THE RELATION OF THE RETICULO-ENDOTHELIAL SYSTEM TO THE FORMATION OF AMYLOID.

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Plates 20 to 22.

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In a recent article (1) Domagk states that he succeeded in producing amyloid in the spleen and liver of normal mice within 10 minutes by intravenous injection of a large quantity of living cocci; furthermore, that he could produce amyloid within 2 minutes in the spleen and liver of a mouse which had several injections of dead cocci previous to the final intravenous injection of living cocci. He also described marked changes in the reticulo-endothelial cells, and finally drew the conclusion that amyloid appears at first in the neighborhood of these phagocytic cells. This substance which he thought to be amyloid did not react to any of the specific stains (gentian violet or iodine), but showed metachromasia when stained with cresyl violet or Giemsa.

The Influence of the Injection of Dead and Living Bacteria upon the Formation of Amyloid.

Since vital staining by the intravenous injection of Congo red has proved in many experiments to be a most delicate and reliable, as well as specific, method for demonstrating even the earliest traces of amyloid (2), experiments were undertaken in order to define the nature of the substance produced in Domagk's experiments.

Each of a series of 10 mice was injected with 0.2 cc. of dead streptococci in the gluteal region four times at intervals of 2 days. Following these injections 0.5 cc. of living streptococci was injected intravenously into each animal. In another series of 10 mice 0.5 cc. of living streptococci was injected intravenously without any previous injections of dead bacteria. Corresponding animals of each group were killed 15 minutes, 30 minutes, 1 hour, 2 hours, 24 hours, 2 days, 3 days and 7 days after injection. Each of these animals received 0.5–0.7 cc. of 1 per cent solution of Congo red intravenously shortly before death.

None of the 20 animals showed even the slightest trace of amyloid in any of the organs, although many of them showed marked lesions in spleen and liver corresponding to those described by Domagk. The changes in the reticulo-endothelial cells are very marked and consist of swelling and vacuolation. These cells contain bacteria for some time after the injections and later on become distended with red blood cells and cellular debris.

These experiments obviously shed no light upon the relation of the reticulo-endothelial cells to amyloid formation since there was no evidence that amyloid was formed. The idea, however, that reticulo-endothelial cells could in some way be responsible for the formation of amyloid is very tempting in many respects. It would at once explain many morphological pictures seen in cases of experimental amyloidosis, the interpretation of which appears to be rather forced so far.

The Relation of the Reticulo-Endothelial Cells to the Site of Formation of Amyloid.

It is surprising indeed to find the phagocytic reticulo-endothelial cells of spleen, liver, kidney, adrenal and intestines located exactly in these places where amyloid is constantly seen. After one or more intravenous injections of 0.2 cc. of India ink in a mouse, the reticulo-endothelial cells filled with ink particles are seen forming black rings in the tissue around all the follicles of the spleen, while there is comparatively little ink phagocytized in other parts of this organ (Figs. 1 and 2). In the liver one finds ink in cells, located beneath the endothelium of the periportal vessels, and sometimes in the endothelial cells themselves. The many phagocytic cells in the capillaries and the Kupffer cells are loaded with ink particles and often appear as dark, solid black spots, their nuclei being unrecognizable. There are only a few of these cells seen around the central vessels (Figs. 3 and 4). In the kidney the ink is found in cells of the capillaries of the glomeruli, and in the medulla between tubules (Figs. 5 and 6); in the adrenals in phagocytic cells of the capillaries between the columns of the cells in the cortex; in the intestines most of the ink is seen in the stroma of the villi, especially at their tips, and also in the capillaries at their bases (Figs. 7 and 8). All of these are the very places where amyloid is invariably and typically found when present.

Another point in favor of the theory that the reticulo-endothelial

cells may play an active part in the formation of amyloid is the solitary appearance of small, isolated patches of amyloid in all of the organs concerned. This phenomenon can, of course, only be observed in very early stages, and is even then rarely seen in the spleen, which fact is responsible for the idea that amyloid appears at once in masses around the follicles. This is not true, for here, as elsewhere, there are first formed small isolated droplets of amyloid which anastomose later and form the solid ring which is so typical of this organ (Fig. 9).

