

# Natural History of Syphilitic Aortitis

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No large studies of cardiovascular syphilis at necropsy have been reported since 1964. We examined at necropsy 90 patients who had characteristic morphologic findings of syphilitic aortitis. None had ever undergone cardiovascular surgery. With the exception of 2 cases seen more recently, the hearts and aortas of the 90 patients were examined and categorized by one of us (W.C.R.) from 1966 to 1990. All 90 had extensive involvement of the tubular portion of the ascending aorta by the syphilitic process, which spared the sinuses of Valsalva in all but 4 patients. The aortic arch was also involved in 49 (91%) of 54 patients and the descending thoracic aorta in 47 (90%) of 52 patients. Syphilis was the cause of death in 23 (26%) of the 90 patients. It was secondary to rupture of the ascending or descending thoracic aorta in 12, severe aortic regurgitation leading to heart failure in 10, and severe narrowing of the aortic ostium of the right coronary artery in 1 patient. Of the 40 patients who had undergone serologic testing for syphilis, 28 (70%) had a positive (reactive) finding. Those patients with a negative or nonreactive test or who did not undergo a serologic test for syphilis had morphologic and histologic findings in the aorta at necropsy similar to the findings of those patients who had had a positive serologic test for syphilis. In conclusion, cardiovascular syphilis has not disappeared. In patients with dilated ascending aortas, with or without aortic regurgitation, a serologic test for syphilis is recommended. If the findings are positive or if characteristic morphologic features of cardiovascular syphilis are suspected, irrespective of the results of the serologic tests, antibiotic therapy appears desirable. © 2009 Elsevier Inc. All rights reserved. (Am J Cardiol 2009;104:1578–1587)

Syphilis was so common in the nineteenth century—estimated to affect 15% of United States adults during that period—that an entire specialty (syphilology) focused on it. Although relatively few with primary syphilis subsequently develop tertiary syphilis, the cardiovascular manifestations of late syphilis are at least life-threatening, if not fatal. The cause of the cardiovascular features of syphilis are unclear, because the spirochete *Treponema pallidum* has never convincingly been demonstrated in histologic sections of the aorta in patients with this complication of syphilis, and *T. pallidum* cannot be cultured. Because of its decreased frequency in the past several decades and because serologic tests for syphilis are now infrequently performed, it seemed appropriate to review a large number of cases of cardiovascular syphilis studied at necropsy by a single investigator during an approximately 50-year period to learn more about the morphologic features of the cardiovascular consequences. Only patients who had never undergone cardiovascular surgery were included.

## Methods

The autopsy files of the Pathology Branch of the National Heart, Lung, and Blood Institute, National Institutes

of Health (Bethesda, Maryland; where W.C.R. was chief for 29 years) were searched for cases coded as “cardiovascular syphilis.” Except for 2 cases seen subsequently, all hearts and aortas were studied by W.C.R. from 1966 through 1990. None of the 90 patients had ever undergone cardiovascular surgery. Of the 90 cases studied, 77 were submitted from Washington, DC area hospitals or institutions (Washington DC Medical Examiners Office, n = 17; Georgetown University Medical Center, n = 17; Washington DC Veterans Affairs Hospital, n = 11; Washington DC General Hospital, n = 12; Howard University Hospital, n = 6; George Washington University Hospital, n = 4; Sibley Memorial Hospital, n = 3; National Institutes of Health, n = 2; Suburban Hospital, n = 2; Franklin Square Hospital, n = 2; National Naval Medical Center, n = 1, and non-Washington, DC area hospitals, n = 13). Patients for whom a serologic test for syphilis was positive (reactive) but in whom the aorta was not involved by the syphilitic process were not included in the present study.

Each heart and aorta was examined initially and later by W.C.R. All hearts had extensive involvement of the tubular portion of the ascending aorta by a process typical of cardiovascular syphilis (to be described subsequently). Many of the hearts and aortas were photographed, and several were drawn by a professional artist (Leon Schlossberg).

Partial or complete clinical records for each case were provided by the submitting institution. Most cases were seen initially by W.C.R. at the submitting institution at a teaching conference. He examined the specimen there and discussed the findings and then brought the heart and aorta back to the National Institutes of Health for additional study. Histologic sections of the aorta and heart were pre-

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Table 1  
Necropsy cases of syphilitic aortitis without operative intervention

Variable	Total (n = 90)	Men (n = 59)	Women (n = 31)
Age (years)			
Range	19–91	19–88 (66 ± 13)	32–91 (70 ± 14)
Mean ± SD	67 ± 14		
Race			
African American	60	44	16
European American	20	12	8
Unclear	10	3	7
Serologic test for syphilis (positive/No. done)	28/40 (70%)	20/27 (74%)	8/13 (62%)
Aortic regurgitation	23 (26%)	14 (24%)	9 (29%)
Systemic hypertension	41/72 (57%)	28/48 (58%)	13/24 (54%)
Heart failure	26/84 (31%)	23/56 (41%)	3/28 (11%)
Cause of death			
Syphilis			
Aortic rupture	12 (13%)	5 (8%)	7 (23%)
Aortic regurgitation → heart failure	10 (11%)	8 (14%)	2 (6%)
Ostial narrowing, right coronary artery	1 (1%)	0	1 (3%)
Coronary artery disease	17 (19%)	14 (24%)	3 (10%)
Stroke	5 (6%)	2 (3%)	3 (10%)
Noncardiac, nonvascular	38 (42%)	27 (46%)	11 (35%)
Unclear	7 (8%)	3 (5%)	4 (13%)
Heart weight (g)			
Range	215–850	260–850	215–750
Mean ± SD	486 ± 135	507 ± 135	443 ± 127
Coronary artery narrowing >75% of cross-sectional area	46/71 (65%)	35/48 (73%)	11/23 (48%)
Left ventricular infarct			
Acute	5 (6%)	4 (7%)	1 (3%)
Healed	28 (31%)	24 (41%)	4 (13%)
Both	1 (1%)	0	1 (3%)
Coronary ostial narrowing			
Right	13 (14%)	9 (15%)	4 (13%)
Left main	2 (2%)	1 (2%)	1 (3%)

pared at the National Institutes of Health in the Pathology Branch for each case and were examined by W.C.R.

## Results

The pertinent findings for the 59 men and 31 women are listed in Table 1. The men ranged in age from 19 to 88 years (mean 66 ± 13), and the women from 32 to 91 years (mean 70 ± 14). The race was known for 80 patients: 60 (75%) were African American and 20 (25%) were European American. At least 23 patients had some degree of aortic regurgitation; 3 others had evidence of aortic valve stenosis (a nonsyphilitic process) at necropsy. All 90 patients had 3-cuspid aortic valves. At least 41 (57%) of the 72 patients in whom it was noted had a history of systemic hypertension or had had a peak systolic pressure >140 mm Hg or an end-diastolic pressure >90 mm Hg, or both. At least 26 (31%) of the 84 patients in whom it was noted had had clinical evidence of heart failure. At least 40 patients had undergone a serologic test for syphilis (either the Venereal Disease Research Laboratory or fluorescent treponemal antibody), and in ≥28 (70%), 1 or both test results were positive (reactive).

