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Final Report on
the Study of the
Use of a Vaginal
Contraceptive 100

Final Report on the Study of the Use of a
Vaginal Contraceptive, Conceptrol Cream, as a
Prophylaxis against Gonorrhoea as carried out by

Graduate School of Public Health
University of Pittsburgh

and

Allegheny County Preventive Medical Clinic
Allegheny County Health Department
Pittsburgh, Pennsylvania

FINAL REPORT

RESEARCH SERVICES TOWARD THE DEVELOPMENT OF A COMBINED
AGENT FOR DISEASE PROPHYLAXIS AND CONTRACEPTION
AID/csd 2822

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SUMMARY OF FINDINGS

The review of the laboratory findings indicate, as would be suggested by review of the content of the vaginal contraceptives approved by FDA for over-the-counter sales, that there is a very substantial degree of anti-bacterial activity in the various chemical preparations with respect to *Neisseria gonorrhoeae*, *Treponema pallidum*, *Candida albicans*, and *Trichomonas vaginalis*.

It is to be noted that no clinical attempt was made during the course of this study to evaluate the eventual study preparation, Conceptrol Cream, the single dose packet of Delfen Cream, or any of the other preparations as a prophylaxis against syphilis. The reason for this is obvious when one notes the low rate of syphilis in the U.S. population and specifically in the Pittsburgh SMSA served by the Allegheny County Health Department. Because of the highly-effective national and local venereal disease (VD) control program in terms of syphilis, it would be extremely difficult to obtain the large number of patients for clinical trial which would be required to provide significant data.

The analysis of the data indicate clearly that in terms of the experimental design and the limitations inherent in it that the vaginal contraceptive, Conceptrol Cream has value in the prevention of infection with gonorrhea in the female when used pre-coitally and as directed for contraceptive purposes.

In light of the evidence presented, there is in the first 6 months after the infection which brings the patient into the study a statistically significant lowering of the incidence of gonorrhea in the patients using Conceptrol Cream as compared to the control group. It now appears that there is available for use in VD control programs a prophylactic preparation which

is applied to the female, for which she alone can take the responsibility, and which offers protection against the transmission of gonorrhoea to her. Furthermore, experience has shown that the vaginal preparation tested when used according to the directions is highly effective as a contraceptive agent. The findings thus suggest the possibility of integrating the concepts of VD control, and even sexually-transmissible-disease-control, into population/family planning programs. Conversely increased use of the vaginal contraceptive Conceptrol Cream and others, should they be shown effective in the family-planning/population programs, would offer increased protection against the transmission of the venereal diseases and possibly others of the group classified as sexually transmissible diseases. It thus appears that there exists an opportunity to use a well-accepted and proven preparation which has been available for many years as an effective over-the-counter contraceptive much more aggressively and actively in programs designed to control venereal disease transmission and thus concurrently diminish the occurrence of unplanned pregnancy. Thus the female now has available for her self protection against both unwanted pregnancy and gonorrhoea a product which she can use without physician intervention or the requirement for cooperation of her sexual partner.

RESEARCH SERVICES DIRECTED TOWARD THE DEVELOPMENT OF A
COMBINED AGENT FOR DISEASE PROPHYLAXIS AND CONTRACEPTION
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INTRODUCTION

In the following pages, a report will be given of the laboratory studies and subsequent clinical trial to test the possible effectiveness of vaginal contraceptives as venereal disease (VD) prophylactic agents. The study has been based upon the hypothesis that the standard, FDA-accepted non-prescription vaginal contraceptives, creams, jellies, foams, and suppositories all contain agents which, in addition to being spermicidal, may also have the properties of being antibacterial with respect to *N. gonorrhoeae*, *T. pallidum*, *C. albicans*, and *T. vaginalis* thus protecting against transmission during sexual intercourse. In addition, they may well be lethal to a number of the other agents which are responsible for the other sexually transmissible diseases. A recent monograph by Bennett (1) on chemical contraception gives details on the chemical bases of currently used preparations. From this the relationship between cellular toxicity with respect to both the sperm cell and various pathogens is evident.

The reasons for this hypothesis are twofold. In the first place a number of the vaginal preparations contain surfactant agents which are known to be antibacterial in nature. In addition, the preparations contain agents such as mercury compounds and numerous other agents also known to be antibacterial. Details of composition of all preparations tested in the project will be found in Appendix A. As the usage of these types of preparations and of the condom has declined over the years since the introduction of the oral contraceptives

and intrauterine devices in the decade of 1960, there has been noted a concurrent rise in rates of infection with gonorrhoea and to a lesser extent, with syphilis. The most obvious epidemiologic explanation is the loss of the chemical and mechanical barriers to transmission of infection resulting from the rapidly growing use of the pill and the IUD and the related discontinuance of the mechanical and chemical-barrier types of contraceptives (2).

In order to prove the hypothesis two steps were necessary. First, the currently marketed FDA approved vaginal contraceptives had to be tested in the laboratory to determine antibacterial effectiveness in vitro. For *N. gonorrhoeae*, *T. vaginalis*, and *C. albicans*, standard procedures were available requiring only slight modifications related to the substances being tested. For the *T. pallidum*, testing required use of the male rabbit which required an 8 month period of observation for each preparation tested. In this study, again, a large background of experience existed. The rabbit is the animal model in which therapy and prophylaxis of syphilis had been studied for almost three quarters of a century so that there exists a firm basis for study. Furthermore, Dr. R. C. Arnold, one of the consultants, had had long experience in work with prophylaxis in the rabbit and in man in the Venereal Disease Research Laboratory (VDRL) of the USPHS at Staten Island, N.Y. (3). When the laboratory studies were completed, a review of laboratory findings, of packaging characteristics, of patient potential-acceptability, and of the anti-bacterial spectrum was carried out so as to permit the selection of the agent for the first field trial. On the basis of all considerations the product Conceptrol Cream, Nonoxynol 9, a single-dose packet of Delfen Cream, manufactured by Ortho Pharmaceutical Corporation, was selected. A clinical field test was planned and carried out in cooperation with the Allegheny County Health Department. The decision to limit the study to gonorrhoea was

made because of the relatively low rates of syphilis in Allegheny County and the consequent difficulty that could be foreseen in conducting a field trial to study any disease other than gonorrhea.

It was hypothesized that if one or more of the vaginal contraceptive preparations were found to be protective against transmission of gonorrhea, for the first time a preparation would be available to the female for her own use and self-protection independent on any male cooperation such as is afforded through his use of the condom. This would provide the female then with the same type of self-administered protection which is offered to the male through the use of the condom. It would in theory offer the female the opportunity for self-protection against both venereal disease and pregnancy through a non-prescription agent. It was further felt that it was desirable from the public health point of view to have available for more widespread use this type of preparation, if it could be shown effective, because of the need to attempt to stem the rapid increase in the rates of gonorrhea in the United States as well as abroad, particularly in the younger age group. It seemed that such a preparation if proven effective and thus accepted by the FDA and then incorporated into VD control programs and effectively promoted as both prophylactic and contraceptive would have a higher probability than any preparation requiring medical intervention of being widely accepted and used by this higher-risk group, not commonly under close medical supervision or accustomed to securing prescription contraceptives from a personal physician. It was further obvious that this type of dual-purpose preparation for use in international programs would offer an effective contraceptive preparation with additional self-protective VD prophylactic characteristics which could then be introduced into VD control programs directed towards the sexually active group so identified because of clinically-demonstrated venereal disease.

There would thus be opportunity for the wider promotion and use of a single preparation offering protection against both pregnancy and venereal disease. Such dual purpose preparations could be expected to be utilized in population and venereal disease control programs of various nations and in the health and population programs of various international agencies. In view of a very strong move on the part of many governments to tie together family planning and general public health programs it was further felt, particularly because of the WHO concern with the sexually transmitted diseases, as reflected in the Technical Discussion of the 28th World Health Assembly (4), that the value of a dual-purpose preparation of this kind could potentially be very great with respect to the goals of both STD/control and population programs. Thus VD prophylaxis promotion in family planning programs would offer the type of protection against both venereal disease and unplanned pregnancy that is felt desirable. Promotion through the VD control programs would then provide the added benefit of helping to cut down on the rates of unplanned pregnancy in a group known to be at high risk of unplanned pregnancy because of an established pattern of sexual practices lacking self-protective components.

It should be noted that there has been very strong informal as well as formal support of this concept from WHO, PAHO, the American Social Health Association, and various other groups concerned with population problems and the sexually transmitted diseases.

STUDY PROPOSAL

There has been a vast experience with the use of prophylaxis as an element of successful venereal disease control programs. The review of the literature has conclusively demonstrated the effectiveness of a prophylactic program involving both the condom and the locally applied agents, either self-administered or as station prophylaxis, in bringing about remarkable reductions of rates of venereal disease infection in World War I and World War II. A detailed report of this experience is found in official reports. Experience to date has further shown that experimental findings with respect to both local prophylaxis and parenteral therapy for syphilis in the rabbit have a very high index of predictability with respect to application to man.

With respect to gonorrhoea, however, the only effective test animal in which the clinical and epidemiological characteristics of the disease are similar to man is the chimpanzee. Thus, practically all of the studies on prophylaxis of gonorrhoea in the male have had to be carried out in the human. Here again, in the reports from the literature, a significant body of experimental studies, both clinical and epidemiologic (5), in humans exists. In addition to the experience with male prophylaxis both self-applied and station-applied in the two world wars, as summarized by Greenberg (6), numerous reports on female vaginal prophylaxis are found in the literature. Various studies reported by Funes and Aguilar (7), Tsukara, et al. (8), Porter, et al. (9), and Edwards (10) demonstrated that certain medicated douches given post contact as well as certain vaginal tablets containing antibiotics and certain organic iodine preparations all of which are used by the female pre

or post contact provide a high degree of protection against the transmission of gonorrhoea.

Thus there was further reason to hypothesize that an agent deposited pre coitally in the vagina and having antibacterial properties sufficient to protect against infection or insemination from the male would also probably provide a similar high degree of protection to the uninfected male partner should his female partner have an infection.

At the completion of Phase I of the project--laboratory studies of the effect of the various contraceptive agents on the four test organisms, *N. gonorrhoeae*, *T. pallidum*, *C. albicans*, and *T. vaginalis*--it was then possible to select the preparation to be used for Phase II of the project. Certain criteria were felt essential in order to assure that the preparation to be field tested would be one which would fit into both family planning and VD control programs both in the AID-assisted projects abroad, as well as in the United States. It was felt necessary that the preparation selected for field testing be available over the counter without medical prescription or physician intervention in a single dose disposable package. It was further necessary that the preparation be one approved for use as a vaginal contraceptive by the Food and Drug Administration. The reason for this was that the requirements for approval for a new use of a preparation already approved for vaginal contraception would not call for long-term and expensive testing for toxic effects in addition to the clinical testing required to meet requirements of FDA with respect to a completely new preparation.

On the basis of these considerations and of analysis of the laboratory findings, a decision was made to use the preparation Conceptrol Cream, the single dose packaging of the vaginal contraceptive also available in the multiple dose tube as Delfen Cream. The Ortho Pharmaceutical Company,

Raritan, New Jersey, which makes these preparations very graciously agreed to supply all the pharmacological data necessary for the filing of an I.N.D. so as to permit the clinical study of Conceptrol Cream as a prophylactic agent in accordance with FDA regulations. The manufacturer also agreed to make available at no cost to the project the unlabeled packets of Conceptrol Cream required for clinical trial. The legal documentation is found in Appendix B.

The decision was made that the first clinical trial should take place within the U.S. and that future testing abroad if and when appropriate would be a replication of U.S. studies, modified as seen necessary as a result of U.S. experience and local consideration.