In the liver the earliest form of amyloid is found in the form of small solitary patches in the tissue surrounding the periportal vessels and in the intermediate zone of the lobules (Fig. 4). These isolated areas soon unite, thus forming a complete layer of amyloid around the vessels. At the same time solid, anastomosing strands of this material are found in the adjoining parts of the liver lobules. The tissue around the central vessels is much less affected but not completely exempt. Some of the patches of amyloid appear to be located in the lumen of the capillaries, often completely surrounded by endothelial cells; this fact is mentioned by many authors and all sorts of explanations, which on the whole are rather unsatisfactory, have been made for this remarkable occurrence which seems to contradict any present theory of the mechanism of amyloid formation.

In the glomeruli and in the tissue of the papillæ of the kidneys, between the columns of cortical cells in the adrenals, in the stroma of the villi of the intestine, as well as in the tissue at their bases, one sees the earliest stage of amyloid represented by small isolated patches which later on form anastomoses which imitate the whole framework (Figs. 6 and 8). The same principle governs the appearance of amyloid in all these organs.

The solitary appearance of small patches of amyloid in different parts of different organs suggests its formation on the very spot where it is located rather than precipitation of a substance circulating in the blood stream. The assumption that amyloid is formed in some way by activities of specific cells would not be contradictory of morphological facts. It cannot, however, be too strongly emphasized that only studies of the early stages of amyloidosis are of any value as far as its genesis is concerned. In this sense the study of

chronic, even advanced cases, would be of about the same value as those of scars in questions of tuberculosis or syphilis.

Delay in Appearance of Amyloid Following Attempt at Blockage of Reticulo-Endothelial System with India Ink.

In order to demonstrate possible corelations between reticulo-endothelial cells and amyloid, 15 of a series of 30 mice (Series 1-b, Table I) were injected intravenously with India ink, and amyloid was then produced by subcutaneous injections of 0.5 cc. of 5 per cent nutrose as used by Kuczynski (3). An injection of 0.2 cc. of India ink was given 1 day before the first injection of nutrose. If such a mouse is killed 1 day after the injection, practically all the reticulo-endothelial cells are found to be loaded with ink particles. Later on one often finds cells, which have to be called reticulo-endothelial cells as far as their morphology and position go, without any ink particles in their protoplasm. This is not surprising since many of the ink-containing cells die and are replaced by new cells, most of which certainly contain no ink. The majority of the reticulo-endothelial cells, however, still show ink particles 2 months after a single injection. In general one can assume that most of the cells containing ink were present at the time of the injection.

On the same day the other half of the series (Series 1-a, Table I) were injected with nutrose only, for control purposes. At certain intervals animals were simultaneously killed from both series. The organs of mice which died spontaneously were fixed in Zenker, formalin and alcohol, and sections of the various organs stained for amyloid with Congo red (4) and gentian violet. All the other animals were injected intravenously with 0.5–0.7 cc. of 1 per cent Congo red at least ½ hour before death in order to mark out the amyloid vitally. Their organs were fixed in saturated corrosive sublimate.

In the mice injected with nutrose alone (Series 1-a, Table I) amyloid was found after about 30 daily injections, while all the previously killed animals showed none. The corresponding animals (Series 1-b, Table I) injected with India ink 30 days previously did not have any amyloid. These results suggested that the appearance of amyloid was retarded in those animals whose reticulo-endothelial cells were loaded with ink, but upon repeating the experiment (Series 2-a and b, Table I) amyloid was found to appear at about the same time in the mice receiving India ink and nutrose, as in those receiving nutrose alone.

In the attempt to settle this question of the possibility of influencing the time of appearance of amyloid by blocking the reticulo-endothelial cells with India ink, four more similar series of animals were studied. Realizing that only one injection of ink was perhaps not enough to block the reticulo-endothelial system very extensively and that this fact might have been responsible for the indecisiveness of

the second experiment, those mice receiving ink of each of these four latter series were injected three to ten times during the course of the experiment.

TABLE I.

The Relation of Attempted Blockage of Reticulo-Endothelial System by Injection of India Ink to the Time of Appearance of Amyloid.

