Role of Acquired Immunity to *T. pallidum* in the Control of Syphilis

JAMES F. JEKEL, M.D., M.P.H.

DURING THE PAST 10 years a marked resurgence of infectious syphilis has occurred in the United States and elsewhere—a marked contrast to its rapid decline in the preceding decade. Fleming listed the following 10 reasons for this resurgence in his excellent review of the subject (*1*):

1. Decreased financial support for venereal disease control activities during the mid-1950's.
2. Increasing urbanization.
3. Decreasing "happenstance" use of penicillin.
4. The shift in treatment of syphilis from public clinics to private physicians' offices, due to the introduction of long-acting penicillin, and the fact that syphilis is not well reported to public health authorities have hindered epidemiologic investigation.
5. Decreased fear of syphilis due to the availability of quick treatment.
6. Increased population mobility.
7. Importation of syphilis from other countries.
8. An increase in syphilis among teenagers.
9. Homosexuality (possibly increasing in importance).
10. Increased consumption of alcohol.

These factors have undoubtedly played a role in the current syphilis control problem, but it is not possible to state with certainty the extent of the contribution of each. Nor is it possible to exclude the possibility of other factors influencing the pattern of reported infectious syphilis during the past 20 years.

Hypothetically, declining levels of acquired immunity to syphilis may have contributed to the increasing difficulty in controlling the disease by placing increased burdens on epidemiologic investigation and control programs. This paper (*a*) reviews evidence which suggests that acquired immunity serves as a barrier to the spread of infectious syphilis, (*b*) reviews evidence for a marked drop in syphilis immunity in the U.S. population in the past 25 years, (*c*) discusses the implications of yaws eradication programs for syphilis control in some developing nations, and (*d*) considers the implications of the hypothesis for syphilis control efforts.

Active Herd Immunity Against *T. pallidum*

In 1926 Chesney wrote his classic review of immunity in syphilis and concluded that syphilis infection produced active immunity in human beings (*2*). Some debate followed as to whether this represented a true immunity, but the work of Magnuson and Rosenau seemed to confirm that, at least in rabbits, a true active immunity develops in response to infection with *Treponema pallidum* (*3*). They infected rabbits with *T. pallidum* and then treated different groups of these animals with penicillin at 0, 3, 6, 12, and 24 weeks after infection in order to prevent further progression of the in-

Dr. Jekel is assistant professor of public health, Yale University School of Medicine, New Haven, Conn.

fection and of the development of active immunity. They then challenged the rabbits by applying different amounts of *T. pallidum* inoculum to their skin. They summarized their findings as follows:

> Starting from a small but demonstrable immunity at 3 weeks, the immunity increased to such a degree that by the 24th week animals were protected (asymptomatic reinfection) against 10^8 minimal infectious inoculums.

By "asymptomatic reinfection" Magnuson and Rosenau meant that *T. pallidum* was discovered in some organs, but no skin lesions developed in response to the inoculum. Their observations were confirmed by Miller and coworkers, who found that after 24 weeks of syphilis infection all of their rabbits were resistant to the development of skin lesions upon reexposure (*4*).

Magnuson and co-workers studied this same phenomenon in human volunteers at Sing Sing prison (*5*). Those who had a definite history of syphilitic infection were classified as to whether their infection had been treated early in its course (before 2 years had elapsed), late in its course (after 2 years), or not at all. Each volunteer was then inoculated on the skin with identical doses of *T. pallidum.* Primary skin lesions and a serologic response developed in response to inoculation in all who had been treated for early syphilis (11 volunteers), but not in those who had had untreated late syphilis (five volunteers). Of 26 volunteers with syphilis treated after 2 years from the time of exposure, skin lesions developed in 10, but only one of these lesions was positive by darkfield examination; in 16 of these volunteers no lesions developed in response to inoculation. The authors concluded that untreated syphilitic persons were highly resistant to the development of infectious skin lesions, that belatedly treated syphilitic persons were partially resistant, and that syphilitic persons treated early were fully susceptible to reinfection.

Some clinical evidence supports the theory that acquired immunity from untreated syphilis protects against the development of infectious skin lesions after reexposure. It has long been known that repeat primary chancres seldom occur in persons with untreated syphilis—presumably because of active immunity, since reexposure is common in persons with a history of syphilis (*2*). Since the introduction of adequate penicillin therapy, however, repeat primary chancres have become more common, and some patients have been seen with a third and even a fourth primary chancre. Cannefax (*6*), in his excellent review of the immunological aspects of syphilis, commented regarding this point:

> It was also well-established that, if the patient was adequately treated, the "chancre immunity" was lost. This was evidenced by numerous instances in which adequately-treated patients developed new primary lesions, whereas inadequately-treated or untreated patents did not develop new or primary lesions.

