AMYLOIDOSIS.

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Investigations have shown amyloid disease to be due to a combination of factors. 1. It is observed as an accompaniment of a large variety of infective and toxic diseases, particularly in those cases in which a discharging lesion is present. 2. It affects especially the spleen and the liver. 3. The condition can be produced experimentally by the injection of sterilised broth cultures of Staphylococcus aureus. 4. Experimental investigation has shown that the spleen is of special importance in amyloidosis because the injection experiments are invariably negative in animals from which the spleen has been removed, whereas the control experiments on normal animals give positive results in 30 per cent. of the cases. The laying down of amyloid substance therefore is in some way related to a derangement of an active splenic function. 5. The chemical analysis of amyloid shows that it has a variety of forms. These forms can be regarded on the one hand as different phases in the process of a physico-chemical change in any one organ, e.g. pre-amyloid, and achro-amyloid as suggested by Lubarsch, while, on the other hand, the variations in composition as seen in different organs may be determined by the specific metabolism of the organ attacked. This is suggested by the results obtained by Wells.

In view of the complexity of this process, the following investigation of a series of cases was undertaken with the purpose of discovering how far the microscopic study of the distribution of amyloid in the spleen, liver, kidney, and intestine throws light on the nature of the process. It was further attempted to determine the particular structure, the derangement of which leads to the deposition of the amyloid substance.

The material was obtained from nine cases of amyloid disease accompanying a variety of conditions. The tissue was fixed in alcohol or Pick's solution. Sections were stained with methyl violet.

The following is a result of a microscopic study of the above cases:

Spleen—1. Diffuse Type.—In many sections the capsule is uniformly thickened. There is frequently a diffuse deposit of
amyloid in the subcapsular region, but more often this area stains diffusely with a blue reaction.

The most marked amyloid lesions in the splenic pulp are under the endothelium of the sinuses. The cells thus embedded have atrophied. A positive intracellular reaction with methyl violet was observed in a few cells forming the splenic reticulum. There is a well-marked hyperplasia of pulp tissue and an abundance of sinuses.

The malpighian bodies show a variety of lesions.

1. Amylosed areas with splenic sinuses are to be found within the apparent boundary of the malpighian body and these are continuous with amyloid deposits in the neighbouring pulp. The lesions may involve only a small portion of the malpighian structure although more extensive depositions of a similar nature are not infrequently seen. Often the lesions are multiple.

2. Other malpighian bodies give a positive methyl violet reaction only in localised areas. This particular type of lesion also exhibits the usual characteristics of affected spleen pulp.

3. In still others, the lesion is entirely one of the malpighian body. Amyloid has collected in greatest density at the periphery and distinctly within the actual boundary of the malpighian body, while the surrounding pulp is either free or only slightly involved.

The walls of the smaller arterioles and capillaries of the malpighian bodies and splenic pulp are involved completely except for the thin intimal coats. The lesions in the larger vessels vary from an extensive infiltration of the adventitia and media to localised deposits in that part of the adventitia which borders on the media. Very many of these vessels of the larger type are free from amyloid.

These localised mural deposits of amyloid have several interesting features. Many are enclosed in endothelial-lined cavities which by position and structure are recognisable as lymph spaces. The indications are that the lesion first appears in the lymphatics and walls of the smaller branches from which amyloid spreads by continuity until it reaches the larger vessel. If a transverse section be made at or about the point of
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division it will appear that the larger artery has a localised mural lesion, whereas it is the smaller branch which is affected up to the point of division from the larger vessels.

Widespread depositions in the arterial coats were repeatedly traced to this type of initial lesion.

2. *Sago Type.*—The capsule in most sections is not obviously thickened. However, only a relative estimate which takes into consideration the previous thickness of the capsule and the degree of splenic enlargement can be of any value.

The pulp is hyperplastic but sinuses are relatively few. There is a conspicuous increase in the number of capillaries and smaller vessels.

In general, the amyloid lesions are very obviously localised and are not restricted to the malpighian bodies. Frequently the malpighian body, together with the surrounding pulp, is embedded in a moderately uniform mass of amyloid. There is nothing to indicate that one lesion has not affected both at the same time.

The deposition in the pulp is not limited to the subendothelial zone of the sinuses but has become more widespread.

In at least one series of sections many individual reticular cells gave a positive intracellular reaction.

