Penicillin Treatment of Patients with Cardiovascular Syphilis in Congestive Failure

By Joseph Edeiken, M.D., William T. Ford, M.D., Mortimer S. Falk, M.D., and John H. Stokes, M.D.

Congestive failure has been considered a relative contraindication to antisyphilitic therapy in cardiovascular syphilis since the arsphenamine era, when severe reactions were reported following administration of this vasculotoxic drug. After having observed no severe reactions to penicillin in a series of patients with cardiovascular syphilis, it was decided to administer the antibiotic as initial therapy for individuals in congestive failure. This report summarizes observations on twelve such patients. There were no severe reactions during the course of treatment in the entire group. Digitalis and other measures to restore compensation were used concomitantly with penicillin. All the patients were improved upon completion of therapy. Case histories of 2 patients who died two months after treatment, are given. The significance of observations on the entire group is discussed.

In a recent communication, observations on 50 patients with penicillin-treated cardiovascular syphilis were presented. Although the number of patients treated was relatively small, statistically speaking, it was felt that there was strong evidence that penicillin has no injurious effects as initial therapy in syphilis involving the cardiovascular system. Emboldened by this experience, we have now ventured one step further and have administered penicillin to 12 patients with cardiovascular syphilis in congestive failure. This report records our observations on these patients during and following treatment.

In the pre-penicillin era, cardiac failure was considered by many to be a contraindication to any antisyphilitic treatment with the exception of iodides. Stokes and his associates differed from the majority in that they felt that patients with cardiovascular syphilis in decompensation did better when weak spirilliciald agents such as mercury were administered concurrently with measures to restore compensation. The majority, however, believed that when decompensation was present the first essential was to relieve the congestive failure before administering more than the absolute minimum of antisyphilitic treatment. It was usually the practice to limit specific therapy to potassium iodide; in the presence of edema, one of the mercurial diuretics was given, principally for its diuretic and incidentally for its antisyphilitic effect. It was believed that some degree of cardiac reserve should be built up before bismuth or small dosages of an arsenical were even considered. This seemingly ultraconservative approach was formulated because several severe and even fatal reactions had been known to occur following the administration of arsenicals. Herrmann and Jamison outlined a method of treatment for patients in congestive heart failure which emphasized again the conservative approach. Their opinion was based on a long and extensive experience which included the observation of "some fatalities" following the direct use of even small doses of neoarsphenamine in decompensated cardiovascular syphilis. Wilson and associates observed electrocardiographic evidence of widespread myocardial disturbances directly following the introduction of arsenicals in the presence of congestive failure in patients with aortic syphilis.

Although there have been several reports on the treatment of cardiovascular syphilis with penicillin, a review of the literature revealed no reference to the treatment of decompensated cardiovascular syphilis with this antibiotic. Of the 12 patients in moderate to severe congestive heart failure whom we have treated...
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<td><strong>Duration of Syphilis</strong></td>
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<td>Case 1, G. N. (M), age 43, asymptomatic neurosyphilis, aortic regurgitation</td>
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<td>Case 2, B. M. (M), age 49, aortic regurgitation, aneurysm intimo- media artery, hypertension, tabes dorsalis</td>
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<td>Case 3, P. I. (M), age 68, aortic regurgitation</td>
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<td>Case 4, W. S. (M), age 39, aortic regurgitation</td>
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<td>Case 5, D. H. (M), age 69, aortic regurgitation, aneurysm ascending aorta</td>
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<td>Case 6, V. R. (M), age 59, aortic regurgitation</td>
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<tr>
<td>Case 7, S. R. (F), age 47, aortic regurgitation, hypertension</td>
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<tr>
<td>Case 8, V. S. (M), age 50, aortitis, hypertension</td>
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<tr>
<td>Case 9, R. W. (M), age 67, aortic regurgitation</td>
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<td>Case 10, H. B. (M), age 58, aortic regurgitation</td>
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### Table 2.—Status of Cardiovascular System Prior to Penicillin and at Time of Most Recent Examination