This change can be explained by assuming that early penicillin treatment in recent years has prevented such patients from acquiring effective immunity to *T. pallidum*, thus leaving them susceptible to reinfection. In his article, Cannefax concluded that the bulk of available evidence favors the view that there is a true acquired immunity to syphilis in persons whose syphilis infection was allowed to proceed undisturbed by therapy for several months. He emphasized that the character of this immunity is primarily to make the patient resistant to the development of new infectious lesions rather than to enable him to destroy treponemes within his body (*6*):

> There is no doubt that the development of a primary lesion in humans results in an immunity sufficient to prevent the occurrence of a subsequent chancre unless challenged with very large numbers of virulent organisms.

Declining Prevalence of Syphilis

No substantial evidence exists to support the theory that the reagin or even the treponemal antibodies are the active agents in producing chancre immunity (*6*). Moreover, one cannot conclude that chancre immunity corresponds to the serologic titer in any one person. Nevertheless, the longer syphilis infection progresses untreated, the more likely it is that a high serology titer will appear and that significant chancre immunity will also develop. Considering the population as a whole, therefore, the prevalence of reactive serologic tests is an approximate indicator of the prevalence of late treated or untreated syphilis and also of levels of chancre immunity.

Table 1. Premarital syphilis reactor rates per 1,000 tested among residents of Virginia, by race

Year	White		Nonwhite	
	Number tested	Reactor rate per 1,000	Number tested	Reactor rate per 1,000
1944	27,571	11.6	14,529	204.7
1962	35,157	2.4	11,640	39.8

SOURCE: Statistics Section, Venereal Disease Program, National Communicable Disease Center, Public Health Service.

Table 2. Results of serologic blood tests[1] for syphilis on the first million Selective Service registrants

Race and age group	Number tested	Number reactors	Percent reactors
White:			
18–25	477,768	4,822	1.0
26–35	372,518	10,183	2.7
Negro:			
18–25	60,238	10,679	17.7
26–35	51,232	16,397	32.0

[1] Tests performed between Nov. 1, 1940, and Apr. 15, 1941.

SOURCE: Statistics Section, Venereal Disease Program, National Communicable Disease Center, Public Health Service.

Serologic screening programs, such as premarital blood testing and screening programs for military recruits, have indicated that reactor rates in the United States in the early 1960's were only a fraction of those in the early 1940's. Table 1 shows the decline in the percentage of premarital serologic tests which were positive in Virginia in 1944 and 1962. In both the white and nonwhite populations, by 1962 the reactor rate had fallen to about one-fifth of the 1944 rate. Table 2 shows the prevalence of positive serologic tests in young U.S. men (both white and nonwhite) based on the testing of Selective Service registrants in 1940 and 1941. Table 3 shows the prevalence of positive serologic tests in the U.S. male population in 1960–62, as determined during the health examination studies of the U.S. National Health Survey.

Comparison of these two sample studies indicates that the reactor rate in the U.S. population has fallen greatly in this two-decade period. However, not every investigator has found this great a decline in premarital serologic reactor rates. Wilbar and Millington found the serologic reactor rates in Pennsylvania had not fallen greatly in the two decades after 1940 (*7*). However, the great increase in Pennsylvania's nonwhite population during this period might explain the lack of significant decline in overall serologic reactor rates. Therefore, although the exact magnitude of the decline in syphilis reactor rates is uncertain, the bulk of evidence supports the contention that current reactor rates are only a fraction of those before World War II. This reduction has presumably been caused by the introduction of effective antibiotic treatment since 1941.

