Amy Lowell

INDEX

ANNOUNCEMENTS

1. SURGERY SEMINARS

WINTER QUARTER - 1934

Thursdays - 4:30 -
Todd Amphitheater.

Jan. 18 Dr. Roscoe C. Webb
Back Injuries

Jan. 25 Joint seminar with the Department of Pediatrics
Drs. Willis Thompson and Herbert A. Carlson
Treatment of Empyema

Feb. 8 Dr. Vernon L. Hart
Lumbosacral Lesions

Feb. 15 Dr. John R. Paine
History of the Use of the Stomach and Duodenal Tube

Mar. 1 Dr. Arthur A. Zierold
Head Injuries

Mar. 8 Dr. Carl W. Waldron
Tumors of the Jaw

ANYONE INTERESTED IS CORDIALLY INVITED TO ATTEND.

2. SURGERY CLINIC FOR SENIORS

Surgery 30w 1934 — Todd Amphitheater 8:00 - Monday

Jan. 8 Dr. Martin Nordland
Goiter

Jan. 15) Dr. Oswald S. Wyatt
" 22) Some Surgical Disorders of Infancy and Childhood

Jan. 29 Dr. Harold E. Hullsiek
Carcinoma of the Colon and Rectum

Feb. 5 Dr. Carl W. Waldron
Fractures of the Jaw

Feb. 19 Dr. John M. Culligan
Renal Calculi

Feb. 26 Dr. Edward Moren
Head Injuries

Mar. 5 Dr. William A. Hanson
Surgery of the Liver

Mar. 12 Dr. James M. Hayes
Acute Infections of the Biliary Tract

II. ABSTRACT

AMYLOID DISEASE

Abstracts and impressions prepared with the help of Medical Fellow Carl Ecklund who is interested in the experimental production of amyloid disease.

References:

General study of 125 cases:

1. Rosenblatt, M. B.
Amyloidosis and amyloid disease.
Am. J. Med. Sc. 186:815 (Oct.) '33.

Amyloid Kidney

2. Bell, E. T.
Amyloid disease of kidneys.
Am. J. Path. 9:185 (Mar.) '33.

3. Noble, J. F. and Major, S. G.
Renal insufficiency in amyloid disease.
Arch. Path. 8:762, '29.

4. Christian, H. A.
Nephrosis syndrome associated with idiopathic amyloidosis.
Med. Cl. North America, 15:805, '32.

5. Shapiro, P. F.
Lipoid nephrosis--pathology. genesis and relation to amyloidosis.
Arch. Int. Med. 46: 137, '30.

Adrenal Insufficiency

6. Bannick, E. G., Berkman, J. N. and Beaver, D. C.
Diffuse amyloidosis.
Arch. Int. Med. 51:978, '33.

7. Philpott, N. W.
Addison's disease in association with amyloidosis.
Ann. Int. Med. 1:613, '27 - '28.

Bowel in Amyloidosis

8. Randall, O. S.
Multiple myeloma complicated by intestinal obstruction due to local infiltration of small intestine.
Am. J. of Cancer, 19:838 (Dec.) '33.

Congo Red

9. Bennhold, H.
Uber die ausscheidung intravenos einverlichten Kongorates bei den verschiedensten Erkrankungen insbesandere bei Amyloidosis.
Deutsch. Arch. fur Klin. Med. 142:32, '23.

10. Also, Klin. Wchnschr. 3:1457, '24.

11. Wallace, J. E.
Diagnosis of amyloid disease by the intravenous injection of Congo Red.
Lancet 1:391, (Feb. 20) '32.

12. Bookman, A. and Rosenthal, J.
The clinical value of intravenous injection of Congo red in the diagnosis of amyloid disease.
Am. J. Med. Sc. 173:396, '27.

Healing of Amyloid Disease

13. Waldenstrom, H.
Uber das Entsthchen und Verschwinden des Amyloids beim Menschen.
Klin Wchnschr. 6: 2255, '27.

Pathogenesis of Amyloid; Reticulo-endothelial and Antibody Reactions.

14. Jaffe, R. H.
Experimental amyloidosis in mice.
Arch. Path. and Lab. Med. 2:149, (Aug.) '26.

15. Jaffe, R. H.
Amyloidosis produced by injection of protein.
Ibid. p. 25.

16. Letterer, E.
Ein Beitrag zur experimentellen Amyloidforschung.
Verhdl. der Deutsch. Path. Gesell, 20:301, '25.

17. Letterer, E.
Experimentelle Studien uber Art and Ent stchung des Amyloids.
Ziet. fur. Inn. Med. 47:417, '26.

18. Grayzel, H. G., Jocalio, M., Moslaw, M., and Worshell, H. B.
Experimental studies of amyloidosis.
Proc. Soc. Exp. Med. 28:172, '30.

19. Loeschcke, H.
Vorstellungen uber das Wesen von Hyalin und Amyloid auf Grund von serologishen Versuhen.
Beit. zur Path. Anat. und Allg. Path. 77:231, '27.

20. Smetana, H.
The relation of the reticulo-endothelial system to the formation of amyloid.
J. Exp. Med. 45: 619, '27.

21. (Review of older literature in English)
Bailey, C. H.
The production of amyloid disease and chronic nephritis in rabbits by repeated intravenous injections of living colon bacilli.
J. Exp. Med. 23: 773, '16.

