Further Observations on Penicillin-Treated Cardiovascular Syphilis

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

One hundred and eleven cases of cardiovascular syphilis were treated with penicillin and, of these, 13 were in congestive heart failure, eight suffered from angina pectoris, and three had a history of coronary occlusion. Except for mild fever in a few instances therapeutic shock was not observed in any of the patients and therapeutic paradox, although sought for, was also not observed. There is evidence to suggest that penicillin has a favorable influence upon cardiovascular syphilis; angina pectoris and congestive heart failure do not contraindicate the use of penicillin in cardiovascular syphilis.

In 1949 we reported the early observations of this group on penicillin-treated syphilitic cardiovascular disease. Although scattered reports of untoward reactions as the result of penicillin treatment of late cardiovascular syphilis appeared in the literature, in none of this series were there reactions which could be construed as due to a serious therapeutic shock, although mild fever occurred in some cases. Therapeutic shock or the Jarisch-Herxheimer reaction is a term applied to an exacerbation of the signs or symptoms of the disease in a syphilitic patient in any stage of the disease immediately following treatment with antisyphilitic drugs. Moreover, despite careful observations for therapeutic paradox, nothing definitely classifiable as such was observed within the observation period. Therapeutic paradox was described by Wile and has been attributed to over-rapid healing, with resulting functional imbalance so that the patient is in a worse condition after treatment than before. It was believed any organ may have its func-

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(The Penicillin-Syphilis Panel consists of representatives of the Institute, Departments of Neurology, Ophthalmology, Dermatology and Syphilology and Pediatrics, Hospital of the University of Pennsylvania; the Division of Venereal Disease Control, Philadelphia City Department of Public Health; the Philadelphia General and Pennsylvania Hospitals, and the Children's Hospital.)

One of the patients was a 41-year-old white man with a history of syphilis for 25 years, with congestive heart failure secondary to syphilis. The patient was treated with 400,000 units of penicillin daily for three weeks, and the course of treatment was followed by clinical examination and electrocardiographic studies. The patient responded to treatment with the disappearance of symptoms and signs of congestive heart failure. The electrocardiographic studies showed a marked improvement in the QRS complex, particularly in the precordial leads. The patient was discharged from the hospital with a diagnosis of syphilis treated with penicillin and congestive heart failure secondary to syphilis.

Later, observations were made on 12 patients with syphilitic heart disease and congestive heart failure in whom penicillin and methods to combat congestive failure were used simultaneously. In this group not only were untoward effects lacking, but the distinct impression prevailed that these patients responded better than most patients with cardiovascular syphilis and decompensation who were treated, as was often the case in the prepenicillin era, with measures aimed only toward combating congestive failure.

Previous to the above reports, Russek, Cutler, Fremer and Lahnman and also Tucker and Farmer reported that patients with cardiovascular syphilis tolerated penicillin well. To these have been added the series of Fluur and Thomas, additional cases by Russek, Nicholson and Lohman, Peralta and Casteneda and the experiences of Webster. Material and Methods

Since the initial reports the series has enlarged to include a total of 111 cases. The purposes of the present study were to determine: (1) To what extent penicillin is tolerated by patients with cardiovascular syphilis, including those with congestive
failure or angina pectoris; (2) by prolonged follow-up studies, to determine: (a) the frequency of therapeutic paradox, and (b) the influence of penicillin treatment upon the subsequent course of cardiovascular syphilis.

criteria mistakes in diagnosis may be made especially in the older age group. A systolic murmur at the aortic area followed by an accentuated and tambour-like second sound in a person under 40, with positive serologic tests for syphilis, and without evi-

### Table 1

<table>
<thead>
<tr>
<th>No. of Cases</th>
<th>Sex</th>
<th>Color</th>
<th>Age Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>B</td>
</tr>
<tr>
<td>Aortitis</td>
<td>48</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Aortic insufficiency</td>
<td>51</td>
<td>42</td>
<td>9</td>
</tr>
<tr>
<td>Aortic insufficiency and aneurysm</td>
<td>9</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>3</td>
<td>3</td>
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### Table 2.—Serologic Data before and after Treatment