The cause of death in the 90 patients was as follows: cardiovascular syphilis from rupture of the ascending or descending thoracic aorta in 12 patients, severe aortic regurgitation producing heart failure in 10 patients, or severe

narrowing of the ostium of the right coronary artery in 1 patient (total 23 patients [26%]); coronary heart disease in 17 patients; stroke in 5 patients; cancer in 14 patients; renal failure in 3 patients; and a noncardiac, nonvascular, and noncancer cause in 28 patients, including chronic obstructive pulmonary disease in 4, amyloidosis in 2, and unclear in 7.

At necropsy, the hearts of the 46 men weighed 260 to 850 g (mean 507 ± 135, median 505). In 33 (72%) of these 46 patients, the heart weighed >400 g (upper limit of normal for men). The hearts of the 23 women weighed 215 to 750 g (mean 443 ± 127, median 420). In ≥18 (78%) of these 23 women, the heart weighed >350 g (upper limit of normal for women).

In all 90 patients, the tubular portion of the ascending aorta was extensively involved by the syphilitic process (Figures 1 to 9). In only 4 of the 90 patients did the process extend into the wall of aorta behind the sinuses of Valsalva. In the other 86 patients, the process began at the sinotubular junction. The aortic arch was available for examination in 54 of the 90 patients. Of the 54 patients, the aortic arch was also involved by the syphilitic process in 49 (91%). The descending thoracic aorta was available for examination in 52 of the 90 patients, and in 47 (90%) the process also involved this portion of the aorta. The abdominal portion of aorta was available for examination in 47 patients, and in 39

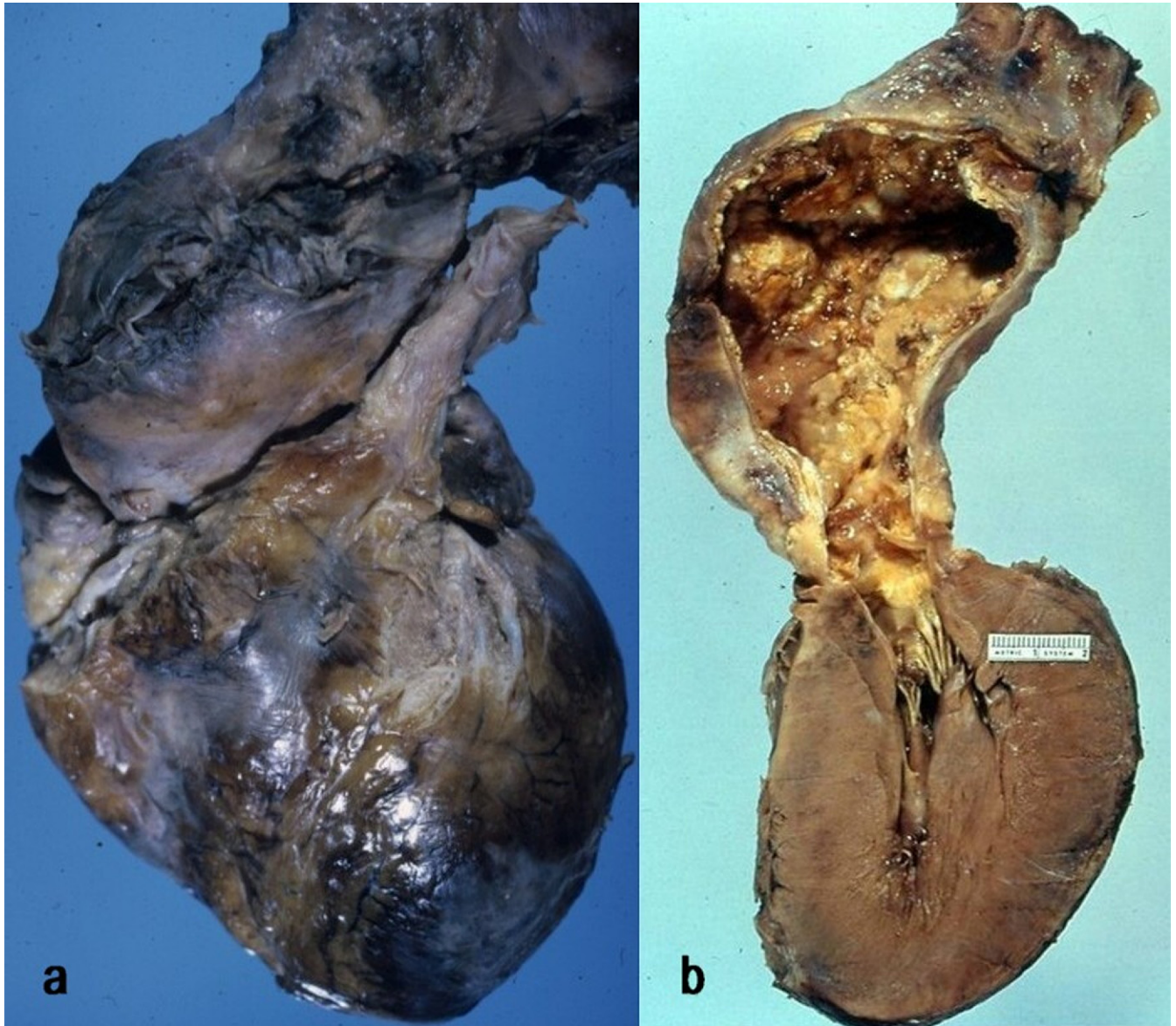


Figure 1. Heart and aorta in 67-year-old European-American woman with positive Venereal Disease Research Laboratory and fluorescent treponemal antibody serologic test results for syphilis with huge fusiform aneurysm of ascending aorta. (a) Anterior view of heart and aorta. Huge aortic aneurysm compresses adjacent pulmonary trunk. (b) Opened aorta showing severe involvement of tubular portion by syphilitic process with sparing of sinus portion. Right ventricle and atria have been excised from remaining left ventricle. The lack of dilation of the left ventricular cavity strongly suggests the lack of aortic regurgitation, of which no evidence was seen during her life.

