CLINICAL CONFERENCES

EDITOR: EDGAR V. ALLEN, M.D.
Associate Editor: RAYMOND D. PRUITT, M.D.

Congestive Heart Failure Induced by Primary Systemic Amyloidosis
A Diagnostic Problem

Arranged by RAYMOND D. PRUITT, M.D., GUY W. DAUGHERTY, M.D., AND JESSE E. EDWARDS, M.D.

Congestive heart failure occurs commonly in males past 45 years of age as a consequence of coronary sclerosis associated with myocardial infarction or with hypertension. The clinical evidences of coronary sclerosis are not always identified readily in patients so afflicted, and this not uncommon basis for congestive heart failure of obscure etiology is not, to be sure, the only cause of such failure. To place all cases of congestive failure for which no cause is evident in the category of "arteriosclerotic heart disease" is to admit a lack of diagnostic sensibilities and to practice an indolent and erroneous form of medicine.

Report of Case. The patient whose problems are to be reviewed in this conference was first examined by a member of the staff of the Mayo Clinic in May, 1939. At that time the patient was 36 years old and came for investigation and treatment of pain in the lower portion of his back. This pain had begun following an accident. Examination of his heart was carried out at this time with negative results. His blood pressure was 112 mm. of mercury systolic and 76 mm. of mercury diastolic.

He was next examined at the clinic on April 21, 1952, at the age of 49 years. He reported that on January 30 he had experienced an episode of pain localized over the anterior aspect of the left side of his chest. This pain had persisted in severe form for 30 minutes and in milder intensity for the next 24 hours. He described the distress as of a sharp, exacerbating character which took his breath away. Its severity was of an order established by the patient as the worst he had ever had. However, he did not consult a physician at this time and, following subsidence of the pain, he felt reasonably well and continued in his work as a maintenance man in a hotel. Three or four days prior to his examination on April 21 he had noted increasing dyspnea associated with exertion and a pitting type of edema had developed over the lower legs and ankles. Blood pressure readings were 90 mm. Hg systolic and 70 mm. Hg diastolic.

A physical examination made on April 21 disclosed no abnormalities other than edema of the lower extremities and a cardiac rate of 96 beats per minute.

Laboratory studies were productive of the following information. Specific gravity of the urine was 1.008 on one occasion and 1.006 on another. Albuminuria was graded 2 and the test for Benee Jones protein was negative. Microscopic study of the urine gave a negative result. The concentration of urea in the blood was 24 mg. per 100 cc. and of serum proteins, 5.10 Gm. per 100 cc., of which 3.67 Gm. was albumin and 1.43 Gm. was globulin. The sedimentation rate of erythrocytes was 29 mm. per hour by the Westergren method. Hemoglobin concentration in the blood, erythrocyte and leukocyte counts, and differential blood counts were within the limits of normal. The result of a serologic test for syphilis was negative. The chest x-ray disclosed no pulmonary pathologic condition. The transverse diameter of the heart was regarded as being at the upper limit of normal (fig. 1).

Further studies were advised but the patient chose to proceed with a program of treatment which included moderate restriction of his intake of salt and an appropriate dose of digitalis. His dyspnea subsided and his edema disappeared. However, he returned on June 3, 1952, to report that in spite of maintenance of therapeutic measures he had recurrence of edema, attended by dyspnea on mild effort, but no orthopnea. Findings on physical examination were unchanged except for the observation

From the Division of Medicine and the Section of Pathologic Anatomy, Mayo Clinic, Rochester, Minn.
that the liver was palpable 2 cm. below the right costal margin when the patient inspired deeply.

On July 22, the patient weighed 169 pounds (about 77 Kg.), an increase of 15 pounds (about 7 Kg.) over his weight on June 3. His dietary intake of sodium had been restricted during the interval. Digitalis had been taken regularly until June 16.

On July 22, he was admitted to the hospital. Principal therapeutic measures included reconstitution of treatment with digitalis, administration of a mercurial diuretic at intervals of two or three days and of a diet containing 130 Gm. of protein and approximately 0.9 Gm. of sodium. On this regimen the patient’s weight declined from 169 pounds to 141 pounds (about 64 Kg.) during a period of 14 days.