<table>
<thead>
<tr>
<th></th>
<th>Aortitis</th>
<th>Aortic Insufficiency</th>
<th>Aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>48</td>
<td>51</td>
<td>9</td>
</tr>
<tr>
<td>STS* Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>41</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td>After treatment</td>
<td>34</td>
<td>42</td>
<td>7</td>
</tr>
<tr>
<td>STS negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>7</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>After treatment</td>
<td>11</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Change in titer†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same</td>
<td>18</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Fall</td>
<td>13</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Rise</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Negative before,</td>
<td>1</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>positive after</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No follow-up</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CNS‡ syphilis</td>
<td>26</td>
<td>17</td>
<td>5</td>
</tr>
</tbody>
</table>

* Serologic test for syphilis.
† Change in titer: Rise—increase of two or more titer in quant. titer; Fall—drop of two or more titers in quant. titer; Same—no change or one titer rise or fall.
‡ Central nervous system syphilis.

The cases included in this study were divided into the following 4 groups:

(1) Simple aortitis
(2) Aortic insufficiency
(3) Aortic insufficiency and aneurysm
(4) Aneurysm

The pertinent data concerning race, age and sex are listed in table 1. In table 2, are presented the pertinent syphilogic data. We are aware that the diagnosis of simple aortitis is frequently most difficult, and it must be admitted that even with rigid

dence of hypertension, arteriosclerosis or rheumatic heart disease was considered suggestive evidence of aortitis, especially when the above were associated with a dilated, elongated ascending aorta with or without calcification; those cases with a definite pulsating bulge of the arch of the aorta or its main branches were considered aneurysm. Angina pectoris and paroxysmal dyspnea in this group were considered possible evidence of coronary ostial involvement. In the older age groups with hypertension and/or arteriosclerosis and positive serologic tests for syphilis, the diagnosis of aortitis was extremely difficult and errors in diagnosis were probable, but only a comparatively few cases (table 1) in whom the aorta was far more dilated than expected for the degree of hypertension, were included in this group. Other patients, in whom the signs could not be considered out of proportion to the degree and duration of hypertension, were treated with penicillin but were not included in this study.

All cases were hospitalized and were given complete physical examinations before treatment. Laboratory studies included electrocardiogram, fluoroscopic study of the heart, complete blood count, urinalysis, serologic tests for syphilis, and such studies as determination of blood nitrogen and blood sugar, when necessary. Electrocardiograms were made approximately every three days during treatment in 42 of the 111 cases. All the patients were given sodium penicillin in aqueous solution intramuscularly on a round-the-clock schedule until a total dosage of 4,800,000 to 9,600,000 units had been given. In some of the earlier cases the initial doses were small, 500 to 5,000 units every three hours. All the later cases were started on larger doses, 40,000 to 50,000 units every two or three hours until a total of 4,800,000 to 9,600,000 units were given and repeated once if indicated. Follow-up studies were made three months after discharge from the hospital and every six months thereafter, whenever possible. In many cases, especially in
those who had congestive failure, opportunity to follow these patients in the cardiac clinic at frequent intervals was afforded. In every follow-up study, complete physical examination, electrocardiogram, and fluoroscopic study of the heart were made, in addition to serologic studies.

Results

Simple Aortitis

Five of the 48 patients who were considered to have simple aortitis, but who probably had coronary ostial involvement also, had paroxysmal dyspnea and four were improved after treatment; one showed little or no change. One patient who had congestive heart failure continued to have nocturnal dyspnea in spite of measures to combat congestive failure, until relieved by treatment with penicillin, and was free of attacks 12 months later. This case has been reported in detail elsewhere. The other three were free of nocturnal dyspnea when examined 10 months, 14 months and three years after treatment. The fifth patient continued to have attacks after three and one half months. One patient who had suffered a coronary occlusion before penicillin therapy, and who did not suffer from nocturnal dyspnea at the time of treatment, was in congestive failure and had nocturnal dyspnea 58 months after treatment.

Angina pectoris was present in three instances. Two were improved three and one half and 19 months after treatment; the other showed no change after 11 months either in severity or frequency of attacks.

