TREATMENT AS A FACTOR IN THE CONTROL OF THE VENEREAL DISEASES*

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This discussion of the control of the venereal diseases will limit itself to a consideration of the role of treatment in the control of syphilis and gonorrhea in particular, with a few comments about the other venereal diseases.

More or less effective attempts to control venereal disease within a single human body date back at least to Paracelsus, but the community control of venereal disease is largely a modern phenomenon which waited on the discovery of effective therapy. Theoretically, there are other approaches to the control of the venereal diseases, among them changing the sex habits of the human being, production of acceptable and effective vaccines, and the use of prophylaxis. The first of these alternatives has been too formidable for thorough consideration by most practical-minded men. No effective vaccine against any venereal disease has been developed nor has a prophylactic been devised that has proved practical for civilian populations.

The burden of control rests heavily on effective treatment. The American plan for the control of the venereal diseases, as set forth in the 1936 report of the Advisory Committee to the Surgeon General, is in essence a program for getting antisyphilitic drugs to syphilis. Later, when drugs became available for gonorrhea, the same goal was set for that disease. Whether or not these treatment programs have greatly reduced the incidence of syphilis and gonorrhea in the United States, one thing, at least, is certain: Widespread treatment programs with effective drugs have markedly reduced the total injury these pathogens are producing in man. Well within the memory of all is the time when physicians scolded irresponsible patients for thinking a case of gonorrhea was no worse than a bad cold. Many who now treat this disease with penicillin wish their own bad colds were no worse than the patients' gonorrhea. As Doctor Mahoney has remarked, gonorrhea, in his opinion, is fast losing its place as a major health problem because penicillin, through widespread early treatment of the disease, has greatly limited its ability to injure the human.

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In a less spectacular way this is also true of the minor venereal diseases. Chancroid responds quickly to the sulfonamides, and in the few cases where the patient cannot tolerate that drug, streptomycin can be used (1, 2, 3). In lymphogranuloma venereum the sulfonamides are usually rapidly successful (3). In granuloma inguinale streptomycin will succeed when antimony fails (4). Streptomycin has provided some remarkable cures in this disease. Even with syphilis, the great imitator, it safely can be said that its power to injure is rapidly being limited by early treatment. In fact, it is probably not altogether facetious to suggest that libraries take care to preserve their copies of Fournier and Stokes because physicians now have practical weapons which, if intelligently applied, can at the very least limit syphilis to the early manifestations of the disease. Gummas are becoming increasingly rare, aneurisms less and less frequent, and paresis less common.

When Doctor Parran started his great program for venereal disease control in the United States he began with about as great a handicap to success as could be imagined. To have to overcome the hostility of misguided public policy toward syphilis was discouragement enough; but to have to face the victims of that disease with the announcement that the best he and the medical profession had to offer in its amelioration was 18 months of weekly treatments with nauseating, painful, and dangerous drugs must have given pause even to so courageous a physician as Doctor Parran. The patients were not so courageous. As you know, from 50 to 80 per cent of those who had the courage to start that schedule of treatment failed to complete it.

Penicillin has changed all this. When Mahoney, Arnold, and Harris demonstrated the effectiveness of penicillin in the treatment of syphilis in 1943 (5), the physician was at last about to take possession of a treatment that could be used with safety and little discomfort and completed in one week or less. Its great and serious limitation was the need for hospitalization during therapy. In the years that followed the dose-time relationships were effectively worked out. The work of the Venereal Disease Research Laboratory has established the superiority of a schedule of therapy of 40,000 units of aqueous penicillin every 2 hours for 85 doses. Since this schedule of treatment was presented in detail in the literature (6) approximately one year ago it will not be necessary to dwell on it in detail at this time. It can be stated, however, that after an additional year of observation of the patients reported in the original article, the staff of the Venereal Disease Research Laboratory has seen nothing that would change its opinion of the efficacy of this schedule of treatment in early syphilis. The 40,000-unit schedule demonstrated that such a schedule was satisfactory as regards a sufficiently high minimum serum level of penicillin over a sufficient length of time. Subsequently, studies were undertaken to determine the minimum length of

