Studies on Development of a Vaginal Preparation Providing Both Prophylaxis Against Venereal Disease, Other Genital Infections, and Contraception. I. Venereal Disease Prophylaxis, Past Experience, Present Status and Plans for Future Studies

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VERY early in the modern era of medicine, it was discovered that silver compounds were effective gonococcicidal agents. In 1881, Crede provided that a two per cent silver nitrate solution instilled into the eyes of the newborn would prevent the development of gonococcal ophthalmia neonatorum, the leading cause of blindness at this period. By 1904, Metchnikoff and Roux[12] had discovered through both animal and human experimentation that it was possible to use mercury preparations, notably 33 per cent mild mercurous chloride, as a post-exposure local application in ointment form to prevent infection with syphilis. Because of the lack of specific therapeutic agents for the treatment of both gonorrhea and syphilis at that time, the importance of prophylaxis was self-evident. Silver and mercury compounds, in addition to the condom, were widely used for many years. During the First World War, the use of prophylactic preparations was a very important element in venereal disease control programs involving the military.

To quote from Stokes on World War I experience with prophylaxis:[16]

"A classical example is Walker's experience at St. Nazaire in World War I, when an incidence rate of 625 per thousand per month was reduced in three months to 110 per thousand by the compulsory application of prophylaxis to all men returning from leave, whether admitting exposure or not. Further application of prophylaxis, and more efficient guards around the camp, reduced the incidence to 35 per thousand. Estimates of the efficiency of station prophylaxis based largely on World War I experience, include such figures as 1.3 per cent failure in 242,000 treatments; one infection in 37 exposures without prophylaxis as against one infection in 274 exposures when prophylaxis was taken."

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The efficacy of prophylaxis as an element of venereal disease control programs was self-evident.

In spite of their effectiveness, the preparations such as calomel ointment and silver compounds required patient cooperation and responsibility. In civilian life, and all too often even in military life, motivation to use the prophylactic was lacking, particularly in situations involving casual contact. In addition, the preparations were somewhat messy, uncomfortable to use, and their true value was not perceived by the individual at risk.

With the onset of the Second World War, protection of the troops against venereal infection was once again a matter of military concern. The prophylaxis program was reinvigorated as an important element in the VD control program of the military. It was complemented by an extensive distribution of the condom and an effective health education program. By this time sulfonamide preparations had become available. Later, antibiotics were also available. Both of these had been studied for use as prophylactics, and had been found when used systemically to offer a substantial degree of protection.

The chief disadvantages of the use of sulfonamides or antibiotics as systemic prophylactic agents were threefold: (1) The risk of development of a resistant strain of the organism; (2) the possibility of sensitization or allergic reactions in the patient; and (3) the close medical supervision necessitated by these types of preparations.

Studies had been carried out for many years in the Venereal Disease Research Laboratory of the United States Public Health Service in an attempt to improve available prophylactic preparations, and to develop better products such as a water soluble preparation effective as a cleansing agent, as well as a prophylactic against both the gonococcus and the spirochete.[1] The combination of 0.1 per cent Mapharsen and one per cent sodium lauryl sulfate in aqueous solution was successful in laboratory studies.[3] In field trials involving both females and males, this preparation was found to be effective in reducing the incidence of infection with gonorrhea.[5]

By 1950, the investigations on the Orvus-Mapharsen preparation had reached a point at which it was considered suitable for widespread use. However, at this time policy decisions were made in both civil and military programs to rely solely on therapy associated with well-developed case finding

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and other public health methods for venereal disease control purposes. Thus, there was a virtual cessation of research work on venereal disease prophylaxis in both laboratory and field operations.

