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CLINICAL PROBLEMS IN THE ANTIBIOTIC TREATMENT OF GONORRHOEA

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SYNOPSIS

After briefly reviewing the history of penicillin therapy in gonorrhoea, the author shows that the number of cures effected with the repository penicillins, although originally very high, has diminished considerably in recent years, despite a general tendency to increase the dosage. The reduced efficacy of PAM and benzathine penicillin is demonstrated by an exposition of the current results obtained with these two preparations in the treatment of gonorrhoea patients in London. Some of the difficulties involved in distinguishing between treatment failures and reinfections are discussed.

The paper continues with an examination of the possible alternatives to repository penicillin in the treatment of gonorrhoea. Data are given on the comparative efficacy of a number of preparations, including mixed penicillins, phenoxymethyl penicillin and various other antibiotics, such as streptomycin and the tetracycline group.

The problem of re-examination of treated gonorrhoea cases is also dealt with, practical reasons being given for restricting the period of follow-up to three weeks.

Finally, in a discussion of possible future developments, the author suggests a number of measures designed to prevent a further loss of sensitivity to penicillin in the gonococcus.

Reduced Efficacy of Repository Penicillins in the Treatment of Gonorrhoea

The introduction of penicillin for the treatment of gonorrhoea during the Second World War was timely, for although the sulfonamides had revolutionized the treatment of the disease but a few years previously, they were already proving ineffective in some parts of the world. Campbell (1944), for example, had reported that failure to respond to sulfonamides was being noted in 75% of cases in Italy in 1943.

From the outset a number of cases of gonorrhoea (approximately 10%) failed to respond to treatment with the sulfonamides, owing to the existence of a naturally resistant strain of gonococcus. In the process of time, the

susceptible strains were largely disposed of and the resistant strains remained. Indeed, in London in 1949 (by which time penicillin had been in general use for gonorrhoea for 4-5 years), Dunlop reported that no less than 176 of 205 cases of gonorrhoea failed to respond to sulfonamides. In addition, it is thought that acquired resistance was also fostered by the indiscriminate use and abuse of the drugs (the taking of small doses by prostitutes, for example, to obscure the results of medical examinations, and the wholesale application by all and sundry for conditions other than venereal diseases, often trivial in nature).

There was no naturally penicillin-resistant gonococcus: all cases responded provided an effective serum level of the antibiotic were maintained for 10-12 hours. The preparations themselves were improved so that the treatment could be given on an ambulatory basis with a minimum of inconvenience to the patient. This was achieved by single intramuscular injections of 300 000 units of penicillin-in-oil beeswax and later, more simply, with a similar dosage of procaine penicillin (alone or with aluminium monostearate), and with benzathine penicillin.

Success in 90%-100% of the cases was reported from many parts of the world with injections of aqueous penicillin (e.g., Heller, 1946; Lakaye, 1946; Cohn & Kornblith, 1948; Fawkes, 1949), with penicillin-in-oil beeswax (e.g., Heller, 1946); with procaine penicillin G (e.g., Eisenberg & Loughlin, 1948; Hirchsberg, 1948; Lodin, 1956; Gjessing, 1956a); with repository penicillins, such as procaine penicillin with aluminium monostearate (e.g., Butler et al., 1952; Lodin, 1954; Sleath & Nelson, 1956); with benzathine penicillin (O'Brien & Smith, 1952) and with combinations of penicillins (Wherritt, Altheide & Duflett, 1956). Similar cure rates were reported with penicillin given orally (e.g., Bushby & Harkness, 1946; Ross, Burke & Olansky, 1947; Horne, 1950) and latterly with phenoxymethyl penicillin or penicillin V (Sheil, 1956).

Failure to control gonorrhoea

Although a cheap and effective treatment for gonorrhoea has enjoyed the widest use the disease has not been controlled. While the incidence of early syphilis has apparently declined consistently in most countries since the Second World War, the situation as regards gonorrhoea is far less satisfactory.

In many countries the numbers of cases of early syphilis treated annually have fallen to 5% or less of the war-time peaks. On the other hand, the numbers of gonorrhoea cases have declined to only about 50% of the war-time levels and in many cases are perhaps only a little below those of pre-war years. During the last five years, moreover, there has been little or no improvement and indeed many countries have reported a rise. Such a state of affairs has, for example, been noted in Canada (Lossing & Allen,

1956); Denmark (Eliot, 1955); Finland (Häro & Pätiälä, 1957); France (Durel, 1956); Hong Kong (Thomson, 1956); India (Rajam, 1956); Poland (Towpik, 1957); Norway (Gjessing, 1956b); Sweden (Tottie, 1956) and the United Kingdom (England and Wales, Ministry of Health, 1957).

