in 1888 by Professors Jolly and von Mering for its soporific properties. It is said to occupy a place between chloral and paraldehyde, two parts being equal to one of the former or three of the latter. Its advantage over chloral is, that it has no depressing effect on the heart. Its smaller dose and less disagreeable odor make it preferable to paraldehyde in many cases. It produces a calm, refreshing sleep, which lasts for six or eight hours, from which the patient awakens without any bad symptoms. It is used in insomnia due to nervousness, debility, mental excitement, and delirium tremens, morphiomania, and in fevers. It has not proved of much use when the sleeplessness is due to pain. It does not cause headache, nausea, or deranged digestion. In very large doses it produces a lowered temperature, shallow respiration, feeble pulse, loss of reflexes, and paralysis of extremities. It is given in doses of ♏ xxx.–xlv. Its taste and odor often prove objectionable, and may be disguised by combining with extract of licorice or some aromatic. It may also be used as an enema with mucilage of acacia, in doses of ♏ xl.–xc. *Beaumont Small.*

**AMYLOFORM.**—A proprietary compound, stated to be a condensation product of formaldehyde and starch. It is a white powder, odorless, non-toxic, and insoluble in all ordinary solvents, and is used as a substitute for iodoform.

*Dextroform* is a similar compound of formaldehyde and dextrin, and it possesses the advantage of being soluble in water and of setting free its formaldehyde more readily. *W. A. Bastedo.*

**AMYLOID.**—(From *amylum*, starch, so called from the fact that the amyloid substance gives with iodine and sulphuric acid a reaction similar to that of starch. Also called waxy, lardaceous, or albuminous degeneration. French, *Dégénérescence amyloïde;* German, *Amyloidentartung, Wachsentartung, Speckentartung.*)

The term amyloid degeneration is applied to the appearance, in the body, of a clear, colorless, shining, homogeneous, highly refractive, and translucent body, greatly resembling wax, firm in consistency, and possessing but little elasticity. When treated with iodine solution, it takes on a mahogany color, which in marked cases may become bluish or green (see Plate VII.) If the specimen thus treated is further subjected to the action of dilute sulphuric acid, zinc, or calcium chloride, the mahogany color may be intensified, or a play of colors—red, violet, blue, or green—may be produced. This action, however, does not always occur.

Because of this characteristic reaction with iodine, so analogous to that of starch, Virchow was led to believe that the newly discovered substance was devoid of nitrogen and closely allied to cellulose or starch, and for this reason gave it the name amyloid. It was further designated as "animal cellulose." On the other hand, Meckel believed it to be closely related to cholesterin. Several years after, the chemical investigations of Friedrich, Kekulé, Schmidt, Rudeneff, and Kühne proved conclusively that the so-called amyloid was in reality a nitrogenous body of an albuminous nature. According to Tschermak, it is a coagulated, albuminous substance, and is possibly an intermediate product between the proteids on one side and fat and cholesterin on the other.

It bears also a very close chemical relation to the hyaline deposit found in blood-vessels and connective tissue, as is shown by the fact that amyloid organs sometimes contain hyaline masses in no way distinguishable from the neighboring amyloid except by the application of specific staining methods. In some cases the periphery of large masses of amyloid give the reactions for hyalin and not for amyloid. Litten found that pieces of amyloid tissue lost their characteristic reactions and became changed to hyaline when introduced into the abdominal cavity of animals. The strong general resemblances between the two bodies, their similarity of location, and the frequent coincidence of occurrence make it very probable that the two substances are very closely related and that they may change from one to the other.

Amyloid differs from other albuminous bodies in its characteristic staining reactions, in its resistance to the action of pepsin, and in its very slight tendency to putrefaction. When exposed for a long time to the action of the gastric juice it slowly dissolves, so that it is possible that its resistance to pepsin and agents of putrefaction is due to its great density, which hinders the penetration of fluids. It is likewise resistant to acids and alkalies, and is not altered by alcohol and chromic acid. Through the prolonged action of dilute sulphuric acid tyrosin and leucin may be obtained from amyloid, its end products thus harmonizing with its albuminous nature.

