PROBLEMS ARISING FROM THE USE OF PENICILLIN IN GONORRHOEA

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Among the problems which have arisen from the penicillin therapy of gonorrhoea are the following: (1) Can the multiple- (five or ten) injection technique used so successfully in the Services be superseded in civilian out-patient practice by a "one-shot" or a "two-shot" method? (2) Does the dosage of penicillin used in the treatment of gonorrhoea "mask" the presence of a concomitantly acquired syphilis, or does it not? (3) Is there any danger that the single-injection method of treatment, if it should fail, will produce a penicillin-fast strain of the gonococcus? (4) Is it advisable to give irrigation when penicillin is used?

Articles that have recently been published show that among those engaged in treating venereal disease there are very decided differences of opinion on these questions. For example, Allan (1946) describes the apparently completely successful use of a single-injection method (dose 200,000 or 300,000 units) in a small group of thirty cases of gonorrhoea, and expresses the hope that "in some clinic dealing with large numbers, and where patients can be under more continuous supervision, the single-injection method will be tried out on enough cases to provide accurate statistics." Allan states that "the single-injection method has several demerits"—for example, "the danger of producing a penicillin-fast strain of the gonococcus" and "the very real danger of masking an early syphilis"—and in this latter connexion he stresses "the necessity for regular serological tests for the following twelve months." On the other hand, Marshall (1946), in commenting on Allan's pronouncements, states that he has "not yet seen any cases where syphilis became evident later than three months after penicillin therapy for gonorrhoea and without another exposure to possible infection." Marshall remarks that "it would be interesting to have . . . reasoned opinions . . . on the length of follow-up necessary after the treatment of gonorrhoea with penicillin in the doses now used."

Various Injection Techniques Compared

The efficacy of multiple-injection techniques in gonorrhoea, either untreated or sulphonamide-resistant, has been emphasized by Harrison (1945), who recommended five 2-hourly doses of 30,000 units, and more recently by Lees (1946), who adduced a cure rate of 98% in 344 sulphonamide-resistant cases treated with ten 3-hourly doses of 10,000 units. Marshall (1945) has stated recently that "the best method of treatment of gonorrhoea with penicillin . . . is with doses of not less than 100,000 units given intramuscularly in four or five separate injections at 2-hourly or 3-hourly intervals over a period of 8-12 hours." On the other hand, from the point of view of civilian practice, multiple-injection techniques have distinct drawbacks, and a "one-shot" or "two-shot" method much more nearly approaches the ideal. But is it practicable by only one or two injections to achieve a cure rate comparable to the high efficiency of the five-injection plan? Romansky and Rittman (1944) have shown that a single dose of 100,000 units could be highly effective when its action was delayed and prolonged by suspending the penicillin in peanut oil containing 2 or 3% of beeswax. Lloyd Jones *et al.* (1946), using suspensions of penicillin containing magnesium sulphate to delay absorption, have described a one-injection method which achieved apparent cure in 95.6% of 113 male out-patients. In the hope of arriving at a satisfactory minimal-injection technique, various methods have been tried in groups of cases at the Edinburgh clinic, and the results recorded are shown in Tables I and II.

Certain cases were considered unsuitable for a one-injection or a two-injection technique, and for these a multiple-injection

method was used; these cases fell into one or other of the following groups: those with metastatic complications, such as arthritis and iritis; those with local complications, such as abscess of the prostate gland in the male or abscess of Bartholin's gland in the female; young girls with gonococcal vulvo-vaginitis; and babies with gonococcal ophthalmia. In one of these cases chosen for multiple-injection treatment—that of a little girl of 4 suffering from gonococcal vulvo-vaginitis—the gonococcal infection showed amazing persistence after what constituted a colossal dosage of penicillin even for this resistant type of case. First of all this child was given fifteen 3-hourly intramuscular doses, each of 20,000 units, which resulted in an apparent clearing-up and temporary disappearance of gonococci from the smears. But slight redness and discharge returned and gonococci reappeared in the smears, so another course of twenty-four 3-hourly doses, each of 20,000 units, was administered. Again there was temporary improvement, and thereafter again recurrence. A third course was now given, comprising sixty 3-hourly doses each of 40,000 units, and, after the usual improvement, again relapse occurred. By this time the child had received no fewer than ninety-nine intramuscular injections of penicillin to a total dosage of 3,180,000 units—more than enough to cure most cases of sero-negative primary syphilis in an adult—and still the gonococcus had not been beaten. In pity for the little patient the idea of still more penicillin was abandoned; instead recourse was had to the sulphonamides, and 15 g. of sulphadiazine caused disappearance of signs and gonococci, though the period of observation has not been long enough to justify claiming a cure.

