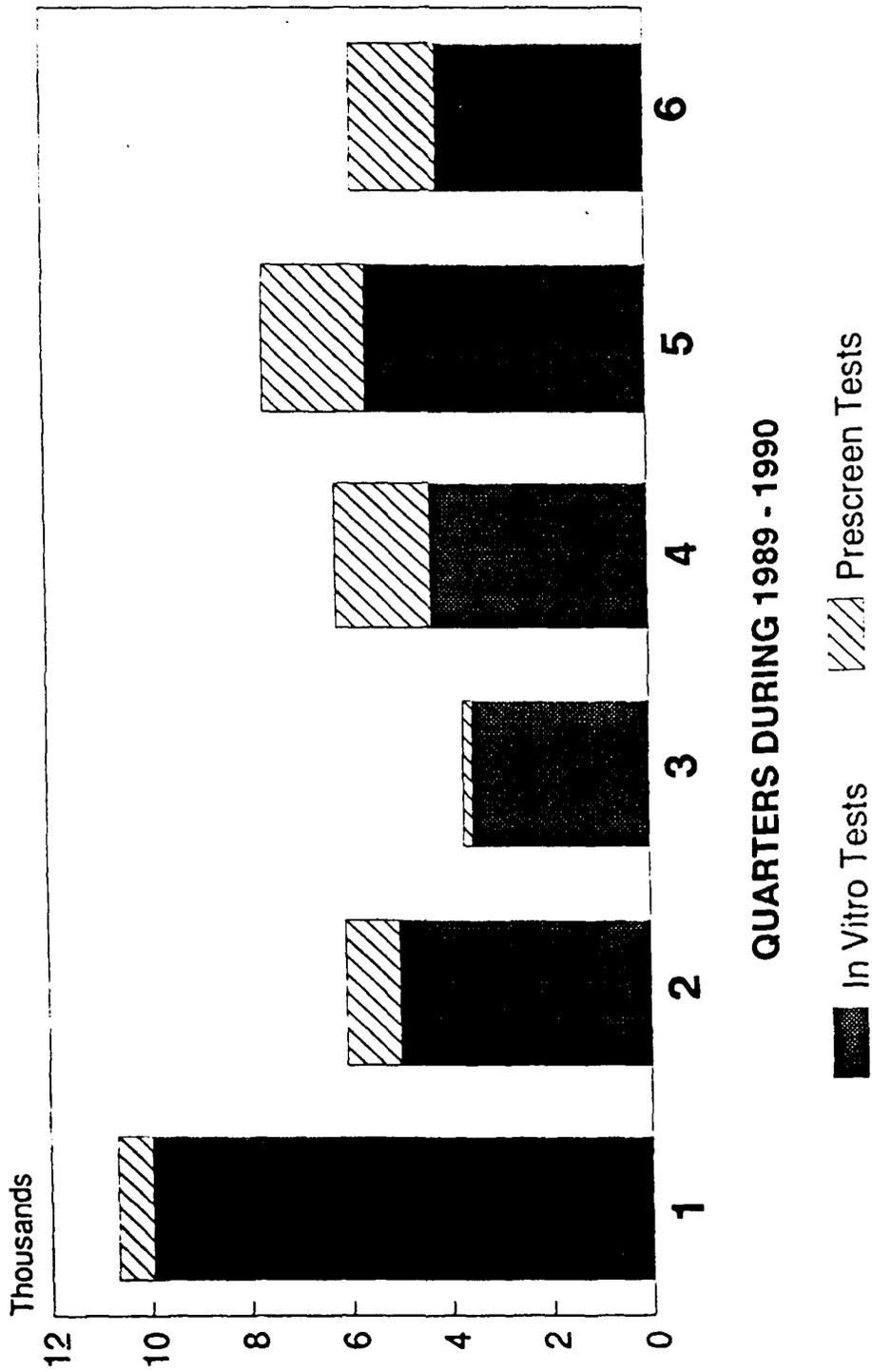


Figure 3

# HIV In Vitro Testing by Reporting