AMYLOIDOSIS: ITS CLINICAL AND PATHOLOGIC MANIFESTATIONS, WITH A REPORT OF 12 CASES *

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Amyloidosis is a generalized disease characterized by the deposition of a homogeneous substance in the media of arteries and perivascular connective tissues. Because of its starchlike staining with iodine, Virchow (1853) considered the substance a carbohydrate moiety, and originated the term "amyloid." The chemical nature of amyloid has never been clearly elucidated, but the studies of Eppinger (1922) and Hass (1940)[21] demonstrated the presence of both protein and polysaccharide elements. It is not known whether the substance is produced locally or transported to the site of deposition, nor is it known whether it is an abnormal substance, or a normal one produced in amounts too great for utilization. Amyloid has been reported in small amounts in the otherwise normal tissues of senile mice and the hearts of aged patients.[27, 28] Because amyloid can be produced experimentally [39, 42] by the injection of colloidal sulfur, selenium, sodium caseinate, bacterial toxins, gelatin and egg albumin, the concept of antigen-antibody interaction has been suggested as a factor in pathogenesis.[34] Amyloid has also been produced by administering nitrogen mustard. ACTH and cortisone used in conjunction with nitrogen mustard enhance amyloid deposition and delay its reabsorption after mustard therapy has been discontinued.[42] The known cytotoxic effect of nitrogen mustard, and inhibitory effect on inflammatory reaction of adrenal cortical steroids, suggest "that a suppression of mesenchymal cells which are in a state of active proliferation is involved in the basic mechanism of the formation of amyloid." [50] Amyloid has been reported in patients with Hodgkin's disease [23, 57] who have been repeatedly treated with nitrogen mustard and who have had unusually long survivals. Amyloid deposition occurs in 15% of cases of multiple myeloma;[8] this has directed speculation as to the rôle of a hyper- or abnormal globulinemic state [24] in the pathogenesis of amyloid. Because of the occurrence of amyloid in connective tissue diseases, it has been suggested that amyloid is another collagen disease.[32]

The disease has been divided into primary and secondary categories on the basis of: (1) presence or absence of inciting disease, (2) distribution of involvement, and (3) the staining reaction. Primary amyloidosis occurs without preëxisting disease and has widespread organ involvement. It

* Received for publication August 13, 1956.

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almost invariably involves the heart,[1, 9] and in two thirds of cases spares the liver, kidney, spleen and adrenal. The heart is rarely involved in the secondary form, and the parenchymal organs (liver, spleen, adrenal, kidney) are invariably involved.[59] The secondary form of amyloid has a constant affinity for certain dyes (Congo red, crystal violet, methyl violet), but the staining of primary amyloid is not predictable. Since there is no known chemical dissimilarity between primary and secondary amyloid, and since there is considerable overlap of organ involvement in the two forms, criticism has been directed at the clinical separation.[9]

By 1950 only 70 cases of primary amyloidosis had been reported.[22] In the last five years 30 additional cases have been added.[32] It is probable that the disease is being suspected more frequently, rather than that there has been a true increase in the number of cases. Of the 70 cases previously reported, in only 14 was the diagnosis made ante mortem.[1, 22] Secondary amyloidosis is common in autopsy series; the incidence has been reported to be as high as 24% with tuberculosis and 20% with rheumatoid arthritis.[6, 17, 40, 49, 53] The frequency in tuberculosis accounts for 80 to 90% of reported cases of secondary amyloidosis. Amyloidosis has also been seen in association with osteomyelitis, bronchiectasis, empyema, actinomycosis, ulcerative colitis, syphilis, subacute bacterial endocarditis, chronic urinary tract infection, carcinoma, lymphoma and leukemia. The incidence is higher where a chronic fistula or sinus tract exists.

Amyloid tumors [46] represent local accretions of amyloid tissue; they are found most frequently in the respiratory tract, but have also been reported involving the eye, urinary tract and central nervous system. These lesions are generally localized and benign, but systemic amyloidosis has appeared after the excision of an amyloid tumor.

Amyloid disease presents itself clinically with a variety of manifestations, which may occur singly or in combination, depending on the extent and severity of the process. Heart failure is responsible for the death of 50% of those with primary amyloidosis.[1, 6, 7, 9] A 70% incidence of renal failure has been reported in those dying of secondary amyloidosis.[6, 30] Liver failure with jaundice,[4, 45, 47, 52, 58] gastrointestinal hemorrhage,[4, 15, 38] adrenal cortical insufficiency [5, 6, 33, 36] and a spruelike syndrome [15] have also been reported in amyloid disease.

The rate of accretion of amyloid is unpredictable. It may be fairly rapid. Tissues have been examined and found free of amyloid within a few months of clinical onset of the disease, with death resulting within two years. It is said that primary amyloidosis is a more slowly progressive disease than the secondary form. This has been used as an explanation for the difference in staining reaction. We know of no statistics that would indicate that the secondary form is more fulminant.

The diagnosis of the disease rests on Congo red absorption and biopsy. Bennhold (1922) originally observed that Congo red was absorbed by

amyloid tissue, and established the figure of 60% loss of Congo red to the tissues between a four and a 60 minute specimen as the requirement for a positive test. Selikoff [43] suggests that the criteria for the diagnosis be made more rigid to exclude false-positives. He would require 90 to 100% removal on two consecutive tests for a positive diagnosis. Unger et al.[54] suggest a method to obviate the inadequacies of the original method. A two or four minute specimen (the 100% figure) does not allow adequate mixing, nor does it measure dye being lost to amyloid tissue during this time. They suggest serial determinations. From these a curve is constructed and a more nearly accurate initial level (100% figure) is obtained by extrapolation back along the curve to the time of injection. Congo red remains in amyloid tissue for at least several days, as witnessed at necropsy.[18] The skin similarly may retain Congo red, and caution has been advised in administering the dye when the skin is known to be involved. Congo red can probably saturate amyloid tissue so that repeated testing within short periods may give conflicting results. The tongue and gingiva are involved sufficiently often in the primary disease that biopsy should be done in suspected cases. Selikoff [44] claims that in secondary amyloidosis gingival biopsy may be equally rewarding. Biopsy may be the only way of establishing the diagnosis in primary amyloidosis when Congo red is not retained. Liver biopsy has been performed frequently to establish the diagnosis. Because an amyloid organ is friable and cannot be readily repaired surgically, caution should be observed in performing aspiration biopsy when amyloid is suspected. Volwiler and Jones [55] report a death from hepatic hemorrhage following biopsy. The spontaneous rupture of amyloid spleens has also been reported.[12, 29]

Case Reports

For purposes of discussion the cases have been arranged according to their predominant manifestations. The first case compounds the phenomena observed in succeeding cases, and is discussed separately.

Case 1. Renal failure—adrenal cortical failure—hemorrhage. A 26 year old white male was found to have Hodgkin's disease by lymph node biopsy in 1945. From 1948 to 1954, during 22 hospitalizations, he received 780 mg. of nitrogen mustard, 185 mg. of triethylene melamine (TEM) and x-ray therapy to the left axilla, spleen and mediastinum. During his early admissions the urine was acid, concentrated well (1.023), and contained no albumin. The liver and spleen became enlarged in 1948. In 1950 albuminuria appeared and persisted. In 1952 polyuria appeared, and the urine did not concentrate beyond 1.012. Congo red was 90% retained by the tissues. In 1953 nonprotein nitrogen elevation (53 mg.%) was first noted. The urine was then alkaline and remained so thereafter. Albuminuria (9.7 gm. in 24 hours) and albuminemia (2.4 gm.%) were present. Alkaline phosphatase was elevated to 20 Bodansky units. In October, 1953, epistaxis, anorexia, diarrhea, abdominal pain, dyspnea, and pain and tingling in the legs developed. Deep and rapid respirations were present. Increased skin pigmentation was noted. No pulses could be felt in the lower extremities. CO_2 combining power was 5 m. mol/L.;

chloride, 90 mEq./L.; sodium, 141 mEq./L.; potassium, 4.3 mEq./L. Nonprotein nitrogen was 137 mg.%. In addition to large amounts of saline, the patient received 788 mEq. of sodium lactate during the first five days. Respirations improved but the CO_2 combining power remained very low (7.5 m. mol/L.). Despite his marked acidosis the urine remained alkaline. One 24 hour urine specimen contained 134 mEq. of sodium and 194 mEq. of potassium. He excreted 2,000 to 2,500 c.c. urine per day.

Diarrhea and anorexia continued after admission, and on the third hospital day hypotension (80/40 mm. of Hg) developed. He was thought to have adrenal cortical insufficiency secondary to amyloid involvement. He received cortisone thereafter, in doses varying from 25 to 150 mg. per day, and improved. In November, 1953, by which time cortisone had been reduced to 25 mg. per day, a minor surgical procedure (skin biopsy) was performed. Following this he developed a pneumococcal septicemia and went into shock (blood pressure, 40/0 mm. of Hg). He was treated with large doses of penicillin, 60 c.c. of aqueous adrenal extract, 20 mg. of DOCA, and 200 mg. of cortisone. His blood pressure rose to 115/70 mm. of Hg, and after 19 hours of anuria he again produced urine.

In early January, 1954, massive gastrointestinal hemorrhage occurred and the patient died.

Postmortem examination revealed extensive amyloid involvement of kidney, adrenal and liver, with lesser involvement of lymph nodes and spleen. There was focal deposition of amyloid in the arterioles of pancreas, prostate, and gastrointestinal tract. The villi of the small bowel contained amyloid. The gastrointestinal tract was filled with blood. Hodgkin's disease was not found.

Comment: This case showed evidence of renal, adrenal, gastrointestinal and vascular involvement with amyloid. The underlying disease had been present nine years. The patient had received a large total dose of mustard. At necropsy there was no evidence of Hodgkin's disease, despite earlier biopsy diagnosis and repeated satisfactory responses to nitrogen mustard and x-ray therapy. In the absence of significant Hodgkin's disease, at any rate, the renal, adrenal, gastrointestinal and hemorrhagic manifestations can be attributed to amyloidosis only.

