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Amyloidosis

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I. AMYLOIDOSIS

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Section 1

The purpose of this paper is to review briefly the several diseases characterized by the deposition of amyloid, especially the form known as primary systematized amyloidosis, to present two cases of this rare type which recently came to autopsy, and, finally, to summarize the findings of some histochemical investigations into the nature of the amyloid substance.

Amyloid disease is customarily divided into four or five, more or less distinct syndromes, dependent primarily on the location of the deposits. The location of these deposits, of course, determines the symptoms, signs and clinical course of the disease produced. One of the commonly used classifications is the following, proposed by Reimann, Koucky and Eklund, at this University, in 1935:[1]

1. Secondary amyloidosis
2. Primary amyloidosis
3. Tumor forming amyloidosis
4. Amyloidosis associated with multiple myeloma.

Secondary amyloidosis is that familiar type in which deposits are secondary to some chronic inflammatory or suppurative process such as tuberculosis, osteomyelitis, rheumatoid arthritis, or ulcerative colitis. The deposits are characteristically parenchymatous in distribution, being found in the reticuloendothelial cells of the liver lobules, the splenic pulp, the glomeruli and tubules of the kidneys, and in the substance of the adrenal glands. The primary type was assumed not to be associated with other inflammatory or suppurative disease. In this type the amyloid is also distributed widely throughout the body, but parenchymal tissue is involved secondarily if at all. The sites of involvement are the blood vessels and connective tissues throughout the body, the muscles, including the myocardium, the gastrointestinal tract, and rarely, the bones and joints and peripheral nerves. The fourth group, amyloidosis associated with multiple myeloma, is very similar to the primary type in its distribution, but in this type, Bence-Jones proteinuria, hyperglobulinemia and plasmocytomas are found. Included in the third group, tumor forming amyloidosis, were those cases in which amyloid is found localized in one, or at most a few, sites in the body. This form is familiar to otolaryngologists and ophthalmologists in the form of nodular or diffuse infiltration of amyloid in the conjunctivae, pharynx, larynx, esophagus and stomach.

Numerous objections have been raised against this classification and attempts, generally unsuccessful, made to improve upon it.[2,3,4,5,etc.] Cases have been reported which cannot be catalogued in the above types.[1] Thus cases in which amyloid was found limited to classical parenchymatous locations but in which no evidence of chronic inflammatory or suppurative disease could be discovered either by history or at autopsy are available in the records of the Department of Pathology at this University.[2] Conversely, cases of the so-called "primary" amyloidosis have been reported following such chronic inflammations as bronchiectasis[6] and pyelonephritis, and nephrolithiasis.[3] It may be argued that in these cases there was no cause and effect relationship between the suppurative processes and the subsequent deposition of amyloid. More important, perhaps, are those cases in which amyloid was found in the blood vessels, connective tissues and muscle, and also in typical parenchymatous distribution in the liver, spleen, kidneys and adrenals in the same individual.[4] To overcome these objections attempts have been made to relabel the so-called primary type. This form has been called a) primary[1], b) primary systemic[7], c) primary atypical[8], d) idiopathic[9], e) atypical[10], f) generalized[11], g) diffuse[12], and h) paraamyloidosis.[13] Unfortunately, none of these terms is completely satisfactory. Contention can be made there is no essential difference between primary systemic amyloidosis and that associated with multiple myeloma. No sharp line can

be drawn between either the clinical or pathologic findings. Indeed, it has been maintained that all cases of "primary" amyloidosis would develop myelomas if they survived long enough, or that the cases called primary have not been examined thoroughly enough to rule out the presence of myelomas. The third group, "tumor-forming" amyloidosis is not free from objection, in that in these cases in which deposits of amyloid are found localized in one organ, for example, the larynx, one cannot be certain that generalization will not occur later.

The above four headings do not include all cases of amyloid deposition. Excluded are those instances in which amyloid appears in degenerating portions of tumors or in sites of chronic inflammation. Excluded also are those instances in which the deposition of amyloid appears to be a manifestation of senile change. Asymptomatic amyloidosis of the seminal vesicles is a common finding in the aged, and King has recently reported the presence of small amounts of amyloid as in incidental finding in the myocardia from five individuals, all over 85 years[3] of age. To a dermatologist, the most glaring defect in this classification is its failure to include a well-defined entity known as lichen amyloidosis, in which deposits of amyloid appear as nodules in the skin, usually grouped and localized to the pretibial region, but rarely, generalized. In this group of cases, no evidence of internal amyloidosis has been found, either clinically or at autopsy.[14] There is no report of this form of cutaneous amyloidosis being associated with localized forms occurring in the mucous membranes composing group 3 of Reimann, Koucky and Eklund's classification.

No completely satisfactory system of classification having as yet been produced, despite repeated effort, it will probably be necessary to await knowledge of the etiology of these conditions before their nosologic relationship will be clarified.