The figures for England and Wales and for Hong Kong, shown in Tables 1 and 2 respectively, are representative of the situation in general.

TABLE 1. NUMBERS OF NEW MALE CASES OF GONORRHOEA, EARLY SYPHILIS, NON-GONOCOCCAL URETHRITIS AND CHANCROID TREATED IN THE VENEREAL DISEASE CLINICS OF ENGLAND AND WALES *

Year	Gonorrhoea	Early ** syphilis	Non-gonococcal urethritis	Chancroid
1939	28 811	3 574	No data	827
1942	17 956	5 470	,,	969
1944	16 629	4 384	,,	628
1946	36 912	10 705	,,	994
1948	25 006	6 603	,,	706
1950	17 007	2 678	,,	433
1951	14 975	1 498	10 794	437
1952	15 510	891	11 552	389
1953	15 242	755	13 157	347
1954	13 962	600	13 279	301
1955	14 079	609	14 269	285
1956	16 377	587	14 829	307

* Based on data published in England and Wales, Ministry of Health (1957)
** Under one year of duration

TABLE 2. NUMBERS OF NEW CASES OF GONORRHOEA, PRIMARY AND SECONDARY SYPHILIS, NON-GONOCOCCAL URETHRITIS AND CHANCROID TREATED IN HONG KONG *

Year	Gonorrhoea	Primary and secondary syphilis	Non-gonococcal urethritis	Chancroid
1951	6 903	863	No data	2 347
1952	8 546	852	,,	2 400
1953	11 625	766	870	2 507
1954	10 785	447	770	2 365
1955	11 309	187	869	2 468

* Based on data published in Thomson (1956)

Thus while the numbers of cases of early syphilis in England and Wales in 1956 were little more than one-twentieth of those of 1946 and the numbers of cases seen each year are still declining, those for gonorrhoea in 1956 had fallen by little more than one-half from their war-time peak and the annual figures are quite definitely rising again. A steady progressive rise since 1951 is shown in respect of non-gonococcal urethritis.

In Hong Kong, over a five-year period, the numbers of cases of primary and secondary syphilis have shown a steady and pronounced decline, while the numbers of cases of gonorrhoea have markedly increased. The reported cases of non-gonococcal urethritis, which have remained steady in number over the last three years, are far fewer in relation to the number of gonorrhoea cases than they are in Europe. Chancroid (also showing no signs of extinction) is a much greater problem.

Increase in the dose of penicillin

This failure to control gonorrhoea has occurred in spite of a general world tendency to increase the dose of penicillin given for the disease.

In the early days of penicillin therapy, the incidence of infectious syphilis was still high in many countries and the possibility that the penicillin given for gonorrhoea might mask but not cure an incubating syphilitic infection was foremost in the minds of venereologists. However, several workers (Cronin, 1947 ; Streitman, 1949 ; MacFarlane, 1950) suggested that the problem had probably been exaggerated and that if simultaneously acquired syphilis were going to appear it would do so within three months of penicillin therapy. With time it became clear that masking happened so infrequently as to confirm the contention that even small doses of penicillin given for gonorrhoea would completely abort incubating syphilis (Bauer, 1949). In consequence, there was a tendency to increase the dose of penicillin so as to ensure this effect (Willcox, 1953 ; Kanee & Nelson, 1954), and a dosage of 1.2 mega units of repository penicillin is now frequently used *(Bulletin of the Vancouver Medical Association*, 1956).

In 1955 the World Health Organization conducted a world survey of the management of venereal diseases in ports (Willcox & Guthe, 1957).

TABLE 3. DOSE OF PENICILLIN USED FOR GONORRHOEA BY PARTICIPANTS IN WORLD HEALTH ORGANIZATION SURVEY, 1955

Participants in survey	Dose in mega units		
	0.3-0.4	0.6-0.9	1.2 and over
Total (148)	23	85	40
Percentage	15.5	57.4	27.0

The findings concerning the dose of penicillin given for gonorrhoea are shown in Table 3.

It is evident that by 1955 no less than 84.4% of participants were using doses of penicillin of 0.6 mega units or more, and 27.0% were using doses of 1.2 mega units or more.

