

“ ONE SHOT ” TREATMENT OF VENEREAL DISEASES EMPLOYING PROCAINE PENICILLIN G WITH ALU- MINIUM MONOSTEARATE (P.A.M.)

BY

R. R. WILLCOX

*Consultant in Venereology, King Edward VII Hospital, Windsor, and
St. Mary's Hospital, Paddington. Lately Adviser in Venereology to the
Government of Southern Rhodesia.*

EVER since the discovery that penicillin was effective against syphilis efforts have been directed to the limitation of the number of injections to be given by the evolution of preparations which are either more slowly absorbed or more slowly excreted. The slow absorption methods gained the initiative with the introduction in 1945 of penicillin in oil beeswax (Romansky and Rittman) and the success of delayed excretion procedures, employing caronamide, came only after the delayed absorption techniques had become established arriving too late to enjoy general use.

Penicillin in oil beeswax, however, proved by no means always easy to administer, especially in the hands of the general practitioner remote from the surgery or clinic. The discovery that procaine combined with penicillin in equimolecular amounts to form a crystalline salt procaine penicillin which, if injected in watery or an oily medium, will give blood levels of penicillin comparable with those obtained with penicillin in oil beeswax (Herrell *et al.*) was heralded as a major advance.

Procaine penicillin was improved still further by the addition of a water-repellent substance, aluminium monostearate, after a single intramuscular injection of 600,000 units, of which detectable penicillin can be found in the blood for three to four days, while after a single dose of 2.0 or 2.4 million units for as long as a week or more (Young *et al.*).

The “single shot” treatment of gonorrhoea, first with penicillin in oil beeswax and then with procaine penicillin plain, has been established for a long time. Procaine penicillin with aluminium monostearate has proved no less successful although, with the more prolonged penicillin blood levels obtained with its use, there is a greater theoretical possibility of masking a concomitant incubating syphilitic infection and, for this reason and also on the grounds of economy,

some clinics have therefore reduced the dose given for gonorrhœa to 100,000 or 200,000 units which, in spite of the lower peak levels obtained, is apparently giving satisfactory clinical results.

Of greater interest, however, has been its use for early syphilis and it appears probable that Ehrlich's dream of curing the disease with one injection has at last been realized. Thomas *et al.* (1949a), employing four schedules consisting of single injections of 1·2 or 2·4 mega units of P.A.M., or divided injections of 1·2 mega units given weekly for two or four weeks, treated 30 cases of early syphilis with promising initial results. By the time that the same writers had treated 143 patients 113 were considered as showing satisfactory response (Kitchen *et al.*). Now Thomas *et al.* (1949b) report 160 cases so treated and after nine months 19 have been lost to observation, 17 still have insufficient follow up but 41 show serologic "cure" and 80 show serological improvement while there have been so far only three failures. Likewise Taggart *et al.* (1949) treated 97 patients with early syphilis by the "single shot" method but only 25 (7 of which were sero-negative primaries) were observed for six months and 2 required retreatment one of which was a probable reinfection.

We can but await the outcome of this American work, before reaching any definite conclusion but the preliminary observations are most encouraging. The type of work for which such treatment, if successful, would be the most applicable is the mass treatment of native populations where ordinary medical facilities are minimal and it would be especially welcomed in tropical and subtropical Africa.

The present paper is written on experience gained during a Venereal Diseases Survey of the African in Southern Rhodesia undertaken during 1949 (Willcox). It was considered desirable to give P.A.M. to in-patients of a Native Venereal Diseases Hospital and compare the initial results with those of other tried methods. Here there was an abundance of clinical material but the opportunities for follow-up were minimal as the African does not usually attend for such matters once the sores have healed. (Of 415 persons instructed to attend for monthly post-treatment blood tests at this hospital, for example, only 64 returned at the end of the first month.) Hence the data presented is concerned solely with the immediate results.

Some 114 venereal diseases patients were given single intramuscular injection of 2·4 mega units of procaine penicillin with 2 per cent aluminium monostearate (Boots) and 17 others received the same dose to assess its prophylactic value against an experimental infection with soft sore.

Penicillin Serum Levels.—Tests were made for the presence of penicillin on 80 sera from 40 patients at varying intervals after injection. Penicillin was found in all of 5 patients tested on the ninth day, all of 10 tested on the eighth day, all of 12 on the seventh day, all of 12 on the sixth day, all of 10 at the fifth day, all of 10 at the fourth day, all of 7 at the third day, all of 8 on the second day and all of 6 tested one day after receiving the injection.