Primary Systematized Amyloidosis

Special attention will be devoted to this particular form of amyloidosis, because it is not as well known as the secondary, parenchymatous type, because it is being recognized and reported more and more frequently by both clinicians and pathologists and because with its varied clinical picture, dependent as that is on the appearance of deposits in a wide range of possible locations throughout the body, it is of importance in differential diagnosis to specialists in almost all branches of medicine.

This syndrome first appeared in the medical literature in 1856.[15] Wild is credited with the first good description of the symdrome in 1886.[16] Since that time, approximately 70 cases of the musculo-gascular-connective tissue type of amyloidosis, not associated with multiple myelomas, have been reported in the world's literature. It is interesting to note that Koletsky and Stecher were able to find only 23 cases up to 1939,[2] so that over two-thirds of the total number have been reported in the past ten years. Most of these later reports have been by American authors. Dahlin recently reported a review of all autopsies at the Mayo Clinic from 1922 to 1946.[4] Out of a total of 44 instances of amyloidosis, 7 were of the primary systemic type, having previously been unrecognized as such. These facts indicate that the syndrome of primary systematized amyloidosis is becoming of increasing importance to clinicians and pathologists alike. Indeed, with the steady drop in the incidence of the secondary, parenchymal type in this country (due to the decreasing amount of tuberculosis and syphilis and better treatment of chronic suppurative diseases), primary systemic amyloidosis heretofore considered an "atypical" form of amyloidosis, may well become the more common, hence "typical" type.

Clinical Course of Primary Systematized Amyloidosis

Primary systematized amyloidosis occurs in all adult ages and with equal frequency in both sexes. The disease may have a wide variety of clinical pictures depending on the organs and tissues which are infiltrated with amyloid material. Because certain organs and systems are preferred sites, however, a certain uniformity results in the majority of

cases. Organs involved in the majority of reported cases are the striated muscles, gastro-intestinal tract, heart, skin and mucous membranes.

Involvement of skeletal muscles is a common occurrence. Almost any muscle may be involved, but favored sites are the calf muscles, the hamstring group, the large muscles of the back and the muscles of the shoulder girdle. Symptoms are pain in the muscles, weakness and easy fatigability. These are often the earliest symptoms of the disease. Physical examination may reveal weakness, tenderness of the involved muscles and sometimes, induration and swelling. Disturbances in gait and limitation of motion may be noted. These symptoms and signs were prominent in one of our cases. The gastro-intestinal tract is also involved in a large percentage of the reported cases. Any part of or all of the tract may be involved. Common symptoms are diarrhea, alternating with or followed by constipation which may become very severe. Anorexia is common and probably accounts for the marked loss in weight which occurred in many of these cases. Nausea and vomiting may supervene. In at least 3 reported cases, ulceration has occurred over localized or diffuse amyloid deposits in the stomach and duodenum. Loss of gastro-intestinal motility may be seen on radiologic examination and rarely complete pyloric or intestinal obstruction occurs. Hemorrhage from the gastro-intestinal tract, manifested by either melena or hematemesis, is not uncommon. In a few instances, such hemorrhage has been massive enough to constitute the immediate cause of death. Abdominal pain and distention may be troublesome and have lead to surgical exploratory operations, often with unfavorable results. In one of our cases, complaints of loss of appetite and abdominal pain led to removal of a myomatous uterus six weeks before death. In the other case, anorexia with weight loss and obstipation were increasingly troublesome up to the time of death. In the case reported by Michelson and Lynch in 1934,[17] there was massive hemorrhage from the bowel.

In a recent review of the reported cases of this disease, Dahlin found evidence of cardiac infiltration with amyloid in 46 instances out of a total of 57 cases reported up to that time.[4] In 25 of these 46, myocardial insufficiency was considered to be the immediate cause of death. Amyloid may be deposited in any of the layers of the heart and may produce cardiac failure in several ways.[18]

1. As a result of deposition of amyloid in the pulmonary vessels and alveolar walls with resulting chronic or pulmona,

2. As a result of deposition of amyloid in the cardiac blood vessels (although the large branches of the coronary arteries have not been reported to be significantly narrowed by amyloid deposits),

3. As a result of extensive pericardial or endocardial deposits of amyloid,

4. Extensive valvular deposits producing stenosis or insufficiency.

5. Diffuse or nodular interstitial amyloid infiltration into the myocardium, with or without secondary degeneration of the myocardium,

6. By combinations of the above involvement.

Clinically the heart may be normal in size or moderately enlarged. The blood pressure is almost uniformly low, commonly being in the range of 90-110 systolic and 65-80 diastolic. The only case with an elevated blood pressure was that of a female, age 18, whose blood pressure was 180/94.[19] At autopsy she was found to have contracted kidneys, each kidney weighing 50 grams. Precordial pain, substernal in location, and sometimes radiating down the arms, is a common complaint. Edema, hydrothorax, ascites, dyspnea and orthopnea frequently result from myocardial insufficiency, and disturbances in rhythm such as auricular fibrillation, have been recorded. Electrocardiograms characteristically show low voltage in all limb leads, sometimes disturbances in conduc-

tion, and occasionally the changes of old myocardial infarction may be simulated. Amyloid disease, then, must be considered as a cause of otherwise unexplained cardiac failure.