Tables I and II show in comparison the results obtained by one-shot and two-shot techniques.

TABLE I.—Results of Giving One Single Intramuscular Injection of 200,000 Units

	Period of Investigation	Nature of Preparation	No. of Cases	No. of Relapses	Cure Rate %
Male cases:					
Group 1 . .	June, 1945, to Feb., 1946	Saline solution without adrenaline	135	31	77.0
" 2 . .	July, 1945, to Oct., 1945	Saline solution plus adrenaline	103	20	80.6
" 3 . .	Nov., 1945, to Dec., 1945	Oil-beeswax suspension	41	4	90.2
Female cases:					
Group 1 . .	July, 1945, to Jan., 1946	Saline solution without adrenaline	35	4	88.6
" 2 . .	July, 1945, to Dec., 1945	Saline solution plus adrenaline	58	7	87.9

TABLE II.—Results from Two Intramuscular Injections, Each of 200,000 Units

	Period of Investigation	Nature of Preparation	No. of Cases	No. of Relapses	Cure Rate %
Male cases . .	Jan., 1946, to April, 1946	Saline solution	190	8	95.8
Female cases	Jan., 1946, to April, 1946	Saline solution	55	5	90.9

Description of Preparations Used

All solutions of penicillin were made up with sterile normal saline, the usual concentration being 200,000 units of the sodium salt dissolved in 4 or 5 ml. of saline. The beeswax-peanut-oil suspensions contained 2.5 or 3.5% beeswax, and the strength of the suspension was 50,000 units per ml.

In the group of cases in which adrenaline was used to prolong the action of the penicillin by delaying absorption and

excretion, 2 minims of 1 in 1,000 solution of adrenaline hydrochloride were added to and mixed with the penicillin solution in the syringe, the adrenaline being used in an attempt to prolong the bacteriostatic concentration of penicillin in the blood according to the method suggested by Fisk, Foord, and Alles (1945). In the second group of cases, which received two intramuscular injections, the second injection was given six to eight hours after the first. With this scheme it is necessary for the patient to report for treatment twice in the same day. So far it has been possible for every patient to arrange to do this. In the event of a person's reporting for the first time in the evening, for the sake of consistency, and to avoid having to give a second injection in the middle of the night, the first injection might be deferred till the following morning. There is, however, an obvious risk in delaying treatment, and it is, on the whole, probably better in these cases to use a single-shot technique, and repeat it the next morning if smears still show gonococci.

Method of Administration, and Tolerance

All injections were made intramuscularly into the upper outer quadrant of the buttock, and when two injections were given both buttocks were used. As a rule the intramuscular injections were well received by the tissues. Reaction, expressed by pain, swelling, redness, and induration, varied with the make and batch of penicillin used, and was apparently due to impurities, being most evident where the sample was dark brown in colour and of low penicillin content, and very slight with light-yellow samples of greater purity and potency. In most cases the local intolerance was negligible, and, in the few where local pain and stiffness were encountered, these were not of an incapacitating nature.

General intolerance has been minimal, though in a few cases faintness, nausea, pallor, sweating, and rapid feeble pulse occurred after the injection. It is thought that in most instances this was psychological, and due to the prick of the needle rather than to the action of the penicillin solution. The majority of the patients exhibiting these features occurred in the series receiving 2 minims of adrenaline in addition to the penicillin, and in these the untoward effects might have been due to the rapid absorption of the adrenaline. This was a transient phenomenon and passed off quickly without special treatment.

Relapses

A certain number of cases in each series had received previous treatment with sulphonamides and some had been treated with penicillin. Those which had received previous sulphonamide treatment were neither more nor less liable to relapse on the dose of penicillin given than those which had had no previous treatment. In each series 91% of the males had no urethral discharge the second day after treatment. The duration of the discharge depended on the severity of the infection before treatment was instituted; in only 2.4% of the male patients did it persist for more than three days.