Despite the absence of a naturally penicillin-resistant gonococcus, the fear that an acquired resistance might be induced has been ever present. Certainly there has been an enormous use (and misuse) of the antibiotic. Sexually promiscuous persons, among others, have been repeatedly exposed to the drug, which in a number of countries can be bought over the counter without restriction. In some places penicillin is given preventively and curatively in a routine manner to prostitutes, and everywhere the antibiotic has been used by physicians on the widest scale.

The following data, which report a recent falling off in the cure rates of gonorrhoea after treatment with the repository penicillins, pertain to London, but the same situation has been noted also in other large cities (Guthe, communication to the World Health Organization, 1957).

Decreased cure rates with PAM

Procaine penicillin in oil with aluminium monostearate (PAM) was for many years the most widely used penicillin preparation for gonorrhoea in venereal disease clinics. It gave good results and its general use for syphilis simplified treatment procedures, since only one preparation was in routine use for both diseases. Through the years, however, the failure rates in the treatment of gonorrhoea have been increasing in spite of a progressively larger dosage. From Table 4 it will be noted that during 1956-57, in the series reported, the failure rates with PAM were nearly four times higher than in 1954, when a smaller dosage was administered.

TABLE 4. RESULTS OF TREATMENT OF GONORRHOEA WITH PAM IN LONDON

Year	Dose in mega units	Treated	Followed up	Failures *	Reinfection **	% Failure in cases followed up
1952	0.15	223	200	18 (8) (13)	42 (20)	9.0
1954	0.3	226	194	9 (5) (9)	22 (20)	4.6
1956	0.6	226	190	34 (23) (36)	23 (17)	17.9
1957	1.2	44	39	7 (6) (7)	15 (9)	17.9
Totals		719	623	68 (42) (65)	102 (66)	10.9

* Bracketed figures show recurrences (i.e., relapses and reinfections) encountered within 2 and 3 weeks of therapy, respectively.

** Bracketed figures indicate reinfections occurring within 3 months of therapy.

Decreased cure rates with benzathine penicillin

If the current results obtained with PAM are poor, those obtained with benzathine penicillin are worse. When benzathine penicillin was first introduced it gave excellent results in the treatment of gonorrhoea. For example, O'Brien & Smith (1952) had no definite failures in 1028 patients given single injections of 0.3-2.5 mega units. At the present time, however, doses of 0.3-1.2 mega units of benzathine penicillin have shown failure rates of up to approximately 30% (Table 5).

TABLE 5. RESULTS OF TREATMENT OF GONORRHOEA WITH BENZATHINE PENICILLIN IN LONDON IN 1957

Dose in mega units	Treated	Followed up	Failures *	Reinfection **	% Failure in cases followed up
0.3	98	76	24 (23) (25)	3 (3)	31.6
0.6	125	92	21 (21) (23)	3 (3)	22.8
1.2	41	33	10 (10) (10)	— (—)	30.3
Totals	264	201	55 (54) (58)	6 (6)	27.4

*** Bracketed figures give recurrences (i.e. relapses and reinfections) encountered within 2 and 3 weeks of therapy, respectively.**

**** Bracketed figures show reinfections occurring within 3 months of therapy. There is less possibility of long-range follow-up than in the case of the PAM series.**

Criteria for failure or reinfection

It is somewhat difficult to distinguish between treatment failures and reinfections. If a case fails to respond and gonococci are still present after 24-48 hours, it may fairly be assumed that treatment has failed. If recurrence is noted after three months' post-treatment observation, the case may be assumed to be a reinfection, notwithstanding the denials of the patient. It is in the cases recurring between these times that uncertainty lies. Although a history of renewed sexual risk within a week of recurrence may be regarded as sufficient reason to suspect a reinfection, proof is usually lacking, for only in a small proportion of contacts is the opportunity given to find gonococci in the consort.

Of a series of 1528 cases of gonorrhoea treated in batches during the years 1952-57 in London, 1280 were followed up. A recurrence was noted in 313, of which 184 (58.5%) were suspected to be relapses to treatment and 129 (41.5%) to be reinfections.

On the assumption that recurrences within two weeks are relapses and recurrences after that time are reinfections, 172 of these cases would be relapses (54.9%) and 141 would be reinfections (45.1%). If, on the other

hand, recurrences within three weeks are relapses, and recurrences after that time are reinfections, the relevant figures would be 197 relapses (62.9%) and 116 reinfections (37.1%). Thus it would seem likely that if all recurrences encountered within two weeks of treatment are regarded as relapses, the numbers of relapses, as compared with those judged on an individual basis, would be slightly understated. If three weeks is taken as the criterion, the treatment failure rate would be slightly overstated.