time that an effective serum level of penicillin must be maintained in order to effect a clinical and serologic cure. The Chicago experience with massive doses of penicillin over a 24-hour treatment period had shown the ineffectiveness of so short a period (7). In the investigation for a shorter treatment time it was decided arbitrarily to triple the time employed by the Chicago group. A schedule of 200,000 units of aqueous penicillin given every 2 hours for 36 doses was used. During the past two years 451 cases of darkfield positive primary and secondary syphilis have been treated with this schedule at the Laboratory. Only patients experiencing their first attack of syphilis and giving no history of penicillin therapy *for any cause* within the preceding three months were admitted to the study. These restrictions were in addition to the requirement that all patients have darkfield positive lesions, which in those with secondary syphilis had to be on the skin of the body outside the genital area. Because of this requirement, the number of secondaries in the series is smaller than that usually seen. The ratio of primaries to secondaries was approximately 70 to 30. About 18 months have passed since this schedule of treatment was begun on 451 patients, and it is possible to draw a tentative conclusion as to the efficacy of a 72-hour treatment period. First of all, it can be said that the results of this schedule practically parallel the results obtained with the previous schedule of 40,000 units every 2 hours for 85 doses, so that it appears possible to obtain the same satisfactory treatment of early syphilis in 3 days that had previously been shown possible in $7\frac{1}{2}$ days.

Of the 451 cases treated on this schedule, 16 patients have been re-treated. Of those cases re-treated, in the judgment of the clinicians who observed the cases, 3 were clinical relapses due to the inadequacy of the treatment for those patients. The other 13 are believed, after careful consideration of each individual case, to be undoubted reinfections. However, in evaluating the schedule, all re-treatments are classified as treatment failures and are therefore counted against the schedule. At the end of the first year's observation of patients treated on the 3-day schedule there is an accumulative re-treatment rate of 5.55 per cent, while with the previously mentioned $7\frac{1}{2}$-day schedule the re-treatment rate was 3.60 per cent at the end of the first year's observation; or, to put it another way, in the 3-day schedule at the end of one year's observation there is a satisfactory condition in 94.45 per cent of the patients treated, while at the end of one year's observation of patients treated with the $7\frac{1}{2}$-day schedule there is a 96.40 per cent satisfactory condition of patients treated. The slight difference between the two schedules has no statistical significance. Among those treated on the 3-day schedule there have been, as yet, no failures beyond the one-year observation period. It is felt, therefore, that early syphilis can probably be effectively treated if an adequate level of penicillin is maintained in the blood stream for a minimum period of 72 hours.

The question then arose whether or not it was possible to decrease the total treatment time still further. It was decided to try a 48-hour schedule using 300,000 units of aqueous penicillin as the dose. A schedule of 300,000 units every 2 hours for 24 doses was tried on 111 patients with darkfield-positive primary and secondary syphilis, using the same standards for admission to the schedule as with the previous schedule. This schedule is of more recent origin, and it has been possible to follow the patients for a minimum of only 6 months. However, there are already enough data to demonstrate that 48 hours is not long enough to produce a sufficiently effective schedule of treatment in spite of the very high doses of penicillin that were used. In six months of observation there have been 7 cases of re-treatment out of 111 in this group. Six are clear-cut treatment failures and the seventh may be, although there is a possibility that in that case so-called pingpong syphilis was transferred back and forth between husband and wife. In six months this schedule has produced approximately ten times as many treatment failures as have accrued in one-and-a-half to three years of observation on the 3- and 7½-day schedule. It can, therefore, be concluded that the minimum time which an effective penicillin level must be maintained for the treatment of early syphilis lies somewhere between 48 and 72 hours.

