THE MODERN TREATMENT OF SYPHILIS.

I.

THE TREATMENT OF SYPHILIS IN ITS EARLIER STAGES.

BY

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AN experience in the treatment of syphilis which extends over a considerable number of years, and has been gained under particularly favourable conditions for estimating the value of antisypilitic remedies, has led us to certain conclusions which we think of some interest.

The great advances which have been made in the diagnosis and treatment of syphilis in recent years enable us now to diagnose this disease from its earliest stages, detect its presence in the absence of naked-eye signs, and effectually control its progress. The old uncertainty of diagnosis in the primary stage has been replaced by the certainty which results from microscopic examination of the exudate from the sore; the signs of syphilis have been increased by one which is the most constant of all—the Wassermann reaction; and, thanks to salvarsan, the slow dragging progress towards recovery which was the rule under exclusively mercurial therapy, a progress which was often marked by many relapses, has given way to one which is at once more rapid and, judged by every test we can apply, more permanent.

It requires no very vivid imagination to realize what these advances mean to the control of syphilis. For ourselves, we believe that, properly used, they give us the power to limit syphilis to its earliest stages, and eventually to abolish, amongst other curses, congenital syphilis. As a contribution to this ideal we will describe the lines on which we think syphilis should now be managed in its earlier stages.

THE IMPORTANCE OF EARLY DIAGNOSIS AND TREATMENT.

The results we have obtained with salvarsan have shown us that it is of the very greatest importance to commence treatment in the earliest possible stage—much earlier, in fact, than that in which the primary sore can be recognized by the naked eye. In each of the various series of cases we have treated with salvarsan on different definite plans the total relapses which followed when treatment commenced in the secondary stage were more than double those which followed when it commenced in the primary stage. Add to this the risk of transmission to others, either directly from the sore or through the seminal fluid, and the chances of the central nervous system becoming seriously infected during the weeks which elapse between the first appearance of the primary sore and the outbreak of secondary signs, and it must be clear that every effort should be made to ensure that treatment commences as early as possible.

The value of a microscopic examination to the diagnosis of early syphilis does not seem to be sufficiently recognized. When a patient presents himself to his medical adviser with an early syphilitic sore, the commonest mistake which is made is to judge it by its naked-eye appearance, assume at once that it is not syphilitic because it has not the look of a Hunterian chancre, and prescribe an antiseptic ointment. Subsequently, when the sore begins to look more typical of syphilis, a blood test is thought of, a specimen of blood is sent to a pathologist, and the result not infrequently returned as doubtful or negative. Still a diagnosis is not made and more time is lost, till, finally, a positive blood reaction, or the outbreak of secondary symptoms, makes the diagnosis clear. All this time the spirochaetes have been multiplying in the patient's tissues, and the latter have been surrounding it with

barriers of new connective tissue, which make it increasingly difficult for remedies eventually to reach the parasite. If in the first instance the surgeon had caused a little serum to ooze from the margin of the sore by scraping it lightly with a scarifier, by rubbing it over with spirit and drying off the spirit, or by rubbing it fairly energetically with a dry swab, had allowed the serum to run into a capillary tube (such as is used for calf lymph), a procedure which is fully as easy as the taking of a blood specimen, and had then dispatched the specimen to a pathologist, a diagnosis in the case of syphilis would have been reached in practically every case within a few minutes of the opening of the parcel. Another mistake which is commonly made is to apply an antiseptic ointment to the sore when it is first seen, and some time later, when the sore takes on a suspiciously syphilitic appearance, to take the specimen for microscopical examination. If by any chance an antiseptic has been applied to the sore, and the specimen has to be posted, less time will be lost in the end if it is dressed for a few days with simple saline solution or boiled water, since the application of an antiseptic to the sore always causes the spirochaetes to retire to the deeper layers.

For over four years we have made a rule of microscopically examining the exudate from every sore, however trivial and unlike syphilis it may appear, and are convinced that is impossible for anyone, however experienced he may be, to recognize a syphilitic sore in its earliest stage without the aid of the microscope. This is the stage, however, in which, as we have said, it is of prime importance to commence treatment, and it follows that the surgeon who would do the best for his patient will never neglect this method of making an early diagnosis.