Involvement of the skin and mucous membranes is of importance in the clinical picture of primary systemic amyloidosis because in those uncommon instances in which the syndrome has been correctly diagnosed before autopsy, examination of these accessible organs, clinically and histologically, has in most cases been the means by which the diagnosis was established. This was true in one of our cases in which the correct diagnosis was made antemortem.

Macroglossia is perhaps the best-known sign of primary amyloidosis. It is not invariably present. Rigdon and Noblin, in a review of 44 cases, found it present in 24.[20] It may be of interest that of the 9 of these 44 cases which were diagnosed before death, 6 had macroglossia. The extent of enlargement varies from slight thickening to one extreme case in which the mouth could not be closed because of massive enlargement of the tongue. The most frequent symptoms are a feeling of swelling of the tongue, dysphagia, and interference with speech. Ingestion of solid food may become impossible, and this, as well as anorexia, may be a cause of the weight loss commonly suffered by these patients. On examination, the tongue is thick, indurated, the movements are limited and speech is muffled. Commonly the papillae are obliterated and the tongue, smooth and diffusely reddened, may be studded with red or yellowish papules and nodules, both dorsally and on the ventral and lateral surface. Ecchymoses may be seen here, as well as in the other mucous membranes and skin. Histologically, both the submucosal connective tissue and muscle are usually involved.

Almost all of the other regions of the oral and naso-pharyngeal mucous membranes may be involved. The alveolar margins, buccal mucosa and inner surfaces of the lips are commonly mentioned sites. Less common are involvement of the nasal mucosa, palate, pharynx, larynx, and trachea. The lesions usually consist of groups of transparent papules and nodules which may be accompanied by submucosal hemorrhage. Localized or diffuse purpura may occur without relation to nodular lesions. The mucous and serous glands may be heavily infiltrated and rendered functionless, the loss of their secretion rendering the ingestion of solids even more difficult. Diffuse infiltration of the nasal mucosa, resulting in epistaxis and finally nasal obstruction has been reported. Lindsay and Knorp's patient had perforation of the nasal septum.[18] Diffuse infiltration of the laryax, resulting in laryngeal obstruction sufficient to require tracheotomy has occurred.

Amyloid infiltration into the skin may produce various lesions. Perhaps the most common is purpura. Purpura may occur associated with the other lesions to be mentioned subsequently and also independently of them into apparently normal skin. In no instance in which biopsy of the purpuric areas has been done, however, has there been failure to find amyloid infiltration into the walls of the small blood vessels. The damage to the blood vessel walls is apparently the cause of the purpura, since other abnormalities in the bleeding and clotting mechanism, as measured by the cuff test, bleeding and clotting and prothrombin times, platelet counts, etc. almost invariably cannot be demonstrated. This was true in our case. Many of the reported cases have been thought at first to be suffering from some allergic or familial type of purpura, the vague abdominal and musculoarticular symptoms also suggesting such a diagnosis. Frequently the purpura is intermittent, often intensified by straining and coughing and in severe cases, by even slight pressure on the involved skin.

Perhaps the most striking and characteristic lesions occurring in the skin are translucent papules and plaques. These vary in size from a millimeter or so in diameter up to two centimeters. Because of their shiny, translucent character, they may appear to be vesicles, but they are firm and smooth to

the touch. Their color is usually a translucent yellowish-white, but they may be various shades or red due to the presence of purpuric hemorrhage. These lesions commonly occur in groups, and in almost all reported cases certain areas of the integument have been favored. These areas are the eyelids, the naso-labial commissures, the corners of the mouth, around the chin, at the base of the neck, in the axillae and in the inguinal folds. Accompanying lesions in these locations, there may be scattered lesions elsewhere. Less common cutaneous lesions include a pseudo-scleroderma due to diffuse involvement of a large area of skin, most commonly of the face and neck, diffuse thickening of the palms and soles, and thickening and redness of the finger pads.[21] Ulcerations may occur, especially over the bony prominences.[22] Lindsay and Knorp reported an eczematous plaque on the ear, the skin underneath being shown histologically to be heavily infiltrated with amyloid.[18] The same patient showed red longitudinal striations under the finger nails which these authors assured to have been due to amyloid deposits, though no histologic examination was done.

Less common manifestations of this syndrome which have been reported included pain in the finger tips, intermittent claudication, compression fractures of the vertebrae, pathologic fracture of the femur, amenorrhea, and evidence of autonomic nervous system dysfunction such as pupillary changes, difficulty in micturition, and impotence.[23]

Direct involvement of the central nervous system has not been reported.