The malpighian bodies, on the whole, are not prominent and are very often amylosed. Lesions in them vary considerably. Many are completely embedded in amyloid, while their arteries often are not affected, especially if the vessel be of the larger type. However, their smaller arterioles and capillaries are usually completely amylosed, even when the "body" includes a medium-sized non-affected vessel.

The accumulation of amyloid at the periphery of many malpighian bodies is very pronounced. Although amyloid material may at the same time be present both in the inner portions of the malpighian bodies and in the surrounding pulp, the heavier zone at the periphery is sufficiently marked to warrant consideration as to its probable relationship with the peripheral sinuses.

The general condition of the vessels in the sago waxy spleen is essentially the same as in the diffuse type. But a study of these sections elucidated a few points. As in the diffuse type, the smaller vessels and capillaries are affected most extensively, and in the larger vessels the changes are localised, as has already been described. However, a pre-
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amyloid substance can also be seen in the mural tissue spaces. Longitudinal sections of vessels show the changes to be peri-vascular in their initial stages.

Liver—1. Early.—In the early phase amyloid changes are limited almost entirely to the smaller arteries of the portal tract in which the lesions involve the greater part if not the whole of the vessel wall. Of the larger arteries relatively few are affected to any degree. Several exhibit localised deposits, while only occasionally is there any marked positive reaction in the adventitia or neighbouring media. The veins are free, although in the walls of several there are masses of a blue-staining homogeneous material, pre-amyloid (Davidsohn).

The liver cells are free from amyloid changes. The Kupffer cells are swollen, and between them and the underlying cells there are small masses of a blue-staining homogeneous material.

2. More Advanced.—Later, most lobules are affected on their middle and outer zones. Positively reacting masses collect between the Kupffer cells and their underlying liver cells. However, very frequently, the amyloid substance infiltrates the surrounding liver tissue which eventually causes atrophy of the involved liver cells, and occlusion of the intercellular canaliculi.

The larger portal tracts are moderately free. A number of the smaller arteries and a higher proportion of the smaller veins have suffered heavily. The central veins contain subendothelial deposits.

3. Advanced.—In the walls of the portal veins, collections of amyloid material are seen frequently when hepatic amyloidosis is very advanced. Such lesions when localised represent either affected branches involving the larger vessels at their junction, or, mural lymphatic channels containing masses of the amyloid substance. In the remainder, the mural deposits are usually associated with amyloid within the lumen of the vessel, or in the subendothelial zone of the intima.

In the hepatic arteries, the adventitia and the adventitial media are the sites usually chosen. Here and there the deposits are circumscribed, while in many of the larger type tissue spaces in the media have been preferred.

The hepatic veins are affected chiefly in their smaller branches.

The central veins are extremely dilated. The majority possess globular subendothelial deposits of a light-blue homo-
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Geneous material, many of which are intermixed with positively reacting masses.

The periductal vessels of the portal tract are in an advanced stage of amyloidosis, while the bile ducts are unaffected.

Within the lobules the middle and outer zones are the areas most frequently the seat of amyloid deposition. Occasionally the lesion has advanced into the central portion although the distribution here is irregular and more localised.

Kidney—1. Early.—In renal amyloidosis the lesion first to appear is in the glomerulus, and localised nodules centering about the capillary tufts are the most prevalent. Occasionally the whole glomerulus is converted into a homogeneous mass of amyloid. At this stage no other amyloid lesions are demonstrable in the kidneys.

2. More Advanced.—Circumscribed lesions in the glomerular tufts are again predominant. The walls of the vessels supplying the affected glomeruli have been completely infiltrated. The capillaries about the loop of Henle have been amylosed thus causing the displacement and atrophy of the neighbouring tubules.

3. Advanced.—To a moderate extent, the larger arteries exhibit mural deposits of amyloid. These vary from a circumscribed deposition in the adventitia to an extensive infiltration of the adventitia and media. Initial lesions in the vascular lymphatics are frequent findings.

The larger vessels are dilated and the arteries atheromatous. Very many of the glomerular tufts are entirely amylosed. Of these an appreciable number exhibit an uneven and nodular appearance as the reaction in different areas of the same glomerulus varied in intensity. The afferent and efferent glomerular vessels, the smaller renal arteries and veins, as well as the capillaries in general, show advanced amyloid lesions. The tubules suffer from displacement and atrophy due to pressure exerted by the amylosed peritubular vessels.