Need for Reconsideration

The world wide resurgence of gonorrhea and syphilis, despite the existence of specific therapeutic agents, has prompted a reconsideration of the methods for handling the problem. There is a suggestion that a change in contraceptive practice, with either increased rates of exposure in oral contraceptive or intrauterine device users or decreased use of the condom and of vaginal contraceptives, some of which appear to have prophylactic qualities, may be factors in the increased transmission of infection.[8]

Thus, it would appear timely and appropriate to restudy prophylactic preparations for topical use. If certain preparations already in use as vaginal antiseptics or for contraception are found to have potential as VD prophylaxis, epidemiologic studies are indicated. In terms of public health programs now directed at venereal disease control or prevention of unplanned pregnancy, the existence of single preparations which could be utilized in either health program has a self-evident significance. Thus, a study supported by AID (US Agency for International Development) has been undertaken.

While syphilis can be maintained in several of the anthropoid species, the animal that has been most widely studied and has been found most useful in the laboratory is the rabbit. The experience of Arnold and Mahoney[3] in both therapy and prophylaxis of syphilis has shown a high degree of correlation between prophylactic and therapeutic findings in the rabbit and in man. Of particular interest is the fact that the Nichols strain of *Treponema pallidum,* which has been the most widely studied and used since its isolation in 1912, produces a disease in man apparently no different from that encountered with street strains of the organism.[10] The gonococcus, however, is not transmissible to any readily accessible experimental animal; therefore, all evaluations of prophylaxis or therapy must be done in man.

Epidemiologic studies in man have indicated that the risk of infection with syphilis for the male following contact with a known diseased partner, but without knowledge of the number of contacts, is roughly one in two. Studies in gonorrhea have indicated that the risk to the male in contact with an infected female is roughly one in 20 for a single contact.[6] The risk to the female following contact with an infected male has not been estimated. The human experimental studies carried out at the Federal Penitentiary at Terre Haute as reported by Mahoney *et al*[11] indicate again, under experimental conditions, the relatively low order of virulence of the gonococcus and the rapid loss of infectivity of cultured strains. These facts point out the difficulties involved in the assessment of the prophylactic value of any agent, and indicate the necessity for utilization of epidemiologic methods of study involving relatively large numbers of individuals, at comparatively high risk of infection and observed over long periods of time.

Studies such as that of Funes and Aguilar[5] on prostitutes utilizing an Orvus-Mapharsen solution as a douche following contact, as well as investigations carried out in the military, offer well controlled populations for the observation of prophylactic effects of different products.[5] Studies involving the exposure of non-infected volunteers to infected contacts in order to observe relative rates of protection have become increasingly difficult, due to the rigid medical research ethics now operative.

Behavioral Studies

Behavioral and motivational studies are also required to determine the acceptability and use of prophylactic agents. The nature of the casual sexual contacts, perhaps in physical surroundings with no facilities for any type of self-medication or washing, demonstrates the need for such studies. A health educational approach was found to be highly effective during both World Wars in the venereal diseases control program of the Armed Services, as well as in selected segments of the civilian population. Prophylactic measures were also successful in some areas in which prostitution was carried out under medical supervision. Long-acting penicillin injections were used rather widely under certain circumstances and found to decrease very rapidly the incidence of transmission of syphilis and gonorrhea.[4] It should be noted, however, that this method was not acceptable to the prostitutes in many cases because one of the side effects of penicillin was the restoration of fecundity, perhaps due to the cure of specific and non-specific cervical or vaginal infections which had previously resulted in relative sterility. Unwanted pregnancies following such prophylactic therapy, rather than the occasional drug reaction, were very important elements in initiating non-cooperation of the prostitute population.[4]

In recent years, following the widespread use of the intrauterine devices and oral preparations as contraceptive methods, with a resulting relative decline in the use of the condom and the vaginal preparations, epidemiologic observations have suggested the probability that vaginal contraceptive preparations themselves do have a certain measure of prophylactic value.[8]

The significance of the condom as a contraceptive agent needs no explanation. It is of interest to note that, because of legal requirements governing the sale and use of contraceptives in many states in the United States, the condom has been permitted to be sold "for the prevention of the transmission of disease only." However, its use is not increasing in proportion to population growth.[15] From the public health viewpoint, it would appear to be feasible to attempt to approach the prevention of both venereal disease transmission and unwanted pregnancies through increased attention to the practice of prophylactic measures.[2]