Case 2. Renal failure. In April, 1945, a 29 year old white male was paralyzed below D-10. He developed osteomyelitis of the right hip with a draining sinus. In November, 1950, liver enlargement was first noted. Prior to 1950 the urine had been albumin-free, concentrated well, and was usually acid. By mid-1950 the urine failed to concentrate beyond 1.010, contained albumin, and was persistently alkaline. Amyloidosis was suspected, and Congo red was 85% retained by the tissue. In November, 1953, the patient developed fever, nausea, vomiting, pericardial friction rub, and edema of the lower extremities. A generalized convulsion occurred. He had a positive Chvostek's sign, nonprotein nitrogen was 55 mg.%; CO_2 combining power, 4.7 m. mol/L.; chloride, 100 mEq./L.; sodium, 134 mEq./L.; potassium, 4.3 mEq./L.; calcium, 6.4 mg.%; inorganic phosphorus, 9.9 mg.%. The white blood cell count was 24,500, and a beta-hemolytic streptococcus was cultured from the blood. Over a 48 hour period, in addition to antibiotics and calcium gluconate, the patient received 178 mEq. of sodium lactate (calculated to raise the CO_2 combining power 10 m. mol/L.). However, several determinations failed to show significant change in the CO_2 combining power. The urine remained alkaline. The patient developed respiratory irregularity, became comatose, and died during a convulsion.

Postmortem examination revealed extensive amyloidosis of the kidney, with tubular atrophy, and hydropic nephropathy of the remaining tubular cells.

Comment: Renal failure related to amyloidosis and septicemia was the cause of death. There was insufficient evidence clinically or at autopsy to suggest that adrenal cortical insufficiency played a rôle. The nature of the renal failure and associated electrolyte disturbance is essentially a duplicate of case 1.

Case 3. Renal and adrenal cortical failure. In April, 1945, a 23 year old white male was paralyzed below D-3. He developed a chronic draining sinus over the right greater trochanter. The urine was persistently alkaline, contained albumin, and did not concentrate beyond 1.010. Congo red was 66% removed from the serum. Because of the demonstrated focus of chronic infection with evidence of secondary amyloidosis, the sinus tract and the head and neck of the right femur were excised. Preoperatively the nonprotein nitrogen was 53 mg.%; CO_2 combining power, 24 m. mol/L.; and chloride, 94 mEq./L. On the eighth hospital day, spasm of the lower abdominal muscles occurred. At that time the patient was hypotensive (55/40 mm. of Hg) and had a positive Chvostek's sign. The nonprotein nitrogen was 52 mg.%; CO_2 combining power, 8.5 m. mol/L.; chloride, 107 mEq./L. Inorganic phosphorus was 12 mg.%; creatinine, 13 mg.%. Calcium was 6.0 mg.%. The urine contained 7.5 gm. albumin (24 hour specimen) and was alkaline. The patient was considered to have amyloid involvement of the kidneys and adrenals, and was treated with 100 mg. of cortisone daily, intravenous saline and calcium gluconate. He responded with a rise of blood pressure 110/80 mm. of Hg. The nonprotein nitrogen stabilized in the range of 70 to 80 mg.%. The CO_2 combining power remained between 9 and 11 m. mol/L. An attempt at dialysis on the artificial kidney had to be interrupted because of blood clotting. In April, 1954, three days after omission of cortisone, the patient was found to be hypotensive and semi-comatose. The nonprotein nitrogen was 69 mg.%; CO_2 combining power, 12 m. mol/L.; chloride, 79 mEq./L.; sodium, 122 mEq./L.; potassium, 3.5 mEq./L.; calcium, 6.5 mg.%; inorganic phosphorus, 12 mg.%. He was treated with 30 c.c. of aqueous adrenal extract initially, and over the next 72 hours received 920 mEq. of sodium, 140 mEq. of potassium, and 1,060 mEq. of chloride. He was also given 200 mg. of cortisone and 5 mg. of DOCA daily. He responded initially, with chlorides rising to 104 mEq./L., sodium to 136 mEq./L. and blood pressure to 100/60 mm. of Hg. However, about two weeks later he developed an otitis media and bronchopneumonia, became increasingly dyspneic and cyanotic, and died on May 24, 1954.

At necropsy the liver, kidney, adrenal cortex and spleen were extensively involved with amyloid, with lesser involvement of the arterioles of the pancreas, gastrointestinal tract, prostate and testes. There was amyloid deposition in the villi of the ileum. There was a recent thrombosis of the right adrenal vein with associated cortical necrosis (weight, less than 1 gm.).

Comment: In this patient, renal and adrenal cortical failure occurred postoperatively. Adrenal insufficiency was initially controlled, but renal insufficiency persisted, with manifestations indistinguishable from those of the preceding cases. The terminal episode of adrenal cortical insufficiency was precipitated by infection, cortisone withdrawal and adrenal cortical necrosis.

Case 4. Renal and probable adrenal cortical failure. On the basis of nystagmus, dorsal column and pyramidal tract signs in a 51 year old white male, the diagnosis of multiple sclerosis was made in 1948. Nine months later he developed ankle edema, nocturia, a greatly enlarged liver, clubbing and plethora. The hematocrit was 62%.

The urine failed to concentrate beyond 1.011 and contained 4 plus albumin. Nonprotein nitrogen was 61 mg.%. Total cholesterol was 357 mg.%. Bromsulphalein was 32% retained after 45 minutes. The alkaline phosphatase was 40.8 Bodansky units. Liver biopsy showed amyloid. The edema increased, ascites appeared and diarrhea developed. Serum albumin fell to 1.6 gm.%. Cholesterol rose to 604 mg.%. The nonprotein nitrogen rose to 147 mg.%, calcium fell to 7.6 mg.%, CO_2 combining power to 13.5 m. mol/L. In early December, 1949, a low blood pressure (80/50 mm. of Hg) was noted. In the succeeding two weeks the patient became weaker, and on December 17, 1949, he died.

Necropsy showed marked deposition of atypically staining amyloid in the renal glomeruli, and extensive tubular necrosis with hyaline droplet deposition in much of the remaining tubular epithelium. The adrenals were extensively infiltrated with amyloid. The pancreas was involved to a lesser degree. The heart, tongue, bone marrow and muscles were free of amyloid.

Comment: This case, by virtue of the distribution of the amyloid, would fall into the secondary category and be related to multiple sclerosis. To our knowledge, such relationship has not been reported. The amyloid stained atypically suggesting the primary disease. This emphasizes the difficulty of attempting classification. The terminal hypotension, nausea, diarrhea and weakness suggest adrenal cortical hypofunction, but this was not substantiated by laboratory test or by therapeutic trial.

Case 5. Renal and adrenal cortical failure. A 57 year old white male was hospitalized in April, 1947, because of rheumatoid arthritis of 25 years' duration. In November, 1947, a Congo red test showed 80% retention, though there was no clinical evidence to suggest amyloid disease. In November, 1949, albuminuria was first noted. The urine did not then concentrate beyond 1.010, was alkaline, and thereafter remained so. Nonprotein nitrogen was 80 mg.%. In November, 1950, a cataract extraction was done. Following the procedure the patient became drowsy and distended, had repeated vomiting, and became hypotensive and oliguric. The nonprotein nitrogen rose to 160 mg.%; CO_2 combining power, 10 m. mol/L. The patient developed pulmonary edema and, terminally, an *Aerobacter aerogenes* bacteremia. He died on his tenth postoperative day.

At autopsy there was pulmonary edema and evidence of septicemia. There was no evidence of pyelonephritis. The adrenals and, to a lesser extent, kidneys, liver and spleen, were involved with amyloid.

Comment: This case was terminated by renal failure, probably adrenal cortical failure, and septicemia, following a relatively minor surgical procedure. Renal failure was not due to pyelonephritis but was probably related to hypotension, septicemia and amyloid involvement. Considering the degree of amyloid involvement, adrenal cortical failure could well have been a factor in the postoperative course. However, studies were inadequate to substantiate this.

Case 6. Adrenal failure. In 1943 a 23 year old white male developed rheumatoid arthritis. In June, 1950, he received ACTH, with temporary improvement. In November, 1950, albuminuria was first noted. The alkaline phosphatase was elevated to 18 Bodansky units. Amyloid disease was suspected. Congo red was 95% removed from the serum. In January, 1951, cortisone was started and continued

thereafter in doses varying between 50 and 150 mg. per day. The patient was at this time excreting large amounts of albumin (10 to 12 gm. per day), and the serum albumin had fallen to 0.8 gm.%. Serum globulin was elevated (5.4 gm.%). Cephalin flocculation was 4 plus; bromsulphalein was 40% retained after 45 minutes; cholesterol, 509 mg.%; alkaline phosphatase, 14 Bodansky units. In August, 1951, the liver first became palpable. Despite evidence of continuing renal disease, the urine concentrated well (1.020), and nonprotein nitrogen was not elevated. By April, 1952, there was massive hepatomegaly (iliac crest), moon face, girdle obesity, striae, hypertension and glycosuria. In August, 1952, petechiae appeared over the abdomen and upper extremities, though there was no abnormality of bleeding or clotting mechanisms. On October 1, 1952, during his twentieth month of cortisone therapy, the patient developed an exquisitely tender right knee, became febrile, went into shock and died. Both a culture of joint fluid aspirated at onset of symptoms and a blood culture taken just before death grew a pneumococcus Type 23.

At necropsy there was an acute, purulent arthritis of the right knee. There was extensive amyloid involvement of the liver and kidney, and lesser involvement of the spleen and adrenals. The gastric mucosa was minimally infiltrated. The liver was massive and was stained with Congo red (given four days prior to death). The hepatic parenchyma was 90% replaced by amyloid. The adrenals were very small (not more than 1 mm. of cortex), and had minimal amyloid involvement. The kidneys were large and extensively infiltrated with amyloid. There was no evidence of pneumonia.