Chronic nephritis of a patchy distribution is fairly pronounced. These areas are more extensively amylosed than the rest.

Intestine.—The lymphatics and vascular channels of the villi have been the seat of an extensive amyloid deposition. The epithelium lining the intestine is atrophic and in several areas the cells approach the spheroidal and flattened types.
Amyloidosis has been produced experimentally by the injection of various substances but without the production of suppuration. It is therefore our first duty to find, if possible, the common factor which exists in the production of both the experimental and the human processes.

Davidsohn and others have produced amyloidosis experimentally by the intravenous injection of broth cultures of Staphylococcus aureus, previously killed by heat. Toxins alone have been effective, as seen in animals used for the production of diphtheria anti-toxin. But in general, in the human subject, amyloidosis accompanies chronic suppurative conditions. A similar process is induced experimentally by the injection of turpentine.

What is the common factor? An organism with its exotoxin, a toxin alone, and a purely chemical substance are all essentially different, and yet the substances can each produce the disease. The common factor in all three is toxicity, and a capacity to damage body tissues. Both of these are present in chronic suppuration as seen in the human subject.

Another coexisting factor in this series is chronic venous congestion, which, according to the post-mortem reports, was present in all cases.

These sufficiently indicate a common process governed by common factors and thereby warrant an investigation as to the causes of the preference constantly shown for certain organs and for certain tissues in those organs.

The spleen, liver and kidneys are chiefly affected, and less frequently the intestine, while rarely nodules have been found in the trachea and other organs. Perhaps, by considering those organs more often chosen by this process, an indication may be found to assist in forming a working basis. The intimate association of the liver and the kidney with the detoxification and excretion of bacterial products and toxins from other sources, the marked response always associated with the spleen under such circumstances indicate that these organs are the ones most liable to alteration through the invasion of organisms or toxins. Moreover, this is emphasised by the fact that the situation of splenic lesions in cases of acute infection and in amyloidosis are strikingly similar.

In the sago type, and to a lesser degree in the diffuse type of waxy spleen, the malpighian bodies are attacked.
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Perivascular amyloid changes were frequent. In both varieties a distinctly heavier deposition of amyloid was repeatedly seen at the periphery of the malpighian body. The situation of these lesions strongly suggests an association of these peripheral deposits of amyloid with the peripheral sinuses of the malpighian body.

The vulnerable points of the spleen in acute infection are much the same. Sections from the spleen of a larger number of such cases show that very frequently there are degenerative areas in the malpighian bodies. Very frequently inflammatory products collect in the perivascular spaces. The peripheral sinuses, too, are often dilated and many have been invaded by haemorrhage from the surrounding acutely congested pulp.

In short, those organs most liable to bacterial and toxic changes appear to be most vulnerable in amyloidosis. Tissue damage probably plays an important part, but it alone does not explain away the similarity. The whole question will be discussed later when all the data have been considered.

Having surveyed the general factors involved, it is now necessary to note briefly the conclusions of several workers before proceeding to the more detailed phase of the inquiry.

That the spleen may have an essential rôle in this disease suggested itself to Davidsohn, on observing that splenic lesions are the first to appear. This view was strengthened when later, in his experiments, he found that after the removal of the spleen of an animal it was impossible to produce amyloidosis. He, therefore, concluded that the spleen produces an enzyme; this enzyme interacts with a soluble product of cell destruction which has been conveyed by the blood; as a result amyloid is formed.

Schmidt considered it probable that an enzyme acting on the soluble precursor of amyloid caused its coagulation or precipitation in the tissue spaces and lymphatics.

After studying the chemical content of amyloid, Wells states that the protein constituent of that substance varies in different organs.

MacCallum's investigation led him to the conclusion that amyloidosis results in an infiltration.

The conclusion of these workers suggests that in amyloidosis some splenic product is essential; that the lymphatics and tissue spaces are involved; that each organ affected contributes through cell destruction the protein portion necessary in the amyloid combination; and that the process results in an infiltration.
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Amyloid disease will be studied now in the light of the microscopic findings recorded above. By reason of Davidsohn's results the spleen will be considered first.

In order to appreciate fully the amyloid findings in the spleen the main features of the organ will be reviewed briefly.

