

## ORAL AMPICILLIN IN UNCOMPLICATED GONORRHOEA

### I. Treatment of Gonococcal Urethritis in Men

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**Abstract.** This article is the first in a series concerning ampicillin in the treatment of gonorrhoea. A comparative investigation of ampicillin and penicillin G in the treatment of gonococcal urethritis in men is presented. During 1 year, 938 patients were treated with one intramuscular injection of penicillin G. During the following year 1 150 patients were treated with oral ampicillin in three different dosage schemes. More than 20% of the patients were harbouring gonococci less sensitive to penicillin G. The statistical evaluation showed that treatment with oral ampicillin, either as 2 g together with 1 g of probenecid in a single dose or as 2 g in two divided doses given with a 5 hour interval (1 day treatment), was equivalent to the routine treatment with one intramuscular injection of 2.2 MIU penicillin G (1.0 MIU Na salt + 1.2 MIU procaine salt). Two grammes of ampicillin in a single dose was an inferior alternative. Thus the patients in the 1 day treatment group must have taken the prescribed second dose. The percentage of treatment failure was consistently lowest for ampicillin in divided dose. Side-effects to ampicillin have been registered in 3 patients. The sensitivity of the gonococcal strains to penicillin and the age distribution have been taken into consideration during the 2 years of examination.

In many parts of the world gonococcal infection is a growing problem. In Sweden the incidence rose by 14% during 1969 with almost 34 500 new cases reported. From South Vietnam and the Philippines, for example, a higher frequency of gonococci with low sensitivity to antibiotics is reported (37).

It also seems that many cases are more serious than one was earlier prone to believe. Gonococcal septicaemia has been reported to appear in approx. 1.9% of the cases (5). Asymptomatic gonorrhoea exists not only in females but also in males and serves as a gonococcal pool (25, 26, 34, 35). An undiagnosed or inadequately treated case of uncomplicated gonorrhoea may appear as a case

of prostatitis, epididymitis, salpingitis, arthritis or sepsis in a later phase of the disease, besides causing infections in contacts.

The present routine therapy for uncomplicated gonococcal urethritis (consisting of penicillin G in a single intramuscular injection) is still very effective in most parts of the world. Penicillin injections are impractical, however, and may give rise to serious allergic reactions. Idsöe et al. (19) found 151 fatal cases of anaphylactic reactions to penicillin reported in the literature. Only 3 of these were caused by oral penicillin preparations and 123 occurred after a single injection of penicillin G.

The search for an oral alternative in the treatment of gonorrhoea is therefore warranted. To be accepted as an alternative to the present routine therapy, a preparation should at least fulfil the following requirements:

1. Oral medication with at least the same efficacy as the present intramuscular dose.
2. Effective in a single dose or in two doses on the same day.
3. Low toxicity even at high doses.
4. Fewer and less serious allergic reactions than with penicillin G injections.
5. Low incidence of strains with low sensitivity.

Ampicillin seems to be the only penicillin fulfilling these requirements from a bacteriological point of view (39). While "normally" sensitive gonococcal strains seem to need approximately twice as much ampicillin as penicillin G to be inhibited, the relation is the opposite in less sensitive strains (38, 49). According to Halverson et al. (17) ampicillin showed a narrower spectrum of

Table I. Male patients treated for gonococcal urethritis during July 1967–June 1968

Treatment	No. of patients
Penicillin G	
(positive culture; sensitivity test)	922
(positive culture; no sensitivity test)	9
(positive smear; negative culture)	7
Tetracycline	122
Treated but not followed	54
Total	1 114

Table II. Male patients treated for gonococcal urethritis during October 1968–September 1969

Treatment	No. of patients
Ampicillin	
(positive culture; sensitivity test)	1 122
(positive culture; no sensitivity test)	4
(positive smear; negative culture)	24
Tetracycline	35
Treated but not followed	98
No treatment	2
Total	1 285

activity than penicillin G against 323 gonococcal strains. 96.6% of the strains had MIC values of 0.5 µg/ml or less for ampicillin, whereas the corresponding figure for penicillin G was 79.6%.

