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CIRCULAR LETTER NO. 20

The Treatment of Syphilis

1. The purpose of this Circular Letter is to outline certain changes in the management of syphilis, based on increasing experience with penicillin therapy. It is, in part, abstracted from WD Technical Bulletin 106, 11 October 1944, with additions based on the experience in ETO.

2. Indications for Penicillin Treatment of Syphilis. Penicillin will be used in the treatment of the following types of syphilis:

a. Untreated primary and secondary syphilis.

b. Untreated latent syphilis. It is essential that a preliminary spinal fluid examination be made in all cases of presumed latent syphilis. If the spinal fluid is abnormal as defined in Circular Letter No. 103, Office of the Chief Surgeon, 9 August 1944, the case must be classified as asymptomatic neurosyphilis and be managed according to par. 8a below.

c. Neurosyphilis.

3. Indications for combined Penicillin-Mapharsen therapy for syphilis.

a. Treated primary and secondary syphilis that has failed to respond to mapharsen-bismuth therapy, or to intensive arsenotherapy, or to penicillin therapy, as the case may be. This includes:

(1) Clinical relapse, such as mucocutaneous, ocular, osseous, or visceral.

(2) Treatment resistance, a rare condition, manifested by failure of the primary and secondary lesions to respond to adequate mapharsen-bismuth therapy, usually accompanied by the presence of living treponemas in the lesions.

(3) Serologic relapse as evidenced by reversal of a negative STS (serologic test for syphilis) at the conclusion of Mapharsen-bismuth therapy to positive during the 6 months post-treatment observation period, or during the 12 month observation period following intensive arsenotherapy or penicillin therapy. The criteria of serologic relapse are discussed in paragraphs 8b and c below.

(4) Serum-fastness as evidenced by a persistent positive STS at the end of mapharsen-bismuth therapy, or six months after intensive arsenotherapy or penicillin therapy.

4. Technique of Penicillin Treatment of Syphilis.

a. Penicillin therapy requires hospitalization of approximately 10 days, including 7 ½ days of therapy, and time consumed for pretherapeutic diagnostic procedures and administrative details.

b. Dosage and technique of administration of penicillin. The total dosage will be 2,400,000 units of penicillin, given in 60 consecutive intramuscular injections of 40,000 units (2 c.c. of solution) each, at 3-hour intervals day and night for 7 ½ days. No additional anti-syphilitic therapy is to be given after the completion of the course of penicillin except in the case of asymptomatic neurosyphilis.

c. Noninterruption of penicillin treatment. Treatment should continue without interruption after its initiation. On the first day of treatment, commonly, and during the couse of treatment less frequently, minor reactions may be encountered. These are almost never an indication for the discontinuance or interruption of therapy.

5. Reactions observed in Penicillin Treatment of Syphilis.

a. Herxheimer reactions. These occur frequently in cases of primary and secondary syphilis, less commonly in cases of latent syphilis, and rarely in cases that have already received some anti-syphilitic therapy. The manifestations may be focal or systemic and are ascribed to the massive destruction of treponemas in the syphilitic lesions and in the blood stream. These reactions may therefore be considered of favorable significance. Both the focal and systemic Herxheimer reactions are encountered on the first day of treatment only. They begin usually some 3 to 6 hours after the

first penicillin injection, gradually become worse and reach a peak, after which they slowly and progressively subside, disappearing within an average of 24 hours. No specific therapy is required although such drugs as aspirin and codeine may be given for relief of symptoms. It must be emphasized that these symptoms disappear spontaneously in spite of the continued regular administration of penicillin, and are not justification for discontinuance of penicillin.

(1) The focal Herxheimer reaction consists of an aggravation of the existing syphilitic lesions. There may be increased swelling of the chancre, further increase of already enlarged regional lymph nodes accompanied by pain, and exaggeration of the secondary eruption. A pallid, sparse, macular eruption often becomes extremely profuse and vividly red, and may resemble measles or scarlet fever.

(2) The systemic Herxheimer reaction may be manifested by a variety of symptoms, such as headache, malaise, nausea, occasionally vomiting, abdominal cramps and weakness, but its most characteristic features are chilly sensations and fever. Peak temperatures above 105°F have been recorded, although generally lower grades of fever prevail.

b. Other reactions to penicillin. Other reactions caused by penicillin have been rare and ordinarily trivial. Most patients will complain of more or less muscle soreness at the site of injections, but usually this is not objectionable. The most common late systemic reactions have been secondary fever occurring toward the end of treatment and terminating immediately on its cessation; urticaria; generalized pruritus; erythema nodosum lesions; mild erythema multiforme; diffuse toxic erythema-like eruptions; herpes simplex; and mild gastro-intestinal symptoms such as abdominal cramps, nausea, and occasionally vomiting.

6. Post-Treatment Observation of Patients Treated for Syphilis with Penicillin.

a. Serologic and Clinical follow-up.