Silica and Amyloidosis

Clinical

22. Carey, J. B.
Pneumosilicosis and amyloidosis.
Ann. Int. Med. 6: 1106, (Feb.) '33.

Experimental

23. Murato, M. and Yoshikawa, W.
Experimentelle Erzehgung von Amyloidose durche orale und parenterale Verabreichung der Kibsilsaure und einer ibrer Verbindungen.
Virch. Arch. 264: 587, '27.

eneral Statement:

The literature on amyloid disease ontains very few summarizing papers robably because the knowledge of the ondition is still too fragmentary for such ummaries to be made. Many papers deal ith the causes and pathogenesis of the isease. Numerous cases are being re-orted with unusual locations of the de-osits. One group of cases which have reated interest are those without any pparent cause. A few papers summarizing he clinico-pathological features of the isease as it involves special organs can e found.

hemistry of Amyloid Deposits

The term "amyloid", meaning starch-ike, was given to the deposits because hey became blue if treated with iodine ollowed by sulphuric acid (Virchow 1853). rawkow (1897) presented the idea that he substance is a chondroitin-sulphuric cid-protein compound since the organs ith amyloid contained this substance, hereas normal parenchymatous organs do ot. Chondroitin-sulphuric acid is made p of sulphuric and acetic acid and car-ohydrates in the form of glycuronic acid nd chondrosamine (anisomer of glucosamine). anssen (1908) mechanically removed amy-oid from spleens and found that it con-ained no chondroitin-sulphuric acid al-hough it was present in the whole amyloid rgan. Mazeda (1909) stated that amyloid ontained no sulphuric acid. In recent ears, the theory advanced by Krawkow is ot generally accepted. The results of everal investigations show that neither ulphur or carbohydrates are present. he substance is a protein, the exact ature of which has not been determined. he excess of chondroitin-sulphuric acid n amyloid-containing organs has apparent-y not been explained.

The staining properties of amyloid re confusing. Regardless of the cause of he amyloidosis, the position of the de-osit or the specie involved (human, horse, ouse, etc.), the substance has about the ame characteristics. The amyloid reacts o a number of substances: iodine, iodine-ulphuric acid, methyl-violet, Congo Red, tc. In the same individual and even in the same area, i.e. within one glomeru-lus, the reaction varies. It is unknown whether the reaction is physical, chem-ical or varies with the age of the deposit.

Pathology:

Specie distribution: The condition is widespread. It occurs in horses, cows, chickens, man and experimentally in mice, rabbits, guinea pigs, frogs and other animals.

The earliest changes have been ob-served in the experimental animals. In these, the early deposits are fine droplets in the cytoplasm of the reticu-lo-endothelial cells. In some cases, proliferation of these cells with actual granulomatous formation has been seen. Other early deposits have been observed in the endothelial cells of capillaries (Bell). Here, there is a definite pro-liferation of the cells. In the next stages, the nuclei of the vascular endothelial and reticulo-endothelial cells disappear leaving a clump of the amyloid material. Whether this clump grows by addition of more material directly or within adjacent cells is not clear but it apparently takes place by the latter method. The significance of these early changes is that the amy-loid is present in both vascular endo-thelium and reticulo-endothelium. The latter type of deposit leads to enlarge-ment of the organ whereas the vascular deposits cause obstruction in the cir-culation and eventually lead to atrophy. This produces the "contracted" kidney sometimes seen and probably is a factor in the development of clinical symptoms when the amyloidosis involves structures such as brain and heart.

Organs involved seem to be any in the body (bone, gonads?). The usual sites are liver, spleen, kidneys and adrenals. In experimental animals (feeding experiments), the amyloid ap-pears first in the spleen, then in the liver and then kidneys. In 1727 autop-sies (Rosenblatt), there were 125 cases of amyloidosis - 7.2%. The distribution was as follows:

Spleen	89	Stomach	1
Kidney	72	Heart	1
Liver	63	Rectum	1
Adrenal	41	Tongue	1
Lymph nodes	8	Myeloid	7
Parathyroid	4.5		
Pancreas	3		
Intestine	2		

A collection of the individual cases from the literature would give a false impression of the areas involved because of the tendency to report cases with unusual distribution.

Special forms of localization: Even a superficial review of the literature shows an odd assortment of areas involved by amyloid either alone or in combination with other areas. Some of these are as follows: nose, larynx, trachea, brain, meninges, skin, muscle, heart, veins, arteries, bladder, seminal vesicles, bone marrow and the viscera. The involvement may be diffuse, localized or nodular. Thus, there may occur odd cases of polyps of the nose, infiltrations of one muscle group (gluteal, heart) or obstructing tumors at the base of the bladder due to amyloid deposits without involvement elsewhere.

Pre-amyloid stages have been described. Sometimes some of the masses are not typical amyloid deposits. They stain faintly, give irregular reactions with the various dyes or histologically appear like hyaline. It has been suggested that these are pre-amyloid stages. In the experimental studies, such as pre-amyloid stages, apparently are not encountered. The interpretation of the hyaline masses as amyloid can be questioned.