The capsule is made up of fibrous tissue including elastic and muscle fibres. Through the rhythmic contraction of the elastic and muscle fibres the spleen pulsates once every minute. From the capsule fibrous trabeculae containing elastic and muscle fibres penetrate into the splenic substance. The trabeculae give rise to fibrils which form the splenic reticulum. The trabeculae contain the larger splenic vessels and lymphatics.

In the splenic pulp and associated with the splenic arteries are the malpighian bodies which are made up of collections of lymphoid tissue in the adventitia of these vessels.

The malpighian body is irregularly pitted on its outer surface. Into these hollows the surrounding splenic pulp is moulded, thus producing splenic pulp projections. The line of demarcation between the malpighian body and the surrounding pulp is therefore seldom distinct. Generally, large lymph sinuses with their walls in contact, form a large part of the boundary of the malpighian body.

From the malpighian body the splenic artery continues into the pulp. The arterial wall becomes perforated at this stage, allowing the blood to come in direct contact with the splenic pulp.

The structure of the splenic pulp centres chiefly about the numerous minute compartments and the sinuses.

The minute compartments are constituted by (1) a reticulum of fibrils which are derived from the trabeculae and which are covered with branched connective tissue corpuscles or reticulum cells. The branching processes from several cells unite to form the minute compartments above mentioned. (2) Splenic phagocytes which are large mononuclear cells and are found in the interstices.

The sinuses are modified venous channels whose walls also are perforated. They are lined by endothelium ribbed longitudinally by fibrils derived from the reticulum and the layer of endothelium is encircled by similar fibrils continuous with those just mentioned.

It is now possible to trace completely the blood flow through the spleen. On leaving the splenic arteries through the perforation in their walls, the blood makes its way into the small
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interstices of the splenic meshwork. Here the blood cells surround the splenic phagocytes.

On leaving these compartments the blood enters the sinuses and passes from the organ by way of the splenic vein.

The lymphatics of the spleen are of two types. One type has both afferent and efferent vessels. The lymphatics of this group are found in the subcapsular region and in close association with the trabeculae.

The other type of lymphatics were described by Weidenreich. They are associated with the splenic reticulum, empty into the sinuses and have no afferent or efferent vessels to and from the spleen.

We will now proceed to consider the findings as observed in the various organs.

Spleen—i. Diffuse Type.—The earliest lesion in the spleen is seen in the smaller vessels. Only at a later stage in the process are those of a larger calibre affected. This would indicate that the process was spreading outwards and that the amyloid material was to a great extent a product of the spleen although some of its constituents may have been contributed from elsewhere.

Another feature must be considered here. The finding in several cases of splenic pulp cells which gave a positive intracellular reaction is sufficient to indicate that whereas the amyloid process elsewhere is in the nature of an infiltration, in the spleen intracellular changes may occur as well. But this intracellular reaction was never directly associated with visible collections of amyloid.

Further significance is gained from the fact that in no other organ was hyperplasia constantly present. It may therefore be inferred that the spleen is in a state of increased activity, and an intracellular substance is produced by the hyperplasia and hyperfunction which is sufficiently concentrated to give a faint but distinct positive reaction. This is additional proof that the spleen produces a factor which probably is carried away by the blood stream by way of the splenic sinuses, and assists in the production of amyloid in other organs. That the factor is disseminated by the blood stream is evident from the distribution of amyloid amongst the various organs.

Let us now consider the changes present in the pulp. Lesions in any organ usually centre about some function or action of that organ. In the case of the spleen it is as yet
impossible to associate the lesions definitely with any function, but the known splenic action may afford some assistance.

The relationship of splenic pulsations with the early stages of amyloidosis is very intimate and important as the following will show.

We will consider the effect of the increased pressure caused by splenic pulsation during contraction. The blood pressure would convert the arteries into relatively non-compressible columns. The malpighian bodies, of firmer consistency than the pulp, become even more so under the pressure of splenic contractions. It has already been stated that available records show chronic venous congestion to be present in every case. Such back pressure would convert the sinuses into firm columns.

With these observations before us, the distribution of amyloid in the pulp of the diffuse waxy spleen can be readily understood, for the deposits are about these comparatively non-compressible parts. It would therefore appear that the splenic pulsations compressed the splenic pulp against these firmer areas, i.e., arteries, malpighian bodies and sinuses, causing a concentration there, of the elements necessary for amyloid production, and the actual deposition occurred in those areas.

