The Specific Treatment of Syphilitic Aortitis

By R. H. Kampmeier, M.D., and Hugh J. Morgan, M.D.

Heart disease is the most common cause of death in the United States. Syphilis is the etiologic factor in about 10 per cent of cases and represents one of the types of heart disease which is preventable. Specific, curative remedies are available for the infection. The advent of penicillin therapy in 1943 was the most important development in the treatment of syphilis since Erlich's introduction of Salvarsan (606) in 1910.

An understanding of the pathology and natural course of untreated syphilitic cardiovascular disease is essential to any evaluation of treatment, old or new, and will be reviewed in some detail. Following this, the role of specific treatment in the management of syphilitic cardiovascular disease will be discussed.

Pathology

The basic lesion of cardiovascular syphilis is aortitis. Syphilitic myocarditis and gummas of the myocardium are rare lesions. The frequency of uncomplicated aortitis cannot be accurately determined. Its complications, aneurysm, aortic insufficiency and stenosis of the coronary orifices, are usually easily recognized. They represent the disabling and lethal manifestations of syphilitic cardiovascular disease.

Syphilitic aortitis is a manifestation of acquired syphilis. Congenital syphilis probably never causes aortitis. The few reported cases of congenital cardiovascular disease of syphilitic origin are not convincing.

Syphilitic myocarditis became a controversial topic following Warthin's report in 1931 that spirochetes could be demonstrated in the myocardium of individuals with syphilis and diffuse myocardial degenerative and inflammatory changes. Although a few investigators agree that diffuse syphilitic myocarditis may occur, the vast majority of pathologists relate the myocardial changes in syphilis to the effects of aortic regurgitation, disturbances in the coronary circulation and gummas. Electrocardiographic studies in the acute stages of syphilis reveal that there may be diffuse myocardial involvement as indicated by abnormal T waves and other minor, transient changes. It rarely happens that these changes in the myocardium in early syphilis result in cardiac enlargement and circulatory embarrassment; we have seen only three such cases at Vanderbilt University Hospital in 30 years experience with 2200 acute syphilitic infections.

Gummatous syphilitic involvement of the myocardium is well recognized, approximately 100 cases having been reported. The lesion occurs most often in the myocardium of the left ventricle, particularly at the base of the interventricular septum where it may cause complete heart block. Gumma of the ventricular wall may cause bundle branch block. Myocardial infarction may be simulated by a gumma insofar as electrocardiographic changes are concerned. Indeed, we have seen an occlusive lesion of a coronary vessel produced by an enveloping gumma.

There seems little reason to doubt that the aorta is invaded by spirochetes early in the course of syphilis. The evidence that spirochetemia occurs in acute syphilis is conclusive. Spinal fluid and electrocardiographic changes in early syphilis are indications of focal lesions in the meninges and myocardium, just as the rash, lymphadenopathy and mucous patches indicate focal lesions in skin, lymph nodes and mucous membranes. The aortic wall probably is invaded by Treponema pallidum either via the mediastinal lymphatics or directly via the vasa vasorum. Lymphatic vessels and vasa vasorum are especially numerous in the ascending and transverse segments of the aortic arch. This may explain the greater frequency of
syphilitic disease in these than in the more distal portions. Whether invasion of the aorta is lymphogenous, hematogenous or mixed the result is involvement of the vasa vasorum and lymphatics of the adventitia and media. Lymphocytic and plasma cell infiltration and obliterating endarteritis of the vasa vasorum is associated with necrosis and fragmentation of the elastic tissue of the media. At some point in the course of the acute, generalized infection, many weeks after the seeding of the aorta with *T. pallidum*, widespread destruction of organisms occurs and the disease progresses from the acute to the chronic stage. In the aorta an exquisitely chronic, low grade inflammatory process may go on for years, possibly with periods of exacerbation and remission entirely unrelated to clinical manifestations of disease. This is uncomplicated syphilitic aortitis. In time, perhaps 10, perhaps 30 years after the acute phase of the infection in the aorta occurred, the complications may become manifest: focal weakness of the aorta may lead to aneurysm, general weakness to diffuse dilatation; dilatation of the aortic ring, separation and sagging of the commissures or actual deformity and destruction of the aortic valve leaflets by inflammation may lead to aortic regurgitation; and finally, deformity or narrowing of the ostia of the coronary arteries by aortitis may interfere with the normal delivery of blood from the aorta to the coronary system.