Pathogenesis:

Causes: The usual causes of clinical amyloidosis are various forms of longstanding suppuration. In one series, of 125 cases, the preceding disease was as follows:

Tuberculosis	110
Carcinoma of lung	4
Pyonephrosis	4
Carcinoma of stomach	1
Carcinoma of esophagus	1
Myltiple myeloma	1
Chronic lymphatic leukemia	1
Syphilis	1
Chronic arthritis	1
No known preceding disease	1

In Bell's group of 65 cases, the preceding diseases were as follows:

Tuberculosis of lungs	23
Tuberculosis of spine	8
Tuberculosis of hip joint	2
Chronic abscess	6
Chronic osteomyelitis	5
Empyema	4
Pyonephrosis	2
Transverse myelitis with secondary infections	2
Syphilis	4
Ulcerative enteritis	1
Bronchiectasis	1
Ulceration of legs	1
Unresolved pneumonia	1
Chronic arthritis	1
None	4

In both of these series, tuberculosis was the causative disease in the highest percentage of cases.

In Bell's group, tuberculosis was associated with extensive chronic suppuration in all cases. Rosenblatt noted that in tuberculosis with suppuration the incidence of amyloid disease was greater than in the general group of tuberculous cases. The same has been observed by others. It is said that the large quantities of leucocytes is the actual factor involved.

In the cases reported in the recent literature, there is an unusually large number in which no preceding disease was present. In Carey's case, the associated disease was silicosis.

In the experimentally produced amyloid deposits, the causative agents may be divided into 3 groups: protein, bacteria and such elements as silicon and manganese. These substances may be given by mouth or by injection. It is surprising to note the wide range of protein and bacteria which may be used. Hirose (John Hopkins Hosp. Bull. 40: 33, 1913) lists 19 bacterial agents alone. The type of protein used likewise is

ariable. One of the common methods of roduction is the peritoneal implantation f homogenic or heterogenic pieces of issue. These pieces on disintegration elease the protein. In these experiments, t is unknown whether the bacteria and rotein, or whether the leukocytic reaction to their presence, is the exciting actor.

Development: Many theories as to he actual development of the amyloid deosits can be found. Some of these theories tate that the amyloid substance is formed n the area of suppuration and is transerred to its final position by the leukoytes or is carried in the serum and is recipitated into the various tissues. ther theories postulate an abnormality f protein metabolism induced by the supuration or by the intake of the protein. his abnormal protein is deposited in the arious parts of the body. Some authors aintain that lipoid nephrosis and amyloid isease are related processes. Another heory is that the amyloid deposit repreents a form of degeneration within the rgan. Osler stated that amyloid disease f the kidney was one of the end results f chronic nephritis, i.e., a degenerative process.

One of the most interesting theories pon which to speculate is that of the ntigen-antibody-precipitin phenomena. t is generally agreed that the reticulondothelial system is the one which is orphologically involved. In brief, the heory is as follows. A protein, either utogenous or not, is the antigen. The eticulo-endothelial system in part or ntirely produces the antibody. Following nother dose of the antigen, a precipitin eaction occurs. The precipitation of he antigen takes place within the retiulo-endothelial cell forming the protein eposit. Some authors claim that the eukocytes alone are the antigenetic actors.

It has been suggested that there is lso an anaphylactoid reaction. It is nown that in this type of reaction cerain tissues become sensitive and they are nown as "shock" tissues, for example ung, bowel, uterus, etc. The isolated ocalization of the amyloid deposits peraps can be explained by the anaphylactoid reaction in "shock" tissues.

This serological theory genesis is receiving considerable attention. In general, these theories seem to be most applicable to the human types. Many things support this theory. It is well-known that horses used for the production of sera frequently develop amyloid disease. (Doerken, E., Virchow's Arch. 286: 487, '32). The widespread presence of the disease throughout the animal kingdom from amphibians to man suggest that some such process as the antigen-antibody reaction is involved. "Blocking" the reticulo-endothelial system by dyes delays the development of amyloid disease. A diet high in fats (also liver and meats) is likewise protective. Apparently amyloid begins to develop when the liver is depleted of fat (Jaffe). The effect of diet on antigen-antibody formation is not clear. Likewise, the development of amyloid after the injection of silica is difficult to explain by this theory.

Clinical Features:

The incidence of amyloid disease is low. In 1727 autopsies, there were 125 cases (7.2%). In the Department of Pathology, University of Minnesota, there are 65 cases on record.

Sex: Males and females are about equally involved.

Age: In Bell's group, the decades from 10 to 60 showed approximately an even division with a maximum between 40 and 50.

General symptomatology: Jaffe noted in the experimental animals a rapid loss of weight coincident with the development of amyloid disease. He also noted a definite anemia, leucocytosis of the polymorphonuclear type and a subnormal temperature. Bernhard, F. (Deutsch. zeit. fur Chir. 221:130, '29) states that the bleeding time is prolonged in amyloidosis. He cites cases that bled to death very much in the same manner as hemophiliacs. He believed that this was due to injury to the liver producing changes in fibrinogen formation.

ymptom Localization:

In generalized amyloidosis, it is said in the older literature that the symptoms of the disease are always those referable to the kidney. It undoubtedly is true that most patients in large series will show kidney signs. In Bell's group of 65 cases, albumen in the urine was present in all but 4. In Rosenblatt's series of 125 cases, the urine was studied in 109 cases and 79 of these showed albuminuria. However, in the more recent literature, cases are being reported in which the presenting symptoms pointed to damage in other organs: adrenal, heart and brain. Some of the cases with odd distribution showed symptoms due to the localization of the deposits in the nose, tongue, larynx, skin, muscle, bladder, etc.