All cases which relapsed on the initial dose of penicillin—i.e., where the urethral discharge persisted or returned (usually within 14 days) and was found to contain gonococci—were cured by further treatment with penicillin, usually by one of the methods using multiple injections of saline solution at 3-hourly intervals. A few of these relapse cases were cured by a course of 25 g. of sulphathiazole or sulphadiazine given in five days.

All cases reported have been under observation for at least two weeks after treatment with penicillin. Most of them have been under observation for some months, and several have been observed for six months and discharged as cured.

Concomitant Syphilis

Five of the male patients in the series now reported on, and two additional males, have during their period of observation developed syphilis, and, so far as has been ascertained, infection with *Sp. pallida* took place at the same time as infection with the gonococcus. In these cases the incubation period before the appearance of the chancre has varied from 39 to 184 days. All the patients strongly denied any exposure to infection after having had their gonorrhoea treated with penicillin. The salient features of these seven cases are now detailed.

Reports of Cases

Case 1.—Age 33. Exposure, Dec. 6, 1944; urethral discharge, Dec. 12. Took 12 g. sulphapyridine. Seen on Jan. 10, 1945; gonococci still present in urethral smear. Blood Wassermann negative. Given 30 g. sulphathiazole, after which discharge stopped. Jan. 24: Reported with return of urethral discharge, and gonococci again present in the smears. Given 30 g. sulphadiazine. Feb. 1: No discharge; urine clear. Feb. 15: Recurrence of profuse purulent urethral discharge containing gonococci. Given penicillin in oil-beeswax suspension, 100,000 units. Feb. 16: No discharge; urine clear. Feb. 19: Routine blood tests showed both Wassermann and Kahn to be strongly positive. March 8: Course of sixty 3-hourly injections, each of 40,000 units, of penicillin started. March 9: Quantitative Wassermann titre, 36 doses. March 11: First appearance noted of indurated sore at the urinary meatus and of a scar in the coronal sulcus. The period between exposure and the development of positive blood tests was 75 days; to the appearance of a "sore," 95 days.

Case 2.—Age 23. Exposure, April 14, 1945; urethral discharge, April 19. April 21: Gonococci very numerous in urethral smear. Blood Wassermann and Kahn reaction both negative. Given 25 g. sulphathiazole, followed after an interval by 30 g. May 22: As the discharge containing gonococci still persisted he was given 4 injections of penicillin, each of 15,000 units 3-hourly (total, 60,000 units). May 23: Indurated lesion on under-surface of shaft of penis. Three successive dark-field examinations of serum were negative for *Sp. pallida*. Lesion healed satisfactorily. Blood Wassermann and Kahn negative. July 18: Blood Wassermann weak to moderately strong positive; Kahn strongly positive. Incubation period to development of "sore," 39 days; to positive blood Kahn, 95 days.

Case 3.—Age 30. Exposure, Aug. 16, 1945; urethral discharge, Aug. 22. Seen on Aug. 23. Urethral discharge contained very numerous gonococci. Blood Wassermann and Kahn both negative. Given one dose of penicillin, 200,000 units, plus 2 minims of adrenaline. Sept. 22: Blood Wassermann negative. Oct. 1: Two small circular abrasions in coronal sulcus, not indurated and with no associated inguinal adenitis. Three successive dark-field examinations of serum were negative for *Sp. pallida*. Lesions healed by Oct. 6, and on this date blood Wassermann and Kahn both negative. Oct. 22: Routine blood Wassermann and Kahn strongly positive. Oct. 27: Slightly indurated swelling in coronal sulcus, with no erosion of skin surface. After scarification a small bead of serum was obtained, and in this a few *Sp. pallida* were demonstrated. Quantitative blood Wassermann strongly positive 10 doses; Kahn strongly positive. Incubation period, 72 days.

Case 4.—Age 35. Exposure, Oct. 30, 1945; urethral discharge, Nov. 2. Seen on Nov. 5. Gonococci very numerous in purulent urethral discharge. Blood Wassermann negative. Given one dose of penicillin, 200,000 units. Relapsed. Nov. 9: Given 4 doses of penicillin, each of 40,000 units, 3-hourly (total, 360,000 units). Jan. 3, 1946: Circular indurated lesion on shaft of penis present for one week, serum from which contained *Sp. pallida*. Blood Wassermann negative. Incubation period, 60 days.