But little is known with certainty regarding the causes and nature of amyloid formation. It is one of the most common pathological conditions of the body, and may exist as a local change, or be widely distributed through many organs and tissues. It usually occurs as a slowly progressing disease in association with various cachectic conditions. In these cases of widespread formation it must be the result of some general disturbance of metabolism. The amyloid substance does not exist in the blood as such, but the material from which it is formed is, without doubt, derived from the blood. Though called amyloid degeneration, the process is not to be classed with the true degenerations of cell protoplasm, but is rather to be regarded as a pathological deposit, in the tissues, of a substance derived from the circulation. It has been conclusively shown that the cells of the affected tissue take no active part in the formation of amyloid. The location of the deposit is practically always in the walls of the blood-vessels or in the interstices of the tissues immediately around the vessels, and the organs which show the greatest degree of the change are those abundantly supplied with blood, as the liver, spleen, and kidneys. It is possible that the amyloid substance is the result of the union of some albuminous material derived from the blood with some constituent of the tissues, and that the lowered vitality of the tissues resulting from general or local disturbances of nutrition favors its formation; or, as the result of impaired nutrition, a peculiarly modified albuminous body may be separated from the blood through the activity of the secretory cells of the blood-vessel walls. As the chief seat of the amyloid deposit is always just outside the endothelium of the blood-vessels, it becomes highly probable that it is a *product of endothelial cell activity*, and is deposited in the tissues outside the endothelium in a manner analogous to the deposit of hyalin, lime salts, or silver pigment. This pathological secretion may be the result of general changes in the circulation whereby the secretory function of the cells of the vessels is changed, or the changes may be primary in the cells themselves. The fact that local deposits of amyloid occur without apparent general changes of nutrition favors this view. In the widespread deposit of amyloid in cachectic conditions the pathological condition of the cells may be produced by the altered state of the blood; in the local deposits it may be due to local changes in the vessels, caused by local inflammatory processes.

In the majority of cases the deposit of amyloid appears as a secondary phenomenon in various cachectic states, being most commonly associated with chronic tuberculosis of the lungs and bones, chronic suppurative processes, syphilis, chronic dysentery, and leukæmia. In these diseases the most extensive deposits may be found. It rarely occurs in the cachexia of carcinoma, and usually only when there is ulceration of the growth. It is also found, though less frequently, in association with pseudoleukæmia, chronic arthritis, nephritis, chronic diarrhœa, typhoid fever, prolonged malaria, and after severe forms of rachitis. Occasionally there may occur in children a widespread deposit of amyloid without any discoverable cause.

According to Cohnheim, amyloid deposits may become well developed in from two to three months. Czerny and Krawkow claim to have produced it in animals in





from three to sixty days through the establishment of suppurative processes, caused by injections of turpentine and of staphylococci. Experiments made in Ziegler's laboratory throw doubt upon these investigations. As a rule, the formation of amyloid takes place very slowly. It occurs most frequently between the tenth and thirtieth years, but may be found in new-born infants (congenital syphilis), and also in extreme old age.

Localization.—Amyloid occurs most frequently as a widespread deposit in one or several organs, especially affecting the spleen, liver, kidneys, and lymph glands. Next to these the mucosa of the intestine, the adrenals, and the omentum may show a marked degree of the change. In all of the organs it may occur to such an extent that it affects greatly the gross appearance. It is less frequently found in the intima of the great vessels, mucosa of the respiratory and urinary passages, thyroid, lungs, ovaries, testicles, prostate, bone marrow, salivary glands, and muscle. In these its occurrence is usually so limited that its presence can be made out only by means of the microscope.

