TREATMENT BEFORE DIAGNOSIS IN VENEREOLOGY*†

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That diagnosis should precede treatment has been a valuable principle during a long phase of our medical history. In recent years, however, as new advances in therapeutics have outpaced those in diagnosis, the epidemiological approach has gained at the expense of the clinical, and in many fields the principle is undergoing modification. That in certain circumstances preventative "treatment" should precede diagnosis is now generally accepted.

Thus suppressive treatment with antimalarial drugs is given to millions prior to exposure to the mosquito. Antibiotic "umbrellas" have been widely used before dental extraction, and before chest and other operations to prevent unpredictable invasion by unknown organisms. Healthy persons are inoculated against typhoid and cholera, children against diphtheria and tuberculosis. Those who are tardy in receiving vaccination against smallpox find that it is obligatory before travelling abroad to many countries and are quick to receive it in the face of an epidemic. Moreover, a doctor might even be held liable if he had failed to give preventative treatment before a diagnosis of tetanus is made. Suspected bacterial endocarditis is not infrequently treated in spite of a negative blood culture, and one does not wait to obtain a positive sputum before treating a radiographically suspected case of pulmonary tuberculosis. Similarly one does not wait to confirm the presence of pediculi before administering DDT in a typhus outbreak, or delay taking tablets for sea-sickness until vomiting has set in.

It is quite natural, therefore, that "treatment" before diagnosis should be applied to the venereal diseases. This method has so far been used principally in the following circumstances:

- (1) In mass-treatment campaigns against the treponemal diseases in areas of high prevalence;
- (2) In persons exposed to unusual risk of syphilis (*e.g.* regular consorts of known infectious syphilitics, especially if pregnant);
- (3) In females where the tests have failed to show the gonococcus but gonorrhoea is suspected on epidemiological grounds.

(4) As a prophylactic against gonorrhoea after risk of infection.

With any new method of treatment there are four questions which should be asked:

- (a) Is it efficient?
- (b) Is it economical?
- (c) Is it ethical?
- (d) Is it safe?

The various indications for treatment of the venereal diseases before diagnosis are considered below in the light of these criteria.

(1) TREATMENT OF PERSONS WITHOUT OVERT SIGNS OF DISEASE IN MASS-TREATMENT CAMPAIGNS.—The World Health Organization has now treated with penicillin well over 3,500,000 persons in its mass-treatment campaigns against yaws, bejel, and endemic syphilis. Experience has already shown that unless the apparently non-infected contacts of detected cases are also treated the campaigns will fail, owing principally to undetected latent and incubating cases. The WHO Expert Committee on Venereal Infections and Treponematoses (1953), in a consideration of these campaigns, has recommended:

Where treponemal diseases constitute a major public health problem, contacts without overt signs of disease should receive preventive ("abortive") treatment with PAM.

This point is well illustrated by the experience in a small village in Bosnia afflicted by endemic syphilis (Guthe and others, 1953). In a village with a population of only 573, secondary syphilis was found in 29 cases (5 per cent.) when the initial case-finding and mass-treatment programme was launched in August, 1948 (First Survey). The Second Survey, when the entire population was again examined, was deferred for 22 months, and, although only five cases of infectious syphilis (? re-infections) were found among those originally treated, 24 additional cases were detected in the remaining population—making a total incidence as high as at the beginning. All cases and *household contacts* were then treated. At a Third Survey made only 4 months later, four additional fresh cases of infectious syphilis were found. A Fourth Survey carried out 2 months later

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revealed no infectious case of syphilis and the village was still free of endemic syphilis in November, 1951 (Figure).

FIG.—Endemic syphilis control programme, Trnaci, Bosnia. Cases of secondary syphilis found in four surveys, (WHO 2024).

Similar experience is forthcoming from Indonesia and Haiti. Thus the principle of treatment before diagnosis is already firmly established in the mass-treatment campaigns against the treponematoses in many parts of the world. This is no small-scale programme, for already, in the six major WHO-assisted mass campaigns, over 13 millions have been examined and over 3,500,000 treated with penicillin (Table). This form of treatment is both efficient and safe; it is certainly economical, for without it the campaigns will fail; and the ethics of the procedure have never been challenged. In case anyone should consider this indication a departure from principle for a “special case”, it must be pointed out that in relation to the world scene this is not a special case.

