

PREVENTION OF VENEREAL INFECTIONS

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SYNOPSIS

In the first part of this paper, a plea is made for a broad view by health administrations of the preventive aspects of venereal disease control, based on epidemiological rather than purely clinical grounds. Stress is laid on the importance of measures directed towards health promotion, specific protection, early recognition and prompt treatment, disability limitation, and rehabilitation. The value of case-finding and contact-tracing and of systematic blood-testing of certain population groups is emphasized.

In the second part, measures for local and systemic prophylaxis are discussed. It is also pointed out that in the past 15 years there has been a rapid reduction in syphilis throughout the world as a whole (although some recrudescence has recently been reported in certain countries), but that over the same period the reservoir of gonorrhoea has been but slightly reduced. The possible epidemiological, immunological and other reasons for this phenomenon are gone into, and the conclusion is reached that the outlook for the control of gonorrhoea is now somewhat less favourable than it was a few years ago. Should apprehension on this score bring about a general orientation away from penicillin (particularly the long-acting preparations) in treating gonorrhoea, the effect on the reservoir of syphilis may also be unfortunate.

I. A WIDER OUTLOOK

Levels of Prevention

The physical and mental harm resulting from venereal infections has been recognized for many years. Efforts to prevent its occurrence can be traced back to ancient rituals. In more recent times, prevention of venereal infections has been attempted more scientifically in view of the dangers to the health of the public associated with their spread and the disability and economic losses they cause. A wider acceptance of venereal infections as ordinary communicable diseases, regardless of the mode of transmission and of moral aspects, has also taken place over the last decades, but further emphasis in this direction is still needed.

Epidemiological knowledge of venereal infections is required if their broad prevention and control are to be successful. We must have knowledge about the micro-organism causing the disease, and, since syphilis is the most important venereal infection from a public health viewpoint, particularly about *Treponema pallidum*. Such knowledge is still limited. Our inability to culture *Treponema pallidum* on artificial media, the absence of an immunizing agent in the treponematoses, the existing limitations in the culturing of the gonococcus as a diagnostic criterion are only so many examples among innumerable others. In addition, we must study the reactions of the human host and the interactions when the agents of venereal infections enter the body. On this point we must appreciate the limitations of our knowledge of the natural course of untreated syphilis and gonorrhoea in man and the importance of the complex processes of immunity, reinfection and prevention of late and systemic manifestations, disability, and death. Finally, the various factors affecting the environment of man, his habits and characteristics, must be known. That such knowledge is incomplete becomes at once apparent when we pause to consider what is known of the differences in patterns of sexual and other behaviour between peoples in urban and rural environments, in hot and cold climates, in higher and lower economic groups, at varying levels of education, in developed and under-developed areas. The forces involved in the epidemiology of venereal infections therefore cannot always be measured accurately, singly or jointly, but they play, of course, a smaller or larger part in the perpetuation of those infections according to the conditions involved.

Great progress has been made in the last 15 years in the control of the world reservoir of the treponematoses through national and international programmes. Some are even talking about syphilis as an eradicable disease. The availability of penicillin and the apparent ease with which the treatment can be carried out today may, however, have lulled the public, and also—to some extent—the medical profession, into a false sense of security. Although further active work should be carried out and the present favourable situation exploited to the maximum within the next few years, it should be realized that there is no reason why penicillin resistance in the treponeme should not develop, or why allergic reactions to the therapy might not become increasingly frequent in the future.¹ It should be noted that the total reservoir of gonorrhoea does not appear to have been appreciably reduced in spite of the effectiveness of penicillin in the individual treatment of the disease. In addition, there are recent indications that the gonococcus is showing signs of lessened penicillin sensitivity and of “resistance”.

If the long-term prevention and control of syphilis are going to be successful the epidemiological and other knowledge at our disposal must be directed—at all levels—towards restraining the forces now favouring

¹ See article on page 427.

the survival of the treponemes. At the same time, research on important outstanding questions on this disease must be stimulated and new problems arising in gonorrhoea must be studied nationally and internationally, so that further progress towards the elimination of some of man's oldest infections can eventually be attained.

The definition of "prevention", as it relates to communicable diseases in general, can be well illustrated by the experience in syphilis, which shows

TABLE 1. APPLICATION IN SYPHILIS OF PREVENTIVE MEASURES BASED ON NATURAL HISTORY

Level of prevention	Agent	Host	Environment
Health promotion	Avoidance of disease-producing micro-organisms by health education in hygiene	Sex education, preparation for marriage, premarital and prenatal examinations as part of general medical examinations	General improvement of socio-economic conditions; recreational facilities; welfare programmes
Specific protection	Prophylaxis—chemical, mechanical, and chemotherapeutic	Prenatal serological examinations, avoidance of promiscuity	Suppression of commercialized prostitution; precaution in handling discharges of syphilitic infants; caution in laboratory workers
Early diagnosis and treatment	Adequate treatment to destroy <i>T. pallidum</i>	Case-finding for early syphilis; advice on infectiousness; immediate and adequate treatment; contact investigation; examination of infants of syphilitic mothers at birth and regularly for 3 months; routine examination of cerebrospinal fluid	Educational media demonstrating urgency of early diagnosis; adequate diagnostic treatment and contact facilities
Disability limitation	Treatment to destroy <i>T. pallidum</i> in brain of those with paresis	Case-finding for latent syphilis and for early signs of late syphilis; adequate examination of heart and central nervous system; routine examination of cerebrospinal fluid; adequate treatment	Educational media demonstrating effects of non-treatment; provision for low-cost treatment facilities for complicated syphilis
Rehabilitation		Preparation for blindness in primary optic atrophy; rehabilitation of the blind and of patients with tabes, paresis, and advanced cardiovascular disease	Improvement of working conditions of the disabled; the cardiac patient, the paralysed, the blind