The degree of the change varies very much in different cases. The kidneys may show a marked deposit, while the other organs may contain but little amyloid; in other cases the liver or spleen may be the chief seat of the change. The primary seat of the deposit and the order in which the different organs are affected vary with the individual case, and bear no definite relation to the associated pathological condition.

Local deposits of amyloid occur in single lymph glands following inflammatory processes (mesenteric glands after typhoid), in scars, local inflammations, hyperplastic growths, tumors (osteo-fibroma of tongue, chondroma of lung), in the tongue, tonsils, and larynx following syphilitic processes, and in the scars of liver gummata. Klebs obtained the amyloid reactions in a hard chancre. Numerous authors have found amyloid in pathological conditions of the cornea and conjunctiva (trachoma, staphyloma, etc.). It has also been found in old blood clots and thrombi, and frequently in the cartilages of old individuals who have presented none of the pathological conditions with which amyloid is usually associated. These local deposits of amyloid sometimes form tumor-like masses under conditions in which it is impossible to establish any relationship between them and any other pathological process. The corpora amylacea found in the prostate, nervous system, lung, etc., sometimes give a reaction resembling that of amyloid (see *Corpora Amylacea*).

Macroscopical Appearances.—When the deposit of amyloid is at all extensive, it is readily recognizable by the naked eye; but the degree and nature of the deposit and of the associated degenerative conditions vary so much that no general description can be given which will apply to all cases. The organ is usually swollen and plumper than normal, its edges are more rounded and its fissures deepened. Its volume and weight are increased, the latter sometimes four- to fivefold. The consistency is greatly increased; in severe cases the organ may have a wooden hardness. There is also a great loss of elasticity, so that pressure indentations made upon the surface of the organ remain for a long time. The blood-content of the affected organ is usually greatly diminished, so that its color becomes grayish or yellow if much fatty change is present. Very characteristic is the shining, translucent, waxy appearance of the cut surface, resembling that of bacon (lardaceous). The differences in histological structure of the various organs lead to individual appearances when amyloid is present, and these will be described separately.

The iodine test is best applied to fresh tissue. A moderately strong Lugol's solution should be used after washing out the blood, as the color resulting from the combination of the red hæmoglobin and yellowish-brown iodine very closely resembles the mahogany red of the amyloid. The iodine solution is poured over the freshly cut surface, allowed to stand for a minute or so, and then washed off. The amyloid areas are reddish brown, the non-amyloid ones yellow. If dilute sulphuric acid is now applied, the amyloid portion becomes dark green to black, or dark violet, while the unaffected tissue is of a clear gray color. This gross reaction is plainly seen, as a rule, only when the amyloid deposit is marked; but sometimes, as in the intima of the large arteries, it may be brought out very distinctly when no other appearances point to the presence of amyloid (see Plate VII.).

Microscopical Appearances.—Microscopically, amyloid appears as a homogeneous, hyaline substance, of rather high refraction, which is deposited almost exclusively in the walls of the capillaries and smaller arterioles. In its earliest stages it appears as a homogeneous layer outside the endothelium, but in more advanced cases, owing to the atrophy of the intervening tissue, the masses of amyloid increase greatly in size and may finally become confluent, so that the entire tissue, or a large part of it, may be replaced by amyloid. In this way large nodules or tumor-like masses are formed. It must be emphasized, however, that in its earliest stages the first appearance of amyloid is always next to endothelium.

It is never deposited in living cells. The tissue cells proper take no active part in the process, and the changes found in these cells are to be regarded as secondary. The lumen of the affected vessel is soon narrowed by the increasing deposit, and the resulting disturbance of blood supply leads to degenerative changes (atrophy and fatty degeneration) of the cells of the affected region. The deposit of amyloid between and around the cells near the blood-vessels leads to similar changes. The individual vessels are not equally affected throughout, and different vessels of the same organ may show the change in very different degrees.