The bacteriological results are supported by positive experiences in clinical trials. Ampicillin has been tried in various dosages and forms of administration as well as in combination with other drugs. Gjessing & Ödegaard (14) noted a failure rate of 3% with a combination of 1 g ampicillin orally plus 600 000 IU procaine penicillin G compared with 11.6% with procaine penicillin G only. Keys et al. (22) state that intramuscular ampicillin in combination with oral probenecid may become the drug of choice for gonorrhoea. 105 of 106 patients with gonococci showing a marked in vitro insensitivity to penicillin and other antibiotics were cured with 2 g of ampicillin sodium in a single intramuscular dose combined with orally administered probenecid.

Ampicillin given in a single oral dose has been tested by Willcox (44, 45, 46), Alergant (2), Marmell et al. (31) and McLone et al. (32). Though Alergant (2) reports a good result with

only 5% failures, most trials with single dose regimens show more disappointing results. Nevertheless, one oral dose of ampicillin gives better results than the same dose of pheneticillin or a higher dose of penicillin V (45).

Two doses of ampicillin orally have been reported to give results comparable to i.m. treatment with penicillin G (15, 45). Oral ampicillin as a single dose regimen combined with probenecid has also given results at least as good as 2.2 MIU of a combination of sodium and procaine penicillin G (16).

A large number of patients present themselves for suspected gonorrhoea at the Outpatient Clinic for Venereal Diseases of Södersjukhuset every year. They are representative of a metropolitan clientele in that many neglect to come for re-examination or may wait several weeks before coming to the first follow-up; others, despite reminder, do not come to a single re-examination. Not so few are abusers of alcohol and narcotics. Many have been previously treated for gonorrhoea on one or more occasions.

Having regard to the category of patients, antibiotics in a single oral dose would be the best form of treatment. It is known that to a large extent patients fail to follow a given prescription (18) and tablets are given to others, with the risk of an increase in the number of undiagnosed and incompletely treated cases harbouring gonococci, and of increased resistance to antibiotics.

Would this category of patients take a prescribed second dose 5 hours after the first? The motivation for taking the second dose should be sufficiently great. In country districts it has been found that patients do take the second dose (15). In this study, however, a very thorough examination could be made of the individual cases with positive culture at re-examination, and in most cases it could be definitely established whether there was a treatment failure or reinfection.

In order to discover whether brief oral ampicillin treatment was an equivalent or better form of therapy than the routine use of a single intramuscular injection of penicillin G, it was decided to compare with one another and with the earlier routine treatment the results of a high single oral dose of ampicillin, a high single oral dose of ampicillin combined with probenecid, and 1 day treatment with divided dose of ampicillin. This comparison was in the first place to be made on

male patients. If the result was favourable, the investigation was to be extended to the female material at the clinic (9). A comparison was also planned of the results of the various forms of treatment in cases with initially positive gonococcal culture in the rectum (10) and likewise between the clinical results on the one hand and the pharmacological and bacteriological on the other (11, 12). In collaboration with Astra Research Laboratories, therefore, an absorption study in cross-over design has been made with the doses in question, and the bacteriological laboratory of the hospital has determined the sensitivity to antibiotics in each case. The present study is concerned with oral ampicillin treatment of men.

### MATERIAL AND METHODS

The diagnosis of uncomplicated gonorrhoea was made on 1114 male patients in the 1 year period 1967-68 (Table I) and on 1285 in 1968-69 (Table II). Samples for direct microscopy and culture were collected at all visits. In vitro antibiotic susceptibility tests were done on all positive cultures. Only patients with positive culture were included in the evaluation of the results.

The trials with oral ampicillin treatment started in the autumn of 1968 (Table II). The patients were divided at random into three groups (Table III). Group A was given a high single oral dose of 2 g ampicillin (Doktacillin®, Astra Läkemedel AB, Sweden). In group B the high single dose was potentiated by probenecid, i.e. 2 g ampicillin + 1 g probenecid (Probecid®, Astra, Sweden). Group C was given the same quantity as group A but on a divided dose basis, i.e. 1 g ampicillin in the Outpatient Clinic and 1 g 5 hours later.

Penicillin G treatment in a fourth group was abandoned, as it was realized that the patients' aversion for injections would make it difficult actually to give every fourth patient an injection.

