NATURAL HISTORY OF SYPHILIS AND LEVELS OF PREVENTION*†

BY

E. GURNEY CLARK

From the Division of Epidemiology, Faculty of Medicine, Columbia University, New York

From the viewpoint of prevention, syphilis, like other disease processes, has its origin before man himself is affected. Therefore, application of preventive measures need not await man's actual exposure to the causative agent. There are possibilities of intercepting the various related " causes " which lead to exposure, as well as of interrupting the process after it begins in man. The complete process, at least for preventive purposes, may be termed the " natural history of the disease ", which begins with the very first forces that initiate it in the environment or elsewhere, and continues through the resulting changes that take place—until equilibrium is reached, or defect, disability, or death ensues. There is a " period of pre-pathogenesis " before man's contact with the disease agent, and one of " pathogenesis " after man harbours the *Treponema pallidum*. Preventive measures may be applied throughout these two periods. The disease may be attacked from at least five preventive points during these two periods :

(*a*) health promotion ;
(*b*) specific protection ;
(*c*) early recognition and prompt treatment ;
(*d*) disability limitation ;
(*e*) rehabilitation.

These represent means of interception common to a majority of disease processes and may be utilized on a community or on an individual basis. They are not static or isolated phases in the natural history of the disease process but form more or less a continuum (Leavell and Clark, 1953).

The relationships of these levels to the natural history of any disease are shown diagrammatically in Fig. 1 (overleaf). The natural history as defined above is shown in the upper part of the diagram and the lower part shows the levels of prevention in relation to the various phases of the natural history. Throughout the natural history, agent, host, and environmental factors may be operating, and their interaction during pre-pathogenesis brings the specific agent into contact with man to initiate the process in man. After this comes the phase of increase in the agent, whether it be through multiplication, as in infectious disease, or through increments of agent, as in non-infectious disease (*e.g.* lead). This is followed by tissue changes, signs and symptoms, and finally by recovery, defect, disability, or death. Prevention must take into account all possible causative factors, from the first environmental forces which bring the host and agent together to those which later maintain this relationship. The multiple causes of disease are active long before the disease involves the subject. Precipitating and predisposing forces may be continuously operative in the occupational or living environment of man. Heredity, social and economic factors, or physical environment may be preparing the way long before pathogenesis is initiated. Malaria illustrates how the knowledge of pathogenesis alone is not sufficient for disease prevention. This disease process produces rather characteristic humoral and cellular changes and more or less typical signs and symptoms, yet complete knowledge of its course in man gives no clue to its prevention. The malarial parasite, the primary specific cause, can be discovered in the blood of those affected. Specific therapy in the individual may prevent subsequent attack but basic prevention is related to the more important environmental causes of malaria outside the individual. Prevention depends upon knowledge of climatic conditions, biologic and geographic environment, the habits and characteristics of the anopheline mosquito, the habits and customs of the

* Received for publication May 26, 1954.
† Paper given before the Medical Society for the Study of Venereal Diseases, London, June 8, 1953. Based on a concept introduced in " Textbook of Preventive Medicine " (1953) by H. R. Leavell and E. Gurney Clark.