Caution should be used in interpreting the data in the tables, since different serologic tests were used. Tables 1 and 2 show pooled data from a number of different nontreponemal antigen tests (such as the Kahn, Kolmer, Hinton, Kline, Eagle, and Mazzini tests). Table 3 shows results from the Kolmer Reiter protein test, which uses a treponemal antigen. In general, the nontreponemal antigen tests are more sensitive than the treponemal tests, and so would be expected to have higher false positive rates. However, as the prevalence of a condition in a population falls, in a screening program for that condition the false positives automatically become a higher proportion of the total positives found, even though the false positive rate of the screening test is unchanged. Therefore, even though

Table 3. Prevalence of reactive Kolmer Reiter protein tests in the general male population, United States, 1960–62

Race and age group	Percent reactors
White:	
18–24	0.3
25–34	1.0
Negro:	
18–24	2.8
25–34	7.3

SOURCE: Findings on the Serologic Test for Syphilis in Adults, United States, 1960–62. PHS Publication No. 1000—Series 11—No. 9.

the Kolmer Reiter protein test would be expected to have a lower false positive rate than the reagin tests, it would also be plagued with false positives, due to the low prevalence of reactive serologic tests. Therefore, in light of this information and supporting data from the marked decline in mental hospital admissions for syphilitic brain disease and rates of congenital syphilis, we can conclude that this fall in the prevalence of syphilis is real.

Significance of Decline in Reactor Rates

The evidence cited indicates that an untreated syphilitic patient eventually acquires active immunity and becomes resistant to the development of a primary skin lesion upon reexposure. Thus, before the advent of effective antisyphilitic treatment, most syphilitic persons could spread infectious syphilis during only one period in their lives, that is, during the first few weeks when the disease was in the primary and secondary stages. Thereafter, except for some relapses into a secondary stage of the disease, they were resistant to the infectious lesions which could spread the disease further. These resistant persons were a barrier to the spread of infectious syphilis, and therefore represented a "herd immunity."

The overall reactor rates in a population need not be very high for a significant herd immunity to be present. The overall reactor rate might be only 10 percent in a population, and yet in the "high-risk" population (that part of the population whose sexual behavior makes exposure likely) the reactor rate might be 50 percent or higher. I believe that during and immediately after World War II the reactor rates in the population at high risk for acquiring syphilis were indeed adequate to provide significant herd immunity against the spread of infectious syphilis, thereby assisting the control programs in process at the time.

The widespread use of antibiotics for the treatment of venereal disease and other ailments during the past two decades has markedly reduced the overall prevalence of untreated and late-treated syphilis and thus prevented the development of active herd immunity to *T. pallidum* in numerous persons who have been infected with the syphilis organism. The susceptible population has increased therefore, whether it is expressed in absolute numbers or as a percentage of the promiscuous population.

Assuming that 50 percent of the promiscuous population was resistant to the development of primary syphilitic lesions in 1948, and that now less than 10 percent of this population is similarly resistant, the average case of infectious syphilis should produce more than 50 percent more new infectious cases now as compared to 1948. This would be an increase in the so-called "lesion-to-lesion index," which is the number of new infectious cases brought to treatment from the contacts of every person with a diagnosed case of infectious syphilis. The Surgeon General's 1962 Task Force report on the eradication of syphilis (*8*) revealed a 50 percent increase in the lesion-to-lesion index from 1953 (0.20) to 1961 (0.30). While this is consistent with the argument just made, the data cannot be claimed to prove the point, because this index may also be increased by better casefinding or by an increase in the average number of sexual contacts in the population. The same report does show an increase in the average number of contacts per case between 1953 and 1961, although the increase was not as great as the increase in the lesion-to-lesion index.

If a drop in chancre immunity did permit a more rapid spread of infection, this would put a greater burden on epidemiologic investigation and control programs to prevent an outbreak from an individual case. The role of herd immunity is epidemiologically similar to that of the "prophylactic treatment" of syphilis contacts, which has proved effective in the rapid control of syphilis epidemics. The similarity consists of the fact that both herd immunity and prophylactic treatment decrease the percentage of exposed persons in whom infectious lesions develop.

The Need for a Vaccine

Assuming that the hypothesis is correct, what are the implications for syphilis control today? The hypothesis provides no reason to suggest a lessening of current casefinding and treatment efforts, for to decrease these would permit the occurrence of even more severe epidemics. On the contrary, the hypothesis suggests that the epidemiology and treatment programs today have an even more difficult task than two decades

ago, and therefore they need even greater support.

The hypothesis does suggest that an artificial active immunizing agent might provide the added tool needed to accomplish the rapid eradication of syphilis. There are several notes of caution, however, that should be mentioned with reference to such a vaccine.

First, a vaccine would not be acceptable for general use if it interfered significantly with the serologic diagnosis of syphilis, which is the foundation of the current control efforts. It might be difficult to develop a vaccine which produced significant immunity but which did not alter the serologic titers. The reality of the problem is illustrated by the current situation of BCG vaccine in tuberculosis control, where use of the vaccine makes interpretation of the tuberculin skin test difficult, thereby decreasing considerably its usefulness in the developed countries with active casefinding and treatment programs.