**Clinical Considerations**

*Uncomplicated Aortitis.* By definition, uncomplicated aortitis is syphilis of the aorta which produces neither sign nor symptom. The condition cannot be recognized clinically. Its presence is accurately determined only at autopsy. It is the forerunner of the three chief manifestations of cardiovascular syphilis: aortic regurgitation, stenosis of the ostia of the coronary vessels, and aneurysm. Speculations relative to its incidence in individuals with chronic syphilis vary from 20 to 90 per cent! It is the one type of cardiovascular syphilis for which therapy holds great promise.

The literature concerning the frequency of uncomplicated syphilitic aortitis contains no really worthwhile figures. Accurate data can be obtained only from necropsies of individuals with chronic syphilis who die of causes other than aortitis. In 15,000 autopsies at the Philadelphia General Hospital between 1927 and 1937, evidence of cardiovascular syphilis was found in 1042 or 6.9 per cent.² There were 192 instances of aneurysm and 216 of aortic insufficiency. The remaining 634 cases were diagnosed simply as aortitis without any statement relative to the presence or absence of angina pectoris or to patency of the coronary artery ostia. Seventy-four per cent of the subjects were males and 68 per cent of these were Negroes. If it is true that the incidence of asymptomatic aortitis is very high in chronic syphilis, it should be related to the fact that only about 10 per cent of patients with chronic syphilis develop lethal syphilitic cardiovascular disease.

The recognition of uncomplicated syphilitic aortitis, in which there are no symptoms referable to the aorta or coronary system and no physical signs of heart or aortic disease, is obviously impossible unless, as some observers believe, diagnostic x-ray changes can be demonstrated. Most students of the subject agree with Kampmeier, Fleming and Glass,³ and White and Wise,⁴ and others that the early diagnosis of cardiovascular syphilis in the absence of aortic regurgitation, aneurysm, or coronary artery narrowing is “practically impossible.” Controlled attempts to recognize uncomplicated aortitis by x-ray examinations have met with failure. Blitch, Morgan and Hiißstrom⁵ were unable to demonstrate aortic dilatation attributable to syphilis in men having “late latent syphilis,” a number of whom almost certainly had uncomplicated aortitis. In this study only men with syphilis and in the “aortitis age” were examined. When hypertension, arteriosclerosis, thyrotoxicosis and severe anemia were excluded, these men with chronic syphilis showed no x-ray evidence of aortic dilatation in spite of the fact that uncomplicated aortitis was almost surely present in a considerable number of them.

Since by definition there is absence of involvement of the ostia of the coronary arteries in uncomplicated aortitis, electrocardiographic changes do not occur.
In summary, it must be said that the diagnosis of uncomplicated syphilitic aortitis is entirely inferential. We know that aortitis occurs in a large number of individuals who have chronic syphilis and that in a much smaller number progression occurs in time with the development of one or more of the following complications: aortic dilatation, aneurysm, aortic insufficiency and narrowing of the ostia of the coronary arteries. Since early uncomplicated aortic involvement is frequent and cannot be recognized, and since it is the forerunner of the most common lethal manifestations of syphilitic infection, all chronic syphilis must be regarded as suspect and managed accordingly. Only in this way will asymptomatic aortitis be given treatment and prevented from progressing to fatal complications. In fact, the rationale of treating chronic asymptomatic ("latent") syphilis resides mainly in the fact that it provides prophylactic therapy for cardiovascular syphilis, that is, therapy for uncomplicated aortitis which cannot be recognized.

Aortic Insufficiency. Among the complications of syphilitic aortitis, aortic insufficiency is the most frequent and the most deadly. Yet in relation to the incidence of syphilitic infection, it is not common. The incidence of syphilitic aortic insufficiency in 2,951 cases of late syphilis at Vanderbilt University Hospital was 3 per cent. Cochems and Kemp found the incidence of serious cardiovascular syphilis to be 14 per cent in persons engaged in heavy labor, whereas it was only 8.7 per cent in persons with sedentary occupations; they suggested that syphilitic aortitis has a better chance of remaining uncomplicated when the circulation is not subjected to the effects of heavy manual labor. In the cases of syphilitic aortic insufficiency at Vanderbilt University Hospital, there were 91 instances in Negro males, 37 in Negro females, 27 in white males and 8 in white females.