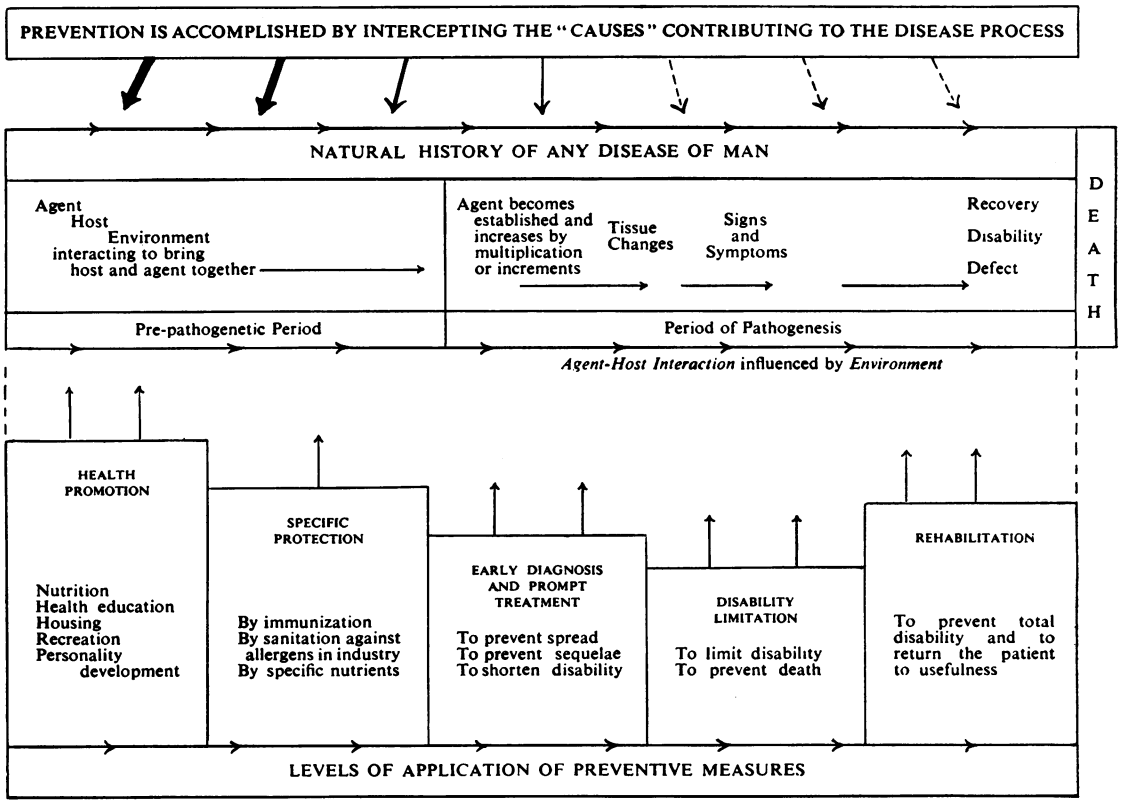

FIG. 1.—Natural history of disease and levels of prevention.

human host, and the application of specific protective devices and prophylactic measures.

The complete definition of causation of any disorder in man must encompass a consideration of *all* the agent, host, and environmental factors which interact to provoke or perpetuate the process. The philosophy of prevention can be put into a single phrase: "To oppose or intercept a cause is to prevent or dissipate its effects" (Perkins, 1938). Prevention at any level of application in the progressive natural history of any disease depends upon the knowledge of these multiple causes relating to agent, host, or environment, and the ease with which these causes may be intercepted or counteracted. Prevention requires the construction and interposition of barriers to the interaction of these elements. The degree of success depends upon the completeness of knowledge and the opportunity to apply it. It is not necessary to know everything about a disease to initiate preventive measures, though often complete success cannot be achieved because current information is too meagre. Nevertheless, the interception of any of the causes of disease at any stage of development may affect the morbid process. This concept permits the inclusion of specific treatment in the scheme of prevention.

Application of Preventive Measures

The five levels at which preventive practices may be applied are as follows:

(1) *Health Promotion.*—This is applied in the period of pre-pathogenesis before man is involved; its aim is to achieve the best state of physical, mental, and social well-being. This includes a good standard of nutrition adjusted to the various developmental phases of life, provision for adequate housing and recreation, and agreeable conditions in the home and at work. Sex education and counselling before and during marriage may have a direct effect upon the exposure to venereal disease.

(2) *Specific Protection.*—This comprises measures applicable to a particular disease or group of diseases to intercept the causes before they involve man. Included