Because of the long standing cooperative relationship between the Allegheny County Health Department and the Graduate School of Public Health, University of Pittsburgh, the County Health Department offered the services of its VD clinic for the conduct of the study. Thus the Allegheny County Health Department, Dr. Frank Clack, Director, and the professional staff of the VD clinic served as collaborators at no cost to the project. It was further understood in planning for the field trial in the County Clinic that the project staff would function as members of the staff of the VD Clinic, taking part in all clinic operations in such a way as to be able to identify the patients, as well as to be able to work with them within the framework of normal clinic operation. In this way it was possible to assure the fullest access to potential patients as well as assure for the study participants the highest quality of medical care by both the project and clinic staff. Finally, it is important to point out that the actual volume of patients coming to the clinic was such that the intimate collaborative efforts of the project staff and the VD Clinic personnel were essential in order to assure that there would

be no interference with normal clinic operation which could then form the basis for community complaint about experimentation being carried out. It should be noted that thanks to the efforts of both the Allegheny County Health Department staff and the project staff, there were no problems whatsoever involving interpersonal relationships of the investigators, the staff of the clinic, or the patients.

In compliance with federal and University of Pittsburgh requirements with respect to human experimentation, procedures were established to secure informed consent and to assure that all laws and regulations were complied with.

Following satisfaction of all legal and other requirements, an agreement between the County Health Department, AID, the Graduate School of Public Health, and Ortho Research Foundation was arrived at and the clinical field trial was finally undertaken.

The details of the laboratory studies, both preceding the field trial and associated with the field trial and the report on the clinical trial design and implementation follow.

PHASE I

LABORATORY STUDIES TO ESTABLISH POSSIBLE PROPHYLACTIC PROPERTIES OF VAGINAL CONTRACEPTIVES

The various chemical preparations that were proposed to be included for testing were as follows:

1. Existing FDA approved vaginal contraceptives which contain spermicides that might be expected to have spirocheticidal and bactericidal properties.
 - a. Certain vaginal contraceptives widely used abroad but not sold or approved for use in the U.S. were tested as submitted from AID, WHO, or other international sources.
2. Certain antibiotics that are used topically for treatment of vaginal diseases.
3. Certain currently-used antiseptic preparations for intravaginal use.
4. Certain new compounds that pharmaceutical companies and other research groups were developing for vaginal use and which appeared to have particularly high potential.

The laboratory facilities especially for venereal disease studies, including animal (rabbit) facilities for syphilis work, were established. Though various conventional and widely-used methods are known for testing bacterial susceptibility to antibiotic and chemotherapeutic agents, preliminary studies were carried out to determine the group of tests that would probably provide the most accurate and applicable methodology for this project. The variety of preparations ranging from foams to suppositories presented unique laboratory problems with respect to comparative testing. In addition to the accuracy of the selected tests, it was also considered that these

tests should relate as closely as possible to the natural situations of sexual contact and related contraceptive behavior.

An extensive review of the literature on prophylaxis, testing procedures and other aspects of venereal disease was compiled (Appendix C).

For perfecting the laboratory testing techniques and other related methodologies, the *N. gonorrhoeae* and certain other isolates from genital infections were obtained from local venereal disease clinics, however, later all studies were carried out with strains of various test microorganisms obtained from Center for Disease Control (CDC), Atlanta, Georgia, and American Type Culture Collection (ATCC), Rockville, Maryland. Various laboratory testing techniques and methodologies were perfected and these standardized procedures were used throughout the life of this project. The details of testing methods and techniques for maintaining syphilis spirochetes (Appendix D), harvesting *T. pallidum* (Appendix E), determination of spirocheticidal activity (Appendix F), bactericidal and bacteriostatic activity (Appendix G), trichomonocidal activity (Appendix H), spermicidal activity (Appendix I), and the method for evaluation of various indices (Appendix J) were published and/or reported in various scientific meetings. A large number of contraceptives, vaginal antiseptics and other experimental products available in this country and abroad were evaluated for their antimicrobial properties.

Techniques were devised and developed to determine optimum conditions for preserving various microorganisms to be used for evaluation of various test products. In vivo rabbit experiments simulating the physical conditions of human male exposure to syphilis infection were initiated. In this, the group was able to utilize the assistance of Dr. R. C. Arnold who had spent many years in this type of research at the VDRL of the USPHS. Serological tests were selected to be used for field screening which were considered to

be sensitive enough to determine any immune or biological response to T. pallidum infection.

While these laboratory studies were being carried out, arrangements were made to provide diagnostic services for venereal diseases, to a local free clinic where almost 50% patient load consisted of cases of sexually transmitted diseases. This was done so as to establish a laboratory resource of experience and proven quality to monitor the Phase II study when initiated. It was further anticipated that the experience gained through this diagnostic clinic work would be very helpful in developing the protocol and procedures for the clinical field trial as required under Phase II of the contract. It was also expected that this action would be followed by the utilization of the clinic as a source of patients for the clinical trial, Phase II. It was anticipated that this would also help to answer many of the basic questions concerning patient management and education, staff-patient relationships, distribution of medication and record keeping, etc. It was expected that once these questions were answered, standard procedures for setting up and running the study in a clinic would be formulated.

FINDINGS

The main objectives of the laboratory studies were to assess in vitro and where possible in vivo, the effectiveness of existing FDA approved vaginal contraceptives and certain antiseptic vaginal preparations against *N. gonorrhoeae*, *T. pallidum*, *C. albicans* and *T. vaginalis*. However, later the potential candidate-products were also tested against certain other microorganisms causing genital infections such as *Haemophilus ducreyi* and Herpes simplex virus type II. The effect of PH and other variations as present in chemical contraceptives were also studied. Data on these in vitro studies and various findings are described in Appendix K.

In addition to the above mentioned laboratory studies, several small complementary experiments and investigations were undertaken because of relevance to the primary objective of the contract and because of the significance with respect to future large-scale use in public-health or population programs.

(1) Chemical susceptibility of *N. gonorrhoeae* on continuous passage in presence of contraceptive: Sequential fifty serial passages of *N. gonorrhoeae* were made on regular chocolate agar media and chocolate agar media containing 0.75% of a chemical contraceptive. After every five passages, gonococci from both sets of media with and without contraceptive products were examined and minimal inhibitory concentrations of penicillin as well as the above-named contraceptive were determined.

No significant change in MIC or resistance or other growth characteristics was found that was persistent at any time during fifty passages of *N. gonorrhoeae* under these conditions. It was concluded that the use of various contraceptives as topical venereal disease prophylaxis will probably not

change the susceptibility of *N. gonorrhoeae* and therefore it is unlikely that the gonococcus will become more resistant with wide use of such non-antibiotic chemical contraceptive preparations.

(2) Survival and recovery of *N. gonorrhoeae* under different environmental conditions: This study was undertaken to investigate various conditions under which gonococci will remain viable before or after standard incubation temperature to ascertain the optimum conditions for survival and recovery of *N. gonorrhoeae* during transport of specimen from the field and for subcultures in the laboratory. The presence of CO_2 was found necessary especially if the transporting period is to be more than 24 hours. It was found that best results can be obtained if the inoculated plates were incubated 24 hours prior to mailing. If the plates were not incubated immediately or were not kept in a candle jar with CO_2 , the optimum period of storage of inoculated plates with positive cultures was found to be 5°C .

With continuous cultivation, the laboratory adopted *Neisseria* strains appear to become less fastidious. It was also found that the alkaline PH is not detrimental to the gonococcus but acid PH is, and the damaging effect of acid PH from 3 to 5.6 is more evident at higher temperatures.

(3) Virucidal effect of certain chemical contraceptives on herpes simplex virus type II: Public health has long been concerned with the control of syphilis and gonorrhea as venereal diseases, but has given little attention to other genital infections; yet herpes genitalis was recognized and described as a venereal disease as early as 1885. The incidence of herpes genitalis is far greater than generally suspected.

In the teenage population the incidence of all common, sexually transmitted diseases has been increasing for the last several years and a large number of unplanned pregnancies are reported each year. It is therefore

not surprising that the majority of patients with primary herpes genitalis infections are teenage girls and unmarried women. Thus, the potential importance of topical prophylaxis for venereal diseases by use of intra-vaginal contraceptives and their impact on all sexually transmitted infections in this particularly vulnerable age group is very evident.

Considering their potential usefulness for topical prophylaxis should any of the preparations be found active against herpes simplex virus type II, a number of chemical contraceptives were studied for their virucidal activity. The virucidal effect of these contraceptives were determined using both tissue culture technique as well as mice inoculation. Several logs of virus inactivation were observed by either or both techniques depending upon the concentration of the contraceptives tested and virus harvest (Appendix L).

(4) The effect of vaginal lubricants on N. gonorrhoeae: The gonococcal infection in a large majority of women does not cause sufficiently marked signs or symptoms to make them aware of the disease and thus report for treatment. Failure to diagnose gonorrhea in women who harbor asymptomatic infection is an important contributing factor in the gonorrhea epidemic. Asymptomatic infected individuals, being unaware, keep spreading the disease. Numerous techniques have been used to identify gonococci in patients suspected of having gonorrhea; however, the culture technique using selective media is the most sensitive method for female patients. Unfortunately, several conditions and procedures carried out in the course of obtaining a cervical specimen for cultural diagnosis can affect the positive yield. Some family planning and ob/gyn clinics prefer to use commercially available lubricants for the speculum during pelvic examinations. Considering this and the possibility that certain components of the lubricating agents might be bacteriostatic or bacteriocidal, decision was made to investigate a possible

interference of commonly used vaginal lubricants in culture diagnosis of gonorrhea by studying in vitro effect of selected lubricants on *N. gonorrhoeae*. Two lubricants i.e., K.Y. Jelly and Lubrifoam, widely used in family planning and other ob/gyn clinics were demonstrated to have bactericidal effect on *N. gonorrhoeae* when tested by several different methods. Gonococci were killed on contact with Lubrifoam even at 10% concentration and an exposure time as little as one minute was sufficient to inhibit the growth on chocolate agar medium. The K-Y Jelly showed less inhibitory effect than Lubrifoam. These findings suggest that certain vaginal lubricants have bactericidal effects and should not be used in association with vaginal and pelvic examination if specimens are to be taken at the same time for diagnosis of gonorrhea (Appendix M).

PHASE II

FIELD TRIAL TO STUDY SELECTED PRODUCT IN HUMANS

In the process of planning for the field trial, there were several advisory committee reviews of the possible procedures and protocol.

Various experimental approaches were considered on the basis of previous studies of prophylaxis. Because of various considerations ranging from federal guidelines for human experimentation through the realities of clinical study possibility based upon the currently applicable Pennsylvania law requiring parental consent for all human experimentation under the age of 21 and the demonstrated patient resources and cooperation at the Allegheny County VD clinic, the resources of which had been volunteered for conduct, the options for study design were limited.

In short, the design which could satisfy both epidemiologic, legal, and ethical considerations was one in which rates of infection in Conceptrol Cream users and control subjects were determined. The fact of risk of infection was established by choosing volunteers with one or two previous infections who were then observed at biweekly intervals following entry into the study.

The clinical design shown in Appendix N was developed and approved by all relevant groups. It is evident that the successful completion of the study is primarily dependent upon patient cooperation. Thus a staffing pattern was set up which was designed to maximize attention to and close relationship with the patient so as to secure cooperation. A system was further set up to assure essentially 24 hours per day, 7 days per week of patient access to the clinical study staff so as to reinforce the patient's realization of the importance of cooperation and the patient's perception of concern for her welfare.

FIELD REPORT

In order to evaluate the field trial results clearly, it is necessary to divide it into time sequences. The first period is the establishment of the field trial methodology, the second is the first six months of patient experience, the third period, the second six months of patient experience, and finally the fourth period following initiation of slight changes in protocol based upon the previous experience.

