Penicillin in Benign Late and Visceral Syphilis*

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For the purpose of this discussion, benign late syphilis may be loosely defined as allergic in type, with chronic, focal inflammatory lesions involving structures not essential to life or vision, and which develop more than two years after infection. In the great majority of patients such lesions involve the skin or mucous membranes (late nodular syphilides, cutaneous or mucosal gummas), the bones (periostitis, osteitis, osteomyelitis) or the muscles or tendons (gummas of muscles, synovitis). Infrequently, patients with the allergic tendency develop gummatous lesions in such important viscera as the liver, spleen, stomach, lungs or testes. Gummatous involvement of the cardiovascular or central nervous systems is rare; and in these situations the granulomatous process may constitute a direct and immediate threat to life. In effect this communication, therefore, resolves itself into a consideration of the effects of intramuscularly administered penicillin on the mucocutaneous, osseous and visceral manifestations of late acquired syphilis, manifestations which, however painful, disabling or disfiguring, seldom if ever kill the patient. The material to be presented represents a review of the literature together with an analysis of the records of the Syphilis Clinic, Department of Medicine, the Johns Hopkins Hospital, including data previously published.[1]

The mode of action of penicillin in benign late syphilis is not entirely clear. The therapeutic activity of the antibiotic, aside from an ill-defined "general tonic effect," probably rests on its direct bactericidal (i.e., treponemicidal) action. The typical gummatous lesion is a chronic, focal granuloma with central caseation necrosis. Although Treponema pallida are seldom demonstrated in these lesions, it is believed by many that the organisms develop about a focus in an individual who has become sensitized or allergic to the parasite or to its by-products. This hypothesis would explain nicely the healing of gummas following the administration of treponemicidal drugs such as arsenic, bismuth or penicillin; it may not explain the occasional lesion which responds to one but not another type of syphilotherapy. Whatever the mode of action of penicillin, in our own experience and in the results reported in the current literature it has proved to be an effective remedy in the treatment of the vast majority of patients with clinical manifestations of benign late syphilis.

Mucocutaneous Benign Late Syphilis. In the early clinical evaluation of penicillin these manifestations of late syphilis were unique in that they could be observed or palpated directly and measured accurately, and the difference between treatment success and failure could be objectively determined. In our own study, for example, we have applied the following criteria for "complete healing": In ulcerative cutaneous gummas we required restored continuity of the skin surface by complete epithelialization and the disappearance of signs of inflammation. Nodular gummas were regarded as healed when swelling, induration and erythema had vanished, although pigmentation might persist. Per-

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forating gummas of the palate were considered healed when the integrity of the mucous membrane had been restored or the residual perforation was completely quiescent and not inflamed or indurated. The use of these or similar criteria enabled investigators to report comparable data.

The first case report[2] described a patient with a nodular syphilide of the nose who was treated with 320,000 units of amorphous penicillin; the lesion healed leaving only residual pigmentation. In 1944 a group of investigators[3] reported on twenty-one cases of benign late syphilis of skin and bones (not separately considered). They found that the lesions healed in twelve to forty-six days under a dosage of approximately 300,000 units and concluded that results were so satisfactory that little further investigative interest or effort was required. In spite of this optimistic conclusion, there were two failures in the group studied: One was a suspected gumma of the orbit and no particulars were given concerning the other.

A year later O'Leary and Kierland,[4] without citing details, wrote that "penicillin is by far the outstanding remedy for the treatment of late cutaneous and osseous syphilis." They recommended two courses of 2.4 million units each, given four months apart. Stokes and his co-workers[5] stated that penicillin in low dosage (300,000 to 600,000 units) cured soft tissue gummas and simple uncomplicated bone lesions. Inadequate data were given concerning the diagnosis and treatment of patients having a satisfactory outcome but one treatment failure was reported. The patient had received arsenobismuth therapy for gummatous osteomyelitis of the sinuses and frontal bone without apparent effect; penicillin administration (2.4 million units in ten days) likewise failed to give improvement during 101 days of post-treatment observation. Hill[6] mentioned a patient with an extensive destructive gumma involving the center of the face, including the nasal septum and hard palate, who was unimproved after 2.4 million units of penicillin. Therapy with induced tertian malaria completely resolved the lesion. Hahn[7] has reported in detail a patient given 4.8 million units of amorphous penicillin for a large granulomatous penile mass which failed to improve. This lesion was likewise unresponsive to therapeutic dosages of tartar emetic and sulfonamide compounds. It had clinical attributes of a gumma and microscopic examination of a specimen taken for biopsy revealed "chronic inflammatory tissue of a nonspecific nature." Ten months after penicillin administration arsenobismuth therapy was given with prompt and complete healing.