Pertinent data regarding roentgen examination before and after treatment are listed in table 3, and in table 4 are listed the electrocardiographic findings before and after treatment; neither the roentgen or electrocardiographic changes noted after treatment can be considered significant. Electrocardiograms were made every three days during treatment in 17 cases. In 11 the tracings remained unchanged, but in six there were slight but probably not significant changes in the T waves. In three there was an increase in amplitude of the T waves in the limb and/or precordial leads, and in three the T waves became lower but not inverted. In all but one, however, the changes were transient, but in this case the improvement persisted after 42 days.

The aorta was considered abnormal in all cases but no attempt was made to evaluate slight changes in aortic measurements. There was no marked change noted following treatment. We have not observed the development of an aneurysm or aortic insufficiency in a single case.

Table 3.—Heart Size in 48 Cases of Aortitis

<table>
<thead>
<tr>
<th>Before Treatment</th>
<th>After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Same</td>
</tr>
<tr>
<td>Normal</td>
<td>22</td>
</tr>
<tr>
<td>Normal but config. of left, vent. hypertrophy</td>
<td>6</td>
</tr>
<tr>
<td>Slight enlargement</td>
<td>14</td>
</tr>
<tr>
<td>Moderate enlargement</td>
<td>4</td>
</tr>
<tr>
<td>Marked enlargement</td>
<td>2</td>
</tr>
</tbody>
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Table 4.—Electrocardiograms in 48 Cases of Aortitis

<table>
<thead>
<tr>
<th>Before Treatment</th>
<th>After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Same</td>
</tr>
<tr>
<td>Normal</td>
<td>28</td>
</tr>
<tr>
<td>Myocardial damage</td>
<td>11</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>6</td>
</tr>
<tr>
<td>Right bundle branch block</td>
<td>1</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2</td>
</tr>
</tbody>
</table>

There was one death attributed to pneumonia 12 months after treatment.

Aortic Insufficiency

Nine of the 51 patients with aortic insufficiency had signs of congestive failure and five others were receiving digitalis but no longer showed signs of failure. All were treated with penicillin simultaneously with measures to combat congestive failure, and all left the hospital feeling much improved. In no case was there evidence of therapeutic shock; one patient who also had auricular fibrillation died two months
later from a pulmonary embolus; one died as a result of unknown causes 66 days after treatment, and one after five months as a result of uremia. The others were in a much improved condition 5 to 17 months after treatment, although they continued on digitalis and mercurial diuretics. One patient who did not have signs of congestive failure before treatment developed signs of failure 36 months later, but

<table>
<thead>
<tr>
<th>Table 5.—Heart Size in 51 Cases of Aortic Insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Treatment</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Normal ..........</td>
</tr>
<tr>
<td>Normal but config. of left vent. hypertrophy ..........</td>
</tr>
<tr>
<td>Slight enlargement ..........</td>
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<tr>
<td>Moderate enlargement ..........</td>
</tr>
<tr>
<td>Marked enlargement ..........</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 6.—Electrocardiograms in 51 cases of Aortic Insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Treatment</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Normal ..........</td>
</tr>
<tr>
<td>Myocardial damage ..........</td>
</tr>
<tr>
<td>Left ventricular hypertrophy ..........</td>
</tr>
<tr>
<td>Right bundle branch block ..........</td>
</tr>
<tr>
<td>Left bundle branch block ..........</td>
</tr>
</tbody>
</table>

This was controlled easily by the usual measures to combat congestive failure.

One patient who had subacute bacterial endocarditis was well eight months following treatment.

Five patients had angina pectoris and four were improved 3 to 28 months after treatment. The fifth case was the patient who died from a pulmonary embolus.

Data regarding heart size before and after treatment are listed in table 5 and in table 6 data relating to electrocardiographic findings before and after treatment. Of the nine cases showing marked enlargement, eight suffered from congestive failure. The other was receiving digitalis although he showed no signs of congestive failure. Six of these nine showed diminution in heart size 5 to 17 months after treatment; the remaining three died before follow-up examinations could be made.