The diagnosis of syphilitic aortic insufficiency usually is not difficult. Clinical manifestations appear most often during the second or third decade of the infection. Thus the age group involved is from 35 to 50 years in white patients and a somewhat younger age group in Negroes. A relatively small number of cases of aortic insufficiency are discovered in the asymptomatic stage by physical examination. For example, among 163 patients with aortic insufficiency studied at Vanderbilt University Hospital, 25 or 15 per cent were discovered during routine examinations. The early symptoms of aortic insufficiency are exertional dyspnea, orthopnea, paroxysmal dyspnea and cough—all manifestations of left heart failure. The physical signs of aortic insufficiency are quite variable depending upon the degree of incompetency of the valve. Left ventricular enlargement of varying degrees is usually present. The smooth, high pitched, diastolic murmur at the second right intercostal space near the manubrium, which is usually transmitted unchanged along the left sternal border to the apex in anterior cusp defects (Belthaezer Foster), and changed to a murmur of rumbling character over the precordium and apex when the posterior aortic cusps are involved (Austin Flint), is characteristic. The signs of aortic regurgitation usually present over the peripheral vessels may be entirely absent if the normal diastolic blood pressure is maintained. If regurgitation is free and there is greatly increased pulse pressure, the classic systolic pistol shot and diastolic Duroziez' murmur over compressed femoral arteries are present together with visible capillary pulsations and abnormally large pulsations over the peripheral vessels. X-ray examination commonly reveals a widened aorta and left ventricular enlargement although early cases may show no abnormalities.

Aneurysm. Another complication of syphilitic aortitis which occurs in the third or fourth decade of infection is aneurysm. The factors of race and sex operate here as in valvular disease.

Incidence figures at necropsy vary greatly. At the Vanderbilt University Hospital only one aneurysm was encountered in 340 consecutive autopsies. Six hundred thirty-three cases of saccular aneurysm were collected from the records of Charity Hospital in New Orleans and Vanderbilt University Hospital by Kampmeier. The ratio of aneurysms in white to Negro patients was 1:3.1. Sixty per cent of the aneurysms were in Negro males, 21 in
white males, 16 in Negro females and 3 in white females.

The diagnosis of aneurysm is usually not difficult. The location of the sac and its relationship to structures which may be compressed determine to a great extent the symptoms and signs. The structures commonly affected are the trachea, major bronchi, lungs, esophagus, pulmonary arteries, vagus and sympathetic nerves, recurrent laryngeal and intercostal nerves, the diaphragm and indirectly the stomach. Pressure erosion of ribs, sternum, and vertebrae by the pulsating tumor occurs not infrequently and rupture may occur externally and into pericardial and pleural cavities, trachea and esophagus. Aneurysm rarely if ever develops after aortic regurgitation has become established in syphilitic aortitis. However, the presence of aneurysm does not protect against the subsequent development of aortic insufficiency. Indeed, the two conditions occur together in about 20 per cent of cases. Expert roentgenologic examination, including fluoroscopy, is essential to diagnosis.

**Stenosis of the Coronary Artery Orifices.** The third major complication of syphilitic aortitis is interference with the myocardial blood supply resulting from syphilitic involvement of the orifices of the coronary arteries. Ostial stenosis results in precordial pain which must be differentiated from angina pectoris due to other more common causes. Years ago Pincoffs and Love called attention to the involvement of the coronary ostia in the aortic syphilitic process and related this to the occurrence of angina pectoris and death. Stenosis of coronary ostia was present in 20 per cent of the cases of cardiovascular syphilis with aortic regurgitation studied by Kampmeier (Charity Hospital). The right coronary artery is involved more frequently than the left. The normal proximity of the aortic valve leaflets and the ostia of the coronary arteries at the root of the aorta and the occasional congenital upward displacement of the openings (Von Glahn) afford explanations for the frequent association of aortic regurgitation and coronary insufficiency in syphilitic aortitis. The same association may explain in part the rapid downhill course of syphilitic aortic insufficiency in comparison with the more benign course of rheumatic aortic insufficiency.