The first tracing was made on June 4, 1952, some six months after the episode of pain and after treatment with digitalis had been instituted. One is impressed immediately by the low amplitude of the QRS complexes in leads I, aVR and aVL. Neither in the extremity leads nor in the precordial leads is there an aberration in QRS configuration which affords specific evidence of a myocardial scar. Significance of the QS deflection in lead aVL is limited, especially since there is no R wave in lead aVR. The R wave in the precordial leads is absent in V1 and of low amplitude in the remainder of the precordial leads. However, at no point is a Q wave discernible. The RS-T segment depression in standard leads II, III, extremity lead aVF and precordial leads V5 and V6, as well as the RS-T elevation in aVR, presumably may be ascribed to the effects of digitalis.

In the electrocardiogram recorded six weeks later (July 23, 1952) the form of the complexes in lead V5 is noteworthy inasmuch as a notch is present in an R wave of very low amplitude.
Unfortunately, records were made from only three precordial positions.

If a myocardial scar is responsible for the peculiarities of this electrocardiogram, its location almost certainly would be in the lateral wall of the left ventricle. I would conclude, however, that both the historical and electrocardiographic evidence of myocardial infarction are inconclusive and that the most substantial reason for suspecting that this patient's illness and death were related to postinfarction congestive heart failure is the frequency of this type of illness as compared with other pathologic processes producing a similar clinical picture in men of 50 years.

May I propose that Dr. Daugherty discuss the second question which was raised, namely what significance should be attached to the preponderance of edema over other manifestations of disability in the evolution of the patient's disease?

DR. G. W. DAUGHERTY: I saw this patient on June 4, 1952. He was moderately edematous. He was continuing to work as a maintenance man in a hotel. This job required considerable walking and some lifting, so while he was aware of dyspnea it was not severe nor was he orthopneic. Urinalyses revealed albuminuria, grade 2 to grade 3, and the concentration of the total serum protein was slightly below normal. However, the reduction was greater rather than less in the globulin than in the albumin fraction. Several collections of urine over a 24-hour period showed the loss of protein to be about 0.1 Gm. per 100 cc. The urinary sediment contained a few hyaline casts and an occasional erythrocyte. The Bence Jones protein reaction was negative. The cardiac silhouette in a roentgenogram of the chest was enlarged and the venous pressure in the right antecubital vein was 14 cm. of water.

The occurrence of edema, without marked dyspnea, tended to draw attention away from a failing left ventricle as a cause of the patient's difficulty. Constrictive pericarditis seemed unlikely since there was no hepatic enlargement and no great elevation of the venous pressure. The urinary findings suggested kidney disease. It was my impression at the time that this patient had a specific renal lesion, either as a primary disease or in association with that heart disease which was causing the cardiac enlargement. I did not feel that the renal findings were to be explained on the basis of congestive heart failure. However, the evidence at the time was not satisfying for the diagnosis of the nephrotic syndrome as an explanation for the preponderant edema nor did subsequent urinalyses and determinations of serum protein values afford more convincing evidence of such a disorder. The lowest value for proteins in the serum was recorded on July 15, 1952, when it was 4.9 Gm. per 100 cc., of which 3.5 Gm. was albumin and 1.4 Gm. was globulin. The concentration of cholesterol in the plasma on this date was only 134 mg. per 100 cc.

Because of the combination of findings suggestive of renal disease and heart disease, I suggested that a Paunz test for amyloid be
performed. This was done on June 5, 1952, and the result was reported as negative.

Dr. Pruitt: I do not understand why you were so confident that the patient had a specific renal lesion. Could not the findings on urinalysis and the altered concentration of proteins in the serum be encountered as effects of congestive heart failure on renal function?

Dr. Daugherty: Certainly that question should be raised. The presence of the abnormal findings in the urine could indeed be due to congestive phenomena in the kidney. However, in mild failure—and recall that this patient did not have hepatomegaly and was still working—I have not seen such changes in the serum proteins. Further, when there are significant congestive changes in the kidneys the concentration of urea in the blood tends to be slightly elevated. In this patient this concentration was 16 mg. per 100 cc. of blood and a urea clearance test, done shortly afterwards, revealed a result within the range of normal values.