Of the 16 whose heart size was normal although the configuration suggested left ventricular hypertrophy, a follow-up study was made in 14 cases. Of these, five showed increase in heart size. Seven of the 11 patients who showed slight cardiac enlargement were studied after treatment and four showed an increase in size of the heart; one of these was the patient with subacute bacterial endocarditis. Of the 15 patients with moderate cardiac enlargement, 10 were followed up; four showed diminution in size of the heart and in six the heart remained the same in size 9 to 17 months after treatment. The most marked improvement in heart size, therefore, was noted in the moderately and markedly enlarged groups. In the latter group all patients were in congestive failure or had a history of failure, and all were treated with digitalis and other measures to combat congestive failure; the diminution in size, therefore, may have been due to the latter measures and not to penicillin.

Electrocardiograms were made every three days during treatment in 20 cases, and in 14 there were no significant changes. In five instances, there were transient T-wave changes in the limb and/or precordial leads; one showed increased amplitude of the T waves and in four the T waves became of lower amplitude or inverted in one or more leads, but all returned to the pretreatment pattern before discharge from the hospital. One patient who had evidence of intraventricular block, developed complete heart block three days after treatment was started, but the electrocardiogram returned to the pretreatment pattern three days later although penicillin was continued. However, he had frequently developed complete heart block for short periods of time before treatment, and penicillin was therefore not considered responsible.

Follow-up study was made in 10 of the 12
patients whose electrocardiograms were considered normal before treatment; in only one of these patients were there T-wave changes, and these were of the type observed in left ventricular hypertrophy. This patient also showed considerable increase in cardiac area following healing of subacute endocarditis, involving the aortic valve.

In seven cases the soft diastolic murmur of early aortic insufficiency could not be heard on repeated examinations 3 to 40 months after treatment; in three cases the intensity of the murmurs was markedly reduced and they were barely audible. In two patients with wide-open aortic insufficiency the murmurs were markedly reduced three to nine months after treatment, but in the remaining 39 patients with wide-open insufficiency there was no detectable change in the intensity or quality of the murmur.

One elderly negro male with aortic insufficiency, hypertension 220/120, and arteriosclerotic was suspected of having developed an aneurysm of the innominate artery nine months after treatment, and this was at first considered the only instance of therapeutic paradox in this study. However, this patient subsequently died of cerebral hemorrhage, and an autopsy revealed a tortuous and sclerotic innominate artery but no evidence of aneurysm.

**Aneurysm and Aortic Insufficiency**

There were nine cases in this group. The aneurysm involved the ascending aorta in six instances, the ascending and transverse arch in one, the descending aorta in another, and the innominate artery in another instance.

The heart was normal in size in three cases, slightly enlarged in one instance, moderately in three and markedly in two. Follow-up study was made in six cases and no change in heart size or aneurysm was noted 8 to 38 months after treatment.

The electrocardiogram before treatment showed changes indicative of left ventricular hypertrophy in three, T-wave changes indicative of myocardial damage in two, a healed posterior infarction in one, and in three the tracings were normal. Electrocardiograms were made every three days in five cases but showed no significant changes.

Ten months after treatment there was considerable improvement in one of the tracings showing myocardial abnormality, and it is also of interest that a soft diastolic murmur had been heard before and during treatment could no longer be heard in this patient on repeated examinations. Three patients were in congestive failure, and also improved under combined treatment. Two of them died subsequently, however, one as a result of uremia 20 months after treatment, and the other after 21 months as a result of unknown causes.

**Aneurysm without Aortic Insufficiency**

There were three patients in this group. One patient had an aneurysm of the left common carotid artery, one of the ascending aorta and in the third patient the aneurysm involved both the ascending and transverse portions of the arch. The latter patient died 34 days after treatment following operation in an effort to prevent further enlargement of the aneurysm.

The heart was normal in size in one instance, moderately enlarged in another, and in the third case the heart was of normal size but the configuration suggested left ventricular hypertrophy.

The electrocardiogram of the patient with moderate cardiac enlargement showed evidence of left ventricular hypertrophy but was normal in the other two cases.

In two cases electrocardiograms were made every three days during treatment. In one there was no change but in the other there was considerable improvement in amplitude of the T waves.

