PROGRESS REPORT

Contract for: Research Services Directed Toward the Development of a Combined Agent for Disease Prophylaxis and Contraception

Contract No. AID/csd - 2822

July 15, 1974

January 1, 1974 - June 30, 1974

TABLE OF CONTENTS

	Page
Report Summary	1
A. General Background	2
A.2. Personnel and Consultant Utilization	3
B. Statement of Project Objectives as Stated in Contract	4
C. Continued Relevance of Objectives	5
D. Accomplishments to Date	
1. Findings	6-8
2. Interpretation of Data and Supporting Evidence	9
3. Research Design	10
E. Dissemination and Utilization of Research Results	11-14
F. Statement of Expenditures and Obligations and Contract Resources	15
Expenditures and Obligations Contract Year	16
G. Work Plan and Budget Forecast for Coming Six Months	17
Proposed Planned Expenditures-Pittsburgh Clinical Field Trial	18
Appendix A - Laboratory Report	19
Appendix B - Third F.D.A. Progress Report	20-27
Appendix C - Clinic Activity Report	28
Appendix D - Abstract and Bibliographic List	29-31
Appendix E - Use of Material	32

REPORT SUMMARY

A. 1. Research Services Directed Toward the Development of a Combined Agent for Disease Prophylaxis and Contraception - AID/csd - 2822.

2. Principal Investigator: John C. Cutler, M.D., Director, Population Division. Contractor: Graduate School of Public Health, University of Pittsburgh. Mailing Address: Fifth & DeSoto Sts., Pittsburgh, PA, 15261.

3. Contract Period: (as amended) June 30, 1970 to June 30, 1975.

4. Period covered by Report: January 1, 1974 - June 30, 1974.

5. Total A.I.D. funding of contract to date: $ 719,284.

6. Total expenditures and obligations to date: $ 531,441.

7. Total expenditures and obligations for contract year: $ 139,640.

8. Total expenditures and obligations for reporting period: $ 68,087.

9. Estimated expenditures for next contract year: $ 162,974.

B. Narrative Summary of Accomplishments and Utilization:

1. The present reporting period covers the second six months of a two-year contract extension to successfully complete the initial human field trial being conducted in cooperation with the Allegheny County Health Department Preventive Medicine Clinic. During this period the principal accomplishments have been: (a) Completing observations on 8 females for a period of one year; (b) Acquiring 15 new participants for the study; (c) Continuation of a trial analysis on infection data to date; (d) Discussions with various pharmaceutical companies for funding to establish additional field trial sites; (e) Submission of third F.D.A. Report (attached).

2. Principal accomplishments prior to this reporting period include: (a) Collection of baseline data; (b) Completion of laboratory assay of products to identify most active products to field test; (c) Development and approval of experimental design, field protocol, and all data forms; (d) Beginning of human field clinical trial with Conceptrol; (e) Agreements with various agencies to assist in the identification and acquisition of study participants.

A. General Background

Various factors such as penicillin, a high degree of public interest, the condom, and public health programs helped decrease venereal disease rates after World War II. As the venereal disease rates declined, however, there ensued a serious decline in medical and public interest, as well as in government funding for research. As a result of this declining interest, we are again faced with rapidly rising rates of venereal disease throughout the world. The increase in venereal disease rates combined with steadily rising numbers of unwanted pregnancies presents one of the major world-wide public health problems today.

In view of the fact that both unwanted pregnancy and venereal disease are often the result of unprotected or casual contact, it is felt that an intravaginal precoital preparation offering protection to the female from venereal disease and pregnancy, as well as to the male from venereal disease, would significantly complement existing contraceptive and venereal disease control techniques. Such a preparation, which could be used alone or in conjunction with other types of contraceptive agents, which would not require medical prescription or intervention, and which would be readily available regardless of age, would appeal to a large number of the sexually active and promiscuous population whose major concern is self-protection. This preparation could be promoted effectively for wide distribution and could be incorporated into existing VD and family planning programs as well as other public health programs, with a high probability of utilization.

Although prophylactic treatment is accepted in many parts of the world, little systematic evaluation of mechanical, chemical or antibiotic agents as a means of preventing venereal disease has been made in recent years. It is hypothesized that a dual-purpose intravaginal agent can be developed through research by identifying existing contraceptive products that have a dual action, and also by combining substances which are effective as local prophylactics against syphilis and gonorrhea with substances that are effective as intravaginal contraceptives.

A. 2. Personnel and Consultant Utilization

Name	Title	Man Month Effort	Salary
J. C. Cutler	Project Director	2.4	$ 1,764
B. Singh	Epidemiologist/Microbiologist	24.0	8,010
O. Nickens	Physician	12.0	6,606
U.A. Carpenter	Project Administrator/Coordinator	24.0	7,494
A. Scarola	Nurse	24.0	4,572
M. Wade	Educator	24.0	3,942
S. Wiemert	Lab Technician	24.0	2,718
F. Steinberg	Secretary	24.0	2,652
N. Sussman	Statistician	6.0	1,062

Salaries	$ 38,820
Fringe	5,241
Indirect	22,283
Other Fees	- 0 -
Total	$ 66,344

Consultants: No consultants were utilized under this contract during this reporting period.