Repeated subcutaneous injections of nutrose 0.5 cc., 5 per cent solution 6 times a wk.				Intravenous injection of India ink before and during the experiment. Repeated subcutaneous injection of nutrose 0.5 cc., 5 per cent solution 6 times a wk.				
Series	Duration of experiment in days	Numbers of mice	Amyloid	Series	Duration of experiment in days	Numbers of mice	No. of intravenous injections of India ink	Amyloid
1-a	30	1–13	−	1-b	30	1–13	1	−
	31	14	+		31	14	1	−
	32	15*	−		36	15	1	−
2-a	13	1–14	−	2-b	38	1–13	1	−
	45	15	+		44	14	1	+
					52	15	1	+
3-a	36	1–13	−	3-b	35	1–12	1–2	−
	38	14	+		37	13	3	−
	42	15	+		41	14	3	−
					50	15	3	+
4-a	6	1–13	−	4-b	14	1–12	1	−
	22	14	−		28	13	2	−
	25	15	+		38	14	3	−
					47	15	5	+
5-a	34	1–13	−	5-b	30	1–13	1–4	−
	36	14	−		36	14	5	−
	42	15	+		42	15	5	−
6-a	18	1–11	−	6-b	18	1–13	1–3	−
	42	12	−		42	14	7	−
	47	13	+		53	15	10	−
	48	14	+					
	53	15	+					

* Received one intravenous injection of India ink 15 days before death.

In each of these four series amyloid appeared later in those animals whose reticulo-endothelial cells were filled with India ink than in the controls receiving nutrose alone (see Table I).

Morphological Relationship of Newly Formed Amyloid and Ink-Containing Reticulo-Endothelial Cells.

In studying the morphological relations of reticulo-endothelial cells and amyloid, especially in differentiating reticulo-endothelial cells present before the appearance of amyloid and those formed during and after its formation, only mice of Series 1 and 2 receiving one injection of ink, were used. The findings are constant but difficult to interpret. The clear-cut structure of the liver makes it easier to study the relationship between reticulo-endothelial cells and amyloid in this organ than in spleen and kidney; therefore, most of the observations were made in the liver. An average periportal field shows the following picture. A ring of amyloid is found between the endothelium of the vessels and the liver cells. Cells containing ink granules may be seen lining the lumen but are more often found outside the zone of amyloid, less frequently within. These cells appear to be intact and their nuclei are present. Embedded in the substance of the amyloid one occasionally sees isolated small particles of ink, having no longer any obvious relationship with living cells; but often there is no trace of ink in relatively large solid masses of amyloid (Fig. 10). In earlier stages the localized patches of amyloid around the periportal vessels are often seen to be completely surrounded by ink particles of various sizes, while there is no trace of ink in the amyloid itself (Fig. 11). In the midzonal areas of the lobules the relations between cells containing ink particles and patches of amyloid are manifold. The area of amyloid may be covered on one or the other side by cells containing ink (Fig. 12). These cells, in addition to other cells which do not contain ink, may also be found completely surrounding the amyloid (Fig. 13). Sometimes, but not frequently, cells or remains of cells with ink granules lie in the center of a small, solid area of amyloid, which is arranged in concentric layers and in turn is separated from the liver cells by ink-containing reticulo-endothelial cells (Fig. 12). Some of these ink granules in the periphery of an area of amyloid do not seem to be located any longer in the cells (Fig. 14). It appears as though these particles represent remains of cells which no longer exist. Not infrequently separate contiguous, crystalline patches of amyloid, completely

surrounded by liver cells, were found. Cells which contain ink granules separate these patches from the liver cells and there are also a few small particles of ink between them (Fig. 15).

In the spleen the cells which contain ink are widely scattered throughout the areas of amyloid, especially in the periphery of the zone of amyloid surrounding the follicles (Fig. 16). Isolated phagocytic cells are frequently found completely embedded in amyloid and free particles of ink are often enough seen lying in this substance (Fig. 17). Solitary patches of amyloid in the pulp are usually surrounded by cells which contain ink, sometimes only by ink granules (Fig. 18).

The interpretation of these findings in the liver and spleen appears difficult. One thing seems to be certain, that the reticulo-endothelial cells as such are not primarily transformed into amyloid. Were this true one would expect to find amyloid constantly containing large numbers of ink granules; this, however, is not the case. The granules which are actually seen included in masses of amyloid all appear to be the remains of cells passively involved in this process.