Prognosis - All reported cases of this syndrome have had a fatal outcome. The duration of life after the onset of symptoms has varied from 4 months to 14 years.

Etiology - The etiology of this condition remains undetermined. Amyloid deposition can be produced in experimental animals by various techniques, but the deposits so produced have a parenchymal distribution, while spontaneous amyloidosis in mice has a distribution corresponding to primary systematized amyloidosis in humans. The theory of some authors that in the case of amyloidosis associated with multiple myeloma the amyloid material is produced by the plasma cells (as maybe Bence-Jones protein, a substance having many similarities to amyloid), does not seem to apply in the primary systematized form, since no large number of plasma cells is present. Many authors follow the lead of Koletsky and Stecher who postulated that amyloid was a product of an antigen antibody reaction occurring in the walls of the blood vessels.[2] There would appear to be little concrete evidence to support this theory. More definite knowledge of the etiology of this form of amyloidosis, to say nothing of the other forms, will have to be gained by future investigations.

Section 2. CASE REPORTS

Following is a summary of two cases of primary systematized amyloidosis which came to autopsy. The first case was studied extensively by Drs. Roehrer, Schultz and Thomes, and attended in her terminal course and autopsied by Dr. Nickerson. We are greatly indebted to these physicians for permission to report their findings. She was seen by us in consultation. The second case is reported with the kind permission of the members of the Department of Pathology. Time does not permit more than a brief presentation of the significant findings in these cases.

Case 1.

Mrs. ., a 43-year old white female first noted purpura of the eyelids four years before death. The purpura later involved the base and sides of the neck and the inguinal regions as well. In the same year she noted ankle edema which was intermittent. One year before death, pain in the lower extremities was noted. This aching pain gradually extended upward and became more severe, requiring narcotics for relief. At about the same time generalized edema and albuminuria developed. These complaints persisted until death. Six months before death pain and weakness in

the arms developed, as well as weakness in the legs. There was anorexia, nausea and vomiting and constipation, and the patient lost thirty pounds in weight.

Physical examination showed the blood pressure to be 102/75. On the eyelids, chin, inner surface of the lower lip, base of the neck, axillae, antecubital spaces, inguinal, and anal areas and vulvar mucous membranes were numerous small, flat-topped waxy papules, yellow-white in color. Some of these were hemorrhagic, as was the surrounding skin. Pigmentation marked the site of former lesions. Palmar erythema was noted. General physical examination was negative. There were areas of hyperthesia on the lower extremities. The deltoid, gluteal, hamstring and iliopsoas muscles were weak.

Laboratory studies: Cuff test, bleeding and clotting and prothrombin times, platelet counts and liver function tests were normal, as was the hemogram. The Congo red test showed no abnormal retention of dye. Sedimentation of red cells was moderately rapid. The serum proteins were normal. The urine showed up to four plus albumen and a few red and white cells. Bence-Jones protein was absent on repeated testing. The bone marrow showed six per cent plasma cells, but they were not of a neoplastic type. Chest x-ray showed a moderately enlarged heart, left ventricular in configuration. The electro-cardiogram showed low R voltage, right axis deviation and a diphasic T_2. The interpretation was myocardial damage.

At autopsy, the heart showed ecchymoses on the visceral pericardium and gross deformity of all valves except the aortic. The valves contained firm nodular deposits of amyloid. Microscopically the myocardium was extensively infiltrated with amyloid, some fibers being completely replaced. The lungs showed large amounts of amyloid in the walls of the alveolar capillaries, the alveolar spaces being almost completely obliterated in places. The muscles of the gastrointestinal tract were extensively infiltrated with amyloid. The liver, spleen and adrenals showed deposits in the walls of the blood vessels but the parenchyma was uninvolved. The kidneys showed moderate amounts of amyloid in the walls of the glomerular capillaries, and there were hyaline casts in the tubules. In the other organs examined, large amounts of amyloid were present in the walls of the blood vessels, the media being especially affected, and lesser amounts of amyloid were seen lying free in the connective tissue. Skeletal muscle showed degeneration and moderate infiltration with amyloid.

Case 2.

, a 47-year old female, noted fatigue and anorexia, beginning four months before death. She soon developed exertional dyspnea and a pressing dull pain over the sternum and upper chest. The patient stated that she had been drinking large quantities of water for the same length of time. Six weeks before death a myomatous uterus was removed because of the above complaints. At that time the roentgenogram of the chest showed left axis deviation and evidence of myocardial damage. The urine showed a trace of albumen and few red and white cells. The immediate postoperative course was without incident, except that the blood pressure, which before operation had been 160/110, dropped to 130/90 and remained at approximately that level. After operation fatigue and anorexia remained the dominant complaint. In addition, there developed insomnia, pounding of the heart, increasing dyspnea and orthopnea. The patient lost thirty to forty pounds in four or five weeks. Five days before death, physical examination showed a blood pressure of 108/90, left ventricular enlargement, basal pulmonary rales, an enlarged and tender liver and two-plus pitting edema of the lower extremities. The electrocardiogram at this time showed negative T waves in the first and fourth leads and widening of the QRS group. The urine failed to concentrate above 1010, showed two-plus albumen, granular casts and a few red and white cells. The hemogram was essentially normal. The patient died suddenly while in a hospital.