B. Statement of Project Objectives as Stated in the Contract

This Progress Report, the eighth such Report since the original contract was awarded in July 1, 1970, covers the period from January 1, 1974 - June 30, 1974. This period of time represents the second six months of a two-year contract extension. Under the terms of this contract extension, the Project proposes to accomplish the objective of successfully completing the human field trial being conducted in cooperation with the Allegheny County Health Department Preventive Medicine Clinic which was begun under the original contract. This objective will be completed by means of (a) Identification and interviewing of possible participants in the County Clinic by Pro-Con staff; (b) Laboratory diagnosis of all smears and cultures obtained from Project participants by Pro-Con staff members in the Graduate School of Public Health; (c) Statistical analysis of data from the study and write-up by Pro-Con staff; (d) Submission of Project data to F.D.A. for possible approval of the new indication - venereal disease prophylaxis - for Conceptrol cream.

C. Continued Relevance of Objectives

Data from both the United States and World Health Organization continue to show a world-wide rise in venereal disease. "Today's VD Control Problem 1974" published by the American Social Health Association states that gonorrhea, the most frequently reported communicable disease, continued to increase in FY 1973 and reached a total of reported cases nearly double that of five years ago. During the same period of time, in no country has there been an abrupt decline in birth rates related to family planning or population programs.

In the reports of the National Commission on Venereal Disease to the Secretary of the Department of Health, Education, and Welfare, particular attention has been paid to the importance of cooperation between venereal disease and family planning programs with respect to prevention. Both the condom and possible chemical prophylactic/contraceptive preparations have been singled out in this regard.

A Bill has been passed in the Pennsylvania Legislature which requires that a course of study in venereal diseases be taught in all public junior and senior high-schools in the state of Pennsylvania.

Thus it would appear that the concept accepted by A.I.D. in funding this study has been fully recognized by experts and workers in the venereal disease field, as well as by state and federal governments. With official increased interest and acceptance of this concept by the United States, the prospect of international acceptance of a combined prophylactic-contraceptive product as another tool for venereal disease control programs appears to be enhanced should clinical studies validate the hypothesis.

D. 1. Accomplishments to Date - 6/30/74

(A) Field

Findings: 71 women have agreed to participate in the field trial and were randomly divided into study and control groups as follows:

Study - 35 individuals assigned to study group
21 have dropped out of study group
3 have completed 1 year of observation
11 are currently on trial in study group
23 individuals have contributed observational time to the trial
4 infections observed
3 individuals infected
3 re-entered after infections
152.7 person months of observation

Control - 36 individuals assigned to control group
16 have dropped out of control group
5 have completed 1 year of observation
15 are currently on trial in control group
30 individuals have contributed observational time to the trial
10 infections observed
8 individuals infected
7 re-entered after infection
252.4 person months of observation

D. 1. (A) cont'd.

During the current reporting period 15 new female participants have been entered into the Project for observation. This has increased the total number of females entered in the Project to 71. While participants have been entering the Project at a lower rate than was projected, only 29 females need to be entered and observed in the Project in order to obtain our objective of entering 100 females. While drop-outs are anticipated, past performance indicates that observation time will be gained with the majority of girls who will enter the Project in the future.

(B) Laboratory

Diagnostic services and laboratory support for field trial participants and potential candidates to be included as participants in the study were provided. A total of 1510 specimens were recieved for diagnostic services during this reporting period of six months (Appendix A). All presumptive cultures were further confirmed by appropriate biochemical and other tests for various isoletes. All positive cultures of Neisseria gonorrhoeae and Candida albicans were preserved for reference and antibiotic susceptibility tests. Every blood specimen was processed and tested by serological tests including RPR and VDRL tests.

The effect of sub-lethal doses of Conceptrol on Neisseria gonorrhoeae was determined based on morphological change and biological activity for penicillin. This study was carried out on gonococcal isolate from field trial patient. No difference was found due to a continuous exposure to this contraceptive (Conceptrol).

A recent publication "Inhibition of Neisseria Gonorrhoeae by a Factor Produced by Candida Albicans", Applied Microbiology, Vol. 27, No. 1:192-196, 1974, prompted us to confirm this report and to find if yeast infection among our field trial patients will cause misdiagnosis or false negative results. Necessary technique was developed and a total of 60 yeast cultures isolated from field trial patients were tested for their possible inhibitory effects on growth of Neisseria gonorrhoeae.