For pictures where the patches of amyloid are completely surrounded by cells containing ink, it is difficult to offer any other explanation except that these patches are situated in capillaries; otherwise how could amyloid, were its position outside the wall of capillaries, be surrounded by reticulo-endothelial cells which contain ink injected 6 weeks previously. Some of these cells may be phagocytic wandering cells, but most of them are certainly reticulo-endothelial cells as far as their morphology goes.

Only occasionally is there a suggestion that amyloid is situated within reticulo-endothelial cells. Fig. 19 shows two of these cells which seem to be filled with both ink and amyloid. Such appearances are very rarely seen.

Although one cannot always clearly interpret these various morphological relationships of amyloid, reticulo-endothelial cells and ink, none of them are contradictory to the idea that amyloid may in some way be formed through the activity of reticulo-endothelial cells. On the other hand, however, certain pictures (Figs. 13–15) demand this interpretation.

Injection of India Ink in Mice Already Showing Amyloidosis.

If one assumes that the reticulo-endothelial cells form amyloid, the question arises whether such an unusual process does not alter the cells greatly, or whether this substance is perhaps only formed by damaged and altered cells.

Should the reticulo-endothelial cells be involved only secondarily one would expect still to find many of these cells, which are yet phagocytic, in areas of already developed amyloid. There should also be ink-containing cells found in the periphery of follicles in the spleen and around the periportal fields of the liver after an injection of India ink in an animal having amyloidosis. One should expect to find their number decreased but there would be definite evidence of the presence of many of them which would take up the ink in a way similar to that of a normal animal. A mouse having received about 50 subcutaneous injections of nutrose was injected for the first time with 0.2 cc. of India ink intravenously 1 day before it was killed, and received $\frac{1}{2}$ cc. of 1 per cent Congo red $\frac{1}{2}$ hour before its death.

The sections of the organs of this animal show striking pictures. There are huge masses of vitally stained amyloid around the follicles in the spleen, and there are amyloidal rings around the periportal vessels of the liver, and some patches of amyloid in the intermediate zones.

There are almost no reticulo-endothelial cells containing ink granules around the follicles except in places where there is no amyloid, or where the mantle of amyloid around the follicles is not complete. Only a few of these cells are seen in large areas of amyloid (Fig. 20).

In the liver there are numerous cells loaded with ink far away from the periportal fields, while they are practically missing in a broad zone around the vessels themselves, where amyloid is most marked (Fig. 21). Identical pictures were seen in organs of mice injected three to five times subcutaneously with 1 cc. of a 1 per cent solution of trypan blue after the development of amyloid.

The striking absence of phagocytic cells in the areas where amyloid is most abundant must mean that the reticulo-endothelial cells of these areas have been destroyed or have been markedly altered physiologically. Were such pictures exceptional one might think that ink had

not reached the reticulo-endothelial cells due to obstruction of the periportal capillaries by amyloid and that ink reached only the reticulo-endothelial cells in the central portion of the lobule through collateral circulation from adjacent lobules. This conception of vascular obstruction is hardly tenable, however, for every capillary throughout the liver shows the usual amount of reticulo-endothelial cells containing ink particles. The additional fact that the amyloid throughout the entire lobule is brilliantly stained vitally by intravenous injections of Congo red also strongly speaks against a vascular obstruction in these areas.

Evidence of destruction of reticulo-endothelial cells is commonly found in cases of progressing amyloidosis in all the involved organs, and by the observations just described the idea of the direct connection of these perishing cells with the formation of amyloid is strongly supported, but there is no evidence that the cells as such are directly and primarily converted into amyloid.

DISCUSSION.

In this paper facts have been assembled which speak in favor of the theory that amyloid is actively formed by specific phagocytic cells (reticulo-endothelial cells) in the place where it appears. It must be said that all of the material collected does not furnish conclusive proof of this theory, but puts forward facts which suggest it rather strongly.

It is remarkable indeed to find most of the reticulo-endothelial cells in the organs in question in the very places where amyloid lies. The objection of having phagocytic cells in numbers in other organs also where amyloid is not commonly found, for instance in the lungs, must not necessarily overthrow this theory. Having phagocytic properties in common with those of the lungs, the reticulo-endothelial cells of spleen, liver, kidney, intestine, adrenal and lymph glands probably have many other special functions besides, each group adapting itself to the function of the organ in which it is located. This special functional relationship may be the explanation why the reticulo-endothelial cells of spleen, liver and kidney should be more concerned than those of other organs in the formation of amyloid.