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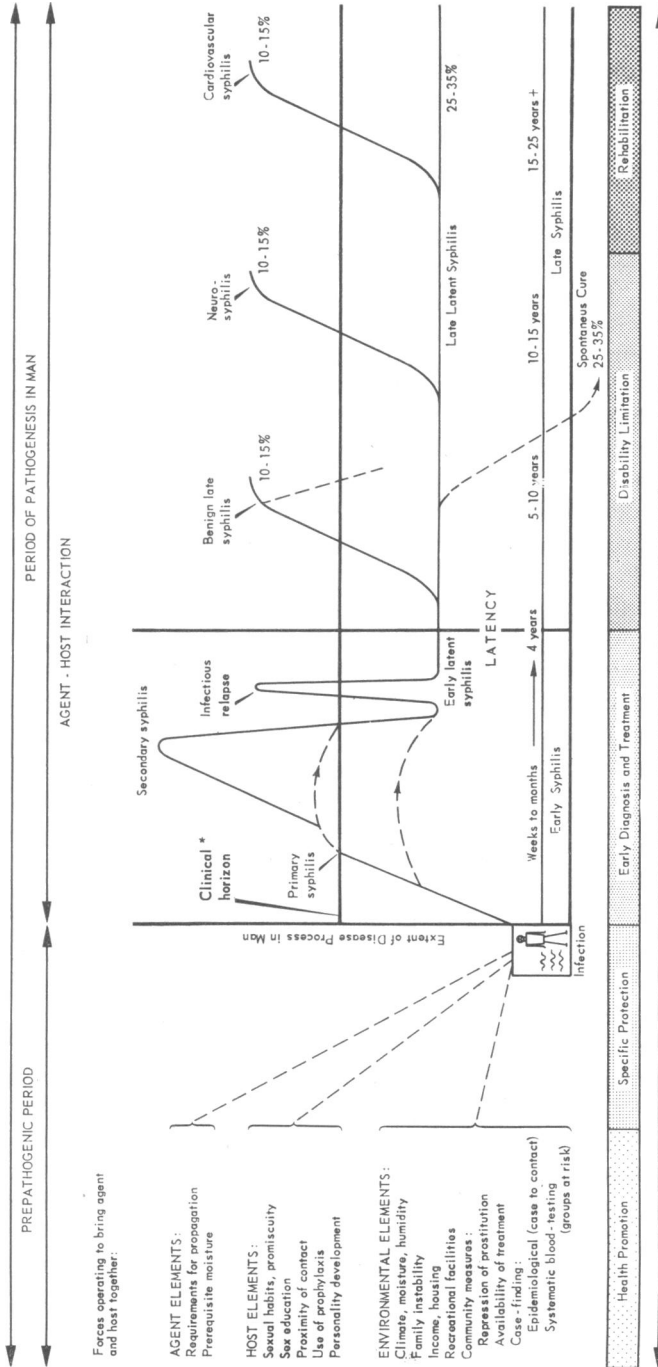
that there are five levels at which preventive public health measures can be applied. These are shown in Table 1: (a) health promotion; (b) specific protection; (c) early recognition and prompt treatment; (d) disability limitation, and (e) rehabilitation. These levels are not isolated groupings but represent rather a connected process in which the preventive measures are the basis for individual and community venereal disease control efforts. Lastly, it is also necessary to distinguish between the forces which operate *before* and those which operate *after* pathogenesis in the individual. The application of preventive measures in relation to pathogenesis is illustrated in Fig. 1.

Case-finding in Prevention

A broad definition must be given to "prevention" to emphasize that it should not be limited to mean a specific procedure at a single level. However, specific intervention through treatment of clinical cases represents a practical means for health agencies to attack the epidemiological chain in venereal disease control. This intervention was in the past in many countries limited to medical inspection and treatment of clinical manifestations at venereal disease dispensaries for prostitutes. This is still the situation in several areas in Asia and in the Americas. In others, epidemiological case-finding (or "contact-tracing") has been added and is being used with varying degrees of success. In highly developed countries with a low prevalence of venereal infections (such as the Scandinavian area and North America), specialized public health nurses, social workers or case investigators are available, and epidemiological case-finding has been found to be a useful further procedure. In countries with much venereal disease, numerous sexual contacts, and less developed health services, such specialized health workers are usually not available to carry out effective epidemiological work. A further case-finding mechanism is therefore needed, particularly in such areas, and systematic blood-testing of segments or groups of the population at particular risk of infection becomes a useful supplementary tool in the prevention and control of venereal syphilis. In order to develop such a blood-testing programme, adequate laboratory facilities and personnel must be available. A training programme is therefore required as part of a national plan if effective prevention and control of venereal disease are to be achieved.

The technical basis for systematic serological testing is today quite different from that only a few years ago. With the establishment through the World Health Organization in recent years of international reference preparations (a) for cardiolipin and lecithin antigens (Pangborn et al., 1955) and (b) for reactive syphilitic sera, it is now possible for national health laboratories to obtain from WHO standard samples whereby the levels of sensitivity and reactivity of seroreactions can be made uniform and comparable within a country and internationally. Furthermore, the

FIG. 1. NATURAL HISTORY OF ACQUIRED SYPHILIS



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* The course below the clinical horizon is asymptomatic and that above is symptomatic.

discovery of the treponemal immobilization (TPI) test at the International Treponematoses Laboratory Center (Baltimore, Md., USA) has also given us another weapon to determine more precisely the extent of false positive serological reagin reactions (Turner & Hollander, 1957).

Maternal and Child Health and Rural Health

Syphilis is the only known microbial disease which infects the foetus through the placenta and where the prenatal infection can be cured. The opportunity for specific prevention of congenital syphilis offered by case-finding and maternal treatment should be taken advantage of in venereal disease programmes. Systematic obligatory blood-testing in pregnant women should be carried out at general health centres, in maternal and child health clinics, and in private and governmental delivery institutions and hospitals. It should be part of the technical policy of the general health programme under a nationally co-ordinated plan. More direct and closer collaboration than exists at present between the venereal disease service, the health centre service and the maternal and child health programme is highly desirable.