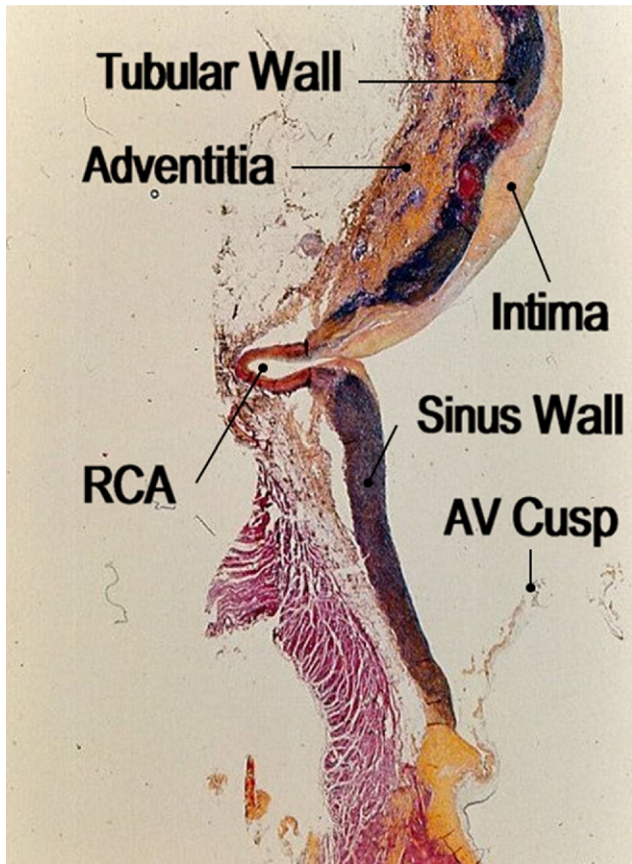


Figure 2. Histologic section of sinus and proximal tubular portion of ascending aorta in 32-year-old African-American woman who was killed in an automotive crash. Ascending aorta had a maximal diameter of 6 cm. Media (black stained) of sinus wall was normal, and no intimal or adventitial thickening seen. Wall of tubular portion was 4 times thicker than that of sinus portion. Thickening resulted from severe thickening of both intima and adventitia by fibrous tissue. Transverse scars replaced medial elastic tissue in 3 different areas. Ostium of right coronary artery severely narrowed by intimal fibrous tissue. Movat stain, original magnification  $\times 5$ . RCA = right coronary artery; AV = aortic valve.

(83%), this portion of the aorta contained atherosclerotic plaques. However, the process was quite different from that involving the more proximal portions of the aorta in that the process involved only the intima and spared the adventitia.

The syphilitic process involving the thoracic aorta caused aneurismal dilation of the involved segment in some patients but not in others. The aneurismal process involved the entire wall of aorta (fusiform) in all patients, and in 10 of them, one or more saccular aneurysms were present within the fusiform dilated portion. (Only a portion of the aortic wall was involved in the saccular aneurysm.)

Histologically, the wall of the thoracic aorta was much thicker than normal, the result of fibrous thickening of the adventitia and fibrous and/or fibrocalcific thickening of the intima (Figures 2 and 8). Within the adventitial fibrous tissue were focal collections of plasmacytes and lymphocytes, often surrounding the vasa vasora, the walls of which were usually quite thickened and their lumens quite narrowed. The media of the aorta was not thickened but its elastic fibers, as demonstrated by Movat stain, were focally interrupted such that in some areas of media no elastic fibers

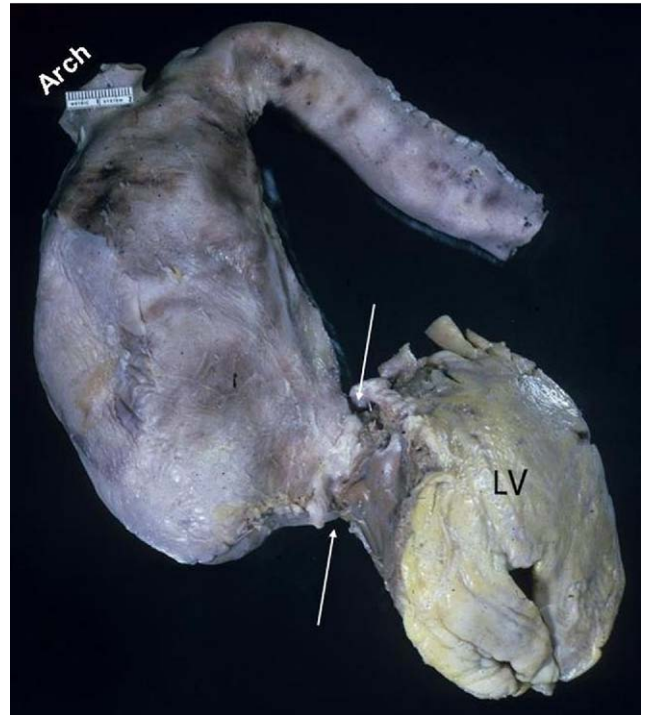


Figure 3. Thoracic aorta and left ventricle from 79-year-old woman who died from cancer. Maximal transverse diameter of ascending aorta was 8.7 cm. Dilation began just above sinus portion (between arrows), which was not dilated. Entire arch and descending thoracic aorta were also diffusely involved by syphilitic process. Both Venereal Disease Research Laboratory and fluorescent treponemal antibody serologic test results for syphilis were negative. LV = left ventricle.

were present and fibrous scars had replaced the medial elastic fibers and smooth muscle cells. The intimal process appeared to be typical atherosclerotic plaque.

At least 46 (65%) of the 71 patients in whom the arteries were carefully examined had  $>75\%$  narrowing in the cross-sectional area of one or more major (right, left main, left anterior descending, left circumflex) epicardial coronary arteries. Of the 85 patients in whom the ostia of the 2 coronary arteries in the aorta were carefully examined, 13 (15%) had definite narrowing of the ostium of the right coronary artery and 2 (2%) had definite narrowing of the ostium of the left main coronary artery.

Grossly visible myocardial infarcts were observed at necropsy in 34 (38%) of 89 patients: acute infarcts only in 5 patients (6%), healed infarcts only in 28 patients (31%), and both acute and healed infarcts in 1 patient (1%).