Special localization: In addition to these bizarre types, there are cases of generalized amyloidosis which also give symptoms due to the special localization. Gastro-intestinal amyloidosis causes cramps, diarrhea, constipation and in such individuals a diagnosis of intestinal obstruction may be made. Involvement of the heart may produce cardiac decompensation. Adrenal deposits lead to symptoms of Addison's disease which may overshadow all of the other symptoms. Philpott reports a case of Addison's disease in which there was no suspicion of amyloidosis until autopsy. He found 7 other such cases in the literature. Bannick, Berkman and Beaver reported 3 cases in all of which the symptoms of suprarenal insufficiency, including pigmentation were present. The presence of these symptoms is probably not always recognized.

Kidney in Amyloid Disease: Many interpretations of the renal symptoms can be found. Some authors have interpreted the clinical findings as evidences of lipoid nephrosis or various forms of nephritis and when amyloidosis has been found at autopsy several theories regarding the inter-relationship of the two have been presented. Although there may be independent kidney damage due to the suppurative conditions it would seem that probably the underlying disease from the beginning as the amyloid deposit.

Many single case studies can be found. Bell's series consist of 65 cases. This author makes the following observations:

Albuminuria was present in all but 4. The absence of albumin is almost conclusive evidence that very little or no amyloid is present in the kidneys. The albumen escapes through injured glomerular capillaries.

Urinary proteins are low in albumin. In amyloid disease, the percentage is 35 to 60 whereas in chronic nephritis and lipoid nephrosis it is usually about 90%.

Serum proteins uniformly show levels below normal.

Edema is variable. It was present in 50% of the cases. It may be dependent upon associated glomerular changes other than amyloid.

Hematuria is occasionally seen.

Hypertension is most often absent. A large number of cases show hypotension (adrenal insufficiency?). A few cases of hypertension have been noted. Bell collected 6 such cases and had 3 in his own series.

Renal insufficiency is a well-known cause of death in amyloid disease. In Bell's group, all of the cases with advanced amyloid deposits showed imparied kidney function. The size of the kidneys is usually large but "contracted" kidneys have been found. The enlargement appears to be partly due to cloudy swelling resulting from the infection. The lesions in the kidney consist of amyloid accumulation in the endothelial cells of the glomerular capillaries, in the muscle layer of the arterioles and under the basement membrane of the tubules. Obstruction of the arterioles may be a significant part of the process. Bell and also Th. Fahr stress the presence of casts in the tubules producing obstruction and atrophy.

Congo Red Test:

The test was introduced by Bennhold (1923) and has since become a standard procedure in diagnosis of amyloid disease. Bennhold stated that the normal absorption of the dye was up to 30%. In amyloid disease, there is 40 to 100% absorption. It is said that over 65% absorption is conclusive. The dye is absorbed by the amyloid deposit and can be found there at postmortem, many months later (Hargrave, M., Arch. Path. 15: 238, Feb. '33). Bennhold found that the dye is also retained within the serum. In a more recent review of the Congo red test, Wallace states that in "tubular and parenchymatous nephritis", the dye disappears through the kidney. Therefore, the urine, as well as the serum, must be examined for the dye. In "splenic tumors of non-amyloid origin," it has been said that the dye also disappears more rapidly than normally. Wallace was unable to confirm this statement in three cases of splenomegaly. The author makes the following observations on the technique of the test: (1) The dye may be injected quickly without ill effects. (2) Perivenous extravasation causes no damage but the dye persists in the tissue up to 4 weeks. (3) Hemolysis and clotting ruin the test. (4) The dye in the blood increases the tendency to clotting. Koller (Scheiz. Med. Schnschr. 62:522, May 28, '32) observed that the granules of the eosinophiles take up the due.

Healing in Amyloid Disease: Waldenstrom in twelve cases was able to watch the changes in the liver by means of diagnostic puncture. In three of these cases, the amyloid disappeared entirely coincidently with the healing of the primary disease. In one of these cases, the liver had extended into the iliac fossa and another case had gone through a period of uremia and marked edema.

Impressions:

1. The literature on amyloidosis contains very few summarizing papers. Particularly in recent years, cases with unusual distribution are being reported. It is notable that in our University group 5 recent papers on amyloidosis have appeared.

2. The term "amyloid" was given to the disease because the deposit turned blue when treated with iodine followed by sulphuric acid. It is not starch. In 1897, investigations showed that amyloid containing organs were high in chondroitin-sulphuric acid and it was assumed that the amyloid was made up of this substance. In 1908, it was shown that although the organs contained excess of this substance the amyloid deposits themselves were free of it. Now, it is assumed that the substance is a protein, the exact nature of which has not been determined.

3. The staining properties of amyloid are poorly understood. It reacts variably with a large number of substances and even in the same specimen the reaction may not be uniform. It is unknown whether the reaction is physical, chemical or varies with the age of the deposit.

4. Amyloidosis is remarkably widespread as it occurs in all types of animals from amphibian to man. It is spontaneously or experimentally induced.