The Patients.—The cases treated were as follows:

| Type of case | No. |
|--|-----|
| Dark field positive early syphilis | 30 |
| Dark field negative sero-positive clinical early syphilis | 22 |
| Dark field negative sero-negative clinical early syphilis | 23 |
| Dark field negative clinical early syphilis without blood test | 5 |
| Soft sore | 19 |
| Lymphogranuloma venereum | 4 |
| Gonococcal epididymo-orchitis | 2 |
| Others | 9 |

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Dark Field Positive Early Syphilis (30 Cases).—This group includes 20 cases of primary syphilis and 10 cases of secondary syphilis. Of the primary cases 9 were sero-negative and eleven sero-positive. In all *T. pallidum* was found in the dark field before treatment. Of 26 patients 15 had had their lesions for under two weeks and 11 over that time. The last admitted sexual contact was under a month previously in 20 and over a month in 10. All but one had made some form of financial payment, it being the customary 2s. 6d. "short time" in 16, and 5s. all night in 9 while in 5 others the money paid ranged from 1s. 6d. to a pre-lobola fee of £3. 3 of the patients had co-existent gonorrhoea. All of the patients were given single intramuscular injections of 2.4 mega units of P.A.M. and in all the dark field had become negative in twenty-four hours and the urethral discharges of the 3 affected rapidly cleared.

The average number of days before the sore had healed and the patient was discharged from hospital was 6.36 days (longest 14). 3 patients required additional treatment before the sore would heal, 2 with oral sulphadiazine and 1 with local calomel ointment. As with other rapid treatments with aureomycin and chloromycetin it was noted that cases of florid secondary syphilis apparently responded more quickly than those of primary syphilis (Willcox, 1949*b*). The average healing time for the 9 secondary cases was 5.5 days as against 6.8 days for the primary cases.

Dark Field Negative Sero-positive Early Syphilis (22 Cases).—These patients all had clinical syphilis as evidenced by the presence of classical syphilitic inguinal adenitis. Repeated dark fields of material from the sores, however, failed to show *T. pallidum* often on account of secondary infection or phimosis (of 310 consecutive admissions to this V.D. Hospital only 10 were circumcised). Gland punctures were not done in this series. In all, however, the serum tests for syphilis were positive. One patient had an additional gonococcal infection and in at least 3 cases, as evidenced by the presence of fluctuant buboes, there was thought to be a superadded chancroidal infection. Such was very common in this area.

Fifteen of 16 of the patients had had their condition for under two weeks. 20 had had their last sexual contact at periods under a month and only 2 longer than this time. 14 paid 2s. 6d. "short time," 4 gave 5s. for the night while 1 paid only 1s. 6d. and 3 paid nothing at all. All patients received single

injections of 2·4 mega units of P.A.M. and the average number of days before the sores were healed was 8·27 (longest 18). 4 of the patients, 2 of which were those suspected of having a superadded soft sore infection, were given oral sulphadiazine, 1 with penicillin in addition, and 2 others were given local calomel ointment. In this group also the three secondary cases (average 4·66 days) healed more quickly than those of primary syphilis. The case of gonorrhœa responded rapidly.

Dark Field Negative Sero-negative Clinical Early Syphilis (23 Cases).—This group of 23 patients had clinical primary syphilis, as evidenced by the sore and typical syphilitic inguinal glands, but no *T. pallidum* was found in two daily dark fields and the serum tests for syphilis were also negative. One patient had co-existent gonorrhœa. It is considered likely that some cases of chancroid were unwittingly included in this group and 1 case was definitely believed to have a double infection. Only 2 of 14 patients had had their lesions longer than two weeks. Of 22 noted the last contact had been less than a month in 20. 5 denied having paid any money; 12 gave the traditional 2s. 6d. for a brief liaison and 3 gave 5s. for the night. 2 others paid 1s. 6d. and £1 respectively.

All were given single intramuscular injections of 2·4 mega units of P.A.M. and the lesions healed in an average of 6·45 days (longest 13). 2 cases required additional treatment (1 with sulphadiazine and 1 with local calomel ointment) while 2 others received systemic penicillin for other reasons, 1 with sulphadiazine in addition. Of 5 other early syphilitics treated, 3 with primary and 2 with secondary syphilis, in whom there were negative dark fields but no record as to serology, the average period before healing of the sores was 5·8 days. 1 required additional treatment with oral sulphadiazine.

Soft Sore: Clinical Infection (19 Cases).—9 cases of clinical soft sore were also treated. The majority had typical multiple sore and 7 had fluctuant tender buboes. Repeated daily dark field examinations were negative in all. The serum tests for syphilis were negative in 15 but positive in 4 persons who were believed to be latent syphilitics with superadded chancroid.