By repeatedly demonstrating the certainty with which a diagnosis of syphilis can be made by means of dark-ground illumination, by enlarging on the trivial appearance of many sores in which we have demonstrated the *Spirochaeta pallida*, and by frequently speaking in the presence of our patients of the advantages of early treatment, we have gradually educated the soldiers under our charge to take serious notice of the merest abrasions of the penis. Certainly the microscope often reveals no spirochaetes, and later events show that the sore was non-syphilitic; but, on the other hand, it is becoming more and more common for soldiers in the London District who are infected with syphilis to "report sick" when the sore is no larger than a split pea. It is worth the trouble of many negative examinations of non-syphilitic venereal sores to have the satisfaction of detecting one case in such an early stage, and commencing treatment at once. Circumstances make it, of course, easier to educate the soldier in these matters than the civilian, but we cannot help thinking that if all practitioners realized the value of an early diagnosis of syphilis and the ease with which it can be carried out, their knowledge would gradually be conveyed to the public.

In connexion with the examination of venereal sores another point may be mentioned here. Occasionally it happens that a patient is doubly infected by one exposure. A few days after exposure a soft chancre develops in which the *Spirochaeta pallida* is not discovered, but the patient subsequently develops secondary syphilis. The early stages of such syphilitic infections may easily be missed if a close watch is not kept on the sore, especially at the end of two to four weeks after it has made its first appearance.

It is not necessary to enlarge on the Wassermann test as a means of diagnosis. Of its value there can be no doubt, but the ideal treatment of syphilis commences before the Wassermann reaction is of any value in diagnosis, and the place of this test is properly in the subsequent observation of the patient.

TREATMENT.

The diagnosis having been made on the lines suggested above, it becomes necessary to lay down a programme of treatment and to see that it is carried out.

In the following remarks we shall speak of salvarsan rather than of neo-salvarsan, because we have chiefly worked with the older preparation. A short experience with neo-salvarsan inclined us to the belief that it is not quite so active as salvarsan in corresponding doses, but our chief reason for adhering to salvarsan is that neo-salvarsan is more easily oxidized than salvarsan, especially at high

temperatures, so that we did not think that it would be suitable for use in the tropics, and preferred to find out what could be done with a preparation which could be used wherever our soldiers serve.

It is hardly necessary now to produce further proof of the superiority of salvarsan and mercurial treatment over exclusively mercurial treatment. This is agreed upon by practically every one who has had an opportunity of comparing fairly the two methods, and we need only mention here the figures we produced at the International Congress of Medicine this year. These showed that of 378 patients treated exclusively with mercury in regular courses 83 per cent. relapsed clinically at least once during the first year, while out of 152 patients treated with two injections of salvarsan and nine injections of mercurial cream, or three of salvarsan and four of mercurial cream, only 3.9 per cent. relapsed clinically within a year of the suspension of treatment. Three months after the suspension of two years' regular mercurial treatment, out of 289 cases, more than 40 per cent. gave a positive reaction to the original Wassermann test, while twelve months after the suspension of a course of treatment with salvarsan and mercury, which lasted not more than nine weeks, 19.4 per cent. gave a positive reaction.

It is of the utmost importance that the patient be impressed with the necessity of undergoing a thorough initial course of salvarsan and mercury, and of subsequently submitting himself to periodical examinations. If the patient will not undertake to submit to a thorough and definite course of salvarsan and mercurial treatment, it would probably be wiser to withhold the salvarsan, since in this case the patient would generally be compelled by a succession of reminders to prolong his treatment over what is really a critical period.

In the early stages of salvarsan treatment a large number of cases in the early primary or secondary stage received a single injection of salvarsan, which caused the rapid disappearance of all clinical symptoms. Impressed by this and believing themselves to be cured, they refused further treatment, if such was advised. A very large proportion of these cases subsequently relapsed; in other words, became infectious again, and doubtless many of them transmitted the disease to others. Further, it is amongst these patients who received what we now know to have been a quite inadequate amount of treatment that practically all the cases of cranial nerve disturbance have occurred. It has been established by the researches of Dreyfus and others that the meninges are infected during the early stages of syphilis in a far larger proportion of cases than was ever imagined (83 per cent. according to Dreyfus), and it is clear that the first course of treatment must be calculated to prevent infection of the central nervous system. We cannot discuss here the question of cranial nerve disturbances being due to salvarsan poisoning as some have asserted. It is sufficient to say they occur for the most part amongst patients who have received considerably less salvarsan than is usual, and that when promptly recognized and treated with salvarsan before the nerve has become irrevocably damaged they almost invariably recover. The only two cases of the kind which we have had support these remarks, since both of them received much less salvarsan than we are in the habit of administering.