The first reported experience from this clinic[1] described results of penicillin treatment in eighteen patients with gummas of the skin and/or mucous membranes. It was found that total doses greater than 1.7 million units of amorphous penicillin gave progressive improvement in most instances. One patient given only 60,000 units during her first course of therapy developed renewed activity in the scar one year later. There were no signs of relapse when last seen 805 days after retreatment with 1.2 million units. A diabetic patient with secondarily infected gummatous leg ulcers and arteriosclerosis of the lower extremities also required retreatment. The lesions failed to heal after 1.2 million units; 106 days later he was given 2.0 million units of penicillin with complete healing within one month. He remained well for seventeen months when a recurrent nodulo-ulcerative syphilide appeared in one of the scars. The administration of 8.0 million units of penicillin G in ten days and a prolonged course of arsenobismuth therapy promoted rapid healing. The other sixteen patients originally reported have undergone no relapses during follow-up periods as long as 1,596 days (mean, 911 days) although one received an additional 10.0 million units for serorelapse; the lesions had remained healed for 541 days at the time of retreatment.

Since the original communication we have treated with penicillin alone sixteen additional patients with cutaneous and/or

mucous membrane gummas. Total dosages ranged from 0.32 to 7.0 million units; ten received crystalline penicillin G. All have been treatment successes in that our criteria of healing were satisfied. The mean period of post-treatment observation, however, has been only 364 days. In the total series of thirty-four cases the gross incidence of failure was 5.9 per cent.

One report[8] has appeared on the treatment of a nodular late syphilide with 7.8 million units of oral penicillin administered over a ten-day period with a satisfactory outcome.

Conclusions. According to Moore[9] there appears to be general agreement that the older methods of syphilotherapy were usually successful in producing rapid healing of skin and mucous membrane lesions, even the largest cicatrizing within forty-two to fifty-six days. As nearly as can be estimated from available data, penicillin, if it is to be effective at all, will likewise promote at least temporary healing in less than two months. There is no good evidence that the rate of healing is more or less rapid following penicillin; nor is there available sufficient material to justify opinion as to the comparative effects of amorphous penicillin and crystalline penicillin G.

Sufficient evidence is at hand to show that a single course of penicillin therapy will not induce prompt healing or prevent gummatous recurrence in all patients with cutaneous and/or mucous membrane gummas. Although there is unquestionably a tendency to report promptly penicillin failures rather than successful results, it would seem from these data that in 5 to 10 per cent of these patients retreatment with penicillin or institution of arsenobismuth therapy would be indicated. As a corollary, too much reliance should not be placed on a single course of penicillin administration as a therapeutic test in benign late mucocutaneous syphilis.

Benign Late Osseous Syphilis. The early reports already cited[3–5] have to a great extent classified benign late syphilis of skin and mucous membranes and of bone together because they are frequently coexistent (e.g., gumma of skin with underlying periostitis of tibia). The criteria for successful treatment differ markedly between the two groups. Whereas the former heal *actively*, a treatment success in late syphilis of bone is usually characterized by arrest or lack of further activity. Serial roentgenograms show that proliferative or destructive activity has ceased; occasionally areas of osseous destruction are repaired completely. Where bone surfaces are near the skin (e.g., tibia, skull) and the overlying soft tissues are involved in a gummatous process with or without secondary infection, it may be impossible to tell what degree of osseous involvement is due to syphilis of soft tissues and how much to the process in the subjacent bone. In short, the division between success and failure of treatment is less sharply delineated, and serial observations over a prolonged period of time must be made before conclusions are justified.

In addition to the five patients with osteitis, osteomyelitis and/or periostitis described in our first report[1] we have since treated eleven more. Dosages of penicillin from 0.6 to 7.0 million units were given; five patients received penicillin G. Post-treatment observation periods ranged from 135 to 1,449 days (mean, 706 days). In only five of the sixteen patients studied were bone lesions unaccompanied by gummatous involvement of the overlying soft tissues. In most cases initiation of penicillin treatment caused a dramatic cessation of local deep bone pain in osseous syphilis. (This was also true following arsenic, bismuth and, occasionally, iodides.) One exception was noted in our series. A twenty year old negress with periostitis of the tibias and fibulas gave a history of severe osteocopic pain of five months' duration. The deep pain in the legs was essentially unchanged following 0.6 million units of penicillin and two months later similar pain began in the right arm. Roentgenograms showed thickened cortex and irregular contour of the right ulna. Without additional antisyphilitic treatment the attacks of ostealgia in all sites

gradually became less severe and troublesome, disappearing entirely during the seventh post-treatment month. These pains have not recurred and roentgenograms taken at 1,109 days showed a static process in the involved bones.