D. 1. (B) cont'd.

Results of this study showed that 89% of all Candidaalbican isolated from the patients exhibited some degree of gonococcal inhibition when grown on selective media presently used for isolation of Neisseria organisms. Based on these findings, necessary corrective steps are taken to eliminate any possible effect of multiple infections on diagnosis and isolation of different organisms.

(C) Administrative

In light of the Project objective of disseminating findings of the Project to the scientific community, abiding by the rules and regulations of the F.D.A. concerning research with human volunteers, and establishing sites and methods for acquiring participants for the Project, the administrative attainments during this reporting period have been consistent with the stated objectives of the Project. The primary accomplishments for this period are: (1) Preparation of an article to be published in Clinical Obstetrics and Gynocology; (2) Preparation of a background paper for W.H.O. session on Venereal Disease Prophylaxis; (3) Preparation and submission of the Third F.D.A. Progress Report (Appendix B) ; (4) Discussions with Clinic Medical Director for incorporating Project patient identification system into new extended therapy regimen begun by the County; (5) Continuing contact with health agencies and hospitals for identifying possible participants; (6) Review of new guidelines on research involving human volunteers to assess status of Project field trial.

D. 2. Interpretation of Data and Supporting Evidence.

During this reporting period, 77 females 21 years old or older who visited the VD Clinic had a past infection during the prior 12 months. Of this group 24 were diagnosed as having a second infection. All 24 females were interviewed and 15 agreed to participate in the study. An additional 37 females were interviewed but did not meet all the criteria for participation in the Project. During this reporting period, one source of possible participants, the Manchester Health Center, was closed and the Medical Care Center did not identify any participants eligible for the study (Appendix C).

In an effort to continue to deliver better medical treatment to Project participants than they would normally receive as a clinic patient, all participants completing their observation time are offered the option of continuing medical examination for venereal disease without payment. One female exercised her option to take advantage of this service.

D. 3. Research Design

Possible modifications of the research design are:

(1) Inclusion of patients under 21 years of age in the field trials when laws governing legal age to give effective consent are revised;

(2) The possibility of changes in regard to the requirements for use of the oral contraceptive and IUD method of preventing unwanted pregnancies;

(3) The use of proven high-risk sexually active females as participants (i.e., prostitutes).

(4) Conducting an intervention trial by giving all females with a first infection the test product to use and measuring the reduction in re-infection rates.

(5) Re-examine all infected females one month after treatment. Information from the Montgomery, Alabama gonorrhea registry showed when positive females re-tested 4-6 weeks after treatment, 19.2% were positive.

E. 1. Dissemination and Utilization of Research Results

Every effort has been made by the Pro-Con Group to disseminate the results of the research findings. These findings have been presented to:

(1) American Public Health Association 1971 and 1972

(2) National Commission on Venereal Disease 1972

(3) International Union Against the Venereal Diseases and the Treponematoses (Venice) 1972

(4) First and Second International Venereal Disease Symposiums (St. Louis) 1971, 1972

(5) Population Club (Hawaii) 1972

(6) American Society for Microbiology (Philadelphia) 1972

(7) W.H.O. Regional Office (Copenhagen) 1971

(8) Pittsburgh Public School System and Parochial School System, 1973 - Seminars as part of instructional programs (Allegheny County Health Department)

(9) Lectures of American and Foreign students of Graduate School of Public Health, University of Pittsburgh and surrounding colleges

(10) Professional staff of local hospitals, health centers and free clinics

(11) Exchange of Pro-Con scientific information via Neisseria Treponema Scientific Memoranda NIAID (NIH) - 2 contributions, 1973

In addition, results of laboratory testing have been supplied to all cooperating pharmaceutical companies concerning the antimicrobial activity of their product.

(12) American Association of Planned Parenthood Physicians (Houston) 1973

(13) American Social Health Association (New Orleans) 1973

(14) Indiana State Physicians Association (Indianapolis) 1973

(15) Department of Health and Welfare of Canada (Ottawa), Oct. 1973

(16) F.D.A. Safety and Efficacy Review of OTC Drug Products, Washington, Nov., 1973

E. 2. Findings of the Project to date include both in vitro results and the data from the human field trial.

Because of the varied lengths of observation time as well as unequal numbers of patients in the study and control group, we will continue to use the number of infections per 100 person months as the index of risk. The values of this index as of this reporting period are 2.6 infections per 100 person months (4/152.7 x 100) and 4.0 infections per 100 person months respectively for the study and control groups. These findings continue to show the encouraging trend presented in the previous report. However these data do not allow for any conclusions to be drawn which could be applied to the problem in the U.S.A. or L.D.C.s.