5. The earliest form of the deposit consists of fine droplets in the cytoplasm of the reticulo-endothelial cells and in the endothelium of blood vessels. The deposit within the cell increases until the nucleus of the cell disappears leaving a clump of amyloid. Further frowth of the deposit beyond this stage is not well known. It probably grows by the addition of more amyloid within adjacent cells rather than by addition to the original deposit.

6. The deposition within the reticulo-endothelial cells leads to enlargement of the organ and the deposition within the endothelium of blood vessels leads to obstruction and circulation and naturally to atrophy.

7. Any organs in the body may be involved with the possible exception of bones and gonads. No instance of involvement of these structures is found in the literature. In cases of generalized amyloidosis the spleen, kidney, liver and adrenals rarely escape.

8. A large number of cases with bizarre depositions of amyloid have been reported. These deposits may be isolated and nodular. They may be present without deposit in any of the other organs.

9. These deposits may occur in the nose, larynx, trachea, brain, meninges, skin, muscle, heart, veins, arteries, bladder, seminal vesicles, bone marrow and other viscerae.

10. Hyaline-like deposits which resemble amyloid have been described as pre-amyloid stages (see last week). Some of the cases showing odd localization have been of this type. The usual causes of clinical amyloidosis are various forms of longstanding suppuration, notably tuberculosis with secondary infection. The other types of associated longstanding suppuration are malignancy, leukemia, syphilis, arthritis.

11. In the recent literature, there is an unusually large number of cases with no demonstrable preceding disease reported.

12. In the experimentally produced amyloid deposits, the causative agent is of 3 types: protein, bacteria or such elements as silica and manganese. These are given by mouth or injection. There is a surprisingly wide range of proteins and bacteria used. One author cites 19 bacterial agents alone. One of the common methods of production is the peritoneal implantation of homogenic or heterogenic pieces of tissue which on disintegration releases the protein? It has been suggested that the leucocytes brought out by the bacteria or the protein are the actual exciting factors.

13. There are many theories as to the actual development of the amyloid deposits which have been presented. It is said that amyloidosis is a manifestation of abnormal protein metabolism; that the amyloid is formed in the area of suppuration and transferred to its final resting place by the serum or leucocytes; or that the amyloid represents a form of degeneration within the organs.

14. One of the most interesting theories is that of an antigen-antibody-precipitin phenomena. It is known that the reticulo-endothelial system is the one which is morphologically involved. The theory is as follows: a protein, either autogenous or not, is the antigen; the reticulo-endothelial system in part or entirely produces the antibody. Following another dose of the antigen, a precipitation reaction occurs within the reticulo-endothelial cells, giving rise to the amyloid deposits.

15. It has often been suggested that an anaphylactoid reaction takes place. Certain tissues become sensitive like the "shock" tissues in true anaphylactoid reactions and the isolated localization of amyloid deposits perhaps can be explained by the anaphylactoid reaction within "shock" tissues.

16. This theory of genesis is receiving considerable attention. It is well-known that horses used for production of sera frequently develop amyloid disease. The widespread presence of the disease throughout the animal kingdom suggests that some such common process is involved. Blocking of the reticulo-endothelial system delays the development of amyloid.

17. Other facts, however, are difficult to explain on the basis of this theory. A diet high in fat and also liver and meat is protective and delays the formation of amyloid. It is said that amyloid does not develop until the liver is depleted of fat. However, the development of amyloid after the injection of silica is difficult to explain.

18. The incidence of amyloid disease is very low. In 1727 autopsies, the incidence is 7.2%.

19. Males and females are about equally involved.

20. In one group of 65 cases in the decades from 10 to 60 show approximately an even distribution with a definite increase between 40 and 50.

21. In experimental animals, a rapid loss of weight coincident with develop-

ment of the amyloid disease has been seen. There is anemia also and a leukocytosis of the polymorphonuclear type. A subnormal temperature has been observed. In some of the clinical cases, there is a tendency to bleed. This has been explained on the basis of liver injury.

22. It is generally thought that the symptoms of amyloidosis are nearly always referable to the kidney. It is probably true that in large series of cases most of the individuals show signs of kidney damage. However, in more recent literature, cases are being reported in which the presenting signs point to damage in other organs, i.e. adrenals, heart, brain, etc.

23. Cases without generalized distribution show signs due to the localization of the deposit in the various organs, such as the nose, tongue, larynx, skin, muscle, bladder, etc.

24. In the picture of generalized amyloidosis, there also may be symptoms due to special localization, for instance, gastro-intestinal amyloidosis causes cramps, diarrhea, constipation and sometimes a diagnosis of intestinal obstruction is made on this basis. Involvement of the heart may produce cardiac decompensation. Several cases are being reported in which involvement of the adrenals gave a picture of Addison's disease.

25. The kidney in amyloid disease has been more intensively studied. Since the symptoms of amyloidosis of the kidney are very much like those of other forms of nephritis, many cases have been clinically diagnosed as nephrosis or parenchymatous nephritis and when the amyloidosis was found at autopsy numerous theories regarding the inter-relationship of the two have been presented. It seems that probably the amyloidosis was usually a primary condition.

26. The absence of albumen in the urine is almost conclusive evidence that there is very little or no amyloid present in the kidney. The albuminuria is due to injured glomerular capillaries. The degree of albuminuria is variable. It may be found only shortly before death or may be present in large quantities over a long period of time.

