PENICILLIN TREATMENT OF CARDIOVASCULAR SYPHILIS*†

BY

HERMAN BEERMAN

*University of Pennsylvania, Departments of Dermatology of the School of Medicine (Professor D. M. Pillsbury)
and of the Graduate School of Medicine (Chairman, H. Beerman), and the Institute
for the Study of Venereal Disease (Director, J. H. Stokes)*

Any evaluation of a new mode of therapy for cardiovascular syphilis is bound to yield inconclusive results because of the many unsolved problems in diagnosis, and because of the lack of suitable controls. It is however the author's conviction that in penicillin practitioners have a safe, effective means of supplementing the medical treatment of cardiovascular syphilis.

Evaluation of Treatment

Among the still unsolved problems in the evaluation of penicillin therapy are :

- (1) uncertain criteria of diagnosis, clinical and post-mortem, of uncomplicated syphilitic aortitis ;
- (2) influence of race and sex ;
- (3) prophylactic effect ;
- (4) amount of treatment adequate in early syphilis to prevent the development of cardiovascular complications.

Furthermore, insufficient time has elapsed to determine the efficiency of penicillin in the management of cardiovascular syphilis. Evaluation of the effect of penicillin therapy on prognosis is also difficult because we do not know whether or not cardiovascular syphilis is changing with the passage of time, so that we are now seeing a different type of this phase of syphilis. The simultaneous occurrence in patients of cardiovascular and other forms of late syphilis, such as neurosyphilis, may alter the picture of therapeutic efficacy, besides increasing the potential reactivity of the patient to a particular treatment system or drug. Other variable factors involved are :

- the presence of diabetes mellitus ;
- hypertension ;
- degree of arteriosclerosis ;
- renal function.

It is not sufficient merely to use past records to obtain a control series against which to evaluate therapy in cardiovascular syphilis. One cannot be certain whether patients in the previously treated group are similar to those now being subjected to the new method of treatment (Densen and others, 1952).

Barnett and Small (1950), moreover, on the basis of a series of 334 cases of cardiovascular syphilis with aortic regurgitation, aneurysm, or both, attest to the statistical difficulties in the evaluation of the effect of antisyphilitic therapy in cardiovascular syphilis. They show that symptomatic and asymptomatic cases must be separated for study. In the former, cases observed for less than a year must be eliminated in order to obtain little- and much-treated groups of comparable initial severity. In the latter, no such elimination can be made, but the results must be expressed in relation to the total years of patient observation, rather than to the number of individual patients involved. Antisyphilitic therapy probably improves prognosis to some extent at any stage of cardiovascular syphilis, but it is definitely more effective when given before the onset of symptoms, and it probably becomes progressively less useful as the disease progresses. Flaum and Thomas (1951) believe that the factors influencing prognosis of cardiovascular syphilis include:

- (1) presence or absence of symptoms of diminishing cardiac reserve ;
- (2) size of heart ;
- (3) age of patient (arteriosclerosis) ;
- (4) type of work performed ;
- (5) amount of previous antisyphilitic therapy and when it was given in relation to the discovery of the cardiac involvement.

Involved also in the evaluation of cardiovascular syphilis therapy is the relative place of medical care, other than so-called specific therapy. Although little mention is made here of the so-called medical treatment of cardiovascular syphilis, this does not indicate any lack of regard for its importance.

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The review of cardiovascular syphilis by Moore (1949) summarizes many of the problems involved in determining the effect of antisyphilitic therapy in this aspect of syphilis. In view of the uncertainty of diagnosis of uncomplicated syphilitic aortitis, information concerning the effect of antisyphilitic treatment must be sought from patients in whom the clinical diagnosis is as nearly as possible verified by the presence of aortic regurgitation, saccular aneurysm, or both. In this connexion, Moore believes that only two methods of study seem applicable; the histopathology of aortic syphilis as affected by treatment and the clinical study of treatment effect.

The study of the effects of therapy on the histopathology of the aorta, however, has yielded contradictory results. While Hood and Mohr (1937) found no histologic differences in the aortas of untreated and adequately treated patients, Howe (1943) and Webster and Reader (1948, 1949) found what appear to be definite differences.

Moore points out certain difficulties in the clinical study of the effect of treatment in terms of symptomatic relief and prolongation of life span. The first clinical intimation of the presence of cardiovascular syphilis may be sudden death, or an attack of congestive heart failure, which is fatal in a few days or weeks. In such cases, there is no way of estimating the value of specific treatment, since there is no time to give it. Because the Johns Hopkins material contains nearly one-third of the cases of cardiovascular syphilis in this category, Moore and his group eliminate from statistical consideration of treatment effect all patients who died within one year of the onset of symptoms. Furthermore, since in a given patient the course of the disease is wholly unpredictable with or without therapy, conclusions may be drawn only from large numbers of individuals and in terms of averages. Aortic regurgitation, saccular aneurysm, or a combination of the two, are usually fatal in the long run, unless the patient dies of an unrelated process.

The uncontrollable factors of the economic situation and physical work are related to mechanical circulatory death. A sedentary occupation is essential to prolong life to the maximum in a patient with aortic aneurysm or regurgitation. The factor of work stress is, according to Moore, as important in prolonging life as antisyphilitic treatment, and account must be taken of it in a statistical analysis of results. Because of the more strenuous occupations of males, sex plays an important role in prognosis. The race of the patient is also important; for example, syphilitic heart disease is not only

more frequent in the Negro than in the white, but it is probably also more rapidly progressive. The duration of infection and the age of the patient are also involved. The probably prolonged symptomless course of aortic insufficiency and aneurysm is a significant item. An estimate of the effect of antisyphilitic treatment can be had only by comparison of various groups of patients receiving various types or amounts of specific therapy with a group receiving none at all. The purely medical management of the several groups must be as far as possible identical. The physician must resist the temptation to try another form of antisyphilitic therapy if one fails to bring about symptomatic relief, or if symptoms recur. Finally, for complete statistical accuracy, Moore suggests that the results of treatment should be reported only for patients followed until death; if possible, with verification of the diagnosis by necropsy.

