Research Needs in Syphilis

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THE PRINCIPLES applicable to the study of venereal syphilis have wide bearing on the general problem of treponematoses. This is especially so, because, as endemic treponematoses are controlled, venereal syphilis will undoubtedly become more prevalent.

Certain generalities can be stated more or less dogmatically. It is obvious that more study of the fundamental problems should be the aim of future students of the treponematoses. A shift in emphasis from the study of the individual to epidemiology has been the trend in recent years. Although money is a big factor in the study of treponematoses, as in other endeavors, the greatest need is the interest of workers in all fields bearing on the problems. Before outlining research needs in syphilis, certain background material must be emphasized.

Remarkable developments in syphilology occur in cycles, and there are periods in which one feels confident that the ultimate has been attained. In 1911, for example, Neisser (*1*) stated that there were three great discoveries which formed the basis of modern syphilotherapy: (*a*) the discovery of *Spirochaeta pallida* by Schaudinn, with the cooperation of E. Hoffmann, (*b*) the discovery by Metchnikoff and Roux that syphilis is transmissible to monkeys, and (*c*) the adaptation to syphilis examinations of the serodiagnostic methods of Bordet and Gengou by A. von Wassermann and his coworkers. The net result of these discoveries yielded much to establish the principles of therapy so that when the climax was reached, the synthesis of salvarsan "606," by Ehrlich, it would seem that the millennium had arrived.

Neisser stated further, "European physicians have known syphilis for more than four centuries, and for almost as long scientific medicine has been using mercury in its treatment. Yet only the last 8 years have improved our knowledge of the nature and pathology of the disease sufficiently, so that we are able to replace a purely empirical, and therefore, uncertain treatment with a rational therapy: a therapy, the principles of which are based not merely upon hypotheses and theoretical speculations, but on actual observations. Seldom indeed has there been such notable progress in any branch of medicine in such a short time as we now note in syphilology. Best of all, these discoveries have been applied directly to the cure of the patient, the highest goal of any medical research. It is important and gratifying that these extraordinary achievements, with all their still-unexplained and unforeseen potentialities, have been attained neither by chance nor by crude empiricism. On the contrary, modern syphilotherapy is the result of exhaustive research in the spheres of etiology, diagnosis and experimental pathology and therapy."

Neisser was not entirely full of optimism, however, for he also stated, "Human indolence and stupidity will arrange that syphilis will never die out but will remain always a dangerous disease, but we know that new and wonderful weapons have been placed in our hands to combat it. Let us practical physicians express our admiration and gratitude to those men who

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created scientific foundations for these therapeutic triumphs: Schaudinn, Hoffmann, Metchnikoff, Roux, Wassermann, Bruck, and Paul Ehrlich."

It did not take long for the syphilologists and venereologists to realize the shortcomings of syphilotherapy even with the arsenicals. The treatment was long, arduous, dangerous, and perhaps not even curative in the biological sense. Therefore, new drugs such as bismuth and new methods of treatment such as intensive, rapid treatment, so popular before World War II, were studied extensively.

Then came the discovery that penicillin had the potential to wipe out syphilis with a minimum of treatment and inconvenience. Again the hopes of the venereologists and syphilologists were at a peak, for at last one had at hand a medicine which was not only effective therapy for syphilis but seemed to have great potential against gonorrhea. Again it seemed that we had really come to a point where syphilis was no longer going to be a problem. In fact, in 1956, Joseph Earle Moore (*2*) stated that "It would now appear that the venereologist (syphilologist) finds himself in the position of having worked himself out of a job."

Unfortunately, the idea that syphilis was no longer a problem was completely erroneous. Little syphilis was found, probably because it was not looked for as a result of decreased appropriations for casefinding. It also appeared that penicillin used for other purposes might be masking the presence of syphilis.

The false confidence of the optimists was well put by Ambrose King (*3*): "The postwar decline in incidence, and the introduction of new remedies, have inspired a false confidence and a move to dismantle some of the organization which has served the public well in the control of these diseases. Because of this attitude it has been difficult to recruit young men of quality to this special subject. There is a case for strengthening rather than weakening the venereal disease scheme and for offering encouragement to new entrants by filling vacant appointments with venereologists and by financing research."

It is hardly necessary to go into details of the recent upsurge in venereal syphilis in the United States. It is amply emphasized by a few statements from a pamphlet of the Public Health Service (*4*) and a joint statement by several health associations (*5*):

1. The 18,781 cases of infectious syphilis reported in the United States during fiscal year 1961 was the greatest number reported in any year since 1950.