## Discussion

The present study has described the cardiovascular findings at necropsy in 90 patients with characteristic morphologic findings in the ascending aorta of tertiary syphilis. Each heart and aorta was examined and categorized by the same investigator (W.C.R.). No patient had ever undergone cardiovascular surgery. Although it was positive (reactive) for only 70% of the patients who had a serologic test for syphilis, the changes in ascending aorta were similar in the patients with reactive and nonreactive findings for syphilis

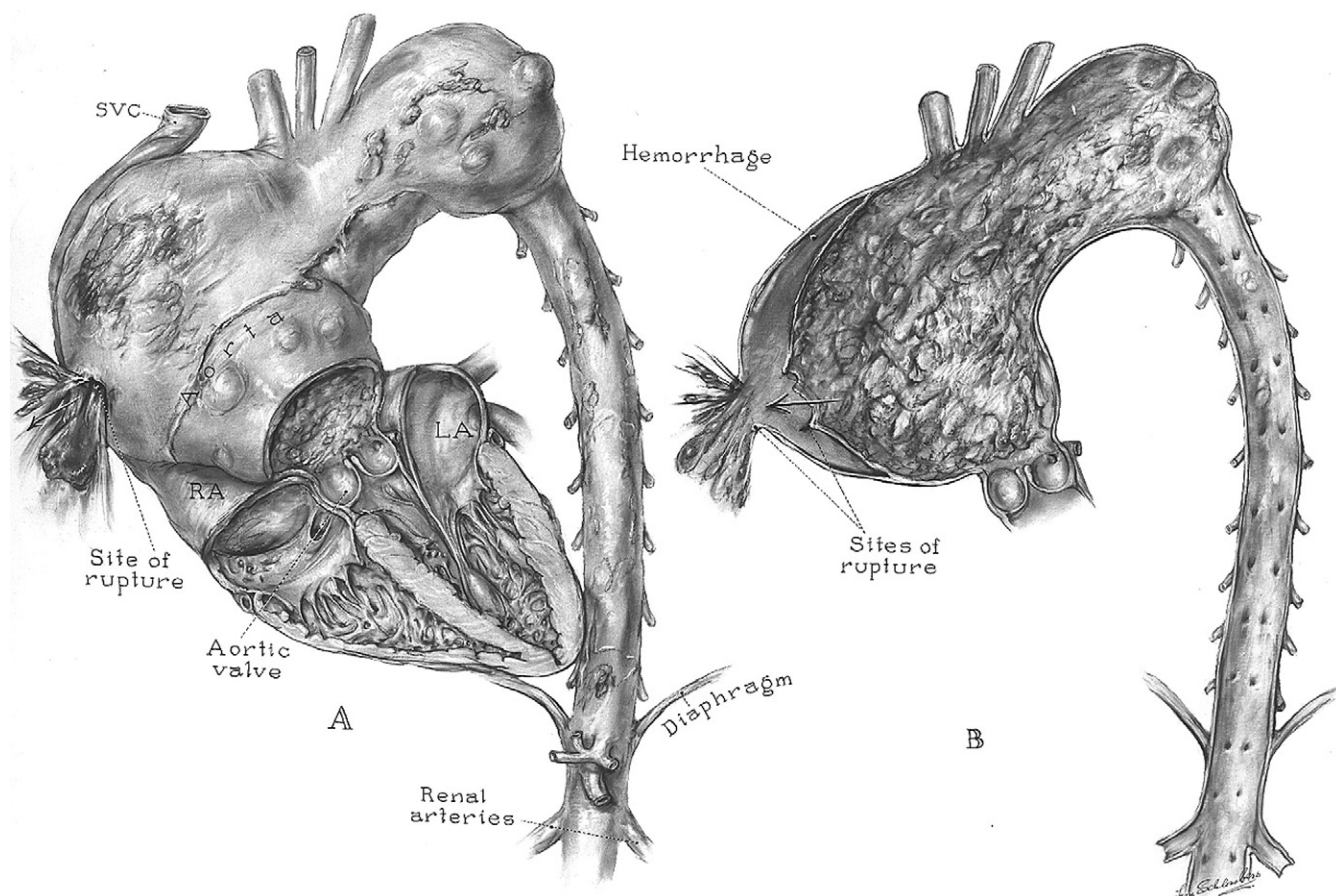


Figure 4. Drawing of thoracic aorta, which ruptured in 60-year-old European-American woman. She had died suddenly at home in the bathroom. Largest transverse diameter of ascending aorta was 9.5 cm. Sinus portion of aorta was normal. The rupture was into the pericardial sac. SVC = Superior vena cava.

and in the patients who did not have a serologic test for syphilis recorded. Of the 90 patients studied, men outnumbered women nearly 2 to 1 and African Americans outnumbered European Americans nearly 3 to 1. Evidence of aortic regurgitation was present clinically in only 1/4 of the patients, and systemic systolic blood pressure  $>140/90$  mm Hg was present in virtually 60% of the patients. Evidence of heart failure was recorded clinically in nearly 1/3 of the patients. The causes of death varied. Syphilis was the cause in only 1/4 of the patients, with nonsyphilitic causes responsible in 3/4. Nearly 70% had one or more major (right, left main, left anterior descending, left circumflex) coronary arteries narrowed  $>75\%$  in cross-sectional area by atherosclerotic plaques (nonsyphilitic), and nearly 40% of the patients had acute or healed myocardial infarct, or both. The ostium of the right coronary artery was very narrow in 15% of the patients.

Examination of our necropsy patients supports the view that cardiovascular syphilis is essentially limited to the thoracic aorta with occasional involvement of the arch arteries. The involvement when present always included the ascending aorta, but any portion of the thoracic aorta can be affected by the syphilitic process. Although some of our patients had severe atherosclerotic involvement of the abdominal aorta, with or without fusiform aneurysm, the process was clearly different from that involving the thoracic aorta in that it spared the adventitia and only indirectly

involved the media (presumably from pressure from the overlying heavy atherosclerotic plaques). Similarly, although the coronary ostia can be narrowed by the syphilitic process in the aorta, the coronary arterial involvement is clearly not a part of the syphilitic process. The narrowing of the coronary arteries themselves resulted from typical atherosclerosis, a process involving the intima only, except for focal thinning of the media, again presumably the result of the overlying heavy atherosclerotic plaques. The adventitia of the coronary arteries was spared (i.e., not thickened).

The syphilitic process appears to involve only arteries in which the vasa vasora are present or at least easily identified histologically. The vasa vasora are either absent from the coronary arteries or difficult to identify. The vasa vasora are present in the entire thoracic aorta but are absent from the abdominal aorta and their absence from this portion of the aorta appears to be the explanation for the absence of syphilitic involvement of the abdominal aorta.

The major consequence of syphilitic involvement of the aorta is thickening of its wall (Figure 10). The thickening results from dense scarring of the adventitia and from less dense fibrous tissue with or without calcium in the intima. The media is not thickened and might be thinner than normal. The media contains many foci of fibrosis, and these scars are usually oriented transversely. In these scarred areas, the elastic fibrils and smooth muscle cells may have vanished completely, and, even in the nonscarred areas of