Table III. Modes of treatment and number of patients in each group

Patient group	Treatment	No. of patients
G	2.2 MIU penicillin G intramuscularly (1 MIU Na salt + 1.2 MIU procaine salt)	922
A	2 g ampicillin orally	379
B	2 g ampicillin + 1 g probenecid orally	364
C	1 g + 1 g ampicillin orally with 5 hour interval	379

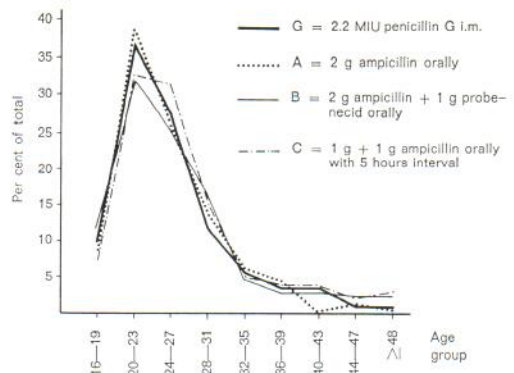


Fig. 1. Age distribution in the different treatment groups.

It was therefore decided to compare ampicillin treatment during a whole year with the previous year's penicillin G treatment, 2.2 MIU penicillin G i.m. = 1.0 MIU Na salt + 1.2 MIU procaine salt (Gonocillin®, AB Leo, Sweden). Great care was taken not to change any feature in the routine of treatment and follow-up of the gonorrhoea material, apart from the recording of side-effects.

In the evaluation, patients with two or three negative follow-up cultures have been counted as *satisfactory* and patients with positive culture at the first check within 14 days or with first or second culture positive within 21 days as *treatment failure*. Only very probable reinfections (contact positive) have been excluded.

A statistical calculation has also been made in which positive culture at first follow-up and positive culture at first or second follow-up have been counted as treatment failure irrespective both of the time of the examinations and of whether reinfection existed or not.

Determination of the sensitivity of the gonococci to penicillin G, chloramphenicol and tetracycline was routinely done by the diffusion method reported by Ericson et al. (8). Furthermore, tests were carried out against streptomycin during the first and against ampicillin during the second year of the trial.

The patients were also divided into two groups according to the sensitivity of the gonococcal strains to penicillin G and ampicillin, namely fully and less sensitive. Strains with MIC  $\geq 0.1$  IU penicillin G and  $\geq 0.1$   $\mu$ g ampicillin per ml have been denoted as less sensitive strains.

The statistical analysis was done in cooperation with the Statistical Research Group at the University of Stockholm. The  $\chi^2$  test was used. Significance limits for the  $\chi^2$  values are:

	$\chi^2 < 3.841$	for	$P > 0.05$
*	$3.841 < \chi^2 < 6.635$	for	$0.01 < P < 0.05$
**	$6.635 < \chi^2 < 10.827$	for	$0.001 < P < 0.01$
***	$\chi^2 > 10.827$	for	$P < 0.001$

Yates' correction has been used, and for small groups the Fisher-Yates' test.

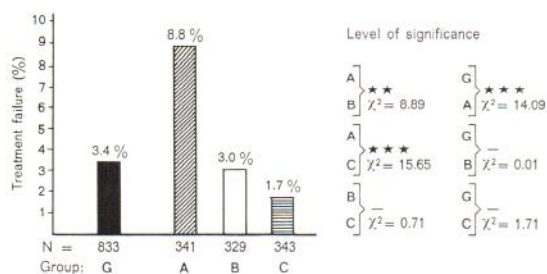


Fig. 2. Result of treatment (all patients). Satisfactory: 2 or 3 negative follow-up cultures. Treatment failure: positive culture at follow-up I within 14 days.

## RESULTS

The number of male patients in the analysis (Table III) is 2 044, of whom 922 were treated with penicillin G (group G) and 1 122 with ampicillin, 379 of whom with a high single dose of ampicillin (group A), 364 with a high single dose of ampicillin combined with probenecid (group B) and 379 by 1 day treatment with ampicillin, i.e. the same quantity as group A but in a divided dose with a 5 hour interval (group C).

The age distribution will be seen from Fig. 1 and shows close conformity of the various groups.

The incidence of all gonococcal strains with reduced sensitivity to penicillin G isolated at the Bacteriological Laboratory at Södersjukhuset in 1967–68 was 23.3% and, in 1968–69, 26.5%. The frequency of strains with reduced sensitivity to penicillin G in the statistically evaluated material in this paper, is for the 2 years 1967–68 and 1968–69 approx. 24.4%.