Since syphilis rarely causes disease of the coronary arteries anywhere except at their orifices, the occurrence of angina pectoris in an individual with syphilis immediately suggests the presence of aortitis and ostial involvement. If aortic regurgitation of moderate degree or aneurysm is present, such a diagnosis can be made with considerable confidence. If marked regurgitation is present, pain may occur without ostial involvement, for it is clear that aortic insufficiency regardless of cause, when associated with a large valvular defect and low diastolic blood pressure, may produce coronary insufficiency in the absence of coronary artery disease. The electrocardiogram is of little value in differentiating such cases from coronary ath erosclerosis.

**The Course of Cardiovascular Syphilis**

Before an evaluation of treatment directed against syphilitic aortitis can be made, it is necessary to be familiar with the natural course of the disease.

Since the diagnosis of uncomplicated aortitis cannot be established with certainty during life, no information is available as to its course. If, as some believe, a large percentage of individuals with chronic syphilis have aortitis then, in a very considerable number, it is uncomplicated and remains of no consequence since not more than 10 per cent develop clinically recognizable cardiovascular syphilis.

Information concerning the prognosis of the complications of aortitis is available. A number of factors appear to be involved in the outcome of untreated aortic insufficiency. The degree of regurgitation is certainly important. Free regurgitation, associated with a low diastolic blood pressure, decreases coronary blood flow and creates a greater burden for the left ventricle than does a slight valvular incompetency with normal pulse pressure. Furthermore, the state of the myocardium, irrespective of syphilis, is an important factor. The myocardium of an old person, experiencing the effects of the aging process, will fail more rapidly in the presence of aortic regurgitation than the myocardium of a younger individual.
Furthermore, coronary atherosclerosis, hypertension, thyrotoxicosis, rheumatic heart disease, anemia or other factors may be present in association with cardiovascular syphilis and exert a very unfavorable influence upon its course. Finally, syphilitic involvement of the ostia of the coronary arteries is commonly present in individuals with syphilitic aortic regurgitation. When the unfavorable effect of aortic regurgitation upon coronary blood flow is augmented by syphilitic narrowing of the orifices of the coronary vessels, or by atheromatous sclerosis of the vessels, the greatly decreased coronary circulation doubtless contributes importantly to an unfavorable course and hastens the development of congestive heart failure.

Studies by Kampmeier and Combs’ at Vanderbilt University Hospital indicate the great prognostic importance in a given case of the occurrence of myocardial insufficiency. Their data show that within a three year period death occurred twice as frequently in the group of patients who had myocardial insufficiency at the time of admission to hospital as in those who had never experienced decompensation. Of course, this observation is not surprising since congestive heart failure is the cause of death in most cases of syphilitic aortic regurgitation. Obviously this point must be considered in evaluating the effect of specific therapy. Our experience indicates that a life of physical inactivity is conducive to relative longevity in syphilitic aortic insufficiency provided, of course, myocardial insufficiency has not already developed. Once the latter has occurred, physical activity is tolerated poorly regardless of the state of cardiac compensation when the patient is at rest.

The prognosis of aortic aneurysm is almost always gloomy. Except for the rare patient with a saccular aneurysm which has not enlarged enough to involve vital structures, life is measured usually in months after the onset of symptoms. Only 18 of 188 cases of aneurysm studied by Kampmeier lived longer than two years after the onset of symptoms. If these 18 are excluded from consideration, the average duration of life of the remaining 170 patients, after the onset of symptoms, was 6.4 months. A large percentage of these patients had received no antisyphilitic treatment.

We have seen that the outlook for the patient with clinically recognizable syphilitic aortitis is poor. To what extent may it be improved by specific antisyphilitic treatment? Obviously, aortic valvular insufficiency and saccular aneurysm are irreversible processes. Antisyphilitic treatment cannot restore the normal structure of valve or aortic wall. The most that can be hoped for is an arrest of the deforming, destructive process involving the wall of the vessel, the valves and the ostia of the coronary arteries. Conceivably, the latter might become further narrowed by post-treatment congestion and edema of syphilitic inflammatory tissue (Herxheimer reaction) or become wider as the syphilitic inflammatory reaction recedes under treatment. Isolated instances of both sudden death and complete relief from angina pectoris in subjects with chronic syphilis following specific treatment do occur. It is reasonable to assume that syphilitic aortitis which has not become complicated by involvement of the orifices of the coronary artery or of the aortic valves and which has not progressed to focal weakness with aneurysm formation may respond to specific treatment by arrest or actual regression and healing. The infrequent occurrence of syphilitic cardiovascular disease in patients adequately treated early in the course of the infection is strong evidence in favor of this assumption. As has been noted above, it is chiefly to the end of arresting the progress of subclinical aortitis and preventing the development of its lethal complications that “latent” syphilis is treated.