(1) All syphilis cases treated with penicillin will have a physical inspection and quantitative STS at the following times after treatment:

Two Months
Four Months
Six Months
Nine Months
Twelve Months

(2) On each specimen of blood the laboratory should be requested by the medical officer to perform the authorized quantitative STS described in TM 8-227, and to report the result in units.

b. Spinal fluid.

(1) In primary and secondary syphilis the spinal fluid will be examined as soon as feasible after the completion of 6 months of observation. In no case will the syphilis register be closed until this examination has been accomplished.

(2) Spinal fluid tests to be performed. Cell count; Pandy or Nonne-Apelt qualitative tests for protein; quantitative estimation of total protein; complement fixation (Wassermann) test, or, if this is not feasible, a flocculation test; and colloidal gold test. The cell count and qualitative protein determination should be performed at the local laboratory within 30 minutes after the spinal fluid is withdrawn.

c. Special administrative features of penicillin treatment.

(1) Because the long-term effects of penicillin in the treatment of syphilis have not yet been determined, it is vital that all concerned cooperate in ensuring that adequate follow-up studies are made. The Commanding Officer of each U.S. Army hospital in the ETO will submit a monthly listing of patients who have received penicillin therapy for syphilis during the month. ETOUSA Form No. 343, 3 November 1944, List of Syphilis patients treated with Penicillin, will be utilized in accomplishing this end. The name, ASN and organization of each patient will be shown. In addition, the race, diagnosis, and highest Kahn titre during treatment will be given. The report will be addressed to Office of the Chief Surgeon, Attn: Medical Records Division, APO 413.

(2) Preparation of the Syphilis Register, W.D.M.D. Form No. 78. This will be filled in completely in the usual manner, and a brief note describing the treatment procedure will be made in the Register. A sample note reads as follows:

> Soldier received intensive penicillin therapy from 1 Nov 1944 to 8 Nov 1944 consisting of 60 consecutive intramuscular injections of 40,000 units each at 3-hour intervals for a total dose of 2,400,000 units. There was a febrile Herxheimer reaction the first day with peak fever of 102.4°F. Lesions were healed when therapy was completed.

(3) Preparation of W.D.,M.D. Form No. 78a (Patient's Record of Syphilis Treatment). This will be prepared as a personal record for the soldier. A brief account of the treatment status of the patient will be entered. This can be done simply by repeating the note made in the syphilis register, described in (1) above. An additional statement will be made regarding the follow-up measures to be carried out.

(4) Closure of the syphilis register.

(a) Primary and secondary syphilis. On completion of the spinal fluid examination and physical examination six or more months after penicillin therapy has been given, providing the results are satisfactory, the Syphilis Register will be sent to the Office of the Chief Surgeon (Attention Medical Records Division, APO 413) for review and safekeeping. The follow-up blood tests required at the end of nine and twelve months will be initiated in the Office of the Chief Surgeon.

(b) Latent Syphilis. The Syphilis Register will be closed in latent Syphilis and transmitted to the Office of the Chief Surgeon, Medical Records Division, after twelve months of observation if there has been no clinical or serologic relapse even though the serologic tests have remained persistently positive. It is anticipated that serum-fastness will not be uncommon in cases that receive penicillin therapy in the latent stage of syphilis.

7. Clinical and Serologic Post-Treatment Course of Favorably Responding Penicillin Treated Syphilis.

a. Primary and Secondary Syphilis.

(1) Clinical Course. The rate of healing of primary and secondary syphilitic lesions varies, depending principally upon the type of lesion. Large ulcerated or deeply infiltrated lesions may not heal completely for 1 to 3 weeks after treatment is concluded. Presence of such lesions, unless physically incapacitating, or requiring extensive local treatment, will not be cause for prolonged hospitalization.

(2) Serologic course. The titre of the STS declines gradually from positive to negative in the post-treatment period, the negative phase being achieved in a variable time. The majority of cases become negative between the second and fourth post-treatment months, although earlier and later reversals occur. In general, the higher the initial titre of the quantitative STS the longer the test will take to become negative.

(3) Critical relapse period on the basis of present information. The critical period for relapse, both clinical and serologic, appears to lie between the third and sixth post-treatment months, although relapses have been observed at earlier and later periods.

b. Latent Syphilis.

(1) Serologic course. The serologic curve may take the same course as that observed in primary and secondary syphilis. This is especially true in cases of very early latent syphilis, notably those which have only recently passed from the secondary

phase into the phase of latency. On the other hand, individuals with older latent syphilis are likely to exhibit serologic refractoriness, the STS showing little or no tendency to fall in titre.