TABLE
PERSONS EXAMINED AND TREATED IN SIX OF THE
LARGER WHO/UNICEF-ASSISTED TREPONEMAL DISEASE
CONTROL PROGRAMMES

Programme			No. Examined (First Survey Only)	No. Treated for First Time (including Later Surveys)
Period	Country	Disease		
To June 30, 1953	Haiti	Yaws	2,124,954	2,124,954
To Sept. 6, 1953	Indonesia	Yaws	5,439,424	888,953
To Aug. 31, 1953	Thailand	Yaws	2,459,503	294,039
To Sept. 4, 1953	Philippines	Yaws	1,609,795	60,091
To Sept. 30, 1953	Iraq	Bejel	120,298	64,099
To Jan. 1, 1953	Yugoslavia	Endemic syphilis	1,472,402	90,235
Total			13,226,376	3,522,371

In spite of the decline of early syphilis in the more civilized countries, the treponematoses in the under-developed areas constitute the greatest world problem. Mass-treatment campaigns are in operation or are planned in many places, and the number of these mass campaigns is increasing annually as are the numbers of persons examined and treated. Already then, in fact, treatment before diagnosis is being more frequently practised in the management of treponemal diseases in areas where the non-venerable and venereal treponematoses are prevalent, than it is being withheld in areas of low prevalence like Great Britain, the U.S.A., Scandinavia, and Europe in general. It is thus we ourselves with our low incidence of syphilis who represent the “special case”. Moreover, to exclude the mass-treatment campaigns against the treponematoses from our arguments would show a distressing lack of historical, geographical, and biological perspective in our understanding of syphilis.

Of the success of the mass-treatment campaigns in producing a “knock-down” effect there is no doubt. New infectious cases are rarely found once two surveys have been made, and successive serological surveys have shown a progressive fall in the incidence of sero-positivity in the treated populations. In the words of Grin (1953), speaking of Yugoslavia:

The epidemiological situation cannot conceivably return to the original situation after one or two follow-up examinations have been made, but constant supervision of previously endemic areas is necessary as part of the long-term programme.

In the words of E. G. Clark (1953), Professor of Epidemiology, Columbia University, New York, also writing of Yugoslavia:

I have never seen public health funds spent to greater advantage.

(2) TREATMENT OF CONSORTS OF INFECTIOUS SYPHILITICS.—Regular consorts of infectious syphilitics are particularly liable to develop syphilis. A number of workers have therefore recommended that these persons be given “abortive” treatment in the pre-primary stage of the disease. This matter was discussed at a United States Public Health Service meeting held at Bethesda, Maryland, in February, 1946; and I then spoke against it. Although many then agreed that such persons, if treated, should receive full anti-syphilitic treatment and follow-up, I felt that this was quite as bad as having had the disease when there was still a sporting chance of escaping it. However, figures are now available to show how high the risk of syphilis actually is in these persons, and also the efficacy of the procedure.

Alexander and Schoch (1949) gave 900,000 units penicillin in oil-beeswax plus 0.05–0.06 g. Mapharsen and 3 ml. bismuth ethyl camphorate to the contacts of 148 known infectious syphilitics. Only six developed syphilis *as against no less than one hundred of 161 contacts left untreated*. The series was enlarged further (Alexander and others, 1949) by the inclusion of a further 108 contacts who were given penicillin and bismuth without Mapharsen, and only thirteen of the new total of 256 treated developed syphilis. Likewise Plotke and others (1949) gave single injections of 600,000 units of penicillin in oil-beeswax to 77 contacts of infectious syphilis, and only 4 per cent. developed syphilis, as against 25 per cent. of a group of untreated controls. Furthermore, in an investigation undertaken in Copenhagen, Marcussen (1953) reported that 60–66.3 per cent. of persons in regular sexual contact with patients suffering from contagious syphilis developed or had developed the disease.

When the high default rates in contacts, the not infrequent occurrence of “ping-pong” syphilis, and the fact that one case of syphilis in five passes through undetected (Berdal, 1950) are considered, it is obvious that the possibility of treatment in the pre-clinical stage must merit our attention. The question to decide is whether, after due explanation to the patient, he or she should be treated exactly as if the disease was known to be present (obviously the safer course in the present state of our knowledge), or, if a minimal dose may achieve the same result for the majority of cases, to give this instead and permit the failures to declare themselves within the shorter period of observation. Future research into the relationship between the dose of penicillin required and the time-interval after exposure when it is given, is necessary to determine this point.