Results of Metal Chemotherapy in Cardiovascular Syphilis

Moore's summary of this problem is so satisfactory that it is quoted below at length:

These complexities are cited in extenuation of the fact that now, nearly 40 years after the first introduction of salvarsan by Ehrlich and the initiation of effective metal chemotherapy, there are available in the world literature only three comparable, and reasonably statistically reliable studies of the effect of antisyphilitic therapy in cardiovascular syphilis. These are by Grant (1933), Padgett and Moore (1941), and Stratton (1935).

Depending on the biostatistical method employed, even Grant's data are not strictly comparable with the other two series. Based on 171 cases of aortic regurgitation followed for 10 years or until death, Grant indicates that the mortality rate is higher, and especially so from cardiovascular syphilis, in patients untreated or inadequately treated (with potassium iodide only) than in those given something approaching reasonable arsenic and heavy metal therapy; and that the proportion of patients still living 'uneventful and unchanged' after 10 years is higher in the treated group. If, however, one re-analyses Grant's material on the basis of average duration of life after onset of symptoms, limiting the analysis to patients already dead, there is no difference in the two groups (89 months in 29 treated patients, 87 months in 89 untreated patients). The average duration of life in Grant's untreated group is greater than in treated patients in the two American series. There is, however, a significant difference in the clinical material. Grant's patients were all white males, British Army pensioners, who were able to lead an essentially sedentary life. In the two American series, the patients are predominantly Negro labourers, in whom the unfavourable influence of hard physical work is repeatedly evident.

The data of Padgett and Moore and of Stratton, combined and refigured to show the average duration of life in sixty patients with saccular aneurysm (32

untreated, 28 treated) and 91 patients with aortic regurgitation (51 untreated, forty treated), all of whom lived at least one year after the onset of symptoms or recognition of the lesion but all of whom were dead at the time of study, indicate that life span may be approximately doubled by the factor of treatment. The actual figures are :

aneurysm untreated, 41 months, treated 74 months ; aortic regurgitation untreated, 45 months, treated, 75 months.

The data of Reader and his associates (1947) cannot be compared for lack of pertinent information, but also strongly suggest that antisyphilitic treatment is effective in prolonging life.

All these results were obtained with prolonged cautious treatment with arsenic, bismuth, and mercury, as outlined in Chapter 18 of my monograph, "The Modern Treatment of Syphilis" (Moore, 1941).

Therapeutic Shock and Paradox

In the conventional therapy of cardiovascular syphilis, two concepts, therapeutic shock and therapeutic paradox, played an important role. These problems are fully discussed in "Modern Clinical Syphilology" (Stokes, Beerman, and Ingraham, 1944), and in papers by Stokes, Wolferth, Edeiken, Falk, and Ford (1951), Butterly and Fishman (1952), and Mohr and Hahn (1952).

Therapeutic Shock.—The former, commonly spoken of as the Jarisch-Herxheimer or Herxheimer reaction, is a flare-up of the disease upon the institution of treatment. Originally described by Jarisch for the secondary eruption under treatment with mercurial inunction, it has been identified in every observable phase of syphilis, early and late. In the use of the arsenicals its intensity up to the point of destructive violence probably depends in part upon the initial intensity and impact of the treatment, though the "allergic" status of the individual also participates in this reaction. Dosage, and the activity of the treatment agent used, both play a role in its production. Its mechanism is still unknown, but the earlier attributing of the flare to lysis of *Treponema pallidum* at lesion sites is certainly untenable, since the reaction appears after the use of relatively nonspirillicidal drugs, for example, mercury and tryparsamide, and can be seen in lesions of late syphilis in which treponemata are few and far between. It is more probable that at least a part of the reaction is in the cellular tissues and of the nature of an immunity response, or even an allergic reaction. Therapeutic shock induced by metal therapy had to be controlled. This was accomplished by two devices : initial low dosage, and the preliminary use, before the more shock-producing arsenicals were administered, of more or less prolonged "preparation" with the slower-acting heavy metals, although bismuth itself may produce therapeutic shock, and neoarsphenamine can be given without serious clinical shock if the dosage is low enough.

Clinically the Jarisch-Herxheimer reaction may be manifested by increased body temperature as well as by a flare-up of obvious or subclinical syphilitic lesions

immediately after treatment with anti-syphilitic agents. In the heart this could result in serious embarrassment. Therapeutic shock, then, has been accepted as a danger in the treatment of cardiovascular syphilis during the middle and later years of the arsenical era, and has discouraged the full use of our therapeutic resources against syphilis in treating the disease in the heart and great vessels. On the other hand, the vasculotoxicity of the arsenicals as such should not be confused with the Jarisch-Herxheimer reaction.

Therapeutic Paradox.—Wile (1922) first described this as the conception that the patient might be injured even fatally by the rapidly induced healing of a syphilitic lesion in a vital structure. This was originally observed in the liver. Syphilitic hepatitis improved rapidly under the arsphenamines, and then with equal rapidity the patient went downhill to uncontrollable ascites, with other evidence of hepatic injury, portal obstruction, and death. Later the concept was broadened to include other late manifestations of syphilis, and supposed fibrous contractile scarring as a phase of the healing process, with shrinkage and distortion of the involved structure, rather than lack of time for functional adjustment, was emphasized as the evil consequence. The mechanism of the therapeutic paradox is still unknown. It may be prevented much in the same way as therapeutic shock. Even substitution of a less toxic arsenical (arsenoxide) may, because of lessened vasculotoxicity, yield fewer therapeutic paradoxes than the arsphenamines.