The criteria for the trial stipulates that each patient asked to participate must have had at least two infections within the prior twelve months. This yields a risk index of at least 16.7 infections per 100 person months for each of the patients for the year preceding entry into the field trial. It might be hypothesized that the measured index for the control group would approach this value if it were to be assumed that the patients continued their prior sexual behavior and patterns. This hypothesis is not reflected by the current risk index for the control group of 4.0 infections per 100 person months. Various reasons for this discrepancy have been proposed. Attention will be given to this question and the reasons involved as the trial approaches completion. It is felt that possible reasons for these types of observations that are being made during this initial venereal disease prophylaxis field trial will be of value not only for future trials but also for planning more effective venereal disease control programs for L.D.C.s as well as the United States.

E. 3. Field experience continues to point out the need for educational and motivational material on V.D. prophylaxis for those sexually active individuals at risk. Plans for the field trial call for the development of appropriate educational and motivational material including information on prophylaxis as well as recognition of symptoms, and how and where to obtain treatment. This material will be directed toward the various population segments at risk.

Preliminary work in this area has begun and can be carried out under current provisions of the contract. It is expected that the Allegheny County Preventive Medicine Clinic and the American Social Health Association will be helpful in this endeavor, as well as in assisting with incorporation of the developed programs into existing school programs and existing venereal disease educational and motivational materials.

Little is known concerning attitudes and preferences toward creams, jellies, foams, suppositories and foaming tablets as intravaginal contraceptives. The Allegheny County Health Department field trials could be utilized to test the various dosage forms to evaluate the acceptance factors of different delivery systems.

Our experience in the clinic, while limited to females, has brought to light the problem presented by the asymptomatic male. The research project could be expanded to define the scope of the asymptomatic male contribution to the V.D. epidemic.

Preliminary findings from this study seem to hint that the sexual behavior of females in this study who acquire repeated venereal infections is not what is 'commonly' thought of as promiscuous behavior in terms of number of partners, nor 'sexually active' in terms of number of acts of coitus per 2 week period of time. Research which included the male partner of these females to determine the male's sexual behavior patterns could shed light on risk the female runs of acquiring an infection from an infected male partner.

E. 4. In as much as the contract extension was granted to complete only the local field trial being conducted in the Allegheny County Health Department and not for additional overseas field trial sites, present plans under this contract do not include involvement of L.D.C.s.

However, proposals for overseas field trials have been submitted to other interested funding agencies. In the event any of these proposals are approved and funded, the Pro-Con concept being supported by A.I.D. will involve L.D.C.s by way of overseas field trial sites.

F. Statement of Expenditures and Obligations and Contract Resources

The most significant factor related to the budget plan for the year continued to be slower-than-projected acquisition of patients. Possible participants for the trial still must be 21 years of age or older to give effective consent for participation. While attempts have been made by the University to expedite lowering the age of consent, the bill pending in the state of Pennsylvania to lower the age to 18 has not yet been passed. It is felt that access to younger females would increase the size of the sample for this Project. In addition to this restriction, a number of women attending the various clinics used for participant identification do not give their correct name, address, and phone number, which makes it impossible to contact them about the Project after they have been identified. This appears to be a common characteristic of female patients attending VD clinics.

The clinic staff of the Project is continuing to make efforts to work out new methods of patient relationship and motivation which may stimulate interest in entering the Project and maintain cooperation for the entire study period.

There have been no significant changes or modifications in Project management, staffing patterns, physical facilities or institutional environment during this contract year.

Expenditures and Obligations Contract Year

July 1, 1973 - June 30, 1974

Salaries and Wages		$ 77,640
Fringe (13.5)		10,481
Consultant		-0-
Travel and Transportation(1)		1,280
Other Direct Costs		3,481
Telephone	$ 176	
Postage	60	
Publication	94	
Participants	3,151	
Supplies and Equipment(2)		2,074
Expendable	1,910	
Non-expendable	164	
Total Direct Costs		94,956
Indirect Costs		44,565
GRAND TOTAL		$ 139,521

(1) Includes local travel

(2) Includes maintenance & repairs

G. Work Plan and Budget Forecast for Coming Contract Year

Under provisions of the approved contract extension, the work plan for the coming six months is to maintain the cooperation of the participants presently in the trial and to increase the rate of participant acquisition to successfully complete the study. To increase the rate of participant acquisition, contacts will be made with additional hospital clinics for cooperation, and with private physicians in an effort to gain their confidence and cooperation. In addition, as the trial progresses, problems in methodology and handling of data which arise will be solved and incorporated into existing protocols and criteria. The overall objective of this effort is to establish precise definitions and methodologies for future trials from problems encountered in this initial field trial.

All laboratory back-up for the reexamination of the participants in the Project will be continually performed. All measurable results from the field trial will continue to be disseminated as widely as possible to the scientific community by means of articles in appropriate journals and by presentations at scientific meetings.

Expenditures for the next contract year reflect the estimated costs for continuation of the local field trial. This budget includes adjustments in salaries, fringe benefits, and indirect costs consistent with recent changes in University of Pittsburgh policy.