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<tr>
<th>Case</th>
<th>Signs and Symptoms</th>
<th>Roentgen Findings</th>
<th>Electrocardiogram</th>
<th>Signs and Symptoms</th>
<th>Roentgen Findings</th>
<th>Electrocardiogram</th>
<th>Treatment with Penicillin</th>
<th>Treatment after Penicillin</th>
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<tbody>
<tr>
<td>11-12, E.G. (M), age 65, aortic regurgitation, Ca of larynx</td>
<td>Unknown</td>
<td>None</td>
<td>Kahn 250 units</td>
<td>5 mos. post-treatment: Kahn 16 units</td>
<td>Crystalline “G” 1,000 × 10</td>
<td>None</td>
<td>Improved</td>
<td>Improved, maintained 8 months post-penicillin</td>
</tr>
<tr>
<td>12, L.H. (M), age 56, aortic regurgitation</td>
<td>Unknown—probably 30 years</td>
<td>40 Bismuth since 1943</td>
<td>Kolmer 44, Kahn 4 units</td>
<td>2 mos. post-treatment: Kolmer 44, Kahn 8 units</td>
<td>Crystalline “G” 40,000 × 120</td>
<td>Temp. 100° 16 hours after first injection</td>
<td>Improved</td>
<td>Improved, maintained 2 months post-penicillin</td>
</tr>
<tr>
<td>1, G.N. (M), age 40, asymptomatic neurosyphilis; aortic regurgitation</td>
<td>Progressive dyspnea and orthopenes 6 mos. Right pleural effusion; Liver moderately enlarged; moderate ankle edema; BP 160/100</td>
<td>Marked cardiac enlargement; left; auricular fibrillation; severe myocardial damage</td>
<td>21 months; improved, moderate dyspnea, slight ankle edema</td>
<td>Same</td>
<td>Digitalis; ammonium chloride; mercurial diuretic</td>
<td>Same</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2, S.M. (M), age 50, aortic regurgitation, aneurysm innominate artery; hypertension and tabs dorsalis</td>
<td>Ankle edema; severe dyspnea; severe upper subternal pain, especially nocturnal BP 160/120</td>
<td>Marked cardiac enlargement; severe myocardial damage</td>
<td>Changes suggesting left ventricular hypertrophy</td>
<td>18 months; initial improvement for about 15 months; now increasing signs congestive failure. BP 200/110</td>
<td>Changes due to digitalis; otherwise same</td>
<td>Digitalis; mercurial diuretic (past 3 mos.)</td>
<td></td>
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</tr>
<tr>
<td>3, P.I. (M), age 50, aortic regurgitation</td>
<td>Severe anemia pectoris and recurrent cardiac decompensation 2 yrs. Right pleural effusion; moderate pretilial edema; BP 150/80</td>
<td>Marked cardiac enlargement; severe myocardial damage</td>
<td>Changes suggestive of left ventricular hypertrophy</td>
<td>2 months: free of decompensation; no angina; then developed thrombophlebitis, pulmonary infarction; manic psychosis; died. (Details in paper)</td>
<td>No follow-up</td>
<td>No follow-up</td>
<td>Digitalis; ammonium chloride; mercurial diuretic</td>
<td>Same</td>
</tr>
<tr>
<td>4, W.S. (M), age 50, aortic regurgitation</td>
<td>Angina pectoris 1 year; progressive dyspnea, orthopenes, nocturnal dyspnea; liver enlarged; rales both bases; moderate ankle edema; BP 150/40</td>
<td>Heart enlarged downwards and to left; T.D. 16 ems.; auricular fibrillation</td>
<td>Changes suggestive of left ventricular hypertrophy</td>
<td>Died suddenly at home 2 mos. post-penicillin. Treatment: cause unknown. (Details in paper)</td>
<td>No follow-up X-ray</td>
<td>No follow-up ECG</td>
<td>None</td>
<td>Digitalis, ammonium chloride, mercurial diuretic</td>
</tr>
<tr>
<td>5, D.H. (M), age 50, aortic regurgitation (early); aneurysm ascending aorta</td>
<td>Dyspnea 4 yrs; progressive orthopenes; nocturnal dyspnea; rales both bases; moderate liver enlargement; moderate ankle edema; BP 120/80</td>
<td>Heart only slightly enlarged; auricular fibrillation</td>
<td>Severe myocardial abnormality; probable damage to anterior surface left ventricle</td>
<td>13 months; marked improvement; some dyspnea on exertion; no ankle edema</td>
<td>Heart normal in size; auricular fibrillation</td>
<td>Digitalis; ammonium chloride; mercurial diuretic</td>
<td>Same</td>
<td></td>
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<tr>
<td>Case</td>
<td>Signs and Symptoms</td>
<td>Roentgen Findings</td>
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<td>6.V.R. (M), age 69, aortic regurgitation</td>
<td>Angina pectoris since 1937; severe dyspnea and occasional orthopnea; marked pretrivial edema; BP 174/60</td>
<td>Marked cardiac enlargement, esp. left ventricular; sorts diffusely dilated</td>
<td>Slight depression RS-T segments in most leads</td>