27. Urinary proteins differ from those found in chronic nephritis and lipoid nephrosis in that the percentage of albumen is low. 35 to 65% in contrast to 90%.

28. The serum proteins in advanced cases show markedly low levels similar to those seen in lipoid nephrosis.

29. Edema is variable. It is present in about 50% of the cases and it may be dependent upon the primary causative disease rather than upon the amyloidosis of the kidney. Occasionally, hematuria is seen.

30. Hypertension is rare. Most cases show hypotension (adrenal insufficiency?). Only a few cases of hypertension have been observed. Bell collected 6 such cases and had 3 in his own series.

31. Renal insufficiency is a well-known cause of death. In a group of 65 cases, all of the cases with advanced deposits showed impaired kidney function.

32. The size of the kidney is usually large but contracted forms have been found.

33. The lesion in the kidney consists of amyloid accumulations in the endothelial cells of the glomerular capillaries, in the muscle layer of the arterioles and under the basement membrane of the tubules. The tubules are filled with casts and lead to obstruction and atrophy.

34. Congo Red test was first introduced in 1923 and since then has become a standard procedure in diagnosis of amyloidosis. Normal absorption of the dye is up to 30%. In amyloid disease, there is from 40 to 100% absorption and it is said that any absorption over 65% is conclusive for amyloidosis. The dye is taken up by the deposits and also retained within the serum. It is said that "tubular and parenchymatous nephritis" leads to excretion of the dye through the kidney. Therefore, urine as well as the serum must be examined. It has also been said that splenomegaly causes disappearance of the dye but this

as not been confirmed.

35. The dye may be injected quickly ithout ill-effects. Perivenous extravaation causes no damage but the dye persists in the tissue up to 4 weeks. Hemolysis and clotting interfere with the test nd the presence of the dye in the blood ncreases the tendency toward clotting.

36. Waldenstrom in 12 cases was able o watch changes in the liver by means of iagnostic punctures. In 3 cases, the myloid disappeared entirely coincident ith the healing of the primary disease.

37. The following points in the literture are noted with particular interest: 1) The tendency to place the disease in he realm of immunology. (2) The odd solated localization of the deposits hich may be tumor-like masses in various arts of the body. (3) The evidence that myloidosis may heal.

R.W.K.

II. CASE REPORT

CHRONIC ARTHRITIS. AMYLOIDOSIS. UREMIA.

Case is of white male, 28 years f age, admitted to Minnesota General ospital 9-26-31 and discharged 3-5-32 161 days); readmitted 10-30-33 and exired 11-3-33 (4 days). Total stay - 165 ays.

ain Right Arm

1922 - Following attack of fever and iarrhea, had weakness and soreness of ight arm which lasted all winter.

nset of Arthritis

1925 - Soreness of right shoulder which ched at night and felt stiff in morning. ymptoms continue.

nkylosis

1927 - Joints now completely ankylosed.

rthritis, Left Side

1929 - Injured left knee. Two days ater, swelling and stiffness developed. nee became acutely inflamed, and limitation of motion persisted up until the time of admission.

Marked Progression

Interval history: Left shoulder, left knee, both elbows, hands, wrists and ankles became progressively involved. Salicylate given for pain.

Admitted

9-26-31 - Physical examination: Questionable systolic murmur at apex. Limitation of practically all the joints, including both mandibular joints. Complete ankylosis of right shoulder. Swelling most marked about knee joints, which contain fluid. Laboratory: Repeated urinalyses negative. Blood - Hb. 61%, wbc's 15,200, rbc's 3,470,000, L 21%, Pmn's 79%. Stools - negative for blood, pus, mucus and parasites. X-rays of right knee and right shoulder show almost complete destruction of right shoulder joint, marked bony destruction and some bony ankylosis. The appearance suggested the end stage of a pyogenic or destructive arthritis. The right knee joint showed some narrowing of the cartilage and beginning destruction of the articular surface of the medial condyle of the tibia.

Vaccine Treatment - Improvement

Progress: Placed on Blaud's pills following which there was an increased Hb. of 10% (?). Received 19 injections of streptococcus viridans vaccine intravenously. At the end of his stay in the hospital, the improvement noted was as follows: Able to chew without pain. Could move neck more freely. Very slight limitation of motion persisted in right elbow but no pain. Marked increase in ability to flex left elbow. Swelling of both knees subsided considerably. Limitation of motion less marked. Both ankles much improved, and could put on own shoes, which he could not do on admission. At time of discharge, he got about with aid of crutches and walked as far as 6 blocks. During this admission, there was one aspiration of synovial fluid from the right knee joint. The fluid was quite cloudy and a small amount of blood was present. There were 10,500 cells per cmm. of which 94% were pmn's. Smears

showed no organisms. Cultures taken but not reported on chart.

Continued Improvement

1932 - Since discharge, has been taking vaccine treatment in the Out-Patient Department from time to time with considerable improvement. His chief difficulty in the 2-year interval was pain in the hips.