Case 5.—Age 39. Exposure Oct. 29, 1945, urethral discharge, Oct. 31. Seen on Nov. 3: numerous gonococci were demonstrated in the purulent urethral discharge. Blood Wassermann and Kahn both negative. Given one dose of penicillin, 200,000 units. Feb. 11, 1946: Erosion on glans penis, in serum from which *Sp. pallida* demonstrated, present for four weeks. Blood Wassermann strongly positive. Incubation period 70 days.

Case 6.—Age 40. Reported on March 8, 1946. Indurated erosion in coronal sulcus present since Feb. 15, serum from which contained *Sp. pallida*. Blood Wassermann strongly positive. Last exposure on Aug. 15, 1945, in Germany. Gonorrhoea treated at that time with penicillin (no record of dosage). Strongly denied any further extramarital exposure. Wife first examined on March 9, 1946. No extramarital coitus; last marital coitus on March 2. Clinical examination negative and both blood Wassermann and Kahn negative. Kept under observation, and last seen on June 1. Blood Wassermann and Kahn tests made on nine further occasions up to that date had proved consistently negative. Incubation period, 184 days.

Case 7.—Age 25. Exposure, last week of December, 1945; urethral discharge, Jan. 1, 1946. Treated with 5 intramuscular injections of penicillin at 2-hourly intervals. Ulcer appeared at root of penis in middle of March. Seen on April 25, when he had florid secondary syphilis. Blood Wassermann strongly positive. Incubation period, 81 days (approximately).

In these seven cases the average incubation period is 82 days, being possibly heightened disproportionately by the phenomenally long period of 184 days recorded for Case 6. After excluding the doubtful No. 2, also No. 6, the average incubation period of the remaining five cases is 70 days, and, if we add to this a further 28 days, which may be

necessary for the serological tests to become positive, it is evident that well over three months may elapse before the syphilis is recognized, provided, as may happen (see Case 2), the dark-field examinations of serum from the "sore" do not demonstrate *Sp. pallida*. This observation, if justified, would seem to have an important bearing on the argument that expectant mothers suffering from gonorrhoea should receive sulphonamide treatment in preference to penicillin in order to guard against the adverse effect on the foetus which might result from the presumed action of penicillin in delaying the recognition of a concomitant syphilis.

Commentary

In so far as the experience set out may help in the solution of the problems enunciated above, the answers provided are:

1. A two-shot technique used on an out-patient basis can provide, in male cases, a cure rate (95.8% in 190 cases) which compares favourably with the efficiency (around 95%) claimed for five- or ten-dose schemes. The two-shot cure rate achieved in 55 female cases was 90.9%.
2. The dosage of penicillin necessary to cure gonorrhoea may apparently prolong the inherently long incubation period of syphilis.
3. There is no evidence that failure of the one-injection or of the two-injection methods of treating gonorrhoea will produce a penicillin-fast strain of the gonococcus.
4. As it is only in a small proportion (2.4% in this series) of penicillin-treated cases that urethral discharge persists after the third day, the practice of giving routine irrigations is not likely to cause a significant increase of efficiency. Cases of gonorrhoea with super-added penicillin-resistant infections must be only a small minority, and, when encountered, it is reasonable to anticipate that some of them may be benefited by irrigations.

Summary and Conclusions

A one-shot or two-shot technique in the treatment of gonorrhoea is more suitable in civilian practice than the multiple-dose methods, and such limited-dose techniques can be conveniently applied to out-patients.

In 190 male and 55 female cases of gonorrhoea a two-injection scheme ($2 \times 200,000$ units) gave cure rates of 95.8% and 90.9% respectively.

The dosage of penicillin employed to cure a gonorrhoeal infection may apparently delay the development of concomitant syphilis, and therefore penicillin-treated gonorrhoea cases should be observed for at least six months, and possibly longer.

Failure of a limited-dose technique is not likely to produce resistance to penicillin. In the penicillin treatment of gonorrhoea routine irrigation is not necessary, but may be tried if a urethral discharge persists for longer than three days.

The two-dose method advocated, using saline solutions of sodium penicillin, is simple and easily applied, the solutions used requiring no special skill in dispensing beyond the care necessary to ensure sterility and asepsis.

We are indebted to Dr. W. G. Clark, the Medical Officer of Health, for permission to publish. Our thanks are also due to the following, whose interest and help we gratefully acknowledge: Drs. Robert Lees, R. P. Jack, M. Scott-Gray, and J. Fegan; and to Sister J. Haig, Wardmaster J. Patterson, and the female and male nurses of the Edinburgh Infirmary Clinic, who carried out the injection treatment so skilfully.