May I suggest that Dr. M. W. Anderson continue the discussion inasmuch as he assumed certain responsibilities in the patient's care approximately at this phase of developments?

Dr. Anderson: I saw this patient on July 28, 1952, approximately two months after Dr. Daugherty's initial observations. During this interval, certain significant developments had occurred. The patient's weight had increased to 169 pounds (about 77 Kg.), of which at least 30 pounds (about 14 Kg.) represented retained fluid. His liver, which had not been palpably enlarged at the time of the initial examination in April, was noted to descend 2 cm. below the right costal margin. A test of hepatic function by the Bromsulphalain method indicated retention of dye, grade 1 (10 per cent). Like Dr. Daugherty, I believed the evidences of renal and hepatic involvement were greater than could be accounted for on the basis of congestive heart failure as manifested in this case. There was no evidence of diabetes nor of cutaneous pigmentation to support the presence of hemachromatosis. The Paunz test was repeated on July 29, 1952, with negative results. The decision was made to proceed with needle biopsy of the liver and this was carried out by Dr. Stauffer on July 31. Examination of the tissue obtained disclosed findings typical of amyloid disease. A clinical diagnosis was made of primary systemic amyloidosis with involvement of the heart, kidneys and liver.

Moderator: Dr. Edwards, would you summarize the significant observations made at the time of necropsy?

Dr. J. E. Edwards: The pathologic features in this case were those of primary systemic amyloidosis, with considerable widespread involvement of blood vessels, as well as heavy infiltration of most of the viscera, including the heart. Evidence of congestive cardiac failure was present in the form of edema of the legs, ascites (300 cc.), bilateral hydrothorax (1,000 cc. each side) and central hemorrhagic necrosis of the liver.

In the heart the infiltration by amyloid was suspected on gross morphologic examination, for fine granular elevations were found in the endocardium of both atria and in the atrioventricular valves. Gross sections of the myocardium revealed translucent, gray, speckled lesions measuring approximately 1 mm. in greatest dimension.

Microscopic examination of the heart revealed extensive involvement of the myocardium. In some regions this took the form of an increase in thickness of the reticulum fibers, brought about by the presence of amyloid (fig. 3a). In other regions this change was associated with atrophy of muscle fibers. In still other regions there were large masses of amyloid in which no muscle fibers remained (fig. 3b). Such regions were probably those which had been observed on gross examination of the myocardium. As in other organs, the myocardial blood vessels and surrounding stroma were greatly thickened with amorphous material, which was amyloid (fig. 3c). There were nodular accumulations of amyloid within the leaflets of the atrioventricular valves (fig. 3d).

In the lungs there was considerable involvement of the blood vessels and the alveolar walls. In addition, the mucosa of the small bronchi contained nodules of amyloid (fig. 3e).

The liver was only slightly enlarged; it
Fig. 3. Sections of heart stained with hematoxylin and eosin. (a) The myocardium. Thickening of basement membranes by deposition of amyloid. In areas of heavier infiltration there is atrophy of muscle fibers (X430). (b) Myocardium. Nodules of amyloid associated with disappearance of muscle fibers (X70). (c) Myocardium. Heavy infiltration by amyloid of blood vessels and surrounding stroma (X65). (d) Tricuspid valve. Nodular infiltration of valve leaflet with amyloid (X50). (e) Small bronchus. Nodules of amyloid beneath epithelium (X235). (f) Liver. In a portal area there is a slight degree of amyloid in the blood vessels and connective tissue. Also there is a picture of extensive central hemorrhagic necrosis (X65).
weighed 1,910 Gm. Of all the viscera, the liver contained the least amyloid. This material was almost entirely confined to the blood vessels and connective tissues of the portal regions. In relation to the parenchymal cords there was little amyloid. Examination of the liver also disclosed the changes of central atrophy, necrosis and hemorrhage, features attributed to cardiac failure (fig. 3f).

The kidneys were slightly enlarged. Together they weighed 440 Gm., which is approximately 150 Gm. heavier than the anticipated normal. The kidneys were of uniform size and were similar in appearance. Scattered, cortical, small, acute infarcts were present. Otherwise the cortices were of relatively thick pinkish-gray appearance. The pelvis, calyces and ureters were unusually resilient, and the mucosa contained foci of amyloid which gave to the surface a raised, speckled character resembling that of the lining of the atria of the heart (fig. 4a). On microscopic examination of the kidneys, nodular deposits of amyloid were found in the glomerular tufts (fig. 4b). The blood vessels throughout the organs, and the connective tissue and fat in relation to the pelvis, also were involved.