2. The rise in infectious syphilis has been particularly sharp since 1959, with more than a 50 percent increase in each of the past 2 years.

3. Health officials have expressed particular alarm over the increase in teenagers. Their reports show that between 1956 and 1960 infectious syphilis among persons under 20 years of age rose more than 130 percent. This figure may be smaller than the actual increase, considering the chains of infection that have been found in many areas in this country.

Factors Influencing Course of Syphilis

In 1944, Stokes, Beerman, and Ingraham (*6*) listed the following factors, said to affect the course of syphilis:

1. The organism: strain, rate of reproduction, route of inoculation.
2. Season: sunlight.
3. Endocrine hormones and activity.
4. Diet.
5. Avitaminosis.
6. Defense mechanism, skin and bone involvement, reticulo-endothelial system.
7. Age.
8. Race: Scattered data but no definitive experimental study.
9. Sex: Cause of milder course in women is still unknown.
10. Pregnancy: Numerous studies on the influence of pregnancy in syphilis are summarized by the aphorism, "Pregnancy is good for syphilis but syphilis is not good for pregnancy."
11. Intercurrent infection: Scattered reports, but our ignorance is still cloaked with words such as "biotropism."
12. Heat, fever: Probable thermal death point has been determined, but the mode of action of fever therapy is still a matter of conjecture.
13. Physical strain.
14. Nervous and mental activity.
15. Physical constitution.
16. Trauma.
17. Treatment.

None of these factors is clearly evaluated; each offers unlimited possibilities for productive investigation.

As a reminder of how little we actually know about these problems, I shall discuss briefly some about which there have been recent contributions.

The Organism

Some of the perplexing questions with regard to *Treponema pallidum* include cultivation of a virulent organism, the life cycle, strains and interrelation among treponemes, the invasion mechanism, asymptomatic infection and carrier state, and immunity and immunization. These can be mentioned only briefly here. Many were discussed extensively by Stokes and Beerman in 1947 and 1948 (*7–9*). Little fundamental progress has occurred since then.

Cultivation. Numerous attempts to cultivate virulent *T. pallidum* have been unsuccessful at the hands of competent investigators (*10–12*) employing various methods including the chorio-allantoic membrane of the chick embryo (*13–15*). The recovery by Steinhaus and Hughes (*16*) of a spirochete from hen's eggs after inoculation with liver tissue from hens was not confirmed by Hård (*14*), who could not find evidence that by dark-field examination or by mercury or silver impregnation *T. pallidum* (Nichols and Ghent strains) is capable of multiplying in eggs (hen or goose). Emulsions of the embryos, when inoculated into rabbits, produced only one positive result. This suggests that treponemes do not occur in eggs in an ultramicroscopic phase of their life cycle, but that occasional organisms may survive their stay in the egg and be reinoculated with their virulence retained.

In another study, Hård (*15*) attempted to cultivate virulent *T. pallidum* in media containing growth factors from plants added to a basal medium. Growth of virulent *T. pallidum* was obtained for several weeks in the medium to which potato had been added.

Cultivation of virulent *T. pallidum* would complete the requirements of the laws of Koch to establish *T. pallidum* as the cause of syphilis and afford an unlimited source of virulent organisms for biologic and chemotherapeutic studies. In addition, knowledge of the survival of treponemes away from the body, in soil, sweat, and insects, might help solve the transmission problems of endemic forms.

Life cycle. The question of life cycle and evolution forms of *T. pallidum* remains unanswered. Ingraham (*17,18*) and later Olsen (*19*) reviewed this question thoroughly. The work of Delamater and others (*20–22*) with phase contrast and electron microscopic techniques is suggestive.

The practical considerations which solution of this problem would yield are far reaching, even to the mechanism of transmitting the disease, since if *T. pallidum* is capable of changing into an ultramicroscopic form and can conceal itself in a spermatozoon, paternal transmission of the disease, now denied, is a possibility.

Certain phases in the life cycle may have an affinity for certain structures and thus remove the usually employed postulate of strains, namely, neurotropic and dermatropic, and even treatment resistant. Proof of the existence of a viral form may also explain certain of the puzzles of immunity in syphilis.

Strains. The existence of strains of *T. pallidum* with distinctive biologic properties is still highly debatable. Although the occurrence of neurotropic and other strains is inferred from experimental and clinical evidence, definite proof is lacking. The concept of strains should have a significant bearing in clinical syphilis, but as yet this influence is little understood.