The Results of Treatment before Penicillin

The evaluation of antisyphilitic treatment in persons with complicated aortitis is an extremely difficult task. Since the diagnosis of uncomplicated aortitis cannot be established accurately the effectiveness of treatment is impossible to determine directly. An indirect approach is to observe the post-treatment developments with relation to the complications of aortitis in persons receiving treatment for so-called “latent” syphilis and comparing the
eventual incidence of recognizable cardiovascular syphilis in them with the eventual incidence in untreated "latent" syphilis. This method of evaluation indicates clearly that uncomplicated aortitis can be arrested, that its lethal complications can be prevented. Maynard and Lingg, in a large group of cases, found that cardiovascular syphilis developed five times more frequently in patients who received no antisyphilitic treatment for early latent syphilis than in those who received chemotherapy, and concluded that the incidence of syphilitic heart disease decreased as the amount of antisyphilitic treatment increased. When treatment was delayed until six or more years after the occurrence of the chancre, the incidence of cardiovascular involvement was four times greater than when treatment was completed within three years after the onset of the disease. Additional confirmation is afforded by Howe's observations that the amount of cellular infiltration of the aortic wall in syphilis bears an inverse relationship to the amount of arsphenamine therapy received. Webster and Reader confirmed these findings in a study of sections from the aortas of 45 subjects. They found that in only 3 among 19 cases adequately treated was there an active inflammatory process; whereas, active syphilitic inflammation was present in each of 19 untreated subjects. The aortas of five of seven cases in which treatment was inadequate exhibited active inflammation.

These observations together with those of the Clinical Cooperative Group, Kemp and Cochems and others indicate conclusively that adequate treatment of early "latent" syphilis with arsenicals, mercury and bismuth and iodides prevents the subsequent development of cardiovascular syphilis; that established, uncomplicated aortitis is arrested and the complications of aortitis prevented.

Many observers are not convinced that antisyphilitic treatment prolongs life when either syphilitic aortic insufficiency or aneurysm are present. Others believe that specific treatment is conducive to prolongation of life. However this may be, it is true that in the prolonged and sometimes enthusiastic chemotherapy of the arsphenamine era those patients who lived longest commonly received the most treatment!

Padget and Moore considered the results of the specific treatment of aortic aneurysm and aortic insufficiency. They concluded that "properly directed antisyphilitic therapy results in a prolongation of life in two-thirds of the patients with saccular aortic aneurysm or syphilitic aortic insufficiency and that the remaining third come under observation with initially bad prognoses and do not survive sufficiently long for proper therapy to be administered."

Kampmeier and Combs reviewed the records of 103 cases of aortic insufficiency at the Vanderbilt University Hospital. Seventy-five per cent of the subjects were dead. Fifty-five per cent of the deaths occurred within three years of the onset of symptoms. Neither the kind nor the amount of antisyphilitic treatment appeared to alter the course of the disease.

The Modern (Penicillin) Era

It is clear that a scientific evaluation of the results of penicillin in the treatment of latent and chronic, active syphilis of all types must await the passage of time. Penicillin has been used in treatment only since 1944. However, the curative results in acute syphilis and the immediate results in latent and chronic syphilis are so impressive and convincing that the antibiotic has replaced the arsphenamines in therapy.