It is the function of the venereal disease service to organize proper training of personnel and to provide laboratory services in co-operation with the laboratory programme in addition to advising on minimal standards of diagnosis, treatment, reporting, etc. The service should further collect and analyse statistical data of clinical and serological manifestations in pregnant women and the newborn; and data on the prevalence of seroreactors among pregnant women should be included in national health reports as a basis for further planning of the prevention and control of venereal infections. The number of seroreactors among pregnant women is often a better index of the prevalence of syphilis in a country than are cases of early clinical disease reported from specialized institutions. A seroprevalence of 3%-4% or more in adequate samples of pregnant women should be a matter of concern for health administrations. It may correspond to 8-10 new infections annually per 10 000 of the population at large.

It has been suggested that the annual comparison of the prevalence of disease in women has limitations. In the case of syphilis, it can, however, be assumed that infection rates in pregnant women are comparable from year to year, since pregnancy is symptomatic of high sexual activity in the relatively young age-groups which are at risk of infection. Furthermore, pregnancies occur in women drawn from comparable social and economic levels from year to year.

When syphilitic pregnant women are treated preventively as a result of the laboratory programme, the opportunity arises at general health centres and maternal and child health institutions for health visitors, home-visiting nurses or social workers to carry out family investigations. The

same opportunity arises in gonococcal ophthalmia neonatorum, where prevention of blindness through the use of silver nitrate—or sometimes of penicillin—is also of social importance. The possibility for epidemiological case-finding of syphilis and gonorrhoea in the family brings into focus therefore not only the expectant mother but also the epidemiologically important “expectant” father. Possible paternal disease may be diagnosed, and congenital syphilis found among other children. The initial approach through pregnant women, the maternal and child health service and the health centre programme thus provides an opportunity for the prevention of disease and disability, as well as for broad health education.

Armed Forces

Armed forces personnel generally belong to the younger, sexually most active age-groups, which are particularly exposed to venereal infection, especially when they are stationed in distant and foreign areas where moderating home-community influences and wholesome recreation are often absent. Individually and as a group, members of the armed forces are of epidemiological importance; and the nature, extent and control of venereal infections among them during wars or in post-war periods—whether on friendly or on other soil—have classically been of concern to the public as well as to the forces themselves. From a broad preventive point of view, there is a responsibility for close co-operation incumbent on the military and the civilian health authorities. The value of exchange of epidemiological information with a view to tracing community sources of infection cannot be overrated and more practical contact should be established between the armed forces medical service, the local health officer and the civilian venereal disease and other clinics. The inclusion of systematic blood-testing in the medical examinations of young recruits prior to their induction is a preventive aspect of particular value to the armed forces. Such systematic examination and blood-testing is, however, from a civilian point of view even more important as a preventive measure on *termination* of service in the armed forces, in order to prevent the spread of venereal infections in the population in distant communities abroad and at home. Reliable laboratory services are required here also, and their provision in some countries is the entire responsibility of the armed forces (in the United States of America, for example), while in others it rests—at least in part—with the civilian health authorities, as in the case in some European countries (e.g., the Scandinavian area).

Occupational Health

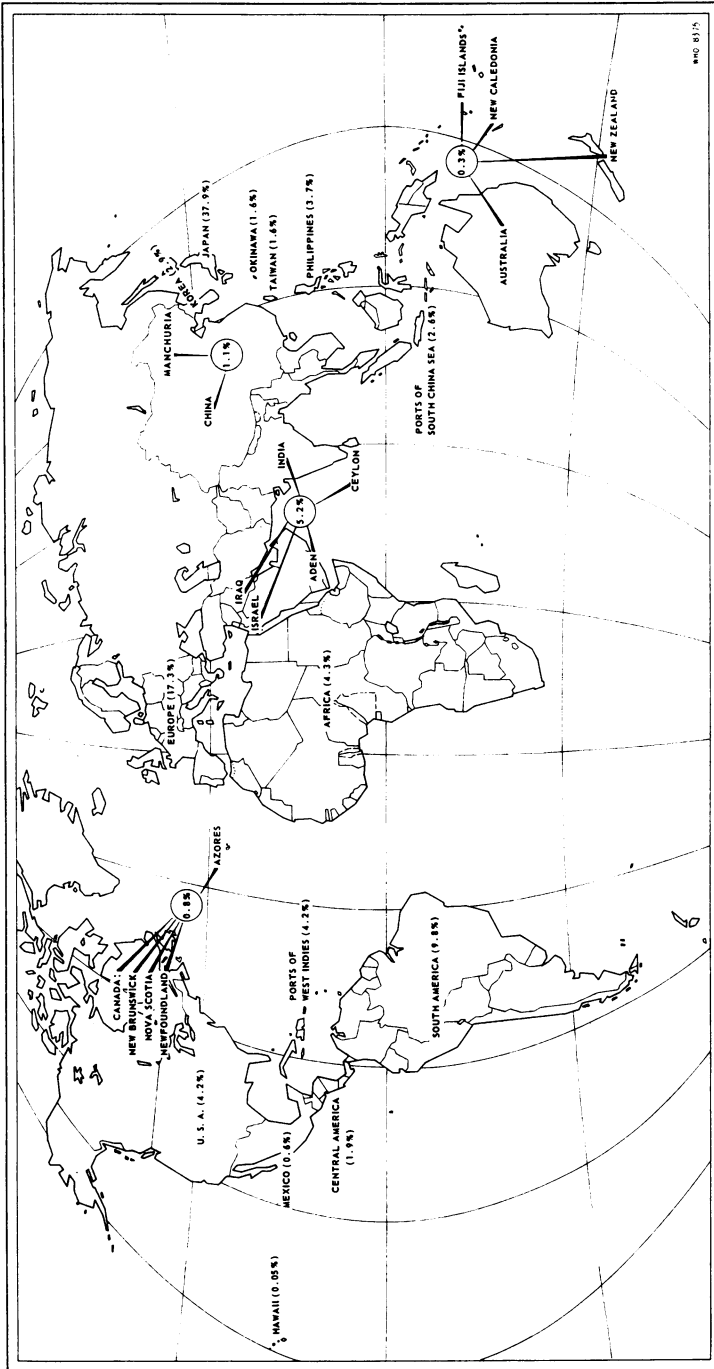
Because of the economic importance of the health of seafarers and in order to prevent international spread of disease, the Brussels Agreement providing for free treatment in major ports to seafarers of all nationalities

was drawn up in 1924. Since then some 60 maritime countries and areas have adhered to it. Special venereal disease services for seafarers have been created or the activity has been included in general or special health plans, as in the United Kingdom, the Scandinavian countries, Italy, and elsewhere. Some important countries, Japan, for instance, have not so far adhered to the Brussels Agreement or made equivalent services available to foreign seafarers free of charge. Infected seafarers from some of these countries have, on the other hand, benefited from the provisions of this Agreement abroad. It has been said that cost is a deterrent. Detailed analysis suggests that this is not so, and it is therefore hoped that further countries will eventually provide free treatment facilities for foreign seafarers in their major ports under the Brussels Agreement, thus accepting their role in the expanding co-operative international programme to improve, through the medium of WHO and the International Labour Organisation, the health of seafarers in general.