<td>14 months: no congestive failure; no dyspnea; no angina; BP 142/60</td>
<td>Heart slightly smaller; T.D. 16.9 cm. compared with 18.5 cm.</td>
<td>Same except for digitalis effects</td>
<td>Digitalis; mercurial diuretic</td>
<td>Digitalis</td>
</tr>
<tr>
<td>7.S.R. (F), age 67, aortic regurgitation, hypertension</td>
<td>Progressive dyspnea 3 years; ankle edema 6 mos. Admitted in acute cardic decompensation; rule both bases; liver mod. enlarged; marked pretrivial edema. BP 160/70</td>
<td>Marked enlargement; sorts moderately dilated</td>
<td>Changes of type seen in left ventricular hypertrophy</td>
<td>13 months: marked improvement; no evidence of congestive failure. BP 170/80</td>
<td>Heart smaller; top normal size, configuration of left ventricular hypertrophy</td>
<td>Digitalis effects; otherwise unchanged</td>
<td>Digitalis; mercurial diuretic</td>
<td>Digitalis, ammonium chloride, mercurial diuretic</td>
</tr>
<tr>
<td>8.V.S. (M), age 60, aorticitis, hypertension</td>
<td>Progressive dyspnea; rule both bases. Marked ankle edema; relieved by digitalis and mercurialis. Severe subternal pain nightly; relieved only by opiates. BP 190/110</td>
<td>Heart markedly enlarged; sorts marke generalized dilatation and elongation</td>
<td>Changes suggesting left ventricular hypertrophy; also digitalis effects</td>
<td>10 months: marked improvement; oppression in upper chest relieved second day of treatment. No recurrence</td>
<td>No change</td>
<td>No change</td>
<td>Digitalis; mercurial diuretic</td>
<td>Same</td>
</tr>
<tr>
<td>9.R.W. (M), age 67, aortic regurgitation</td>
<td>Progressive dyspnea for 2 years; orthopnea; marked ankle edema; liver enlarged 5 cm. below costal margin; right pleural effusion. BP 160/100</td>
<td>Marked cardiac enlargement especially to left; sorts markedly and uniformly dilated</td>
<td>Auricular fibrillation; changes of type seen in left ventricular hypertrophy</td>
<td>7 months: marked improvement; slight dyspnea; no bilateral ankle edema</td>
<td>Heart slightly smaller</td>
<td>Unchanged</td>
<td>Digitalis; ammonium chloride; mercurial diuretic</td>
<td>Same</td>
</tr>
<tr>
<td>10.H.B. (M), age 56, aortic regurgitation</td>
<td>Angina pectoris, progressive ankle edema and dyspnea; orthopnea 45 years; liver 3 cms. below costal margin. BP 180/70</td>
<td>Marked cardiac enlargement; sorts dilated and dense</td>
<td>Signs suggesting left ventricular hypertrophy. Minor grade heart block</td>
<td>7 months: much improved, no evidence of congestive failure; no angina</td>
<td>No change</td>
<td>No change</td>
<td>Digitalis; mercurial diuretic</td>
<td>Same</td>
</tr>
<tr>
<td>11.E.G. (M), age 67, aortic regurgitation, Cus of larynx</td>
<td>Ankle edema; severe dyspnea; rule in both bases; liver enlargement. BP 180/70</td>
<td>Marked cardiac enlargement and dense</td>
<td>Numerous extrasystoles; left ventricular hypertrophy</td>
<td>8 months: no rales in bases. Slight dyspnea on exertion</td>
<td>No change</td>
<td>No change</td>
<td>Digitalis; Salyrgan; oxygen; amphetamine</td>
<td>Digitalis and mercurial diuretic</td>
</tr>
<tr>
<td>12.L.H. (M), age 55, aortic regurgitation</td>
<td>Ankle edema; orthopnea; moist rales throughout chest; liver enlargement. BP 160/60</td>
<td>Marked cardiac enlargement and diffuse dilatation of the sorts</td>
<td>Signs indicative left ventricular hypertrophy</td>
<td>2 months: marked improvement; moderate dyspnea on exertion; no nocturnal dyspnea</td>
<td>No change</td>
<td>No change</td>
<td>Digitalis; Salyrgan, ammonium chloride; Dilaudid</td>
<td>Digitalis and Salyrgan</td>
</tr>
</tbody>
</table>
with penicillin, none was prepared with less potent spirocheticidal agents. All were closely observed in the hospital under complete bed rest and low-salt diet. Digitalis, ammonium chloride and mercurial diuretics were started at the same time as the penicillin in all but one patient. The initial penicillin dosage ranged from 500 to 50,000 units every two hours and the total dosage from 4.8 to 9.6 million units of crystalline penicillin G. Examinations which included electrocardiograms and fluoroscopic studies were made before and at varying periods after treatment. In addition, electrocardiograms were made at approximately three-day intervals during the period of penicillin treatment. The pertinent facts concerning each patient are outlined in tables 1 and 2.