It may be said here that it is easy to prescribe a thorough course, but it is another matter to get a free and independent patient to carry it out. We grant that it is a much more difficult question with civilian patients than with military, but if the medical adviser thoroughly believes in the truth of his advice he can do a great deal towards making his patient carry it out.

Another question of interest is the safety to life of salvarsan injections. We consider that when due regard is paid to the precautions which we will shortly mention it is fully as justifiable to recommend a salvarsan injection as a mercurial. No death or symptom causing any alarm has followed any of the 3,800 injections which have been given at the Military Hospital, Rochester Row. Out of some thousand injections which have been given at the Portobello Military Hospital, Dublin, there has been one death, and out of nearly 6,000 injections given by American army surgeons, one death can be attributed to salvarsan. In each of these cases the death followed the second of two injections given within fourteen days of one another.

For ourselves, we think that the administration of salvarsan is safe enough to justify its recommendation in all ordinary cases of syphilis.

Precautions in Special Cases.

There are cases in which it is advisable to proceed cautiously, and amongst these we would include all suffering from disease of the central nervous system, of the heart, lungs, or other viscera. In these it may be necessary to commence with 0.2 to 0.3 gram salvarsan, and so to administer the total amount of salvarsan considered necessary by means of a number of small injections rather than in a few larger ones. We make a practice of examining the urine of every patient before injecting salvarsan, and when albumin is found administer a first dose of 0.2 to 0.3 gram, according to the condition found, and repeat the dose or slightly increase it a week later if the first injection produced no untoward symptoms. Neisser recommends that in all cases a cautious start should be made so as to make sure that one is not dealing with an idiosyncrasy to salvarsan. This can, of course, always be done provided that in the end the patient receives in a reasonable time the total amount which is considered adequate, but in ordinary cases of syphilis, where the patient appears to be otherwise healthy, we prefer to give the total amount of salvarsan which we consider necessary for one course in a few full doses rather than subject the patient more frequently to the inconvenience of preparation for and the after-treatment which an intravenous injection of salvarsan entails.

Considerations Concerning the Intervals between Doses.

Another question connected with the safety of salvarsan concerns the intervals of time at which full doses can be injected. It has been the practice of some surgeons to give full doses at intervals as short as forty-eight hours, but more and more are now advocating longer intervals than this. Quite possibly in the great majority of cases it may be safe enough to give two injections of 0.6 gram within two days of one another, but, as far as we can judge from the literature, in practically every one of the cases in which epileptiform convulsions followed by coma and death on the fourth or fifth day after an injection has occurred, it was after two or more full doses had been administered at an interval which was something less than fourteen days. The number of cases in which these symptoms, which we think must be attributed to salvarsan poisoning, have followed the first injection must be very small, since we had been able to find records of only three. It seems to us, therefore, that we have to reckon with a very occasional idiosyncrasy to salvarsan, and that this is manifested practically only when the remedy exercises a cumulative action. There is no point in running even the very slight risk of such a calamity as we have described if it can be avoided by sufficiently spacing out the injections, and, for reasons given below, we think that the periods between full doses of salvarsan can be lengthened to more than fourteen days without lessening the therapeutic effect if mercurial injections are given in the intervals.

Preparation and After-Treatment.

The preparation and after-treatment of patients are of some importance to the safety of salvarsan. We recommend the administration of a purgative on the night before, and allow no food for four hours previous to an injection. The patient is made to rest in bed till the following day, being allowed solid food for the first time three to four hours after the injection, provided there is no vomiting or diarrhoea. Though he gets up on the following day, the patient is not allowed to do anything more than lounge about. Possibly this is an excess of caution, but a certain proportion of patients have a slight rise of temperature on the second evening, and it is from those who have dined out, gone to the theatre, or otherwise dissipated on the second day that we have had the most complaints of slight malaise and headache for a few days after the injection.