The solitary patchy appearance of young amyloid seems to indicate

its formation right on the spot where it appears rather than a precipitation of a substance circulating in the blood stream. That it appears in this form just at the very place where phagocytic cells are found in great number is also in favor of the theory that it might have been formed actively by specific cells. The presence of masses of amyloid in the lumen of capillaries of the liver, surrounded completely by Kupffer cells, could only be explained in this way.

The presence of two or more patches of amyloid lying independently but close together in the lumen of one capillary seems to indicate the mechanism by which continuous streaks of this material are formed. This is the form in which amyloid is seen in advanced cases.

It seems much easier to explain the endothelial covering of amyloid in chronic cases, which makes the amyloid appear to be outside the lumen, by a new growth of endothelial cells making an effort to preserve the smooth lining of the capillary than to interpret the presence of endothelial cells around the amyloid by a new growth of endothelium between amyloid and liver cells. The latter would mean a complete reorganization of the capillary system.

There are signs of severe damage and disintegration of reticulo-endothelial cells, during the process of formation of amyloid, as seen by direct observation and by the absence of cells which phagocytize India ink in the areas of newly formed amyloid. The presence of amyloid itself is a manifestation of such an unusual unphysiological condition that it is not difficult to believe that the material is formed by reticulo-endothelial cells, in an abnormal state.

The reticulo-endothelial cells are also secondarily involved in this process; they become partly and completely surrounded by amyloid and are often found embedded in this substance. Finally the cells die, leaving only their phagocytized granules in their places. It is impossible to say what becomes of their cell substances, whether they turn into amyloid or whether they are simply replaced by this substance.

The results of the experiments in which the attempt was made to block the reticulo-endothelial system with India ink have limited value for two reasons. In the first place it is impossible to block these cells completely; secondly there is a considerable irregularity in the time necessary for the experimental production of amyloid follow-

ing even standardized injections of nutrose. But since the attempted blockage of the reticulo-endothelial cells did result in marked delay of the appearance of amyloid, this fact, though itself inconclusive, at least supports the other observations leading to the idea that these cells are concerned in the formation of amyloid.

CONCLUSIONS.

The facts presented suggest strongly that reticulo-endothelial cells are actively concerned in the formation of amyloid. Points in favor of this theory are as follows:

1. The appearance of amyloid in places where reticulo-endothelial cells are normally present, sometimes in very large number.
2. The formation of early amyloid in the small solitary patches, which suggests its local formation.
3. The occurrence of solitary patches of amyloid apparently located within the capillaries of the liver.
4. The manifold relations between reticulo-endothelial cells marked out by phagocytized ink granules, loose ink particles and amyloid, described in the text.
5. The impossibility of demonstrating reticulo-endothelial cells in areas of forming amyloid by intravenous injections of India ink.
6. The delayed appearance of amyloid in animals after blockage of the reticulo-endothelial cells by repeated intravenous injections of India ink.

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EXPLANATION OF PLATES.

PLATE 20.

FIG. 1. Follicles of spleen. Reticulo-endothelial cells containing phagocytized ink particles around follicles. Three intravenous injections of 0.2 cc. of India ink. Unstained section. × about 75.

FIG. 2. Follicles of spleen. Vitally stained amyloid around follicles. Unstained section. × about 75.

FIG. 3. Peripheral vein of liver. Reticulo-endothelial cells with phagocytized ink particles beneath the epithelial lining and in capillaries. Ink granules in endothelium of vein. One intravenous injection of 0.2 cc. of India ink. Unstained section. × about 110.

FIG. 4. Peripheral vein of liver. Vitally stained solitary patches of amyloid in tissues around the vein and in the intermediate zone of liver lobule. Unstained section. × about 110.

FIG. 5. Cortex of kidney. Phagocytized ink particles in reticulo-endothelial cells of glomeruli. One intravenous injection of India ink. Unstained section. × about 110.

FIG. 6. Cortex of kidney. Vitally stained patches of amyloid in glomeruli. Unstained section. × about 110.

FIG. 7. Intestine. Reticulo-endothelial cells containing ink particles in tissues of villi. Three intravenous injections of India ink. Unstained section. × about 75.

FIG. 8. Intestine. Vitally stained amyloid in stroma of villi. Unstained section. × about 75.