Interrelation among treponemes. Specific information about the interrelationship among treponemes is limited. This is independent of strains as such, although the differences are more functional than morphologic (*23,24*). There is some evidence that the organism causing yaws produces an infection which sometimes protects against syphilis (*25–27*). The organism causing bejel and that producing pinta may also be functional variations of *T. pallidum*, but this is not yet demonstrated.

The biological relationship between the agents of syphilis and yaws and that of venereal spirochetosis in rabbits, which is morphologically similar, has just begun to be clarified by Turner and his associates. In comparative studies on *T. pallidum*, *Treponema pertenue*, and *Treponema cuniculi*, Turner and his coworkers (*28*) showed that the organisms have many common characteristics. Studies using the *T. pallidum* immobilization (TPI) test

show no substantial immunologic difference between *T. pallidum* and *T. pertenue*. Penicillin does not help to differentiate the organisms from the various treponematoses. Although their work, carefully controlled, indicated that the different results produced were due to substantial biological differences between the three spirochetes studied, we are no nearer solution of the question of whether the treponematoses, yaws, bejel, and pinta are syndromes of the same disease or independent processes (*29*).

In addition, immunity and allergy in syphilis need reevaluation. In a review, Urbach and I (*30*) pointed out that much of the information on immunity is based on experiments in which cure was attained by the use of arsenicals. In accordance with Worms' ideas (*31*), unless the lymph node transfers made to determine cure are performed at least 1 year after treatment, the infection may be only suppressed by residual arsenical in the organism. Since penicillin is rapidly eliminated and presumed to be curative in animals, future study can be turned in this direction. So far no definitive results have been reported.

Turner and Hollander (*27*) suggest (*a*) study of the adaptive and mutational patterns of the pathogenic treponemes, (*b*) immunochemical studies of pathogenic treponemes, (*c*) study of the nature of the Wassermann antigen, and (*d*) continued efforts to cultivate virulent pathogenic treponemes.

Laboratory Diagnosis

There is no completely satisfactory stain for *T. pallidum*, as exemplified by the multitude of methods of staining spirochetes recommended by a host of investigators. Even dark-field examination presents innumerable problems and, to be sure, is of limited value when the desired information is most useful. Clinicians long for a simple bacteriological method which will enable them at the earliest possible moment to establish, with certainty, a positive diagnosis of syphilis.

When the serologic tests for diagnosis of syphilis were introduced by Wassermann, Neisser, and Bruck, their specificity was accepted by the medical profession with implicit faith. Soon, however, it was found that falsely negative (nonreactive) reactions in syphilitics, as well as falsely positive (reactive) reactions, were repeatedly reported with all tests, not only in many nonsyphilitic diseases of human beings but in presumably normal nonsyphilitic persons as well.

Despite stepping up sensitivity and specificity and the introduction of the TPI, TPCF (*T. pallidum* complement fixation), RPCF (Reiter protein complement fixation), RPR (rapid plasma reagin), and FTA (fluorescent treponemal antibody) tests, verification procedures, special antigens such as the treponemal antigens, and numerous other clinical and laboratory devices, we are still far from a satisfactory solution of the serologic problem. Recognition of the many factors involved in interpretation of a serologic reaction has resulted in somewhat less confidence in the tests and a great deal of confusion in the minds of practitioners. As Stokes (*32*) has aptly stated, "This new question of how often a positive means syphilis; of how to identify the positives that do not; in what diseases and with what frequency nonspecific or nonsyphilitic positives are obtained, suddenly rises to disturb the diagnostic peace." Nevertheless, there is hope for the future (*33*, *34*).

In 1945 I made a survey of recent literature on the subject of biologic false positive reactions to the tests for syphilis (*35*). Among the more than 300 references cited, I was able to gather little more than a mere statement of the reported incidence of false positive reactions in many disease processes, plus many conjectures about the possible cause of the reactions, and a rather feeble program for handling such cases in practice. Although much effort has recently been directed toward this question from various angles, much of a productive nature could be uncovered by further study.

Not only do we not have a simple, reliable, easily performed test for syphilis or the endemic treponemal diseases which will always allow diagnosis of syphilis at the earliest possible moment when it is present and fail to give a reactive result when it is absent, but we lack a test which is able, even if it gives a reactive result, to indicate whether the syphilis is active or quiescent, infectious or noninfectious. No real knowledge is available yet concerning the

relationship of blood factors to the serologic outcome, although work is progressing in this field. There is no definitive information as to the effect of external factors on the serologic result. We have no standardized quantitative procedure. We know little about reagin or even the mechanism of our present tests.