Period

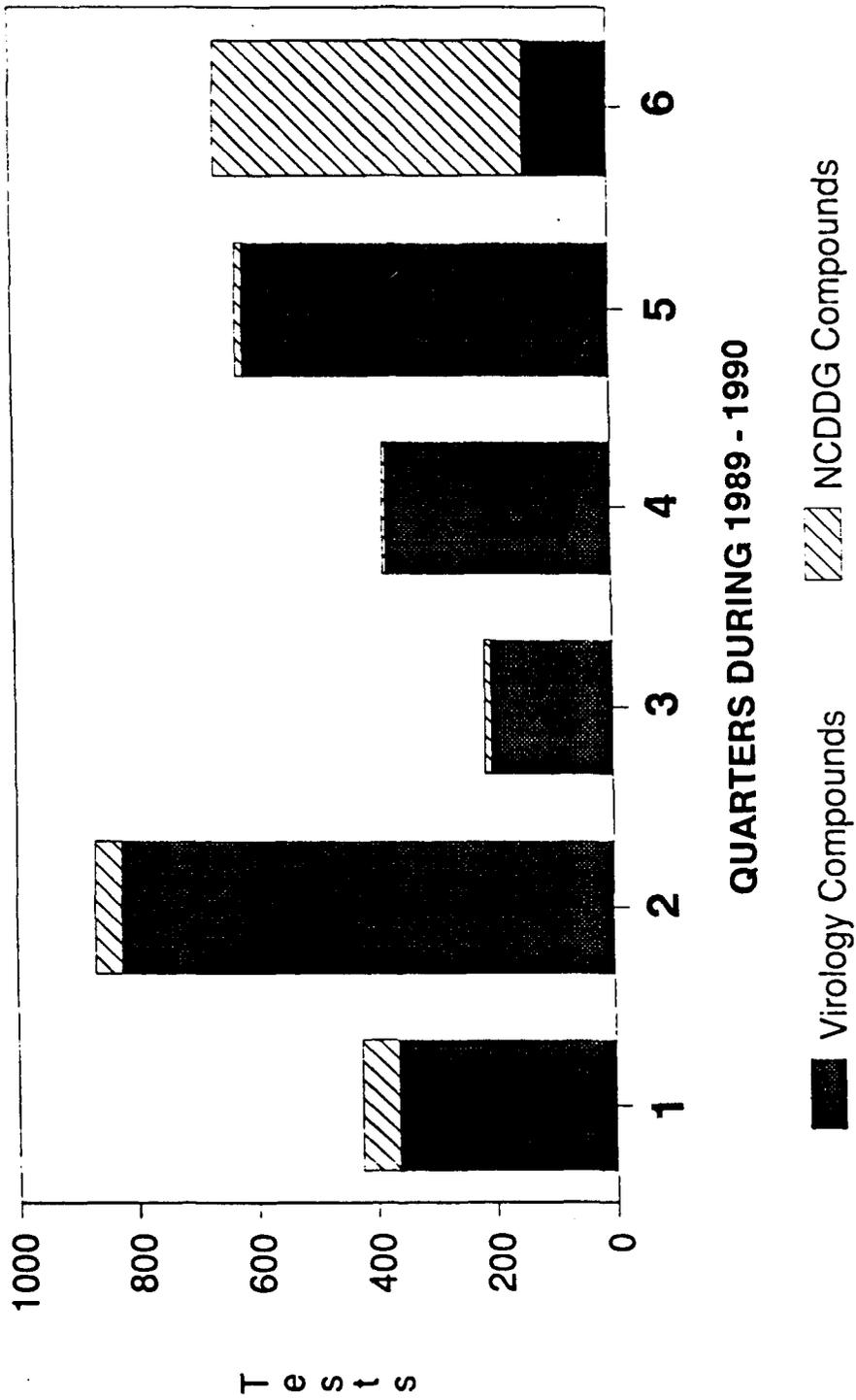
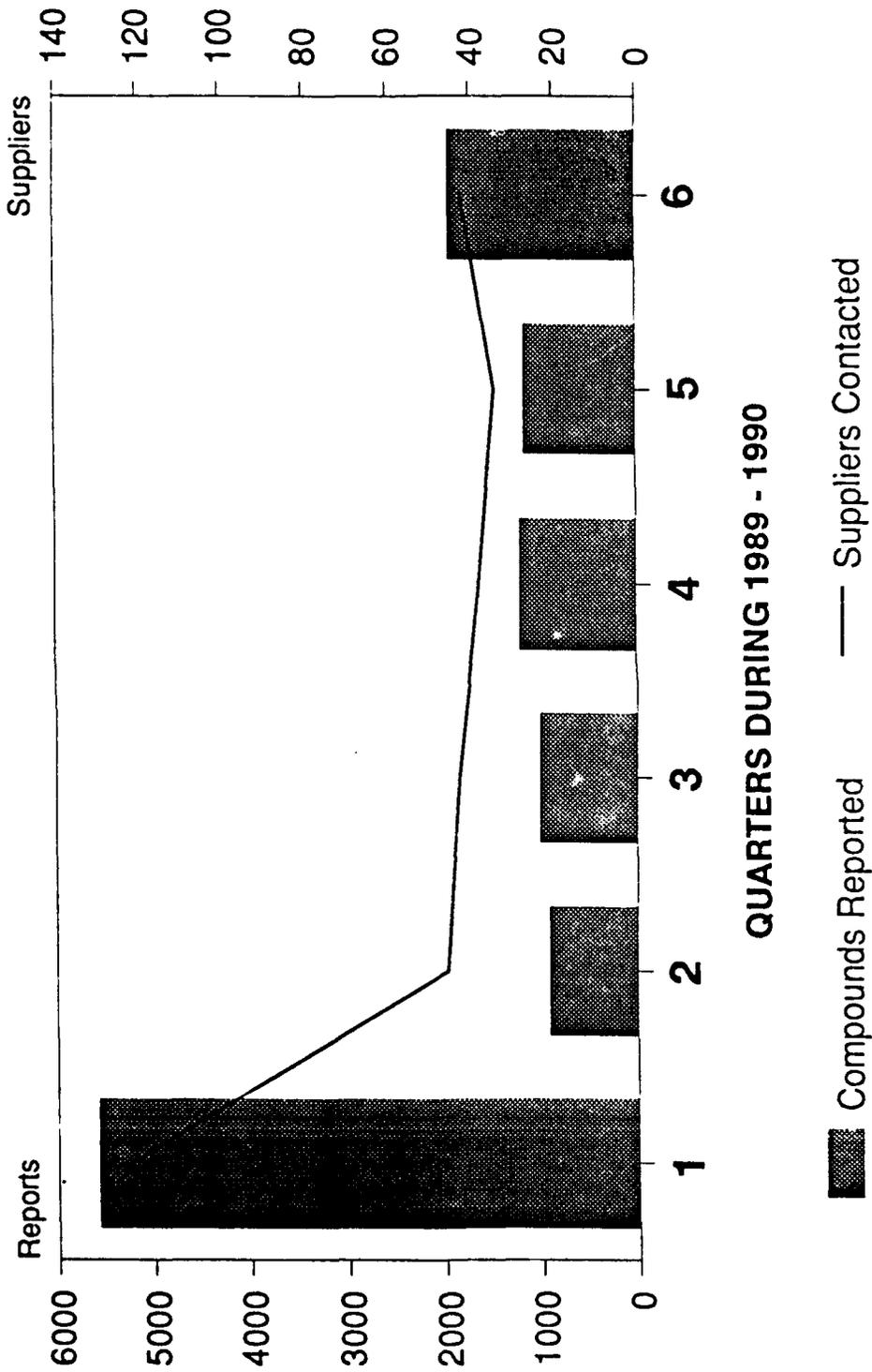