Studies are now under way to assess *in vitro* the effectiveness of certain commercial vaginal contraceptives against *T. pallidum, N. gonorrhoeae, C. albicans,* and *T. vaginalis.* A few such agents have already been placed under observation to determine the prophylactic value against syphilis in the rabbit, with pre- and post-exposure application to the genital mucous membrane and surrounding areas.[13]

Human Testing Problems

In order to test the true value of these agents, they must be tested clinically on a human population. The classical approaches to testing the efficacy of a prophylactic against any infection in the human entail either: (1) the deliberate expo-

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sure to the infection of human subjects, with and without the prophylactic measure, or (2) the prophylactic treatment of a large number of susceptible subjects, and parallel administration of a placebo prophylactic to a similar number of controls, prior to a predicted epidemic, or at least a season of known high incidence of infection, in the community at large.

The first approach has been used with such trivial and self-limiting infections as the common cold. The second has been used in the large-scale field trials of whooping cough and poliomyelitis vaccines.

Venereal diseases, however, present special problems, both ethical and epidemiological. Although both syphilis and gonorrhea are accepted as completely curable in the early stages, they are certainly never trivial, and rarely self-limiting. It is highly questionable whether it would be acceptable to deliberately expose volunteers to the risk of such infection. The required experimental circumstances, i.e. of deliberate sexual intercourse by volunteers with a person known to have active gonorrhea and/or infectious syphilis present problems of social, political, and ethical concern, which must be weighed against national attitudes and practices and the seriousness of the problem to be studied.

It is to be noted that the Terre Haute[10] and Sing Sing[10] studies in penal institutions could be carried out with cooperation of volunteers because of the certainty of cure and consequent low risk to the patient, and because of the fact that the technique for infection was experimental innoculation. There was enthusiastic cooperation of patients in part because of an evident desire to assist in working out solutions which would benefit their fellow men and themselves as well.

From the epidemiologic point of view also, the venereal diseases, by definition, are for practical purposes uniquely transmitted by sexual intercourse. Therefore, despite the current existence of an upward trend of venereal disease incidence, which in the case of gonorrhea at least is of truly epidemic proportions, the susceptible population at large is not universally a risk of infection, as it would be, for example, to influenza. Exposure to risk of venereal infection is dictated, not only by the prevalence of venereal disease in the infectious stages in the population, but equally upon the patterns of sexual behavior of individuals. For any prophylactic trial therefore, attention must be focused upon identified high risk individuals. Prostitutes are an obvious choice but, in a community where prostitution is officially illegal, there are inherent difficulties in their employment as an experimental group.

High risk individuals of both sexes are, however, self-identified by frequent contracting of venereal infections. The clientele of every established VD clinic or general medical clinic at which VD cases commonly present, includes a small proportion of "recidivists" who, by reason of the immutability of their sexual habits and failure to profit by experience, return to the clinic with fresh venereal infections with monotonous regularity. Those who, by reasons of stability of residence, employment, or habit, regularly return to the same clinic, are readily identified from clinic records. From such records, a baseline re-infection rate, or average interval between re-infections, can be determined for such individuals. If such a recidivist group could be induced to co-operate in the regular use of a prophylactic measure against VD, on the assumption that their sexual habits and milieu (and by inference their exposure to VD) remain otherwise unaltered, they do constitute a potential experimental group. By the very nature of their reckless unconcern for the repeated consequences of their promiscuity, VD recidivists present a considerable challenge to the experimentalist from the point of view of securing reliable co-operation in the use of prophylaxis, for they have already, almost by definition, defied the efforts of health educators. However, if the prophylactic application is easy, convenient, and does not interfere with sexual pleasure, it should be possible to promote its use. Free supplies of the prophylactic will be issued to the experimental subjects and they will be asked to return to the clinic for re-examination, swab culture etc., at regular monthly intervals, regardless of whether they have VD symptoms or not. This will require energetic follow-up calls and visits by a project field worker, such as are conducted by the better run VD clinics.