Clinical Syphilology

The need for better appreciation and reevaluation of the finer points of clinical diagnosis of syphilis is emphasized by the still imperfect laboratory tests. Some authorities even state that after long study it is almost impossible to identify *T. pallidum* with certainty. The great propensity for false serologic results even with today's best techniques casts great doubt on the infallibility of the blood test in diagnosis.

To a great extent then, we must revert to the days of the old clinical masters and differentiate, by careful attention to clinical signs and use of the multiple diagnostic approach of Stokes (*36*), the various dermatoses which might be mistaken for syphilis, and vice versa. It is not desirable or safe to assume the syphilitic character of a lesion and apply treatment (penicillin) on "suspicion" because it is harmless. The situation of medical as well as dermatological training without full grounding in syphilology is aptly expressed by a British reviewer (*37*) of MacKenna's "Aids to Dermatology": "Syphilis is now entirely omitted, which in a book on dermatology rather suggests the tragedy of Hamlet with the character of the Prince of Denmark left out."

The need for exact knowledge of the manifestations of syphilis opens a wide field for careful study of the nature of the disease and the discovery of exact means for clinical differentiation.

Although clinical contributions are of little help in solving laboratory problems, the clinician may act as a control in keeping laboratory workers in line. He may stimulate further work and evaluate the results. For example, recognizing the problem of nonspecific reactions to blood tests for syphilis is essentially the outcome of clinical studies in which the serologic results are not in agreement with the clinical findings. The occurrence of an unusual clinical phenomenon or sequence in the course of syphilis may afford the laboratory man unlimited possibilities for study.

Some of the unsolved problems of clinical syphilis were discussed in 1939 by Moore (*38*). The four he considered of paramount interest are still enigmas today.

1. Mode of infection, both in acquired and congenital syphilis.
2. Localization of syphilitic lesions.
3. Course of syphilitic infection as modified by human constitution and other factors.
4. Importance of syphilis as a cause of death.

We know little about the mechanism of asymptomatic infection. In congenital syphilis, we have little unequivocal evidence as to when and why the fetus is infected (*39,40*). The question of third-generation syphilis, despite numerous reports (*41*), is still a matter of theory. Although we complacently accept the fact that syphilis has a special affinity for certain tissues, notably the skin and the cardiovascular and nervous systems, among others, we have no adequate explanation. Nor have we worked out the mechanism or reason for spontaneous cure, not only in animals but in man. What takes place is still a matter of surmise.

Relapse, reinfection, and superinfection. Differentiation of relapse, reinfection, and superinfection in syphilis, closely bound with immunity and cure, have assumed renewed importance with the reintroduction of intensive therapy, especially with penicillin. The situation is far from clarified (*42*). For example, cases of reinfection, infrequent during the pre-arsphenamine era, became much more numerous shortly after introduction of the arsenicals into syphilotherapy. Soon, however, a reaction tending toward more critical consideration of criteria of reinfection set in, and by 1931 Stokes and co-workers (*36*) rated reinfection as "a comparatively rare event in the course of syphilis today." Since 1931 the literature is replete with suggestions as to the uncertainty of what is meant by reinfection, and cases of so-called reinfection are reported as "suspected reinfections," "probable reinfections," "questionable reinfections," and "presumable reinfections."

Intensive therapy, especially penicillin treatment, is presumed to cure syphilis so rapidly that the host has no opportunity to develop im-

munity. Therefore, reinfections are not only possible but may be frequent after this type of treatment (*43*). Although animal studies permit precise control of certain factors which can affect development of immunity in experimental syphilis—time factor, quality (virulence) and quantity of inoculum, methods and sites of first and superinoculations, and reaction of animal to first inoculation (*31*)—the results of these studies are not directly applicable to man. Animal studies, however, indicate certain trends which may apply to human reinfection.

The Sing Sing Prison study by Magnuson and co-workers (*44*), in which nonsyphilitic and syphilitic human volunteers were inoculated intracutaneously with virulent *T. pallidum* and heat-killed organisms were inoculated in patients previously treated for early syphilis, points the way to future possibilities. Clinical studies of reinfection in man, despite the best efforts of competent observers in the prepenicillin era, yielded only inferential evidence of the existence of possible second infection with syphilis. Deliberate attempts to reinoculate syphilitics with treponemes had yielded some so-called superinfections, but reinoculation of cured syphilitics had rarely been successful (*45*) until the Sing Sing study.