Preventive work dealing with venereal foci in ports is obviously a problem of a broad social as well as medical nature. On the medical side, the elimination of such foci must rely, in addition to the provision of free treatment for all seafarers, on adequate facilities for treatment, control and health education of promiscuous port females. Here the problem is no different from that encountered in dealing with any similar promiscuous group of females, whether or not they are recognized officially by legislation as "prostitutes". One aspect, however, is somewhat different, and that is the overseas ramifications of epidemiological case-finding in maritime venereal disease control. Thus, in 1952, more than 45% of the cases of fresh syphilis occurring in the port of Copenhagen were the result of importation from overseas by seafarers. The need for further co-operation between health administrations is also illustrated by Fig. 2, which shows in what parts of the world infected seafarers medically examined in the USA acquired their infection.

In the countries of the Americas, a system of epidemiological notification slips to trace sources of infection is currently being used between health administrations. Similar efforts are made in some parts of Europe. This approach might well be more widely tried. Its practical results are obviously dependent on the wholeheartedness of the effort made at either end of the epidemiological line. There can be little doubt that there is room for further activities aimed at the elimination of foci of venereal infection in ports. It was demonstrated in Great Britain in 1948-49 that the incidence of early syphilis in six port cities was 10.1 per 10 000 population as against 5.4 per 10 000 population in six comparable inland cities, and that there were two-thirds as many cases of early syphilis among the female port population as in the comparable population in inland cities. In many countries (United Kingdom, United States of America, Scandinavian countries), periodical medical examinations among seafarers have now

FIG. 2. PERCENTAGE DISTRIBUTION OF 4384 CONTACTS OF 2426 MERCHANT SEAMEN INFECTED WITH VENEREAL DISEASE, BY GEOGRAPHICAL AREA OF EXPOSURE* (JUNE-NOVEMBER 1951)



* Unidentifiable ports of seamen's contacts are excluded.

Data supplied by courtesy of the Public Health Service, US Department of Health, Education, and Welfare, Washington, D.C., USA.

become obligatory and include systematic blood-testing for syphilis, this being based on the above observation that the prevalence of venereal infections is higher in seafarers than in inland populations. This has also been shown in Norway, where young seafarers had a seropositivity prevalence three times that found among young recruits of comparable age-groups (Kronstad, 1955). Seropositivity was found to be 1.5% among Norwegian seafarers. In Japanese seafarers the corresponding rate has been shown to be 7.3%-8.1% in 1954-55.

Occupational health activities have obviously also been carried out in many other professional groups because of the rapid development of industry and the economic importance of venereal infections in various industrial areas of the world. Pre-employment medical examinations and periodic control have become part of a pattern of health protection for the industrial workers. They represent, therefore, one of the most important occupational groups where systematic blood-testing for syphilis can be readily carried out as part of medical examinations and where the procedure is of preventive as well as of curative value.

Prostitutes

Periodical genito-urinary inspection, smear-taking, treatment, and blood-testing have been the preventive procedures used among prostitutes and similar groups (tea-house girls, waitresses, entertainers, etc.) to limit the spread of venereal infections. Epidemiological case-finding and health education are also sometimes done, and individual prophylaxis is often encouraged.

There can be little doubt that periodic blood-testing of prostitutes and similar groups is of some value in these sexually hyperactive females who may, for purposes of gain, sometimes have 200-300 contacts in a month. The practice of serological testing should be encouraged if reliable laboratory services are available. Inadequate serological testing and a lack of liaison between the performing laboratory and a central serological reference centre which appraises the test performance continuously are likely to give results of little value either to the venereal disease service or to the prostitute.

The value of smears varies obviously with the quality of the method of securing a specimen, the staining and microscopic techniques, as well as with interpretation. The high percentage of positive smears often diagnosed microscopically in prostitutes at periodical medical examinations (ranging from 30% to 60% in different areas) raises the question of the criteria for diagnosis of gonorrhoea. What is the reliability of microscopic diagnoses as compared to gonococcal culturing? How can laboratory services be improved? Why do there continue to exist differences of 40%

to 90% between recognized good laboratories as regards verification of microscopic diagnoses of gonorrhoea by culture? Why are the phagocytized intracellular gonococci considered to be dead by some and alive by others, and under what circumstances should their tinctorial characteristics serve as the sole microscopic criterion for specific diagnosis in gonorrhoea? More knowledge in this field is required, and further research necessary. Further staining techniques might be explored, taking into account new knowledge in other fields of pathology. The study of these and other aspects might lead to more knowledge on which to base better control measures in the future.

In many under-developed countries, the concept of venereal disease control has by tradition been—and often still is—limited to the periodical medical examination and treatment of prostitutes or equivalent groups (tea-house girls, waitresses, entertainers, etc.), the health administration having often accepted this as its responsibility. Whether prostitution is formally outlawed or not, such inspection will undoubtedly continue to be carried out in different ways in many countries and is of a certain epidemiological value, although reports to the contrary are to hand (Lentino, 1955). It should be realized, however, that prostitutes and other promiscuous female groups represent a relatively small part of the total female population of any one country and that modern venereal disease control programmes have much broader functions. The venereal disease service should assume responsibilities for active co-operation in the planning, evaluation and work in maternal and child health and other collateral sectors of the general programme of the health administration, so that a broad view of prevention may result, based on epidemiological rather than purely clinical concepts.