Autopsy examination revealed an enlarged heart and liver. The iodine sulfuric acid test for amyloid was positive in the myocardium, spleen and kidneys. The cranial contents were not examined microscopically, small amounts of amyloid were seen in almost all the glomeruli, chiefly subendothelial in location, but also in Bowman's capsule. The myocardium showed amyloid in the walls of the blood vessels and also involving the fibers themselves. Considerable amounts of amyloid were seen in the follicles and pulp of the spleen, but none in the hepatic parenchyma. The walls of small blood vessels throughout the body were extensively infiltrated with amyloid. Careful examination of the bone marrow showed no evidence of myeloma and there was no gross or microscopic evidence of any focus of chronic inflammation or suppuration.

Section 3

Following is a brief report of some histochemical investigations into the nature of the amyloid substance in primary systematized amyloidosis and in amyloid deposits localized to the skin, the so-called lichen amyloidosus. The usual form of amyloid, occurring in parenchymal amyloidosis secondary to other diseases, has been suspected for many years of being a protein carbohydrate complex.[24] Hass and his co-workers definitely demonstrated by macrochemical methods on amyloid extracted from the organs of patients dying from secondary amyloidosis that this type of amyloid does indeed contain polysaccharide elements. The polysaccharide was found to make up 0.5 to 1.5% of the total mass of the extracted amyloid substance. Chemical analysis showed the polysaccharide to be similar to, if not identical with, chondroitin sulfuric acid isolated from normal cartilage. Unfortunately, these findings cannot be assumed to apply to all forms of amyloid disease, since there is evidence that there is considerable variation in the nature of the substance in the different forms of amyloid disease. Thus, Hass's studies[25] showed that amyloid from muscle in a case associated with multiple myeloma was considerably more resistant to the action of alkaline solvents than was parenchymatous amyloid secondary to tuberculosis. That amyloid of the primary systematized type has atypical reactions to staining with dyes used to demonstrate the secondary type has been repeatedly demonstrated and this failure to give typical staining reactions has, in fact, been used to differentiate the types. Thus, primary amyloid may or may not stain metachromatically with methyl violet, has a weak affinity for Congo Red if it takes up this dye at all, and may or may not give the characteristic reaction to the iodine sulfuric acid test. Our two cases were not stained metachromatically by methyl violet and had no affinity for Congo Red, while control section of tissue from cases of secondary amyloidosis gave characteristic reactions to these methods. We have not been able to find any report of studies concerning the chemical nature of the amyloid substance in either primary systematized amyloidosis or lichen amyloidosus.

The small amount of amyloid in the tissues in relation to the total mass of the organs in these forms of amyloidosis as well as the fact that only fixed tissue was available to us, precluded the use of Hass and co-workers' methods of extraction and macro-chemical analysis. We were therefore forced to rely on histochemical techniques.

Methods Used

Tissues were fixed in formalin and mounted in paraffin in the usual manner. Sections were then stained with hematoxylin and eosin, Congo Red, methyl violet, toluidine blue, periodic acid - Schiff's reagent after the method of McManus, for tyrosine by Millon's reaction and for arginine by Thomas' method.[26] Sections from organs infiltrated with secondary amyloid were stained in an identical manner.

The hematoxylin-eosin-stained sections were used as control sections for positive localization of the amyloid. Congo Red staining was used for the sake of completeness rather than for any informa-

tion it would give about the chemical nature of the amyloid, since the affinity of amyloid and related substances for Congo Red is based on unknown chemical properties. The stains for arginine and tyrosine are the only satisfactory stains available for amino acids and were used to confirm the protein nature of the amyloid substance. Methyl violet and toluidine blue are both basic aniline dyes and both share the property of many such dyes of being rendered metachromatic by substances of high molecular weight with an acidic function, chiefly mucopolysaccharides. In various situations the amount of metachromatic material has been shown to be proportional to the content of such mucopolysaccharides as hyaluronic acid, and mucoitin and chondroitin sulfuric acids. The periodic acid-leucofuchsin stain of McManus is based on the release of aldehyde groups from polysaccharides by periodic acid and the selective staining of these aldehydes by Schiff's leukofuchsin reagent. Although other compounds may give the same reaction, recent studies by McManus indicate that this method has in practice proved highly specific for polysaccharides.[27]