Applying our criteria: the procedure is economical in so far as it prevents a high percentage of infections and saves many a re-treatment for the consort, and it is safe provided the patient is treated and followed-up exactly as if syphilis had been proved to be present. I can find nothing unethical in it.

If we do not accept it *in toto*, most of us, I think, already do so in part. If we have the wife of an infectious syphilitic in the last trimester of pregnancy we tend to treat before diagnosis for the sake of the child. Likewise, if any pregnancy is far advanced we are far less critical in the exclusion of possibly false-positive serum reactions for syphilis when insufficient time exists for their exclusion.

(3) TREATMENT OF GONORRHOEA IN FEMALES IN WHOM THE GONOCOCCUS IS SUSPECTED BUT NOT

PROVED.—This involves treatment before diagnosis of the female consorts, with and without signs, of males known to have gonorrhoea, and females with clinical signs of gonorrhoea but in whom the gonococcus is not found.

Some doubt must always exist as to the complete efficiency of our diagnostic methods, and indeed not all clinics have a satisfactory culture service. Moreover, there is always the possibility that the patient may have passed water or douched herself prior to the tests being taken. Today one might say the rule is “if in doubt, treat”. Marcussen (1953) considers the risk of transmission of gonorrhoea to contacts as being 84.9–87.8 per cent., so that this procedure would seem to be fully justified.

As one never knows which patient will lead the doctor to the courts to give evidence, I personally like to make at least two tests for gonorrhoea before giving penicillin, and to know that the serum tests for syphilis are negative. The procedure is simple, ethical, and safe. No reliable evidence is forthcoming to suggest that syphilis will be masked. Indeed the rarity of syphilis following the treatment of gonorrhoea with penicillin suggests that it is usually aborted completely. For safety, however, the ordinary follow-up for 3 months should still be undertaken but the patient would be recommended to undergo follow-up examination even if no treatment were given.

This opens up another problem. Should this treatment be adopted when the consort is suspected of having some venereal condition, the nature of which is not precisely known? It is only dangerous to give penicillin where a male partner has syphilis, and every effort should therefore be made to determine the diagnosis of the consort before treatment is administered. When this is not possible, judgment must be employed.

(4) PROPHYLAXIS AGAINST GONORRHOEA AFTER EXPOSURE.—It is concerning the question of the chemoprophylaxis of venereal diseases that the greatest controversy concerning “treatment before diagnosis” rages, but we must not allow strong personal convictions, religious or other prejudices, on this particular point to influence our judgment on the more acceptable indications already discussed. Neither must red-herrings in the form of arguments against prophylaxis as a whole be introduced into a discussion of a particular method, for it must not be forgotten that most of us have been or are committed to the giving of prophylaxis after exposure. The so-called “Early Treatment Centres” which were established for the Forces in wartime were conducted by many of us. Also, “as part of the

Government's campaign against venereal diseases", a brochure has been issued to seamen by the Central Council for Health Education (1944) which, albeit urging continence, states :

In all British and in many other clinics early preventative treatment is available.

Thus the pertinent point is not whether we approve of prophylaxis but whether we consider that chemoprophylaxis with antibiotics is a more effective method than those hitherto employed.

(a) *Service Personnel in Areas of High Prevalence.*—Chemoprophylaxis employing penicillin after exposure (which is really "abortive treatment" rather than true prophylaxis—an example of our confusion in terminology in these matters) has been quite extensively tried in the United States Navy and has been shown to be capable of reducing considerably the incidence of gonorrhoea. Eagle and others (1948, 1949) divided a group of seamen into two sections :

(i) controls ;

(ii) those given penicillin orally immediately after returning from 6-8 hrs shore leave.

In 24 weeks there were 43 cases of gonorrhoea in the controls (11.9 infections per 1,000 shore leaves), while there were only five cases in 16 weeks (1.8 per 1,000 shore leaves) in those receiving 100,000 units penicillin in a buffered tablet. The dose was then increased to 250,000 units penicillin ; in the next 8 weeks only one additional case was noted and this patient admitted that he had not taken the tablet. The study, conducted in the Mediterranean area, ultimately involved 24 ships and 12,000 men.