Epigastric Pain, Diarrhea, Nosebleeds, Stupor

1933 - For the year prior to admission, he has had epigastric distress with vomiting after eating numerous kinds of food. It usually came on two hours after meals, was not associated with any particular type of actual pain. The attacks occurred at intervals. About 6 weeks prior to admission, he began having diarrhea with pain in the upper abdomen. Stools contained bright red blood. No chills or fever. Diarrhea stopped approximately three weeks prior to admission. Two weeks prior to admission, nosebleeds began and have been almost continuous since onset. Appeared to become more ill, being sleepy and stuporous.

Admitted

10-30-33 - Physical examination: Temperature 96.4. Pulse 100. Blood pressure 64/40. Dehydrated and drowsy, answers questions very slowly. Cheyne-Stokes respirations present. Breathing is gasping in type. Blood is present in the mouth and nose. Pulse weak and thready. Marked muscular atrophy. Joints enlarged but not tender. Several of the joints fixed. Mucous membranes pale. Lungs negative. Heart - negative. Abdomen - sunken, no masses felt, no tenderness or rigidity, spleen not palpable, liver not enlarged. Laboratory: Urine (3) - specific gravity 1,015, 1,020, 1,016; albumen: 3+, 4+, cloudy; sediment - hyaline casts, granular casts, waxy casts, occasional wbc's. Blood - Hb. 50%, rbc's 2,420,000, wbc's 12,800, Pmn's 75%, L 25%. Blood sugar - 94 mgs., B.U.N. - 46.9, creatinine 11.4.

Uremia pericarditis?

11-1-33 - Very drowsy. Temperature 98.6. Appears to be a friction rub over left chest. Respirations slow. Periods of apnea. Complains of pain in left lower chest. Paraoral fluids given. B.U.N. - 123.5 mgs., creatinine 12.2.

Congo Red - protein

11-2-33 - More drowsy. Congo red test - 200 mgs. in 200 cc. triple distilled water injected intravenously. No Congo red in blood serum in 60 minutes. Blood Wassermann and Kahn - negative. B.U.N. - 133.3 mgs., creatinine 11.35, calcium 5.2. Examination of fundi - media cloudy preventing detailed examination of fundus; moderate degree of optic neuritis; retinitis edematous; vessels apparently normal; no hemorrhages or exudates. P.S.P. - no return in 2½ hours. Blood Chemistry: Total Protein 4.71; Fibrinogen 1.29; Globulin 2.67; Albumin .74 (corrected readings)

11-3-33 - Comatose. 9:47 A.M. - Expired. Clinical Impressions: 1. Chronic arthritis. 2. Gall-bladder disease, possible typhoid focus. 3. Perforated abdominal viscus, gall-bladder or duodenal ulcer. 4. Tuberculosis of peritoneum. 5. Diverticulum of lower end of esophagus or stomach. 6. Glomerulonephritis, uremia. 7. Amyloid disease with uremia.

Note: Uremia, hypotension, absent edema (?)

Autopsy:

Arthritis - slight Edema

Body is that of a well-developed, poorly nourished, white male, 28 years of age, measuring 170 cm. in length and weighing 130 lbs. Rigor is just beginning. Hypostasis is purplish and posterior. There is 1 to 2+ edema of the feet, 1+ of chest wall, abdominal wall and neck. No cyanosis or jaundice. The pupils are regular, each measuring 6 mm. in diameter. There is ankylosis of the shoulder joints. There is contracture about both knee joints with the knees held in partial flexure and they cannot be extended. Both ankle and knee joints are definitely enlarged. There is probable enlargement of the elbow joints. Subcutaneous fat over the abdomen and chest shows very definite edema. There are numerous puncture wounds.

Effusions into Serous Cavities

There is excess of clear fluid in the Peritoneal cavity. Appendix is not examined.

Pleural cavities: On the left side, there is about 1000 cc. of clear fluid with flecks of fibrin. On the right side, the cavity is partially obliterated along the interlobar fissure and apex of the lung, and in the interstices between the adhesions there is about 800 cc. of clear yellowish fluid. The Pericardial sac contains a slight excess of fluid.

Normal

The heart weighs 250 grams. No fibrosis of myocardium. No infarctions. The mural endocardium is smooth. The valves are well formed and show no recent or old endocarditis. The root of the aorta is of normal size and shows no atheromatous changes. The coronaries are soft and patent throughout.

Pulmonary Edema

The right lung weighs 900 grams, left 650. There is very marked edema in both lungs, being extremely marked on the right side throughout both the upper and lower lobes. The upper lobe has a consistence almost that of lobar pneumonia in an early stage but on cross section the infiltration apparently is due to edema. The pleura is stripped up in many places over both lungs with subpleural collection of fluid. There is some compression of both lower lobes due to the fluid in the pleural cavities.

Amyloid, Spleen and Liver

The spleen weighs 140 grams, is firm, has a leathery consistence and is bright red in color. It is dry and no pulp can be scraped away. A Lugol's-sulphuric acid test for amyloid shows a very strong positive reaction. Large, bluish blotches of amyloid show up throughout the examined surfaces.

The Liver weighs 1540 grams, has a pinkish color (Congo red), is quite soft, does not cut with increased resistance, The liver markings are fairly well retained. No change about the periportal spaces. The amyloid test is done and likewise shows a strong positive reaction.

The gall-bladder has a thin wall. No stones or polyp. The ducts are patent throughout and are not dilated or thickened.