8. Definition of Penicillin Failure. Care should be exercised in the determination of failure since patients may develop intercurrent skin eruptions of nonsyphilitic character. Intercurrent infections and smallpox vaccination may produce a temporary elevation of the titre of the quantitative STS. All forms of clinical relapse are generally accompanied by serologic relapse, or by persistently high serologic titres. Treatment failures may be divided into nine categories.

a. Mucous and/or cutaneous relapse is manifested by the appearance of syphilitic lesions of the mouth, genitals, and skin, the latter especially in the anogenital region. Darkfield examinations should be performed to corroborate the diagnosis. If Darkfield examination is negative, repeated quantitative STS should be performed which will reveal a progressively rising titre.

b. Serologic relapse is manifested by a rising titre of the quantitative STS after the test had become negative or has previously manifested a falling trend. When a serologic relapse is suspected, the patient should be thoroughly and completely examined, since serologic relapse is usually accompanied or shortly followed-up by mucocutaneous or some other clinical relapse. Since the titre of the quantitative STS may vary from time to time, as a result of laboratory technique, and in different laboratories, it is not sufficient to accept minor fluctuations in the titre as evidence of serologic relapse. Serologic relapse should be diagnosed only when a series of consecutive tests, performed preferably in the same laboratory, shows persistently increasing titres over a period of 3 to 4 weeks.

c. Serum-fastness in primary and secondary syphilis is manifested by a failure of the quantitative STS to show a marked decline within an arbitrary period of six months after completion of therapy. Minor fluctuations in the titre may be observed, but there is no consistent, gradual and maintained fall to negative. This condition will apparently be uncommon in primary and secondary syphilis, where it will be considered a treatment failure when present 6 months after completion of therapy. It will not be uncommon in latent syphilis, in which it will not be considered a treatment failure.

d. Neurologic relapse (neurorecurrence) may occur as acute syphilitic meningitis, with headache, dizzy spells, fever, and rigidity of neck. In fulminant cases, coma may supervene rather rapidly. Less commonly relapse in the nervous system may appear as an isolated cranial nerve palsy or paralysis of one or more extremities. Diagnosis should be confirmed by spinal fluid examination, and a neurologist should be consulted for diagnostic assistance.

e. Asymptomatic neurosyphilis is manifested only by an abnormal spinal fluid.

f. Ocular relapse may be manifested by iritis, usually unilateral, or optic neuritis, or neuroretinitis, which may be unilateral or bilateral. An ophthalmologist should be consulted.

g. Osseous relapse is manifested by severe pain, often nocturnal, in the long bones, most often the tibias, or severe headaches when cranial bones are affected. Local tenderness is often very acute.

h. To date, no instance of true treatment resistance to penicillin, insofar as failure of mucocutaneous lesions to heal or treponemas to disappear, has been observed.

9. Management of Penicillin Failures.

a. Cases of neurologic relapse and asymptomatic neurosyphilis will receive a total of 4,000,000 Oxford units of penicillin while in hospital, and then be managed in accordance with the directions contained in Circular Letter No. 103, "Management of Neurosyphilis", Office of the Chief Surgeon, 9 August 1944. The penicillin will be administered in 80 consecutive injections of 50,000 units each at 3-hour intervals day and night for 10 days. In patients in whom the possibility of a severe Herxheimer reaction may be considered to have serious potentialities, the initial doses of penicillin may be reduced to 10,000 units, but it should be possible to reach the full dosage schedule within 48 hours. Patients with Grade I and II spinal fluids will be continued on standard mapharsen-bismuth therapy after completion of the penicillin course.

b. Patients with other types of treatment failure will receive a second course of treatment consisting of <u>concurrent</u> administration of penicillin and Mapharsen, as follows:

Penicillin:	80 injections of 50,000 units each given intra-muscularly at 3 hour intervals day and night for ten days, a total of 4,000,000 units.
Mapharsen:	60 mgms intravenously daily for 8 days, a total of 480 mgms.

(1) Management of reactions to Mapharsen. Certain patients will prove more or less intolerant to Mapharsen given in accordance with the above schedule. However, unless the patient has previously received Mapharsen, it is not likely that such reactions will develop prior to the 5th day of treatment. The reactions to be looked for are:

(a) Fever. Severe reactions to intensive arsenotherapy of this type almost never occur in the absence of accompanying or preceding fever. In any patient showing a rise

in temperature above 100°F, the patient should be carefully examined clinically, expecially for the reactions listed below, and adequate laboratory studies performed.

(b) Toxic encephalopathy

(c) Neutropenia.

(d) Toxicodermal reactions of various types, usually a morbilliform or scarlatiniform eruption accompanied by fever.

(e) Hepatitis.

(2) A reaction to Mapharsen of more than slight severity is an indication for discontinuance of such medication. The penicillin course will be continued to completion, and the patient then placed on observation.

(3) Patients with severe reactions to Mapharsen should be treated with injections of BAL, four injections of 2 c.c. each during the first 24 hours, and 2 c.c. daily for the next four days.

10. Management of patients already on standard Mapharsen-bismuth treatment for syphilis who receive penicillin for a surgical wound or an intercurrent medical infection. Insofar as is possible without prejudice to the general medical and surgical treatment of such patients, penicillin therapy to a total of 2,400,000 units should be given while the patient is in hospital. The patient will then be placed on observation as far as his syphilitic infection is concerned. It is impossible at present to evaluate the influence of partial courses of penicillin in the cure of syphilis, and it is important, therefore, that the full course of penicillin be given before the patient is placed on observation.

By order of the Chief Surgeon:

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Executive Officer.