Proposed Planned Expenditures- Pittsburgh Clinical Field Trial

July 1, 1974 - June 30, 1975

Salaries & Wages		$ 85,644
Fringe (13.5%)		11,562
Consultant		1,250
Travel & Transportation (1)		770
Other Direct Costs		9,155
Telephone	$ 300	
Postage	150	
Publications	705	
Participants	8,000	
Equipment & Supplies (2)		5,814
Expendable	2,614	
Non-expendable	3,200	
Total Direct Costs		114,195
Total Indirect Costs		48,779
GRAND TOTAL		$ 162,974

(1) Includes local travel

(2) Includes maintenance & repairs

Laboratory Report

January 1, 1974 - June 30, 1974

Culture	Total Diagnosed	No. of Positives
N. gonorrhoeae	974	2
T. vaginalis	225	39
C. albicans	244	53
Serology	67	1
Total	1510	95

APPENDIX B

Third F.D.A. Progress Report of Clinical Investigation

I.N.D. 8788 - June 30, 1974

This is the third progress report of the clinical field trial to investigate the potential prophylactic value of Conceptrol Cream against the organisms causing venereal diseases which was begun in August, 1972. The following charts describe current participants on trial, drop-outs, side effects and subjective complaints and re-infections in participants while on trial.

To date, 71 women have agreed to participate in this study. Of the 35 women assigned to the test group, 23 individuals have contributed observational time to the trial (152.7 person months of observation). Of the 36 women assigned to the control group, 30 individuals have contributed observational time to the trial (252.4 person months of observation). As of June 30, 1974, in the test group, 11 individuals are currently on trial, 3 have completed one year's observation, 4 infections have been observed, and 21 females have dropped out of the study. In the control group, 15 individuals are currently on trial, 5 have completed one year of observational time on trial, 10 infections have been observed, and 16 females have dropped out of the study (Chart 1). A more detailed breakdown of the study and control groups is shown in Charts 2 - "Individuals Currently Participating in the Trial", and Chart 3 - "Drop-outs".

Side effects encountered during the trial continue to be slight to moderate and for the most part self-limiting, as shown in Chart 4.

The total number of re-infections occurring in both groups is shown in Chart 5, and the females completing one year of observation are shown in Chart 6.

Chart 1

Field Trial Summary

June 30, 1974

Seventy-one women have agreed to participate in the field trial and were randomly divided into study and control groups as follows:

Study - 35 individuals assigned to study group

21 have dropped out of study group

3 have completed 1 year of observation

11 are currently on trial in study group

23 individuals have contributed observational time to the trial

4 infections observed

3 individuals infected

3 re-entered after infections

152.7 person months of observation

Control - 36 individuals assigned to control group

16 have dropped out of control group

5 have completed 1 year of observation

15 are currently on trial in control group

30 individuals have contributed observational time to the trial

10 infections observed

8 individuals infected

7 re-entered after infection

252.4 person months of observation

Chart 2

Individuals Currently Participating in the Trial

June 30, 1974

STUDY			CONTROL		
ID#	Entry Date	Weeks* on Trial	ID#	Entry Date	Weeks* on Trial
155199	8/6/73	43.7	058323	4/12/73	62.7
160704	9/17/73	40.9	041855	6/4/73	50.6
159656	10/12/73	35.9	056877	6/22/73	53.3
161701	11/14/73	31.3	058842	6/26/73	49.3
161893	11/16/73	30.6	051359	6/29/73	51.3
148467	11/19/73	30.4	028476	7/3/73	50.3
150864	1/25/74	22.3	059335	8/20/73	43.4
163220	3/15/74	13.3	055528	11/5/73	32.6
159347	3/26/74	13.7	060699	11/15/73	32.4
163589	4/23/74	9.7	028831	11/29/73	30.4
164688	5/23/74	5.4	063263	2/25/74	temp
			043127	2/25/74	16.4
			062983	3/8/74	16.3
			061040	5/23/74	5.4
			062459	--	--
			064732	--	--

* Time on trial is calculated from 'entry date' to date of last contact. Time under antibiotic therapy is not included.