Fig. 2 shows the results of treatment of the four groups, all patients possible to evaluate being

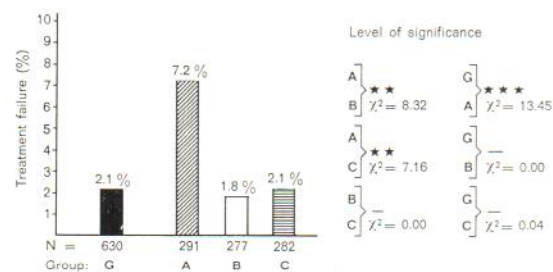


Fig. 3. Result of treatment in patients harbouring sensitive strains ( $MIC < 0.1$  IU penicillin G/ml and  $< 0.1$   $\mu$ g ampicillin/ml). Satisfactory: 2 or 3 negative follow-up cultures. Treatment failure: positive culture at follow-up I within 14 days.

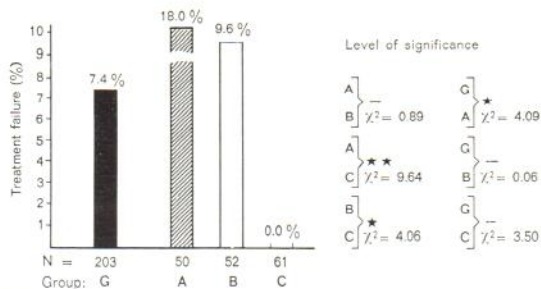


Fig. 4. Result of treatment in patients harbouring less sensitive strains ( $MIC \geq 0.1$  IU penicillin G/ml and  $\geq 0.1$   $\mu$ g ampicillin/ml). Satisfactory: 2 or 3 negative follow-up cultures. Treatment failure: positive culture at follow-up I within 14 days.

included, and with positive culture at first follow-up within 14 days counted as treatment failure. The results for group G is seen to be better than those for A ( $P < 0.001$ ). Between groups G and B and between G and C, on the other hand, there is no significant difference. A comparison within the ampicillin material shows better results both for B and C than for A ( $0.001 < P < 0.01$  and  $P < 0.001$  respectively), while there is no significant difference between B and C.

The same comparison, but only as regards sensitive strains (Fig. 3), shows almost the same result. The difference is, however, smaller between A and C ( $0.001 < P < 0.01$ ).

The same comparison, but as regards reduced sensitivity to the respective penicillins (Fig. 4), shows that the difference between groups G and A has diminished,  $0.01 < P < 0.05$ . Within the ampicillin groups, C shows the best result. The difference between A and C is significant on the  $0.001 < P < 0.01$  level and, between B and C on the  $0.01 < P < 0.05$  level.

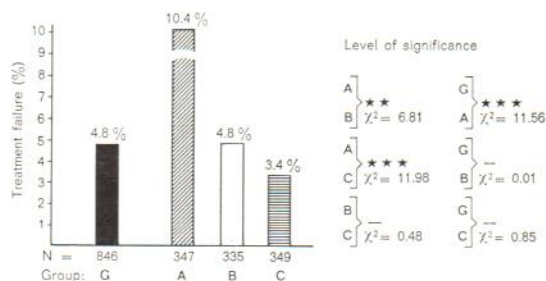


Fig. 5. Result of treatment (all patients). Satisfactory: 2 or 3 negative follow-up cultures. Treatment failure: positive culture at follow-up I or II within 21 days.

Counting as treatment failure, positive culture at the first or second follow-up within 21 days (Fig. 5), and comparing the various treatment groups, the statistical results are roughly the same as for follow-up within 14 days (Fig. 2) as regards the total material.

Comparing the failure group 21 days after treatment in cases with sensitive strains (Fig. 6) with the corresponding group 14 days after treatment (Fig. 3), the result is largely the same. Group A still seems to be least favourable, but the differences are smaller between G and A ( $0.001 < P < 0.01$ ), between B and A ( $0.01 < P < 0.05$ ) and between C and A ( $0.01 < P < 0.05$ ).

Cases with less sensitive gonococci show roughly the same results at the check-up within 21 days (Fig. 7) as at that within 14 days (Fig. 4), but the difference between B and C has disappeared.

Comparing the various groups and, as earlier, counting patients with at least two negative cultures as satisfactory and, as treatment failure, patients with positive culture at first follow-up and with positive culture at the first or second follow-up irrespective of time or reinfection, the results are essentially the same as in previous comparisons (Table IV).