The microscopical appearance of amyloid in sections stained with hæmatoxylin and eosin is so similar to that of hyalin that a differential diagnosis between the two deposits can be made only by means of some specific staining reaction. Of these the best and most practical is the Van Gieson's method. The sections are overstained in hæmatoxylin and then stained for one-half to one minute in a concentrated water solution of picric acid to which enough of a concentrated water solution of acid fuchsin has been added to give it a distinctly red color. By this method amyloid is stained a pinkish brown or yellow, while hyalin takes a deep red color.

The iodine reaction does not show so well in hardened material, so is best applied to fresh tissue. The specific reactions of amyloid with various aniline dyes are classic in the history of microchemistry, and it is largely to the wonderful amount of interest bestowed upon these that this branch of pathological technique owes a very great part of its development. The aniline stains most commonly used are methyl and gentian violet, methyl green, and iodine green. The amyloid tissue is best hardened in alcohol and cut without embedding. The sections are then stained for five to ten minutes in a two to five per-cent. solution of the stain, differentiated with dilute acetic acid, and mounted in glycerin or syrup. With all of these stains amyloid exhibits a metachromatosis. Methyl and gentian violet and iodine green stain the amyloid portion ruby red, while the non-amyloid is stained blue. Methyl green stains the amyloid a sky-blue, the non-amyloid a bright green. None of these reactions is permanent; the sections so treated gradually fade. On the whole, the Van Gieson's method, which can be applied to either paraffin or celloidin sections, is the most convenient and practical stain for the differentiation of amyloid.

*Liver.*—This organ is very frequently the seat of amyloid deposit. Outside the endothelium of the liver capillaries, between it and the liver cells, there is deposited a layer of amyloid, which, as it increases in thickness, presses upon the liver cells and separates them from their normal relations with the blood, so that they undergo atrophy and degeneration, and finally may entirely disappear. The amyloid masses thus become confluent, the only cells

left in the area are the endothelial cells, which may persist for a long time. The intermediate zone of the lobule is almost always affected to a greater extent than either the central or the peripheral one. The walls of the larger blood-vessels may also show the deposit. In more advanced cases the entire lobule may be replaced by amyloid. This marked change is usually confined to single scattered lobules, so that these appear to the naked eye as grains of boiled sago (sago liver). More rarely the greater part of the liver may be replaced by confluent masses of amyloid, whereby the organ acquires a wooden hardness and on section resembles the translucent portions of bacon (*Speck-Leber*).

*Spleen.*—In the spleen the amyloid deposit takes place in the fine reticulum of the pulp beneath the endothelium of the blood spaces. The follicles may alone be affected, appearing enlarged and translucent like boiled sago (sago spleen); or the chief deposit may be throughout the pulp, or may involve both pulp and follicles (*Speck-Milz*, lardaceous spleen). The arterioles of the follicles are often the only portions of the organ which show the deposit, and it is in these that the earliest appearance of amyloid in the body as a rule occurs.

*Kidney.*—The afferent arterioles of the glomeruli are usually first affected, then the glomerular capillaries and efferent vessels, and finally the smaller vessels throughout the entire organ. The change is never so marked in the medullary pyramids as in the cortex, but it may appear early in the straight vessels of the former. As the disease advances the deposit extends from the intertubular capillaries to the basement membrane of the tubules, which may appear as if surrounded by a hyaline ring. The intima of the larger branches of the renal artery may show small and irregularly scattered deposits. Since the glomeruli are the chief seat of the deposit, they appear on the freshly cut surface of the organ as small, firm, translucent dots usually about the size of pinheads.

*Lymph Glands.*—Extensive amyloid deposit is not common in the lymph glands, but scattered masses are very frequently found in them; and the walls of their small arterioles usually show a moderate degree of change in all cases in which the liver, spleen, and kidneys are extensively affected. Local inflammatory changes, both of the lymph glands and the tonsils, are very frequently accompanied by the formation of small masses of amyloid in connection with hyaline deposit, and the close relation of these substances is nowhere else so well shown as in these organs. In advanced cases the deposit may extend from the neighborhood of the capillaries into the reticulum, causing atrophy of the lymphadenoid cells.