Comment: Twenty months of cortisone therapy suppressed adrenal cortical function and produced the adrenal atrophy observed pathologically. In the presence of a cortisone-concealed pneumococcal septicemia, additional endogenous cortisone could not be produced, supplementary cortisone was not given, and the patient died, essentially of acute adrenal cortical insufficiency.

Case 7. Hemorrhage (vascular failure). In April, 1945, a 19 year old white male developed urethritis, arthritis and conjunctivitis, and the diagnosis of Reiter's syndrome was made. He remained symptomatic. In August, 1951, ACTH was started and, save for brief trial periods with cortisone and compound F, he remained on either intravenous or intramuscular ACTH for the next three and a half years. The picture of Cushing's disease developed, with obesity, hypertension and osteoporosis. In May, 1952, Congo red was found to be totally retained by the tissues. Except for 45% retention of bromsulphalein after 45 minutes, all liver function studies were normal. In late 1952 the liver became enlarged and albuminuria appeared (2.0 gm. in 24 hours). In January, 1955, a large, spontaneous hemothorax occurred. He then began to lose small amounts of blood through the gastrointestinal tract, and bleeding was noted at the sites of parenteral injection. Investigation of bleeding and clotting mechanisms revealed no abnormality.* Hemorrhage continued and he died.

At necropsy there was evidence of Cushing's disease (iatrogenic), and arthritis. There were 3,000 c.c. of blood in the left chest with a large hematoma at the left hilum. The site of intrathoracic hemorrhage could not be found. The liver was massive and the hepatic parenchyma was considerably replaced with amyloid. The adrenals were huge (28 and 38 gm. respectively), and showed slight amyloid infiltration. The kidneys showed a moderate glomerular involvement and extensive tubular

* The following were done and found normal: bleeding time, clotting time, platelet count, prothrombin time, prothrombin consumption, recalcification time, clot retraction, and fibrinogen level. There was no circulating fibrinolysin.

necrosis. The stomach mucosa was atrophic and largely replaced by amyloid. A focal myocarditis was present, and there was hemorrhage into the papillary muscles, but no amyloid was present in the heart. There were amyloid deposits in the arterioles of the pancreas, and gastrointestinal tract.

Comment: This patient died of exsanguination. With normal clotting mechanism, and evidence of arteriolar involvement with amyloid, it is probable that death was related to hemorrhage from a disrupted medium or small posterior mediastinal vessel, despite the failure to identify the specific vessel at necropsy.

Case 8. Liver failure and hemorrhage. A 57 year old white male physician developed albuminuria in 1952 and was found to have macroglossia, hepatomegaly and a right interlobar effusion. Hemoglobin was 16 gm.%; the urine was acid and concentrated to 1.015, and contained 10 gm. of albumin in a 24 hour specimen. The serum albumin was 2.6 gm.%. Alkaline phosphatase was 9.9 Bodansky units. Bromsulphalein was 20% retained after 45 minutes. Serum cholesterol was 558 mg.%. Liver and tongue biopsies both revealed amyloid disease. By February, 1954, the liver edge was at the level of the iliac crest, and marked peripheral edema had developed. The urine had become and remained persistently alkaline. Nonprotein nitrogen had risen to 59 mg.%. In April, 1954, pain developed in both lower extremities, and a large ecchymosis appeared over the right thigh after minor trauma. Petechial lesions appeared on the thorax and upper extremities. Urinary 17-hydroxycorticoid excretion was measured before and after intravenous ACTH. There was good adrenal cortical response (3.37 mg. before and 32.58 mg. after ACTH). In May, 1954, jaundice appeared. In June, 1954, the patient developed pain in the right forearm and hand and lost his radial pulse. An ischemic, painful ulcer developed on the left leg, and no pulse could be felt below the femoral. Serum bilirubin gradually rose to 20.4 mg.%, and alkaline phosphatase to 41.5 Bodansky units. An electrocardiogram was abnormal, showing nondiagnostic ST-T wave changes. In July, 1954, gastrointestinal bleeding developed, the nonprotein nitrogen rose, the patient became acidotic, showed potassium retention, remained deeply jaundiced, became oliguric and comatose, and then died.

At autopsy there were purpuric lesions over the thorax and ischemic necrosis of the lower two thirds of the right leg and foot. There were ascites and hydrothorax. The heart was enlarged, dilated and heavy, and contained amyloid. The liver parenchyma was 90% replaced by amyloid. The spleen, kidneys and both adrenals were also extensively involved. The esophagus and small bowel contained amyloid, and there was blood in the gastrointestinal tract. There was minimal involvement of the bone marrow, prostate and alveolar septa. There was extensive vascular involvement, particularly of the smaller arterioles. Both the aorta and the pulmonary artery showed some involvement of the media. The smaller vessels of the heart, pancreas and gastrointestinal tract contained amyloid. The skin and skeletal muscles did not contain amyloid.

Comment: This case represents primary amyloidosis by virtue of the widespread involvement (including the heart and the tongue), and the absence of pathologic evidence for predisposing disease. Included among the involved organs were the liver, spleen, adrenal and kidney. There was evidence of renal and hepatic failure. This is unusual in the primary group, and again emphasizes the difficulty of classification.

Case 9. Heart failure. In late 1946 a 51 year old white male developed hepatomegaly and ascites. There was 35% bromsulphalein retention after 30 minutes. His heart was enlarged, and the electrocardiogram showed evidence of an old anterior myocardial infarction. Liver biopsy showed amyloid infiltration. By January, 1947, he had marked venous distention, a right pleural effusion, ascites, and edema to the iliac crests. The heart was enlarged to the anterior axillary line. The urine concentrated to 1.021 and contained 1 plus albumin. Nonprotein nitrogen was 34 mg.%. He did not respond to measures for congestive failure, gradually deteriorated, and died on March 21, 1947. Postmortem examination was not permitted.

Comment: Inasmuch as this case clinically represents cardiac and hepatic involvement without known predisposing disease, it must be classified as primary amyloidosis. It is conceivable that the myocardial infarct shown by the electrocardiogram could have been produced by amyloid involvement of the coronary arteries.

Amyloidosis in patients dying of underlying disease:

Case 10. In 1944 an 18 year old white male developed Hodgkin's disease. During the ensuing years he was treated repeatedly with nitrogen mustard, x-ray and TEM. In February, 1952 (eight years after onset), a left lower lobe consolidation and empyema developed. At thoracotomy, in July, 1952, a large empyema cavity was found. The diaphragm was partly destroyed, and the process had extended to involve the spleen. The left lower lobe of the lung, spleen, necrotic diaphragm, a portion of adherent stomach, tail of the pancreas, and tumor-infiltrated left lobe of the liver were removed. None of these tissues contained amyloid. In August, 1952, evidence of impaired renal function appeared. The urine did not concentrate beyond 1.012, contained albumin, and became and remained alkaline. The alkaline phosphatase was 30.5 Bodansky units. In December, 1952, the possibility of amyloid disease was considered, but Congo red was only 46% retained by the tissues. Over the next three months the temperature remained elevated, the left chest continued to drain purulent material, and the white count remained above 40,000. The patient's weight fell to 88 pounds, and he died in March, 1953, essentially of persistent sepsis and profound inanition.

Postmortem examination revealed extreme emaciation, a large left empyema cavity, and Hodgkin's involvement of lungs, liver, left adrenal, diaphragm and retroperitoneal lymph nodes. There was moderate amyloid infiltration of the kidneys and liver, right adrenal, stomach, pancreas and small arterioles.

Case 11. In 1942 a 50 year old white male developed a persistent cough. There was no evidence of pulmonary infection or malignancy. In 1943 left chest pain and hemoptysis occurred, and a diagnosis of carcinoma was made on the basis of a bronchoscopic biopsy of the left main stem bronchus. The lesion was deemed inoperable, and between 1943 and 1946 the patient received three courses of x-ray therapy. In April, 1947, the liver was found to be greatly enlarged. The urine concentrated to 1.025, contained 4 plus albumin and was alkaline. Nonprotein nitrogen was elevated. Bromsulphalein was 14% retained after one hour. Congo red was 67% retained by the tissues. Liver biopsy done through a peritoneoscope revealed minimal amyloid involvement. A second biopsy of the left main stem bronchus confirmed the original diagnosis. Increased pulmonary involvement with cavitation gradually developed. The cholesterol rose to 648 mg.%, and hypoalbuminemia became marked (0.7 gm.%). In January, 1948, the patient had a large hemoptysis and the sputum became positive for tuberculosis. Hemoptyses continued and in October, 1948, he died suddenly as a result of a massive pulmonary hemorrhage. Autopsy was not permitted.

Case 12. A 36 year old white male was hospitalized in January, 1948, because of cough and weight loss. He was febrile and had generalized lymphadenopathy and a slightly enlarged liver. There were multiple old fracture deformities of the extremities. One sputum was negative for acid-fast bacilli. Lymph node biopsy revealed no abnormality. X-rays and bone biopsy were consistent with the diagnosis of dyschondroplasia. A chest x-ray showed a pneumonia that slowly cleared with penicillin. An anemia of 8.0 gm. was unexplained. Four years later (1952) he developed massive hepatosplenomegaly. There was no adenopathy. Hemoglobin and albuminuria were present. Nonprotein nitrogen was 51 mg.%; 8.5% of bromsulphalein was retained after 45 minutes. Congo red dye was entirely retained by the tissues. The patient deteriorated rapidly. The nonprotein nitrogen rose to 171 mg.%, creatinine to 11.8 mg.%. The CO_2 combining power fell to 10 m. mol/L. During his last week of life he received 1 gm. of streptomycin daily. He died on March 17, 1952, following a convulsion.

Necropsy revealed miliary tuberculosis. There was a tuberculous pyelonephritis. There was moderate involvement of the liver, kidneys, adrenals and spleen with amyloid, but insufficient involvement of any organ to have caused death.