Second, the vaccine might not always prevent a person from acquiring an internal infection following exposure, even though it prevented the development of infectious skin lesions. Some of the experimental studies cited previously showed that lymph node infections with *T. pallidum* developed in some immunized rabbits following heavy inoculation, even though infectious skin lesions did not develop. The primary justification for a syphilis vaccine, therefore, would be epidemiologic (for herd immunity) rather than clinical (for individual immunity). The individual would be protected, but by other people's immunity more than by his own. Smallpox is an example of this, where herd immunity, by reducing spread of infection, accomplished its eradication.

Third, Cannefax (*6*) and others have mentioned that a syphilis vaccine would probably be unacceptable to the general population. Nevertheless, a syphilis vaccine could be quite effective if used only in the high-risk (promiscuous) portion of the population. One method might be to immunize every venereal disease patient after his initial treatment is completed. This could be done by clinics working in cooperation with syphilis epidemiologists. Even private physicians who are unwilling to report the names of syphilis patients they treat might be willing to call in such patients and immunize them in private. This would not be as satisfactory as reporting a patient to public health authorities, but it would produce longer lasting results than penicillin treatment alone.

Fourth, there are many technical problems in the preparation of a syphilis vaccine. No one to date has convincingly demonstrated satisfactory immunity levels from any vaccine developed in a laboratory. Moreover, up to this time it has not been possible to grow *T. pallidum* on an artificial medium, which would be needed in the development of a vaccine and in its subsequent mass production.

Immunity in Other Treponematoses

In 1927 Butler and Peterson (*9*) proposed the "unitarian" theory of the treponematoses, which was reviewed and expanded by Hudson in 1946 (*10*). According to this theory, all of the treponematoses, or at least venereal syphilis, nonvenereal syphilis, and yaws, are caused by the same organism—*T. pallidum*. The differences in clinical and epidemiologic behavior between the diseases are thought to be due to the differing conditions under which the organism is found. Thus, in tropical areas where most of the body surfaces are constantly moist, the spirochete can survive almost anywhere on the body, and the scant clothing facilitates spread by casual skin contact. Under these circumstances, infection with *T. pallidum* produces the clinical syndrome of yaws. In colder climates, where skin surfaces are not constantly moist and where clothing protects against spread by casual contact, the mucous membranes provide the only surfaces where the organism can survive outside the body, and sexual contact is the most common type of contact conducive to the spread of the spirochete.

Those who support the unitarian theory point to the fact that *T. pallidum* and *Treponema pertenue* are indistinguishable in the laboratory (*11*). Whether or not the strains are identical is not so important to this discussion, however, as the fact that cross immunity occurs between them. In areas of the world (or within one country) where yaws has been highly endemic, venereal syphilis is rare, and in areas where yaws is not prevalent, venereal syphilis is usually found (*12*, *13*). It appears that one side

benefit of endemic yaws is an acquired active immunity to syphilis. According to Wilcox (*13*):

> The question of the introduction of venereal syphilis into areas of yaws and endemic syphilis which have been cleared by mass campaigns is therefore one of current concern for WHO. While the endemic treponematoses are prevalent they provide an immunity against venereal syphilis.

In the developing countries where endemic treponematoses have been prevalent, social changes such as urbanization, increasing mobility of the population, and the breakdown of the older patterns of rural living are making the spread of syphilis easier. Thus, there is concern that if a substitute is not provided for the acquired immunity which yaws provided, venereal syphilis may replace yaws in these countries (*14*). A satisfactory immunizing agent against syphilis may therefore be the best method to prevent this feared side effect of the yaws eradication programs. In fact, such an immunizing agent might be far more effective in these countries than would syphilis casefinding and treatment programs, since immunizing programs are generally less costly, easier, and require fewer highly trained personnel than do casefinding and treatment programs.

Conclusions

Often an advance in medicine brings about an undesirable side effect which requires further medical advances to counteract it. For example, paralytic poliomyelitis emerged as an international problem when living standards were improved. The development and use of excellent antitreponemal antibiotics in this country (for the treatment of syphilis and other diseases) and in tropical areas (for yaws eradication campaigns) have served to decrease acquired active immunity to *T. pallidum*. This in turn is having adverse effects upon the control of syphilis. As with poliomyelitis, the most effective solution to the worldwide syphilis problem, and our best hope for eradication, may be an effective immunizing agent.

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