Follow-up study in the first case 15 months after treatment showed no change clinically or in the electrocardiogram or orthodiagram.

**DISCUSSION**

During the five years of this study certain facts concerning the use of penicillin in cardiovascular syphilis have become clear, and some of the question marks which loomed so conspicuously six years ago are no longer present. Only time, however, careful clinical study and postmortem examinations will determine
whether a number of impressions gained during
these five years, which at present must be
labeled "Not Proved," are sound. However,
there is suggestive, but by no means convincing,
evidence that penicillin has had a beneficial
effect in the large majority of patients treated
in this series and conversely, there is ample
evidence both from our own study and from the
literature that harmful effects are rarities.
This evidence may be briefly summarized as
follows:

1. The reduction in intensity or possible
disappearance of the diastolic murmurs in some
cases. In seven patients in whom the murmur
was the soft type, suggestive of early aortic
insufficiency, the murmur could not be heard
on repeated examinations after treatment, and
in three cases the murmur became barely au-
dible. In no case did the loud, blowing, high-
pitched diastolic murmur, suggestive of wide-
open insufficiency disappear, but in two cases
there was a marked diminution in intensity of
the murmur, which could not be explained by a
drop in blood pressure, change in cardiac rate
or blood count. One may speculate in these
instances that the inflammatory process which
caused widening of the commissures was still
in a reversible stage; if insufficiency were due
to dilatation of the ring, the resultant fibrosis
of healing was sufficiently great to counter-
balance the dilatation. We are aware that this
is pure speculation, but the frequency of this
finding is strongly presumptive evidence of the
validity of our impression that these patients
are benefited by penicillin. We have not ob-
served similar results in the prepenicillin era
except in cases where the murmur was produced
by some hemodynamic factor which was cor-
rected or alleviated.

2. The favorable effect upon patients with
paroxysmal dyspnea and congestive failure.
Paroxysmal dyspnea was present in five pa-
tients with simple aortitis and probable coro-
nary ostial involvement in nine cases of aortic
insufficiency and in one of aortic insufficiency
and aneurysm, or a total of 15 instances; in all
the patients with aortic insufficiency, one with
aortic insufficiency and aneurysm and one with
simple aortitis but with probable coronary
ostial involvement, there were evidences of
severe congestive failure. Two other patients
with aortic insufficiency and aneurysm had
signs of congestive failure but not paroxysmal
dyspnea. In these, measures to combat con-
gestive failure were used simultaneously with
penicillin.

The group of patients with cardiovascular
syphilis and congestive heart failure tolerated
combined treatment very well; nevertheless,
we do not have sufficient evidence to state
definitely that penicillin alters the course or
prognosis of patients with cardiovascular syphi-
lis and cardiac decompensation. Because the
clinical course and prognosis of this group is
frequently altered by many variables such as
duration of infection, amount of early treat-
ment, complicating conditions such as hyper-
tension, arteriosclerosis, nephritis and diabetes,
or social and economic status, a control group
could not be studied especially in view of the
paucity of material; furthermore, we were re-
luctant to deprive a seriously ill patient of a
therapeutic measure which, to us, seemed of
definite value.

Of the four cases of aortitis with paroxysmal
dyspnea, but without signs of chronic congestive
failure, paroxysmal dyspnea was relieved by
penicillin alone in three instances, but in one
case, the symptoms remained unchanged.

One of us (J. E.) treated a patient with
aortitis complicated by hypertension and se-
vere congestive failure for several years before
this study was undertaken. Although this pa-
tient had hypertension, the dilatation of the
aorta was so marked and the history of syphilis
so definite, that there was little doubt about
the diagnosis. Notwithstanding full digitaliza-
tion, ammonium chloride, a salt-free diet and
frequent injections of a mercurial diuretic, noc-
turnal dyspnea was so incapacitating that resort
to one of the morphine derivatives became
necessary. Finally, penicillin was advised as a
last resort, in full awareness of the cardiologic
teaching that it was extremely hazardous to
give antisyphilitic treatment in the presence of
congestive failure. The favorable response was
so dramatic that we were prompted to treat
our other patients with congestive failure with
penicillin concomitantly with the time-honored
drugs for congestive failure; details of this case
and the results of this study have been reported elsewhere.\textsuperscript{8} We have lost sight of this first patient, but for 12 months following treatment he was free of attacks of nocturnal dyspnea.