Results

With hematoxylin and eosin staining amyloid appeared the same in all three types investigated. It had its characteristic hyaline, accellular, faintly eosinophilic appearance. The three forms of amyloidosis could be distinguished only by the location of the deposits, not by their appearance. With Congo Red staining, differences began to appear. Amyloid in the organs from cases of secondary amyloidosis was stained an intense red by this dye while in both primary cutaneous amyloid and purely cutaneous amyloid were stained a lighter, orange red. In none of the sections was there a complete failure to stain with this dye, but in some instances the amyloid stained very little more intensely than the surrounding normal connective tissue, which stains a faint pink with the method used. Stains for both arginine and tyrosine were positive in all sections, both in the amyloid substance and in the surrounding connective tissue. In no instance was the staining intense, and no quantitative difference could be noted between the amount of these amino acids in the amyloid and in the surrounding tissue. It is felt, however, that the reactions were such as to confirm the expected protein nature of amyloid in all three types of the disease.

The toluidine blue stain yielded consistent differences in the staining among the three types of disease. Amyloid in sections from secondary amyloid disease showed no affinity for the dye. In sections from primary systematized amyloidosis and from lichen amyloidosus, on the other hand, the amyloid showed a pronounced affinity for the dye, though no metachromasia was induced despite use of various concentrations of the alcoholic solvent. It is felt that this failure to induce metachromasia is a reflection on our techniques, rather than an indication of the absence of polysaccharides in the amyloid, since such structures as mucous glands, which should induce an intense metachromasia because of their content of mucin, also gave a negative reaction. The most interesting result from the use of the toluidine blue stain was the finding of an intense affinity of primary systematized amyloid and lichen amyloidosus amyloid for the dye, while uninvolved connective tissue and muscle were only weakly stained.

This intense staining of the amyloid in contrast to the surrounding uninvolved tissue proved to be very useful as a differential stain, particularly in the myocardium and muscles of the gastrointestinal tract. It is felt that the toluidine blue stain was far more useful than any other stain used, in localizing and determining the extent of amyloid involvement of the individual muscle fibers.

The periodic acid-leucofuchsin method resulted in a negative reaction in the sections of secondary amyloidosis, a strongly positive reaction in sections from primary systematized amyloidosis, and a less strongly positive reaction in the sections of lichen amyloidosus. The failure of secondary amyloid to stain by

this method, as well as its lack of affinity for toluidine blue, is surprising in view of the fact that this is the type of amyloid which Hass and others have shown to contain a small percentage of chondroitin sulfuric acid or closely related polysaccharides. One can speculate that perhaps 0.5 to 1.5% of polysaccharides is not a high enough proportion to produce a positive reaction. Quantitative conclusions from the results of a study conducted by such methods as those used here are obviously unwarranted, but it is possible to speculate that the great difference in results in these three types of amyloid may indicate a significant difference in the proportion of polysaccharide to protein.

SUMMARY AND CONCLUSIONS

The classification of the various types of amyloid disease has been discussed, and the clinical picture of primary systematized amyloidosis reviewed. Two cases of this rare syndrome, with autopsy findings, have been presented. Results of some histochemical investigations into the nature of the amyloid substance in primary systematized amyloidosis and in lichen amyloidosus have been presented, and evidence produced that in these two types, as in secondary amyloidosis, amyloid is composed of a protein-polysaccharide complex. The proportion of carbohydrate to protein may be considerably greater in the former two types than in the latter.

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II. MEDICAL SCHOOL NEWS

Coming Events

February 15	E. Starr Judd Lecture: "The Surgical Treatment of Constrictive Pericarditis," Emile Holman; Medical Science Amphitheater; 8:15 p.m.
February 15 - 17	Continuation Course in Cardiovascular Diseases for General Physicians
March 1	Clarence M. Jackson Lecture: "Fractures About the Hip -- Early and Late Therapy," Carl E. Badgley; Museum of Natural History Auditorium; 8:00 p.m.
March 1 - 3	Continuation Course in Fractures and the Surgery of Trauma for General Physicians
March 26 - 28	Continuation Course in Pediatrics for General Physicians

Dr. Emile Holman to Give Judd Lecture

Dr. Emile Holman, Executive Head and Professor of Surgery, Stanford University School of Medicine, San Francisco, California, will deliver the annual E. Starr Judd Lecture at 8:15 p.m. on Thursday, February 15, in the Medical Science Amphitheater. His subject will be, "The Surgical Treatment of Constrictive Pericarditis." During his visit to our campus, Dr. Holman will also participate in a continuation course in Cardiovascular Diseases which will be presented for general physicians at the Center for Continuation Study. Dr. Holman's presentation in the continuation course is concerned with arteriovenous communications, a subject which he has studied extensively both in the laboratory and in the clinic. He will also participate along with Dr. Owen H. Wangensteen, Dr. Richard L. Varco, Dr. Ivan D. Baronofsky, and other members of the surgical staff in a surgical colloquium on cardiovascular diseases on Saturday morning, February 17, from 10:00 a.m. to 12:00 noon.