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INDIVIDUAL RESISTANCE TO MALIGNANT DISEASE

ILLUSTRATED BY A CASE IN WHICH A METASTATIC DEPOSIT FROM A CARCINOMA OF THE BREAST OCCURRED IN THE APPENDIX AND LED TO PERFORATION AND PERITONITIS

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In general we are liable to think of the human body as capable of mustering only pathetic resistance to malignant disease. It has long been recognized, however, that in certain individuals an extraordinary power of resistance can be shown. Teacher (1908), Pearce Gould (1910), Bashford, Murray, and Cramer (1907), and Schmidt (1903) proved that a varying proportion of metastatic deposits can be strangulated successfully by the natural mechanisms of defence, and probably most cancer cells carried in the blood fail to establish themselves. Unfortunately, in most cases the enemy's reserves seem to be interminable, and in the end a proportion of the secondary deposits succeed in establishing themselves, and, by spreading, finally win the battle and the patient dies.

Histologically, the local defence reaction of the body to malignant disease is manifested by fibrosis and lymphocytic and eosinophil infiltration; it would appear that the body attempts to restrain tumour growth by encapsulation and strangulation. As compared with most normal tissues, malignant tumours require a correspondingly greater supply of nutrient fluid, containing especially glucose and oxygen, because of the rapidity of their growth and their wasteful methods of metabolism. Warburg (1925, 1925-7, 1930) has shown that in most malignant cells glycolysis, or fermentation of glucose to lactic acid, overshadows the normal respiratory process, in which glucose is split into carbon dioxide and water. Thus encapsulation, associated with constriction of the blood vessels supplying the tumour, may succeed in destroying malignant cells in a certain proportion of the foci. Teacher (1908) demonstrated the success of these local defence mechanisms against isolated metastatic deposits of chorion-epithelioma, one of the most actively proliferative of all tumours. He investigated the histological processes of defence in great detail and showed that metastatic deposits of tumour cells became encapsulated by an even more active proliferation of connective-tissue cells, which surrounded, constricted, starved, and finally replaced the tumour. Haemorrhage followed by coagulation, which is a characteristic feature associated with the growth of many of the most malignant nodules, also plays an important part in the destruction of tumour cells. It obstructs the supply routes to peripheral areas by pressure from within, and Teacher (1908) believes that it also stimulates the peripheral connective-tissue cells of the host to proliferate and form a fibrous encirclement. Pearce Gould (1910), Bashford, Murray, and Cramer (1907), and Schmidt (1903) have all described cases in which the local success of the defence mechanisms against isolated metastatic deposits has been proved histologically.

In 1939 Atkins made the interesting suggestion that the fibrosis occurring in chronic mastitis is part of the mechanism of defence against the onset of malignant disease. He confirmed the important work of Bloodgood (1932), who followed up a long series of cases for some years and who concluded that the incidence of breast cancer in patients suffering from a chronic mastitis is no greater than in the general population. The various types of chronic mastitis show varying degrees of epithelial and fibrous-tissue proliferation. Such epithelial activity might conceivably progress towards carcinoma if further stimulation occurred. Atkins (1939) says: "If now this fibrosis accompanies epithelial changes, which threaten cancer but rarely fulfil their threat, it is possible that the fibrous tissue may be produced in response to that threat and may play a part in preventing it from coming to fruition. Consequently it would be just those patients who are able to develop a fibrous-tissue reaction to epithelial overgrowth—that is, those who complain of the symptoms of chronic mastitis—who would be unlikely to develop cancer."

The Minister of Health, in exercise of his powers under Section 2 of the Water Act, 1945, has appointed the members of the Central Advisory Water Committee. Its terms of reference are to advise the Minister of Health, or any other Minister concerned, upon matters connected with the conservation and use of water resources; on the amendment of enactments which relate to, or in any way affect, the conservation or use of water resources or the provision of water supplies; and on any question that may be referred to the Committee by the Minister in connexion with the operation, or proposed amendment, of relevant enactments. It will also consider the operation of any such enactments, and make recommendations for their extension or modification. Communications concerning the work of the Committee should be sent to the secretary, Mr. M. R. P. Gregson, at the Ministry of Health.