Chart 3

Drop-outs

June 30, 1974

STUDY GROUP

ID#	Entry date	Drop-out date	Weeks on trial	Reason
152993	8/15/72	---	0	never returned-unable to contact
150368	8/28/72	8/13/73	43.4	pregnant
153258	10/3/72	10/5/73	56	completed 1-year observation
153509	10/10/72	---	0	never returned-unable to contact
154324	10/13/72	---	0	unstable working hours
150412	1/9/73	---	0	never returned-unable to contact
149596	2/9/73	---	0	lives too far
146723	2/20/73	4/30/73	10	switched to control
151543	4/3/73	---	0	never returned-unable to contact
155449	4/6/73	---	0	numerous reasons
148323	5/8/73	6/7/73	4.4	unable to contact
128831	5/29/73	11/29/73	26.4	switched to control
154701	6/11/73	---	0	lives too far
150723	7/3/73	---	0	never returned-unable to contact
159736	7/27/73	8/24/73	4	pregnant
155526	8/14/73	---	0	never returned-unable to contact
156486	2/6/73	5/13/74	57.9	completed 1-year observation
157526	3/2/73	11/23/73	3.8	new job commitments
116511	4/18/73	5/3/74	54.3	completed 1-year observation
160134	8/28/73	5/16/74	37.4	temporary -- off birth control
158203	10/1/73	---	0	never returned-unable to contact
160200	11/26/73	---	0	too busy
161552	2/13/74	---	0	never returned-unable to contact
163125	2/22/74	3/8/74	2	children - too hectic

Chart 3 (cont'd)

Drop-outs

June 30, 1974

CONTROL GROUP

ID#	Entry date	Drop-out date	Weeks on trial	Reason
045139	10/9/72	10/30/72	3	new job
053785	10/13/72	8/24/73	45.1	angry; positive culture
052434	10/17/72	7/26/73	40.4	moved to Florida
052077	10/18/72	---	0	pressure at home
049012	11/16/72	---	0	never returned-unable to contact
043853	11/17/72	---	0	never returned-unable to contact
052568	12/22/72	---	0	unable to keep frequent appointments
053890	2/6/73	2/27/74	53.3	completed 1-year's observation
051408	2/14/73	2/21/74	53.1	completed 1-year's observation
051489	3/1/73	4/20/74	55.7	completed 1-year's observation
029207	3/23/73	4/19/74	55.3	completed 1-year's observation
048331	4/10/73	11/2/73	28.4	never kept appointment
054740	4/11/73	5/14/74	52.4	completed 1-year's observation
046723	4/30/73	5/17/74	51.4	changed birth control
049596	5/29/73	11/16/73	23.7	unable to re-contact
060342	8/20/73	11/26/73	14	unable to re-contact
047328	8/28/73	11/2/73	8.7	unable to re-contact
096843	10/8/73	---	0	does not want to participate
061882	11/16/73	3/15/74	17	interfering with job
063263	2/25/74	5/23/74	12.6	went to Chicago for summer
055945	3/22/74	4/20/74	4.1	working, unavailable

Chart 4

Test-Patient Side Effects and Subjective Complaints

June 30, 1974

160134	none	messy
153258	itching (first five weeks)	sometimes interferes with sex pleasure, messy
116511	chafing	messy, partner objects to use
157526	none	sometimes interferes with sex pleasure, messy
156486	none	messy
128831	itching-rash	too wet
148323	none	interferes with sex pleasure
146723	itching/burning	interferes with sex pleasure, messy, objected to use
150368	itching/burning	messy, wet
161701	none	messy
160704	none	applicator uncomfortable, product not convenient
163589	none	messy, drains after intercourse

Chart 5

Infections

June 30, 1974

Study			Control		
ID#	Infection date	Weeks on trial	ID#	Infection date	Weeks on trial
153258	8/13/73	44.6	053785	8/24/73	45.1
	11/15/73	11.4	058842	7/9/73	2.
150368	3/23/73	30.	049596	8/9/73	10.4
161893	5/30/74	26.4		11/14/73	11.
			051359	8/24/73	8.
			053890	3/16/73	5.6
			046723	10/31/73	26.4
				12/28/73	7.4
			055528	11/16/73	2.
			041855	1/25/74	30.7

Chart 6

Completed Observations

June 30, 1974

STUDY				CONTROL			
ID#	Entry Date	Final Exam	Time on Trial	ID#	Entry Date	Final Exam	Time on Trial
153258	10/3/72	11/15/73	55.9	053890	2/6/73	2/27/74	53.3
156486	2/6/73	5/13/74	57.9	051408	2/14/73	2/21/74	53.1
116511	4/18/73	5/3/74	54.3	051489	3/1/73	4/20/74	55.7
				029207	3/23/73	4/19/74	55.3
				054740	4/11/73	5/14/74	52.4

CLINIC ACTIVITY REPORT

January 1, 1974 thru June 30, 1974

Total female visits 3239 Non GC 1071 Non-diagnostic 920 GC visits 1248

GC visits		% of total GC visits
21+	650	52.08
18-20	308	24.68
-18	290	23.24
	1248	

Past infections		% of GC visits
21+	122	18.77
18-20	73	23.70
-18	38	13.10
	233	

Past infections-prior 12 months		% of past infections
21+	77	63.11
18-20	60	82.19
-18	34	89.47
	171	