Faculty News

Doctors Clarence Dennis, Richard L. Varco, Arnold J. Kremen, Davitt A. Felder, and Frederick M. Owens will attend the annual meeting of the University Surgeons Society at Duke University, Durham, North Carolina, February 8-12. Dr. Varco will present a paper on the subject, "Prevention of Dilatation in Autogenous Venous and Pericardial Grafts in the Thoracic Aorta: An Experimental Study." Dr. Kremen will also present a paper. His subject will be, "Cancer of the Tongue: A Surgical Technique for a Primary Combined and En Bloc Resection of Tongue, Floor of Mouth, and Cervical Lymphatics." Dr. Dennis is the secretary of the Society.

Medical Library

The following regulations have gone into effect recently and are announced in the Bulletin at the request of E. W. McDiarmid, University Librarian, and James Kingsley of the Bio-Medical Library.

1. The current issue of all periodicals will be kept in the library and not be allowed to circulate until the succeeding issue has been received.
2. Bound and unbound periodicals for the last five years will be permitted to circulate over-night only. They may be charged out at 5:00 p.m. Foreign language journals which are less in demand will circulate as formerly.
3. The Senate Library Committee has authorized duplicate subscriptions for some 30-50 periodicals, which will be allowed to circulate.

III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

Visitors Welcome

February 11 - 17, 1951

Sunday, February 11

University Hospitals

9:00 - 10:00 Surgery Grand Rounds; Station 22.

10:30 - Surgical Conference; Todd Amphitheater.

Monday, February 12 HOLIDAY

Tuesday, February 13

Medical School and University Hospitals

9:00 - 9:50 Roentgenology Pediatric Conference; L. G. Rigler, I. McQuarrie and Staffs; Eustis Amphitheater, U. H.

9:00 - 12:00 Cardiovascular Rounds; Station 30, U. H.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

1:00 - 2:00 Physiology Seminar on Cardiac Metabolism; 129 Millard Hall.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

4:00 - 5:00 Physiology-Surgery Conference; Todd Amphitheater, U. H.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

5:00 - 6:00 X-ray Conference; Eustis Amphitheater, U. H.

8:00 p.m. Journal Club; E-101, U. H.

Ancker Hospital

1:00 - 2:30 X-ray Surgery Conference; Auditorium.

Minneapolis General Hospital

8:00 - 9:00 Pediatric Rounds; Forrest Adams; 4th Floor Annex.

8:30 - Pediatric Allergy Rounds; Dr. Nelson; 4th Floor Annex.

Tuesday, February 13 (Cont.)

Veterans Administration Hospital

8:45 - Surgery Journal Club; Conference Room; Bldg. I.

8:30 - 10:20 Surgery Conference; Seminar Conference Room, Bldg. I.

9:30 - Surgery-Pathology Conference; Conference Room, Bldg. I.

10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and E. T. Bell.

10:30 - Surgery Tumor Conference; Conference Room, Bldg. I.

1:00 - Chest Surgery Conference; J. Kinsella and Wm. Tucker; Conference Room, Bldg. I.

1:30 - Liver Rounds; Samuel Nesbitt.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III.

3:30 - 4:20 Clinical Pathological Conference; Conference Room, Bldg. I.

Wednesday, February 14

Medical School and University Hospitals

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-109, U. H.

8:00 - 9:00 Roentgenology-Surgical-Pathological Conference; Allen Judd and L. G. Rigler; Todd Amphitheater, U. H.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Medicine Case; O. H. Wangensteen, C. J. Watson and Staffs; Todd Amphitheater, U. H.

12:00 - 1:00 Radio-Isotope Seminar; Civilian Defense Radiation Problems; G. E. Moore; 113 Medical Sciences.

4:00 - 6:00 Ophthalmology Seminar; Todd Room, 5th Floor, U. H.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Eustis Amphitheater.

5:00 - 7:00 Dermatology Clinical Seminar; Dining Room, U. H.

8:00 p.m. Dermatological Pathology Conference; Todd Amphitheater, U. H.

Ancker Hospital

8:30 - 9:30 Clinico-Pathological Conference; Auditorium.

3:30 - 4:30 Journal Club; Surgery Office.

Wednesday, February 14 (Cont.)

Minneapolis General Hospital

9:00 - 10:00 Pediatric Rounds; Dr. Robin; 5th Floor Annex.

11:00 - 12:00 Pediatric Rounds; Franklin Top; 7th Floor Annex.

12:15 - Staff Meeting; ACTH and Cortisone in Allergic Conditions; Sheldon Siegel; 4th Floor Annex.

1:30 - Pediatric Rounds; E. J. Huenekens; 4th Floor Annex.