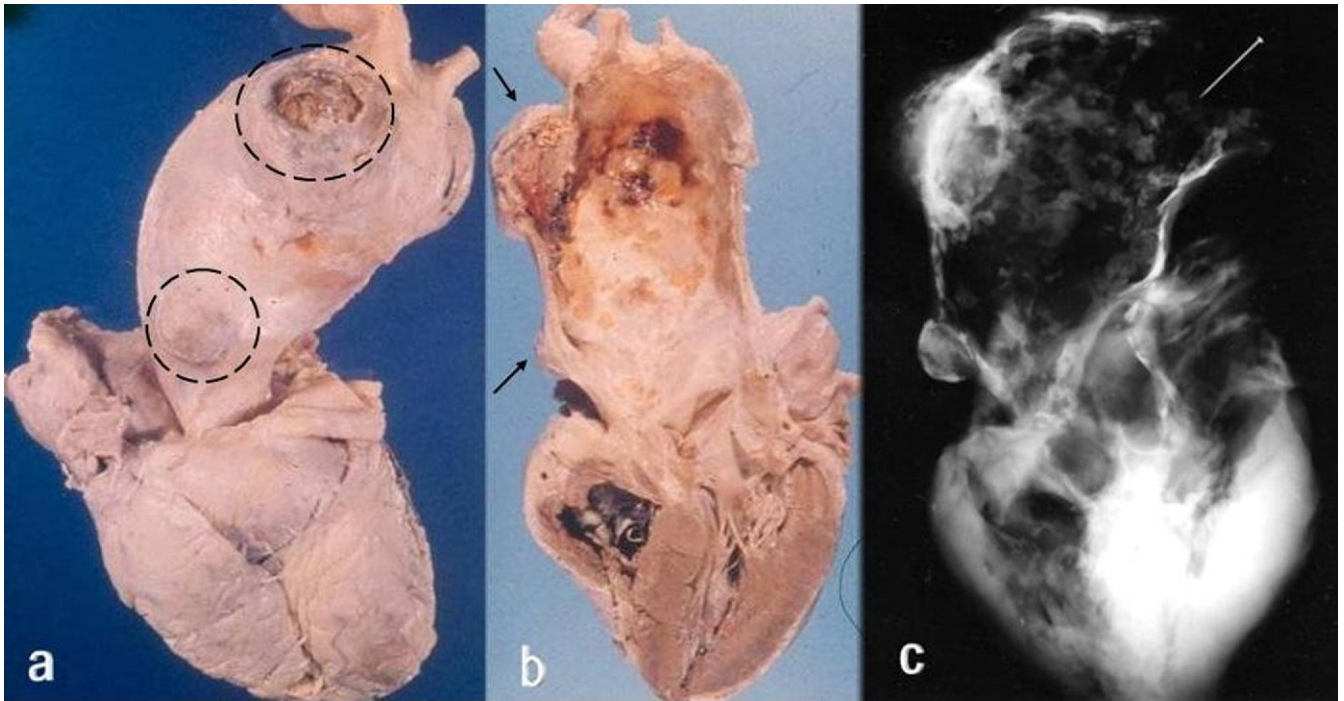


Figure 5. Fusiform and saccular aneurysm of ascending aorta in 81-year-old African-American man who died from a diabetic coma. (a,b) One of 2 saccular aneurysms (arrows and circles) within fusiform aneurysm had burrowed into the sternum. Thrombus was present in both saccular aneurysms. Sinus portion of aorta was normal. Heart size was normal. (c) Calcific deposits present in aortic wall.

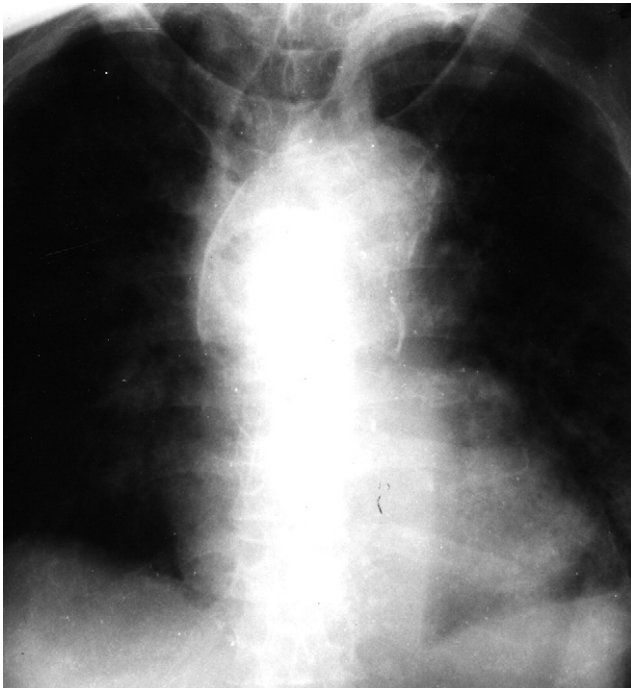


Figure 6. Radiograph of chest in patient described in Figure 5. Linear calcific deposits present in tubular portion of ascending aorta. Calcific deposits present only in intima of aorta.

the media, the elastic fibers are often disrupted. Despite the thickening, the involved arterial wall is weaker than normal because of the disruption of the elastic fibrils and smooth muscle cells of the media. Because the strength of a vessel

is dependent on the integrity of its media, which is disrupted, the involved portion of the aorta usually dilates. Where the media has been totally disrupted, the dilation will be particularly severe, resulting in an increase in focal saccular aneurysms.

Accurately reported information on patients in whom cardiovascular syphilis was found at necropsy is relatively limited, primarily because the data obtained was from autopsy protocols and not from examination by the same investigator of a large number of cases or from re-examination by one or more investigators. Clawson and Bell<sup>1</sup> in 1927 reported the findings from necropsy protocols of 126 patients with syphilitic aortitis: 104 (83%) were men and 22 (17%) were women (the ratio of men to women in their total autopsy cases, however, was 2:1). Aortic regurgitation had been evident in 46 patients (37%), rupture of aortic aneurysm occurred in 35 (28%), and myocardial gummas were found in 3 (2%). Sudden death from coronary ostial narrowing occurred in 25 (20%) and the cause of death was nonsyphilitic for 17 (13%).

Martland,<sup>2</sup> in 1930, described necropsy findings from autopsy protocols in 101 patients with morphologic evidence of cardiovascular syphilis: 28 (28%) had ascending aortic aneurysms, 36 (36%) had aortic regurgitation, and 15 (15%) had narrowing of one or more coronary arteries.

Carr,<sup>3</sup> in 1930, briefly described the autopsy findings in 119 patients with morphologic features of cardiovascular syphilis: 13 (11%) had aneurysmal dilation of the ascending aorta and 24 (20%) had morphologic evidence of aortic regurgitation;  $\geq 49$  patients (41%) had atherosclerotic coronary artery disease.