*Side-effects*

Owing to incomplete hospital records it has not been possible to report the number and type of side-effects of penicillin G treatment in 1967-68. During 1968-69, when ampicillin was used, the patients were questioned about side-effects at follow-up. Three of 1 150 patients reported side-effects.

*Case 1.* Two days after a single dose of ampicil-

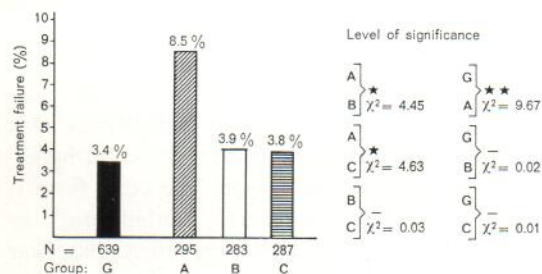


Fig. 6. Result of treatment in patients harbouring sensitive strains (MIC < 0.1 IU penicillin G/ml and < 0.1 µg ampicillin/ml). Satisfactory: 2 or 3 negative follow-up cultures. Treatment failure: positive cultures at follow-up I or II within 21 days.

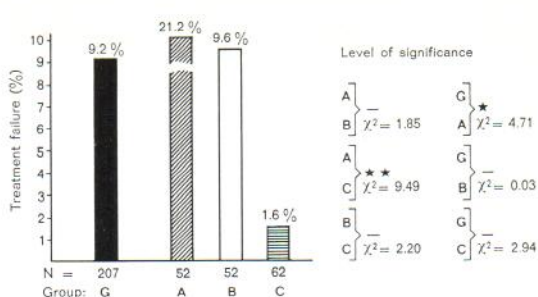


Fig. 7. Result of treatment in patients harbouring less sensitive strains. (MIC ≥ 0.1 IU penicillin G/ml and ≥ 0.1 µg ampicillin/ml). Satisfactory: 2 or 3 negative follow-up cultures. Treatment failure: positive culture at follow-up I or II within 21 days.

lin (group A) diarrhoea and small eruptions on the lips. No objective symptoms when examined 7 days later. Eleven days before this treatment the patient had received a single injection of penicillin G for gonorrhoea without complication.

*Case 2.* General exanthema 3 days after ampicillin in divided dose (group C). Serum sickness when re-examined 7 days later. About 6 months earlier the patient had been treated for gonorrhoea with the combination of ampicillin and probenecid in a single dose (group B) without complication.

*Case 3.* One hour after a single dose of ampicillin (group A) a feeling of swelling in the throat and difficulty in breathing. Asymptomatic 1 hour after hydrocortisone i.v. and antihistamine i.m. Not known whether the patient had been earlier treated with penicillin.

DISCUSSION

*Choice of therapy*

The Swedish standard treatment for uncomplicated gonorrhoea with an intramuscular injection of

Table IV. Findings at follow-up in all evaluated cases

Treatment group	Number of negative cultures		Positive culture at follow-up number		
	1	2 or 3	I	I or II	III
G	50	805	43	60	7
A	19	311	36	46	3
B	16	319	15	26	3
C	17	337	11	17	8

*penicillin G* has shown satisfactory results (13, 15, 26, 38).

The *tetracyclines* were earlier recommended in high doses during 5–8 days but have recently been tried also in one or alternatively two doses (27, 48). In most parts of the world a fair proportion of the gonococcal strains are initially less sensitive to tetracycline and a rather quick development of resistance has been reported. An antibiotic with bactericidal effect is to be preferred with short-time administration (3, 7, 20, 41).

The *sulphonamides* were used early for treatment of gonorrhoea and may still be very useful in the treatment of patients infected with sensitive strains which have been found resistant to the commonly used antibiotics. A more common use would most probably lead to a renaissance of the high incidence of sulphonamide-resistant gonococcal strains earlier noticed (4).

The *cephalosporines* have been reported to give promising results (29). Keys et al. (22) achieved less encouraging results in a clinical study using 2 g of intramuscular cephaloridine in 97 patients and also report a rather high level of resistance with a median value for MIC of 7  $\mu\text{g/ml}$  compared with 0.25  $\mu\text{g/ml}$  for penicillin G and ampicillin. The allergic cross-reactions with penicillin have also to be considered (1, 43).