The thyroid gland was, for the most part, replaced by amyloid which was represented by infiltration within the blood vessels and in the stroma (fig. 4c).

On microscopic examination of the adrenal glands, amyloid was found deposited on the surface of the fat cells around the organs, in the capsule and in the blood vessels related to the capsule. The zona fasciculata and zona reticularis were particularly heavily infiltrated and this infiltration was associated with disappearance of parenchymal cells (fig. 4d).

Examination of the testes revealed amyloid deposited intramurally within the blood vessels and in the connective tissue supporting these (fig. 5a). None was found in direct relation to the seminiferous tubules.

In the gastrointestinal tract amyloid was found within the walls of blood vessels, and particularly striking was deposition of this material in the connective tissue of the tunica propria of the mucous membranes (fig. 5b).

There were striking nodular deposits of amyloid in the corium immediately beneath the epithelium (fig. 5c).

The tongue was heavily involved. This included deposition within the walls of the blood vessels and in the salivary glandular tissue of the tongue and among the muscle bundles (fig. 5d and e).

A submaxillary gland was heavily infiltrated, the degree of infiltration resembling that in the thyroid (fig. 5f).

The spleen was considerably involved, particularly the malpighian bodies and related blood vessels. The bone marrow was essentially normal.

Examination of the sciatic nerves revealed small amounts of amyloid within the walls of blood vessels related to the nerves and in an occasional area there was infiltration of the walls of blood vessels within nerve bundles.

MEDIUM: Dr. Daugherty, patients with systemic amyloidosis are said to develop a nephrotic syndrome. In your discussion you emphasized the absence in this patient of features prerequisite to a diagnosis of the nephrotic state. Have other patients with systemic amyloidosis exhibited the characteristic findings of the nephrotic syndrome or has that designation been applied loosely or mistakenly as it might have been in this case?

DR. DAUGHERTY: About a third of patients with renal amyloidosis develop certain nephrotic features. These include findings that range all the way from albuminuria with edema, to what one considers the full-blown picture of nephrosis: heavy albuminuria, massive edema, hypoproteinemia with reversal of the albumin-globulin ratio and elevation of the plasma lipids. Although there are instances of the full-blown picture, more frequently the patients seen are in the other category. Most certainly there are all gradations of the nephrotic picture, and it may worsen or improve at different times in the same case. Therefore, I would say the term is used loosely, but perhaps justifiably, to designate the patient with renal amyloidosis who has clinical features indicating a rather advanced stage of the disorder. In so far as I am aware, amyloidosis of the kidney presents the same.
CONGESTIVE HEART FAILURE INDUCED BY AMYLOIDOSIS

Fig. 4(a). Kidney. Focal infarcts. In the lining of the pelvis are many tiny nodules representing amyloid infiltration within the mucosa. (b) Kidney. Nodular infiltration of amyloid in glomerular tuft (hematoxylin and eosin; X305). (c) Thyroid. Extensive infiltration in blood vessels and connective tissue by amyloid, leaving only isolated acini (hematoxylin and eosin; X85). (d) Adrenal gland. Amyloid within the capsule and an associated blood vessel, as well as within the cortex. In the latter location the infiltration is associated with loss of parenchymal cells (hematoxylin and eosin; X75).

picture clinically whether it be secondary, or so-called primary amyloidosis.

Moderator: Dr. Pruitt, was the electrocardiographic evidence in this case typical of amyloidosis?