Sources of Pertinent Information

For the student of the treatment of cardiovascular syphilis, a number of good sources are available. Among these are : Stokes, Beerman, and Ingraham (1944), Fleming (1948), Kampmeier (1946), Cole and others (1936), Hinrichsen (1943), Woodruff (1948), de la Chapelle (1947), Nicol (1950), Cormia (1935), Eisenberg (1948), Chapman and Morgan (1947), Prebble (1951), Webster (1947), Barnett and Small (1950).

Penicillin in Cardiovascular Syphilis

Since penicillin should theoretically behave like the other fast-acting spirillicides, the arsphenamines, it could produce not merely a febrile reaction, but an overall exacerbation of the syphilitic process, transient and serious in proportion to the vital location of the lesion and the size of the initial dose. Early in the penicillin era, workers attempted to control an anticipated shock effect by reduction in dosage, but the observation of Olansky (1947) seemed to indicate that reductions in dosage to as low as 1,000 units were without effect in preventing Herxheimer reactions, though their intensity might conceivably be reduced. Tucker and Farmer (1947) showed that a febrile Herxheimer reaction fails to appear only below such small doses as 1 to 10 units

kg. body weight. One-tenth of the dose that will render a syphilitic lesion darkfield negative is capable of causing a Jarisch-Herxheimer reaction. Purified crystalline penicillin G appears to yield fewer severe local flares and immediate serious reactions as compared with the arsphenamines. Certain groups (notably at the University of Pennsylvania) have made a complete study of the effects on cardiovascular syphilis, but other investigators have been extremely conservative in their exhibition of a rapid-acting drug like penicillin, *e.g.*, Wile (1945), Peralta and Castaneda (1949), Tung (1948), Eisenberg (1948), Blomquist (1948), and Willcox (1951). For example, Wile advised against the use of too intensive methods. He felt that after the disease had reached a clinical horizon, treatment reactions were more apt to occur. This relates to either the arsenicals or penicillin, both of which are fast-acting drugs. This point of view seemed somewhat justified at first because in a disease process, such as cardiovascular syphilis, where sudden death, with or without treatment, is frequent, treatment with even small doses of penicillin seemed to be unsafe. Early reports, although admittedly equivocal, featured reactions, even fatal, in patients with cardiovascular syphilis under penicillin therapy. (Dolkart and Schwemlein, 1945; Callaway and others, 1946; Moore, 1949; Scott and others, 1949; Porter, 1948.) Subsequent experience indicates that penicillin is not only well tolerated, but may actually induce relief of symptoms and prolongation of life. Data obtained from the literature have been tabulated in chronological order in the Table (pp. 22-27).

Jarisch-Herxheimer Reaction and Therapeutic Paradox.—The literature on penicillin therapy of cardiovascular syphilis shows how groundless were the fears that it would produce an excessive number of therapeutic shocks and paradoxes. Moore, Farmer, and Hoekenga (1948) stated that the febrile response of the Herxheimer reaction was rarely observed in cardiovascular syphilis, and then only in patients with an associated neurosyphilis with active cerebrospinal fluid findings. They observed no clinical suggestion of increased cardiovascular damage, nor could any evidence of this be detected by serial electrocardiograms, leukocyte counts, and sedimentation rate estimations. The Johns Hopkins group believed that

the risk of a serious Herxheimer reaction in cardiovascular syphilis has been grossly exaggerated.

Wheeler and Curtis (1951) of the University of Michigan analysed the reported deaths and reactions as follows:

Of the eight possible reactions, there are reported three fatalities. The patient reported on by Porter

had received four months of bismuth and iodide therapy before penicillin was administered. Two days after 9.6 million units of penicillin had been given the patient died of rupture of a huge aneurysm. It was evident before treatment that rupture of this aneurysm was imminent and it is impossible to say whether treatment had anything to do with the course of events. In the case presented by Moore the cause of death was likely cardiac failure which developed on the fourth day of treatment. The aorta was filled with plaques of syphilitic aortitis each of which contained fresh hemorrhage. Evaluation in this instance is complicated by the patient's being treated with malaria as well as penicillin. Scott and Maxwell's patient suffered from purulent meningitis of unknown cause. Response to penicillin seemed satisfactory, but the patient died suddenly during convalescence of rupture of a previously unsuspected aneurysm. The possibility of bacterial involvement of the vessel was not discussed.

Of the eight possible reactions there are five reports indicating temporary interference with cardiac function. One of Porter's two patients had received 2 weeks and the other had received 2 months of potassium iodide and bismuth therapy before penicillin was given. Each had aortic insufficiency and one also had an aortic aneurysm. Both were in congestive failure before penicillin was given. As good 'compensation as possible' was obtained by use of digitalis, diuretics, and bed rest. Each developed increasing evidence of congestive failure 2 weeks after penicillin was begun. Each responded satisfactorily to diuretics and greater curtailment of activity. The observation that congestive failure associated with syphilitic aortic insufficiency may be refractory to treatment and that it tends to recur casts some doubt on the conclusion that these patients present evidence of the therapeutic paradox.

Dolkart and Schwemlein's first patient was seen in 1941, at which time diagnoses of latent syphilis and rheumatic heart disease with mitral stenosis and aortic stenosis were made. From 1908 to 1935 the patient had received an unknown amount of arsenic and bismuth. During 1942, an aortic diastolic murmur became evident. On two occasions in 1943, the patient was hospitalized because of chest pain and dyspnea. In 1944, he was again hospitalized and treated for congestive failure. In the summer of 1944, anginal pain on strenuous effort was noted. During 1942 and 1943, fifty doses of bismuth were given. The patient was rehospitalized in September, 1944, for penicillin therapy. Ten thousand units of penicillin given on September 24 produced no reaction. After 20,000 units on September 25, the patient noted four episodes of anginal pain. Twenty thousand units were given again on September 25 and 20,000 units 3 times on September 26. Seven episodes of anginal pain were noted on September 26 and ventricular extrasystoles appeared on physical and electrocardiographic examination. The penicillin was stopped. The extrasystoles disappeared. Because of the associated rheumatic heart disease, the amount of pretreatment, the evident cardiac dysfunction before penicillin was given, it is hazardous to claim that this is an example of a Herxheimer reaction.