As a result of planning with the staff of the Preventive Medicine Clinic of the Allegheny County Health Department, where the VD Clinic is located, the procedures for collecting and managing participants for the study were established. It is to be noted that the study staff functioned as members of the clinic staff so as to facilitate patient acquisition and follow-up, since full involvement of the entire clinic and laboratory staff was an essential element of success. Based on these discussions, projections were made as to the time required for acquiring and following the participants. Much care went into the hiring of the field trial staff with particular emphasis placed on the attitudes of the candidate considered so as to assure that the final team working with patients would have effective relationships with the study group. Since venereal diseases can cause strong unfavorable emotional responses, a staff that was open-minded and non-judgmental was deemed essential. The field staff consisted of a gynecologist, a registered nurse and a health educator. The main duties of the gynecologist consisted of clinically supervising the field staff, doing a pre-determined, pre-trial medical work-up of all participants, follow-up care of any physical problems the participants had during the trial, search for and management of any patient health problems, search for potential side effects, and teaching

sessions with the field staff.

The field nurse functioned in the Preventive Medicine Clinic as a staff nurse and assisted as appropriate in interviewing, drawing blood, obtaining cultures, and in other appropriate ways to facilitate patient management. She also screened all clinic patients for possible participation in the field trials. She acted as a liason between the participant and the physician, conducted field trial clinics when physician was absent, and did whatever was necessary to try to find volunteers and to assure cooperation.

The health educator was also a member of the field trial staff. She was mainly responsible for screening patients in the Preventive Medicine Clinic for their possible eligibility in the field trial. She interviewed possible participants, filled out preliminary interview forms, set up appointments, paid participants, and contacted delinquent patients. While doing all of these, she was also responsible for establishing and maintaining rapport.

Once started, it soon became apparent that the repeater rates were not so high as projections based on data received from clinic personnel in the preceding years which had formed the basis for the study design. It became necessary to secure further data with respect to the numbers and socio-economic characteristics of women who used the facilities. Interviewing techniques were revised in consultation with the Public Health Representatives who were responsible for contact interviewing and tracing. As expected, numerous other problems soon became evident. Since we were working with a social group that is generally conceded, with respect to behavioral patterns, to be less reliable than the group of society not so

infected, numerous problems in scheduling appointments soon became evident, so that the physician, nurse or educator could not see the participant as planned, scheduled and promised by the study participants. Because of social expectations inherent in our culture, it was questioned whether a woman would admit to the physician or other health professional that she had more than one sexual partner. There was some suggestion based upon culture studies and upon study case histories that the contact history was not always fully reliable. Certain bias may have been introduced into the study due to the behavioral characteristics of persons who would say "yes" to the interviewer in the field trial when admitting to such matters as failure to follow agreed upon procedures with respect to the study.

Review of the first few months of experience based upon considerations such as those, brought about certain changes in procedures of patient management. In addition to screening the Preventive Medicine Clinic patients for possible participants, candidates were further furnished by the family-planning and ob/gyn clinics at West Penn Hospital, Magee Womens Hospital and the Manchester Health Center where gonorrhea screening programs were being conducted. Arrangements were further made to schedule weekend and evening appointments at the office of the project physician so as to accommodate potential participants who could not attend at the usually scheduled clinic sessions. Slight revision of the preliminary interview procedure was made so as to make it more persuasive. A possible participant was interviewed as soon as she was known to be eligible rather than after she had completed treatment including test of cure in the Preventive Medicine Clinic. Although acquisition of participants was considerably improved with these changes, the projected rate of acquisition was never

reached. The reasons for the failure can only be speculated upon. But several factors seemed to be involved. The time required for follow-up visits interfered with work and life style of potential and actual participants. Furthermore, there seemed to be a very evident lack of fear of the disease so that the usual clinic patient was not motivated to participate out of concern for protection of her health. A number of women were not interested in securing and using the effective contraceptive techniques required by the study design. Finally, the pattern of lack of cooperation, as in giving false addresses and phone numbers, which has been found to be a common characteristic of the VD clinic population, was evident in this group even though they had volunteered to cooperate.

The last major phase of the study occupied the final nine months when the criteria of two infections in the past 12 months prior to entry was dropped to one infection prior to entry in the study. The decision to make the modification to require only one infection and a history of sexual activity was based upon the observation that in the Preventive Medicine Clinic experience, the second infection most commonly occurs during the first 3-6 months after treatment of the initial infection. Thus our candidate population was rapidly enlarged. Once more the product and patient information forms were reviewed and revised. At this point all women clinic patients over 21 were approached to inform them of the project; it was hoped to encourage more women to return for a test of cure so that more women could be interviewed for entry into the study. At this point the project was finally coming closer to obtaining the number of participants originally projected by the field staff members. Another factor that had become evident was that in terms of prophylaxis, patient behavior

with respect to self-protection appeared to show the same pattern as has been found in the use of the pill or the IUD as measured by continuation rates or, for instance, the pattern of compliance with medical regimens as found in the diabetic patient taking oral or injectable antidiabetic preparations or in maintaining a diet. As the time between the initial, acute disease-episode lengthens without further patient-threatening manifestations of the disease as the patient is under therapy or prophylaxis, the motivation for compliance with medical therapeutic or preventive regimens seems to diminish. Thus it was felt desirable to limit the observation period for the prophylactic study to six months rather than the year as originally planned. This had the advantage of observing the patients when the motivation for compliance with the experimental design was highest. In order to secure adequate months of patient observation, it was necessary to deal with patient behavior as it is found in clinical practice rather than with the theoretical, desired behavior and to set a period of observation which was realistic in terms of the ability to secure patient cooperation. For it was observed that patient compliance with the experimental regimen, including visits for culture and supply pick-up fell off with passage of time.

It is also to be noted that contrary to the popular belief, the fact that the patient has had the disease seems to provide no assurance that she will be concerned enough about the disease to bring herself to the point of practicing self-protective behavior or that she will desire to take part in any sort of program providing measures which have potential for protecting her health. It will be noted that many patients refused to take part in the study because the time involved and the nuisance of

frequent clinic visits were felt to be too great, and there was no perceived benefit in participation on the part of the patient. The financial reward of \$5.00 for her time and \$1.50 for transportation for each visit was not sufficient to bring about compliance with the study design and there seemed to be on the part of many no concern with self-protection. This has relevance to the entire matter of self-protective behavior whether with respect to unwanted pregnancy, venereal disease, or other types of diseases in that the patient who is the object of preventive programs all too often is completely unmoved by the fear of disease or unplanned pregnancy, or even by the actual event or disease itself.

In terms, however, of the pro-con concept and the hope to be able to use this technique as one more element of programs designed to prevent unplanned pregnancy and venereal disease, it is felt that use of this type of self-protective behavior by even a small section of the group at risk of unplanned pregnancy or venereal disease can have significant long-term community impact as shown in the Lee epidemiological model (11).

According to the model, it can be postulated that use of a preparation only 50% effective by 20% of the population would bring about a great reduction in incidence over a 5-year period. It is to be recalled that all programs of disease control by immunization accept the fact that 100% success, whether with coverage or immunity, is not an essential factor for success.

Widespread use of this preparation, if found effective, in accordance with the epidemiologic theory should then have a significant effect in helping to reduce the spread of gonorrhoea within the community. It must be realized, however, that no single prophylactic preparation or thera-

peutic agent is to be looked upon as the perfect or unique single answer to the venereal-disease-epidemic increase because of the related problems of patient motivation and behavior. However, in view of the present day concern with the health-related ill effects of both unplanned pregnancy and venereal disease there is now the potential availability, for the first time, of a preparation which the high risk female can secure without necessity for physician intervention and use without necessity for cooperation by her partner and which will offer her a substantial degree of protection against both pregnancy and gonorrhoea. For recent analyses of data on efficacy of vaginal contraceptives have shown the high degree of contraceptive effectiveness of various of their preparations as well as wide ranges of effectiveness apparently related to certain characteristics of groups studied (12).

ADMINISTRATIVE REPORT

From an administrative standpoint conducting a clinical field trial with an experimental pharmaceutical product requires a series of approvals from federal, university and local-governmental agencies prior to the trial getting underway and further requires continued monitoring of all aspects to assure the collection of accurate data after the trial has begun as well as compliance with all legal requirements with respect to human experimentation.

Critical in any field trial is the development of experimental designs and protocols which will permit scientific proof or disprove the hypothesis being tested. The project epidemiologist, microbiologist, statistician, and principal investigator, and relevant consultants developed the necessary designs and protocols for this project. In the process, a review of the proposed study was held at the University of Pittsburgh, November 1971, with leading experts in the field of venereal disease research. A list of those in attendance is attached as Appendix O. The strengths and weaknesses inherent in this type of research were discussed and the best possible compromise was agreed to for the experimental design and protocols for this field trial.

These final documents were submitted to the Allegheny County Health Department, in whose facilities the trial would be conducted, the Committee on Research Involving Human Volunteers, GSPH, University of Pittsburgh, and Ortho Research Foundation, the pharmaceutical company whose product, Conceptrol Cream, was to be tested. After further minor modifications, an I.N.D. was prepared, agreed upon by all, and submitted jointly by Ortho Research Foundation and the Graduate School of Public Health, University

of Pittsburgh, to FDA for approval to begin the clinical field trial. During this same period of time, discussions were held with eight other pharmaceutical companies concerning the possible testing of their products in other sites. Ten additional trial sites expressed interest in conducting clinical trials, and site visits were made to Guatamala and Jamaica where permission was received from the Ministers of Health to conduct trials in these areas. For various reasons, trials at these sites were never begun, and all efforts were directed towards successfully completing the trial begun at the Allegheny County Health Department Preventive Medicine Clinic, Pittsburgh, Pennsylvania.

In that this clinical field trial of a chemical intravaginal contraceptive as a venereal disease prophylactic was the first of its kind, problems were expected to occur. Some of these problems were easily overcome by minor modifications while others presented major obstacles to successful completion of this trial.

From a design standpoint, the most serious problem encountered which could not be solved was the lack of a placebo for the control group to use while on trial. This problem was twofold in that the Committee on Research Involving Human Volunteers ruled that a placebo could not be used in the trial since it would be of no expected preventative value, but partners of females using a placebo might feel that it had protective value, fail to use whatever methods they normally would use to protect against venereal infection and, in essence, become uninformed participants at risk in the trial. In addition to this committee decision, it was later determined by Ortho Research Foundation that it was impossible to formulate a completely bactericidally-inert placebo to be used in such a trial. In that

all potential-placebo formulations tested exhibited some degree of anti-microbial activity, the effort was discontinued. Hence, no suitable placebo is available for this type of a trial.

From an enrollment standpoint, the Committee on Research on Human Volunteers when considering the question of informed consent determined that participants in this project must have reached the age of majority to give effective informed consent. In the State of Pennsylvania, it was ruled that the age of majority is 21 years of age. Consequently, this project was denied access to the younger female who not only represents the largest proportion of venereal disease patients but who also tends to acquire repeat infections more frequently in the clinic field trial site experience. The policy of the County Health Department has been not to require parental consent for any sort of clinic procedures including therapy for clients under 21 because of the fact that this requirement of parental or spousal consent would be counterproductive to the venereal disease control operation. It was the thought of the County that an attempt to enroll into the study any patient under the age of 21 and thus require parental consent would be counterproductive in terms of the community trust in and utilization of the clinic. It was thus agreed that no patient under the age of 21 would be approached or accepted. The implications of this in terms of enrollment of patients is obvious. This limiting age factor is felt to be the major reason for the slower-than-projected enrollment of participants into the trial.

In addition to the age factor, it was felt during the planning stages that the cooperation of other clinics could be gained and possible participants referred into the project. While many clinics and private

physicians were contacted and agreed to cooperate with the project, it was found that the continued personal contact and motivation needed to assure this cooperation was impossible to achieve outside of the County Health Department clinic in which the project staff functioned on a daily basis as members of that staff. Not only were the other clinics so busy that frequent contact was almost impossible, but it also became apparent that this represented yet another task to be carried out by already "overworked" clinic staff members. Consequently, cooperation of outside clinics "peaked and valleyed" throughout the trial and, over all, contributed very little to the enrollment of participants.