Results

Each of the 12 patients in cardiac failure tolerated his course of penicillin without serious untoward immediate reaction. The only suggestion of therapeutic shock was a slight febrile reaction in 2 patients, H. B., case 10, starting six hours after initiation of penicillin therapy, and L. H., case 12, starting sixteen hours after the first injection. In no instance was it considered necessary to interrupt the treatment schedule. None of the patients showed increasing evidence of congestive failure, but on the contrary, all seemed to be symptomatically improved within forty-eight to seventy-two hours after initiation of treatment. Electrocardiographic studies revealed T-wave abnormalities and other changes which could be attributed to digitalis, but in no instance was there evidence of intraventricular conduction defects. All of the patients were able to leave the hospital immediately after completion of penicillin therapy (usually in ten to twelve days) in an improved state. Maintenance doses of digitalis were prescribed and 7 were continued on mercurial diuretics. The post-treatment follow-up now ranges from two to twenty-one months.

Two of our patients died two months following completion of penicillin.

The first patient, a 58 year old white man (Case 3) had experienced angina and several episodes of severe cardiac failure over a period of fifteen months. Advanced aortic insufficiency of syphilitic etiology was discovered in December 1946 at the time of his first admission to the hospital in acute left ventricular failure. There was no history of previous anti-syphilitic treatment. His reaction to the blood serologic test for syphilis was strongly positive and the spinal fluid examination was negative.

In January 1948 he was admitted to the Institute for the Study of Venereal Disease in severe decompensation. Treatment consisted of a total of 4.8 million units of penicillin (40,000 units every two hours), digitalis, ammonium chloride and Salyrgan. He was much improved symptomatically at the time penicillin therapy was completed and was discharged on a maintenance dose of digitalis and a mercurial diuretic. Following his return home, however, his course was gradually downhill; he became increasingly weak, and developed nausea and vomiting. On February 19, 1948 (just one month after completion of penicillin) he was admitted to the medical ward "in a shocklike state." He complained of severe pains in his calves and was experiencing hemoptysis. He was in acute left ventricular failure, and had a right pleural effusion. X-ray study of the chest revealed irregular densities in both lung fields believed to be due to pneumonia or infarcts. During his period of hospitalization from February 19 to March 12, 1948, he became manic and was to have been transferred to the psychiatric ward of a municipal hospital with the diagnoses of acute manic psychosis, thrombophlebitis, and pulmonary infarct, in addition to the cardiovascular disease previously described. It appears that his family took him home in preference to admitting him to the psychiatric ward, and he died one week later. No autopsy was performed.

The second patient, who died two months following penicillin therapy, was a 39 year old Negro who had acquired syphilis about twenty-three years before. He had been rejected for military service in 1940 because of "heart disease" and a positive serologic test for syphilis, and was referred to a public health clinic for treatment. This consisted of weekly intramuscular injections (? bismuth) and "drops" (? potassium iodide) for one year. Following this, he allowed his treatment to lapse. He gradually began to experience dyspnea on exertion and weakness until about a year prior to his admission, when he developed increasing symptoms and signs of cardiac failure (paroxysmal nocturnal dyspnea, orthopnea, ankle edema, precordial pain). Examination at the time of admission to the hospital revealed marked cardiac enlargement (transverse diameter 18.0 cm.), a "to-and-fro" aortic murmur, blood pressure 150/40, 2-plus ankle edema, and occasional basal rales. Signs of congestive failure diminished on bed rest. His serologic test for syphilis was strongly positive; the cerebrospinal fluid was negative. He was given penicillin without any supportive cardiac therapy (10,000 units every two hours for eight doses, and then 40,000 units every two hours to a total of 4.8...
million units). There was no evidence of a febrile or other untoward reaction during the course of treatment. He was discharged symptomatically improved but returned to the cardiac clinic a month later with an upper respiratory infection and with a recurrence of symptoms and signs of moderate cardiac failure. A digitalis glycoside was prescribed. He seemed to be holding his own on a regimen which included digitalis, ammonium chloride and mercurial diuretics until he "suddenly became very ill" at home, sixty-six days after completion of penicillin therapy, and was taken to a municipal hospital where he was pronounced dead on arrival. Autopsy was not obtained.