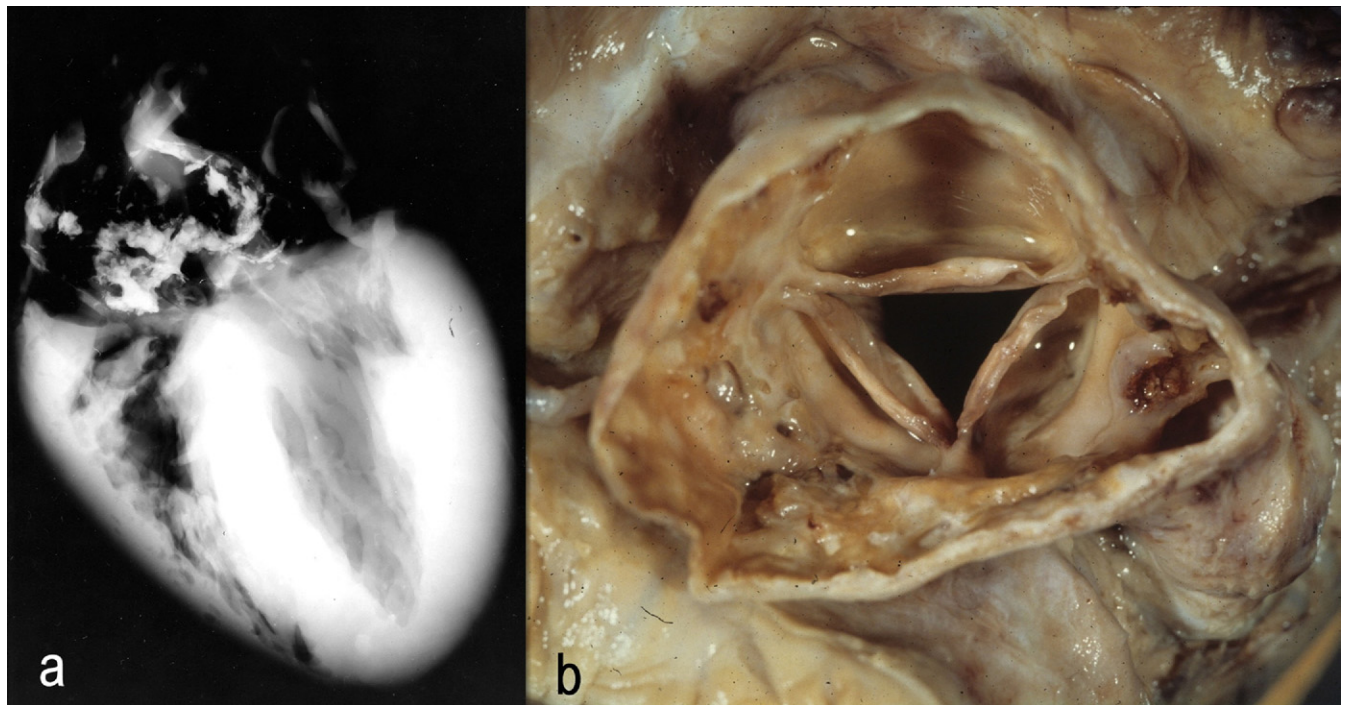


Figure 7. Radiograph of heart and proximal aorta (a) at necropsy and of aortic valve and proximal aorta from above (b) in 68-year-old African-American woman who had clinical evidence of aortic regurgitation and died from heart failure. Radiograph shows heavy calcific deposits in proximal aorta (a). Aortic valve orifice was triangular owing to dilation of ascending aorta. Tubular portion of aorta is diffusely involved by syphilitic process. Venereal Disease Research Laboratory serologic test result for syphilis was nonreactive.

Heggtveit,<sup>4</sup> in 1964, summarized findings from necropsy reports in 100 patients with syphilitic aortitis studied at Kings County Hospital Center (Brooklyn, New York). A clinical diagnosis of syphilis was established in only 17 of the patients. The patients' age range was 30 to 92 years (mean 63): 57 were European American and 43 were African American. Only 23 had ever been treated for syphilis. The blood serology findings (Venereal Disease Research Laboratory and Kolmer) was positive in 40, negative in 28, and not done in 32 patients. Of the 100 patients, 36 had "uncomplicated" aortitis, 40 had aortic aneurysm, 29 had evidence of aortic regurgitation, and 26 had coronary ostial stenosis. In 14 (35%) of the 40 patients with thoracic aortic aneurysms, fatal rupture occurred. In 43 of the 73 men, the heart weighed >400 g and in 18 of the 27 women, the heart weighed >350 g. No large studies of cardiovascular syphilis at necropsy have been reported subsequently.

The frequency of cardiovascular involvement among patients with untreated syphilis has been derived primarily from 2 large studies: the Oslo study and the controversial (i.e., unethical) Tuskegee, Alabama, study, both of which yielded numerous publications in medical journals. The Oslo study<sup>5</sup> analyzed native Oslo patients initially hospitalized with primary syphilis from 1890 to 1910 and followed thereafter for 40 to 60 years. Cardiovascular syphilis (with or without "saccular" thoracic aortic aneurysm, aortic regurgitation or coronary ostial stenosis) was diagnosed in 45 (15%) of the 303 men and in 47 (8%) of the 584 women. Of the patients who were studied at necropsy, 9% of the men had uncomplicated aortitis and 25% had complicated (aneurysm, aortic regurgitation,

coronary ostial stenosis) aortitis, and 11% of the women had "uncomplicated" and 10% had "complicated" disease of the aorta.

The Tuskegee study involved 408 African-American men hospitalized with primary syphilis initially in 1932 and followed through 1972.<sup>6-9</sup> None were treated with penicillin, which had become available in the United States in 1943. By 1952, about 1/3 of the patients had died, and necropsy findings were available for 89. "Fusiform aneurysm of the thoracic aorta" was present in 40 patients (45%), "saccular aneurysm of the thoracic aorta" in 7 (8%), and "aortitis" (by histologic examination) in 41 patients (46%). Of the 89 patients studied at necropsy, 60 (67%) had had positive blood serologic test findings for syphilis when last tested, 3 had "doubtful" test results, and 24 had negative results. Of the 69 hearts (those with weights available), 48 (70%) weighed >400 g. A clinical diagnosis of cardiovascular syphilis corresponded with the necropsy diagnosis in 88% of the patients.