Eight of 9 questioned had had the infection for under seven days and 1 over this time. The most recent sexual intercourse admitted had been under two weeks in 13 and over two weeks in 6. 17 had paid 2s. 6d. for this, 1 gave 5s. and 1 no payment. All were given one injection of 2·4 mega units of P.A.M. and the patients were ready for discharge in an average of 5·5 days (longest 13); buboes being aspirated as required. 3 were regarded as failures and required additional treatment with oral sulphadiazine.

Under ordinary European conditions penicillin is not a satisfactory drug for soft sore as its very use implies at least a two-year follow up as for syphilis in case the infection was in reality syphilitic. Penicillin, therefore, has never been recommended for this condition and is seldom used and indeed, on the basis of laboratory tests, has not been considered as particularly effective. Reports from persons treating patients in the tropics, however, have indicated that it may have a beneficial action in man. For example Lahiri (1947)

reported 32 cases of chancroidal bulbo successfully treated with penicillin in India and Pereyra (1948), also apparently with success, gave penicillin by local iontophoresis to 13 patients.

The objections to its use, if the treatment proves effective, cease to be valid in those countries where a proper follow up of treated patients is not possible provided the same treatment is given for soft sore as that currently employed for syphilis. Hence, should the "one shot" treatment be proved effective for syphilis, if it is likewise effective for soft sore its general use for all cases of penile sore would become not only the most expedient method administratively but also medically desirable. The efficacy of the "one shot" penicillin treatment was, therefore, also tested in the experimental infection.

Soft Sore: Experimental Infection.—If a minute amount (0.05 c.c.) of pus from a chancroidal bubo is injected intradermally into the forearm of the patient himself, or into other volunteers, a small pustule will form at the site of injection in two to three days which, unless treated, progresses into a chancroidal



ulcer (*see fig.*). If the lesion is needled when in the pustular stage, and the patient treated with curative drugs of which penicillin was found to be one, the ulcer stage may be avoided.

On the other hand if drugs curative for soft sore are given to the recipient at the time of inoculation of the bubo fluid, or to the donor at least twenty-four hours before aspiration of the bubo, no such reactions will be observed in the recipients. Thus the relative value of curative agents may be compared.

Five series of such experiments performing single injections of P.A.M. were performed. The donors all had fluctuant buboes with typical penile soft sores, repeated dark fields of which were negative. The serum tests for syphilis were likewise negative but the Dmelcos skin tests were positive. Although organisms resembling Ducrey's bacilli could be demonstrated in scrapings from the penile sores they were not seen either in the bubo pus or in smears taken from aspirated arm pustules.

(a) *Treating the Donor.*—A man with a chancroidal bubo received a single injection of 2.4 mega units of P.A.M. and six days later 0.05 c.c. of the by then milky bubo fluid was injected intradermally into the patient himself and 2 volunteers. Neither of the volunteers showed any reaction although a pustule formed on the arm of the donor which was successfully treated with oral sulphadiazine and a more concentrated penicillin course.

(b) *Treating Recipients at the Time of Inoculation.*—0.05 c.c. of bubo fluid from an untreated donor, which invoked a local reaction in 2 of 3 untreated volunteers injected, was also injected into the arms of 7 persons who had received single injections of 2.4 mega units of P.A.M. from one to eight days previously (the intervals between the P.A.M. injection and inoculation being one, four, four, five, seven, seven and eight days respectively). There were no less than 5 "takes" in these persons the only 2 unaffected had received P.A.M. one day and seven days before.

The same amount of bubo fluid from another untreated donor, which produced a "take" on himself and on one other volunteer control, was injected intradermally into 8 others who had been given single injections of 2.4 mega units P.A.M. one to eight days previously (the actual intervals being one, two, three, four, six, seven, seven and eight days respectively). In this group there were only 3 "takes" in those who had been given P.A.M. seven, seven and eight days prior to inoculation. All those recently injected were unaffected.

Bubo fluid from yet another untreated donor, which produced a "take" on himself and 2 controls, was injected intradermally into 1 volunteer who received a simultaneous injection of 2.4 mega units of P.A.M. No reaction followed.

It will be noted of the volunteers in the last three experiments that 8 had received the P.A.M. one to four days prior to inoculation and 8 between five and eight days. Only 2 "takes" occurred in the first group and no less than 6 in the second.

It thus appears that penicillin certainly has some action upon a chancroidal infection in man but that the small amount of penicillin present in the blood four days after a single injection of 2.4 mega units of P.A.M. while sufficient for syphilis is insufficient to check an incubating soft sore infection. That such is probably the case is indicated by a further experiment in which a more sustained penicillin regime was used with complete success. The fluid from an untreated donor was injected into himself and into 2 controls with a "take" on all. It was then injected into 19 volunteers 2 of which were treated with

streptomycin, 4 with aureomycin, 4 with sulphathiazole and 9 with eight daily injections of 600,000 units of penicillin in oil beeswax with a "take" on none. It is therefore concluded that a single injection of 2.4 mega units of P.A.M. has a definite action upon soft sore although a cure is not as certain than if a traditional eight-day course is given.