The end results in these sixteen patients, in terms of disappearance of symptoms referable to the skeletal system and roentgenographic evidence of osseous arrest or repair, were all adjudged to be satisfactory. One unusual treatment failure, however, deserves special mention. A nineteen year old negress with syphilitic osteomyelitis and periostitis of one radius was treated with 1.62 million units of amorphous penicillin. Although this lesion responded nicely, eight months later a typical nodular serpiginous syphilide of the forearms and hand appeared. A specimen for biopsy was described (Dr. L. W. Ketron) as characteristic of tertiary syphilis and arsenobismuth therapy was instituted.

We have treated two patients with uncomplicated syphilitic osteomyelitis with a satisfactory outcome in each following 1.0 and 1.62 million units of amorphous penicillin, respectively. Miller[10] has reported a case similar to ours in which clinical, pathologic and roentgenographic evidence was presented. Following 2.4 million units of penicillin the pain subsided, the patient gained weight and roentgenograms showed improvement; sequestrum formation was not present. The case of Stokes[5] responded neither to arsenobismuth treatment nor to penicillin; presumably sequestra were present.

Whether or not results of penicillin administration in patients with Charcot joints properly belong in this discussion, it may be briefly said that penicillin exerts no appreciable beneficial effect.[5,11]

Conclusions. Although the cases thus far reported concerning penicillin in benign late osseous syphilis are relatively few in number, results appear to be satisfactory in the patients with uncomplicated periostitis, osteitis or osteomyelitis. Syphilitic osteomyelitis with sequestrum formation appears to respond poorly to treatment and probably requires a combined attack by the surgeon and syphilologist for best results. When there is extensive gummatous involvement of adjacent skin or mucous membrane,[5,6] results of treatment with penicillin alone may be disappointing. The clinician faced with the patient with extensive gummatous involvement of the nasopharynx and paranasal sinuses may be wise in prescribing penicillin plus metal chemotherapy and/or fever.

Gummatous Visceral Syphilis (Excluding Cardiovascular and Neurosyphilis). Active late syphilis of the liver is a condition rarely demonstrated clinically. The initial and essential lesion is the gumma which arises in a highly localized or focal manner and on healing leaves a stellate scar. Because of the great functional reserve and capacity for regeneration of this organ, symptoms or signs of hepatic insufficiency are rare. Clinical observations, laboratory and roentgenographic studies do not permit more than a presumptive diagnosis. To prove the presence of active hepatic gummas two procedures are available. The more reliable (but somewhat dangerous) method is to take a specimen for biopsy. The second is the therapeutic test which requires a post-treatment observation period of months or years.

The only report[12] dealing with this type of benign late syphilis described a satisfactory result in each of two patients (one with late congenital syphilis) with gummatous hepatic syphilis treated with 3,200,000 and 920,000 units of amorphous penicillin. These patients have remained well over observation periods of 487 and 1,449 days, respectively.

We have not treated a patient with late gastric syphilis with penicillin in this clinic. Knight and Falk,[13] however, report clinical, gastroscopic and pathologic data on a fifty-four year old white male who was given "intensive antisyphilitic therapy" (dosage not specified). Although clinical, roentgenographic and gastroscopic studies all showed definite improvement, partial gas-

trectomy was performed. The pathologic picture was compatible with gastric syphilis. T. pallida organisms were not demonstrated.

Benign late pulmonary syphilis is seldom demonstrated clinically. Kulchar and Windholz[14] reviewed the available literature (pointing out that T. pallida have been demonstrated in only two instances), and presented one patient treated with penicillin. A twenty-nine year old white male had syphilitic bone involvement in three sites, an area of increased density in the left lung field, together with a pleural exudate on that side. Following 2.5 million units of penicillin, bone pain subsided and less than one month later the exudate had disappeared and the area of density had been replaced by fibrosis and increased parenchymal markings. No pathologic evidence was presented. A more convincing case recently came to our attention. This patient had a large globular mass in the right lung which failed to respond either to penicillin or to metal chemotherapy given in another clinic; it increased in size during treatment. Pneumonectomy was done since such thorough therapy with no resulting improvement was believed by the attending physicians to be strong presumptive evidence of neoplasm. The gross specimen showed central caseation necrosis, and sections for microscopic study were examined by competent pathologists who believed that the diagnosis of gumma was the most probable one.