Normal Bowel

Gastro-intestinal tract: There is no diaphragmatic hernia, diverticulum, enlargement or change in the lower part of the esophagus or the upper part of the stomach. There is no ulceration or hypertrophic inflammation of the stomach or duodenum. No adhesions about the duodenum or gall-bladder. The small bowel shows no thickening or evidence of amyloid deposits. No reddish discoloration of the bowel, indicating no absorption of the Congo red. The bowel is opened. There is some edema of the colon. No evidence of chronic ulcerative colitis. The mucosa is smooth throughout. No polyps or ulceration.

The pancreas is soft, shows no fibrosis, tumors or cysts. No pinkish discoloration.

Amyloid in Adrenals

The adrenals are well-developed on both sides. No adenomas present. The cortex of the adrenal, instead of a normal golden-yellow color, has a very decided reddish-orange tinge, apparently due to the absorption of the Congo red. The medulla shows no change.

Kidneys Involved

The right kidney weighs 100 grams, left 110. The capsules strip fairly easy on both sides. The kidneys appear small. They are not firm or hard. They cut with approximately normal resistance. The kidney fat is slightly increased in amount. The pelves show no evidence of hydronephrosis or infection. The kidney cortex appears slightly diminished in amount. The surface of the kidney after removal of the capsule is smooth. The amyloid test applied to the kidney is strongly positive. The ureters are not dilated or inflamed.

No Genito-Urinary Infection

The bladder shows no cystitis, diverticulae or trabeculations.

The prostate is approximately normal in size. No abscesses or evidence

of chronic infection. The seminal vesicles are thin walled. No pus, adhesions or fibrosis.

The aorta is of good caliber throughout. No atheromatous changes.

Lymph Nodes Not Enlarged

The lymph nodes are not appreciably enlarged either in the abdominal or thoracic cavities.

Organs of Neck - not examined.

Normal

Head: - The scalp and calvarium show no change. The meninges are thin and smooth throughout. No excess fluid. Externally, the brain shows no change. On cut surface, no hemorrhage is present. The ventricles are not dilated. The choroid plexus appears normal.

Arthritis

Joints: - The right knee and shoulder joints are exposed. There is an excess of clear, slightly turbid joint fluid in the right knee joint. This is aspirated aseptically and taken for culture. There is hypertrophy of the synovial membranes with numerous reddish tags, particularly in the suprapatellar fossa. The patella has an approximately normal surface. Greatest change is on femoral and tibial surfaces of the joints. There is atrophy of cartilages with irregular plaques. At the edge of the joints, there is a ledge of cartilage extending over the edge of the adjacent bone. The bone immediately under this ledge of cartilage appears eaten away for a distance of about 5 to 7 mm. to form a groove following the junction of bone and cartilage. This groove has a striking resemblance to the groove seen in wood eaten away by a worm.

Here and there, a projection of bone is seen which suggests hypertrophic bony change. The cartilage and bone of the tibia shows approximately the same changes as described. Resection of portions of the joints is done. This resection shows that the bone above the joint is thinned out. There is an atrophy of the cortex and cancellous bone. The marrow cavity is filled with yellow, fatty material. The shoulder joints are very difficult to expose. There appear to be adhesions of the muscle tendons and the capsule to the bone. Part of the cavity is obliterated by bony union. There appears to be only irregulr spaces remaining in the joint cavity on the superior posterior side. The anterior and inferior surfaces of the joints are obliterated by the bony union. No cartilage can be recognised as such, apparently is entirely atrophic. The bone adjacent to the joint is extremely thin, can be easily broken down with the fingers, exposing the same type of yellow marrow described for the femur.

Diagnoses:

1. Chronic arthritis.
2. Atrophy of cartilages of bone.
3. Hypertrophic synovitis.
4. Ankylosis, bony and fibrous.
5. Edema (anasarca).
6. Ascites.
7. Pleural effusion.
8. Pericardial effusion.
9. Pulmonary edema.
10. Amyloidosis of spleen, liver, kidneys and adrenals.
11. Uremia (clinical).

Microscopic Sections:

Prostate, bladder, brain, lungs, heart and pancreas - show no deposits of amyloid and there is no significant histological change.

Kidney - Practically all of the glomeruli are involved. The amyloid infiltration is extremely advanced. Only a few capillaries within the glomeruli are patent and many glomeruli appear to be completely obstructed. In some of the patent capillaries, proliferation of the endothelium can be seen. The tubules are atrophic. Many casts are seen in the collecting tubules. Some of the tubules are dilated. In the smallest arterioles, the amyloid infiltration is within the muscle layers. No amyloid is seen in the large vessels.

Spleen - In all the sections, there is a wide collar of amyloid surrounding the Malpighian Bodies. The lymphocytes within these bodies are diminished in number. The pulp is

also invaded but to a less extent.

Liver - Generalized infiltration with amyloid extending into the lobules from the perportal spaces. At the periphery of the lobule, the liver cells have been completely choked out. At the edge of the amyloid, it can be seen that the deposit is entirely within the sinuses and the atrophy of the liver cells is a secondary process. The centers of the lobules are free of amyloid.

Adrenals - Medullae are free of the deposit. In the cortices, there are extensive deposits particularly in the inner and middle zones. The periphery shows only slight invasion. The amyloid is deposited in the stroma cutting off clumps of the adrenal cells. The cytoplasm of these is vacuolated and appears to be degenerating.