The present study had many limitations. First, we had virtually no information on the presence or absence of primary syphilis in the distant past. Second, the results of the serologic tests for syphilis for most patients were not available to us. Third, the entire aorta of many patients was unavailable for examination by us. Fourth, whether syphilitic cardiovascular disease had been diagnosed clinically was not known for most patients. Finally, the number of patients who had ever received antibiotic therapy for syphilis was unknown to us. Nevertheless, the morphologic data were collected and studied extensively by a single investi-

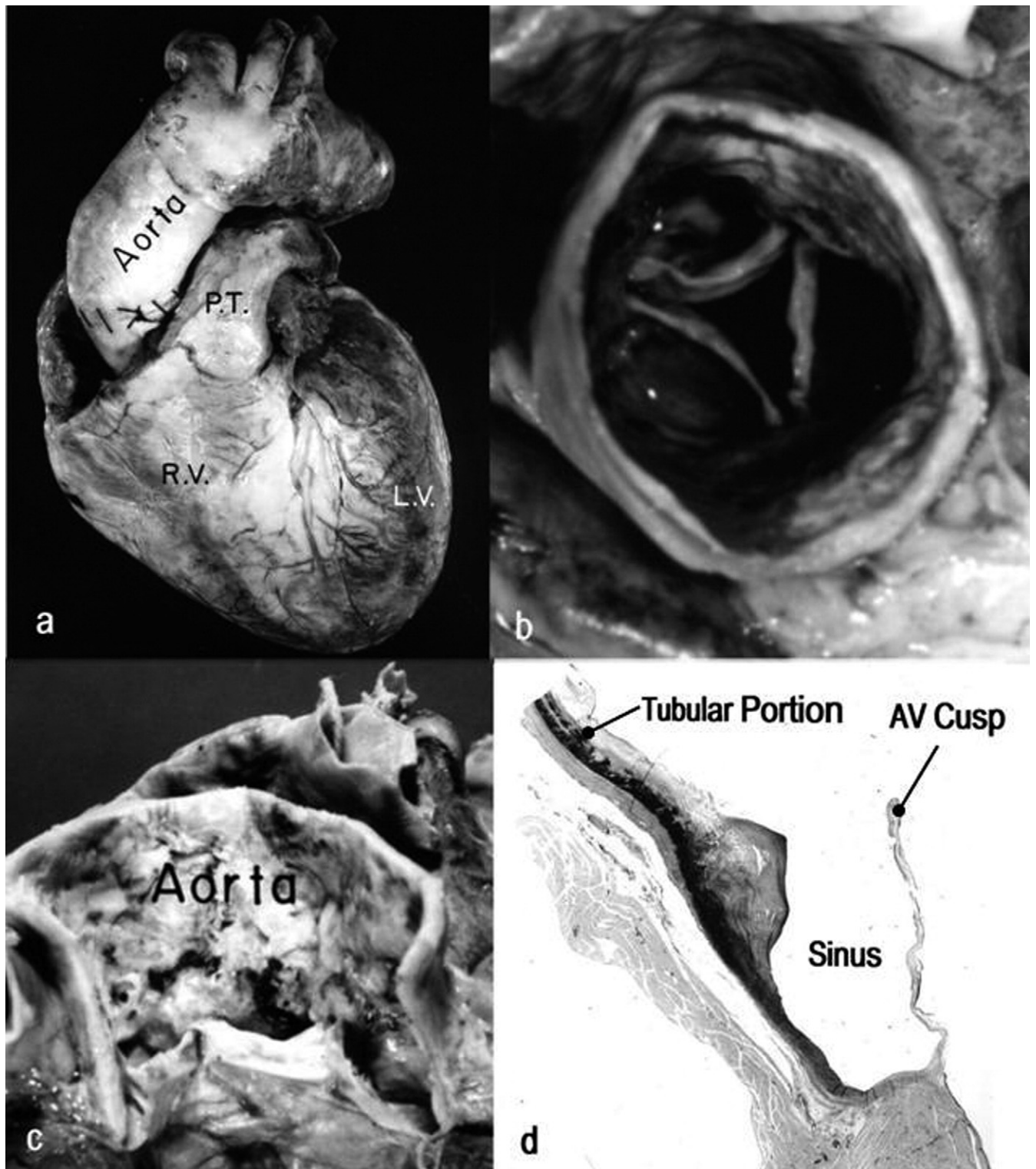


Figure 8. Heart and aorta from 69-year-old African-American man who died from heart failure secondary to severe aortic regurgitation (systemic blood pressure 170/50 mm Hg). Venereal Disease Research Laboratory serologic test result for syphilis was positive (reactive). (a) Heart, which weighed 640 g, and dilated ascending aorta. L.V. = left ventricle; P.T. = pulmonary trunk; R.V. = right ventricle. (b) Aortic valve from above with eccentric triangular orifice. Wall of aorta was very thick. (c) Opened aortic valve and aorta showing diffuse syphilitic involvement of tubular portion. (d) Photomicrograph of aortic valve cusp and proximal aorta. Wall behind sinus portion was normal, and wall in tubular portion was about 3 times thicker than aortic wall behind sinus. Elastic van Gieson stain, original magnification  $\times 5$ .