On the other hand, two patients who were free of signs of congestive failure developed nocturnal dyspnea, but in neither case could treatment be implicated as a possible causative factor because of the long interval after treatment. One patient with simple aortitis who had previously suffered a coronary occlusion developed paroxysmal dyspnea and other evidences of congestive heart failure 58 months after treatment; the other, a patient with aortic insufficiency, was much improved for three years, but then developed congestive heart failure and nocturnal dyspnea. His symptoms were easily controlled with digitalis and weekly injections of a mercurial diuretic.

3. Improvement under penicillin in some cases of angina pectoris. Eight patients, five with aortic insufficiency, and three with simple aortitis, suffered from angina pectoris. Four of the former group and one patient with aortitis were free of angina pectoris or markedly improved after treatment in that the frequency and severity of attacks were reduced; one with aortitis was only moderately improved, and two, one with aortic insufficiency and the other with simple aortitis, showed no improvement. We are aware that, as a group, some of the patients comprising this study were very unreliable and open to suggestion, but in two there was considerable improvement in the electrocardiogram, and in another the soft diastolic murmur could not be heard after treatment. Thus there is suggestive objective evidence that angina pectoris may be favorably influenced by penicillin treatment and that angina pectoris is not a contraindication to treatment with penicillin.

It might be added that three other patients who had recovered from coronary occlusion but who did not have angina pectoris, were treated with penicillin without untoward symptoms, and another patient, not included in this study, who suffered from an acute myocardial infarction, was treated with penicillin because of a complicating pneumonia without untoward reaction.

4. The subjective improvement experienced by most patients supports the efficacy of penicillin. The feeling of well being which is manifested by these patients and the appearance of improved health on leaving the hospital was striking. Good food, frequent bathing, a clean bed and a roof over their heads were undoubtedly contributing factors of more than minor significance to some, but the frequency with which the improvement continued for periods of months and years left little doubt that penicillin was also a factor.

It must be emphasized that even if the ultimate aim of treatment is achieved—cure of the syphilitic infection—the patient, unless treated before complications have occurred, is left with a badly damaged heart or aorta, and this may eventually lead to death. Aneurysms may become larger and cause pressure symptoms or rupture, although the active syphilitic infection has been cured. Patients with partial occlusions of the coronary ostia, may continue to have angina pectoris and nocturnal dyspnea, and those with wide-open aortic insufficiency may continue to show progressive left ventricular hypertrophy and eventually heart failure. There are, however, at present no reliable data to indicate that the infection in cardiovascular syphilis has been eradicated by treatment with penicillin. Although a great deal of information regarding heart size and electrocardiograms before and after treatment has been accumulated, there are so many complicating factors that cannot be evaluated, such as arteriosclerosis, hypertension, drugs, congestive failure, type of work, or social position, which may influence heart size and the electrocardiogram, that they cannot be used to gage accurately the results of penicillin therapy in syphilitic aortitis and its complications. Comparison of measurements of the diameter of the aorta is admittedly inaccurate, and unless there are marked differences they cannot be considered as significant. The available data, however, would indicate that treatment of cardiovascular syphilis with or without angina pectoris or congestive failure with penicillin, can be carried out without fear of serious reaction, and that therapeutic paradox, if it does occur, is a rarity.

Sudden death from syphilitic aortitis is not
uncommon and may be due to a rupture of an aneurysm or to coronary ostial involvement. We can recall a number of these catastrophes, sometimes when syphilitic aortitis was not suspected and before any treatment was instituted. Therefore, in a study comprising a large number of cases of cardiovascular syphilis over a span of years, a sudden death, totally unrelated to treatment but merely coincidental, is probable. Recently we observed a young negro who had a very large heart with loud to and fro murmurs over the base, and a marked and diffuse dilatation of the aorta on roentgen examination. In spite of negative serologic tests the findings were so suggestive of syphilitic aortitis with aortic insufficiency that treatment with penicillin was instituted. He had complained of paroxysmal dyspnea on admission but was much improved on rest in bed, digitalis and mercurial diuretics. Five days after penicillin was started his symptoms became markedly exaggerated and death occurred suddenly during one of the attacks of nocturnal dyspnea. This case strongly suggested that the increase in symptoms and finally death was due to penicillin. Postmortem examination, however, disclosed that not only was penicillin not the cause of his death, but there was no pathologic evidence of syphilitic aortitis. The diffusely dilated aorta and murmur were due to a dissecting aneurysm starting in the beginning of the ascending aorta; there was also double abdominal aorta, probably congenital.