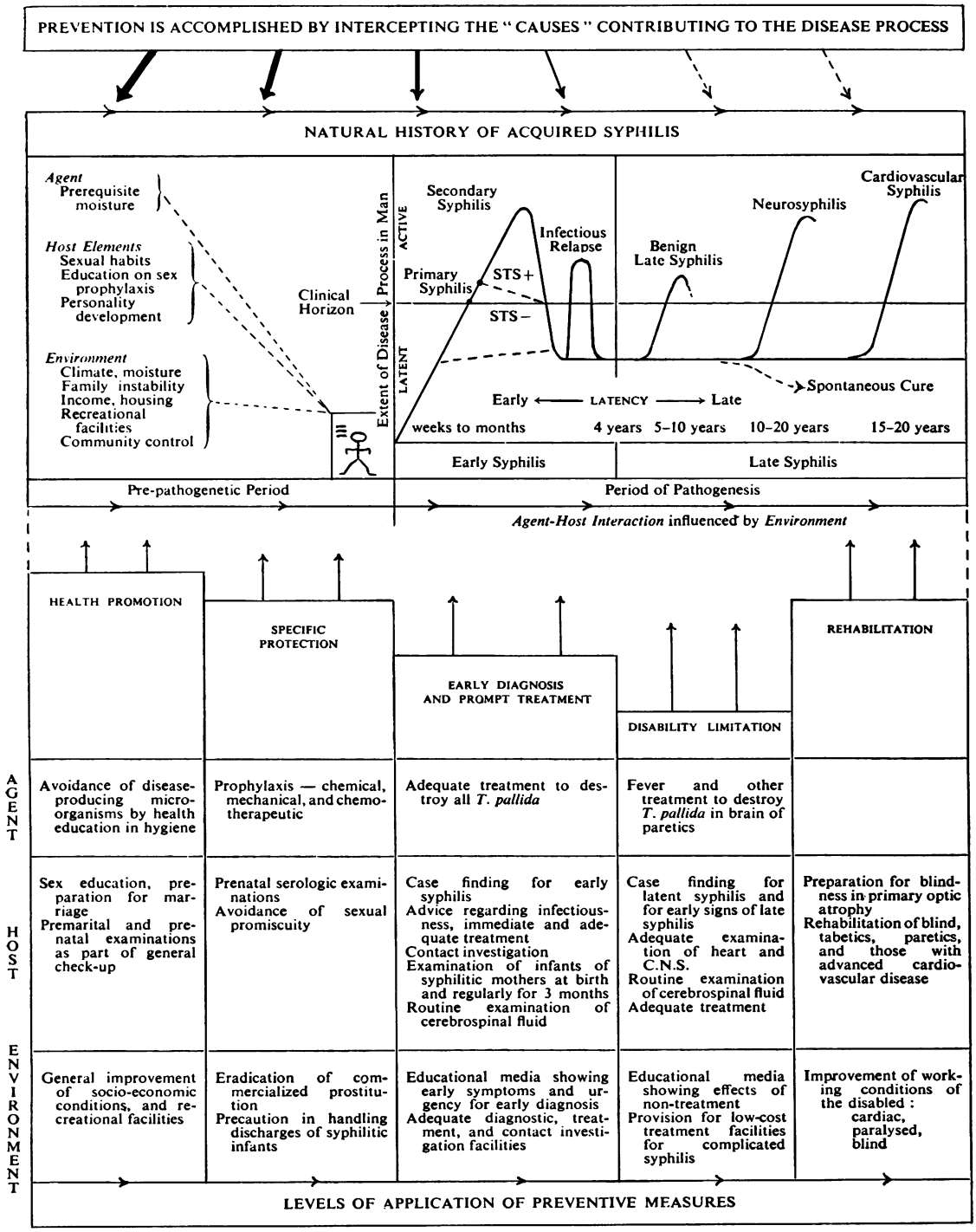

FIG. 2.—Application of preventive measures in the natural history of syphilis.

here are immunizations against infectious disease, pasteurization of milk, purification of water, waste disposal, prevention of air contamination, protection against industrial dermatitis, and control of insect vectors. The avoidance of accidents and allergic conditions would also be included under this category.

(3) *Early Recognition and Prompt Treatment.*—This aims at checking the spread of infections and effecting cure or arrest of disease processes, and hence at preventing complications and shortening the period of disability. The basis of the ideal disease control programme is "case finding" in the early stages of disease, when treatment is most effective. This has been the backbone of modern syphilis and tuberculosis control programmes, and now has become the watchword in the control of chronic diseases.

(4) *Disability Limitation.*—Only the time factor and our scanty knowledge of disease processes separate this phase from the previous one. This stage of disease development involves treatment of a more or less advanced disease process, and points to the failure of prevention at some earlier phase. The large number of persons coming for medical attention with advanced detectable disease emphasizes the need for medicine to apply existing preventive knowledge on a wider scale.

(5) *Rehabilitation.*—This means the prevention of complete disability after anatomical and physiological changes are no longer reversible and its positive objective is to return the affected individual to a useful place in society.

The present concept places health promotion and disease prevention into a framework based upon the natural history of disease. It is the first step in directing those interested in health to a common focus for their own specific contribution to man's health and welfare. Its foundations lie in the evaluation of health on a graded scale and in the concept that the decline from health to disease is a process involving the interaction of disease agents, man himself, and man's environment.