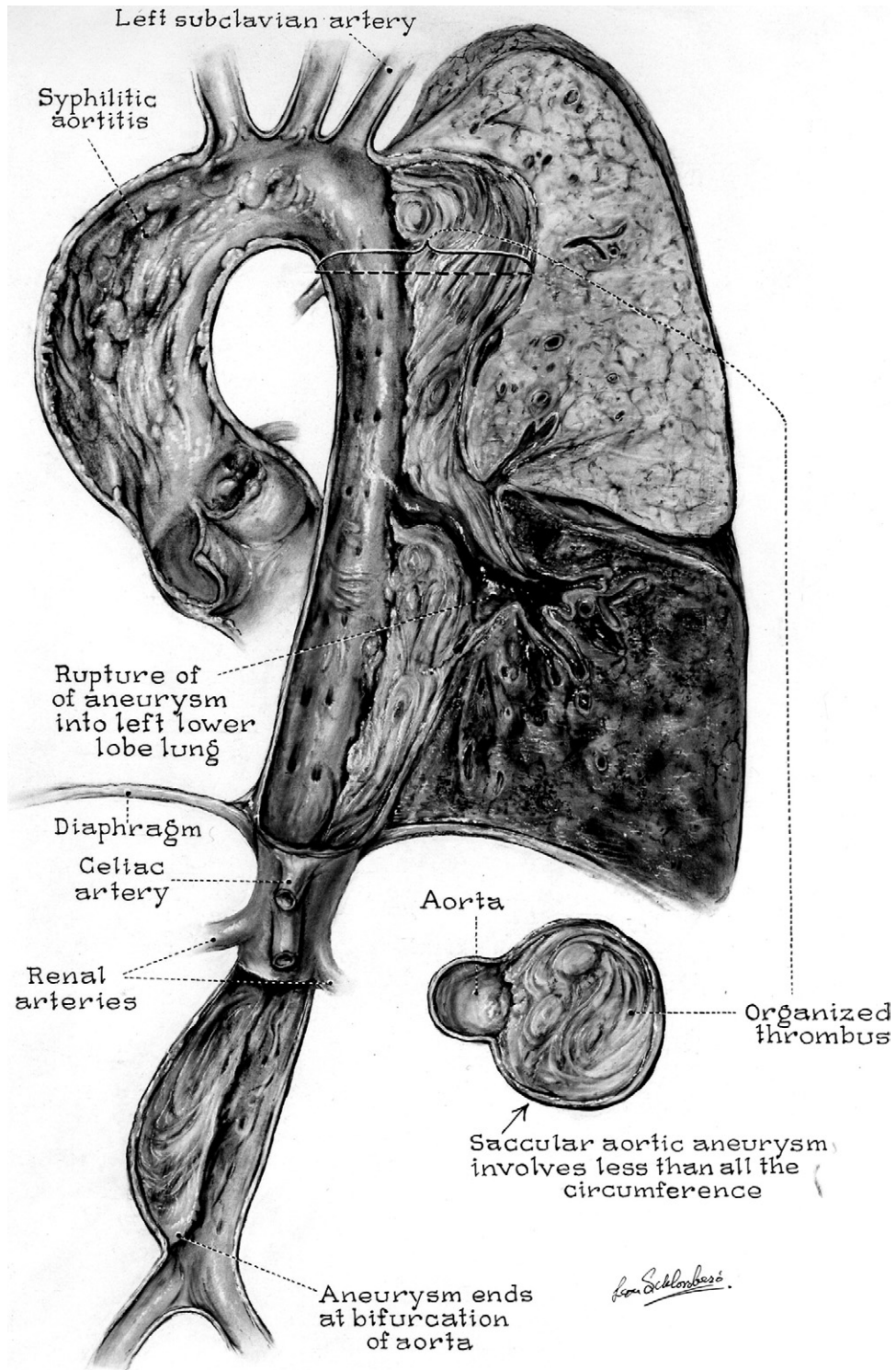


Figure 9. Drawing of aorta and portion of lung from 44-year-old African-American man who died from rupture of descending thoracic aneurysm into his left lung. Ascending aorta was typical of syphilitic aortitis. Wall of aorta behind sinuses was normal. Heart weighed 350 g.

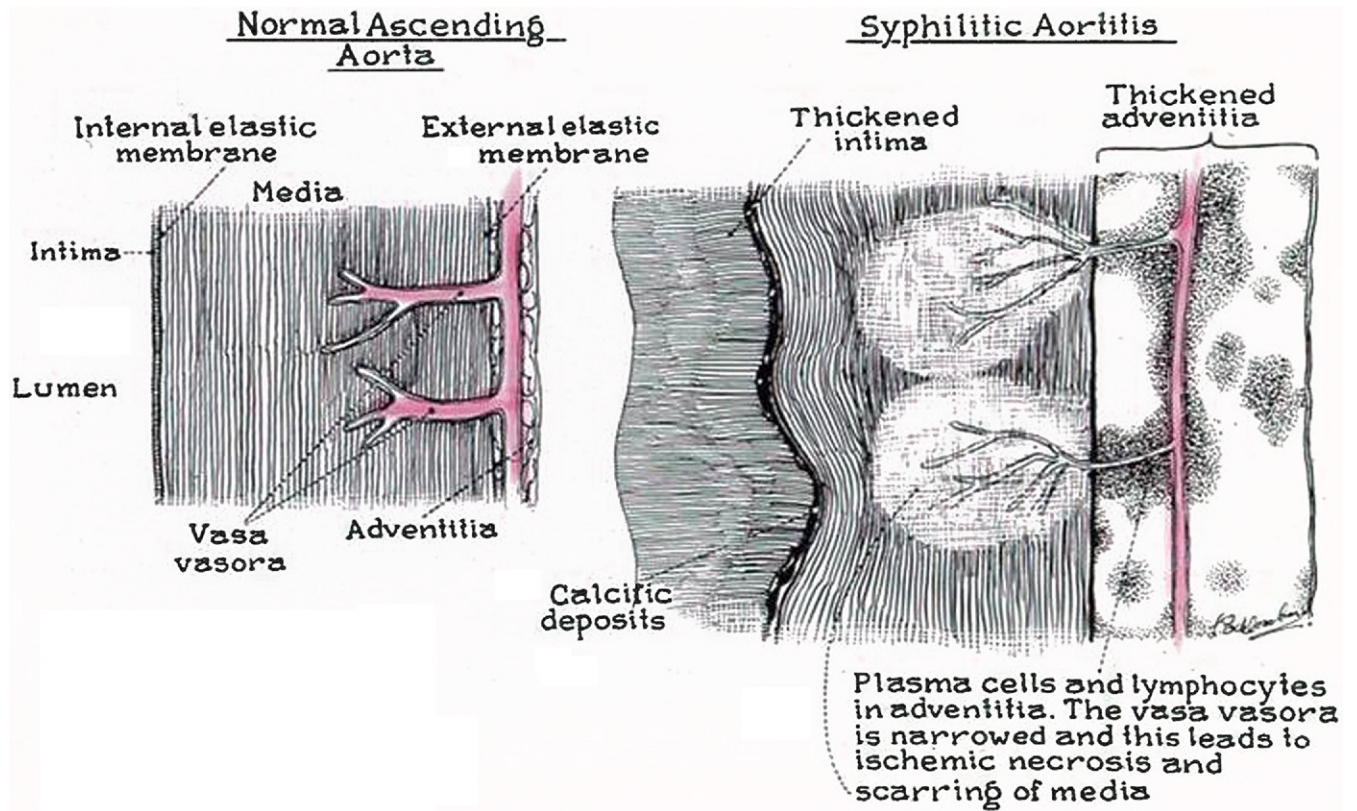


Figure 10. Diagram showing normal aorta (Left) and syphilitic aorta (Right).

gator, an occurrence made possible only by not discarding the specimens soon after necropsy.

1. Clawson BJ, Bell ET. The heart in syphilitic aortitis. *Arch Pathol Lab Med* 1927;4:922-936.
2. Martland HS. Symposium on cardiovascular syphilis: syphilis of the aorta and heart. *Am Heart J* 1930;6:1-29.
3. Carr JG. The gross pathology of the heart in cardiovascular syphilis. *Am Heart J* 1930;6:30-36.
4. Heggveit HA. Syphilitic aortitis: a clinicopathologic autopsy study of 100 cases, 1950 to 1960. *Circulation* 1964;29:346-355.
5. Clark EG, Danbolt N. The Oslo study of the natural history of untreated syphilis: an epidemiologic investigation based on a rest-

udy of the Boeck-Brussgaard material. *J Chronic Dis* 1955;2:311-344.

6. Peters JJ, Peers JH, Olansky S, Cutler JC, Gleeson GA. Untreated syphilis in the male Negro: pathologic findings in syphilitic and non-syphilitic patients. *J Chronic Dis* 1955;1:127-148.
7. Rockwell DH, Yobs AR, Moore MB Jr. The Tuskegee study of untreated syphilis: the 30th year of observation. *Arch Intern Med* 1964; 114:792-798.
8. Caldwell JG, Price EV, Schroeter AL, Fletcher GF. Aortic regurgitation in Tuskegee study of untreated syphilis. *J Chronic Dis* 1973;26:187-194.
9. White RM. Unraveling the Tuskegee study of untreated syphilis. *Arch Intern Med* 2000;160:585-598.