FIG. 9. Spleen. Vitally stained patches of amyloid around follicles and in pulp of spleen. These patches are seen to become confluent in a semicircular area around the follicles. Unstained section. × about 75.

PLATE 21.

FIG. 10. Peripheral vein of liver in the center; the light zone around the endothelial lining represents amyloid. Patches of amyloid in the intermediate zone of lobule. Ink particles are found in endothelium, in reticulo-endothelial cells around the amyloidal ring, embedded in amyloid and in capillaries of the liver lobule. The solitary patches of amyloid are partly or completely surrounded by these cells. Fine ink granules in amyloidal zone around the vein. Amyloid vitally stained with Congo red; tissue stained with iron-hematoxylin. × about 345. Mouse 14. Series 2-b.

FIG. 11. Part of the wall of a periportal vein of liver. Small area of amyloid (*a*) in wall of vein, surrounded by loose ink particles. Amyloid vitally stained with Congo red; tissue stained with iron-hematoxylin. × about 650. Mouse 15. Series 2-b.

FIG. 12. Intermediate zone of liver lobule. Solitary and confluent patches of amyloid. Reticulo-endothelial cells marked out by ink are found around these patches, lining them partially or completely. Ink-containing cells and fragments in the centers of two patches which show a concentrical arrangement (*a*). Fragments of cells and ink granules around small solitary patches of amyloid (*b*). Amyloid vitally stained with Congo red; tissue stained with iron-hematoxylin. × about 345. Mouse 14. Series 2-b.

FIG. 13. Intermediate zone of liver lobule. Solitary patch of amyloid showing outspoken crystalline structure. Reticulo-endothelial cells with phagocytized ink particles surrounding the amyloid completely. Amyloid vitally stained with Congo red; tissue stained with iron-hematoxylin. × about 650. Mouse 14. Series 2-b.

FIG. 14. Intermediate zone of liver lobule. Solitary patch of amyloid showing outspoken crystalline structure. The amyloid is surrounded by reticulo-endothelial cells containing ink and by ink granules. Amyloid vitally stained with Congo red; tissue stained with iron-hematoxylin. × about 650. Mouse 14. Series 2-b.

FIG. 15. Intermediate zone of liver lobule. Three solitary patches of amyloid all showing crystalline structure. *a* and *b* are contiguous, but not confluent. Reticulo-endothelial cells containing ink around *a* and *b*. Fine ink particles between *a* and *b*. Cells with and without phagocytized ink particles around *c*. Amyloid vitally stained with Congo red; tissue stained with iron-hematoxylin. × about 650. Mouse 14. Series 2-b.

PLATE 22.

FIG. 16. Follicle of spleen. *a*, central artery. Zone of amyloid around the follicle. Reticulo-endothelial cells containing ink are scattered throughout the amyloid, but are more frequently seen in the periphery of the amyloidal zone and adjacent tissue. Isolated ink-containing cells and loose ink granules embedded in substance of amyloid. Amyloid vitally stained with Congo red; tissue stained with iron-hematoxylin. × about 190. Mouse 14. Series 2-b.