The diffuse subcapsular reactions, both blue and violet, tend to confirm this view, i.e., that pressure influences the amyloid distribution in the spleen; and for this reason. In the initial stages of tissue damage diffuse staining is common. Here, evidently, tissue damage is in close association with a capsule, largely muscular, and whose contractions are frequent.

The lesions in the malpighian body are varied. (1) There are one or more portions of amylosed malpighian bodies which very obviously are connected with similarly affected areas in the pulp proper. The amyloid in both localities reacts similarly to methyl violet. As the malpighian body boundary is ill defined and irregular, and as the splenic pulp fits into these indentations, it can be understood how the irregularities or indents in the boundary of the malpighian body becomes more obvious and the splenic pulp which dovetails into these becomes more apparent, when amyloid has been deposited in this pulp tissue surrounding the malpighian body. Moreover, it is also understandable how amylosed areas exhibiting splenic sinuses may be present within the apparent but not real boundary of the malpighian body.

(2) In the microscopic description it was stated that localised
Fig. 1.—Kidney. × 100.

Fig. 1.—Capillaries of the glomerular tuft show extensive amyloid lesions. This is the only type of amyloid change present in this section.

Fig. 2.—Kidney. × 60.

Fig. 2.—The walls of the larger arteries are affected only in a portion of the outer media and adventitia, while the wall of the smaller vessels are completely affected. In the larger vein the mural collections are similar to those seen in the portal veins.

The peritubular vessels are very markedly involved. In many areas lesions are so extensive that the tubules have largely disappeared through pressure atrophy.
Fig. 3.—Kidney. $\times 60$.

Fig. 3.—Section showing amyloid changes in the outer media of a larger artery. Many of these deposits can be traced to adventitial tissue spaces where such changes had also occurred. Several glomeruli and many of the smaller vessels have been completely involved.

Fig. 4.—Amyloidosis—Spleen (Diffuse). $\times 60$.

Fig. 4.—1. A definite accumulation of amyloid at the periphery of the malpighian body.
2. Infiltration into the malpighian body from the periphery.
3. Partial involvement of the wall of the central artery only.
4. The walls of the smaller arteries are completely affected.
Fig. 5.—Amyloidosis—Spleen (Sago).  $\times 100$.

Fig. 6.—Amyloidosis—Spleen (Sago).  $\times 60$.

Fig. 5.—Longitudinal section of an artery. The amyloid changes are limited to the adventitial region where the deposit is heaviest and the neighbouring lymphoid tissue. The vessel wall is affected only in a part.

Fig. 6.—The vessel wall is unaffected except in the adventitia where there is a marked deposit. Infiltration has occurred into the malpighian body to a limited degree.
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lesions are present within the malpighian body. These also contain splenic sinuses. Sections cut at right angles to those mentioned in (1) above would give the picture. Hence it is safe to assume that the lesions in both (1) and (2) are in the splenic pulp which had moulded into the crevices of the malpighian body.

(3) Another type of lesion requires explanation, i.e. those present particularly at the periphery of the malpighian body. They appear to be in and about the peripheral sinuses. As already stated, this increases the suspicion that the splenic response in amyloidosis is related to that induced by bacterial and toxic diseases.

That amyloid was present in the perivascular and adventitial channels of the arteries and to a lesser degree in the veins was repeatedly seen. There were also collections of pre-amyloid—(a substance recognised by Davidsohn and Lubarsch)—in similar positions. If the splenic sinuses are modified blood channels, they probably are accompanied by minute lymphatics and their perivascular set would be in the subendothelial zone where amyloid is regularly deposited.

The distribution throughout therefore is entirely along perivascular channels: some of these are definitely known to be lymphatic while the others are probably such. At any rate the latter appear to conform in position with those lymphatics described by Weidenreich.

There still remains another question to answer. If amyloidosis in this organ progresses by lymphatics, why should the central artery of the malpighian body alone be affected? More especially is this to be considered, because this body is a collection of lymphoid cells in the adventitia of a splenic artery, the adventitia being a zone commonly occupied by lymphatic channels.

If the splenic pulsations again be considered, it will be evident, on the one hand, that in a compressed malpighian body there is little opportunity for infiltration into its tissue spaces as these to all intents and purposes have been occluded by pressure. On the other hand, there are available perivascular and adventitial lymph channels associated with the splenic artery of the malpighian body. The walls along these passages are sufficiently firm to resist a moderate degree of pressure, and this alternate route would present less resistance to the advance of amyloid or its precursor.