Our principle in regulating the intervals between doses is based on the following conception:

That the first full dose probably destroys every *Spirochaeta pallida* which it can easily reach through the

circulation, but that in the midst of infiltrated areas a certain number of spirochaetes escape complete destruction since the remedy does not reach them properly.

That after the first injection the surviving spirochaetes remain inactive; nature begins to remove the infiltrations which resulted from the previous activity of the parasite, and in doing so sets free the spirochaetes buried there. This process of repair, as is well known, takes a few weeks (witness the length of time the induration remains round a well-developed primary sore), and until it is fairly well advanced it seems to us that another dose of salvarsan is practically wasted.

That it is necessary to ensure that as these sclerosed areas are opened up and the spirochaetes within them are freed the latter are allowed no headway. This we think can be done by keeping a containing force in the form of a small amount of mercury continually circulating in the blood.

Our conception may be quite wrong, but is supported by this, that in a large proportion of relapses the symptoms which characterize the relapse are an exact reproduction of those for which the patient first sought treatment. This is especially marked in primary cases, in which the relapse is very frequently manifested by a return of the primary sore without other symptoms.

Plan of Course.

Regarding the course which can be considered the minimum, it is as yet impossible to speak quite definitely, since we have not been able to devise one course which is at once the most economical and followed by no relapses. We have administered salvarsan or salvarsan and mercury on certain definite plans to successive series of cases, and have subsequently followed the progress of as many of our patients as possible in order to determine which plan of treatment is followed by the smallest proportion of relapses. The results of our investigation on these lines have been published from time to time and were read to the International Congress of Medicine this year. They dealt with the following schemes:

1. A single intramuscular injection of salvarsan.
2. Two intravenous injections of 0.6 gram salvarsan at an interval of a fortnight.
3. An intravenous injection of 0.6 gram salvarsan, followed at intervals of fourteen days by three intravenous injections of 0.3 gram salvarsan.
4. Three intravenous injections of 0.6 gram salvarsan at intervals of fourteen days, with four weekly injections of calomel, all within the same month.
5. An intravenous injection of 0.3 gram salvarsan, followed by nine mercurial injections, and lastly, an intravenous injection of 0.3 gram salvarsan.
6. An intravenous injection of 0.6 gram salvarsan, nine weekly injections of mercurial cream, and lastly, an intravenous injection of 0.6 gram salvarsan.
7. An intravenous injection of 0.6 gram salvarsan, five weekly injections of mercurial cream, a second intravenous injection of 0.6 gram salvarsan, five more mercurial injections, and lastly, an intravenous injection of 0.6 gram salvarsan.

Disregarding (5), which proved an utter failure, the use of mercury in conjunction with full doses of salvarsan gave better results than the exclusive use of salvarsan. The last course mentioned (three salvarsan and ten mercurial injections) promises to give the best results of all, though we have not yet treated a sufficient number of cases to judge its merits fairly. This course is more intensive than one consisting of two salvarsan and nine mercurial injections, which our tables showed to have given the best results up to date. It can, therefore, be expected to be followed by fewer relapses, and as it is necessary to improve on the course of two salvarsan and nine mercurial injections, which was followed by 5 per cent. clinical and 18 per cent. Wassermann relapses within twelve months of suspending treatment, we can only consider that for the present the minimum course should consist of three salvarsan and ten mercurial injections distributed in the manner we have described.

In cases in which it is necessary to make a cautious start by giving 0.2 to 0.3 gram salvarsan, provided that the patient has shown no untoward symptoms after the first dose, we inject the balance to make up 0.6 gram within five to seven days of the first injection. When the central nervous system is obviously involved, although it is neces-

sary to commence cautiously, the total amount of salvarsan administered in one course should be greater (even double the amount) than that which is given in ordinary cases, and the cerebro-spinal fluid should be examined at the end of the course.

In primary cases it is important to treat the sore, either by excision, cautery, or with calomel ointment. This is the order of preference, and the choice must depend on the site of the sore.

All Cases to be Kept under Observation.

Subsequent observation of the patient is indispensable. As a routine measure in dealing with soldiers we excuse attendance for three months after the first course, as we have found that relapses do not occur during this period. At the end of three months a clinical examination is made and the blood tested for the Wassermann reaction by the original and by Stern's method. Subsequently, in secondary cases a clinical examination is made every month, and the blood is tested every three months till the end of the first year. In primary cases a clinical examination is made every month for three months, and then every three months till completion of the period of observation, the blood being examined every three months as in secondary cases.