*Muscle, Fat Tissue, etc.*—In striated muscle amyloid deposit is rarely found. It has been found in the tongue and in the muscles of the larynx in the shape of nodular masses. The deposit takes place first in the walls of the capillaries of the endomysium, and as it increases in size the sarcolemma comes to be surrounded by a clear, hyaline mass. As the muscle fibre is thus separated from its blood supply it undergoes atrophy and degeneration, finally disappearing so that the deposits of amyloid become confluent into nodular masses. A similar process may take place in heart muscle and in unstriped muscle, but is of rare occurrence. The amyloid deposits in striped muscle occur very frequently in the scars of gummata, but occasionally no evidences of preceding pathological changes can be made out. Adipose tissue is often extensively affected by amyloid disease, the deposit taking place in the walls of the larger blood-vessels and of the intercellular capillaries, so that the fat cells come to be surrounded by a thin hyaline layer.

*Mucous Membranes.*—The mucous membranes of the respiratory tract are very rarely affected. Scattered deposits may occur in the mucosa of the stomach and intestine, producing more or less extensive thickenings of the mucosa, which show the characteristic homogeneous, glassy appearance of amyloid. Large elevations may undergo ulceration, and at the bottom of the ulcer remains of the amyloid may be preserved. The large intestine is more frequently affected than the small. The deposit is in the walls of the capillaries of the mucosa and submucosa. Only in very rare cases is amyloid found in the mucosa of the genito-urinary tract.

General Nature of Amyloid Disease.—As stated above, the formation of amyloid is almost always secondary to other processes which are ulcerative or inflammatory in character, and of infective nature. While not in itself a true degeneration of cell protoplasm, the process is essentially degenerative in character, in that it leads to marked disturbances of nutrition. The deposit in the walls of the blood-vessels leads to partial or complete obliteration of their lumina, thus producing permanent interference with the circulation. As a result of this disturbance of nutrition, atrophy, fatty degeneration, or necrosis of the tissue cells takes place. The pressure of the amyloid deposits between the cells leads to similar results. Fatty degeneration and infiltration are almost always present to a greater or less degree in amyloid disease, and to a certain extent must be regarded as coincident processes produced, perhaps, by the same general disturbances of metabolism which give rise to amyloid. Severe anæmia is usually associated with the condition, and death takes place as a rule from a gradually increasing marasmus.

Symptoms.—The marked alterations in the structure of the affected organs and tissues lead to functional disturbances, which, however, may be very slight when compared to the extent of the deposit. The general clinical picture of the condition will vary, of course, with the organ affected and with the extent of the disease, so that a comprehensive description is not possible. Moreover, from the nature of the case, it is manifestly difficult or impossible to separate the symptoms of amyloid deposit from those of the disease leading to or associated with it. The nature of the primary process will modify very much the clinical appearances dependent upon the amyloid change. Frequently the beginning of the condition is shown by a rapid increase in the marasmus already existing, and by the enlargement of liver and spleen. These phenomena are always more marked in syphilis and in chronic ulcerative processes than in pulmonary tuberculosis. In such conditions as chronic varicose ulcers of several years' standing a rapid increase of the cachexia is usually pathognomonic of amyloid disease.

Associated with enlargement of the liver certain disturbances of digestion go hand-in-hand: absence of bile pigment in the fæces, fecal decomposition, meteorism, etc. Icterus is rarely present, and ascites only as associated with a general hydræmic or cachectic anæmia. Marked amyloid deposit in the kidneys is not always shown by disturbances of its function. The urine may show no changes; but as a rule albumin is present, the amount is increased, and the sediment contains hyaline casts, though usually not in great numbers. The latter never give the amyloid reaction, in spite of the repeated statements that they do. As amyloid deposit in the kidneys is, in the majority of cases, associated with chronic inflammatory changes, the character of the urine may vary greatly. Marked amyloid disease of the intestine is usually accompanied by foul diarrhœa.