II. PROPHYLAXIS AND PREVENTIVE TREATMENT

In the first part of this article five levels at which preventive public health measures could be applied against venereal infections were described and the need for a broader epidemiological concept of venereal disease control was discussed. *Specific protection* against infection can be afforded in several ways, and prophylaxis and preventive treatment of venereal diseases are considered in further detail in the present part of the paper. In regard to the use of preventive procedures in other fields of medicine, the reader is referred to a previous publication (Guthe, 1955).

Prevention of Congenital Syphilis

The complete suppression of congenital syphilis by prenatal treatment of syphilitic women, already placed within the realm of possibility by the pioneer work during the era of the arsenicals, has become a distinct possi-

bility with the discovery of penicillin. The value of treatment in preventing the passage of syphilis from the mother to the child *in utero* approaches perfection. The outcome of pregnancies in a large material studied by Ingraham (1951) and comprising more than 10 000 deliveries at the Philadelphia General Hospital, Pennsylvania, USA, is shown in Table 2.

TABLE 2. OUTCOME OF PREGNANCY AND EFFECT OF ADEQUATE PREVENTIVE TREATMENT IN THE PREGNANT SYPHILITIC MOTHER*

Outcome	Non-syphilitic mothers (%)	Untreated syphilitic mothers (%)	Mothers treated for early syphilis (%)	
			As and Bi	penicillin
Normal full-term living infant	86.3	18.2	91.4	94.0
Living syphilitic infant	—	40.9	2.2	1.1
Premature non-syphilitic infant	9.0	2.3	0.7	0.4
Full-term infant	0.5	1.8	1.9	0.2
Premature infant	1.7	11.8	0.0	0.9
Still-born, full term	0.5	18.2	3.4	2.3
Premature (miscarriage)	2.1	6.8	0.4	1.1

* Based on data from Ingraham (1951).

Local Prophylaxis

The classical work of Roux and Metchnikoff and of Grandmaison many years ago demonstrated experimentally the local prophylactic effectiveness of mercury ointment against *T. pallidum*, and Castellani showed the usefulness of silver nitrate and permanganate against *N. gonorrhoea*. A number of lubricants containing bactericidal as well as spermicidal substances has in recent years been added to the prophylactic armamentarium and the use of antibiotics in vaginal suppositories has also been shown to be highly effective.¹

It should be noted that—epidemiologically speaking—it is quite possible to control the spread of venereal infections by simple ablutions and local prophylaxis, as was demonstrated during the Second World War when, in one instance, among more than 277 000 brothel clients an incidence of 0.31 cases of venereal infection occurred per 1000 over a period of 8 months (Campbell, 1946). Local prophylactic measures, including urination and use of soap and water, have played—and should continue to play—a useful role in the prevention of syphilis, gonorrhoea, and the “minor” venereal infections in the incidental promiscuous males and to some extent also in the promiscuous females. The protection afforded by

¹ See the note by T. Ohno and co-authors on page 575 of this issue.

mechanical prophylaxis is also considerable, but does not prevent extra-genital infection; this is the case also with chemical prophylaxis. Ethical and sometimes religious considerations limit the acceptance of these procedures, and for the individual opportunity or time for their use is not always available. In the last instance, its acceptance is linked with its promotion as part of the activities in the health education of the public.

In this paper, prophylaxis and preventive treatment are discussed from the point of view of their possible broad epidemiological effect on the reservoir of syphilis and gonorrhoea, which, in some countries, is considered to be represented by professional prostitutes, while in others the "good-time girl" or other singly promiscuous females make up the main pool of infection.

Systemic Prophylaxis

Syphilis

The application of systemic prophylaxis or preventive treatment in venereal syphilis of the adult has been a matter of dispute for decades and there have been two schools of thought: "Never treat before diagnosis" and "Prevention is better than cure". Interesting discussions of these questions have been published by Durel & Hardy (1957), and by Willcox (1954) and King (1954), who took widely different points of view. Even in the arsenicals era, preventive treatment was used in the incubation period of suspected syphilis; or prenatally in pregnant women on "proof" of contact with infectious lesions. It is logical that the "consolidation" treatment with bismuth previously applied for several years following *traitement d'attaque* of early syphilis had a prophylactic value against reinfection with *T. pallidum*. Bismuth prophylaxis was also used systematically in some countries and was among the preventive measures available for prostitutes. It is therefore not surprising that similar procedures using penicillin have subsequently been found to be effective, and there has been a growing recognition of the importance of a wider use of penicillin for preventive purposes in all the treponematoses.

The effectiveness of preventive as well as therapeutic treatment in early treponemal disease is based on the ability of penicillin to maintain a sufficient level of the drug in the blood long enough to kill the treponemes present. When pathogenesis is about to begin, the exposure time to penicillin necessary to kill the few existing treponemes at the moment of invasion is probably very short, while in secondary, florid syphilis, with its abundance of treponemes in the tissue fluids, an exposure of the treponemes to penicillin of 10 days or more may be needed. There thus exists a quantitative time-dose relationship, which was originally demonstrated by the work of Eagle (Eagle et al., 1948). Further observations in accidental syphilitic infections

in laboratory workers (Durel, 1957) and experimental inoculations in human volunteers (Magnuson et al., 1956), as well as the increasing practical experience of many investigators (Samamé, 1951; Thomson, 1956) in respect of prostitutes, have demonstrated the preventive effectiveness of parenteral penicillin. In applied public health programmes against the non-venereal endemic treponematoses, particularly endemic syphilis (Grin, 1953; Murray et al., 1956) and yaws (Second International Conference on Control of Yaws, 1957), preventive treatment has become part of the WHO technical policy for their eradication in under-developed areas (Hackett & Guthe, 1956). The following figures will serve to illustrate the results obtained in yaws campaigns from application of this policy:

(a) *Effect of total mass treatment*
(Nsukka Division, Eastern Nigeria)

	Population examined	Percentage of active yaws	
		infectious	total
Initial treatment survey	327 769	3.18	14.28
Resurvey after 1 year	255 046	0.09	0.21

(b) *Effect of treating clinical cases only*
(Indonesian yaws campaign)

	Percentage of total active yaws in four subdistricts				Subdistrict V	
	I	II	III	IV	infectious	total active
					yaws (%)	yaws (%)
Initial treatment survey	19.0	14.3	8.0	17.6	3.7	13.6
1st resurvey	12.0	5.7	4.0	3.6	0.9	4.5
2nd resurvey	8.0	2.2	1.0	1.8	0.5	2.4
3rd resurvey	2.4	1.14			0.5	1.6
4th resurvey	1.0				0.4	1.3

Note: Resurveys were carried out at 9-12 month intervals. The population in each subdistrict was approximately 25 000.