Allegheny County Preventive Medicine Clinic

Total Positive cultures, prior 12 months 21+	24	% of prior 12 months	31.17
Total never returned	0		
Total interviewed meeting criteria	24	% of 21+ positives	79.22
Total acceptors	15	% of interviewed	62.50
Total Non-acceptors	9		
Interviewed, didn't meet final criteria	37		
Total interviewed	61		
Acceptors identified by other sources	0		
Total acceptors this report period	15		

E.1.(1) Papers and publications developed under this contract fall into the following categories: (1) the role of prophylaxis in the control of venereal disease; (2) description and results of laboratory studies on the development of a vaginal preparation to provide venereal disease and genital infection prophylaxis as well as contraception; (3) statistical models for predicting relative risk contracting gonorrhea versus syphilis; and potential impact of chemical prophylaxis on incidences of venereal diseases; (4) description of Pittsburgh clinical field trial design.

(1) Role of Prophylaxis - points discussed are: the history of prophylaxis, the success of venereal disease prophylaxis in both World Wars, discontinuance of interest in prophylaxis after World War II, importance of reconsidering prophylaxis once again in light of current epidemics, importance of providing protection against unwanted pregnancy as well as transmission of venereal disease with one product, the importance of research to evaluate effectiveness of available products, and studies involving individual motivation, practice, responsibility, and delivery of public health services.

(2) Description and Results of Laboratory Studies - describes procedures used for testing, discusses survival and recovery of *N. gonorrhoeae* under different environmental conditions, reports the antimicrobial effects of a number of commonly used intravaginal contraceptives and other preparations on *N. gonorrhoeae*, *T. pallidum*, *C. albicans*, and *T. vaginalis*, and indicates that results are encouraging and postulates that an agent simultaneously offering prophylaxis against venereal disease and contraception would be of great value to both existing family planning and venereal disease control programs.

(3) Statistical Models - describes the development of a theoretical model and uses the model to predict the possible dramatic change in the prevalence of gonorrhea if topical venereal disease prophylaxis is incorporated into existing venereal disease programs and is used by population at risk. Also based upon joint probability of transmissibility and prevalence, the relative risk of contracting gonorrhea versus syphilis is calculated and used in an equation to predict effectiveness of contraceptive products tested *in vitro*.

(4) Description of Pittsburgh Clinical Field Trial Design - outlines the detailed field trial protocol under which Pittsburgh field trial is being conducted.

"Anti-VD Contraceptives Tested in Field Trials," VD Clinical News, 3:3:4, 1973.

Arnold, R. C. and Cutler, J. C., "Search for a Preparation to Prevent Venereal Disease and Pregnancy," Public Health Reports, 85:1062, 1970.

Cutler, J.C., "The Future of Prophylaxis in V.D. Control," The V.D. Crisis: The 1972 International Venereal Disease Symposium, 1972, pp. 92-93.

Cutler, J.C., "Prophylaxis in the Venereal Diseases," Medical Clinics of North America, 56:1211-1216, 1972.

Cutler, J.C., "The Role of Prophylaxis," The V.D. Crisis: The 1971 International Venereal Disease Symposium, 1971, pp. 29-30.

Cutler, J.C., Singh, B., Utidjian, H.M.D., and Arnold, R.C., "Development of a Vaginal Preparation Providing Both Prophylaxis Against Venereal Disease and Contraception," British Journal of Venereal Disease, 49:149, 1973.

Cutler, J.C., Utidjian, H.M.D., Singh, B. and Arnold, R.C., "Studies on Development of a Vaginal Preparation Providing Both Prophylaxis Against Venereal Disease, Other Genital Infections, and Contraception: I. Venereal Prophylaxis, Past Experience, Present Status and Plans for Future Studies," Military Medicine, 138:88-91, 1973.

"Do Spermicides Prevent VD?," Family Planning Digest, 2:1:8, 1973.

"Encouragement of VD Prophylaxis Seen Imperative," Ob. Gyn. News, 7:18:13, 1972.

Lee, T.Y., Utidjian, H.M.D., Singh, B., Carpenter, U. and Cutler, J.C., "The Potential Impact of Chemical Prophylaxis on the Incidence of Gonorrhea," British Journal of Venereal Disease, 48:376-380, 1972.

Lee, T.Y., Utidjian, H.M.D., Singh, B., Carpenter, U. and Cutler, J.C., "The Relative Risk of Contracting Gonorrhea Versus Syphilis Based Upon the Joint Probability of Transmissibility and Prevalence," HSMHA Health Report (in press).

Singh, B., Cutler, J.C. and Utidjian, H.M.D., "Studies on Development of a Vaginal Preparation Providing Both Prophylaxis Against Venereal Disease, Other Genital Infections and Contraception: II. In Vitro Effect of Vaginal Contraceptive and Non-contraceptive Preparations on Treponema Pallidum and Neisseria gonorrhoeae," British Journal of Venereal Diseases, 48:57-64, 1972.