Treatment of Gonorrhoea with Preparations other than Repository Penicillin

Penicillin by injection

Two mixed penicillin preparations are available in Great Britain. One is " Penidural All Purpose ", provided in doses of 1.2 mega units containing 300 000 units of potassium penicillin G, 300 000 units of procaine penicillin G and 600 000 units of benzathine penicillin. The other is " Trilopen ", manufactured in 1.25 mega unit doses, each containing 500 000 units of sodium penicillin G, 250 000 units of procaine penicillin and 500 000 units of benzathine penicillin. Mixed penicillin preparations are more expensive than procaine penicillin alone. One dose of mixed penicillins costs 2/-—3/- ($0.28-$0.42) as against 8½d ($0.10) for 600 000 units of procaine penicillin.

Results currently achieved in London (1957-58) with procaine penicillin and with " All Purpose " penicillin are shown in Table 6.

TABLE 6. RESULTS OF TREATMENT OF GONORRHOEA IN MALES WITH PROCAINE PENICILLIN AND " ALL PURPOSE " PENICILLIN

Preparation	Total dose in mega units	Treated	Followed up	Failures	Reinfection	% Failure in cases followed up
Non-white patients						
Procaine penicillin	0.6 *	81	63	10	3	15.9
" All purpose "	1.2	55	51	5	12	9.8
White patients						
Procaine penicillin	0.6 *	71	53	3	2	5.7
" All purpose "	1.2	40	36	2	4	5.6
Total patients						
Procaine penicillin	0.6 *	152	116	13	5	11.2
" All purpose "	1.2	95	87	7	16	8.0

* In a single dose, or in 2 doses 24 hours apart

Failure rates are higher in non-whites than in white patients, but the over-all results are better in both series than with repository penicillins.

Penicillin given orally

Numerous authors (e.g. Bushby & Harkness, 1946; Ross, Burke & Olansky, 1947; Horne, 1950, Sheil, 1956) have shown that gonorrhoea can be adequately cured by penicillin given orally. Most authors, however, have used multiple doses. Such treatments are open to abuse when used on a mass scale in a venereal diseases clinic and, unless single-dose—or at the most two-dose—schedules are employed, oral administration of penicillin for gonorrhoea cannot compete with single injection procedures.

Benzathine penicillin and phenoxymethyl penicillin (penicillin V) have been administered orally, in single and double doses, for the treatment of gonorrhoea.

TABLE 7. TREATMENT OF GONORRHOEA WITH BENZATHINE PENICILLIN

Schedule	Treated	Followed up	Failures	Reinfection	% Failure in cases followed up
0.6-4.8 mega units in single dose	46	44	16	7	36.4
4.8 mega units in 2 doses	28	23	4	2	17.4
Total	74	67	20	9	29.9

Benzathine penicillin. In single doses benzathine penicillin was ineffective. Thirty-four patients had single doses of 3.0-4.8 mega units. Of 33 cases followed up there were 10 failures and 6 reinfections (Willcox, 1954). Somewhat improved results were obtained by using a higher dosage (4.8 mega units) given in two moieties 6 hours apart (Table 7).

Phenoxymethyl penicillin. A total of 85 patients were treated with 2-3 mega units of phenoxymethyl penicillin given in one single dose or in two

TABLE 8. RESULTS OF TREATMENT IN 85 PATIENTS WITH 2-3 MEGA UNITS OF PHENOXYMETHYL PENICILLIN GIVEN ORALLY, IN ONE OR TWO DOSES

Patients	Treated	Followed up	Failures	Reinfection	% Failure in cases followed up
White	33	27	—	4	—
Non-white	52	49	14	6	28.6
Totals	85	76	14	10	18.4

TABLE 9. RESULTS OBTAINED BY SINGLE OR DOUBLE ORAL DOSES OF PHENOXYMETHYL PENICILLIN

Schedule	Treated	Followed up	Failures	Reinfection	% Failure in cases followed up
2 mega units in single dose	21	20	4	2	20.0
2 mega units in two doses	18	16	5	1	31.3
3 mega units in single dose	22	17	1	3	5.9
3 mega units in two doses	24	23	4	4	17.4
Totals	85	76	14	10	18.4

doses 6 hours apart. The over-all results in white and non-white patients are shown in Table 8.