A reduction of 74 per cent. in the incidence of gonorrhoea over previous experience was obtained with the oral use of penicillin (Babione and others, 1952). On the other hand single doses of 200,000 units penicillin orally given as long as 15 hours after exposure have not proved so successful. Campbell and others (1949) were only able to reduce the incidence of gonorrhoea by 50 per cent. with this method. Success in the chemoprophylaxis of gonorrhoea with penicillin has also been reported by Belcher (1952), and sulphonamides in doses of 2 g. were used to good effect against both chancroid and gonorrhoea by Bergsma (1946). It is apparent also from these trials that although, if the inoculum is small, syphilis may be aborted by prophylactic penicillin given orally such is by no means always the case. Certainly, however, no *masking* of syphilis has been noted, and the disease if present has manifested itself in the usual way. Also many persons attribute the striking fall in the incidence of early syphilis to penicillin given for other reasons by practitioners and hospitals, during the incubation period. Theoretically, if prophylaxis leaves one spirochaete, the patient is in the same position as if he had been infected without prophylaxis by a single spirochaete. It must be remembered, however, that such treatment is designed for men who will not be subsequently followed-up, and there is some danger from this,

unless provision is made for periodical serum tests.

The possibility that the widespread use of antibiotics in this way might encourage resistant bacteria, as has happened with the skin staphylococcus, cannot be ignored, but with no other pathogens has resistance to penicillin become a serious problem (Shooter, 1953). Certainly we see no penicillin-resistant gonorrhoea, and experiments to create a penicillin-resistant treponeme by giving sub-curative doses of penicillin to animals have failed (Probey, 1953). The question of inducing sensitivity of the patient to penicillin is also pertinent.

The method fails as a practical proposition, however, in the matter of cost. If 1,000 treatments have to be given to prevent ten attacks of gonorrhoea it is scarcely economical (Willcox, 1953) ; but the scheme merits some consideration in certain circumstances when infection rates in troops or in particular ports are exceptionally high, as a temporary measure while other means are being used to control the focus of infection. Apart from such circumstances, the uncertainty of the prevention of syphilis does not encourage the use of oral penicillin as a good prophylactic method.

(b) *Individuals.*—For the clinician dealing with individual civilian cases the problem is different. If an anxious patient consults him shortly after exposure, desiring the risks to be minimized, it is his duty to relieve that anxiety by the best means possible. We do not deny anti-malarial prophylaxis to those who expose themselves needlessly, and if we are willing to give men who have run the risk of contracting venereal disease urethral irrigations or applications of mercury ointment, I can see no reason why these persons should not have an injection of repository penicillin if it is more effective, provided that possible dangers are safeguarded. The dangers of masked syphilis are probably no greater than if the patient has no injection, and the possibility of later clinical syphilis is greatly reduced. If the treated person defaults without follow-up he is better off than the untreated one who does likewise, since one case of syphilis in five is unnoticed by the patient. If he does not default, the follow-up of 3 months is the same for both, and the treated person is in no different position from an ordinary gonorrhoea patient treated with penicillin, after which clinical syphilis is a rarity and masked syphilis is at the most a medical curiosity, at the least a doubtful entity.

Some will argue that if it becomes generally known that prophylaxis with penicillin after exposure is generally available, the clinics may become full of undesirable persons demanding it. We already give prophylaxis and advise the public accordingly. We do not tell them that it is inefficient and the public expect to receive the best available. We have not been worried in the past concerning the numbers who have sought prophylaxis, for these have been proportionately very few. I can see no reason, therefore, why the numbers should necessarily increase appreciably in the future. Should they do so we can deal with the situation when it arises.

My own views are that this procedure should not be used indiscriminately but that it is definitely indicated

whenever an innocent party is at risk. For example, when a man who has taken a risk consults the clinic on the way home to join his wife. The giving of the treatment will in most cases protect the innocent party and possibly save the home, in circumstances where the alternative enforced abstinence for 3 months would not pass unquestioned, and would be unlikely to be put into effect. The possible disadvantages should be explained clearly to the patient and a preliminary serum test should be taken. The fact that a follow-up is still necessary should be strongly emphasized. With the facts before him the patient can decide whether he will take chemoprophylaxis. He usually takes it. There is nothing unethical in protecting an innocent party. When the patient is seen within 24 and possibly 48 hrs after exposure, a dose of 300,000 units procaine penicillin with aluminium monostearate may be given. We know that 300,000 units penicillin will in fact cure sero-negative primary syphilis—a much later stage than the one envisaged (Bauer and others, 1950). As we are still in the dark as to what the correct dose and follow-up should be for patients treated after this time, and whether this is justified, such cases are probably best left untreated at present. When no innocent party is at risk, I do not suggest such treatment, but should a patient ask for it I consider it provided he was seen soon after exposure and was prepared to accept the conditions suggested.