It is obvious that all of the schedules discussed so far must be administered in a hospital, a circumstance which greatly limits the usefulness of the schedules on a world-wide basis. To overcome this difficulty many have sought, since the early days of penicillin production, to produce a delayed-absorption product which would widen the interval between injections. Romansky and his group developed the first practical method of delaying absorption of amorphous penicillin by the use of beeswax and oil. This has become the familiar POB. As a commercial product POB showed a considerable variation in its ability to maintain blood levels, with the result that the practitioner could not be certain his patient had a therapeutic level from one dose to the next when the interval between injections was 24 hours or longer. Nevertheless, good results in the treatment of syphilis with POB have been reported by Evan Thomas (8) and others. But POB must take its place alongside of mercury, arsenic, and bismuth among the eventually-to-be-forgotten drugs of syphilis therapy.

Procaine penicillin made beeswax unnecessary in the delayed-absorption use of the antibiotic. Levels can be maintained as long or longer with procaine penicillin in oil as was possible with the soluble penicillin salts in oil and beeswax. One of the limitations of procaine penicillin in oil, however, is the fact that the absorption time is dependent upon the crystal size, i.e., the larger the crystal the longer the absorption time. Unfortunately, when large crystals are used there is a tendency for them to settle out of the oil and form a hard mass which is difficult to break up

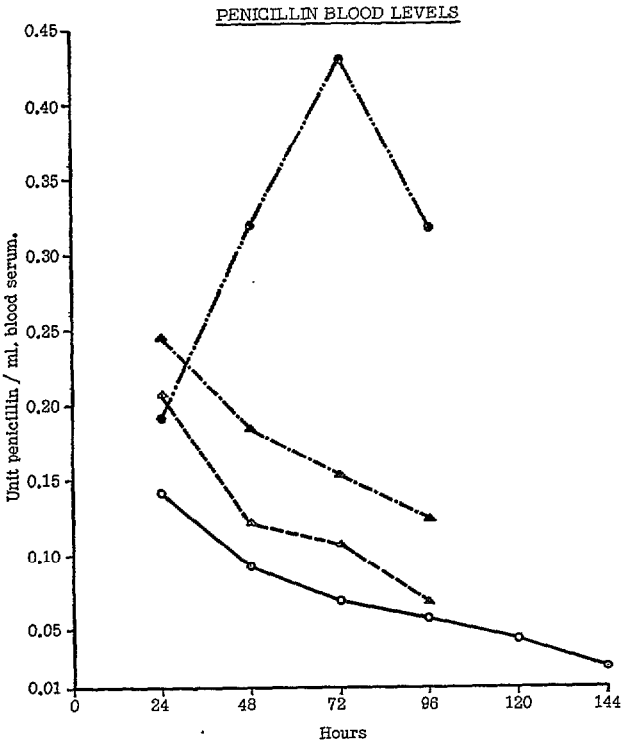
when the drug is to be administered. In addition, large crystals cause clumping with clogging of the syringes and needles and is therefore quite difficult to use. A new product has now been made available which, in all probability, will make previous preparations obsolete. It was discovered, in the course of investigations carried out during the war, that aluminum monostearate is a powerful hydrophobic compound which will prevent the absorption of water into the skin when it is applied as an ointment. The substance was used extensively to prevent what was commonly known in the war as "immersion foot," a condition which had to be guarded against among seamen and military personnel who were stranded in water-filled life rafts and life boats after accidents at sea. This compound was produced in a laboratory where penicillin was also being produced and it was considered as a possible device for prolonging the absorption time of penicillin. When 2 per cent aluminum monostearate is added to procaine penicillin in oil the absorption time is strikingly prolonged. Further investigation demonstrated that contrary to experience without aluminum monostearate, the smaller the crystal the more prolonged was the absorption time, so that commercially there is now being produced a microcyrstal-procaine penicillin with a particle size of 5 microns or less. This product, suspended in peanut oil with 2 per cent aluminum monostearate, forms a permanent suspension from which the crystals do not settle out, making it possible to dispense the drug more accurately and much more easily.

At the Venereal Disease Research Laboratory extensive studies of blood serum levels have been carried out after the injection of various amounts and kinds of procaine penicillin. The findings parallel and confirm those of Kitchen (9) and others as to the remarkably long serum levels possible with microcrystal-procaine penicillin in peanut oil with aluminum monostearate.