The second patient reported by Dolkart and Schwemlein was given penicillin for an upper respiratory infection. After 700,000 units given over a

TABLE
PENICILLIN TREATMENT OF CARDIOVASCULAR SYPHILIS

Author	Date	No. of Patients	Diagnosis	Therapy	Reaction	Remarks
Dolkart and Schwemlein	1945	2	Aortitis with dyspnoea and precordial pain	<i>Patient 1.</i> Daily injection of penicillin <i>Patient 2.</i> 700,000 u. penicillin in doses, 20,000 u. every 2 hours	<i>Patient 1.</i> On third day after 60,000 u. penicillin, 4. original attacks, 4th day 60,000 u. (in 3 doses), 7. anginal attacks with frequent extra systoles <i>Patient 2.</i> Precordial pains after 700,000 u. penicillin	Penicillin should not be used in cardiovascular sypilis because of reactions
Morginson	1946	—	—	—	Jarisch-Herxheimer reaction to penicillin indicated efficacy. May be avoided by lowered dosage	Advised against use of penicillin in cardiovascular sypilis
Hill	1946	—	—	—	No adverse effects	—
Russek, Cutler, Fromer and Zohman	1946	15	Aortitis. Four with aortic aneurysms	Penicillin, 40,000 u. every 2 hours for 85 doses	One patient had mild substernal pain on third day of therapy. Continued on treatment uneventfully	Jarisch-Herxheimer uncommon. Therapeutic paradox rare
Moore	1947	12	Aortic regurgitation. Aortitis with ostial stenosis aneurysm (six had neurosyphilis)	Penicillin started in small doses	One patient with large aneurysm of thoracic aorta died of rupture 6 months after treatment	One possible therapeutic shock. Patient died on 4th day. Combined penicillin and malaria. Denies existence of therapeutic paradox. Risk of therapeutic shock greatly exaggerated
Callaway, Noodin, Flower, Kuhn, and Riley	1946	1	Aortitis and neurosyphilis	Penicillin	Rupture of aortic cusp 10 days after completion of penicillin therapy	—
Pokrass	1947	—	—	—	—	Penicillin will cause Jarisch-Herxheimer reaction and therapeutic paradox in cardiovascular sypilis
Dennie and Dwyer	1947	—	—	Prepare patient with 6-12 injections of bismuth and daily potassium iodide before penicillin, which is given in gradually increasing doses. Conclude with one year or more of bismuth therapy	—	—
Tucker and Farmer	1947	30 (34)*	22 (25)* aortic regurgitation. 8 (9)* thoracic sacular aortic aneurysm	Penicillin started in doses ranging from 500 to 100,000 u. every 3 hours in total	Five patients had temperature rise 37.8 and 39.0 during penicillin therapy (had neurosyphilis). Two with angina attacks prior to therapy had attacks during and after therapy. No change in blood counts, sedimentation rates and electrocardiogram	Insufficient evidence to prove previously reported cases died of therapeutic shock

PENICILLIN IN CARDIOVASCULAR SYPHILIS

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Chapman and Morgan	1947	No data	Aortic aneurysm	Penicillin 10,000 u. followed by 15,000 u. at 2-hour intervals. Total dosage 6 million u. Potassium iodide orally and bismuth intramuscularly every other day during treatment	No reactions	—
Syphilis Study Section, National Institutes of Health	1948	—	—	—	—	Since small doses of penicillin produce Jarisch-Herxheimer reaction in early syphilis, it should be avoided in cardiovascular syphilis
Woodruff	1948 1949	—	—	Advises bismuth before penicillin	—	—
Porter	1948	6	Cardiovascular syphilis	Penicillin	No reactions. Decompensation which was present before became worse during therapy, but was controlled medically	Five of six patients improved symptomatically. One with thoracic aneurysm died of rupture of aneurysm 2 days after 9.6 million u. penicillin
Kossmann and Flaum	1948	49	Cardiovascular syphilis (eleven had no previous treatment)	Penicillin	One patient had recurrent attacks of precordial pain during therapy. Another had paroxysmal dyspnoea. Both had congestive failure, and one complained of angina prior to treatment	—
Peters	1948	About 20	Cardiovascular syphilis with coexisting neurosyphilis	Aqueous penicillin. Some cases started on 5,000 u. Dose gradually increased to 10,000, 20,000, 30,000, 40,000 u. every 3 hours; total 6 million u. Others 40,000 u. every 3 hours to total 2.4 million u.	Few complications	—
Eisenberg	1948	About 20	Uncomplicated aortitis	Penicillin oil-beeswax. Initial dose 100,000 u. Increase by 100,000 u. after the third and fifth day to 300,000 u. Total dose 4.5 million u. in 15 to 20 days	No untoward reaction	—
Webster and Reader	1949	—	—	Penicillin. 20,000 u. every 3 hours, or 300,000 daily for two weeks (preferably procaine penicillin followed by 300,000 u. twice a week for next 10 weeks	—	Hazard of therapeutic shock and paradox is hypothetical
Scott, Maxwell, and Skinner	1949	—	—	—	Death of patient from rupture of aneurysm 49 hours after penicillin had been started for meningococcus meningitis	—