Figure 4

# HIV In Vitro Testing by Reporting Period



QUARTERS DURING 1989 - 1990

Figure 5

### *Recommendations for Future Work*

Additional emphasis may be placed on determination of activity of the 432 compounds with confirmed activity in animal studies. The focus will require methods to prioritize the 432 samples. *In vitro* screening may be continued since so much effort has been applied to developing production type assays and achieving the desired throughput and reproducibility.

Database capabilities also may be continued, maintained and enhanced to keep pace with reporting to suppliers and to provide the utilities to handle and to use large volumes of data. Reporting in a timely and accurate fashion to suppliers is critical to the continued support of the program.

Access to, and the ability to do multivariable analysis of the data, provides the state-of-the-art edge necessary to expedite the discovery and development of new antiviral drug therapies especially for virus-induced diseases important to the Army and other DOD components.

### *Problems Encountered and Solutions Implemented*

No major problems were encountered in this contract. The minor problems and the corrective actions taken were reported in each of the Quarterly Reports.

### *Project Staff and Labor Distribution*

Table 2 lists all the project staff associated with this contract at BRFF. The team was headed by Dr. Edward Stephen and included several highly qualified staff members. The level of effort of each member is also given as hours spent on this contract.

It may also be noted that the contract was performed within the budget.

**TABLE 2. PROJECT TEAM MEMBERS AND THEIR LEVEL OF EFFORT**

<b>Employee Name</b>	<b>Hours Worked</b>
E. STEPHEN (Principal Investigator)	2,324.00
J. GALLALEE	2,819.00
B. HANDELMAN	2,798.75
Y. TEKLU	2,696.50
E. ABEBE	2,425.50
C.R. ETHRIDGE	2,229.75
M. JONES	1,946.00
F. NEFFLEN	1,304.00
C. LU	1,251.50
R. KARPFF	1,146.70
E.S. OONNITHAN	913.00
J. KNEER	849.50
R. GARRITY	786.00
B. KLINE	757.50
T. STEPHEN	728.50
M. DAVOLI	536.00
E. BONHAM	334.50
D. RAPP	193.00
B. GROVE	182.50
P. STEPHEN	27.00
	-----
Total Hours Used	26,249.20

*Transfer of the Contract back to USAMRIID*

On November 6, 1990, the BRFF management was informed of USAMRIID's decision of not exercising the option of continuing the above contract for an additional 6 month period from December 19, 1990 to June 18, 1991 as per original contract.

Immediately we set up a transition schedule to smoothly transfer the contract on or before December 18, 1990. The transition plan included scheduling of moving the VAX computer, computer accessories, the chemicals in the repository, the cold rooms, and all the documents to COR, Dr. John Huggins.

A meeting took place at BRFF on December 7, 1990 which was attended by the contract specialist, Ms. Margorie Troiano, the COR, Dr. Huggins, the P.I., Dr. Stephen, the Project Administrator, Ms. Handelman, BRFF Contract Administrator, Mrs. Rebecca Iype, and the President of BRFF, Dr. Iype.

In this meeting, it was resolved that as of December 7, 1990, the actual work with the computer will stop and during the remaining period, all remaining equipment and property will be transferred. The COR or his representative will sign off on all the items that were to be transferred. In answer to Dr. Iype's inquiry about the performance of this contract, Dr. Huggins said that he was completely satisfied by the outcome of the contract and the performances of each of the team members.

A list of government property transferred to Fort Detrick signed by LTC Childs is attached.

BRFF would like to thank the contract specialist and COR for the smooth transfer of this contract to USAMRIID.