Diagnosis.—The nature of the primary affection must first be considered. If in patients affected with any one of the chronic diseases known to be associated with amyloid (chronic tuberculosis, syphilis, chronic suppurative processes), painless swellings of the liver and spleen arise, in association with albuminuria and extreme paleness of the skin and mucous membranes, the diagnosis of amyloid is made very probable.

Duration.—The earliest stages of amyloid change cannot be ascertained clinically. It is probable that in many cases the process develops through several or even many years with alternate periods of improvement and exacerbation. It may, however, develop within shorter periods, as in a case observed by Cohnheim, in which suppuration of bone after a fracture led to well-developed amyloid disease within a few months. The duration of well-marked cases depends upon the organ chiefly af-





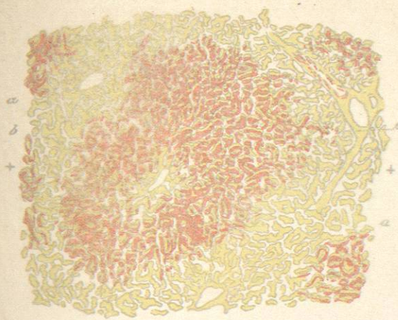


Fig. 1.

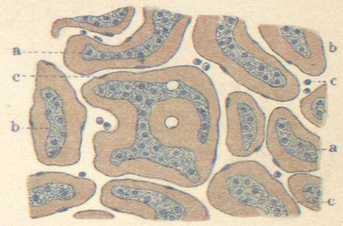


Fig. 3.

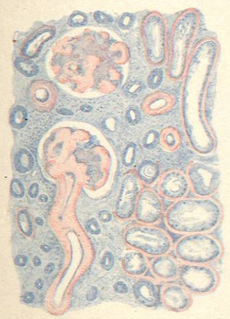

Fig. 2.

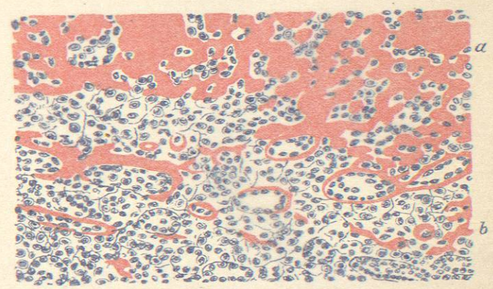


Fig. 4.

## AMYLOID DEGENERATION IN DIFFERENT ORGANS

Fig. 1.—Section of an Amyloid Liver, Showing the Effects of Staining it with a Solution of Iodine. *a*, Normal liver tissue; *b*, tissue that has undergone amyloid degeneration; *c*, Glisson's capsule magnified 35 diameters. (Ziegler.)

Fig. 2.—Amyloid Kidney, Stained with Aniline Violet. The amyloid is stained red. The deposit is most marked in the capillaries of the glomeruli and in the small arteries, and is seen also as a fine hyaline ring surrounding the membrana propria of the tubules. Magnified 400 diameters. (Ribbert.)

Fig. 3.—Section of an Amyloid Liver After being Treated with Methyl Violet and Acetic Acid. *a*, Elongated masses of liver cells; *b*, amyloid substance; *c*, endothelium of the capillaries; *e*, colorless blood corpuscles. Magnified 150 diameters. (Ziegler.)

Fig. 4.—Amyloid Degeneration of the Follicles and Pulp of the Spleen. (Alcohol; methyl violet; hydrochloric acid.) *a*, Follicular tissue in a marked state of amyloid degeneration; *b*, pulp tissue in which the degeneration has begun. Magnified 300 diameters. (Ziegler.)