The *rifamycines* have also been tried in gonorrhoea and Willcox (1968) reports promising results with rifampicin. The rifamycines should perhaps be reserved for tuberculosis and certain infections resistant to other therapy as long as there are other drugs with satisfactory activity against gonococci.

The *aminoglycosides*, streptomycin and kanamycin, cannot be recommended for routine therapy because of their ototoxic effect, but may still have a place singly or combined with other antibiotics in special cases.

The different *oral penicillin preparations* have also been evaluated in the treatment of gonorrhoea (45, 47).

The earlier experiences with *ampicillin* in clinical trials are discussed above.

The simultaneous administration of *probenecid* affects the duration of ampicillin and other semi-synthetic penicillins in serum. Since the secretion of these antibiotics by the tubules may be inhibited by probenecid, an elevation of the am-

picillin concentration in serum is attained (28). A satisfactory clinical effect on uncomplicated gonorrhoea with strains of reduced sensitivity has recently been reported with sodium penicillin G intramuscularly and probenecid orally (22, 33). The combination of ampicillin and probenecid in oral form has, as already noted, also been reported to yield satisfactory results in uncomplicated gonorrhoea (16).

Penicillin–probenecid combinations administered for several days (in streptococcal infections) proved to provoke a remarkably high incidence of allergic reactions (6, 40). The incidence of these reactions seemed to be related to the duration of therapy rather than to the amount of probenecid given (6). This duration/response ratio might explain the low incidence of allergic reactions to treatment with the ampicillin–probenecid combination in a single dose.

The low toxicity, which the penicillins have in common, permits administration of very high doses. The allergic reactions with penicillin G have already been discussed.

The reported frequency of "drug rashes" with ampicillin varies from less than 1% in gonorrhoea patients treated with 1–2 g in one or two doses (15, 16, 47) to 95% in 19 patients with mononucleosis (36).

In a complete survey of the published clinical literature (23) including 13 638 patients treated with ampicillin, 2.8% of the subjects were reported to have had skin eruptions of one kind or another.

Consideration of the type of infection associated with the higher incidence of rashes might suggest that the use of ampicillin for the treatment of conditions that in themselves are often associated with a rash (typhoid and paratyphoid fever, mononucleosis etc.), tends to increase the overall incidence of skin eruptions (24).

The rashes with ampicillin, as with other penicillins, seem to present in two main forms. One form, probably representing true penicillin hypersensitivity, is of urticarial type. The other form is of an irritant erythematous "morbilliform" or maculopapular type which may often disappear if the course of treatment is continued. It has been questioned whether the latter type of rash has an immunological or allergic origin.

The erythematous rash might also be associated with rapid lysis of intestinal organisms, due to the

bactericidal action of ampicillin with release of endotoxins (39) or "skin-sensitizing" agents (24).

In our continued investigations we are (since November 1969) using ampicillin purified from immunogenic protein impurities and have so far seen no further "drug rashes" in connection with the treatment for uncomplicated gonorrhoea. In one clinical series of 2 145 patients (24) this type of purification has been found to reduce the frequency of "drug rashes" with ampicillin from 3.1% to 1.4%. This reduction seems to concern mainly the group of erythematous "morbilliform" or maculopapular type of rash, which further stresses the question of the origin and implications of this type of rashes.

#### *Dosage in the various groups.*

The importance of high serum concentrations for gonorrhoea treatment has been pointed out (26). The concentration should preferably be at least 5 times above the MIC for the bacterial strain. Therapy type A was chosen in order to obtain a high serum concentration. A dose of 2 g ampicillin should be sufficiently high according to earlier absorption studies (30). With type B therapy the intention was to reinforce the high single dose of ampicillin (2 g) by probenecid (1 g). By simultaneous administration of probenecid one can count on attaining almost twice as high a serum concentration (42) and also on prolonging the duration of active ampicillin concentration in serum. Type C was chosen in order to investigate the significance of the duration of treatment.

When a male patient presents for gonorrhoea, the diagnosis in most cases is made by direct microscopy and treatment is given in a situation when nothing is known about the sensitivity of the gonococcal strain to antibiotics. During the 2 years of the investigation the patients have been told to return for a check-up three times at 1 week intervals, which is the routine procedure for such cases at the Clinic.