Comment: These last three patients died of their underlying disease and not of amyloidosis. In case 10, some idea of the time required to develop moderate amyloidosis can be adduced from the interval of time between examination of an uninvolved large multi-organ operative specimen and the postmortem examination (nine months). Hodgkin's disease existed for eight years without amyloidosis, but within a year of the establishment of an empyema, amyloidosis appeared. It seems probable, therefore, that the amyloid was related to the chronic suppuration and not to either the Hodgkin's disease or the therapy he received (nitrogen mustard and x-ray). In case 11 there was the unusual situation of a six year survival with a bronchogenic carcinoma treated by x-radiation only. By clinical evaluation his amyloid disease was extensive but was not responsible for death. Pulmonary fibrosis, cavitation, tuberculosis and carcinoma were all present terminally. Case 12 died of renal failure, but pathologically renal tuberculosis was the cause and not the moderate amyloid involvement.

Discussion

Twelve cases of amyloidosis have been presented. Three of these cases are considered to be primary amyloidosis. Of these one was not verified pathologically (case 9), and one may be construed to be amyloidosis secondary to multiple sclerosis (case 4), an association not previously reported. Only the remaining one (case 8) filled all the requirements for the diagnosis of primary amyloidosis. Classification therefore proved difficult in two of three cases.

The remaining nine are of the secondary form. Of these nine, three cases occurred in patients with arthritis. In two the arthritis was a progressive, disabling form of rheumatoid arthritis. The third had a similar form of arthritis, associated with Reiter's syndrome. Two patients with Hodgkin's disease developed amyloidosis. Both were patients who had

long survivals (eight and nine years). Amyloidosis occurred in two patients with traumatic paraplegia, both of whom had osteomyelitis and chronic draining sinuses. In the remaining two cases (of the nine with secondary form of the disease), tuberculosis played a rôle in one, and tuberculosis, pulmonary carcinoma and infection in the other.

Of the 12 cases, nine died of causes directly related to amyloid involvement of one or more organ systems. The remaining three died of their underlying disease in the presence of mild or moderate amyloid involvement. In these three, death was related to Hodgkin's disease and sepsis (case 10), miliary tuberculosis (case 11), and hemoptysis from combined pulmonary tuberculosis and carcinoma (case 12).

In all 12 cases amyloid disease was suspected ante mortem. In eight cases there was significant Congo red retention, in two there was a false-negative test, and in two the test was not done (table 1). One of the false-negatives (case 9) occurred in a patient with primary amyloidosis. Another case of primary amyloidosis showed 100% retention of the dye,

TABLE 1

Congo Red Retention

Case	% Dye Retained
1	90
2	85
3	66
4	100
5	80
6	100
7	100
8	— (Biopsy)
9	54 (Biopsy)
10	46
11	67
12	— (Biopsy)

emphasizing the variable affinity for Congo red in this form of the disease. The other false-negative (case 10) was obtained in a patient who must have had little amyloid at the time the test was done. A large multi-organ operative specimen contained no amyloid six months prior to the test. Three months after the test he died of his underlying disease, and at that time there was only minimal amyloid involvement.

Congo red tests were repeated in several of the patients. Usually this was not done within five or six months of the original test. In one patient, however, only 25% of Congo red was retained when the test was repeated three weeks after a previous positive (100% retention). This suggests that amyloid can be saturated with the dye for brief periods. One patient died four days after his last Congo red test. The amyloid tissue was still intensely stained at postmortem examination.

In only four of this series of 12 proved cases was more than 90% of Congo red retained. If this level of retention be required to make a positive diagnosis, there will be many false-negatives. The method of Congo red

testing suggested by Unger and associates involves serial determinations and construction of a disappearance curve. We have had insufficient experience with the method to verify its reliability, but it would seem a reasonable method to obviate the inaccuracies of the older method.

Pathologic material was available in all 12 cases. In two the material was obtained by biopsy. The remaining 10 had complete necropsies. Consistent pathologic findings were observed in all cases where amyloid was the cause of death. Involved viscera were greatly enlarged except in two instances. In one of these, adrenal cortical atrophy had been produced by protracted cortisone therapy, and in the second, adrenal cortical necrosis had resulted from adrenal vein thrombosis. The livers were two to three times normal size, the largest weighing 5,900 gm. (table 3). The kidneys were large, contained many totally amyloid effaced renal glomeruli, and showed hydropic degeneration of the tubular epithelium. The adrenal involvement was always maximal in the juxtamedullary region. The adrenal medulla was invariably spared. The livers were usually diffusely involved, with compression replacement of normal hepatic parenchyma. Maximal involvement was observed in the viscera (liver, spleen, kidney, adrenal). Diffuse involvement of arterioles of the gastrointestinal tract, pancreas and prostate also occurred. Involvement of gastric mucosa and villi of small bowel was seen. In only one of the autopsied cases was the heart involved.

Since amyloid is deposited in the arterial wall and perivascularly, continued accretion interposes a block to metabolic exchange and compromises the organ cell by pressure. Failure of specific organs and vascular complications produced the clinical pictures observed.

I. *Renal failure.* Amyloid is deposited in the glomerular capillary. Capillary permeability is altered and albuminuria results. This is the earliest manifestation of renal involvement. The albuminuria frequently becomes massive and leads to albuminemia and edema—the picture of amyloid nephrosis. As the disease progresses, whole glomeruli become nonfunctional. Glomerular insufficiency results in azotemia. Organic acids, and anions normally excreted, are retained, and acidosis of glomerular origin results. The tubular vascular supply is derived from postglomerular vessels; therefore, the involvement of the glomerular capillary deprives the tubule of adequate blood supply. The interposition of amyloid between capillary and cell further restricts metabolic activity of the tubular cell. The tubular cells show hydropic degeneration. Tubular insufficiency appears, manifested initially by polyuria and the failure to concentrate urine. As tubular insufficiency progresses, the cations Na^+ and K^+ may not be saved, NH_4^+ not produced and the urine not acidified. Thus, in the presence of acidosis of glomerular insufficiency, acidosis of tubular insufficiency is superimposed. The chemistry of these alterations is worth considering briefly, since it explains the pathophysiology of the chemical deviation observed in the serum and urine of five of this group of patients.

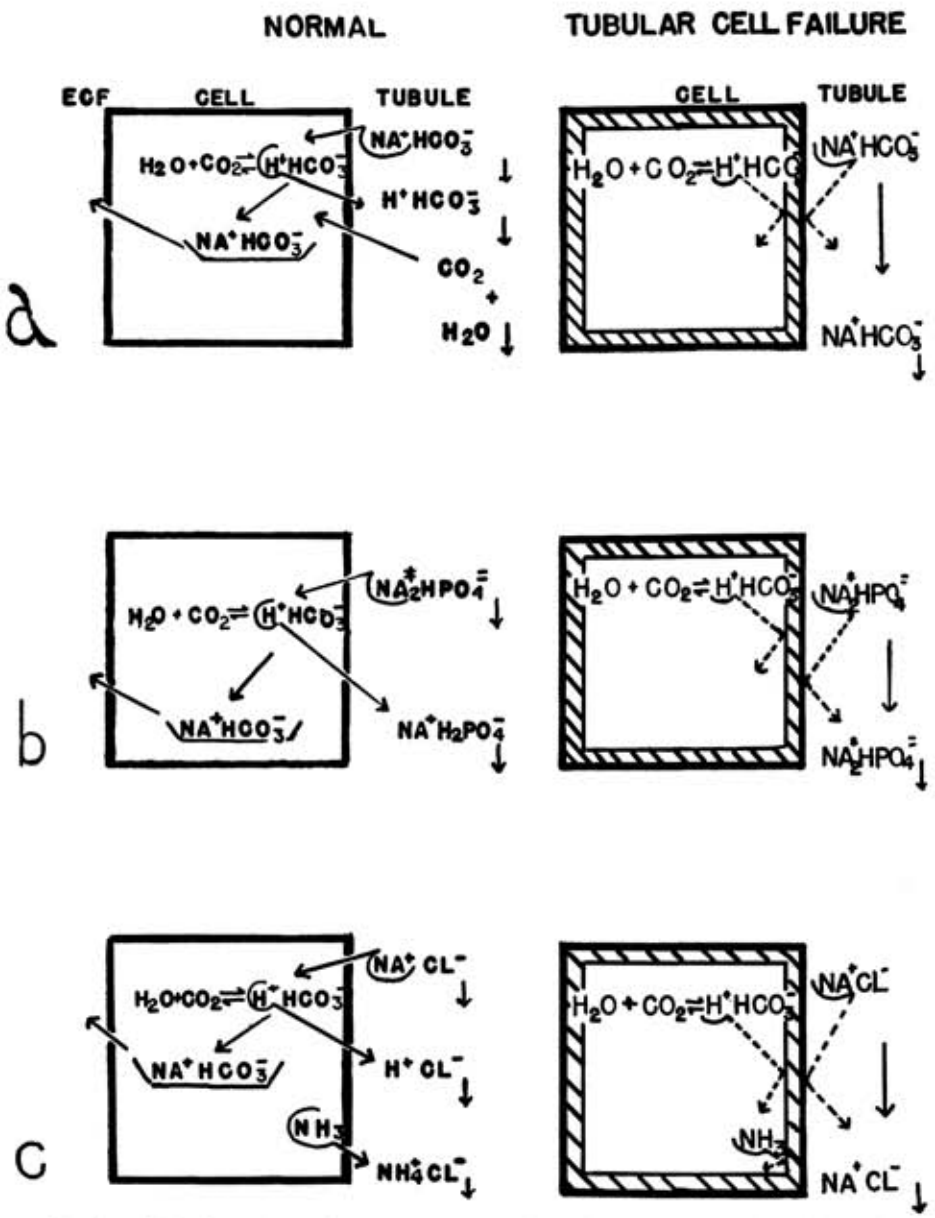

FIG. 1. This is a schematic representation of function of the renal tubular cell in conservation of electrolytes. The diseased tubular cell is compared with the normal. For details see text.

The kidney normally protects and regulates the cation consistency of extracellular fluid by (1) reabsorbing sodium bicarbonate, (2) acidifying the urinary buffer salts, and (3) excreting ammonium ion rather than sodium ion (figure 1).