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In general, the vascular lesions therefore indicate that the spread of amyloid has been along the walls of the capillaries, along the smaller vessels, and finally along the larger arteries. The earliest lesion is in the associated vascular lymphatics, both perivascular and adventitial. Amyloidosis has therefore spread by continuity. The direction of spread indicates the spleen as the seat of production of splenic amyloid.

2. Sago Type.—Here, again, evidence is rather strongly in favour of the view already expressed. Hyperplasia of the pulp and cells giving an intracellular reaction are two findings similar to those seen in the diffuse waxy spleen. They suggest a similar conclusion, namely, that a splenic function has been strained in order to produce amyloidosis.

The outstanding feature in the pulp is that it contains localised lesions which are irregularly distributed. There is again the outward perivascular spread to imply that the spleen has been the seat of manufacture of this substance. The vascular lesions in the pulp and the malpighian bodies are not essentially different from those in the diffuse type of amylosed spleen.

The malpighian bodies proper have been affected in several ways. Frequently there is a heavy deposit peripherally. But the central artery within such a malpighian body is surrounded by an unaffected area even when that vessel is in part the seat of amyloid change. In others the artery is affected while the lymphoid tissue is not involved. In many, infiltration into the malpighian structures penetrates from the surrounding pulp, and in still others, from the periphery of the malpighian body, while in none is there evidence to show that the infiltration has been from the central artery into the malpighian lymphoid tissue.

What, then, determines the character of the distribution? Again we must consider the influence of splenic contractions. In their absence, a uniform concentration of the various elements necessary to produce amyloid would be lacking. The tendency would therefore be for the formation of irregularly distributed localised deposits such are found in the sago waxy spleen.

In the malpighian bodies the problem is different. These structures, in themselves, are collections of lymphoid tissue in the adventitia of splenic arteries. They are largely surrounded by lymph sinuses. Therefore, if the amyloid precursor spreads by the lymphatics, it can readily be seen how these malpighian
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structures may be involved if they are not under pressure. But the principal perivascular lymphatics of the malpighian vessels frequently are involved alone. For the present an explanation of this preference is not available, except that local pressure from amyloid nodules may have been acting on those malpighian bodies. For this reason the process may have advanced preferably by the perivascular lymphatics, a route which offered less resistance.

Several other features have still to be considered. In the pulp hyperplasia and positive intracellular reactions were noted. The hyperplasia had resulted in a more compact cellular formation than that seen in the diffuse type.

A further contrast exists in that there is a very conspicuous abundance of small vessels rather than sinuses. The amyloid reaction, too, in all organs when the splenic lesions are of the sago type give a more reddish reaction with methyl violet, and this was confirmed by a colour analysis with colour filters. In all, this suggests that although the stimulus may be similar, the splenic response in the sago type of amyloidosis has varied appreciably. Otherwise the general features are similar to those already discussed in the foregoing section.

The process within the spleen has been discussed. Splenic participation can be assumed on a fairly substantial basis. The hypothesis which is implied explains how the amyloid factor is disseminated by the blood stream by way of the splenic sinuses; it further combines the doctrines of Wells and Schmidt by introducing the splenic lymphatics of Weidenreich.

Liver.—The earliest changes are in the smaller vessels of the liver, while the larger vessels and the liver lobules are affected only at a later stage. It would therefore appear that here as elsewhere amyloid was a local product and was spreading outwards. Within the liver lobules the amyloid substance is deposited under the endothelium of the blood canaliculi of the middle and outer zones. Later, infiltration involves the liver cells which then become atrophic. Subsequently, the sinusoids become occluded by amyloid masses. An additional feature is that small masses of amyloid have formed within the lumen of several portal veins but not in any arteries. Therefore, it may be asked, "Does the whole process take place within the portal vein?" Another explanation is possible.

As the wall of the portal vein is very thin, and as many collections of amyloid are separated from the lumen only by
a layer of endothelium, in a more liquid phase, such as when amyloid is spreading along the lymphatics, a quantity may have permeated the endothelial layer and given rise to those masses seen within the lumen. But why is this not seen in other organs? The portal vein functions as an artery and it can therefore be supposed that it may acquire those lesions to which arteries are prone.