(c) *Prostitutes*.—Chemoprophylaxis after exposure is indicated for prostitutes in certain parts of the world. Whether we like it or not, there are many places where prostitution is not just a sordid affair in a few back streets of the cities but flourishes almost as part of the social fabric, and where, as is not the case in Great Britain, it is responsible for the bulk of venereal disease. In some places, such as Teheran, prostitutes live in a more or less separate community; in others they are to be found in certain well-defined districts and follow certain occupations, e.g. the "special waitresses" of Taiwan. Decades, or even centuries, may be necessary to change these social conditions. In the meantime there is a potential and fruitful field for abortive treatment before diagnosis, for confirmation of a diagnosis of venereal diseases is often actively resisted by prostitutes.

In countries where prostitutes are registered and regularly examined, and therefore fear admission to hospital in case they are found to have venereal disease, many women are now seeking regular injections of penicillin. The venereologist at Izmir, Turkey, told me that he was convinced that the striking decline of syphilis in that town was due to the weekly private treatment he had given to the prostitutes (Willcox, 1951). Stokes and others (1944) mention a number of workers who give chemoprophylaxis to prostitutes, sometimes successfully with bismuth. Today some workers (e.g., Durel, 1953) justify more prolonged consolidation therapy after short but intensive treatment of syphilis with penicillin by its prophylactic effects in reducing the risks of re-infection. Certainly the objection that prophylaxis increases promiscuity cannot be applied to its use by prostitutes.

Thus when a relatively circumscribed group of women

among whom venereal disease is rife is known to supply the sexual needs of a fairly fixed population of men, it is reasonable to consider some form of chemoprophylaxis to limit the number of infections caused by any one female while she is infectious. Colonel Harrison has spoken of considerable success by orthodox methods in reducing the venereal disease rate of a garrison in India by concentrating on a particular group of women. In many such places there is no medical organization to do this thoroughly. I have seen mining compounds in Southern Rhodesia where relatively small numbers of women were admitted by pass to a community of Africans where chemoprophylaxis with penicillin would have been most useful. In this part of Africa men leave their villages to work in the mines and plantations. Few have any settled family life while they are there and their sexual needs are usually satisfied by prostitutes. Venereal disease is therefore rife. Here more than anywhere, a "shot" in time would save more than nine.

At the present time an interesting programme is being carried out on the Californian-Mexican border, where an attempt is being made to reduce the incidence of venereal disease by giving an injection of 300,000 units PAM every 7 days to a "specific group of persons who, by reason of their activities, may be exposed to venereal diseases, thus becoming reservoirs of infection"! Already there has been a striking fall in the incidence of venereal diseases in the nearby garrison (Samamé, 1951).

These new developments in the management of prostitutes, whether we approve or disapprove, are not without interest; they indicate a possible return to what has often been termed the "French school of thought" in these matters. They have come about through the striking new discoveries in repository penicillins, and we now face a situation in which the techniques which have failed in the past, owing to the inadequacy of available measures, may now succeed with penicillin. The new diamine penicillins may also be useful in this respect.

(5) *PROPHYLAXIS AGAINST GONORRHOEA AND SYPHILIS BEFORE EXPOSURE*.—Here we are on very much thornier ground, and, as there are as yet no results by which to judge this procedure, this possibility has been deliberately omitted from my list of accepted indications. It may fairly be argued that the availability of chemoprophylaxis before exposure might, as an antiveneral measure, defeat its own ends by leading to increased promiscuity. Any form of prophylactic, be it tablet or condom, may deflect the waverer to the path of venery, and the power of the fear of pregnancy and the fear of venereal disease in tending to limit promiscuity has already been drastically reduced by the introduction of the condom. In the last analysis it is the acquisition of stable sexual relations which counts. There is little doubt that had gonorrhoea and syphilis proved