From a practical point of view the introduction of penicillin in the treatment of syphilis was a development of inestimable importance: it substituted for the relatively toxic arsenicals a relatively nontoxic agent equally potent in treponemical action and equally effective in causing resolution of gummatous inflammatory tissue. Intravenous therapy is no longer necessary and the time required for treatment with penicillin can be telescoped into a small fraction of the minimum requirement for the arsenicals. Thus, the technic of the specific treatment of syphilis has become a relatively simple matter. Therapy can be carried out as an office procedure and in a period of a few days. Because of penicillin the number of patients with acute syphilis who receive adequate treatment is being increased enormously. Since this is usually curative treatment it seems certain that the incidence of cardiovascular syphilis, a late result of chronic infection, will diminish greatly.
However bright the outlook for curative treatment of early syphilis by penicillin, it must be categorically stated that no results are available to indicate that the antibiotic will alter significantly the course of events in the established complications of syphilitic aortitis. The factors of importance in prognosis enumerated above apply equally to the cases treated with penicillin and with the arsenicals.

In the pre-penicillin era it was common practice to avoid specific treatment in cardiovascular syphilis if congestive heart failure was present. Patients with cardiac decompensation bore chemotherapy poorly. Therefore, except for the relief of pain in aneurysm and in coronary involvement, arsenicals were avoided under such circumstances. On the other hand, specific treatment was usually employed in all of the complications of aortitis provided the heart was in a state of good compensation. We have seen that uncomplicated aortitis was favorably affected by this treatment. It is probable that on occasions when the complications of aortitis were treated quite early, they became arrested and lethal progression was delayed or prevented. It seems fairly certain that patients with well-developed aneurysms, aortic regurgitation and coronary ostial stenosis were benefited but little if any by arsenotherapy with the usual supplement of bismuth and iodides. It is not likely that penicillin will change this. However, it seems certain that many more patients with cardiovascular syphilis will receive relatively nontoxic, inexpensive penicillin in recommended doses than received arsphenamine.

Recent literature contains reports of the treatment with penicillin of approximately 250 cases of cardiovascular syphilis. In addition to this, 34 cases were treated by us at Vanderbilt University Hospital and Thayer Veterans Administration Hospital. All reports deal with the immediate effects of treatment. Penicillin seems to be tolerated well regardless of either the type of lesion present or the presence or absence of congestive heart failure. Febrile reactions develop within the first 24 hours of treatment in a considerable number of cases but are almost always of short duration and unassociated with untoward developments. A few isolated patients have developed serious complications while under treatment, such as angina pectoris and rupture of aneurysm. It is difficult to interpret these exceptions. They constitute the reason for the practice which is still recommended by us of "preparing" the patient with cardiovascular syphilis for intensive treatment by several weeks of bismuth and iodide therapy or several days of markedly reduced penicillin dosage. Such preparation has been omitted in most clinics in recent years.

The antibiotic may be administered in single daily injections of 600,000 units of procaine penicillin or in six or eight injections daily of aqueous penicillin. In either case therapy should be continued for 8 to 10 days or until 4.8 to 6 million units have been given. Doses two and three times as large have been employed. Another plan of treatment providing slowly absorbed penicillin over a prolonged period is the injection of 600,000 units of penicillin intra-muscularly twice a week for six weeks.

Experience indicated that bismuth and iodides probably were beneficial when used with the arsenicals in the treatment of chronic syphilis. It seems reasonable to allow for this possibility and to employ these slowly acting remedies before and after the administration of penicillin. The use of them before penicillin is given in syphilitic cardiovascular disease provides, in addition, the possible advantage of "preparing" the patient for the rapid, powerful action of penicillin.

**Summary**

Penicillin has made the specific treatment of cardiovascular syphilis easy to give and easy to take and has all but abolished dangerous treatment reactions. Just as the curative therapy of acute syphilis with penicillin is simple and feasible, so is the prophylactic treatment of cardiovascular syphilis in individuals with latent syphilis and uncomplicated syphilitic aortitis simple and feasible. In spite of the fact that the effectiveness of such treatment has not been conclusively established, the prospects seem bright that the incidence of cardiovascular syphilis will decrease sharply in the immediate future.

Cardiovascular syphilis may be treated, with or without preliminary bismuth and iodide "preparation," by the administration of 4.8 to
6 million units of penicillin in a period of 8 to 10 days. Larger doses and longer periods of treatment have been employed. Experience thus far does not indicate that penicillin therapy of established complications of syphilitic aortitis will be any more successful than was therapy of the pre-penicillin era.

REFERENCES


31 McDermid, W. J.: Personal communication.
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R. H. KAMPMEIER and HUGH J. MORGAN

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