Constant administrative monitoring of the trial took place to assure accurate data collection for reports that were submitted to AID, FDA and Ortho Research Foundation, as well as to detect problem areas in need of improvement, and to modification of the protocol when necessary.

The modification of the protocol that had the most striking effect was the changing of criteria for participation in the trial from two previous infections in previous twelve months to one infection, and observing the participant for six months rather than one year. The rationale for this change was that the fact that a female presented herself at the clinic with a positive culture for gonorrhoea was proof of risk-taking behavior so that, logically, re-infection could be expected. The second element involved in this modification grew out of field experience. The reduction in observation time from one year to six months was based on the fact that the majority of re-infections for the females in the clinic population occurred in the first six months. It was felt that observation over longer periods of time would not only fail to con-

tribute meaningful data, but would also unnecessarily increase the overall cost of the trial. Furthermore, the patient cooperation and compliance with procedures seemed to decline in the second six months.

The experience in the day-to-day management of the volunteers and the insights gained for future application are reviewed in a paper prepared by the project nurse which is being considered for publication.

A five year budget for this research project is presented in Appendix P.

STATISTICAL REPORT

The data collection for each individual participating in the clinical trial included information on demographic variables (Table I, Table II and Table IV), method of birth control (Table III) and pre-trial sexual activity (Table V and Table VI). Calendar dates were recorded for entry into trial, acquisition of product by treatment individuals, appointments kept and missed, antibiotic therapy of any kind, venereal disease infections and final examinations. Participants completed a sexual activity questionnaire during each appointment which indicated number of partners and frequency of intercourse in the preceding two week period. The frequency distribution of the responses is presented by three month interval of participation in trial in Table VII and Table VIII respectively. The distribution of average responses for indicated use of the product, also acquired on the sexual activity questionnaire for the treatment group, is presented by three month interval in Table IX. A presentation of all information on participants infected while on trial is given in Table X and Table XI.

The clinical trial design determined that volunteers be randomly assigned to treatment and control groups. However, several factors had to be taken into consideration in the statistical estimation of the proportion of infections in each group and further determination of any statistical difference between these proportions. Observation times varied between individuals and between treatments and control groups due to drop-outs and censored* individuals. Removal of time on antibiotic therapy from each participant's total observation period further contributed to the variability

*Censored individuals are those who were currently active in the clinical trial at its termination date. With respect to the statistical analysis, dropouts and censored are treated the same.

of time on trial. Time to first infection also varied between infected individuals. In addition, after receiving and having been treated for a first infection, a participant remained in the originally assigned group (was not rerandomized). Thus, while the trial summary was based on all observation times and all infections, more detailed treatment data was limited to first infections and corresponding observation times.

Because there was some doubt as to the consistent use of the product by treatment individuals, particularly after six months of observed time, it was decided to analyze the data based on the total trial, and also, based on a six months trial (24 weeks). Also, due to the random assignment of individuals of both criteria to treatment and control groups, the data from new criteria individuals was combined with that of the old criteria for all statistical testing. The clinical trial summary is presented in Table XII. The total trial includes total observation time for all participants and all infections observed. The sixth month trial includes only the first 24 weeks for all participants.

The remainder of the analysis of the clinical trial data was based on the data after removal of all infected individuals and their additional observation times after a first infection. A systematic approach for analyzing the results of the trial, taking additional factors into consideration at each step, was applied for both the total trial and six month trial.

The summary information for the total trial (participants removed after first infection) is given on the following page.

A first look at the data for the total trial ignored both the varied time contributions of the two groups and of the individuals on trial and the varied times to first infection. Thus the proportion of infected in the treatment group was 5/37 and the proportion in the control group was 17/50.

	Treatment	Control
# Participants	37	50
# Infections	5	17
% Lost or censored	73	46
Ave. months per participant	5.8	6.6
PM observed	213.5	329.4
# Infs/100PM	2.34	5.16

A (chi-square) test (corrected for continuity) of the difference between the two proportions was just short of the significant level of $\alpha = .05$ ($P = .055$, two tailed test).

The second level of evaluating any difference between treatment and control groups took into consideration the varied accumulated observation times between groups ignoring the varied observation times between individuals and the varied times to first infection. Here, the two poisson parameter estimates of 2.34 infections per 100 person months for the treatment group and 5.16 infections per 100 person months were compared (13) and the difference was not significant at $\alpha = .05$ ($P = .17$, two tailed test).

The final level of evaluating the difference in performance of the treatment and control groups accounted for the difference in observation times between group and between individuals, and in addition, took into account the observation interval of first infection in each of the groups. The format for this approach is the life table classifications presented in Table XIII and Table XIV. The proportion remaining infection free for the total trial was .63 (SE=.029) for the treatment group and .49 (SE=.066) for the control group, having 95% confidence intervals of (0.921, 0.349) and (0.687, 0.303) respectively (14). A test for the overall difference between

the life table populations (15) was not significant at $\alpha = .05$ ($P = .18$, two tailed test). A non-parametric procedure (16, 17) specifically testing for the difference in time to first infection in the two groups, was just short of significant at $\alpha = .05$ ($P = .0576$, two tailed test).

The same systematic approach was next employed for the first six months (24 weeks) of the clinical trial. The summary information is presented below.

	Treatment	Control
# Participants	37	50
#Infections	1	11
% Lost or censored	51	24
Ave. months per participant	3.9	4.1
PM observed	144.4	206.7
# Infs/100PM	0.69	5.22

The first look at the data for the first six months (24 weeks) of the clinical trial ignored both the varied times of observation of the two groups and of the individuals and the interval of time of infection. The proportion of infected in the treatment group of $1/37$ was compared to $11/50$, the proportion infected in the control group. A test (corrected for continuity) of the difference was significant at $\alpha = .05$ ($P = .024$, two tailed test).

The second level of evaluation of the two groups, as before, took into consideration the varied accumulated observation times between groups ignoring the varied observation times between individuals and the varied times to first infection. The test for the difference between two poisson rates (13), i.e., 0.69 infs/100PM for the treatment group and 5.32 infs/100PM, was significant at $\alpha = .05$ ($P = .034$, two tailed test).

The final level of evaluation of the data, accounting for differences in observation times between groups and between individuals as well as for differences in time intervals of first infection, is based on the first six rows (month intervals) of Table XIII and Table XIV. The proportion of treatment individuals remaining free of infection for six months (24 weeks) was .97 (SE=0.146) and the proportion of controls was .75 (SE=0.098), having 95% confidence intervals of (1.000, 0.914) and (0.880, 0.622) respectively (14). The test (15) for overall difference between treatment and control groups for the first 24 weeks of observation, was significant at $\alpha=0.05$ ($P=.044$, two tailed test). The non-parametric procedure (16, 17) testing for a difference in time to first infection was also significant at $\alpha=0.05$ for the first six months of the clinical trial ($P=.030$, two tailed test).

Because of the consistently non-significant but suggestive results for the twelve month trial and the consistently significant outcomes based on the first twenty-four weeks of observation, it was decided to examine the data for the second six months of the trial. The summary information for this portion of the trial is presented below.

	Treatment	Control
# Participants	17	27
# Infections	4	6
% Lost or censored	47	41
Ave. months per participant	4.1	4.4
PM observed	69.25	120.18
# Infs/100PM	5.78	4.99

All tests applied previously were very non-significant. Indeed, the relative number of infections were quite similar with slight reversal in favor of the control group.

In summary, the analysis of the data of the first 24 weeks of the clinical trial gave consistently significant results to all levels of testing the difference between the treatment and control groups. However, the second six months of the trial showed no difference between the two groups. Thus the analysis of the combined time groups (12 month trial) gave results that, though suggestive, were no longer statistically significant.

TABLE I FREQUENCIES AND PERCENT OF CLINICAL FIELD TRIAL PARTICIPANTSAGE BY CRITERIA BY GROUP

Age	<u>Treatment</u>			No Time
	Old Criteria	New Criteria	Combined	
21-24	17 (65%)	6 (55%)	23 (62%)	21 (72%)
25-28	6 (23%)	3 (27%)	9 (24%)	3 (10%)
29-32	3 (12%)	1 (9%)	4 (11%)	3 (10%)
33+	0 (0%)	1 (9%)	1 (3%)	2 (7%)
	26 (100%)	11 (100%)	37 (100%)	29 (100%)

Age	<u>Control</u>			No Time
	Old Criteria	New Criteria	Combined	
21-24	25 (66%)	5 (42%)	30 (60%)	14 (88%)
25-28	8 (21%)	4 (33%)	12 (24%)	1 (6%)
29-32	2 (5%)	2 (17%)	4 (8%)	0 (0%)
32+	3 (8%)	1 (8%)	4 (8%)	1 (6%)
	38 (100%)	12 (100%)	50 (100%)	16 (100%)

TABLE II FREQUENCIES AND PERCENT OF CLINICAL FIELD TRIAL PARTICIPANTSMARITAL STATUS BY GROUP

	<u>Treatment</u>			No Time
	Old Criteria	New Criteria	Combined	
Single	19 (73%)	6 (55%)	25 (68%)	16 (55%)
Married	2 (8%)	3 (27%)	5 (14%)	3 (10%)
Sep-Div	4 (15%)	2 (18%)	6 (16%)	9 (31%)
Widow	1 (4%)	0 (0%)	1 (3%)	1 (3%)
	26 (100%)	11 (100%)	37 (100%)	29 (100%)

	<u>Control</u>			No Time
	Old Criteria	New Criteria	Combined	
Single	19 (50%)	10 (84%)	29 (58%)	10 (63%)
Married	1 (3%)	1 (8%)	2 (4%)	2 (12%)
Sep-Div	16 (42%)	1 (8%)	17 (34%)	4 (25%)
Widow	2 (5%)	0 (0%)	2 (4%)	0 (0%)
	38 (100%)	12 (100%)	50 (100%)	16 (100%)

TABLE III FREQUENCIES AND PERCENT OF CLINICAL FIELD TRIAL PARTICIPANTSBIRTH CONTROL BY CRITERIA BY GROUP

	<u>Treatment</u>			
	<u>Old Criteria</u>	<u>New Criteria</u>	<u>Combined</u>	<u>No Time</u>
Oral Contra.	17 (65%)	5 (45%)	22 (59%)	19 (66%)
IUD	5 (19%)	4 (36%)	9 (24%)	8 (28%)
Surg. Sterlzn.	4 (15%)	0 (0%)	4 (11%)	1 (3%)
Menopause	0 (0%)	1 (9%)	1 (3%)	0 (0%)
Infertile	0 (0%)	1 (9%)	1 (3%)	1 (3%)
	26 (100%)	11 (100%)	37 (100%)	29 (100%)

	<u>Control</u>			
	<u>Old Criteria</u>	<u>New Criteria</u>	<u>Combined</u>	<u>No Time</u>
Oral Contra.	22 (58%)	8 (67%)	30 (60%)	11 (69%)
IUD	13 (34%)	3 (25%)	16 (32%)	5 (31%)
Surg. Sterlzn.	2 (5%)	0 (0%)	2 (4%)	0 (0%)
Menopause	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Infertile	1 (3%)	1 (8%)	2 (4%)	0 (0%)
	38 (100%)	12 (100%)	50 (100%)	16 (100%)