However, another mode of formation is possible. The blood in the portal veins has been drained from a large area where some degree of tissue damage is likely by virtue of the function of those parts. The necessary protein moiety may be present, therefore, in the veins.

The splenic contribution would be abundant, as the splenic vein empties directly into the portal vein. Then all the necessary factors of amyloid production may be present within the portal vein, and endothelial damage due to toxins or faulty metabolism, as from chronic venous congestion, could supply the final necessity, a site.

If Wells' contention be correct, only a chemical examination of these masses, together with a comparison of the results obtained from similar examinations on amyloid found within the liver substance, would prove which of these two processes had actually taken place.

It must finally be observed that the hepatic sinusoids are vascular channels. By reason of the similarity of distribution of amyloid lesions about the various types of blood vessels, and because in the larger vessels the deposition is definitely in lymphatics, it is reasonable to suppose that here, too, some form of minute lymphatics are involved. In the liver, therefore, the disturbance causes lesions essentially perivascular and probably lymphatic in their distribution.

Kidney.—The earliest lesions are in the glomerular tufts in the form of localised nodules. Any of the involved capillaries which had been cut transversely showed these amyloid accumulations again to be peripherally and therefore perivascular. The vessels about the loop of Henle are next involved, together with the larger arteries supplying the glomeruli. At a later stage the glomerular tufts become more extensively affected. The amyloid substance finally reaches the larger vessels through their lymphatics.

In the renal amyloid process, the combination of factors seen elsewhere is again present. The chief excretory structure,
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the glomerulus, is first attacked. By virtue of its function, it is frequently liable to cell damage, and this no doubt accounts for the preference. Amyloidosis then spreads successively to the afferent and efferent glomerular vessels and finally to the larger vessels. Besides the disablement directly inflicted on the kidney by the amyloid deposition, much damage follows through compression of tubules.

One case in particular exemplifies the importance local tissue damage plays in this process. There were the typical lesions seen in chronic nephritis of patchy distribution and in the damaged areas amyloid changes were most marked.

A further point in the process was disclosed by the glomerular lesion in the advanced cases. Besides varying in intensity, the amyloid varied in reaction. In many glomeruli nodules of amyloid were intermixed with blue-staining homogeneous material — pre-amyloid. It clearly indicates that there are stages in the amyloid process and that the process is gradual.

Intestine.—Here, again, the picture is of a similar type. The changes begin about the capillary tuft in the villi and amyloid spreads by infiltration. Abnormal absorption or excretion, resulting in cell damage, is probably the local determining factor.

After examining in detail the process at work in the various organs, the question arises as to whether the disease has resulted in a degeneration or infiltration. On the one hand, no evidence was found to support the theory that it was a degeneration, for only in the spleen was there any intracellular reaction, and even then, there was no extracellular association of amyloid.

On the other hand, by the application of a solution of barium hydroxide or ammonium hydroxide followed by a solution of barium hydroxide, the amyloid substance was removed, leaving behind atrophic parenchymal cells. Therefore, the microscopic findings obtained by focussing at various levels were confirmed. Treatment of sections by macerating fluids gave similar results. As sections from the various organs in all stages of amyloidosis were examined in the above manner, and as the results were invariably the same, it was concluded that the amyloid process results in an infiltration and not a degeneration.
There still remain to be considered several other contentions regarding the amyloid process. Some workers have contended that amyloid is conveyed in a soluble state to the organ by the blood stream. Only on rare occasions, in the liver alone, was a connection demonstrable between the amyloid present in the wall of the portal veins and similar collections within the lumen. As already stated, those amyloid collections seen within the lumen of portal veins were the result of a peculiar combination of factors, and even these only locally involved the endothelial and subendothelial layers. In no other organ were there any intravascular amyloid masses.

The general impression therefore suggests that an amyloid precursor does not penetrate from the lumen into the vessel wall and later into the tissues. Nor was there any suggestion of an influence from the blood stream activating the cells of the various organs into complete amyloid production.

**Summary.**—The main conclusions are that:

1. The spleen makes a necessary contribution to the whole amyloid process. This product is blood spread as shown by the intravascular masses in the portal veins.
2. The presence of a toxin appears to be essential. Local damage determines the site for deposition in the organ as shown by the amyloid lesions in the chronic nephritic kidney.
3. The amyloid substance is of local manufacture.
4. Amyloid spreads by lymphatics from the original site in the organ.
5. It results in an infiltration.

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