Our practice during the second year varies with the nature of the case when first treated. Primary cases are excused further attendance when the blood has continuously given a negative reaction, and there have been no clinical signs for twelve months after suspension of treatment. Secondary cases are observed at regular intervals throughout the second year. A patient is considered to have relapsed, and to require further treatment, if at any time he either shows clinical signs of syphilis or his blood serum gives a positive Wassermann reaction.

In case of relapse, there is a temptation, especially if the only manifestation is a weakly positive Wassermann reaction, to prescribe only a single dose of salvarsan, in the hope that this, added to the previous treatment, will complete the defeat of the spirochaete. We think this a mistake, and that, on the slightest sign that the disease is not eradicated, the patient should receive a course which is as strenuous as, or more strenuous than, that at first prescribed.

Standard of Cure.

There is nothing more difficult than the laying down of a standard of cure for syphilis. It is well known that absence of clinical signs for many years is of little value, and the Wassermann test is of too recent date to enable us to judge what reliance we can place on a series of negative reactions.

As a routine measure we have adopted the standard mentioned in speaking of the observation of patients—that is, in primary cases twelve months, and in secondary cases two years, freedom from signs, clinical or Wassermann, from the date of the last injection.

In a number of special cases, such as when the patient wished to marry at an early date, we have given the provocative injection of a small dose of salvarsan, followed by three blood tests at intervals of two, six, and thirteen days, which has been advocated by Gennerich and by Milian, but in only one did the previously negative serum become positive, and we have not adopted it as a routine test for cure.

SUMMARY.

We have endeavoured in the above remarks to convey our views as to the lines on which we think early cases of syphilis should be managed. Summed up, they amount to this:

1. Commence treatment in the early primary stage whenever possible.
2. Destroy the primary sore whenever possible and insist on the patient receiving not less than three salvarsan and ten mercurial injections in the manner described.
3. On no account neglect subsequent observation, and prescribe a definite course which is just as strenuous as in the first instance if the patient shows the least sign, clinical or Wassermann, that his disease has not been eradicated.
4. Be cautious about pronouncing a patient cured in any case, but certainly do not do so till he has continued free from all signs, clinical or Wassermann, for at least a year.

after suspension of treatment in primary cases, and two years in secondary cases.

The price of salvarsan and the amount of special work which such a scheme entails make it inapplicable under present conditions to patients in poor circumstances, but it is hardly necessary to say that the control of syphilis in its earlier stages affects the lives and happiness of a sufficiently large percentage of the population, present and future, to make it of national importance.

When we had to rely on mercury, it was practically hopeless to attempt such a control, but with salvarsan, which renders the patient non-infectious so quickly, and has so markedly shortened the duration of treatment, our course, though still difficult, has become clearer, and it is not too much to hope now that we shall be assisted with adequate measures in removing a great curse from our midst.

II.

THE TREATMENT OF SYPHILIS AT THE ROYAL NAVAL HOSPITAL, CHATHAM :

RESULTS DURING THE LAST TWO AND A HALF YEARS,
AND THE INFERENCES TO BE DRAWN
FROM THEM.

By SURGEON GILBERT BODLEY SCOTT, R.N.

To those members of the medical profession who have not had much experience in the modern treatment of syphilis, and who are considering it from the practitioner's point of view, the following observations may be of value.

During the period in which I was in charge of this work 1,100 cases were treated by salvarsan and neo-salvarsan and 2,500 injections were given. For its proper control Wassermann reactions are necessary, and in the period mentioned over 3,000 reactions were carried out.

There are between 108 and 130 beds at Chatham Hospital set apart for venereal disease only. The cases come from ships, chiefly in the North Sea, and the disease is contracted at the various ports on the East Coast of Scotland and England. In addition every few months batches of invalids arrive from ships abroad.

VARIATIONS IN VIRULENCE.

Three points in the incidence of the disease are worth mention. Some towns produce a much more virulent infection of syphilis than others do, and I always consider that the Bombay and Gibraltar infections are not only much more severe than English and Scottish, but are not so amenable to mercury. Syphilis contracted in China will produce in Europeans a very rapid and virulent form of the disease.