1. Carbonic anhydrase in the tubular cell catalyzes the reaction $CO_2 + H_2O \leftrightharpoons H^+ + HCO_3^-$, providing H^+ for exchange for Na^+ in the tubule. Na^+ is absorbed, and is returned to the extracellular fluid as bicarbonate. H^+ combines with HCO_3^- in the tubule and becomes H_2O and CO_2. CO_2 readily diffuses into the cell, where, in combination with H_2O, H^+ HCO_3^-

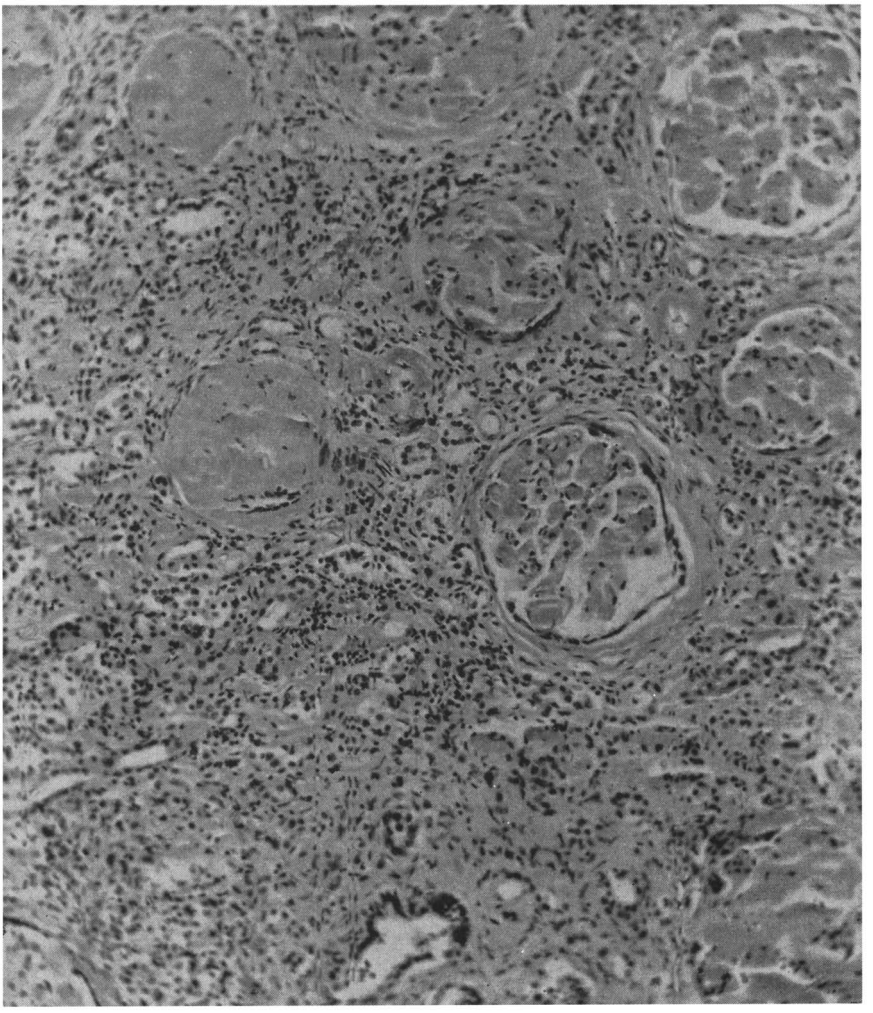

FIG. 2A. Representative section of amyloid involved kidney.

is reformed (the initial step repeated) and another hydrogen ion is made available for excretion (figure 1A).

2. In a similar fashion, H^+ is exchanged for Na^+, acidifying the buffer salt Na_2HPO_4 (figure 1B).

3. NH_3 is produced in the kidney, diffuses into the tubule, and there is

converted to NH_4^+, which displace Na^+ as the excretory cation. By this mechanism, not only is a cation saved but a strong acid (HCl) is also removed from the urine. Such an acid would quickly reduce the urinary pH to a point where further H^+ exchange would cease (figure 1C).

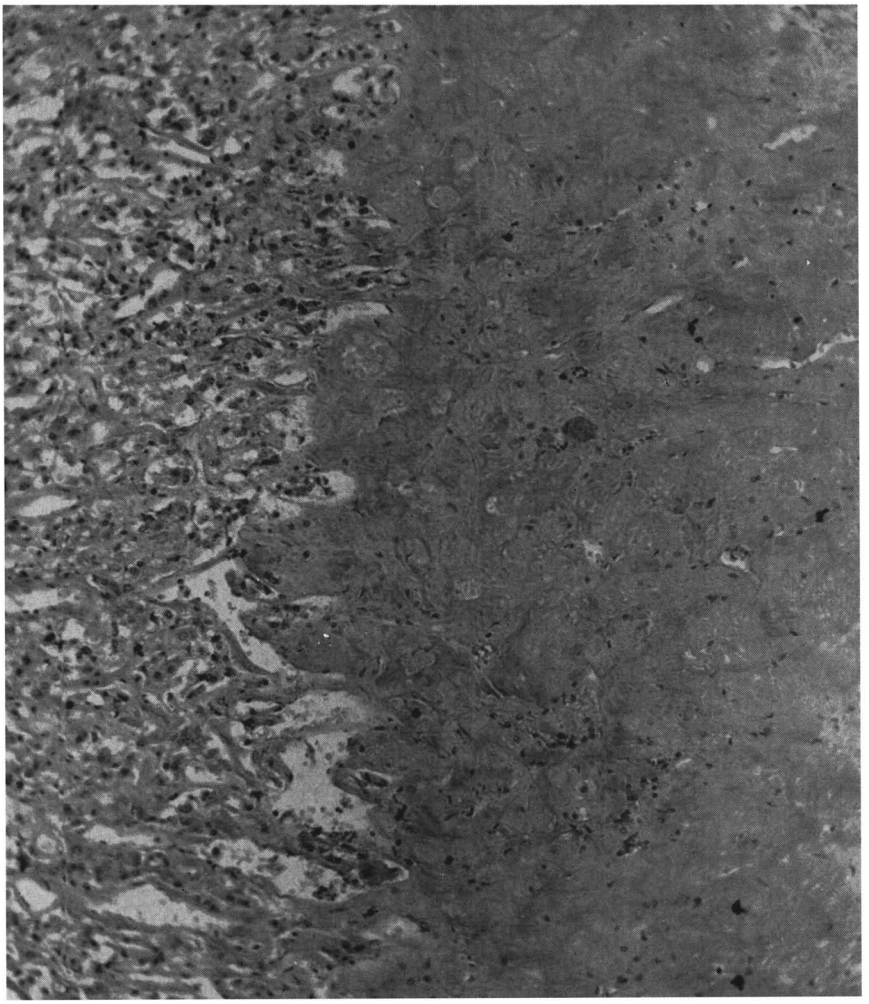

FIG. 2B. Representative section of amyloid involved adrenal.

These mechanisms are dependent upon the integrity of the reaction $CO_2 + H_2O \leftrightharpoons H^+ HCO_3^-$. In order that this reaction proceed rapidly enough to be functionally significant, carbonic anhydrase is essential. When carbonic anhydrase is inhibited (Diamox administration), or when renal tubular cell failure is present, the following occur: fewer H^+ ions are available, Na^+ is not spared, bicarbonate cannot be saved, NH_4^+ is not produced,

and an obligatory cation (Na^+) diuresis occurs (figure 1). The urine becomes alkaline and an acidosis of renal tubular origin is produced.

All 12 cases showed evidence of renal amyloidosis (table 2). Albuminuria was present in all, and in nine was massive. Eight showed inability to concentrate urine. Six patients showed evidence of renal failure, with

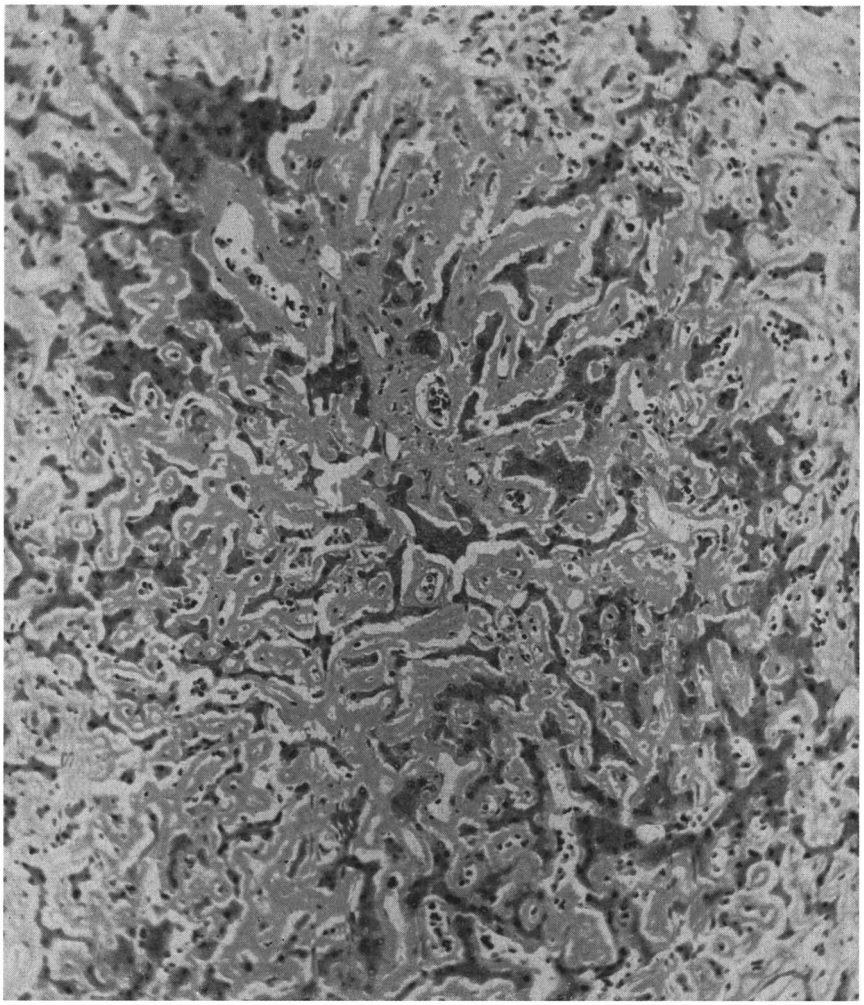

FIG. 2C. Representative section of amyloid involved liver. Note the infiltrative replacement of normal parenchyma, strikingly exemplified in the liver.

fixed specific gravity, albuminuria, elevated nonprotein nitrogen and lowered serum bicarbonate. In five of these (cases 1 to 5) there was no renal disease save amyloidosis. The sixth (case 12) had renal failure secondary to tuberculous pyelonephritis. In all cases serological test for syphilis was negative.