Since we have no absolute criteria of biological cure nor adequate means to identify asymptomatic infections in man, it is possible that reinfection takes place on a scale larger than hitherto suspected. It is unlikely that any discussion of past experiments, regardless of their value, will lead to a definitive opinion as to possible superinfection or reinfection for the individual.

Prophylaxis. Individual prophylaxis against the treponemal infections, with chemicals and, recently, antibiotics of all types, has received considerable attention. The mass treatment of endemic foci of treponematoses is, in effect, mass prophylaxis intended to eradicate possible sources of further exposure. Although efforts in some areas have resulted in a hard core of cases, continued search for methods to effect eradication or prevention is necessary. Periodic treatment of prostitutes with penicillin derivatives, advocated by Durel (*46*), is an application of the mass-treatment principle to a specific group.

Suitable means of immunization are still far from available. To what extent yaws confers protection against venereal syphilis has long been unanswered.

Treatment. It is hardly necessary to elaborate on the present status of the treatment of syphilis. With the advent of penicillin therapy, all seemed settled, but even now we are faced with gaps in our knowledge of the usefulness of treatment and the proper modes of therapy. Much has been learned about the action of the antibiotics as a result of intensive study in the past two decades, but we still lack a really satisfactory drug.

It is becoming more apparent that the drugs now used, especially penicillin, are reaction producing, and the long-term effects, as well as the usefulness of antihistamines and cortisone (*47–50*) with the antibiotics, have not received enough study. Although we recognize the great advances of our present armamentarium, we still need safe, effective, convenient, and inexpensive preparations or a combination of medicaments for venereal syphilis and endemic treponematoses.

Prognosis. Although remarkable retrospective studies of the effects of syphilis have been made (*51–61*), the prognosis for the individual with a treponematosis still needs means for determining the investigation. Age, sex, color and race, socioeconomic considerations, and therapy are only a few of the factors determining the ultimate outcome of a treponemal infection.

Epidemiology and Public Health

Although there are some differences in the biological and clinical aspects of venereal syphilis and the endemic treponematoses, there is most variance in their epidemiology. The major considerations in endemic treponematoses include mode of transmission and entry of treponemes into the body, influence of geographic ecology, socioeconomic and hygienic factors, penicillin from whatever source, age incidence, effects of other diseases, and cross-immunity between syphilis and yaws.

Some of these apply also to venereal syphilis. In addition, we need to know what besides penicillin has caused the recent decline in syphilis

and, conversely, what the factors are in the present upswing. We also need to know the various legal, local, and ecologic factors in different countries; the private physician's role in epidemiology (*62,63*); the part played by migrants, teenagers, prostitutes, and homosexuals in the spread of syphilis; new methods of casefinding; the value of prenatal and premarital tests and cluster testing; and the best methods of education.

The recently organized Government task force includes in its six-point, 10-year goal development of a comprehensive and dynamic education program for professional workers and the general public and continuation of research in syphilis immunology, therapy, and laboratory procedure, together with expansion of research in adolescent and young-adult sex behavior.

Of special interest is the relative importance of prostitutes, teenagers, and homosexuals in transmitting venereal syphilis. It is not possible to determine to what extent syphilis is due to prostitution, as only those caught are counted. It is probably a big factor (*64–66*). The teenage population of the United States, now 17 percent of the total population, will be about 19 percent by 1965 (*67*). Many of the teenagers will come from rural to urban areas. Boys and girls have many emotional problems; some are promiscuous and indulge in heterosexual and homosexual activity. The role of homosexuals in transmitting syphilis is beginning to become clear (*68–69*). But female homosexuality appears not to be a factor in transmission of venereal disease. Why?

Conclusion

This review illustrates that the treponematoses offer a fruitful field of study for all types of investigators. There are many problems which must be solved if these diseases are to be eradicated (*70*). (More detailed lists of problems are available in WHO's Technical Report Series of 1960.) Fiumara (*71*) has aptly summarized the situation: "It is important to realize that the venereal diseases cannot be eradicated by present control methods alone. Until new and better procedures can be devised, all that clinical and public health medicine can expect is a reduction of these diseases. How much they can be reduced depends directly upon the efficiency of practitioners in both groups."

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