Syphilis

Syphilis provides an excellent illustration. Knowledge of the characteristics of the specific treponemal agent of syphilis and of the reactions to it of the human host has taught us much about this disease pattern that has aided its prevention and control. Yet, for its ultimate eradication or its reduction to minimal importance, certain environmental factors must be taken into account. Some causes of syphilis infection are in operation well before agent-host relationships (pathogenesis) begin. The groundwork of congenital syphilis may be laid before marriage through the infection of the potential mother or father. It may be affected by absence of pre-marital examination, inadequacy of examination and treatment, the attitude of the parents to pregnancy and pre-natal care, extramarital relationships, and lack of prophylaxis. Finally, the course of congenital syphilis may be related to the cost and availability of medical care at the time of delivery and in the succeeding few months.

The factors involved in acquiring and transmitting syphilis are complex. They have their origin in variations of human behaviour, sexual promiscuity, marital maladjustments, and in some of the inadequacies of our social and economic life; they are rooted in prudery, ignorance, and defeatism on the part of the public. Such attitudes present obstacles to the application of the usual methods of control utilized against other types of infectious disease.

Fig. 2 shows in detail the natural history of acquired syphilis and the levels of application of preventive measures by the general scheme of Fig. 1. The specific microorganism reaches the biologic orbit of man through the interaction of host and environmental factors during the pre-pathogenetic period. Whether or not man becomes infected depends on the biologic characteristics of the microorganism and the habits and defence mechanisms of man.

The period of pathogenesis, after infection has taken place, may be illustrated by a graph (Morgan, 1941; see Fig. 2). The division between the symptomatic and asymptomatic stages is designated the "clinical horizon". Syphilis as it progresses may be symptomatic (above the horizon) or asymptomatic (below); early (under 4 years' duration) or late (over 4 years); infectious (primary, secondary, and infectious relapse) or non-infectious (late). There may be "spontaneous cure" or lifelong freedom from symptoms (clinical latency), or the infection may terminate in death, defect, or disability. The opportunities for prevention are shown at the bottom of the diagram.

Agent Factors.—The biologic requirements of *T. pallidum* explain why syphilis is a disease of intimate contact. This organism is very fragile, unable to resist drying, unfavourably affected by many common antiseptic agents, and said to be destroyed more quickly by a soap solution than by many strong disinfectants. It dies under bloodbank conditions in a short time, but will survive rapid freezing to −76° C. for one year. It is found infective for 26 hours in syphilis autopsy material. It is immobilized at 41° C. in 2 hours. Man is a necessary host, experimental infections in animals are not persistent, and the agent has not been cultivated on artificial media.

These facts have a direct bearing on the behaviour of the organism in nature. In more primitive treponematosis (yaws, bejel, etc.), the organism finds widespread favourable conditions for existence on the moist skin of persons living in tropical areas and is spread by close bodily contact as a non-venereal disease. These propitious conditions are absent in less humid areas, and are also removed by the advance of civilization, and the use of clothing. In such circumstances, it is only on the mucous membranes about the genitalia and in the mouth that conditions are consistently found which permit the survival of *T. pallidum* for periods long enough for invasion. These biologic characteristics therefore determine the reservoir of infection, dictate the means of transmission, and materially affect the host-parasite interaction.

Host Factors.—In syphilis these are chiefly concerned with the habits and customs of man and the host-agent interaction (Fig. 2). Man is the sole reservoir of syphilis infection. Infection can be transmitted artificially to certain animals but dies out spontaneously without transmission to others of the same species. Whether man as the reservoir of the disease transmits it to others depends on (*a*) the outcome of the complicated host-agent interaction and (*b*) the habits and customs of the host. In view of the fact that the viability of this microorganism depends upon moisture, the chance of exposure to it is dependent upon intimacy of contact, the sexual behaviour of the host, and the habits of the host in respect to prophylaxis.

Host-Agent Interaction.—When the infected moist secretion of the diseased host comes into relationship with a new host one of three things may happen :

(*a*) the organism may fail to gain access and lodgement ;

(*b*) it may gain access, lodge, multiply, and produce infection without early clinically discernible tissue reaction (symptomless infection) ;

(*c*) it may gain access, lodge, multiply, and produce the characteristic discernible reactions of early syphilis.

After the treponeme has gained admission to and settled in the tissues, reproduction occurs at the inoculation site. Dissemination from the portal of entry by means of the lymph and blood streams occurs within several hours, with the result that local prophylaxis delayed longer than this time, even to the extent of excision of the inoculation site, will not prevent disease. It is apparent that syphilis is a generalized infection almost from the beginning, the organism being carried from the original site of entry to all tissues of the body by means of the blood stream as a passive carrier. Thus it is possible for the organism to be transmitted to another host by blood transfusion before there is any clinical or serologic evidence of infection in the infected donor. The bloodstream spread of the treponeme during this early incubation period probably lays the foundation for all the late manifestations.