TABLE—continued

Author	Date	No. of Patients	Diagnosis	Therapy	Reaction	Remarks
Peralta and Castaneda	1949	25	Two aortic insufficiency (one acute cardiac insufficiency) two aneurysm, one myocarditis, one coronary stenosis (infarct) aortitis and coronary arteritis	Penicillin G 2,500 u. initial dose. 50,000 to 100,000 in non-coronary cases. Total 4.5 to 8.0 million u.	28 per cent. of patients had symptoms during therapy. 3.9 per cent. had precordial pain. 7.8 per cent. had electrocardiographic changes without symptoms during treatment (disappearing later). One patient died of cardiac insufficiency 1 month later	—
Flaum and Thomas	1949	39	Thirty aortitis (insufficiency) nine aortic aneurysm (eight no previous therapy). Additional group of 22 patients in above, syphilis of the cardiovascular system was suspected and treated with penicillin (not included in study)	All but three had three injections bismuth preceding penicillin (30,000 to 50,000 u. every 3 hours to a total of 3 to 6 million u. Three patients received penicillin in oil beeswax, 300,000 to 600,000 u. a day to totals 4.2, 7.2 and 9.0 million u. respectively	No reactions <i>per se</i> . Two patients admitted with cardiac failure and died, one 5 weeks and the other 2 months after therapy	No danger of therapeutic shock, but believe patients should be prepared with 0.2 gm. bismuth every 5 days for three doses
Russek, Nicholson, and Zohman	1949	78 males 35-58 years	Nine aneurysms; ten coronary ostial stenosis; one congestive failure	58 received 40,000 u. penicillin for 85 doses. Twenty received 600,000 u. penicillin in oil for six doses	No Jarisch-Herxheimer reactions. One patient had attack of subnormal fever during therapy. He had had similar attack prior to treatment. Patient in congestive failure died 1 week after completion of treatment	Jarisch-Herxheimer reaction, in cardiovascular syphilis, if it occurs at all, is rare
Falk, Edeiken, Ford, and Stokes	1949	12	In decompensation	Medical therapy concurrent with penicillin G 500-40,000 u. every 2 hours to total of 4.8-9.6 million u.	Two had rise in temperature from 6-16 hours after first penicillin injection	All improved. Penicillin plus medical better than the latter alone
Edeiken, Falk, and Steiger	1949	50	23 with aortitis; twenty with aortic insufficiency (eighteen with neurosyphilis); five with aortic aneurysm and aortic insufficiency	Penicillin, 1.2-9.6 million u. Forty patients had received previous therapy, four as recently as 3 months prior to receiving penicillin	Four aortitis patients had rise in temperature during treatment. One had angina 10 months after completing treatment. Three aortic insufficiency cases had temperature rise. No pyrexia among aneurysm patients	Eight patients had electrocardiographic changes during therapy. Six patients with decompensation did well. No therapeutic paradox observed
Moore ..	1949	31	Six aneurysm; 25 aortic regurgitation	21 survivors followed 158-1243 days (average 567 days, or 18 months). Fifteen never in failure before penicillin. None since. Six in failure prior to treatment. Three doing well—two with aneurysm dead (1 and 158 days after treatment) Four living 29-773 days. Four aortic	—	—

Flaum ..	1949	55	Cardiovascular syphilis	Nineteen not previously treated. Twelve given preliminary bismuth. Seven not treated with bismuth. 28 of 36 patients who had received previous therapy 1 or more years prior to admission. Four of these were given bismuth (1 to 3 injections) prior to penicillin	No data	No adverse reactions. Five had fleeting presternal pain. Two had nocturnal paroxysmal dyspnoea. All seven had aortic insufficiency
Diefenbach ..	1949	1	Aneurysm	Penicillin. Three days of treatment	Expansion of aneurysm. Occlusion of left bronchus and death	—
Hayward ..	1949	—	Aortitis ; aneurysms	2-3 months preparation with bismuth and iodides previous to 8-10 million u. penicillin in 10 days	—	Herxheimer reactions are uncommon
Coale, Allen, and Delp	1950	70	48 aortitis ; eighteen aortitis with insufficiency ; four aortic aneurysm	47 previous therapy ; 23 no previous therapy. Penicillin. 6 million u., 600,000 u. per day for 6 days (except Sunday), then 400,000 u. daily for 6 days. Four of patients received 10 to 15 million units	Two with neurosyphilis developed fever during treatment	Penicillin is safe. No necessity for preparatory treatment with bismuth and iodides
Edeiken, Ford, Falk, and Stokes	1950	12	Cardiovascular syphilis in congestive failure	4-8-9-6 million u. penicillin (two cases were started on 500 u. doses, 8 on 10,000 u., two on 40,000 u. every 3 hours). Duration of treatment 12-15 days	No untoward reactions, except febrile reaction in two. Two deaths, cause undetermined	All improved. Penicillin plus medical treatment better than latter alone
Leech ..	1950	17	Five uncomplicated aortitis ; seven aortic insufficiency ; one aortic insufficiency and aneurysms of ascending aorta ; one aortitis, probably aneurysm ; three patients with syphilis and probably nonsyphilitic cardiovascular disease ; two patients had no previous therapy	Penicillin oil beeswax, 300,000 u. per day for 20 days (600,000 u. on Saturday, none on Sunday)	Three patients died, but death was not related to penicillin	Penicillin alone is good treatment. No need for preparatory treatment
Weir, Roberts, and Tullis	1950	43	31 aortic insufficiency without aneurysm. Six with aneurysm, one aortitis. Three aortic insufficiency with aneurysm. Two not stated	Preparatory, penicillin G in beeswax and peanut oil, procaine penicillin G in peanut oil, crystalline penicillin G in sesame oil with 20 per cent. aluminium monostearate. 400,000 or 6 million u. per day (1 dose) for 15 days. (‡, 6 million ; §, 9 million u.)	16 per cent. had febrile Jarisch-Herxheimer reactions, not severe in 16-8 per cent. of patients	Therapeutic shock and paradox have been overemphasized