Lymphogranuloma Venereum.—Whether or not penicillin has some action upon this disease is another matter which has given rise to a difference of opinion. Certainly in the past penicillin has not been recommended as it is liable to mark syphilis. However, now that aureomycin has been found to be effective in lymphogranuloma venereum (Wright *et al.*, 1948) (one case was successfully treated in Southern Rhodesia), and now that aureomycin has been found to be strongly spirochaetocidal and able to heal the lesions of early syphilis (O'Leary *et al.*, 1948; Willcox, 1949c) it is evident that this objection is being ignored.

Several years ago, when serving in West Africa, the writer treated 25 Gold Coast Africans and 2 Europeans with climatic bubo with what today would be regarded as small doses of penicillin. 17 cleared up without further therapy (Willcox, 1946). The type of lymphogranuloma venereum seen in Southern Rhodesia, where it is not so prevalent as in West Africa, is principally in the form of climatic bubo of males. 4 such cases, all mild and in all of whom the serum tests for syphilis were negative, were treated with single injections of 2.4 mega units of P.A.M. In none were the buboes fluctuant before treatment. One proceeded to fluctuation and was aspirated but all were discharged from hospital in an average of seven days.

Other Disorders.—2 cases of epididymo-orchitis associated with a purulent urethral discharge in which gonococci were found in the smears responded excellently to a single injection of 2.4 mega units of P.A.M. being ready for discharge in a painless state four and five days respectively after treatment. A third case of epididymo-orchitis also with a purulent urethral discharge but in which no gonococci could be seen in the smear was also treated but did not respond. Bilharzia ova were not able to be demonstrated in the urine of this patient.

Good results were also obtained with a case of scrotal abscess which, after evacuation of pus, healed in twelve days and also in 3 cases of septic scabies, 1 of balanitis and 1 of septic penile abrasion. 1 case of hydrocele and 1 of penile warts, not surprisingly, did not respond.

It is concluded that single injections of P.A.M. will initially benefit most venereal conditions with the exception of granuloma inguinale and non-specific urethritis which respond to streptomycin, aureomycin and chloromycetin.

SUMMARY AND CONCLUSIONS

- (1) The "single shot" treatment of gonorrhoea is well established.
- (2) The "single shot" treatment of syphilis is undergoing trial in the U.S.A. and the preliminary reports are very promising.

(3) If such a treatment can produce a success of only 70 per cent, and all the evidence points to a better anticipated result than this, then it will have the greatest application in the mass treatment of native populations where the follow up of individual cases has of necessity to be ignored.

(4) If it proves a success the nature of the immediate results to be expected in Bantu natives under short-term observation are indicated in this paper. "Single" injections of 2.4 mega units of P.A.M. were given in all cases, 4 c.c. into each buttock.

(5) 30 cases of early syphilis proved by dark field had their sores healed on an average of 6.36 days after treatment. 3 required additional measures which were given for other reasons to a 4th.

(6) 22 cases of clinical early syphilis with a positive serology, but in which the dark fields were negative, were likewise treated and the sores healed in an average of 8.27 days. 6 required additional treatment.

(7) 23 patients, in whom the dark fields were negative and also had a negative serology, and 5 others in whom the dark field was also negative without record of their serology, received similar treatment and were discharged in an average of 6.2 days. 3 required additional treatment and it was given to 2 others for other reasons.

(8) 19 cases of soft sore were also treated healing in an average of 5.6 days, other treatment being necessary in 3.

(9) Its effects in preventing an experimental infection of soft sore in humans was also tested. It was successful in doing so in 6 out of 8 persons inoculated one to four days after receiving an injection and in only 2 out of 8 inoculated five to eight days after. The bubo fluid of a patient treated six days previously was still virulent to himself but not to 2 others.

(10) P.A.M. was also successful in 4 cases of mild climatic bubo, 2 of gonococcal epididymo-orchitis, 3 of septic scabies and 1 of scrotal abscess and certain other conditions.

(11) The average in-patient time for the 114 venereal diseases patients was 6.6 days. 12 of 80 early syphilitics were given additional treatment.

(12) If, as a result of the American work at present in progress, the "single shot" treatment of syphilis achieves its present expectations this method will be of inestimable value in treating venereal diseases in native populations especially in those places where a doctor can visit only once a week or less often and diagnostic facilities are minimal.

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