The results obtained with the different schedules are given in Table 9.

It is evident that good results can be obtained in white patients with 2-3 mega units of phenoxymethyl penicillin give orally. In all patients the best results were obtained with a single dose of 3 million units. Such treatment is, however, expensive (5/11, or $0.83, per case as compared with 8½d, or $0.10, for 600 000 units of procaine penicillin by injection).

Other antibiotics

The results obtained by the author in treating gonorrhoea with antibiotics other than penicillin are shown in Table 10.

TABLE 10. ANTIBIOTICS OTHER THAN PENICILLIN IN TREATMENT OF GONORRHOEA

Antibiotic	Dose (g)	Year	Treated	Followed up	Failures	Re-infection	Recurrence within two weeks	%Recurring within two weeks
Streptomycin	0.5-1.0	1951	62	52	5	6	4	7.7
,,	0.5-1.0	1956	109	88	11	6	9	10.2
Oxytetracycline	2.0	1952	202	170	16	7	16	9.4
Erythromycin	2.4	1955	50	42	6	2	6	14.3
Spiramycin	2-4	1956	54	47	6	4	7	14.9
Novobiocin	2-12	1956	27	27	11	4	11	40.7
Totals			504	426	55	29	53	12.4

The oral antibiotics listed were generally given either in a single dose or in two doses six hours apart.

Two streptomycin series, which were undertaken in 1951 and 1956, are reported. No obvious deterioration in results was noted in five years. Should an alternative to penicillin be required streptomycin would probably be the test. The cost of 1 g is only 1/6 ($0.21) and usually a single injection would suffice. If streptomycin were used on large scale the gonococcus might soon become resistant. Already cases of streptomycin-resistant gonorrhoea have been reported (e.g., Davey, 1957).

Failing penicillin or streptomycin the tetracycline antibiotics, erythromycin or spiramycin give fairly good results but are relatively very expensive. The eight capsules or tablets necessary cost 11/4-13/4 ($1.59-$1.87).

Follow-up in Gonorrhoea

One final problem is to decide what period of follow-up is best for patients with treated gonorrhoea. As was shown earlier, the great majority of relapses are detected by examinations before the third week. It has been the practice in many countries to follow up treated gonorrhoea patients for three months and then to do a final serum test, since three months is the maximum period in which incubating syphilis might declare itself in the serum.

It has now been shown that incubating syphilis is probably completely aborted by the penicillin given for gonorrhoea; the larger doses administered nowadays make this eventuality more likely. In countries with a minor syphilis problem it would seem hardly justifiable to hold all gonorrhoea patients for three months in order to detect the development of simul-

TABLE 11. FOLLOW-UP OBTAINED IN 661 CASES OF GONORRHOEA TREATED IN LONDON

Follow-up	White patients		Non-white patients	
	Followed	%	Followed	%
0	295	100	366	100
1-3 days	239	81.0	299	81.7
4-7 days	190	64.4	225	61.5
8-14 days	129	43.7	154	42.1
15-21 days	91	30.8	102	27.9
22-28 days	72	24.4	70	19.1
1-2 months	60	20.3	56	15.3
2-3 months	35	11.9	32	8.7
Over 3 months	18	6.1	20	5.5

taneously acquired syphilis—an event which very seldom happens. In any case, from the practical standpoint, even when such a procedure is adopted, only a small minority do not default before the three months' period is completed.

Table 11 shows the results obtained in an attempt to follow up 295 white and 366 non-white male gonorrhoea patients. Even these figures are artificially high, since many of the patients who reported after three months had previously defaulted and only returned because they had again become infected.

It is apparent that only approximately 1 out of 10 patients attend for 2-3 months and less than 1 in 3 for the short period of 3 weeks. It is emphasized that these data refer to a large city and that many of the gonorrhoea patients are itinerant. When dealing with gonorrhoea on a large scale in urban areas, in the light of the data presented, it is therefore considered reasonable deliberately to restrict the follow-up of treated cases to examinations made at 3, 7, 14 and 21 days from treatment. This period, or less, has been accepted for some years in parts of the USA.