TABLE IV FREQUENCIES AND PERCENT OF CLINICAL FIELD TRIAL PARTICIPANTSEDUCATIONAL LEVEL BY CRITERIA BY GROUP

	<u>Treatment</u>			
	<u>Old Criteria</u>	<u>New Criteria</u>	<u>Combined</u>	<u>No Time</u>
8-9th	1 (4%)	0 (0%)	1 (3%)	2 (7%)
10-12th	20 (77%)	5 (45%)	25 (68%)	17 (59%)
Fresh-Soph	2 (8%)	4 (36%)	6 (16%)	3 (10%)
Jr-Sr	3 (11%)	2 (18%)	5 (13%)	4 (14%)
Grad	0 (0%)	0 (0%)	0 (0%)	0 (0%)
No Information	0 (0%)	0 (0%)	0 (0%)	3 (10%)
	26 (100%)	11 (100%)	37 (100%)	29 (100%)

	<u>Control</u>			
	<u>Old Criteria</u>	<u>New Criteria</u>	<u>Combined</u>	<u>No Time</u>
8-9th	3 (8%)	0 (0%)	3 (6%)	0 (0%)
10-12th	22 (58%)	7 (58%)	29 (58%)	13 (81%)
Fresh-Soph	6 (16%)	3 (25%)	9 (18%)	1 (6%)
Jr-Sr	5 (13%)	2 (17%)	7 (14%)	1 (6%)
Grad	1 (3%)	0 (0%)	1 (2%)	0 (0%)
No Information	1 (3%)	0 (0%)	1 (2%)	1 (6%)
	38 (100%)	12 (100%)	50 (100%)	16 (100%)

TABLE V

FREQUENCIES AND PERCENT OF CLINICAL FIELD TRIAL PARTICIPANTS

PRE TRIAL NUMBER OF PARTNERS IN PAST 12 MONTHS BY CRITERIA BY GROUP

	<u>Treatment</u>			
	<u>Old Criteria</u>	<u>New Criteria</u>	<u>Combined</u>	<u>No Time</u>
1	5 (19%)	2 (18%)	8 (22%)	5 (17%)
2	6 (23%)	4 (36%)	10 (27%)	4 (14%)
3	4 (15%)	2 (18%)	6 (16%)	4 (14%)
4-9	6 (23%)	2 (18%)	8 (22%)	8 (28%)
10+	2 (8%)	1 (9%)	3 (8%)	2 (7%)
No Information	3 (12%)	0 (0%)	2 (5%)	6 (21%)
	26 (100%)	11 (100%)	37 (100%)	29 (100%)

	<u>Control</u>			
	<u>Old Criteria</u>	<u>New Criteria</u>	<u>Combined</u>	<u>No Time</u>
1	11 (29%)	5 (42%)	16 (32%)	2 (12%)
2	7 (18%)	4 (33%)	11 (22%)	2 (12%)
3	3 (8%)	2 (17%)	5 (10%)	0 (0%)
4-9	8 (21%)	0 (0%)	8 (16%)	6 (38%)
10+	6 (16%)	0 (0%)	6 (12%)	0 (0%)
No Information	3 (8%)	1 (8%)	4 (8%)	6 (38%)
	38 (100%)	12 (100%)	50 (100%)	16 (100%)

TABLE VI

FREQUENCIES AND PERCENT OF CLINICAL FIELD TRIAL PARTICIPANTS

PRE TRIAL AVERAGE FREQUENCY OF INTERCOURSE PER WEEK BY CRITERIA BY GROUP

	<u>Treatment</u>			
	<u>Old Criteria</u>	<u>New Criteria</u>	<u>Combined</u>	<u>No Time</u>
1-2	11 (42%)	8 (73%)	19 (51%)	12 (41%)
3-4	7 (27%)	3 (27%)	10 (27%)	4 (14%)
4-9	2 (8%)	0 (0%)	2 (5%)	3 (10%)
10+	2 (8%)	0 (0%)	2 (5%)	3 (10%)
No Information	4 (15%)	0 (0%)	4 (11%)	7 (24%)
	26 (100%)	11 (100%)	37 (100%)	29 (100%)

	<u>Control</u>			
	<u>Old Criteria</u>	<u>New Criteria</u>	<u>Combined</u>	<u>No Time</u>
1-2	16 (42%)	4 (33%)	20 (40%)	3 (19%)
3-4	14 (37%)	6 (50%)	20 (40%)	5 (31%)
4-9	2 (5%)	1 (8%)	3 (6%)	3 (19%)
10+	1 (3%)	0 (0%)	1 (2%)	0 (0%)
No Information	5 (13%)	1 (8%)	6 (12%)	5 (31%)
	38 (100%)	12 (100%)	50 (100%)	16 (100%)

AVERAGE NUMBER OF PARTNERS PER 2 WEEKS BY 3 MONTH INTERVAL BY GROUP
(COMBINED CRITERIA)

	<u>Treatment</u>			
	0-3 mo	3-6 mo	6-9 mo	9-12 mo
1	18 (49%)	12 (63%)	9 (60%)	6 (50%)
1-2	9 (24%)	5 (26%)	6 (40%)	5 (42%)
2-3	4 (11%)	0 (0%)	0 (0%)	0 (0%)
3-4	1 (3%)	0 (0%)	0 (0%)	0 (0%)
4-9	4 (11%)	1 (5%)	0 (0%)	1 (8%)
No Information	1 (3%)	1 (5%)	0 (0%)	0 (0%)
	37 (100%)	19 (100%)	15 (100%)	12 (100%)

	<u>Control</u>			
	0-3 mo	3-6 mo	6-9 mo	9-12 mo
1	32 (64%)	18 (51%)	16 (57%)	11 (58%)
1-2	13 (26%)	14 (40%)	4 (14%)	5 (26%)
2-3	2 (4%)	1 (3%)	6 (21%)	2 (11%)
3-4	1 (2%)	1 (3%)	1 (4%)	0 (0%)
4-9	2 (4%)	1 (3%)	1 (4%)	1 (5%)
No Information	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	50 (100%)	35 (100%)	28 (100%)	19 (100%)

TABLE VIII

FREQUENCIES AND PERCENT OF CLINICAL FIELD TRIAL PARTICIPANTS

AVERAGE FREQUENCY OF INTERCOURSE PER 2 WEEKS BY 3 MONTH INTERVAL BY GROUP
(COMBINED CRITERIA)

	<u>Treatment</u>			
	0-3 mo	3-6 mo	6-9 mo	9-12 mo
1	3 (8%)	0 (0%)	0 (0%)	0 (0%)
1-3	9 (24%)	7 (37%)	6 (40%)	2 (17%)
3-4	4 (11%)	4 (21%)	3 (20%)	3 (25%)
4-6	15 (41%)	5 (26%)	5 (33%)	5 (42%)
6-9	2 (5%)	1 (5%)	1 (7%)	2 (17%)
9-14	3 (8%)	1 (5%)	0 (0%)	0 (0%)
No Information	1 (3%)	1 (5%)	0 (0%)	0 (0%)
	37 (100%)	19 (100%)	15 (100%)	12 (100%)

	<u>Control</u>			
	0-3 mo	3-6 mo	6-9 mo	9-12 mo
1	9 (18%)	2 (6%)	1 (3%)	1 (5%)
1-3	10 (20%)	6 (17%)	9 (32%)	5 (26%)
3-4	9 (18%)	8 (23%)	5 (18%)	2 (10%)
4-6	13 (26%)	9 (26%)	3 (11%)	6 (32%)
6-9	4 (8%)	5 (14%)	5 (18%)	3 (16%)
9-14	5 (10%)	5 (14%)	5 (18%)	2 (10%)
No Information	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	50 (100%)	35 (100%)	28 (100%)	19 (100%)

TABLE IX

FREQUENCIES AND PERCENT OF CLINICAL FIELD TRIAL PARTICIPANTSAVERAGE INDICATED USE OF PRODUCT BY TREATMENT GROUP BY 3 MONTH INTERVAL(COMBINED CRITERIA)

	Treatment Group			
	0-3 mo	3-6 mo	6-9 mo	9-12 mo
Always	19 (51%)	13 (68%)	9 (60%)	4 (33%)
Most of Time	16 (43%)	4 (21%)	5 (33%)	8 (67%)
Sometimes	1 (3%)	1 (5%)	1 (7%)	0 (0%)
Never	0 (0%)	0 (0%)	0 (0%)	0 (0%)
No Information	1 (3%)	1 (5%)	0 (0%)	0 (0%)
Total	37 (100%)	19 (100%)	15 (100%)	12 (100%)

TABLE X

CHARACTERISTICS OF CLINICAL FIELD TRIAL PARTICIPANTSINFECTED WHILE ON TRIAL AS INDICATED BY PARTICIPANT

TREATMENT

I.D. Number	Age	Marital Status	Contraceptive Method	Education	Pre-Trial Average Number of Partners Per Week	Pre-Trial Average Number of Sex Acts Per Week	Number of Partners 2 Weeks Preceding Infection	Number of Sex Acts 2 Weeks Preceding Infection	* Use of Product 2 Weeks Preceding Infection
150368	21	S	OC	10-12	---	---	1	5	A
153258	21	S	OC	10-12	---	---	1	6	M
161893	21	S	IUD	10-12	3	3-4	1	1	N
							1	12	M
							1	2	A**
159656	24	M	IUD	10-12	1	5-6	2	3	M
168884	23	S	OC	10-12	2	3-4	1	5	A
							2	3	M

*A=Always, M=Most of the time, N=Never

**Used product improperly

TABLE XI

CHARACTERISTICS OF CLINICAL FIELD TRIAL PARTICIPANTS

INFECTED WHILE ON TRIAL AS INDICATED BY PARTICIPANT

CONTROL

I.D. Number	Age	Marital Status	Contraceptive Method	Education	Pre-Trial Average Number of Partners Per Week	Pre-Trial Average Number of Sex Acts Per Week	Number of Partners 2 Weeks Preceding Infection	Number of Sex Acts 2 Weeks Preceding Infection
053785	24	S	OC	10-12	---	---	1	6
053890	29	S	OC	Fr-So	2	3-4	1	7
049596	22	D	OC	---	4-9	---	3	6
046723	26	W	OC	Jr-Sr	10+	3-4	4-9	14+
041855	23	S	IUD	Fr-So	1	3-4	4-9	14+
058842	34	S	IUD	10-12	1	1-2	1	6
051359	22	Sep	In. Fert.	10-12	2	3-4	1	4
055528	26	Sep	OC	10-12	4-9	3-4	1	2
059335	21	S	IUD	10-12	10+	1-2	2	5
067994	21	S	OC	10-12	4-9	1-2	2	6
064732	21	S	OC	Fr-So	2	3-4	1	4
058203	35	W	Ster.	10-12	4-9	1-2	2	9
060389	26	Sep	OC	Jr-Sr	10+	1-2	1	4
069467	23	S	OC	10-12	3	3-4	3	11-14
026334	26	Sep	IUD	10-12	2	3-4	2	2
070927	33	M	OC	10-12	1	3-4	2	2
071733	22	S	OC	Fr-So	1	3-4	2	8
							2	8
							3	3
							1	1

TABLE XII

CLINICAL FIELD TRIAL SUMMARYTotal Trial: all observation time for all individuals participating in the trialTREATMENT GROUP

	<u>Old Criteria</u>	<u>New Criteria</u>	<u>Combined</u>
Time (weeks)	801	154.8	955.8
*Time (months)	200.3	38.7	239.0
Infections	8	0	8
Individuals inf	5	0	5
# Infs/100 PM	3.99	0.00	3.35

CONTROL GROUP

	<u>Old Criteria</u>	<u>New Criteria</u>	<u>Combined</u>
Time (weeks)	1446.5	203.6	1650.1
*Time (months)	361.6	50.9	412.5
Infections	17	7	24
Individuals inf	13	4	17
# Infs/100 PM	4.70	13.8	5.82

Six Month Trial (24 weeks): observation time censored after 24 weeks participationTREATMENT GROUP

	<u>Old Criteria</u>	<u>New Criteria</u>	<u>Combined</u>
Time (weeks)	459.8	140.3	600.1
*Time (months)	115.0	35.1	150.1
Infections	1	0	1
Females Inf	1	0	1
# Infs/100 PM	0.89	0.00	0.67