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TABLE — continued

Author	Date	No. of Patients	Diagnosis	Therapy	Reaction	Remarks
Forsey ..	1950	From 161 cases (25 aortic insufficiency eleven aneurysm valid)		Penicillin	No case of serious reaction	—
Sinclair and Webster	1951	53	Nine aortitis (six previous therapy). 36 aortic regurgitation (20 had previous treatment). Eight aortitis and sacular aneurysm (seven had previous treatment)	2-12 million u. penicillin	No therapeutic paradox. Two aortitis had Jarisch-Herxheimer reactions (febrile). Four aortic regurgitation had Jarisch-Herxheimer reactions. All patients with reactions also had neurosyphilis	Two aortitis died 1 month and 2 years after treatment (non-cardiac). Six aortic regurgitation died 2 months to 3 years after treatment (four cardiac, two non-cardiac deaths). Penicillin alone is treatment of choice in cardiovascular syphilis
Flaum and Thomas	1951	69	Aortic insufficiency and/or aneurysm	Procaine penicillin in oil with 2 per cent. aluminium monostearate, 600,000 u. dose daily, every other day or three times a week for ten doses	No adverse reactions	Danger of therapeutic shock is greatly exaggerated
Edeiken, Ford, and Stokes	1951	61 additional cases (111 in whole series) (50 or 46 per cent. had neurosyphilis); 48 aortitis; 51 aortic regurgitation; nine aortic regurgitation with aneurysm, three aneurysm		Recent scheme, procaine penicillin ambulatory, 600,000 u. in a single injection daily for ten days. (Total 6 million u.)	No serious reactions in entire series. No unequivocal example of therapeutic paradox	—
Bruetsch ..	1951 (a, b)	—	Cardiovascular syphilis	Penicillin 25 million u., 400,000 to 600,000 u. a day	—	Occurrence of untoward reaction in cardiovascular syphilis has been overemphasized
Wheeler and Curtis	1951	21	Cardiovascular syphilis. Thirteen previously untreated. Eight previously inadequately treated. All but five symptomatic	Penicillin dosage varied widely, 12-40,000 u. aqueous penicillin G every 3 hours for 100 doses (4 million u.)	Ten patients eliminated from evaluation of reaction. Of remaining eleven, three febrile rise within 24 hours after starting penicillin. Two of these had inactive paresis, two possible examples of therapeutic paradox	No need to prepare patient with iodides or bismuth
Johnson and Shapiro	1951	17	—	Penicillin G. Total dosage 4,008,000 u. Injections three times a day, 1,000 u. first day, 2,000 u. second day, 3,000 u. third day, 5,000 u. fourth day	10,000 u. fifth day, 20,000 u. sixth day, 30,000 u. seventh day, 40,000 u. thereafter. No febrile reaction	—
Packer ..	1951	60	Aortic regurgitation	Penicillin. Schedule similar to neurosyphilis	No mishaps	See Weir, Roberts, and Tullis (1950)

Willcox	1951	—	—	—	—	Preparatory bismuth and iodide used by British physicians
Whorton and Denham	1951	1	Gummatous syphilitic aortitis	Sodium penicillin. 140,000 u. every 3 hours	Died suddenly 27 hours after therapy was begun	Jarisch-Herxheimer reaction is uncommon. Cause of death undetermined
Lian, Nedey, and Cassimatis	1951	24	Aortitis—nineteen with insufficiency, two with aneurysm, three with insufficiency and aneurysm	Six injections of aqueous penicillin daily for 10–15 days. Initial dose 200,000 to 1,000,000 u., total dose 3,000,000 to 15,000,000 u. Several patients had repeated courses	Two patients died, one on third day of penicillin treatment, one on third day after therapy was terminated. Neither due to penicillin. No Herxheimer reactions. Some slight febrile reactions	Advise preparatory medical therapy as if the patient were nonsyphilitic. Use penicillin only if treatment fails. Also suggest few mercury cyanide and bismuth injections and repetition of course if necessary
Prebble	1951	—	—	After* preparatory treatment, procaine penicillin with 2 per cent. aluminium monostearate, 600,000 u. Total dosage of not less than 12 million u. Rest 1–2 months followed by alternate courses of bismuth once a week for 10 to 12 injections. Rest 1 month, then penicillin (another 600,000 u. per day to a total of 12 million u.)	—	Preparation with iodides orally or intravenously (10–12 per cent. sodium iodide). Bismuth oxychloride 0.2 gm. (total of twelve each) given twice a week
Stokes, Wolferth, Edelken, Falk, and Ford	1951	111 cases observed from about 3 months to about 58 months following therapy	48 uncomplicated aortitis; 51 aortic insufficiency; nine aneurysm and aortic insufficiency; three aneurysm	Earliest cases aneurysms, penicillin, but mostly with crystalline penicillin G 40,000 to 80,000 u. every 2 hours to a total of 4.8 to 9.6 million u.	No unequivocal cases of therapeutic paradoxes. Little evidence of therapeutic shock	Advocate 2 hour schedule crystalline penicillin G 40,000 to 80,000 u. total 9.6 million u. or 600,000 or 300,000 u. procaine penicillin single or two a day injection schedule respectively to total 6 million u.
Curtis, Kitchen, O'Leary, Rein, Schoch, Shaffer, and Wile	1951	—	—	Penicillin daily or two times a week for 5 weeks. Ten injections of 600,000 u. penicillin aluminium monostearate each for a total of 6 million u. Course may be repeated 2–3 times	—	—
Butterly and Fishman	1952	1	Syphilitic aortitis. Coronary ostial involvement	300,000 u. penicillin for upper respiratory infection	6–8 hours after injection developed cough and chest pain. Died 3 days later	Autopsy proved presence of syphilitic aortitis with coronary ostial involvement
Mohr and Hahn	1952	4	Neurosypphilis—no cardiovascular involvement before treatment	Varying amounts with or without fever	6–18 months after treatment all four developed aortic insufficiency	Not certain whether these are therapeutic paradoxes

3-day interval, precordial pain appeared. The penicillin was stopped and the pain disappeared by the following morning. This patient had aortic insufficiency and *tabes dorsalis*, the diagnosis being made in 1936, nine years before penicillin therapy. From 1936 to 1939, he was given intermittent treatment consisting of iodides, bismuth, and neoarsphenamine. In 1938 and 1939, several episodes of precordial pain had occurred, but the patient denied precordial pain from 1939 to 1945. He also denied knowledge of syphilis or of specific treatment for it. Besides a possibility that the history was unreliable, the re-appearance of the precordial pain at the time of penicillin therapy may have represented only coincidence. It might even be that the pain was tabetic.