To attribute death unequivocally to penicillin without postmortem evidence is contrary to known clinical facts. Theoretically swelling of a syphilitic lesion near the coronary ostia may cause an increase in angina pectoris or sudden death during treatment, but we have not observed either complication in our series. Undoubtedly, many thousands of patients with syphilitic aortitis have been treated with penicillin because of unrelated infections long before a diagnosis of syphilis or its complications was suspected, but we have not observed any sudden increase in sudden deaths in infectious diseases, nor have we been aware of any reports of an unusual number of deaths in infections treated with penicillin. If such were the case, then treatment of infections with penicillin would be hazardous unless syphilitic aortitis were ruled out, a procedure which would require hours of ill afforded time, even if the diagnosis could be made with certainty. We were encouraged to start treatment with large doses of penicillin because we observed several surgical cases who had syphilitic aortitis, but in whom this diagnosis was not suspected, and who were given large doses of penicillin without therapeutic shock. The lack of reaction to such a powerful spirochetical agent as penicillin and conversely the frequent reactions to arsenicals suggests that the latter was not due to rapid destruction of spirochetes, but to vasculotoxic action of the arsenicals.

Therapeutic paradox, although sought for, was not observed. We have not observed a single patient who developed aortic insufficiency or aneurysm after treatment; there is a possibility that aortic insufficiency may develop at a later date in some of our cases as the result of stretching of an already damaged ring or as the result of hypertension, but this cannot be considered a therapeutic paradox and may be due to a natural deterioration of a damaged aorta. Angina pectoris may subsequently occur not only as a result of an increase of fibrosis around the ostia, the result of healing, but as the result of coronary disease, unrelated to syphilis, especially in the old age group, with or without hypertension.

The lack of therapeutic shock, except for slight fever, would argue for treatment with penicillin in cases of syphilis with doubtful cardiovascular findings. It is hoped that delayed action penicillin will be as efficacious as aqueous penicillin in the treatment of cardiovascular syphilis, and that treatment may, therefore, be carried out on an ambulatory basis. We have already treated 13 patients with severe cardiovascular syphilis with procaine penicillin on an ambulatory basis without untoward symptoms; details of these cases will be included in a later report.

**Summary**

1. We have treated 111 patients with cardiovascular syphilis with penicillin.

2. At first we started with very small doses, fearing (a) therapeutic shock which might close
off a stenosed coronary orifice or, (b) therapeutic paradox which, despite healing of the lesions, might give rise to mechanical difficulties as a result of the scars of healing.

3. As time went on, we became bolder, and started therapy with the full dose of 40,000 to 80,000 units of aqueous penicillin every two or three hours until 4,800,000 to 9,600,000 units were given.

4. We never saw evidence of either therapeutic shock or paradox, although a few patients developed a mild fever.

5. As to the favorable effects of penicillin in cardiovascular syphilis, it is reasonable to believe that they will occur in some patients. It was difficult to measure the benefits in our patients because there were no controls. Moreover, in addition to penicillin, we used the other recognized methods of treatment in those patients with signs or symptoms of congestive heart failure.

6. The beneficial effects which we thought we observed were: (a) Some patients with nocturnal dyspnea and symptoms of congestive heart failure improved to a degree we did not expect from therapy other than penicillin. This also occurred in a few patients with anginal pain. (b) In a few patients, a soft aortic diastolic murmur seemed to disappear, or a loud murmur became softer.

7. The main point we wish to stress is that it does not appear to be dangerous to treat patients with cardiovascular syphilis with penicillin.

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