After a variable incubation period ranging from 10 days to 10 weeks (average 3 weeks), the first manifest lesion of the disease appears. This is portrayed in Fig. 2 by the graph line reaching the clinical horizon. This is primary syphilis, and at the time of the appearance of the chancre the serologic test is usually negative. It is important to remember that, although in most instances infection is followed by visible tissue reaction at the inoculation site, and generalized tissue reactions usually follow the dissemination of the organism, either or both of these phenomena may fail to occur or may be so slight as to evade notice. Infection may thus progress without any demonstrable lesions. The precise mechanism operating to suppress the visible early reaction is not well understood ; it may depend on a single factor or a combination of such factors as the size of the infective dose, the site of inoculation, the patient's age, the hormonal influence of sex or pregnancy, or the administration of penicillin during the incubation period either for prophylaxis or for the therapy of some other disorder.

The mild, superficial, non-destructive primary lesion enlarges and is usually followed by a painless swelling of the regional lymph nodes. Soon " reagin " and perhaps more specific antibodies are detectable in the blood, and the conventional serologic tests as well as treponemal immobilization tests become positive. Over the next 4 to 6 weeks or longer, even without specific treatment, the chancre begins to involute spontaneously, and the result of the earlier blood-stream dissemination and subsequent reproduction of the treponeme may become manifest in generalized lesions on the skin and mucosal surfaces—the secondary outbreak. During this secondary stage there may occur also a mild or moderate constitutional reaction characterized by malaise, general lymphadenopathy, or other manifestations of toxaemia. These and the clinical lesions persist for a variable length of time ranging from a few days to several months and in their turn disappear spontaneously, as is shown in Fig. 2 by the line falling below the clinical horizon. These early lesions of syphilis are characterized by a mild tissue reaction and the presence of large numbers of *T. pallidum*. They are superficial, non-destructive, highly infectious lesions and usually heal without scarring. With healing, the treponemes usually disappear from the skin and mucous surfaces.

Thereafter follows an indeterminable period of clinical latency (weeks to years) without outward signs of infection, during which the infected individual is recognized as syphilitic only by means of a positive test of the blood. The latent period may be interrupted during the first few years by recurrences of infectious lesions in the skin, mucous membrane, eyes, or central nervous system. After an unpredictable number of years, late, non-infectious tissue reactions may also occur in almost any part of the body. This agent-host interaction represents a biologic struggle between the treponeme and the host. The struggle may produce a more or less symbiotic relationship with no impairment to health, but this does not mean that no effort should be made to improve the chances of the host since it is not possible to predict the outcome. The agent-host relationship may end in "spontaneous cure", a condition of life-long latency, the only evidence of syphilis being positive blood-tests, or, in a smaller proportion of cases, disabling syphilis of vital organs.

There is no natural immunity to syphilis in man. The host reacts to the presence of the organism by developing a state of acquired immunity or resistance which influences the spontaneous healing of early lesions, protects against new organisms introduced from without, withstands to a variable degree the aggressiveness of the organisms present in the tissues, and in most instances maintains clinical latency throughout life. There is some evidence that such factors as sex, pregnancy, race, and constitution affect this host-parasite relationship.

The transmission of syphilis depends on certain conditions :

(a) that the organism escapes from the infected host in sufficient numbers ;

(b) that it is appropriately transmitted under conditions which satisfy its biologic requirements ;

(c) that it gains access by finding appropriate portals of entry in the new host.

Moist surfaces provide the avenues by which the organisms escape from the reservoir, and intimate contact by sexual intercourse or kissing furnishes the condition necessary for conveyance to a corresponding portal of entry in a new host. The newly implanted microorganism becomes established under conditions of moisture and warmth lasting long enough to enable it to penetrate host barriers.

Infectious moist lesions are present only during primary, secondary, and recurrent secondary syphilis. Body fluids and secretions (saliva, semen, vaginal discharges) from syphilitic persons in various stages of the disease have been studied experimentally and have been shown to contain the organism during the early stages of syphilis when lesions are present, but only rarely, if ever, during the later stages when there are no obvious lesions. Blood is a passive carrier of the organism and appears to be infective chiefly during the incubation period and while primary and secondary lesions are present. At the present time the accepted explanation of *in utero* infection is that occasional spirochetaemia occurs and results in the circulatory transfer of organisms to the foetus, but this has not been proved experimentally. Intimate contact with primary and secondary lesions provides the most favourable conditions for transmission ; yet, despite the presence of infectious lesions, unprotected sexual intercourse does not invariably lead to infection.