The report of Callaway and his associates concerns a 42-year old carpenter who received penicillin in the treatment of neurosyphilis. At the time of treatment compensated aortic insufficiency was observed. No reaction during therapy was noted. When the patient returned to work 10 days after therapy, precordial pain appeared. The pain was progressive. About 6 weeks later the patient went into congestive failure. The murmur had taken on a harsh quality suggestive of a ruptured aortic cusp. Treatment for congestive failure restored compensation but the cardiac reserve was too low to permit the patient to return to work. Rupture of a valve was not proved by autopsy. In the event of valve rupture, it is unlikely the patient could regain compensation. It is impossible to prove whether the breakdown of cardiac reserve was a result of the penicillin therapy or whether it represented a natural progression of the disease.

A review of the present literature dealing with the use of penicillin in cardiovascular syphilis indicates that about 190 cases have been reported. About 35 of these patients carry diagnoses of uncomplicated aortitis. Since a diagnosis of uncomplicated aortitis is subject to considerable possibility of error, results pertaining to this group of patients should be accepted with reserve. The remaining 155 patients present evidence of either aneurysm, aortic insufficiency, or both, and as such permit diagnoses of cardiovascular syphilis. Of this latter group, approximately 130 patients have been given varying amounts of iodide and metal therapy before penicillin administration, and about 25 have received no pretreatment before penicillin therapy. In no instance has an unquestionable adverse reaction to penicillin therapy been recorded.

Whorton and Denham (1951), who reported the occurrence of a possible Jarisch-Herxheimer reaction after penicillin treatment in a patient with gummatous syphilitic aortitis, also commented on the rarity of the Jarisch-Herxheimer reaction in cardiovascular syphilis, in contrast with early syphilis and central nervous system syphilis.

Encouraged by the relatively lessened reaction tendency of penicillin G over the more crude product, Edeiken and others (1949), reported the results of the treatment of fifty cases of cardiovascular syphilis with penicillin therapy alone, without preparation; and of twelve patients with cardiovascular syphilis and congestive 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 pre-penicillin era, with measures aimed only toward combating congestive failure. Experience with these two groups of cases led to the belief that therapeutic shock in cardiovascular syphilis treated with penicillin is indeed uncommon; and that therapeutic paradox, if it occurs, is a rarity. Various hypotheses, including that of a toxic action of arsenicals upon already diseased tissues, rather than a wholesale sudden liberation of toxic spirochaetal disintegration products, were discussed to explain therapeutic shock. If therapeutic paradox occurs, they do not believe it is common or that it is caused by too rapid cure with disturbance of function and resultant rapid fibrosis.

Subsequently Edeiken and others (1951) reported observations on 111 penicillin-treated cardiovascular syphilitic patients (simple aortitis, 48; aortic regurgitation, 51; aortic regurgitation and aneurysm, 9; aneurysm, 3), with re-emphasis of the virtual absence of significant therapeutic shock and paradox.

Serologic Effects.—The serologic effects of penicillin therapy on cardiovascular syphilis are bound to be disappointing. The frequent association of neurosyphilis with syphilitic cardiovascular involvement (for example, 45.2 per cent. of the 111 patients mentioned above also had central nervous system syphilis) may account for much of the poor serologic effect of treatment. Edeiken and others (1951) found, disregarding the six cases without follow-up, that there were 85 cases (80.9 per cent.) positive before, and 86 cases (81.9 per cent.) positive after therapy. Twenty cases (19.1 per cent.) were negative before, and nineteen cases (18.1 per cent.) negative after treatment. Although seven of the cases with a sero-positive reaction yielded negative reactions after treatment, eight of the original twenty cases that had negative reactions before treatment were sero-positive after penicillin therapy. Thirty-six (42.3 per cent.) of the 85 patients with positive results in their tests showed a drop of two or more tubes in the quantitative test, and 37 (43.5 per cent.) showed no change in the quantitative tests. Coale and others (1950) had similarly poor serologic results, and Weir and others (1950) and Johnson and Shapiro (1951) found a post-penicillin therapy drop in serologic titre in their relatively small

series of cases. Leech (1950) found that three out of seventeen patients developed negative reactions to the Wassermann or Hinton tests after treatment.

Clinical Effects.—Assuming that all the deficiencies previously mentioned as inherent in the determination of the effect of penicillin therapy of cardiovascular syphilis are corrected, one could not make definite statements regarding the clinical effectiveness of such treatment because the period of observation is as yet rather short. Up to 1951, 1,243 days was about the longest period of observation reported (Johnson and Shapiro, 1951). However deficient the data, some of the information available on this aspect of the problem is worth mentioning.

Coale and others (1950), for example, noted no striking results, but the overall picture was good.

Flaum and Thomas (1949) stated that seven of their patients with aortic insufficiency, "claimed to be improved after treatment". This apparent improvement could be due to a general systemic improvement following the eradication of the chronic low-grade syphilitic infection.

Leech (1950) reported that all but two of his patients were improved or unchanged. Death in three was not attributable to treatment.

Chapman and Morgan (1947) observed relief of pain in patients with aneurysm, but their treatment schedule included potassium iodide and bismuth simultaneously.

Wheeler and Curtis (1951) also reported improvement in symptoms, but there were two possible therapeutic paradoxes.

Johnson and Shapiro (1951) found significant orthodiagraphic and roentgenographic changes indicating enlargement of an aneurysm in one patient who died of tracheal obstruction 2 days after completion of treatment. Five patients died 2, 270, 350, 537, and 854 days, respectively, after treatment. Most of the patients experienced weight gain and a feeling of well-being.