Possible Future Developments

In this paper some evidence is given of a decline in the effectiveness of repository penicillins for the treatment of gonorrhoea. Is this the first weakness in the antibiotic defences against the venereal diseases ? If so, will the breach widen, and will the gonococcus soon become as resistant to penicillin as it is to the sulfonamides ? It is dangerous to prophesy but the writer doubts such a development for the following reasons :

1. Resistance to penicillin is at present only relative (a reduced sensitivity) and is a developing phenomenon, whereas resistance to the sulfonamides was in some cases complete and was a natural resistance from the outset.

2. At present the problem is limited to repository penicillins, which produce low, if prolonged, serum levels. Good results are still obtained with penicillin preparations which give a high serum level, and cases of gonorrhoea that continue to show gonococci after the administration of reasonable doses of such preparations are not being reported in the literature. It has taken nearly 15 years of penicillin usage to reach this situation, so that, at the present rate, a very long time is likely to elapse before the considerable powers of penicillin in gonorrhoea are exhausted.

3. At the time when sulfonamides were first used there were no effective alternatives. In consequence, sulfonamide-resistant organisms soon became widespread. Today we have streptomycin, tetracycline (alone or with oleandomycin), oxytetracycline, chlortetracycline, spiramycin, erythromycin and chloramphenicol—all of which have been shown to give reason-

ably good results in the treatment of gonorrhoea. Resistant cases can thus be effectively treated by other means before widespread dissemination of the organism occurs. Moreover, as has been shown in the case of acquired penicillin resistance in staphylococci, if the use of penicillin is discontinued for some time the resistant organisms may once more become sensitive. Thus, although the situation is one which requires close watching, it is not likely to deteriorate by the rapid emergence of complete clinical resistance of the gonococcus to penicillin. Should this happen the disease could still be effectively treated—albeit at a much greater cost.

In the meantime one should do all possible to prevent a further deterioration. Apart from the general preventive measure against all microbiogenic and allergic effects of penicillin, which consists in restricting, where possible, the indiscriminate use of the drug,[1] one should try to ensure that the gonococcus is not presented with subcurative serum levels of penicillins. This means using larger doses of quicker-acting penicillins or preparations or mixed penicillins.

At once arises the question of the routine "penicillinization" of prostitutes. This technique has been used in some parts of the world—such as, for example, in Singapore (Ram, personal communication, 1956) in Mexico (Campos Salas, 1952, 1953; Samamé, 1951), in Thailand (Vuletic, personal communication, 1956), in Hong Kong (Thomson, 1956); in Nigeria (Nigeria, Department of Medical Services, 1954) and in France (Durel, 1956)—mainly by means of procaine penicillin with aluminium monostearate (PAM) and with benzathine penicillin (Guthe, 1955). Although some investigators (e.g., Ram, 1956) consider that "penicillinization" has played a major role in the decline of syphilis, the procedure was generally introduced at a time when there was already a widespread fall in incidence. The evidence suggests that although syphilis in prostitutes has been reduced, the measures have been much less decisive against gonorrhoea. Some writers (e.g., Willcox, 1956) have queried the effectiveness of such schemes, considering the small fraction of the sexually promiscuous population which is covered by them, but admit that in exceptional instances, where known brothels supply the sole sexual outlet of a limited community, and when the prostitutes concerned are already under medical supervision, it is not illogical to give penicillin regularly. In order to prevent the fostering of acquired penicillin resistance of the gonococcus in prostitutes, it is suggested that either mixed penicillin preparations should be used or that the usual prophylactic dose of repository penicillin given to prostitutes should be reinforced with shorter-acting penicillin preparations giving higher peaks of penicillinaemia.

It is a general impression that gonorrhoea has become a milder disease. Certainly with modern treatments, in spite of a considerable prevalence in many areas, the frequency of severe complications such as rheumatism,

[1] See paper by T. Guthe, O. Idsöe & R. R. Willcox on page 427.

arthritis, iritis, and—even if to a lesser extent—epididymitis and acute prostatitis, is extremely low in relation to the numbers of clinical cases of acute gonorrhoea seen.

The possibility that, as a result of modifications induced by antibiotic treatment, the disease may sometimes become so mild that some males are virtually asymptomatic carriers has been suggested by a number of authors. For example, Norgaard (1956) has stated that in Aarhus, Denmark, some 10% of male cases of gonorrhoea had no subjective symptoms. Seven such cases have been reported in Great Britain by Bittiner & Horne (1955), and an additional case has been noted by Clements (1955) (see also, *British Medical Journal*, 1955). In the USA the problem has been discussed by Jones & Price (1957).