Not only will the intramuscular administration of 1.2 mega-units of benzathine penicillin¹ eradicate *T. pallidum* in the individual when the disease is in the incubation period, but 2.4 mega-units of benzathine penicillin (or the equivalent amount of PAM) will result in a protective treponemicidal penicillinaemia for three to four weeks when applied preventively in prostitutes (Guthe, 1955; Durel & Hardy, 1957). The results obtained by this procedure are illustrated in Table 3, and the duration of the actual treponemicidal effect of the serum up to four weeks under this regimen is presented in Table 4. Such parenteral preventive treatment is now being used in many countries among promiscuous females.

It is difficult to appraise to what extent the general use of penicillin therapy and its preventive application in venereal disease control, its wide

¹ This corresponds to 2.4 units of PAM meeting international minimum requirements (WHO Expert Committee on Venereal Infections and Treponematoses, 1953).

TABLE 3. INCIDENCE OF INFECTIOUS SYPHILIS IN PROSTITUTES

Number of months after beginning of trial	Test group (monthly "maintenance" doses*)						Control group (clinical cases treated)					
	number examined	seroreactors		primary, secondary lesions **		cumulative percentage	number examined	seroreactors		primary, secondary lesions **		cumulative percentage
		number	percentage	number	percentage of total			number	percentage	number	percentage of total	
0	32	14	43.7	1	—	—	54	23	42.5	0	—	—
1	31	13	41.9	0	0.0	0.0	53	22	41.5	2	3.8	3.8
2	29	12	41.4	0	0.0	0.0	51	20	39.2	1	2.0	5.8
3	30	12	40.0	0	0.0	0.0	49	19	38.8	0	0.0	5.8
4	28	11	39.3	0	0.0	0.0	51	22	43.1	0	0.0	5.8
5	29	11	37.9	0	0.0	0.0	50	21	42.0	1	2.0	7.8
6	29	10	34.5	0	0.0	0.0	49	20	40.8	0	0.0	7.8
7	30	11	36.7	0	0.0	0.0	50	21	42.0	0	0.0	7.8
8	29	9	31.0	0	0.0	0.0	49	22	44.9	1	2.0	9.8
9	28	8	28.6	0	0.0	0.0	49	21	42.9	0	0.0	9.8
10	27	7	25.9	0	0.0	0.0	50	20	40.0	0	0.0	9.8
11	28	8	28.6	1	3.9	3.9	49	22	44.9	2	4.1	13.9
12	29	6	20.7	0	0.0	3.9	50	22	44.0	0	0.0	13.9

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* 2.4 mega-units of benzathine penicillin G given preventively at monthly medical examinations.

** Clinical cases were treated with 4.8 mega-units of PAM in one session.

TABLE 4. PERCENTAGE IMMOBILIZATION OF TREPONEMA PALLIDUM OBTAINED IN A 1/10 DILUTION * WITH 5-10 MILLION ORGANISMS BY THE ACTION OF SERA OF PROSTITUTES HAVING RECEIVED 2.4 MEGA-UNITS OF BENZATHINE PENICILLIN INTRAMUSCULARLY

Number of days after injection	Persons							
	1	2	3	4	5	6	7	8
7	100	100	100	100	100	100	100	—
14	100	100	96	100	100	100	100	96
21	100	100	74	91	100	100	100	71
28	54	32	25	74	87	65	87	50

Reproduced in translation and with slight modification from Durel & Hardy (1957) by kind permission of the editors of *Revue d'Hygiène et de Médecine Sociale*.

* 50 % immobilization in this dilution probably corresponds to 100 % in the circulating blood.

use for other conditions in medicine, and its general misuse by the public in all countries have contributed to the impressive world-wide decline in syphilis observed over the last decade. In spite of the reported increasing incidence of penicillin reactions in all fields of medicine,¹ it is quite conceivable that a general "penicillinization" has taken place, together with the wide use also of some other antibiotics active against *T. pallidum*, and that this has acted as a sort of broad social prophylaxis. Even in countries where little organized venereal disease control effort has been made, early clinical syphilis apparently is now rarely seen. It has also been said that the general decline in syphilis could, at least in part, be due to a "natural cycle" of the disease, a phenomenon spoken of by syphilologists after the First World War. But no further information on the nature of such a cycle is available. It should be remembered, however, that syphilis has been shown to be extremely sensitive to its environment, and during periods of social and economic growth, venereal diseases are apt to decline. On the other hand, epidemic rises in incidence occur very rapidly during, for example, war conditions. Medical interference with the treponeme through "saturation" of the environment with treponemicidal antibiotics would certainly tend to enhance the balance of the host-treponeme relationship in favour of the host.

Gonorrhoea

Why then, if syphilis has declined so remarkably, has gonorrhoea over the same period receded only slightly, despite the fact that both these

¹ See article on page 427.

infections have the same mechanism of transmission, occur in similar environments, and rely on the same drug for individual therapy and on similar means for their prevention?

When discussing this question from an epidemiological point of view, it should first be realized that many more people are susceptible to gonorrhoea than to syphilis, because a certain percentage of urban adult populations are seroreactors and hence relatively immune to a new syphilitic infection, and in tropical rural areas relative cross-immunity from yaws to *T. pallidum* is frequent. Furthermore, gonorrhoea, by and large, is three to four times more frequent than syphilis and has a short incubation period; the statistical chance of infection and spread is therefore greater. In addition, gonorrhoea is more infectious than syphilis and the proportion of "takes" in the susceptibles, although not 100%, is apparently high.