Weir, Roberts, and Tullis (1950), in a preliminary comparison of the post-treatment with the pre-treatment status of their patients, indicated that, although a few patients were graded as "worse" in the post-treatment period, in no case was deterioration hastened by penicillin therapy.

Edeiken and others (1951) found that :

penicillin is admirably tolerated by the decompensated heart, with clinical improvement in a high proportion of cases. Anginal pain was relieved without recognizable shock or paradox in four out of five cases. In syphilitic aortitis 'uncomplicated', observed for from 3 to 58 months, one-third were improved, one-half unchanged, and only one-sixth were worse (one death of

bronchopneumonia). In aortitis with regurgitation, 64 per cent. were improved, 20 per cent. unchanged, and 16 per cent. worse. In aneurysm with regurgitation the number was too small for analysis, but four or five kept under observation improved. Of three patients with large saccular aneurysms, one lapsed from observation, one died in a wiring operation, and one showed no change.

Electrocardiographic Changes.—In this phase of the subject, it is necessary to differentiate the electro-cardiographic effects induced by penicillin *per se* and those incidental to the changes in cardiovascular status that this therapeutic agent induces. Steiger and Edeiken (1948), in their studies on the electro-cardiographic changes before, during, and after penicillin treatment in early syphilis, found alterations in 42.5 per cent. of a second series of forty cases. In an earlier report (1947), they had found a 50 per cent. incidence among thirty cases, making an aggregate of 45.7 per cent. of seventy cases. The electrocardiographic changes, which were T-wave and in some cases RS-T sequent changes in limb or chest leads, or both, occur in all phases of early syphilis. Penicillin does not seem to be responsible for these changes. The changes are usually transient, but may be permanent.

Binder and others (1950) encountered transient T-wave inversion in three patients who developed severe reactions during penicillin treatment. These resemble changes observed in other allergic reactions. With respect to the electro-cardiographic changes produced by penicillin in the treatment of cardiovascular syphilis, there are only scattered data, the exact significance of which is not clear. Edeiken and others (1949) state that, although a large percentage (50 per cent.) of their cases showed electrocardiographic abnormalities either before, during, or after penicillin treatment, one cannot conclude that they are all directly or solely due to the syphilitic infection. Significant T-wave changes were noted during the course of treatment in eight patients. Moore (1949) observed that tracings taken during the course of treatment did not indicate that penicillin irritated the heart, and in several instances improvement was seen. Peralta and Castaneda (1949) noted that 7.8 per cent. of their patients had altered electrocardiograms. Coale and others (1950) concluded that nothing definite could be concluded by following the electrocardiograms. Johnson and Shapiro (1951) observed that :

the electrocardiographic tracings, except for changes which go with left ventricular strain due to aortic insufficiency or changes due to coronary involvement, showed no pattern which could be considered pathognomonic of cardiovascular syphilis.

Summary Statement and Proposed Therapeutic Regimen

The problems of penicillin therapy of cardiovascular syphilis may now be summarized by asking and answering the questions posed by Edeiken, Ford, and Stokes (1951). We emphasize again the relatively subjective character of the available information:

(1) *Can penicillin therapy be given safely to patients with cardiovascular syphilis?*

Penicillin is relatively free from severe reaction.

(2) *How common is therapeutic shock and therapeutic paradox in penicillin-treated cardiovascular syphilis?*

Relatively few unequivocal reactions have been observed, and the University of Pennsylvania group observed no serious examples in 111 cases. The role of coincident neurosyphilis in producing febrile Herxheimer reactions is re-emphasized.

(3) *Are there any contraindications to the use of penicillin in cardiovascular syphilis?*

Patients exhibiting a variety of processes, previously contraindicating arsenical therapy, have been given penicillin treatment without serious untoward effects.

(4) *Does penicillin stop the progress of cardiovascular syphilis?*

There is evidence to suggest that the course of the disease is favourably influenced by penicillin, but no definite statement can be made before a long follow-up period of at least 10 years has elapsed, and before a large number of cases have been studied clinically and pathologically.

(5) *What effect has treatment on the serologic test for syphilis?*

The information indicates that little may be expected from treatment in the way of serologic reversal. The coincidence of neurosyphilis with the cardiovascular process plays a large role in this lack of serologic reversal.

(6) *Should patients with suggestive, but not positive, signs of aortitis be treated with penicillin?*

We agree with Edeiken, Ford, and Stokes in saying "yes" to this question. In view of the uncertainties in the diagnosis of uncomplicated syphilitic aortitis and the safe and probable effectiveness of penicillin therapy, the patient should be given the benefit of the doubt, not only because it is practically without danger, but also because it is inexpensive and not time-consuming. In the past, many patients were not treated because even a presumptive diagnosis condemned them to a prolonged, costly, and even dangerous therapeutic regimen.

To these questions may be added:

(7) *Is treatment with bismuth and iodides necessary before penicillin therapy of cardiovascular syphilis?*

Although, according to Willcox (1951), most British physicians are employing such preparatory treatment, it is obvious from the data presented above that this seems unnecessary at least from the reaction standpoint. Whether the eventual outcome of treatment will be

better with combined therapy or penicillin alone is still unanswered.

Assuming, from the data presented, that penicillin is the safest agent yet produced for treating cardiovascular syphilis, we suggest that the treatment scheme of the University of Pennsylvania group (Edeiken and others, 1951) be employed until a more convenient or effective regimen is evolved.

The advocated treatment includes hospitalization and a 2-hour schedule of crystalline penicillin G (4,800,000 to 9,600,000 units in 40,000 to 80,000 unit individual doses), but procaine penicillin may be given to hospitalized patients on a 600,000 unit single, or a 300,000 unit two-injection daily schedule to an equivalent total dosage. The ambulatory use of this salt is under investigation. By present standards, repetition of courses in excess of two of 9,000,000 units seems unnecessary. . . . The concomitant or subsequent use of heavy metals was not studied in this series, but seems on general experimental grounds to be unnecessary.

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