Transmissibility, therefore, depends on

(*a*) duration of infection ;

(*b*) presence of moist lesions ;

(*c*) infectiousness of secretions ;

(*d*) tissue reservoirs of organisms ;

(*e*) intimate contact with the organism in sufficient numbers ;

(*f*) accessible portals of entry in a susceptible individual.

Environmental Factors.—For preventive purposes these may be defined as the aggregate of all the external conditions (physical, social, biologic, and economic) and influences affecting the life and development of an organism.

The influence of any one or any group of these factors cannot be measured with precision, but environment plays a major role in the initiation and perpetuation of syphilis. Some of the factors are analysed by Ennes (1948). The effect of the physical environment (geography, weather, climate, etc.) has been shown by Hudson (1946) to have altered the manifestations of the disease to such an extent that lesions due to morphologically indistinguishable treponemes are given many different names : endemic syphilis, yaws, bejel, pinta, etc.

The social environment may be particularly conducive to the spread of infection. Low income, poor housing, and inadequate recreational opportunity all contribute to the perpetuation of syphilis. The success of organized community control depends on the extent and availability of public health and medical facilities, the adequacy of case finding and case holding, the "index of suspicion" of medical agencies, the availability of laboratory services, the extent of contact investigation, and the application of premarital and prenatal examination procedures.

The lower portion of Fig. 2 shows the details of prevention in syphilis based upon knowledge of natural history. Preventive action must be directed against the agent, the host, and the environment at each of the levels of prevention in so far as our present knowledge will permit.

The success achieved in the control of syphilis is the result of the application of such measures as these, despite gaps in our knowledge about this disease.

Much has been accomplished in syphilis control and optimism pervades medical and public health circles in respect to its eventual elimination. Yet there are still many unknowns which stand in the way of complete eradication of this disease. For example, *T. pallidum* has not yet been cultivated on artificial media ; we have no immunizing agent ; we know very little about the mechanisms contributing to the natural history of untreated infections, about the duration of infectiousness, the mechanism of immunity, the mechanism of infection *in utero*, the selectivity of the microorganism for certain tissues, or the nature of reagin, upon which serologic tests are based. Furthermore, to those who subscribe to the concept that yaws, bejel, pinta, etc., are different clinical entities of the same disease—the view of " treponematosis " put forward by Hudson (1946)—it is " an illusion to hope for a syphilis-free civilization, while yaws remains rampant in the world ".

The gaps in our knowledge are ample warnings that vigilance must not be relaxed. This is the moment not for the demobilization of the vast forces that have been developed to combat syphilis, as some advocate, but rather for the consolidation of all efforts to prevent the disease in all its aspects.

Summary

(1) Measures for the prevention of syphilis can be applied before man is affected.

(2) This requires knowledge of the " natural history of syphilis ", which for preventive purposes has its origin with the very first forces which act to bring agent and man together.

(3) Such a concept provides a " period of prepathogenesis " and one of " pathogenesis " during each of which multiple causes relating to agent, host and environment are in operation to initiate and perpetuate the disease process.

(4) There are at least five levels at which preventive measures may be applied :

(*a*) health promotion,

(*b*) specific protection,

(*c*) early diagnosis and treatment,

(*d*) disability limitation,

(*e*) rehabilitation.

(5) The relationships of agent, host, and environmental factors to the natural history of syphilis and its prevention are discussed.

REFERENCES

Ennes, H. (1948). " The Social Control of Venereal Disease. Report of a National Inquiry of Professional Opinion." Cooperative Studies Publication No. 2, New Haven, Conn.

Hudson, E. H. (1946). " Treponematosis." *In* " Oxford Loose-leaf Medicine ", ed. H. A. Christian. Oxford University Press, New York.

Leavell, H. R., and Clark, E. G. (1953). " Textbook of Preventive Medicine ", p. 11. McGraw-Hill, New York and London.

Morgan, H. J. (1941). *Amer. J. Syph.*, **25**, 233.

Perkins, W. H. (1938). " Cause and Prevention of Disease ", p. 5. Lea and Febiger, Philadelphia.