The effects of antibiotics on the clinical aspects of venereal disease have been considered by Ricciardi (1956). Lodin (1956) posed the question whether the gonococcus was becoming attenuated and the incubation period was lengthening. In a study of 1120 males he noted that up to 1943 the incubation period was 5 days, whereas in 1954-55 it was 6 days.

While these observations indicate that a degree of watchfulness is required before a cure is pronounced in the male, and that cultures should be more widely used, in addition to smears, the author is not currently of the opinion that—whatever the future holds in store—the problem is as yet a very great one.

RÉSUMÉ

L'introduction de la pénicilline dans le traitement de la blennorragie, au cours de la deuxième guerre mondiale venait à son heure, car le gonocoque était déjà devenu résistant aux sulfamides qui, quelques années auparavant, avaient révolutionné la thérapeutique. Dès le début de la sulfamidothérapie, la résistance du gonocoque avait causé l'échec du traitement dans 10% environ des cas de blennorragie. Au contraire, aucun gonocoque ne se montra d'emblée résistant à la pénicilline, pour autant qu'une pénicillinémie de 10-12 heures était assurée — cela grâce à une injection intramusculaire de 300 000 unités de pénicilline dans l'huile et la cire d'abeille, plus tard de PAM ou de benzathine-pénicilline. L'injection de pénicilline aqueuse assurait 90-100% de guérisons.

Cependant la maladie n'a pas été jugulée et, comparée à celle de la syphilis, la situation est beaucoup moins favorable. Tandis que le taux de morbidité par syphilis s'abaissait dans certains pays à 5% du niveau observé pendant la deuxième guerre mondiale, la blennorragie ne diminuait pas au-delà de 50%. Au cours des dernières années, on a même signalé une recrudescence, malgré la tendance générale à augmenter les doses de pénicilline. On a noté, dans une série de relevés comparatifs, que les taux d'échecs du traitement par le PAM étaient quatre fois plus élevés en 1956/57 qu'en 1954 — année où pourtant la quantité de pénicilline injectée était plus faible.

Evaluant les risques résultant de cette diminution d'efficacité de la pénicillinothérapie, l'auteur souligne qu'actuellement, elle est limitée aux pénicillines-retard. Les préparations donnant une pénicillinémie élevée continuent à donner de bons résultats, et il est probable que la pénicilline conservera son importance pendant de longues années encore. D'autres antibiotiques (streptomycine, tétracycline, oléandomycine, spiramycine, érythromycine

et chloramphénicol) donnent également de bons résultats dans le traitement de la blennorragie, de sorte que les cas rebelles à la pénicilline peuvent être traités avec succès, avant que les organismes résistants aient pu prendre le dessus et se répandre. L'étude des staphylocoques résistants a du reste montré que la suppression du contact avec l'antibiotique entraînait une perte de la résistance. Il semble que l'on n'ait pas à craindre pour le moment une résistance clinique des gonocoques à la pénicilline. La vigilance s'impose cependant. Outre les mesures recommandées en vue de restreindre, dans la thérapeutique générale, l'emploi indiscriminé et abusif de la pénicilline, il importe d'éviter le contact du gonocoque avec des doses sous-curatives de pénicilline dans le sang. Cela implique l'emploi de fortes doses de pénicilline à action plus rapide ou de mélanges de pénicillines. La question de la « pénicillinisation » des prostituées, appliquée dans certaines parties du monde, se pose dès lors. Cette mesure que l'on considère comme ayant largement contribué au déclin de la syphilis n'a pas eu le même succès dans la lutte contre la blennorragie. Dans les cas où les conditions socio-économiques le justifient, il est suggéré d'employer soit une dose plus élevée de pénicilline-retard, soit des mélanges de pénicillines, afin d'éviter l'apparition de souches résistantes. Il semble que, d'une façon générale, la blennorragie ait quelque peu perdu de sa gravité; les complications graves de la maladie sont moins fréquentes.