In the five cases of renal failure due to amyloidosis (table 2, cases 1–5), alkaline urines were present in the face of severe acidosis (CO_2 4.7 to 13.5 m. mol/L.). Serum chloride in these cases was either normal or slightly increased. Sodium and potassium levels were normal, except in two individuals who developed adrenal cortical insufficiency. The discrepancy

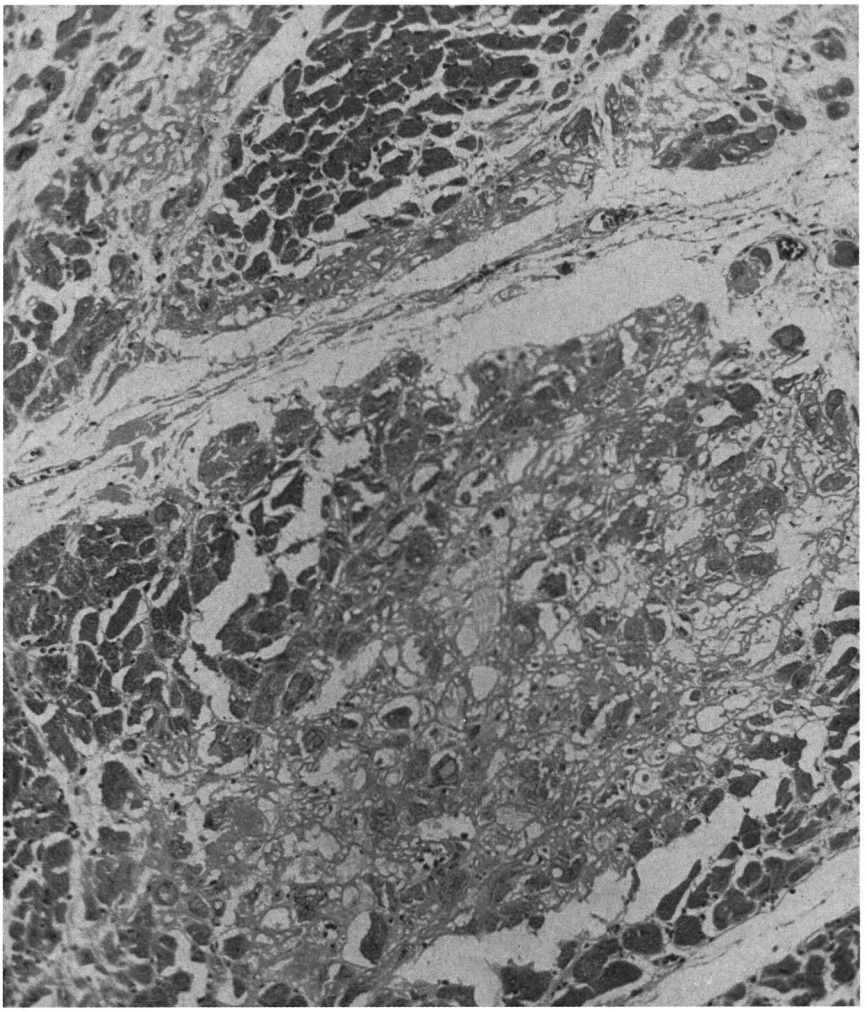

FIG. 2D. Representative section of amyloid involved heart.

between measured cation and anion is explained by increased level of inorganic phosphorus (9 to 12 mg.%), retention of organic acid radicals, and slightly elevated chloride. The significance of these findings was not originally appreciated, and in one patient only (case 1) were urinary electrolytes measured. On two determinations 134 and 120 mEq. of Na^+ and

194 and 175 mEq. of K^+ were excreted in 24 hour periods. As a result of these findings, a recently observed living case with similar urinary findings, elevated nonprotein nitrogen and 100% Congo red retention was more extensively studied. Repeated determinations showed daily urinary excretion of 200 to 300 mEq. of Na^+ and 50 to 70 mEq. of K^+. We feel that these observations substantiate the occurrence of renal tubular acidosis, and suggest that such is a fairly frequent manifestation of amyloid-induced renal failure.

II. *Adrenal cortical failure.* Adrenal cortical hypofunction has been reported rarely in amyloidosis.[8, 33] Stemmerman reported no incidence in a series of 468 cases of amyloidosis,[48] yet O'Donnell[36] lists amyloid as the third most common cause of Addison's disease. Many reports of amyloidosis are in pathology series, which do not indicate whether amyloid was the cause of death or merely an associated finding. If the cause of death

TABLE 2
Manifestations of Renal Disease

Case	S. G.	Albumin Gm./24 Hrs.	Reaction	NPN	CO_2
1	1.012	9.7 gm.	Alkaline	80–100	5
2	1.010	(4+)	Alkaline	55–75	4.7
3	1.010	7.5	Alkaline	70–80	8.5
4	1.011	8.0	Alkaline	61	13.5
5	1.010	(4+)	Alkaline	60–80	10.
6	1.020	10.	Acid	30	Normal
7	1.018	(2+)	Acid	30	Normal
8	1.010	10.	Alkaline	30	Normal
9	1.020	(1+)	Acid	30	Normal
10	1.012	(2+)	Alkaline	20	Normal
11	1.025	(4+)	Alkaline	30	Normal
12	1.011	(4+)	Acid	171	10

is the underlying disease, it is understandable that the associated amyloidosis may not have progressed sufficiently to cause organ failure. The adrenals in this series, like other amyloid-involved organs, were enlarged in all cases except in the instances (case 3) where necrosis had resulted from adrenal vein thrombosis, and (case 6) where cortisone-induced atrophy had occurred. None of the cases escaped involvement of the adrenals, but only two showed good clinical evidence of adrenal cortical insufficiency. In none of the cases was the adrenal medulla involved. The cortex was variably involved—always, however, with the juxtamedullary layers most heavily infiltrated. We have no explanation of why this distribution should exist. It is interesting to speculate that the secretory products of an organ might determine its affinity to amyloid.

To produce hypofunction of the adrenal cortex, almost complete replacement is required. This is demonstrated in case 8, who had an excellent

response to an ACTH test despite advanced amyloid involvement. There can be little doubt that cases 1 and 3 had adrenal cortical insufficiency. Both responded clinically to cortisone therapy, and both experienced addisonian crises in association with cortisone withdrawal. Adrenal cortical failure is also offered as an explanation for the terminal events in cases 4 and 5. In case 6 death was due to acute adrenal cortical insufficiency, which was related not to amyloidosis but rather to an unrecognized septicemia in the presence of cortisone suppression of the adrenal cortex. The incidence of adrenal cortical insufficiency is probably higher than the literature indicates. The availability of more accurate methods of measuring adrenal cortical function may make possible earlier recognition of adrenal cortical involvement in amyloidosis.

III. *Liver failure.* Liver involvement is almost universal in secondary amyloidosis, and it occurs in 30 to 40% of cases of primary amyloidosis.

TABLE 3
Manifestations of Hepatic Involvement

Case	BSP (% retention) after 45 min.	Cholesterol (Mg.%)	Alk. P'tase (Bodansky U.)	Serum Bilirubin (direct/indirect)	Alb./glob. gm.%	C. Floc. (Degree)	Thymol Turbidity (Units)	P. Time (%)	Liver Wt. (gm.)	Est. Amyloid Involvement (%)
1	4.9	179	14.2	0.2/0.4	2.4/3.3	0	2.0	63	4,000	90
2	10.0	—	3.9	0.2/0.2	1.8/3.6	0	1.0	—	2,850	80
3	—	—	—	—	—	—	—	—	—	—
4	32.0	604	45.0	0.2/0.2	1.3/4.7	0	0.6	100	3,350	75
5	8.8	—	1.6	0.2/0.2	4.2/2.1	—	—	—	2,150	50
6	40.0	740	25.0	0.2/0.4	0.8/5.4	4+	10.0	43	5,900	90
7	54.0	—	7.0	0.2/0.4	4.9/3.2	0	1.0	100	4,000	75
8	22.0	600	41.0	20.4 (total)	2.6/2.5	0	—	100	3,800	90
9	35.0	225	—	—	3.3/1.8	0	—	—	—	—
10	—	—	30.0	—	1.5/1.8	0	1.0	—	1,420	50
11	14.0	600	6.1	0.2/0.2	3.3/1.8	0	1.0	—	—	—
12	8.5	153	12.6	0.2/0.2	4.1/3.2	0	1.6	50	3,800	50

Only rare cases of jaundice have been reported;[34, 45, 60] most reports have dealt with other manifestations of amyloid-induced hepatic dysfunction.[51]

Eight of nine livers whose weights were recorded were enlarged; many were massive, with a weight of 5,900 gm. recorded in one instance. Amyloid accounted for 50 to 90% of the recorded weight (table 3). By virtue of the distribution of hepatic amyloid, it could be anticipated that a picture of intrahepatic block would be observed and that, if the process became sufficiently extensive, parenchymal failure could be produced. It was surprising in the present series to observe the extreme degrees of bromsulphalein retention, elevation of alkaline phosphatase, and cholesterol in association with normal serum bilirubins (table 3). The degree of impairment of excretory function was almost invariably associated with lack of evidence for other hepatic dysfunction.