Conclusions. It is obvious that involvement of the viscera by a gummatous process represents a considerable, and sometimes insurmountable problem in diagnosis; it may be even more difficult to adjudge the results of a given therapeutic method. It is in this situation that the qualities of penicillin appear to recommend it particularly. In contrast to the older methods of syphilotherapy, penicillin treatment is brief and essentially free of risk. Since, as far as the therapeutic test is concerned, the treponemicidal properties of a given drug appear to be most important, penicillin probably yields a definite answer as frequently as metal chemotherapy. When roentgenographic evidence of disease is being considered (e.g., possible gumma of lung), it must be kept in mind that penicillin is bactericidal for many organisms. We have had the experience of seeing a solitary area of increased pulmonary density resolve promptly following administration of penicillin. Although the patient had gummatous lesions elsewhere, in retrospect it was impossible to rule out non-syphilitic disease, such as a patch of bronchopneumonia.

Gummatous Keratitis. The keratitis pustuliformis profunda of Fuchs is the only type of corneal syphilitic disease to show a spectacular response to older types of antisyphilitic therapy.[15] It has shown an equally satisfactory response to penicillin in the only case thus far reported.[1]

COMMENTS

From the practical standpoint, benign late gummatous syphilis of skin, mucous membranes and of bone are the most important types. In this series of thirty-nine patients with one or more of these manifestations, a single course of treatment with penicillin alone yielded satisfactory results in all but three. These failures were: (1) recurrence of cutaneous gumma, (2) initial failure to heal promptly after a second course of penicillin, followed by recurrence of cutaneous gumma and (3) initial appearance of a nodular syphilide eight months after penicillin therapy of late osseous syphilis. The only comparable series published,[3] in which twenty-one patients with benign late syphilis of skin and bone were treated with penicillin alone, mentioned two treatment failures. The gross incidence of failure in the combined material was 8.3 per cent (five failures among sixty patients studied). This figure is sufficiently large to show that caution must be used in the interpretation of the therapeutic test in benign late syphilis.

Total dosages employed in our series ranged from 60,000 to 7,000,000 units. In general, the patients treated earlier received smaller dosages. No failures were encountered in the eleven patients treated with crystal-

line penicillin G. This was probably due to two factors, both associated with the recent availability of this product. First, larger total dosages were employed and, secondly, post-treatment observation periods have been shorter. There is no real evidence as yet that crystalline G is superior to amorphous penicillin in the treatment of benign late syphilis.

The majority of our patients with benign late syphilis also had recognizable syphilitic disease involving the cardiovascular or central nervous systems. Twenty-three had neurosyphilis and in one of these a saccular aortic aneurysm was also found. Eighteen had late asymptomatic neurosyphilis, three had tabes dorsalis and two had unclassified late meningovascular neurosyphilis. The two patients in the last category and one with asymptomatic neurosyphilis had "active," group III cerebrospinal fluids (Dattner-Thomas); in the remainder the cell count and protein values were within physiologic limits and the major abnormality noted was the positive Wassermann reaction with relatively large volumes of cerebrospinal fluid (0.2 to 1.0 cc.). These abnormal fluids responded to penicillin administration in the usual fashion. Elevated cell counts and protein contents rapidly fell to normal; the colloidal mastic and Wassermann tests responded more slowly. Laboratory evidence of neurosyphilis disappeared during the periods of observation in eleven of the patients with group II cerebrospinal fluids. In one patient eight positive or doubtful spinal fluid Wassermann reactions in low dilutions were reported before the first entirely normal one taken 1,385 days after penicillin therapy. None of the "inactive" fluids became worse during the period of observation. Serologic blood titers were more recalcitrant. One patient was seronegative before and after treatment. The other thirty-eight patients were seropositive at the time of the most recent observation and in eleven of these the most recent titer was higher than the pretreatment one. These data merely emphasized the fact that most patients with symptomatic late syphilis were seroresistant and that penicillin was no more effective in reversing the serologic reaction to negative than have other types of syphilotherapy.

In our experience the febrile Jarisch-Herxheimer reaction did not seem to be associated with particular types of gummatous lesions. A rise in temperature over 100.4°F. within the first twenty-four hours after the initiation of therapy was noted in five patients; the highest fever was 103.2°F. All these patients had "inactive" cerebrospinal fluids. Fever in excess of 100°F. was noted in two of the three patients with group III, six with group II and in two patients with normal pretreatment cerebrospinal fluids. In a single instance only was significant increase in local erythema and swelling noted. One patient with a gumma of the left vocal cord (and of the hard palate and nasal septum) suffered no ill effects following initiation of therapy with the usual doses (100,000 units every three hours).

SUMMARY

The current literature dealing with the use of penicillin in benign late syphilis of skin and mucous membranes, the bones, liver, stomach, lungs and cornea is briefly reviewed. On the basis of reported data and an analysis of our own material satisfactory results may be obtained in approximately 90 per cent of such cases by the administration of a single course of penicillin alone.

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