Singh, B., Cutler, J.C. and Utidjian, H.M.D., "Studies on Development of a Vaginal Preparation Providing Both Prophylaxis Against Venereal Disease, Other Genital Infections and Contraception: III. In Vitro Effect of Contraceptives and Non-contraceptive Preparations on Candida albicans and Trichomonas vaginalis," Contraception, 5:402-411, 1972.

"Study Suggests Vaginal Infections May Lead to Missed GC Diagnosis," VD Clinical News, 3:2:1, 1973.

"Vaginal Contraceptives Declared Anti-VD," VD Clinical News, 2:1:1, 1972.

"Vaginal Prophylactic Research Advances," Family Practice News, 3:6:41, 1973.

"VD Prophylactic That Answers Contraception Seen Promising," Ob. Gyn. News, 7:22:26, 1972.

Singh, B., "Anti-VD Effect of Spermicides", Medical Aspects of Human Sexuality, Sept. 1973, Vol. VII, No. 9.

PAPERS PRESENTED IN NATIONAL AND INTERNATIONAL MEETINGS

Cutler, J.C., Singh, B., Utidjian, H.M.D. and Arnold, R.C., 1971. "Studies on a Combined Venereal Disease Prophylactic-Contraceptive Agent," APHA. Official Program and Abstracts, Page 109.

Cutler, J.C., 1971. "The Role of Prophylaxis," The International Venereal Disease Symposium.

Cutler, J.C., 1972. "The Future of Prophylaxis in V.D. Control," The International Venereal Disease Symposium.

Cutler, J.C., Singh, B., Utidjian, H.M.D., 1972. "Studies on the Development of a Vaginal Preparation Providing Both Prophylaxis Against Venereal Disease and Contraception," XXVII General Assembly of the International Union Against the Venereal Diseases and the Treponematoses. Presented by Bruce Webster, M.D. - Chairman, National Commission on V.D.

Cutler, J.C., Nickens, O.J., and Balinsky, H., 1973. "Pro-Con Vaginal Contraceptives as Venereal Disease Prophylactic Agents," American Association of Planned Parenthood Physicians.

Nickens, O.J., 1973. "The Pro-Con Project," Indiana State Physicians Association.

Singh, B., 1972. "Survival and Recovery of Neisseria gonorrhoeae Under Different Environmental Conditions," APHA.

Singh, B. and Swab, G., 1972. "Antimicrobial Effect of Contraceptives on Treponema pallidum, Neisseria gonorrhoeae and Candida albicans," Abstracts of the Annual Meeting of the American Society for Microbiology.

Cutler, J.C., Oct. 1973, "In Search of Solutions to the Problem of Gonorrhea Vaginal Contraceptives as V.D. Prophylaxis", WHO Programme of the International Symposium on Gonorrhoea, Ottawa, Canada.

Cutler, J.C., Nov. 1973, "Efficacy of VD Prevention Using Certain Vaginal Preparations", FDA Safety and Efficacy Review of OTC Drug Products, Washington, D.C.

ABSTRACTS AND SCIENTIFIC COMMUNICATIONS

Cutler, J.C., Military Medicine abstracted in Medical Digest (in press).

Lee, T. Y., "Clinical Efficacy Trial of Prophylaxis-Contraceptive Compounds in Preventing Gonococcal Infection. I. Field Trial Design," WHO/VDT/RES/GON/73.74.

Singh, B., "Antimicrobial Effect of Chemical Contraceptives on Neisseria gonorrhoeae," Neisseria Treponema Scientific Memoranda, Memo NT-5/1 May, 1972.

Singh, B. and Cornesky, R., "Antigenic Fractions from Protoplasm of Neisseria gonorrhoeae," Neisseria Treponema Scientific Memoranda, Memo NT-24/1 January 1973.

Singh, B. and Cutler, J.C., "Effect of Intravaginal Chemical Contraceptives on Treponema pallidum," Neisseria Treponema Scientific Memoranda, Memo NT-4/1 May, 1972.

Singh, B. and Lee, T.Y., "Resistance of Gonococci Before and After Serial Passage in Presence of Prophylactic-Contraceptive Agent," Neisseria Treponema Scientific Memoranda, (in press).

Singh, B., Lumpkin, H.L. and Cutler, J.C., "Survival and Recovery of Neisseria gonorrhoeae Under Different Environmental Conditions," Neisseria Treponema Scientific Memoranda, Memo NT-18/1 July, 1972.

APPENDIX E

E. 1. (2) During this reporting period, material from the project was utilized as follows:

(a) Presentation to the WHO International V.D. Conference on Gonorrhea by the Department of Health and Welfare of Canada, Ottawa, Canada, October 1973.

(b) Presentation to the FDA Review Committee on Safety and Efficacy of OTC Drug Products, Washington, D.C., November 1973.