The duration of infectiousness can be very long when gonorrhoea remains undiagnosed, unsuccessfully treated or untreated, particularly in women. Treatment time with antibiotics is very short and no substantial immunity is produced by the acute gonorrhoeal infection; in addition, the rate of reinfection with the gonococcus is much higher following antibiotic therapy than with the long-lasting local therapy used previously.

Syphilis is less contagious than gonorrhoea, and perhaps only 50% of those exposed to infectious genital lesions may acquire the disease. Furthermore, the incubation period is long (3-5 weeks) and epidemiological case-finding, undertaken as a result of a diagnosed infectious case, leaves a relatively long period at the disposal of the case-investigators to find and treat interim contacts before they become infectious.

The widespread use of penicillin for conditions other than venereal infections, and the general misuse, may—as has been stated above—be not insignificant factors responsible for the decline in the incidence of syphilis as compared with gonorrhoea. There is also a greater chance that penicillin will be given for unrelated conditions during the long incubation period of syphilis than during the short incubation period of gonorrhoea. Furthermore, *T. pallidum* is a micro-organism often more sensitive to penicillin than the gonococcus and a lesser blood concentration of the antibiotic is therefore required to eradicate *T. pallidum* in the incubation period than is the case in gonorrhoea, where some strains of gonococci now require penicillin blood levels several times as high as those for *T. pallidum*.

When penicillin was introduced in the treatment of gonorrhoea 15 years ago as little as 100 000 units cured acute cases of the disease. The use of single intramuscular injections of 300 000 units became standard practice when long-acting penicillin in oil beeswax (POB) and later procaine penicillin G in aluminium monostearate (PAM) came into being. Success in 90%-100% of the cases was reported from many parts of the world. Therapeutic dosages now required to achieve similar results far exceed those previously applied. In addition, increasing failure rates have been

reported with various long-acting penicillin preparations which have gradually come into use over the last years. In a world-wide survey in 1955 the World Health Organization (Willcox & Guthe, 1957) found that increasing dosages of penicillin were being used in the treatment of gonorrhoea. Eight times the dose of PAM was required to obtain the same cure rates in the United Kingdom in 1957 as in 1952. With benzathine penicillin, failure rates of 30.8% are now encountered and a failure rate of 28.6% has been reported with phenoxymethyl penicillin or penicillin V, although this is a preparation with high rather than long blood concentration characteristics. These increasing failure rates on the *clinical* side are also pictured in the concurrent *laboratory* developments. There were originally no known strains of the gonococcus "resistant" to penicillin. In 1948, suggestive evidence of developing resistance was shown to be due to non-gonococcal urethritis (Hughes & Carpenter). A certain range in the penicillin sensitivity of the gonococcus was shown by some investigators in 1949 (Cohn et al.) and 1950 (Gocke et al.). Others (Horne, 1945; Marcuse & Hussels, 1954) found no evidence of increased resistance, the sensitivity ranging from 0.005 to 0.03 units/ml. More recently, however, as many as 10 units/ml have been required to kill isolated strains of gonococci *in vitro* (Ehrman & Granits, 1955). In fact, this concentration was defined as a quantitation limit, synonymous with "resistance". Suggestive correlation between the clinical and the laboratory findings has recently been shown (King, 1958; Gradock-Watson, Shooter & Nicol, 1958). G. M. Thomson in an unpublished document has for practical purposes defined "resistance" in males on the basis of failures following treatment with 400 000 units of PAM. Other similarly arbitrary definitions on clinical or laboratory grounds have been made, signalling that the problem is to some extent a quantitative one of practical nature. Ehrman & Granits (1955) in fact cured even their "resistant" cases with massive doses of penicillin, presumably because of the very high blood levels achieved. It is interesting to note that in the recent experience of R. R. Willcox¹ dosages of phenoxymethyl penicillin two to three times as high as those used by Marmell & Prigot (1956) in gonorrhoea have resulted in 18.4% failures while Marmell & Prigot only a few years previously had encountered no failures. Blood levels varied from 2.7 to 4.6 units/ml. For practical purposes, however, it must now be accepted that many strains of gonococci are "resistant", although penicillin may well continue to be relied on as the first weapon against this disease for some time to come.

Penicillin in all its forms has over the years also been used for *prophylactic* purposes in gonorrhoea. In this respect its value was demonstrated in 1946 and other experience has subsequently been made in France (Durel, 1957), Panama (Fabrega, 1955), in the USA (Weinstein, 1955), and else-

¹ See the article by R. R. Willcox on page 503 of this issue.

where. Various contributions to this subject have also been made from Asian countries.

The value of penicillin (used parenterally or orally) for purposes of systemic prophylaxis, as it is in therapy, is obviously based on the sensitivity (despite the "resistance") of the gonococcus to penicillin. With the current changing sensitivity it is to be expected that also the prophylactic value of penicillin will in the future become less effective. This might, however, take more time to manifest itself than it has in the therapy of the clinical disease. Prophylactic benzathine penicillin (2.4 mega-units) is, for instance, still effective in the prophylaxis of gonorrhoea in some countries, particularly France.

Discussion

It has been said that it took nearly ~~15~~ years of penicillin use to reach the present situation and that it will therefore take a very long time before penicillin is exhausted as our main weapon against gonorrhoea. Admittedly, the situation is different from that existing in the sulfonamide era, when a second bowstring of effective drugs against the gonococcus was not available; now there are also, among others, streptomycin, the tetracyclines and polymyxin. Many of these are also effective against the non-gonococcal genito-urinary infections which are becoming increasingly frequent.