Bromsulphalein retention was greater than 5% after 45 minutes in nine

of the 10 cases so studied. In four the retention was minimal (8.5%, 8.8%, 10% and 14%), but in the remaining seven it was elevated from 22% to 54%. Alkaline phosphatase was elevated in eight of the 10 cases. Extremely high elevations were noted in four cases (45, 25, 41 and 30 Bodansky units). The cholesterol level was greater than 500 mg.% in four of seven cases. Serum bilirubin was normal except in one patient (case 8). In this instance jaundice was present preterminally (bilirubin, 20 mg.%). Hypoalbuminemia was present in nine of 11 cases. It seems probable that this can be better correlated with the universally present massive albuminuria than with hepatic dysfunction. The cephalin flocculation and thymol turbidity were significantly altered in only one case.

Except for the preservation of a normal serum bilirubin, the chemistry of the hepatic alteration produced by amyloid mimics that of biliary obstruction. Other intrahepatic disease, such as metastatic carcinoma and hepatoma, may also produce a fragmentary picture of obstruction, with elevation of the alkaline phosphatase as the most characteristic abnormality.

IV. *Heart failure.* Heart failure is a product of replacement of normal muscle by amyloid. Decreased contractility of the organ results in intractable congestive failure. Cardiac failure in this disease has been mistaken for constrictive pericarditis. This is not unreasonable, since amyloid, in essence, must produce restrictive involvement of the myocardium. There are no identifying characteristics of amyloid heart disease other than its refractility to therapy. The electrocardiogram usually shows nothing more than nonspecific T wave changes. Suspicion of the true nature of the heart disease must come from evidence of additional organ involvement. Amyloid heart disease was undoubtedly the cause of death in case 9, and may well have been the cause of the electrocardiographic changes suggesting infarction (autopsy not allowed). In case 8 there was amyloid heart disease, but death was due to amyloid involvement of other organs.

V. *Peripheral vascular failure.* When amyloid infiltrates the media of smaller vessels, the elastica is replaced, the vessel is weakened, and hemorrhage and thrombosis may occur. Case 7 terminated of exsanguination purely as a result of amyloid vascular involvement. Three cases had gastrointestinal bleeding that led to death, two had arterial occlusion, which, in one, terminated in ischemic necrosis of an extremity. In none of the cases who bled was there evidence of impairment of the clotting mechanism.

VI. *Gastrointestinal tract involvement.* The gastrointestinal tract was intrinsically involved in cases 1, 6, 7, 8 and 10, but all cases showed some degree of involvement of the submucosal vessels. In the five instances of intrinsic involvement, the usual site of deposition was in the mucosa of the stomach and the villi of the small bowel. Diarrhea occurred in two cases. In three cases of extensive amyloidosis (cases 1, 7 and 8), gastrointestinal hemorrhage resulted in death. Steatorrhea and malabsorption (impaired oral glucose tolerance test) have been reported in amyloidosis.[52]

VII. *Blood picture.* Most patients showed anemia related to their underlying disease. However, in two instances (both cases of primary amyloidosis) a high hemoglobin and hematocrit were observed. Amyloid involvement of the bone marrow was demonstrated in one of these cases. The possibility is suggested that amyloid involvement of the bone marrow can produce anoxia and lead to polycythemia. Polycythemia in primary amyloidosis with marrow involvement has been previously reported.[59]

VIII. *Blood pressure.* Despite the frequency of significant renal disease, hypertension was not observed. Only two patients displayed moderate elevation of the blood pressure. Both of these patients had been on ACTH or cortisone in excess of 20 months and showed obesity, striae, moon face, osteoporosis and, in one case, glycosuria. Neither showed renal failure; both concentrated urine well and had normal nonprotein nitrogens. Their blood pressure elevation was believed to be related to their ACTH and cortisone therapy. Elevated blood pressure was so conspicuously absent otherwise that we believe its presence in renal amyloidosis is fortuitous.

IX. *Miscellaneous.* Patients with amyloid disease may be unusually susceptible to infection. Septicemia was recorded in four patients (two pneumococcus, one beta hemolytic streptococcus, one *Aerobacter aerogenes*). An additional patient had metastatic abscesses at post mortem.

One patient who had biopsy-verified Hodgkin's disease, and who had repeated satisfactory responses to nitrogen mustard, TEM, and x-ray, died after nine years with extensive secondary amyloidosis. At necropsy there was no evidence of Hodgkin's disease. The paucity or absence of Hodgkin's disease under these circumstances has been previously observed.[5] Since it is possible to produce amyloidosis with nitrogen mustard experimentally, these observations suggest that it may be the therapy, and not the Hodgkin's disease, that is responsible for the amyloidosis.

Treatment

There is no known satisfactory therapy for either primary or secondary amyloidosis. Crude liver extract and ACTH and cortisone have been recommended.[19, 14] Some of this series of patients were treated with crude liver preparations, without discernible benefit. Others either developed amyloidosis while on ACTH or cortisone, or received such therapy without improvement. Treatment for the large part was directed at the underlying disease or at the manifestations of amyloidosis. In a few instances, recognition of a treatable complication (i.e., adrenal cortical insufficiency) prolonged life, but in all instances the amyloid disease progressed to termination without measurable remission.

Summary

The nature, incidence, pathology, pathogenesis and clinical manifestations of amyloidosis are discussed.

Twelve cases of amyloidosis are presented. Of these, three are considered to be of the primary and nine of the secondary variety. These three cases of primary amyloid disease bring to about 100 the cases reported in the literature to date. The nine cases of secondary amyloidosis are related to arthritis in three instances, to Hodgkin's disease in two, to infections occurring in traumatic paraplegia in two, and to tuberculosis and carcinoma in one each. Nine of the cases died of amyloidosis. Three died of their underlying disease. Pathologic verification of the disease was made in all 12; in 10 complete necropsy was done. The Congo red test established the diagnosis in eight of 10 cases.

All had evidence of renal disease, and five cases had renal tubular acidosis and died of renal insufficiency.

Two cases of adrenal cortical insufficiency due to amyloid disease are reported.

Hepatic function was altered in all, and jaundice was present in one instance. The chemistry of the hepatic disturbance closely resembled that of obstructive hepatic disease.

Involvement of the vascular tree led to thrombotic episodes in two cases and to massive hemorrhage in three. Gastrointestinal hemorrhage and diarrhea were observed as evidence of intestinal amyloidosis.

Comment is made on the frequency of septicemia, the absence of hypertension, and the nature of myocardial involvement in this disease. A suggestive relationship is noted between the appearance of amyloidosis and the use of nitrogen mustard in Hodgkin's disease.

Acknowledgment

The invaluable assistance and advice of J. R. Browning, M.D., D. S. Moses, M.D., and Ira A. Gore, M.D., and the coöperation of the Paraplegia and Pathology Services in the preparation of this manuscript are gratefully acknowledged.

Summario in Interlingua

Amyloidosis es un morbo generalisate que es characterisate per le deposition de un complexo de proteina e polysaccharido in le vasos sanguinee e in le tessutos conjunctive perivascular. In iste sitos, disfallimento de organos specific resulta in parte ab necrosis pressori de cellulas e in parte ab obstruction de normal activitates metabolic. Iste concepto pathophysiologic explica le diversitate del manifestationes de amyloidosis. Le litteratura reporta circa 100 casos de amyloidosis sin morbo antecedente (i.e. amyloidosis primari). Circa 50 pro cento de iste casos se terminava in disfallimento cardiac. Amyloidosis secundari occurre como un complication commun de tuberculose, arthritis rheumatoide, e myeloma multiple. In series autoptic, inter 15 e 25 pro cento del casos del mentionate tres morbos se revela como complicate per amyloidosis. Le condition ha etiam essite reportate in casos de osteomyelitis, sepsis chronic, morbo de Hodgkin, carcinoma, leucemia, e subacute endocarditis bacterial.

Es presentate un reporto de dece-duo casos de amyloidosis. In tres illo pareva esser primari, in nove secundari. Materiales pathologic esseva disponibile in omne 12 casos. Necropsias complete esseva reportate pro 10. Le forma secundari del morbo esseva associate con arthritis in tres casos, con morbo de Hodgkin in duo, con paraplegia traumatic con osteomyelitis in duo, con carcinoma in un, e con tuberculose

etiam in un. In octo ex 10 casos, rubio congo esseva retenite in ultra de 60 pro cento. Duo reactiones esseva false negative. In un de iste casos le amyloidosis esseva minimal, in le altere il se tractava del forma primari del morbo. Omne le 12 casos manifestava affectiones renal. In sex casos, le patientes moriva con disfallimento renal. In cinque casos le disfallimento renal esseva characterisate per nephrosis amyloide, elevate valores de nitrogeno non-proteinic, e urina alcalin in le presentia de extreme acidosis metabolic. Iste ultime constatation es explicate per le incapacitate de conservar natrium e kalium, le perdita de bicarbonato, e le incapacitate de excerner iones de hydronium e ammonium (acidosis reno-tubular). Disfallimento adreno-cortical esseva constatate in duo patientes. Ambes experientiava crises addisonian, e ambes respondeva a cortisona. Un patiente moriva de acute insufficientia adrenal in le presentia de septicemia. Dysfunction hepatic esseva manifeste in signos de obstruction intrahepatic con marcate elevationes del valores de phosphatase alcalin seral e de cholesterol e un basse excretion de bromsulphaleina. Un sol caso revelava un augmento del bilirubina seral. Tres patientes moriva ab hemorrhagia massive connectite con affection vascular. Thromboses de vasos major occurreva in duo casos. Septicemia esseva demonstrate in cinque casos. Le possibilitate que il existe un relation etiologic inter amyloidosis e le therapia a mustarda a nitrogeno in morbo de Hodgkin es signalate a causa del occurrentia tardive de iste complication e proque amyloidosis pote esser producite experimentalmente per medio de mustarda a nitrogeno. Hypertension non occurreva in le presente serie in despecto de avantiate morbo renal. Polycythemia esseva presente in duo casos. In un de istos, affection del medulla ossee esseva demonstrabile. Nulle therapia effectuava un remission de forma mesurabile. Cortisona, ACTH, e preparatos de hepate crude esseva omnes sin beneficio.