Veterans Administration Hospital

8:30 - 10:00 Orthopedic-Roentgenologic Conference; Edward T. Evans and Bernard O'Loughlin; Conference Room, Bldg. I.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker.

7:00 p.m. Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, February 15

Medical School and University Hospitals

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-109, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

12:00 - Physiological Chemistry Seminar; Effect of Adrenal Steroids on Enzymes Responsible for Urinary Ammonia; D. Simmons; 214 Millard Hall.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - Bacteriology Seminar; 214 Millard Hall.

5:00 - 6:00 X-ray Seminar; Eustis Amphitheater, U. H.

5:00 - 6:00 Radiology Seminar; Intussusception in Children; Elliott Lasser; Eustis Amphitheater, U. H.

7:30 - 9:30 Pediatrics Cardiology Conference and Journal Club; Review of Current Literature 1st hour and Review of Patients 2nd hour; 206 Temporary West Hospital.

*8:15 p.m. E. Starr Judd Lecture; The Surgical Treatment of Constrictive Pericarditis; Emile Holman; Medical Science Amphitheater.

Minneapolis General Hospital

8:00 - 9:00 Pediatric Rounds; Forrest Adams; 4th Floor Annex.

11:30 - Pathology Conference; Main Classroom.

Thursday, February 15 (Cont.)

Minneapolis General Hospital (Cont.)

1:00 - 2:00 EKG and X-ray Conference; Classroom, 4th Floor Annex.

2:00 - 4:00 Infectious Disease Rounds; 8th Floor.

4:00 - 5:00 Infectious Disease Conference; Classroom, 8th Floor.

Veterans Administration Hospital

8:00 - Surgery Ward Rounds; Lyle Hay and Staff.

9:15 - Surgery Grand Rounds; Conference Room, Bldg. I.

11:00 - Surgery Roentgen Conference; Conference Room, Bldg. I.

1:00 - Chest Rounds; William Stead.

Friday, February 16

Medical School and University Hospitals

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U.H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:45 - 12:50 University of Minnesota Hospitals Staff Meeting; Wilms's Tumors; Milton P. Reiser; Powell Hall Amphitheater.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

2:00 - 3:00 Dermatology and Syphilology Conference; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

3:00 - 4:00 Neuropathology Conference; F. Tichy; Todd Amphitheater, U. H.

4:00 - 5:00 Clinical Pathological Conference; A. B. Baker; Todd Amphitheater, U.H.

4:15 - 5:15 Electrocardiographic Conference; 106 Temp. Bldg., Hospital Court, U.H.

5:00 - Urology Seminar; Neurogenic Vesical Dysfunction; E. A. Webb; Eustis Amphitheater, U. H.

Ancker Hospital

1:00 - 3:00 Pathology-Surgery Conference; Auditorium.

Friday, February 16 (Cont.)

Minneapolis General Hospital

9:00 - 10:00 Pediatric Rounds; Dr. Tobin; 5th Floor Annex.

9:30 - Surgery-Pediatric Conference; O. S. Wyatt and T. C. Chisholm; 4th Floor Annex.

11:00 - 12:00 Pediatric Rounds; Franklin Top; 7th Floor Annex.

Veterans Administration Hospital

10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.

1:00 - Microscopic-Pathology Conference; E. T. Bell; Conference Room, Bldg.I.

1:30 - Chest Conference; Wm. Tucker and J. A. Myers; Ward 62, Day Room.

3:00 - Renal Pathology; E. T. Bell; Conference Room, Bldg. I.

Saturday, February 17

Medical School and University Hospitals

7:45 - 8:50 Orthopedic X-ray Conference; Wallace H. Cole and Staff; M-109, U. H.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; E-221, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie & Staff; Eustis Amphitheater, U.H.

9:15 - 10:00 Surgery-Roentgenology Conference; J. Friedman, O. H. Wangensteen and Staff; Todd Amphitheater, U. H.

10:00 - 11:30 Surgery Conference; O. H. Wangensteen & Staff; Todd Amphitheater, U.H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:00 - Anatomy Seminar; Electron Microscopy of Sections of Central Nervous System, J. F. Hartmann; Effects of X-rays on Ovarian Tissue; Albina Yakaitis; 226 Institute of Anatomy.

Ancker Hospital

8:30 - 9:30 Surgery Conference; Auditorium.

Minneapolis General Hospital

8:00 - 9:00 Pediatric Rounds; Forrest Adams; 4th Floor Annex.

11:00 - 12:00 Pediatric Clinic; Charles May; Classroom, 4th Floor Annex.

Veterans Administration Hospital

8:00 - Proctology Rounds; W. C. Bernstein and Staff; Bldg. III.

8:30 - Hematology Rounds; P. Hagen and E. F. Englund.

*Indicates special meeting. All other meetings occur regularly each week at the same time on the same day. Meeting place may vary from week to week for some conferences.