It now becomes possible to envisage what Ehrlich so energetically sought—a therapia sterilisans magna—a single-injection treatment of syphilis. If it is true that early syphilis can be effectively treated when an effective blood level of penicillin is maintained for 72 hours, then it is only necessary to demonstrate that the levels obtained with microcrystal penicillin and aluminum monostearate are effective. Such studies are now under way.

Groups of patients are being given 1,200,000 units, i.e., 4 cc. of the preparation, in one injection; other groups are being given 900,000 units in one injection; and still another group is receiving 300,000 units in one injection. It is important not only to demonstrate that early syphilis can be cured with a single injection of penicillin, but it is also important to determine the minimum amount of penicillin that can be safely administered with an expectation of cure in a very large per cent of the cases treated. This is especially true from the standpoint of world control since the cost of the drug will undoubtedly determine the extent of the

treatment program in many areas. Perhaps it is not too much to hope that within our lifetime Ehrlich's dream will come true and syphilis will become a rarity and Fournier's classic will become a curiosity.



Procaine penicillin G (microcrystals) in peanut oil containing 2% (w/v) aluminum monostearate. One injection 300,000 units. 35 patients.

Procaine penicillin G (microcrystals) in peanut oil containing 2% (w/v) aluminum monostearate. One injection 900,000 units. 21 patients.

Procaine penicillin G (microcrystals) in peanut oil containing 2% (w/v) aluminum monostearate. One injection 600,000 units. 84 patients.

Procaine penicillin G (microcrystals) in peanut oil containing 2% (w/v) aluminum monostearate. 600,000 units q. 24 x 3. 28 patients.

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EL TRATAMIENTO COMO FACTOR EN EL CONTROL DE LAS ENFERMEDADES VENÉREAS (*Sumario*)

Expónese en este estudio sobre el papel de la terapéutica en el control de la sífilis y la blenorragia, que entre los medios de confrontar el problema se hallan la modificación de los hábitos sexuales; el empleo de vacunas eficaces, y la profilaxis, pero que resultando el primero de gran magnitud para abordarlo en forma práctica, y no disponiéndose de vacuna eficaz contra dichas enfermedades, la responsabilidad de su control recae en la terapéutica. La blenorragia está cediendo rápidamente ante la penicilinoterapia, y lo mismo puede decirse de las enfermedades venéreas menores; el chancro blando responde rápidamente a las sulfonamidas, pudiendo emplearse la estreptomicina en caso de intolerancia a la droga; en el linfogranuloma venéreo las sulfonamidas resultan de acción rápida y eficaz. En la actualidad es posible vislumbrar lo que con tanto tesón buscara Ehrlich: un tratamiento de la sífilis consistente de una sola inyección. Si es cierto que la sífilis temprana puede ser tratada eficazmente cuando se mantiene durante 72 horas un nivel sanguíneo adecuado de penicilina, sólo resta demostrar que son adecuados los niveles obtenidos con penicilina microcristalina y monoestearato de aluminio, a cuyo fin se están realizando estudios actualmente. A ciertos grupos de enfermos se les están administrando 1,200,000 unidades, esto es, 4 cc de la droga en una sola inyección; a otros grupos se les dan 900,000 unidades en una sola inyección, y otro grupo recibe 300,000 unidades en una sola inyección. Es importante comprobar que la sífilis temprana puede ser curada con una sola inyección de penicilina; y desde el punto de vista de control mundial, también precisa definir la cantidad mínima de penicilina que puede administrarse sin peligro y con esperanzas de curación en un porcentaje muy elevado de los casos tratados, ya que el costo de la droga indudablemente determinará en muchas regiones la magnitud de los problemas de tratamiento. Tal vez no sea demasiado optimista esperar que dentro de nuestra vida el sueño de Ehrlich se traduzca en realidad y la sífilis se convierta en enfermedad rara; quizás aun, la obra clásica de Fournier se convierta en curiosidad.