This geographical factor should undoubtedly influence the initial intensity of the treatment, its duration, and the prognosis. By prognosis I do not mean danger to life, but likelihood of relapse to active disease and a permanent positive Wassermann reaction.

EXTRAGENITAL INFECTION.

The treatment of extragenital chancres is influenced in the same manner. I have found that the fingers and lips are the most frequent sites.

Naval medical officers thoroughly realize the danger of lip infection on board ship, and men liable to pass on the infection are segregated in the sick-bay or sent to hospital.

Were this precaution not taken lip chancres would be far more frequent. It is just as necessary to instruct syphilitic patients in the prevention of the spread of disease as it is the tuberculous. The old stone fountain and chained drinking cup must have caused in hot weather many cases of syphilis and other communicable diseases. The prevention of finger chancres lies not with the removal of offending nails, splinters of wood, and other excuses, but in improving the morals of man.

DIAGNOSIS.

The early diagnosis of syphilis is of vast importance, and the bearing on the treatment, the prognosis, and the patient's life is not yet properly realized by three-quarters of the medical profession and not at all by the public.

If there is to be no return to the Contagious Diseases Act of 1864, then the abolition of the hidden plague in relation to syphilis must still lie in the treatment of men and women immediately they become sources of danger. Early diagnosis and treatment must go hand in hand, and to carry out this ideal successfully some kind of institution analogous to the tuberculin dispensary must be formed.

Importance of Early Diagnosis.

I will take the subject of early diagnosis first and summarize beforehand what I am going to say.

1. For our purpose the diagnosis by the Wassermann reaction is practically useless.
2. The only useful means of diagnosis of early syphilis is the demonstration of the *Spirochaeta pallida*.

I am firmly convinced that if all cases of syphilis were examined in the first stage of the disease, and in the first few days of that stage, before antiseptics have been applied, the spirochaete could and would be easily found.

I am also firmly convinced, although I cannot give definite proof, that if these early cases are treated by two or three injections of salvarsan or neo-salvarsan and a short course of mercury, 99 per cent. of these will be cured.

When once the Wassermann reaction has become positive or the sore hard and indurated this treatment will not cure more than 60 per cent., and I should remain doubtful of that 60 for the next fifteen years.

If, however, a prolonged course of mercury—two to three years, with intermissions—is given to these cases in conjunction with salvarsan, a better outlook is obtained.

Not many years ago we allowed our patients to reach the secondary stage before we made a diagnosis and treated them. What would be said if we to-day waited to see if secondary deposits of cancer occurred in the liver in a suspected case of epithelioma of the lip, or a tumour in the region of the appendix to burst before diagnosing an abscess?

It sounds ludicrous, but it is really not more absurd than at the present day to wait for a positive Wassermann reaction or secondary symptoms. I am of the opinion that when once a man has developed secondary syphilis at least 60 per cent. of his chances of being cured have gone. When the disease has been established for a year I do not believe there are more than 20 per cent. in whom a cure is effected or in whom the infection dies out. I except from this statement McDonagh's method of treatment, because I have had no practical experience of its results and am not qualified to give an opinion. Why should we condemn our patients to such a poor outlook when early diagnosis and treatment give such a good one?

Demonstration of the Spirochaete.

The diagnosis of early syphilis by demonstration of the spirochaete is easier than examining for tubercle bacilli in the sputum.

The methods are two: (1) By Chinese ink; (2) by the dark-ground illumination. Both these methods are described in any book dealing with laboratory work, but a laboratory is not required, only the most simple apparatus, a microscope, and experience in recognizing the various forms of spirochaete.

If we do not get our patients in this early stage these methods are still easily employed, provided that no antiseptic has been applied to the sore, and that it is not a healing one.

Under these two latter conditions a diagnosis must be made from its character or by Wassermann's reaction. A hard indurated sore, if not malignant, is almost certainly syphilitic. A soft shallow one more often turns out to be syphilis than "chancreoid." Therefore, the nature of a soft sore cannot be diagnosed by its appearance.

Date of Wassermann's Reaction.

Wassermann's reaction becomes positive about three to four weeks after the appearance of the sore in most cases. Sometimes it is earlier, sometimes later. I refer here to reactions done by Fleming's method, or the original when using cholesterin antigen.

The appearance of the reaction probably means that the infection has passed beyond the local stage, that it is