Such an experimental design falls far short of the classical controlled trials previously outlined. The use of a placebo prophylactic with a controlled group on a blind or double blind basis is not contemplated, for fear that the infections occurring in the control group would completely discredit the whole concept of VD prophylaxis with a section of the identified high risk group. Moreover, it is felt that it will be difficult to obtain the sustained cooperation of an adequate number of experimental subjects as it is, without halving the number using the actual prophylactic. In the proposed design, the subjects will act as their own controls on the basis of their known 'preprophylactic' infection rate.

Current Project

The specific prophylactic products which this project is currently working on are intravaginal chemical contraceptive preparations, which are introduced immediately prior to intercourse. However, the trial of prophylactic efficacy will not be confined to female subjects. The product will also be issued to males instructing them to insist upon its intravaginal introduction by their female partners prior to intercourse, in the interests of their own protection. It is postulated that a suitable prophylactic chemical barrier should prevent the transmission of infection in either direction, so to speak, from male to female or from female to male.

The experimental design outlined above is ethically unobjectionable. In the event that the prophylactic proves incompletely effective, or even totally ineffective, the subject is no worse off than if he or she had not been selected for the trial. By their recidivist history, the subjects have demonstrated their proclivity for contracting venereal disease, which will scarcely be increased by the sense of false security that might be engendered by the use of an incompletely effective prophylactic. The inducement to attend the clinic for regular check-ups, even when symptom-free, engendered by the trial, can only be in their best interests, in that it will bring them to diagnosis and treatment earlier than would otherwise have been the case. If and when an experimental subject contracts VD during the trial, he or she will be withdrawn from further participation for, once the prophylactic under test has failed for a particular individual, that subject is unlikely to place much reliance upon it subsequently, and therefore little reliance could be placed upon further results from the same

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individual. Of course, if, following apparent failure of a prophylactic the subject admits to failure in its invariable use in every single sexual exposure, such a result will not necessarily invalidate the prophylactic. Needless to say, every effort will be made during the trial to persuade subjects: (1) to attend only the clinic from which the trial is being conducted; (2) not to self-administer antibiotics or other chemotherapy for whatever reason; and (3) to report antibiotic or other medication which may be prescribed by any physician for any other non-venereal health problem.

Some rather large-scale epidemiologic surveys following in general terms the model described above have already been instituted in several countries, in an attempt to assess the effectiveness of certain vaginal agents in preventing venereal disease in prostitute populations.[7]

While it is recognized that many elements, of which one is therapy, make up the total program required for the control of venereal disease, it should be apparent once again that it would seem to be highly desirable to build upon past experience and to attempt to reintroduce the concept of prophylaxis as an important measure. As well as being provided with prophylactic agents, the individual must increasingly be motivated to take some responsibility in protecting himself or herself from infection. When planning to intensify public health programs to control VD, the budgetary competition to meet the growing demands for other health services must be recognized. It is evident that in order to reduce the costs of prevention of infection the cooperation of the individual himself is necessary.

It has been obvious, through the rise in venereal disease rates, that therapy alone cannot be counted upon to meet the world wide problem. The early hopes for the possibility of "eradication" because of existence of specific chemotherapeutic agents have not been realized. Therefore, in order to approach the problem realistically, it seems essential to not only reintroduce prophylaxis to the armamentarium of the public health control methods but also to enlist the patient's cooperation in terms of self-protection, through the use of some agent which may prevent infection. The potential and need have been recently reviewed by Smartt.[14]

Summary

In view of the increasing world-wide concern, not only with the problem of the unwanted child and the massive population increases but also with the pressures for integration of population programs into the framework of total public health services, it would appear most opportune to be able to combine venereal disease prophylactic efforts with those designed to prevent unwanted pregnancies.

With that thought in mind it becomes obvious that there is both an opportunity and a need for substantial increases in research efforts directed at the assessment of the prophylactic values of existing contraceptive agents. In addition, other studies, involving individual motivation, practice, and delivery of public health services should be established in such a way as to determine how most effectively the knowledge and tools now at hand can be used.

An experimental model for the study of venereal disease prophylaxis in human subjects is described.

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