CONTROL GROUP

	<u>Old Criteria</u>	<u>New Criteria</u>	<u>Combined</u>
Time (weeks)	787.0	189.7	976.7
*Time (months)	196.8	47.4	244.2
Infections	8	7	15
Females Inf	7	4	11
# Infs/100 PM	4.06	14.77	6.14

FREQUENCIES OF TRIAL PARTICIPANTS BY STATUS

	<u>TREATMENT GROUP</u>		<u>CONTROL GROUP</u>	
	<u>Old Criteria</u>	<u>New Criteria</u>	<u>Old Criteria</u>	<u>New Criteria</u>
15 Censored	3	3	4	5
42 Drop (time)	15	6	18	3
30 Completed	8	2	16	4
45 Drop (no time)	18	11	8	8
132	44	22	46	20

*Months refers to 28 days on trial

TABLE XIII

LIFE TABLE CLASSIFICATION OF FREQUENCIES AND FIRST INFECTIONS FOR INDIVIDUALS IN THE PRO CON TRIAL BY GROUP

Month After Entry x to x + 1	Treatment Group (Combined Criteria)							Cumulative Proportion Uninfected
	Uninfected at Beginning of Interval	Infected During Interval	Lost or Withdrawn During Interval	Effective Number At Risk	Proportion Infected	Proportion Uninfected	Proportion Uninfected	
0-1	37	1	6	34.0	0.02941	0.97059	0.97059	0.97059
1-2	30	0	3	28.5	0.00000	1.00000	0.97059	0.97059
2-3	27	0	5	24.5	0.00000	1.00000	0.97059	0.97059
3-4	22	0	3	20.5	0.00000	1.00000	0.97059	0.97059
4-5	19	0	1	18.5	0.00000	1.00000	0.97059	0.97059
5-6	18	0	1	17.5	0.00000	1.00000	0.97059	0.97059
6-7	17	1	1	16.5	0.06061	0.93939	0.91176	0.91176
7-8	15	1	3	13.5	0.07407	0.92593	0.84423	0.84423
8-9	11	0	1	10.5	0.00000	1.00000	0.84423	0.84423
9-10	10	1	2	9.0	0.11111	0.88888	0.75043	0.75043
10-11	7	0	0	7.0	0.00000	1.00000	0.75043	0.75043
11-12	7	1	1	6.5	0.15385	0.84615	0.63497	0.63497
12+	5							

TABLE XIV

LIFE TABLE CLASSIFICATION OF FREQUENCIES AND FIRST INFECTIONS FOR INDIVIDUALS IN THE PRO CON TRIAL BY GROUP

Month After Entry x to x + 1	Control Group (Combined Criteria)							Proportion Infected	Proportion Uninfected	Cumulative Proportion Uninfected
	Uninfected at Beginning of Interval	Infected During Interval	Lost or Withdrawn During Interval	Effective Number At Risk	Proportion Infected	Proportion Uninfected				
0-1	50	4	3	48.5	0.08247	0.91753	0.91753	0.91753	0.91753	
1-2	43	3	2	42.0	0.07143	0.92857	0.92857	0.85199	0.85199	
2-3	38	2	4	36.0	0.05555	0.94444	0.94444	0.80466	0.80466	
3-4	32	1	2	31.0	0.03226	0.96774	0.96774	0.77870	0.77870	
4-5	29	0	1	28.5	0.00000	1.00000	1.00000	0.77870	0.77870	
5-6	28	1	0	28.0	0.03571	0.96429	0.96429	0.75089	0.75089	
6-7	27	1	3	25.5	0.03922	0.96078	0.96078	0.72144	0.72144	
7-8	23	1	2	22.0	0.04545	0.95454	0.95454	0.68865	0.68865	
8-9	20	0	2	19.0	0.00000	1.00000	1.00000	0.68865	0.68865	
9-10	18	0	3	16.5	0.00000	1.00000	1.00000	0.68865	0.68865	
10-11	15	2	1	14.5	0.13793	0.86207	0.86207	0.59366	0.59366	
11-12	12	2	0	12.0	0.16667	0.83333	0.83333	0.49472	0.49472	
12+	10									

EPILOGUE

It appears from the studies carried out to date that Conceptrol Cream does have value in the prevention of gonorrhoeal infection in the female. It further seems that a significant number of patients will cooperate and use the preparation according to directions and in a responsible fashion so as to protect themselves against reinfection. The laboratory evidence further suggests that this preparation and a number of others currently widely used as vaginal contraceptives may also have very real potential for the prevention of certain other sexually transmitted diseases such as syphilis and those caused by *T. vaginalis*, *C. albicans*, Herpes virus type II infection and others. The full potential of this will have to be determined through further studies. It is thus felt that it is highly desirable to move ahead rapidly, aggressively and imaginatively to introduce Conceptrol Cream into VD control and family planning programs as a preparation which, for the first time, will offer the female opportunity to protect herself against acquiring gonorrhoea and at the same time will offer her very real protection against unplanned pregnancy. In light of today's patterns of sexual behavior, particularly among the younger age group and the resultant health problems that are seen with a rise in rates of gonorrhoea and the continued high rate of unplanned pregnancy particularly in the teenagers, it appears that this preparation, if effectively introduced into various public-health and population/family planning programs would offer a very important tool to the public health workers, educators and others concerned and dealing with this problem. While this is being done it is felt desirable and necessary to build up a reservoir of experience with respect to methods

of patient motivation, techniques for assuring utilization of the "tool" in various public-health and family planning programs. At the same time it is felt necessary to determine the effectiveness as prophylactic of the other vaginal contraceptives such as foams, jellies, suppositories and foaming tablets so as to provide a spectrum of types of preparations that will be compatible with the wide variety of personal preference for agents for self-protection in the cause of sexual practices.

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Test Material Classified as Contraceptives or Vaginal Antiseptics
with Active Ingredient

Test Material	Active Ingredient	
<u>Contraceptives</u>		
Certane Vaginal Jelly	Phenylmercuric acetate Oxyquinoline sulfate Boric acid Sodium sulfodiocetylsoccinate	0.02%
Contra Creme	Phenylmercuric acetate Triethanolamine Glycerine Glycol monostearate Stearic Acid	0.06% 0.06% 2.5 % 3.5 % 3.5 %
Cooper Creme	Trioxymethylene Sodium oleate	0.04% 0.67%
Delfen Cream	Nonoxynol 9	5.0 %
Delfen Foam	Nonoxynol 9	12.5 %
Emko Concentrate	Nonylphenoxypolyoxyethylene ethanol Benzethonium chloride	8.0% 0.2 %
Emko Concentrate + Agent A	Nonylphenoxypolyoxyethylene ethanol Benzethonium chloride, Agent A	8.0 % 0.2 %
Emko Concentrate + Agent B	Nonylphenoxypolyoxyethylene ethanol Benzethonium chloride Agent B	8.0 % 0.2 %
Immolin Vaginal Cream-Jel	Methoxypolyoxyethyleneglycol 550 laurate Nonylphenoxypolyethoxyethanol	5.0 % 1.0 %
Koromex A	Phenylmercuric acetate Polyoxyethylenenonylphenol Boric acid	0.02% 0.5 % 2.0 %
Lanesta Gel	Chlorindanol Sodium chloride Sodium lauryl sulfate Ricinoleic acid	0.1 % 10.0 % 0.2 % 1.0 %
Lorophyn Suppositories	Phenylmercuric acetate Methylbenzethonium chloride Methylparaben	0.02% 0.2 % 0.1 %

Test Material Classified as Contraceptives or Vaginal Antiseptics
with Active Ingredient (continued)

Test Material	Active Ingredient	
<u>Contraceptives Con't</u>		
Milex Cresent Jelly	Sodium lauryl sulfate	0.008%
	Ricinoleic acid	1.0 %
	Sodium chloride	5.0 %
Ortho Creme	Ricinoleic acid	
	Nonoxynol 9	
	Sodium lauryl sulfate	
	Boric acid	
Ortho Gynol Jelly	Ricinoleic acid	
	p-diisobutylphenoxyethoxy- ethanol	
Preceptin Gel	Ricinoleic	
	p-diisobutylphenoxyethoxy- ethanol	
Ramses Vaginal Jelly	Dodecaethyleneglycol mono- laurate	5.0 %
Not included: Emko Concentrate and Spermicide		
<u>Vaginal Antiseptics</u>		
Betadine Vaginal Gel	Providone-iodine 1.0% available iodine	
Candeptin Vaginal Tablets	Candicidin 0.3% activity dispersed in starch, lactose and magnesium stearate	
Iso-sol- Argyrol	Mild Silver Protein	20.0 %
Neo Silvol	Silver iodide	20.0 %
Penigin	Crystalline penicillin G	
Penigin C	Crystalline penicillin G Benzethonium Chloride Chloramphenicol	
Progonasyl	Ortho-iodobenzoic acid	1.0 %
	Triethanolamine	11.0 %

Test Material Classified as Contraceptives or Vaginal Antiseptics
with Active Ingredient (continued)

Test Material	Active Ingredient	
<u>Vaginal Antiseptics con't</u>		
Propion Gel	Calcium propionate	10.0%
	Sodium propionate	10.0%
Silver Protein	Silver nucleinate	19.0 to 23 silver
Sporostacin Vaginal Cream	Chlordantoin	1.0%
	Benzalkonium chloride	0.05%
Trib Vaginal Cream	Triclobisonium chloride	0.1 %
Trimo-San Vaginal Jelly	Phenylmercuric acetate	1.4000%
	Sodium lauryl sulfate	
Vabal D Cream	Phenylmercuric acetate	0.05%
	Dichlorophene	0.5 %
Vagisec Liquid Douche	Polyoxyethylene nonylphenol	
	Sodium edetate	
	Diocetyl sodium sulfosuccinate	
Not included:	Emko concentrate (no active ingredient)	
	Koramex A base only	
	Vabal D Base	

Material Classified as Contraceptives or Vaginal Antiseptics
with Active Ingredient

<u>Test Material</u>	<u>Active Ingredient</u>
<u>Chemicals</u>	
CN 23577	Composition not given
CN 35458	Composition not given
CN 59895	Composition not given
CN 60563	Composition not given
CN 60684	Composition not given
CN 67 013 27	Composition not given
7828	Composition not given
CN 83402 B	Composition not given
Cortone	Cortisone acetate

Source: Facts and Comparisons, Inc., pp. 404-412 and 509

Test material packages

GRADUATE SCHOOL OF PUBLIC HEALTH

UNIVERSITY OF PITTSBURGH

MEMO TO: Dr. Cutler

FROM: Dr. Griffin, Dean

DATE: 5 April 1972

SUBJECT: Proposed Research Project Entitled "A Field Efficacy Trial of Intravaginal Precoital Prophylactic Agents as Preventive Treatment of Venereal Disease Infection"

I have approved the 29 March recommendation of the Committee on Research Involving Human Volunteers that your proposal, in the revised form, be assigned to Category A as defined in the ground rules established by this School with the approval of the Public Health Service.