BIBLIOGRAPHY

1. Ballinger, J.: Amyloid heart disease, Am. J. M. Sc. **217**: 308–313, 1949.
2. Bannick, E. G., Berkman, J. M., and Beaver, D. C.: Diffuse amyloidosis; three unusual cases; a clinical and pathological study, Arch. Int. Med. **51**: 978–990, 1933.
3. Bayrd, E. D., and Bennett, W. A.: Amyloidosis complicating myeloma, M. Clin. North America **34**: 1151–1164, 1950.
4. Berris, B., and Wolff, H. J.: Primary systemic amyloidosis with jaundice and hemorrhage, Gastroenterology **13**: 67–72, 1949.
5. Case Records of Massachusetts General Hospital, New England J. Med. **241**: 497–500, 1948; **252**: 994–999, 1955.
6. Clinico-pathologic conference: Amyloidosis of the liver and cardiac failure, Am. J. Med. **17**: 280–290, 1954.
7. Dahlin, D. C.: Amyloidosis, Proc. Staff Meet., Mayo Clin. **24**: 637–648, 1949.
8. Dahlin, D. C.: Secondary amyloidosis, Ann. Int. Med. **31**: 105–119, 1949.
9. Dahlin, D. C.: Primary amyloidosis with report of 6 cases, Am. J. Path. **25**: 105–123, 1949.
10. Dahlin, D. C.: Classification and general aspects of amyloidosis, M. Clin. North America **34**: 1107–1111, 1950.
11. Dahlin, D. C., Stauffer, M. H., and Mann, F. D.: Laboratory and biopsy diagnosis of amyloidosis, M. Clin. North America **34**: 1171–1176, 1950.
12. Drapiewski, J. F., Sternlieb, S. B., and Jones, R.: Primary amyloidosis with spontaneous rupture of the spleen and sudden death, Ann. Int. Med. **43**: 406–412, 1955.
13. Ensign, W. G.: Macroglossia as a manifestation of primary systemic amyloidosis, J. A. M. A. **149**: 136–138, 1952.
14. Fiese, M. J.: Primary systemic amyloidosis; therapeutic failure of desiccated liver; report of a case, Stanford M. Bull. **11**: 30–32, 1953.

15. Findley, J. W., Jr., and Adams, W.: Primary systemic amyloidosis simulating constrictive pericarditis with steatorrhea and hyperesthesia, Arch. Int. Med. **81**: 342–351, 1948.
16. Forbus, W. D.: Reaction to injury—pathology for students of disease, Vol. II, 1952, The Williams and Wilkins Co., Baltimore, pp. 370–378.
17. Gedda, P. O.: On amyloidosis and other causes of death in rheumatoid arthritis, Acta med. Scandinav. **150**: 443–452, 1955.
18. Golden, A.: Primary systemic amyloidosis of alimentary tract, Arch. Int. Med. **75**: 413–416, 1945.
19. Grayzel, H. G., and Jacobi, M: Secondary amyloidosis; results of therapy with desiccated whole liver powder, Ann. Int. Med. **12**: 39–58, 1938–39.
20. Guttman, P.: Addison's disease, Arch. Path. **10**: 742–785, 895–914, 1930.
21. Hass, G., and Schulz, R. Z.: Studies of amyloid. II. The isolation of a polysaccharide from amyloid-bearing tissue, Arch. Path. **30**: 240–259, 1940.
22. Higgins, W. H., and Higgins, W. H., Jr.: Primary amyloidosis; a clinical and pathological study, Am. J. M. Sc. **220**: 610–615, 1950.
23. Hochman, A., and Czerniak, P.: Hodgkin's disease and amyloidopathia, Radiology **63**: 716–721, 1954.
24. Jackson, A.: Amyloidosis: report of 3 cases with some consideration as to etiology and pathogenesis, Arch. Int. Med. **93**: 494–502, 1954.
25. Jackson, A., and Slavin, M.: Primary amyloidosis. A report of two cases, Am. Heart J. **47**: 839–844, 1954.
26. Jacobi, M., and Grayzel, H.: Generalized secondary amyloidosis; a clinicopathological study of 84 cases, J. Mt. Sinai Hosp. **12**: 339–363, 1945.
27. Josselson, A. J., Pruitt, R. D., and Edwards, J. E.: Amyloid disease of heart, M. Clin. North America **34**: 1137–1144, 1950.
28. Josselson, A. J., Pruitt, R. D., and Edwards, J. E.: Amyloid localized to the heart—analysis of 29 cases, Arch. Path. **54**: 359–367, 1952.
29. King, F. H., and Oppenheimer, G. D.: Rupture of amyloid spleen, Ann. Int. Med. **29**: 374–378, 1948.
30. Lindsay, S.: Primary systemic amyloidosis with nephrosis, Am. J. Med. **4**: 765–772, 1948.
31. Marriott, H. J. L.: Primary systemic amyloidosis, Ann. Int. Med. **38**: 620–626, 1953.
32. Mathews, W. H.: Primary systemic amyloidosis, Am. J. M. Sc. **228**: 317–333, 1954.
33. Mendel, D. L., and Saibil, M.: Amyloidosis of adrenals as a cause of Addison's disease, Canad. M. A. J. **39**: 457–459, 1938.
34. Moschcowitz, E.: The clinical aspects of amyloidosis, Ann. Int. Med. **10**: 73–88, 1936.
35. Newmann, W., and Jacobson, A. S.: Paraplegia and secondary amyloidosis—report of 6 cases, Am. J. Med. **15**: 216–222, 1953.
36. O'Donnell, W. M.: Changing pathogenesis of Addison's disease with special reference to amyloidosis, Arch. Int. Med. **86**: 266–279, 1950.
37. Parker, R. L., Odell, H. M., Logan, A. H., Jr., Kelsey, J. R., Jr., and Edwards, J. E.: Primary systemic amyloidosis; report of 2 cases, M. Clin. North America **34**: 1119–1135, 1950.
38. Pocock, D. S., and Dickens, J.: Paramyloidosis with diabetes mellitus and gastrointestinal hemorrhage, New England J. Med. **248**: 359–363, 1953.
39. Pirani, C. L., Bly, C. G., Sutherland, K., and Chereso, F.: Experimental amyloidosis in guinea pigs, Science **110**: 145–146, 1949.
40. Reece, J. M., and Reynolds, T. B.: Amyloidosis complicating rheumatoid arthritis, Am. J. M. Sc. **228**: 554–559, 1954.
41. Reimann, H. A., Sahyoun, P. F., and Chaglassian, H. T.: Primary amyloidosis; relationship to secondary amyloidosis and report of a case, Arch. Int. Med. **93**: 673–686, 1954.

42. Richter, G. W.: The reabsorption of amyloid under experimental conditions, Am. J. Path. **30**: 239–261, 1954.
43. Selikoff, I. J.: Diagnosis of generalized amyloidosis by Congo red test: definite diagnostic criteria, Am. J. M. Sc. **213**: 719–727, 1947.
44. Selikoff, I. J., and Robitzek, E. H.: Gingival biopsy for diagnosis of generalized amyloidosis, Am. J. Path. **23**: 1099–1111, 1947.
45. Spain, D. M., and Riley, R. L.: Jaundice in amyloidosis of liver, Am. J. Clin. Path. **14**: 284–288, 1944.
46. Stark, D. B., and New, G. B.: Amyloid tumors of larynx and trachea, M. Clin. North America **34**: 1145–1150, 1950.
47. Stauffer, M. H.: Hepatic manifestations in secondary amyloidosis, M. Clin. North America **34**: 1165–1169, 1950.
48. Stemmerman, M. G., and Auerbach, O.: Adrenal amyloidosis, Arch. Int. Med. **74**: 384–389, 1944.
49. Teilum, G., and Lindahl, A.: Frequency and significance of amyloid changes in rheumatoid arthritis, Acta med. Scandinav. **149**: 449–455, 1954.
50. Teilum, G.: Studies on pathogenesis of amyloid. II. Effect of nitrogen mustard in inducing amyloidosis, J. Lab. and Clin. Med. **43**: 367–374, 1954.
51. Teilum, G.: Cortisone, ascorbic acid interaction and pathogenesis of amyloidosis: mechanism of action of cortisone on mesenchymal tissues, Ann. Rheumat. Dis. **11**: 119–135, 1952.
52. Tiber, A. M., Pearlman, A. W., and Cohen, S. E.: Hepatic function in patients with amyloidosis, Arch. Int. Med. **68**: 309–324, 1941.
53. Unger, P. N., Zuckerbrod, M., Beck, G. J., and Steele, J. M.: Amyloidosis in rheumatoid arthritis; a report of 10 cases, Am. J. M. Sc. **216**: 51–56, 1948.
54. Unger, P. N., Zuckerbrod, M., Beck, G. J., and Steele, J. M.: Study of disappearance of Congo red from blood of non-amyloid subjects and patients with systemic amyloidosis, J. Clin. Investigation **27**: 111–118, 1948.
55. Volwiler, W., and Jones, C. M.: Diagnostic and therapeutic value of liver biopsies, with particular reference to trocar biopsy, New England J. Med. **237**: 651–656, 1947.
56. Wald, M. H.: Clinical studies of secondary amyloidosis in tuberculosis, Ann. Int. Med. **43**: 383–394, 1955.
57. Wallace, S. L., Feldman, D. J., Berlin, I., Harris, C., and Glass, I. A.: Amyloidosis in Hodgkin's disease, Am. J. Med. **8**: 552–557, 1950.
58. Wollaeger, E. E.: Primary systemic amyloidosis with symptoms and signs of liver disease; diagnosis by liver biopsy—report of a case, M. Clin. North America **34**: 1113–1118, 1950.
59. Wolf, R. L., Hitzig, W., and Otani, S.: Amyloidosis unassociated with predisposing disease, Arch. Int. Med. **95**: 141–152, 1955.
60. Zetzel, L.: Hepatomegaly with jaundice due to primary amyloidosis, Gastroenterology **8**: 783–787, 1947.