REFERENCES

Bauer, T. J. (1949) *J. vener. Dis. Inform.*, **30**, 185
Bittiner, J. B. & Horne, G. O. (1955) *Brit. J. vener. Dis.*, **31**, 155
Brit. med. J., 1955, **2**, 1548
Bull. Vancouver med. Ass., 1956, **32**, 389
Bushby, S. R. M. & Harkness, A. H. (1946) *Lancet*, **2**, 783
Butler, P. G., Brenner, A. F., Condit, P. K. & Johnston, J. (1952) *Amer. J. Syph.*, **36**, 269
Campbell, D. J. (1944) *Brit. med. J.*, **2**, 44
Campos Salas, A. (1952) *Bol. epidem. (Méx.)*, **16**, 62
Campos Salas, A. (1953) *Arch. mex. Venereol. Derm.*, **12**, 63
Clements, P. A. (1955) *Brit. med. J.*, **2**, 1540
Cohn, A. & Kornblith, B. A. (1948) *Amer. J. med. Sci.*, **215**, 506
Cronin, E. (1947) *Brit. J. vener. Dis.*, **23**, 15
Davey, A. C. C. (1957) *Brit. J. vener. Dis.*, **33**, 179
Dunlop, E. M. C. (1949) *Brit. J. vener. Dis.*, **25**, 81
Durel, P. (1956) *Brit. J. vener. Dis.*, **32**, 145
Eisenberg, H. & Loughlin, M. E. (1948) *J. vener. Dis. Inform.*, **29**, 269
Eliot, T. D. (1955) *Brit. J. vener. Dis.*, **31**, 2
England and Wales, Ministry of Health (1957) *Report of the Ministry of Health for the year ended 31st December, 1956. Part II. On the state of the public health*, London, pp. 252, 253
Fawkes, M. A. (1949) *Caribbean med. J.*, **11**, 64
Gjessing, H. C. (1956a) *Acta derm.-venereol. (Stockh.)*, **36**, 122
Gjessing H. C. (1956b) *Brit. J. vener. Dis.*, **32**, 86
Guthe, T. (1955) *Brit. J. vener. Dis.*, **31**, 160
Häro, A. S. & Pätiälä, R. (1957) *Brit. J. vener. Dis.*, **33**, 70
Heller, J. R. (1946) *J. Amer. med. Ass.*, **131**, 1880
Hirchsberg, N. (1948) *Amer. J. Syph.*, **32**, 141
Horne, G. O. (1950) *Brit. J. vener. Dis.*, **26**, 23
Jones, R. F. & Price, K. A. (1957) *J. nat. med. Ass.*, **49**, 19
Kanee, B. & Nelson, A. J. (1954) *Amer. J. Syph.*, **38**, 354
Lakaye, R. (1946) *Arch. Serv. Santé Armée belge*, **99**, 389

Lodin, A. (1954) *Svenska LäktT.*, **51**, 1724
Lodin, A. (1956) *Svenska LäkT.*, **53**, 16
Lossing, E. H. & Allen, R. H. (1956) *Brit. J. vener. Dis.*, **32**, 150
MacFarlane, W. V. (1950) *Brit. J. vener. Dis.*, **26**, 69
Nigeria, Department of Medical Services (1954) *Annual report on the Medical Services for the year 1952-53*, Lagos
Norgaard, O. (1956) *Acta derm.-venereol. (Stockh.)*, **36**, 150
O'Brien, J. F. & Smith, C. A. (1952) *Amer. J. Syph.*, **36**, 519
Rajam, R. V. (1956) *Brit. J. vener. Dis.*, **32**, 79
Ricciardi, L. (1956) *Prophyl. San. Morale*, **28**, 167
Ross, S., Burke, F. G. & Olansky, S. (1947) *New Engl. J. Med.*, **236**, 817
Samamé, C. (1951) *Bol. Ofic. sanit. panamer.*, **30**, 42
Sheil, L. P. (1956) *Brit. J. vener. Dis.*, **32**, 251
Sleath, G. W. & Nelson, A. J. (1956) *Canad. J. publ. Hlth*, **47**, 383
Streitman, B. (1949) *Wien. klin. Wschr.*, **61**, 919
Thomson, G. M. (1956) *Brit. J. vener. Dis.*, **32**, 82
Tottie, M. (1956) *Brit. J. vener. Dis.*, **32**, 157
Towpik, J. (1957) *Brit. J. vener. Dis.*, **33**, 78
Wherritt, H. R., Altheide, H. E. & Duflett, N. R. (1956) *Missouri med.*, **53**, 767
Willcox, R. R. (1953) *Progress in venereology*, London, p. 15
Willcox, R. R. (1954) *Amer. J. Syph.*, **38**, 469
Willcox. R. R. (1956) *Int. Rev. Criminal Policy* (in press)
Willcox, R. R. & Guthe, T. (1957) *Bull. Wld Hlth Org.*, **16**, 1033