A copy of the Committee's memorandum of recommendation is attached for your information. Please note that the questions shown on Sample 3, Attachment D, should be eliminated.

ek

cc: Dr. Minardi ✓
Miss Tomko ✓

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TECHNIQUE FOR TESTING SPIROCHAETICIDAL EFFECT

The spirochaeticidal property of various test samples was studied according to the previously reported methods of Arnold and Cutler (1956) as well as those of Turner, Hollander, and Schaeffer (1953). Each test sample was diluted to 50, 20, 10 and 1 per cent concentrations (weight/volume) with physiological saline. For preliminary screening, one drop of *T. pallidum* suspension was placed on the microscope slide next to one drop of the diluted test sample. The two drops were mixed with an applicator stick and the stop-clock was started for timing. The coverslip was then placed and the slide was examined by darkfield microscopy. The time required to immobilize spirochaetes was noted and recorded, 1 to 1.5 minutes were required for the preparation and thorough darkfield examination of five different fields of each wet smear slide; accordingly the dilutions of the test sample that were effective in rendering the spirochaetes non-motile within 1 to 1.5 minutes were further tested. For this purpose a more quantitative method was used in which 0.5 ml *T. pallidum* suspension was mixed with an equal volume of diluted test sample. At various intervals slides were prepared and examined for the motility of spirochaetes. The time required for the immobilization with each dilution was recorded. Physiological saline solution was used as a control and the number of spirochaetes and their motility was recorded at the end of the experiment. The pH of the saline control solution was adjusted with 1N HCl or NaOH to that of the test sample.

HARVEST OF SPIROCHAETES

A rabbit infected with pathogenic *Treponema pallidum* (Nichols strain) received from the Venereal Disease Research Laboratory, Center for Disease Control, Atlanta, Georgia, provided the source of the strain which has been maintained by regular passage in rabbits for subsequent testing. At the peak of acute orchitis, the rabbit is killed by injecting air into the ear vein. The testicles are removed aseptically, sliced, and minced into small pieces. Physiological saline solution with 20 per cent rabbit serum is added in a quantity of 15-20 ml. for each pair of testicles. The spirochaetes are extracted by shaking the flask for 1½ hours, using a low-speed mechanical shaker at room temperature. Then the material is centrifuged for 15 minutes at 110 G and the supernatant suspension of treponemes is removed. The harvest is considered satisfactory for the test if ten or more actively motile spirochaetes are present per 40 darkfield in each of five different fields. For regular passage and maintenance of *T. pallidum*, 0.2 to 0.5 ml. of the spirochaete harvest is injected by the intratesticular route into a healthy normal rabbit. The next spirochaete harvest from the injected rabbit is made in about 11 days at the time of acute orchitis.

EFFECT ON MOTILITY OF T. PALLIDUM

Twenty contraceptive and seventeen non-contraceptive vaginal antiseptic preparations were tested for their spirochaeticidal effects on *T. pallidum* in vitro. The results in Table I show the effective concentration of contraceptives which inhibited the motility of actively motile *T. pallidum*. As shown in Table I the various contraceptives are grouped according to the concentrations required to immobilize spirochaetes within 1 to 1.5 minutes. Only two contraceptives were effective at 1 per cent. concentration and were placed in Group A. The pH of these two contraceptives at 1 per cent. concentration were 6.2 and 7.1 respectively. Group B included twelve different contraceptives all of which were effective at 10 per cent. concentration. The pH alone within this range was not responsible for reducing the motility of spirochaetes as judged by the controls in this range. Three contraceptives (Group C) were effective at 20 per cent. concentration and two at 50 per cent. (Group D).

The results with non-contraceptive preparations tested for this purpose are shown in Table II. Several of these test samples were to be found to be spirochaeticidal by the criterion of motility.

Nine preparations (non-contraceptive Group B) out of seventeen immobilized spirochaetes within 1 to 1.5 minutes. The pH of test samples in Group B ranged from 3.5 to 7.2. The more alkaline preparations, with the exception of one (Group E), were effective at high dilution (1 per cent.) as shown in Group A; the pH of two preparations was 8.8 and 9.4.

Groups of Contraceptives according to the dilutions required to immobilize
T. pallidum spirochete suspension within 1 to 1.5 minutes ^a

Group	Name of Contraceptive	Conc.	Number of Contraceptives	pH range
A	Emko Concentrate + B, Ortho Cream	1%	2	6.2-7.1
B	Certane Vaginal Jelly, Contra Foam Cooper Creme, Delfen Cream, Delfen Foam, Emko Concentrate, Emko Concentrate + A, Finesse, Immolin Vaginal Cream-Jel, Lorophyn Suppositories, Ortho Gynol Jelly, Preceptin Gel	10%	12	4.6-7.5
C	Contra Creme, Lanesta Gel, Ramses Vaginal Jelly	20%	3	5.5-6.9
D	Koromex A Vaginal Jelly, Milex Cresent Jelly	50%	2	5.5-5.6

a) Control from pH 4.6 to 7.5 did not immobilize spirochetes in 5 minutes

Highest Dilution of Contraceptives Required to Inhibit the Growth
of N. gonorrhoeae by Time Exposure Method

Group	Name of Contraceptives	Conc.	pH range	Growth After Exposure ^a (minutes)		
				1	5	10
A	Cooper Creme, Preceptin Gel	1%	5.6-6.7	-	-	-
	Ortho Creme	1%	6.2	+	-	-
B	Emko Foam, Milex Crescent Jelly,	10%	5.7-7.3	-	-	-
	Certane Vaginal Jelly, Contra Foam, Koromex A Vaginal Jelly, Lanesta Gel, Lorophyn Suppositories, Ortho-Gynol Jelly	10%	4.6-7.5	+	-	-
C	Delfen Cream, Emko Concentrate + Sp.	20%	5.2-7.0	+	+	-
D	Delfen Foam, Emko Concentrate, Emko Concentrate + A, Emko Concentrate + B, Immolin Vaginal Cream Jel	50%	4.9-7.4	-	-	-
	Contra Creme, Ramses Vaginal Jelly	50%	6.7-6.9	+	+	-

a) Bacterial suspension for these experiments contains about 10^6 CFU per 0.1 ml., the inoculated Thayer-Martin selective medium plates were incubated at 37° in CO₂ incubator.

Highest Dilution of Contraceptives Required to Inhibit the Growth
of N. gonorrhoeae by Plate Dilution Method

Group	Name of Contraceptives	Conc.	pH of medium	Growth on Plate ^a	
				I	II
A	Ortho Creme, Preceptin Gel	1%	7.4	-	-
B	Certane Vaginal Jelly, Contra Creme, Contra Foam, Cooper Creme, Delfen Cream, Emko Concentrate + Sp. Immolin Vaginal Cream Jel, Lanesta Gel, Lorophyn Suppositories, Milex Crescent Jelly, Ortho Gynol Jelly	10%	7.4-7.6	-	-
C	Delfen Foam, Emko Concentrate, Emko Concentrate + A, Emko Concentrate + B, Emko Concentrate	20%	7.2-7.6	-	-
D	Koromex A Vaginal Jelly Ramses Vaginal Jelly	50%	7.5	-	-

a) Bacterial suspension for these experiments contains about 10^6 CFU per 0.1 ml., the inoculated Thayer-Martin selective medium plates were incubated at 37° in CO₂ incubator.

EFFECT ON GROWTH OF T. VAGINALIS

All contraceptive preparations when tested by the time exposure or tube dilution technique were effective in inhibiting the growth of T. vaginalis as shown in Table IV. In the time exposure method, most of the preparations were found effective at 1% concentration. By the tube dilution, method 19 preparations were effective at 10% concentration and the minimum inhibiting concentration (MIC) was higher for most of the preparations as compared to their MIC by the time exposure method.

Table IV
 Highest Dilution of Contraceptives Required to Inhibit
 the Growth of *T. vaginalis* by Two Methods^a

No.	Contraceptive	Time Exposure Method		Tube Dilution Method	
		Conc %	No. Live/Total 5 min 10 min	Conc %	No. Live/Total
1	Certane Vaginal Jelly	10	NG ^b	50	2/4
2	Conceptrol	1	0/1	10	NG
3	Contra Creme	1	NG	10	NG
4	Contra Foam	1	NG	10	NG
5	Cooper Creme	1	NG	20	NG
6	Delfen Cream	1	NG	10	NG
7	Delfen Foam	1	NG	100	NG
8	Emko Concentrate	1	NG	10	NG
9	Emko Concentrate + Spermicide	10	0/3	10	NG
10	Emko Foam	1	NG	100	NG
11	Finesse	1	0/2	10	NG
12	Immolin Vaginal Cream-Jel	1	NG	10	NG
13	Koromex A Vaginal Jelly	10	NG	10	NG
14	Lanesta Gel	1	NG	10	NG
15	Lorophyn Suppositories	1	NG	10	NG
16	Lorophyn Jelly	1	1/1	10	NG
17	Milex Crescent Jelly	1	NG	10	3/5
18	Ortho Creme	1	NG	10	NG
19	Ortho-Gynol Jelly	1	NG	10	NG
20	Preceptin Gel	1	NG	10	NG
21	Ramses Vaginal Jelly	1	NG	10	NG
	Control (mean average)		13/16		7/10
			12/15		

a) Growth in SIS medium (B.B.I.) with 5% Horse Serum. Mean count from 10 fields of duplicate tubes.
 b) NG indicates no growth when examined under microscope using low dry (10X) objective.

TEST FOR SPERMICIDAL QUALITY

The spermicidal quality of the contraceptives and vaginal antiseptics was determined by using the Modified Sander-Cramer Dilution Test. Under this method the test material is diluted to varying concentrations with a saline solution. 0.5 ml of this dilution is then mixed with 0.1 ml semen and examined microscopically under high dry power (40x). The greatest concentration of material capable of immobilizing the spermatozoa within 20 seconds is determined. Results are then confirmed by examining five fields for sperm motility. All the contraceptives and vaginal antiseptics which are found to be effective will be tested further by using the International Planned Parenthood Agreed Test for total spermicidal power.

The source of spermatozoa is human semen obtained through volunteers payed a nominal fee. This approach has been approved by the University Committee on Human Experimentation.

The Ranking of Contraceptive Products
(Performance Index)

There are over 20 contraceptives which have been screened and tested quantitatively in vitro. The performance index has been developed in order to make a selection among the contraceptives tested. In the epidemiological field, the difficult problem that often arises in practice is that of how to select the best subject in terms of several traits at one time. In the process of evaluating the performance of several contraceptives against the spirochete and gonococcus, the relative importance of gonorrhoea and syphilis can be treated as weighting coefficients. By employing the compound probability of transmissibility of a single act of sexual exposure and prevalence adjusted for under-reporting, the epidemic of gonorrhoea is weighted as 2.8 times as important as that of infectious syphilis.

From laboratory results, the performance of contraceptives are scaled by considering the effective concentration and time needed to immobilize N.gonorrhoeae and T.pallidum. For each tested product, points will be given according to the following scales:

Effective Concentration	Effective time (in min.)		
	1	5	10
1%	12	11	10
10%	9	8	7
20%	6	5	4
50%	3	2	1

For example, in Table 13 attached, Certane Vaginal Jelly attained 9 points on the anti-spirochete scale which indicates that it is effective at 10% concentration within one minute. Similarly, Certane Vaginal Jelly is effective at 20% concentration for one minute exposure to N. gonorrhoeae.

The Performance Index (P.I.) for each product is arrived at by combining the anti-spirochete and anti-G.C. scale measurements with the corresponding weighting coefficient stated above. For example, the performance index of Contra Creme is derived by:

$$\begin{aligned}
 \text{P.I.} &= X_1 + 2.8 X_2 \\
 &= 6 + 2.8 X_2 \\
 &= 11.6
 \end{aligned}$$

where X_1 = The scale measurement for anti-spirochete

X_2 = The scale measurement for anti-G.C.

The final selection was made by ranking products from 1 to 19 based on their performance index.