**Discussion**

We do not have sufficient evidence as yet to show that penicillin alters the course or prognosis of decompensated cardiovascular syphilis, but it seems significant that the patients in this study were apparently able to tolerate large doses of this powerful spirillicidal agent, even though they were in acute congestive heart failure when treatment was started.

It has been shown that penicillin is well tolerated by patients with late cardiovascular syphilis. In the paper previously alluded to we reported our observations on 50 cases of late cardiovascular syphilis treated with penicillin. Physical examinations and electrocardiographic studies made before, during and within the available period of observation after treatment failed to disclose any deleterious effects upon the cardiovascular system during or following the use of penicillin.

The apparent lack of immediate unfavorable effects when penicillin is given to patients with cardiovascular syphilis and congestive failure is significant, for it is this type of patient who received little or no antisyphilitic treatment before the penicillin era. It is not unlikely that some of the arsenicals, defects, which were attributed to the Jarisch-Herxheimer reaction were due to the toxic effects of the drug on an already damaged cardiovascular apparatus. Wilson and associates observed the development of an abnormal idioventricular rhythm following the administration of 0.2 Gm. of arsenicals to a syphilitic patient who showed right bundle branch block in the electrocardiogram; death occurred a few days later. Two other patients with syphilitic aortitis, with practically normal electrocardiograms, developed diphasic QRS complexes, suggesting incomplete bundle branch block, following intensive arsenical therapy. We have treated with penicillin over 100 patients, including the 12 in cardiac failure (and 3 with healed myocardial infarctions), and although transient T-wave changes were noted, conduction defects, except those due to digitalis, were absent.

If the Jarisch-Herxheimer reaction is accepted as the cause of most immediate untoward reactions in patients with cardiovascular syphilis treated with arsphenamine, how then can we reconcile the apparent lack of reaction in the same type of patient treated with penicillin? It might be argued that the difference in mode of action of the two drugs on the spirochete could of itself account for this seemingly marked difference in toxicity. However, one has merely to note the frequent occurrence of Herxheimer reactions in patients with early syphilis treated with penicillin, as compared with the arsenicals, to realize that penicillin is more likely than arsphenamine to produce this type of reaction. A tenable hypothesis is that the difference lies in the inherent toxicity of arsphenamine for the damaged cardiovascular system.

What about the phenomenon of therapeutic paradox? We can state with some certainty, that if it occurs at all, it is apparently uncommon in penicillin-treated cardiovascular syphilis. It is not possible to determine clinically whether progression of the process in a particular patient is the result of his disease or is due to too rapid healing with scar formation and contracture in a vital structure. If aortic regurgitation happens to occur following treatment of syphilitic aortitis, it seems as reasonable to assume that the process has progressed to involve the aortic ring and valves as it is to attribute it to therapeutic paradox. Such a sequence sometimes occurs quite rapidly without any treatment at all; the course of syphilitic heart disease is often unpredictable, as has been shown by Reader and associates. It is to be expected that some patients may decline coincidentally with or after treatment. Of course, this is speculation which will not be substantiated or refuted.
until many more patients have been treated and autopsies obtained on those who die following treatment.

It is not possible at the present time to predict what the long-term effect of immediate penicillin treatment upon decompensated cardiovascular syphilis will be.

**SUMMARY AND CONCLUSIONS**

1. Twelve patients with syphilitic cardiovascular disease and congestive failure were treated with penicillin.

2. No untoward reactions, except for slight early febrile reactions in 2 patients, were observed during treatment. The total dosage varied from 4,800,000 to 9,600,000 units. Two patients were started on 500 unit doses; 8 patients on 10,000 units; 2 patients received large initial doses—40,000 units every three hours. The duration of treatment was twelve to fifteen days.

3. There were two deaths, the case histories of which are presented. Unfortunately, autopsies were not performed in either patient.

4. All patients were improved on leaving the hospital. We cannot yet state how much of this improvement was due to penicillin; longer and more extensive experience is needed. It is also impossible to predict whether or not therapeutic paradox may not ensue and a new decompensation or death be precipitated more readily because of the use of penicillin.

5. It is our present impression that patients with syphilitic cardiovascular disease in cardiac failure react better to the combined treatment with penicillin than those who receive only treatment for congestive failure. We are encouraged by our observations to date. If penicillin can convert an active process in the aorta to an inactive one, it seems reasonable to assume that life can be prolonged in patients in whom the process is not too far advanced.

**REFERENCES**


Penicillin Treatment of Patients with Cardiovascular Syphilis in Congestive Failure

JOSEPH EDEIKEN, WILLIAM T. FORD, MORTIMER S. FALK and JOHN H. STOKES

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