The experience with resistance in man and insects suggests, however, that once the process has begun, its rate of increase does not follow a straight line, but takes place at an accelerating speed. The continued use of repeated, relatively small doses of penicillin in gonorrhoea may thus defeat our purpose, and may assist the gonococcus to increase quantitatively its tendency to resist the antibiotic, just as can be demonstrated to be the case *in vitro*. More strains with somewhat lowered sensitivity to penicillin will thus be allowed to survive. Natural selection and survival of the least sensitive strains will add to the problem and accelerate the quantitative and qualitative composition of the over-all reservoir from which new infections are drawn. This process is already under way. Under these circumstances, the broad preventive value of the long exposure time of the gonococcus to repository penicillin preparations by wide prophylactic and therapeutic use may no longer remain an effective factor in reducing transmission of gonorrhoea. The use of short-acting penicillins with high blood level characteristics—although temporarily effective in individual cases—will not solve the problem of gonorrhoea. An already weakening epidemiological barrier may in the long run only be further weakened. The public health prognosis of gonorrhoea from the point of view of broad prevention and control is therefore less favourable than even a few years ago.

It has been suggested that there is a need to use more widely other antibiotics in gonorrhoea or urgently to develop a new repository, non-toxic,

inexpensive antibiotic preparation which—apart from having a rapid curative effect—must have particularly long-acting characteristics. This is undoubtedly true. Should such a preparation become available it would be essential from the beginning to use substantial doses so that the chances of selection and of a gradual development of resistance are reduced to a minimum. The use of relatively small drug doses, repeatedly and over a period of time, is the biological mechanism whereby resistance may develop either through adaptation of the gonococcus to the antibiotic or through natural selection by the survival of increasingly tolerant strains. Had large dosages of long-acting penicillin been used from the beginning, the result might have been a more persistent and significant decline in the gonorrhoea reservoir over these 15 years. The epidemiological potential of any new preparation to control gonorrhoea will depend on a long exposure of the gonococcus to the drug in the host by a wide preventive and therapeutic use. A persistent reduction in the reservoir and the transmission might then follow. The effect of such wide use—along with that of other measures at all levels of prevention—would be of broad epidemiological value, as contrasted with temporary therapeutic success in individual clinical cases.

Finally, it is tempting to refer to the possible effect on the reservoir of syphilis which might result from a switch from long to short-acting penicillins and the increasing general use in all medical conditions of other antibiotics, not necessarily effective against *T. pallidum*. Would the general decrease in use of long-acting penicillin preparations affect the broad social prophylaxis against syphilis now considered to be a factor in its control? Is such a reorientation already taking place and is it related to the increase in the incidence of venereal syphilis reported in several countries since 1955?

RÉSUMÉ

Les connaissances épidémiologiques variées qui doivent présider à l'organisation de la lutte contre les maladies vénériennes, sont encore limitées. L'impossibilité de cultiver *T. pallidum* en milieu artificiel, l'absence d'un agent immunisant, les difficultés rencontrées dans la culture du gonocoque, sont autant d'obstacles. Il en est d'autres encore, tels que le peu d'information que l'on a sur le cours naturel chez l'homme de la syphilis et de la blennorragie non traitées, les réactions d'immunité, la réinfection, les incapacités de travail et la mort, les différences de comportement sexuel chez les populations urbaines et rurales, sous des climats froids ou chauds, à divers degrés de développement économique et culturel. Tous ces facteurs difficiles à évaluer jouent évidemment un rôle, plus ou moins grand, dans la persistance des maladies vénériennes.

De grands progrès ont été accomplis au cours des 15 dernières années, grâce à la lutte menée sur le plan national et international. Le succès du traitement par la pénicilline a créé un sentiment de sécurité, pourtant fallacieux. Il faut certes tirer le plus grand parti possible des avantages de la situation présente. Mais rien ne permet d'exclure, pour l'avenir, l'apparition d'une résistance à la pénicilline chez le tréponème, ou une fréquence accrue des réactions allergiques au traitement. Il semble, d'autre part, que

les sources d'infection blennorragique n'aient pas diminué d'intensité, comme celles de la syphilis. Le gonocoque paraît donner des signes de résistance à la pénicilline. Il importe donc, si l'on veut avoir raison un jour de ce groupe de maladies, de concentrer et d'intensifier les efforts afin de dominer les éléments favorables à la survivance des tréponèmes, et d'étudier sur le plan national et international les problèmes nouveaux que pose la blennorragie.

La prévention peut s'exercer à cinq échelons: *amélioration du niveau général de la santé* (hygiène personnelle, éducation sexuelle, examen pré-nuptial, amélioration des conditions socio-économiques et de l'utilisation des loisirs); *protection spécifique* (prophylaxie, examen sérologique prénatal, suppression de la prostitution commercialisée); *diagnostic et traitement précoces*; *limitation des séquelles incapacitantes* (traitement en vue de la destruction des tréponèmes dans le tissu cérébral, recherche de la syphilis latente, éducation du public dans ce sens); *réadaptation* (des aveugles, paralysés ou des sujets atteints de maladies cardiovasculaires avancées).

L'auteur décrit divers aspects de la prophylaxie. Il discute ensuite la question du traitement préventif, puis de la protection généralisée créée par l'usage constamment accru des antibiotiques, et de la pénicilline en particulier, contre diverses maladies, enfin le problème de la blennorragie, qui n'a pas suivi la même courbe descendante que la syphilis. La résistance du gonocoque à la pénicilline et ses conséquences lointaines permettent de penser que la situation, à cet égard, est moins favorable qu'elle ne l'était il y a quelques années.

On a proposé d'utiliser de façon plus générale d'autres antibiotiques contre le gonocoque et de mettre au point une préparation antibiotique-retard non toxique, peu coûteuse, qui, tout en ayant un fort pouvoir curatif aurait une longue action retard. Si un tel médicament devenait disponible, il faudrait l'utiliser tout de suite en fortes doses, de façon à éviter les risques de sélection de souches résistantes ou d'adaptation, résultant de l'utilisation prolongée de faibles doses de substance active. Au cas où l'insuccès partiel du traitement de la blennorragie par la pénicilline-retard motiverait l'application moins générale de cette thérapeutique, ou le retour à l'emploi de pénicillines rapides, on peut se demander quelles seraient les répercussions sur la prophylaxie antisiphilitique, et s'il existe un rapport entre cette réorientation des méthodes de traitement, déjà amorcée, et la recrudescence de la syphilis vénérienne dans certains pays depuis 1955.

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