Table 13
Scaling Measurements and Performance Index

Number	Contraceptive	Scales		P. I.*	Rank
		Anti-spirochete	Anti-G.C.		
1.	Certane Vaginal Jelly	9	6	25.8	9.5
2.	Contra Creme	6	2	11.6	19
3.	Cooper Cream	9	12	42.6	2.5
4.	Delfen Cream	9	5	23.0	12.5
5.	Delfen Foam	9	3	17.4	16
6.	Emko Concentrate	9	3	17.4	16
7.	Emko Concentrate + Spermicide	9	4	20.2	14
8.	Emko Foam	9	8	31.4	6
9.	Finesse	9	3	17.4	16
10.	Immolin Vaginal Cream-Jel	9	5	23.0	12.5
11.	Koromex A Vaginal Jelly	3	8	25.4	11
12.	Lanesta Gel	6	8	28.4	7
13.	Lorophyn Suppositories	9	9	34.2	4.5
14.	Milex Cresent Jelly	3	9	28.2	8
15.	Ortho Creme	12	11	42.8	1
16.	Ortho-Gynol Jelly	9	6	25.8	9.5
17.	Preceptin	9	12	42.6	2.5
18.	Ramses	6	3	14.4	18
19.	Lorophyn Jelly	9	9	34.2	4.5

*P.I. = Performance Index

EFFECT OF pH ON THE VIABILITY OF *N. GONORRHOEAE* AND *C. ALBICANS* IN PHYSIOLOGICAL SALINE SOLUTION AFTER VARIOUS EXPOSURE TIMES (a)

SAMPLE NO.	pH	GROWTH AFTER EXPOSURE -- MINUTES (b)					
		<i>N. GONORRHOEAE</i>			<i>C. ALBICANS</i>		
		1	5	10	1	5	10
1	2.5	+	-	-	+	+	+
2	3.0	+	+	+	+	+	+
3	3.5	+	+	+	+	+	+
4	5.5	+	+	+	+	+	+
5	6.9	+	+	+	+	+	+
6	7.6	+	+	+	+	+	+
7	9.2	+	+	+	+	+	+
8	10.5	+	+	+	+	+	+
Control	6.8	+	+	+	+	+	+

(a) 0.1 ml culture containing about 10^6 CFU was mixed with 1 ml Phy. Sal. Solution and plates inoculated by streaking

(b) Thayer-Martin Selective Medium for *N. gonorrhoeae* and Sabouraud Agar for *C. albican*. Plates read after 24 hours incubation at 37°C

TITRATION OF HERPES VIRUS TYPE 2 IN TISSUE CULTURE BEFORE AND AFTER TREATMENT WITH CHEMICAL CONTRACEPTIVES

CONTRACEPTIVE TESTED	ASSAY SYSTEM	VIRUS TITRATION* (Log TCID ₅₀ /0.1 ml)	
		BEFORE	AFTER
A	VERO CELL	6.0	≤ 2.5
B		6.0	≤ 2.5
A	HUMAN FIBROBLAST (HUF)	6.5	≤ 3.5
B		6.5	≤ 3.5

*Virus suspension mixed with equal volume of contraceptive (10% solution) and after 10 minutes serial dilutions inoculated in Vero cells from 10⁻³ to 10⁻⁸ and HUF from 10⁻⁴ to 10⁻⁹

TITRATION OF HERPES VIRUS TYPE 2 IN MICE BEFORE AND AFTER TREATMENT WITH CHEMICAL CONTRACEPTIVES

CONTRACEPTIVE TESTED	TITRATION IN MICE BY I.C. (Log LD ₅₀ /0.03ml)*
NONE	5.3
C	≤ 0.5
A	≤ 1.5
B	≤ 2.5
D	1.7
E	≥ 4.5

*LD₅₀ titers calculated by Reed-Muench method.

Growth Inhibition Effect of LubriFoam on
Neisseria Gonorrhoeal by Two Methods

I. TIME EXPOSURE METHOD

Dilutions*	Inhibition of growth** after exposure (Minutes)		
	1	5	10
Undiluted	—	—	—
50%	—	—	—
20%	—	—	—
10%	—	—	—
Control (Phy. Sal. Sol.)	+	+	+

II. PLATE DILUTION METHOD

Dilutions*	Inhibition of growth** on duplicate	
	I	II
10%	—	—
5%	—	—
2%	—	—
1%	+	+
Control (Phy. Sal. Sol.)	+	+

*Dilutions prepared in Physiological saline solution. For plate solution method it represents the final concentration in the medium.

**Growth after 24 hours incubation at 37°C in CO₂ incubator; + indicates confluent growth and - indicates complete inhibition of growth.

Growth Inhibitory Effect of Ky Jelly on Different
Strains of *N. gonorrhoeae*

Test Method	Concentration* of Ky Jelly	Growth** of 3 Strains								
		53258			55528			63220		
		1 min.	5 min.	10 min.	1	5	10	1	5	10
Time Exposed	90%	+	+	+	+	+	+	+	+	+
Method	70%	+	+	+	+	+	+	+	+	+
	50%	+	+	+	+	+	+	+	+	+
	30%	+	+	+	+	+	+	+	+	+
Plate Dilution Method	10% 8% 6% 4%	Growth of 3 Strains on Duplicate Plates								
		I		II		I		II		
		—	—	—	—	—	—	—	—	
		+	+	+	+	+	+	+	+	

*Dilutions made in Physiological saline solution, for Plate Dilution Method it represents the final concentration in the medium.

**Growth on Chocolate Agar medium plates after 124 hours incubation at 37°C in CO₂ incubator;

+ indicates confluent growth

— indicates complete inhibition of growth

POPULATION DIVISION

DEPARTMENT OF EPIDEMIOLOGY & MICROBIOLOGY
March 16, 1972

TO: Dr. David Minard, Chairman for the Committee on Human Experimentation
FROM: John C. Cutler, M.D., H.M.D. Utidjian, M.D., and B. Singh, Ph.D., DVM
SUBJECT: Request for Consideration to Conduct a Field Efficacy Trial of
Intravaginal Precoital Prophylactic Agents as Preventive Treatment
for Venereal Disease Infection

One of the major world-wide public health problems today is the rapidly rising rates of venereal disease combined with steadily rising numbers of unwanted and casual pregnancies.

It is felt that a commercially available, FDA approved intravaginal precoital preparation offering protection to the female from venereal disease and pregnancy would significantly complement existing contraceptives and venereal disease control techniques.

In view of this, field efficacy trials will be necessary upon completion of laboratory screening and quantitative testing, in vitro and in vivo of a number of compounds against T. pallidum and in vitro against N. gonorrhoeae.

The field trials will be Phase II of a three-year project sponsored by the Agency for International Development titled "Development of a Combined Agent for Genital Infection Prophylaxis and Contraception."

1. The field efficacy trial of an intravaginal, precoital prophylactic agent as preventive treatment against venereal disease will employ a completely randomized control design without a placebo. Clinic patients selected for possible participation in the field trial will be those adult females:
 - a. Who present themselves to the clinic with medically established gonorrhea after the field trial has begun.
 - b. Who have had one or more venereal disease infections prior to the index infection, ascertained by clinic records or confirmed medical history.
 - c. Who are currently using oral contraceptives, the I.U.D., or have undergone surgical sterilization procedures.
 - d. Who have been judged by the clinic staff to be suitable subjects with reference to:
 - (1) Level of past co-operation and judgment as revealed by treatment and follow-up attendance at the clinic.
2. Those patients who meet the criteria described will be initially contacted by the treating physician to determine whether they would be willing to talk with Pro-Con personnel about their possible participation in the field trial.

3. Once selected, these patients will be interviewed by a Health Educator and their voluntary cooperation in the field trial solicited.
 - a. The purpose of the trial will be thoroughly explained (Attachment A). The selected patients will be informed that:
 - (1) The investigational drug has been proven safe to use by the F.D.A. and is currently available on the market. We are testing the drug for its usefulness in the preventive treatment of venereal disease.
 - (2) The investigational drug has practically no inherent risk of serious side effects.
 - (3) The investigational drug has shown a high degree of effectiveness against venereal disease organisms in the laboratory tests.
 - (4) The investigational drug is expected to be effective as preventive treatment against future venereal disease re-infection.
 - (5) The patient must sign an "informed consent" form (Attachment B) before being allowed to participate in the field trial. A summary statement describing the study and its risks which is the basis for the discussion with the prospective subject will be on the reverse side of the "informed consent" form. Each patient who agrees to participate in the trial will be required to initial this summary statement after the discussion with the Health Educator.
4. Each patient who agrees to participate will come on trial immediately after successful termination of antibiotic treatment for their most recent attack of venereal disease. Since random assignment to test or control group occurs after the patient has agreed to participate, all patients will be given information about:
 - a. The intravaginal preparation and applicator to be used.
 - b. The proper use of the preparation.
 - c. The free supply of the preparation they will be given if assigned to the test group. The investigational drug that is supplied to the test group will be adequately labeled CAUTION: NEW DRUG -- LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE to fulfill the requirements of F.D.A.
5. Observation will be carried out for one year to see whether there is a significant reduction in the rate of re-infection of the test group as compared to the control group. To accomplish this statistical comparison, the following will be done:
 - a. Twice-a-month routine examination of all female patients in the study regardless of whether they have venereal disease symptoms or not. These examinations will include:
 - (1) Clinical examination of the genitalia for venereal disease and local skin reactions to the preparation.
 - (2) Cultures for gonococcus and examination for trichomonas and candidiasis infection.
 - (3) Dark field microscopy of any suspicious lesions.
 - (4) Prompt treatment for those patients who contract a venereal disease infection while on trial.
 - (5) History of use of preparation and sexual activity pattern.
 - (6) Serology for syphilis monthly.
 - (7) Search for problems encountered.
 - (8) Re-instruction or re-inforcement of instructions.
 - (9) Issue further supplies for their own personal use.
 - (10) Regular screening which will be medically beneficial in detecting vaginal infection particularly asymptomatic gonorrhoea.

6. Each patient who agrees to participate will receive \$5.00 plus \$1.25 for transportation tokens or parking cost per re-examination visit.
7. The Hypothesis: Use of a clinical venereal disease prophylaxis will significantly reduce the venereal disease re-infection rate of the test group, in contrast to the control group who will not be receiving this prophylactic measure.
8. To insure confidentiality of the information derived from the study, review of medical records will be conducted by the treating physician, and information vital to the study will be kept on coded cards. This coding will be done at the site of the trial and the names of the subjects will not leave that location (Attachment C). All Master Code Cards and identifying data will be destroyed at the termination of the study.
9. Any changes in the proposed procedure will be brought before the Committee for reconsideration.
10. It is respectfully requested that the Committee authorize the Department of Epidemiology and Microbiology and the Population Division of the Graduate School of Public Health to conduct the described field efficacy trials of an intra-vaginal pre-coital prophylactic against venereal disease.

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	<u>6/70-12/70</u>	<u>1/71-12/71</u>	<u>1/72-12/72</u>	<u>1/73-12/73</u>	<u>1/74-12/74</u>	<u>1/75-12/75</u>	<u>TOTAL</u>
Salaries	17,409	50,321	73,789	84,891	79,583	67,582	373,575
Fringe	1,741	6,243	9,897	11,019	10,924	9,619	49,443
Travel	522	2,044	3,380	1,531	1,299	854	9,630
Equipment ¹	3,961	9,023	976CR	256	144	20	12,428
Supplies	2,605	12,462	10,584	5,110	2,529	583	33,813
Consultant	- 0 -	500	738	- 0 -	- 0 -	- 0 -	1,238
Telephone	49	327	492	224	518	895	2,505
Postage	2	12	37	27	44	5	125
Publication	- 0 -	- 0 -	109	252	- 0 -	28	389
Pay to Participants	- 0 -	<u>25</u>	<u>500</u>	<u>2,250</u>	<u>2,500</u>	<u>1,750</u>	<u>7,025</u>
Total Direct	26,289	80,957	98,550	105,560	97,541	81,334	490,231
Indirect Cost	<u>10,184</u>	<u>31,876</u>	<u>57,415</u>	<u>47,180</u>	<u>41,400</u>	<u>41,480</u>	<u>229,535</u>
Grand Total	<u>36,473</u>	<u>112,833</u>	<u>155,965</u>	<u>152,740</u>	<u>138,941</u>	<u>122,816</u>	<u>719,766</u>

1. Includes repair and maintenance

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