Section of Medicine

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Penicillin in the Treatment of Syphilis

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ON the basis of the observation by Mahoney that penicillin has marked spirocheticidal effects in both rabbit and human syphilis, a study of penicillin therapy in 15 patients with early syphilis was recently undertaken at the 2nd General Hospital, U.S. Army. This report will deal only with the immediate effects of treatment, inasmuch as insufficient time has elapsed to allow any conclusions as to the rate of reversal of the blood serologic test for syphilis (STS) or of the eventual outcome as to cure of syphilis in these patients. The patients selected were from non-combat units, in order that adequate follow-up studies could be assured.

The types of syphilis present were as follows: 3 sero-negative primary, 8 sero-positive primary, and 4 secondary. 13 patients had lesions from which *Treponema pallida* could be demonstrated, and the rate of disappearance of treponemata was determined by examinations made at intervals of two hours during the initial day of treatment.

Two schedules of treatment were employed: 5 patients received an injection of 20,000 units of penicillin intramuscularly every four hours, night and day, until a total of 1,000,000 units had been given over a period of just over eight days; 10 patients received an injection of 20,000 units of penicillin every four hours until a total of 500,000 units had been given over a period of four days.

The immediate effects of treatment may be summarized briefly:—

Herxheimer reaction.—Two of the 15 patients had brisk Herxheimer reactions consisting of fever of 103° and 101° F., respectively, between eight and twelve hours after the initial injection of penicillin. In both of these patients there was marked accentuation of the presenting lesions of syphilis, in one patient a maculo-papular eruption on the trunk, in the other a chancre of the lip. Seven patients had oral temperatures of 100° F. within twelve hours after the initial injection; 6 patients had no fever. None of the reactions noted interfered with continuance of treatment.

Disappearance of Tr. pallida.—The presenting lesions of syphilis became negative for spirochetes of syphilis within fourteen hours in 12 of the 13 patients in whom serial examinations were done. Spirochetes were recovered from one patient fourteen hours after treatment was started; they were not present when the next examination was done ten hours later.

Healing of lesions.—All types of lesions, including clean and secondarily infected chancres, macular and papular secondary lesions, and peri-anal condylomata, healed more quickly than after Mapharsen (Mapharside) therapy. Using the rate of epithelization as a criterion of healing, the time required varied from three to seven days, with a mean of between four and five days. Satellite lymphadenopathy subsided more slowly. The rapidity with which lesions of early syphilis melted away was striking and impressive.

Blood serologic tests.—Quantitative Kahn tests were done daily or every other day during the period of observation in the hospital. There were no changes which could be regarded as outside the limits of error of this method of determining the amount of

syphilis reagin, but it is felt that administration of penicillin probably has the effect of increasing the Kahn titre during the first week of treatment in patients with early syphilis. Following completion of treatment, Kahn tests are being taken at weekly intervals on all patients. In five patients who had a positive STS at the beginning of treatment, and who have now been followed for five weeks, the STS has become negative. This is in accord with Mahoney's observation in four patients, that the STS became negative in from four to seven weeks after administration of 1,280,000 units of penicillin over a period of eight and one-half days.

SUMMARY

Penicillin has a strikingly beneficial effect in the treatment of early syphilis. In our small series, the rate of disappearance of spirochetes and the healing of early lesions were both more rapid than that observed after arsphenamine therapy, either of the conservative or intensive type. The absence of reactions to treatment, and the short time during which treatment may be compressed, make this method of treatment of great potential value in military medicine. Prolonged arsphenamine bismuth therapy for syphilis is unsatisfactory at best, and under conditions of war the difficulties of carrying it out regularly may at times be insurmountable. Intensive therapy offers the advantage of assuring the patient of completion of treatment and prospect of cure in 85 to 90 per cent. of patients, but requires hospitalization for twenty to twenty-five days, and must be given under expert direction if undue reactions to treatment are to be avoided. The immediate effects of penicillin are greatly superior, and it is hoped that the initial promise of this method will be confirmed by the extensive studies now proceeding in the United States and elsewhere.

Some Aspects of Bacterial Metabolism in Relation to Chemotherapy

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THE antibacterial drugs of the sulphanilyl group, beginning with prontosil and sulphanilamide, were evolved without knowledge of the target to be attacked within the disease-producing bacteria. But the introduction of these drugs took place at a time when great advances had been made in our knowledge of bacterial biochemistry. A turning point came when it was shown by Woods (1940) that p-aminobenzoic acid was a specific antagonist of bacterial growth-inhibitions caused by sulphanilamide. This observation directly linked the growth-inhibitory effects of the antibacterial drug with the growth processes of the bacterial parasite in a way which threw unexpected light on the target in the parasite at which the drug should be aimed—namely its metabolic processes. The chemical relation between the drug sulphanilamide, i.e. p-aminobenzene sulphonamide and its natural antagonist p-aminobenzoic acid, is very striking, the drug having a sulphonamide group in place of the carboxyl group of its antagonist. Woods suggested that p-aminobenzoic acid itself was really an important metabolite for the streptococci with which he was working, and that it was the normal utilization of this essential metabolite with which the sulphanilamide interfered. Soon after, p-aminobenzoic acid was indeed found to be an essential growth factor for several different species of bacteria, as Woods had predicted (Rubbo and Gillespie, 1940; Lampen and Peterson, 1941; Lampen, Underkofler and Peterson, 1942). This substance is now recognized as an essential metabolite for many bacterial species as well as for other types of organism. Woods showed that the relation of sulphanilamide to p-aminobenzoic acid in his case was analogous to that found in the competitive inhibition of an enzyme reaction. This suggested that the sulphanilamide competed with p-aminobenzoic acid in the utilization of the latter by an enzyme system of the bacterial cell for which p-aminobenzoic acid was the normal substrate, this enzyme reaction being essential for the growth of the bacterial cell.

The generalization which followed from this was put forward by Fildes (1940) namely, that bacteriostatic substances could be designed deliberately to interfere with metabolic reactions which were essential to the growth of the bacteria it was desired to inhibit, by making the inhibitor to have a chemical structure related to, but sufficiently different from, one of the essential metabolites of the cell. The drug might then be expected to interfere with the use of the normal metabolite, by some form of enzyme inhibition.