#### *Satisfactory result*

Only patients with at least two negative follow-up cultures have been regarded as satisfactory. According to the recommendations of the Swedish Board of Social Welfare a patient treated for gonorrhoea should have two negative cultures be-

fore he is pronounced healthy. As appears from Table IV, 50 of the patients treated with penicillin G and 52 with ampicillin did not come for more than one check-up. In the statistical analysis these patients have not been included in the satisfactory group; they might have been positive at a second check-up.

#### *Treatment failure*

If we look at the time of examination of patients positive at the first check-up, we see that it varies between 5 and 85 days after treatment for the penicillin G patients and between 5 and 123 days for the ampicillin. It has been difficult to prove definite reinfections even among the patients who came very late to the first check-up. This applies likewise to patients with negative first and positive second culture. The few patients who were positive at the third check-up (Table IV) have not been included in the statistical evaluation. They would have been assigned to the satisfactory group if they had not appeared at the third check-up! The number of reinfections among these patients, furthermore, must have increased still further.

A comparison of the four groups at a first check-up within 7 days of the date of treatment has proved impossible statistically owing to the small number of patients who had returned within that time. The longer the time that elapses before the first check-up, the more difficult it is to discover differences in therapeutic effect and the greater the number of reinfections (45) which obscure the primary differences. These reinfections affect a metropolitan clientele to a greater extent than a material from a smaller place, where the individual cases can be charted in a quite different way (15). With random selection, however, the various groups should be affected equally in this respect.

The earliest possible time for calculation of treatment failures at the first check-up has in this material been judged to be 14 days. Another assessment has also been considered of value, namely to count cases with a negative culture at first but positive at second follow-up as treatment failures. The time limit has then had to be put at 21 days after the treatment. In the analysis only very probable reinfections (contact positive) within these groups have been excluded.

*Homogeneity of the material*

The age distribution of the four groups is closely similar. The proportion of strains with reduced sensitivity to penicillin G is virtually the same during the 2 years. An extensive comparison of clinical results and sensitivity of the bacterial strains will be made in a coming study (12).

*The value of the various forms of treatment*

Summing up the total result in the different groups (compare Table III), the tendency in all tests is least favourable for group A, less favourable than for G, B and C. This applies whether one counts as treatment failure a positive culture at first follow-up within 14 days, a positive culture at first or second follow-up within 21 days, a positive culture at first follow-up irrespective of time and reinfections. Treatment type A should therefore not be used in the future.

This material reveals no statistically significant differences between groups G and C. As regards the groups with less sensitive strains and treatment failure after 14 and 21 days (Figs. 4 and 7) the  $\chi^2$  value in a comparison between G and C is higher than in other tests, in favour of C.

In a single test (evaluation after 14 days and occurrence of gonococci with reduced sensitivity) treatment type C is found to be significantly better than B ( $0.01 < P < 0.05$ ). The groups showing the most equivalent results are G and B.

In group C the treatment appears to be equally satisfactory in the presence of less sensitive gonococci (Figs. 4 and 7) or of sensitive (Figs. 3 and 6). This does not seem to apply in the other groups, which show a higher percentage of treatment failures in the presence of less sensitive gonococci.

From this material, accordingly, treatment type C seems to be preferable to G in infections with less sensitive gonococci. Type B has proved to be fully equivalent to G. The disadvantage of type C would be that the dose of ampicillin is divided. But the patients must nevertheless have taken the second dose, for type C with a first dose of 1 g shows throughout statistically better results than A (with a single dose of 2 g). The advantage of type B is that it is a single-dose treatment. Its disadvantage is that patients are given still another drug with known allergenic properties.

In principle, as expected, the greatest differ-

ences between the various forms of treatment occur in the group of patients who had gonococcal strains with reduced sensitivity and when the result of treatment was assessed after 14 days. The therapy in this group was put to a more severe trial both because the infection was more difficult to treat and because the number of re-infections was reduced. That the large percentual differences do not yield clearer statistical differences in this group may be due to its smallness. It should be noted that only about 16% of the investigated strains had a reduced sensitivity to ampicillin. As this part of the ampicillin material was smaller than expected, it was considered warranted to continue the investigation with groups B and C in order to check the reliability of the existing tendencies and also to get a clearer picture of the side-effects.

As group A showed throughout the least favourable results and C seemed to be best, attention must be paid not only to the peak concentration but also to the duration. A comparison of the clinical result and the serum concentrations attained with the various doses of ampicillin will be presented in a coming paper (11).

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