Dr. Pruitt: The role of the electrocardio-
gram in the diagnosis of cardiac amyloidosis is, at best, a supportive one. Study of the tracings obtained from 15 patients who had cardiac amyloidosis of various types led us here to conclude that definitive evidence of the disease cannot be had from the electrocardio-
CONGESTIVE HEART FAILURE INDUCED BY AMYLOIDOSIS

M. H. Stauffer: It is well known that in secondary amyloidosis, biopsy of hepatic tissue usually will afford evidence sufficient to establish the diagnosis, since in most cases the liver is involved along with the spleen, adrenal glands and kidneys. In primary amyloidosis the myocardium, blood vessels, skeletal muscles and skin are predominantly involved, whereas the liver has been said by some authors to be seldom affected. Reports have appeared, however, of several cases of primary amyloidosis in which the principal clinical manifestations have been those of hepatic disease. These reports indicate that the liver may be severely involved in the primary type of this disease. This fact, along with many other peculiar aspects of amyloidosis, suggests that there is not always a clear-cut difference between the primary and secondary syndromes. Therefore, when my colleagues have asked me to attempt to secure evidence definitive of amyloidosis by biopsy of the liver of a patient who presents clinical features favoring the primary type of the disease, I have undertaken the procedure with some optimism. In the past two years I have secured hepatic tissue containing deposits of amyloid from seven patients, on whom preceding clinical studies had indicated existence of the primary type of the disease.

The Paunz or the Congo red test often gives a negative result in primary amyloidosis since, in this form of the disease, the amyloid has less affinity for Congo red than in secondary amyloidosis. This feature of the primary type of the disease makes the results of examination of tissue obtained for biopsy more critical in determining the diagnosis. When a patient does not have macroglossia or cutaneous lesions, it appears to me that the liver should be considered a fruitful source of tissue for microscopic study. This is especially true if that organ is enlarged and firm or if there are associated signs of hepatic dysfunction not
readily accounted for by such congestive heart failure as may be present. If congestive heart failure is quite evident, then appropriate treatment should be instituted and maintained for several days prior to biopsy of the liver in order to lower the venous pressure as much as possible. There is a report in the literature of death occurring as a consequence of needle biopsy of the liver of a patient who had amyloidosis. This report, combined with the frequent presence of congestive cardiac failure among patients with amyloidosis, suggests that the risk of performing biopsy may be increased if individuals are afflicted with this disease. However, we here have now performed needle biopsy on nine patients who had amyloidosis without untoward incident; this series includes the seven patients already mentioned who had primary amyloidosis, and two additional patients who had the secondary form of the disease.

MODERATOR: Dr. Edwards, would you integrate this case of primary systemic amyloidosis with the general problem of cardiac amyloidosis?

DR. EDWARDS: Cardiac amyloidosis may be encountered as part of the three following conditions: Primary systemic amyloidosis, secondary amyloidosis and amyloidosis complicating multiple myeloma. In addition, deposition of amyloid may be restricted to the heart, the remaining organs failing to show deposition of this material.

Characteristically, as in the case here presented, primary systemic amyloidosis is associated with involvement of the heart, and in this disease congestive cardiac failure is not an uncommon cause of death.

In secondary amyloidosis cardiac involvement may be encountered at times, but this circumstance is relatively uncommon, the amyloid being deposited mainly in the abdominal viscera.

In approximately 20 per cent of patients who die from multiple myeloma, amyloidosis is an associated pathologic finding. While the deposition of amyloid may be considered secondary to the presence of multiple myeloma, the characteristics of its deposition simulate those of primary, rather than secondary, amyloidosis. In amyloidosis complicating multiple myeloma, therefore, cardiac involvement is a frequent occurrence.

Deposition of amyloid restricted to the heart has in recent years become recognized as occurring more commonly than was appreciated in the past. This manifestation of amyloid disease usually is limited to individuals in the decade of life from 70 to 79 years and beyond. While the degree of deposition in the usual case in which amyloid is confined to the heart is less than in cases of primary systemic amyloidosis, there are isolated cases in which heavy deposition occurs and in which congestive cardiac failure is attributable to this deposition.

SUMMARY

This conference has been concerned with a case of primary systemic amyloidosis in which death occurred in the course of severe, congestive heart failure. Major emphasis has been attached to the diagnostic problems which were posed by a patient so afflicted. If comments regarding treatment have been of limited extent, so have been the results of treatment when applied.
Congestive Heart Failure Induced by Primary Systemic Amyloidosis: A Diagnostic Problem
RAYMOND D. PRUITT, GUY W. DAUGHERTY and JESSE E. EDWARDS

Circulation. 1953;8:769-778
doi: 10.1161/01.CIR.8.5.769
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1953 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/8/5/769