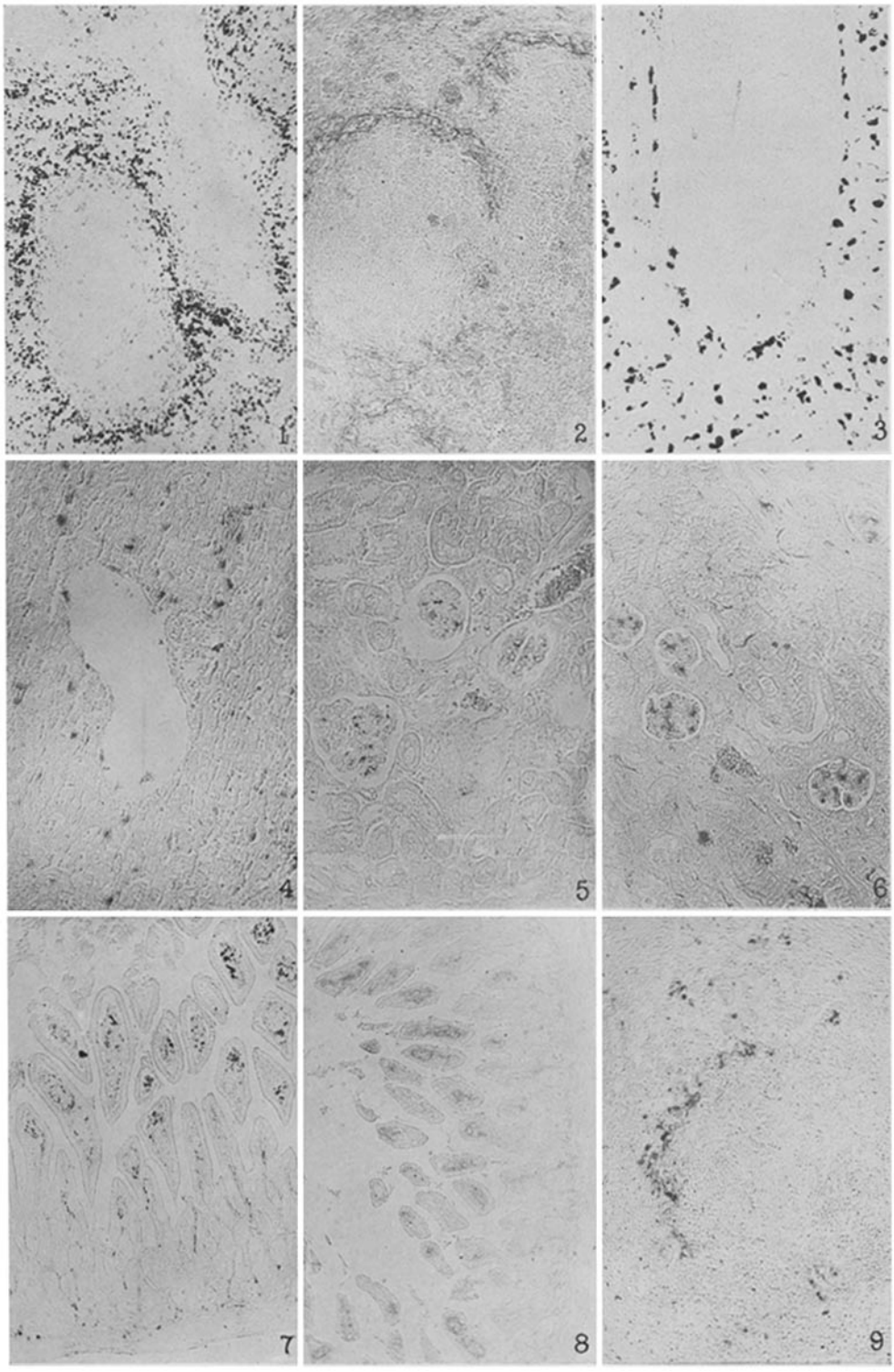
FIG. 17. High power magnification of one part of Fig. 16. Malpighian body (central artery *a*) surrounded by amyloid (unstained). Isolated cells, some containing phagocytized ink particles embedded in amyloid. Also fine ink granules in substance of amyloid. × about 345.

FIG. 18. Splenic pulp. The large light areas are solitary patches of amyloid in tissue of pulp surrounded by reticulo-endothelial cells containing ink and also by ink granules. Amyloid vitally stained with Congo red; tissue stained with iron-hematoxylin. × about 345. Mouse 15. Series 2-b.

FIG. 19. Intermediate zone of liver lobule. Two small solitary patches of amyloid; *a*, almost surrounded by a solid black zone of ink; *b*, enclosed by ink particles which show a bipolar arrangement. Amyloid vitally stained with Congo red; tissue stained with iron-hematoxylin. × about 345. Mouse 14. Series 2-b.

FIG. 20. Follicles of spleen partially surrounded by large masses of vitally stained amyloid. 0.2 cc. of India ink was injected 1 day before death. No reticulo-endothelial cells containing ink around follicles except in area *a* where the amyloidal zone around the follicle is not complete. (Compare with Fig. 1.) Unstained section. × about 75.

FIG. 21. Two periportal vessels of liver. Vitally stained rings of amyloid around vessels, patches of amyloid in intermediate zone. 0.2 cc. of India ink was injected 1 day before death. No reticulo-endothelial cells in tissue around both vessels, no ink granules in endothelium. The capillaries show the usual amount of phagocytic cells loaded with ink. (Compare with Fig. 3.) Unstained section. × about 115.



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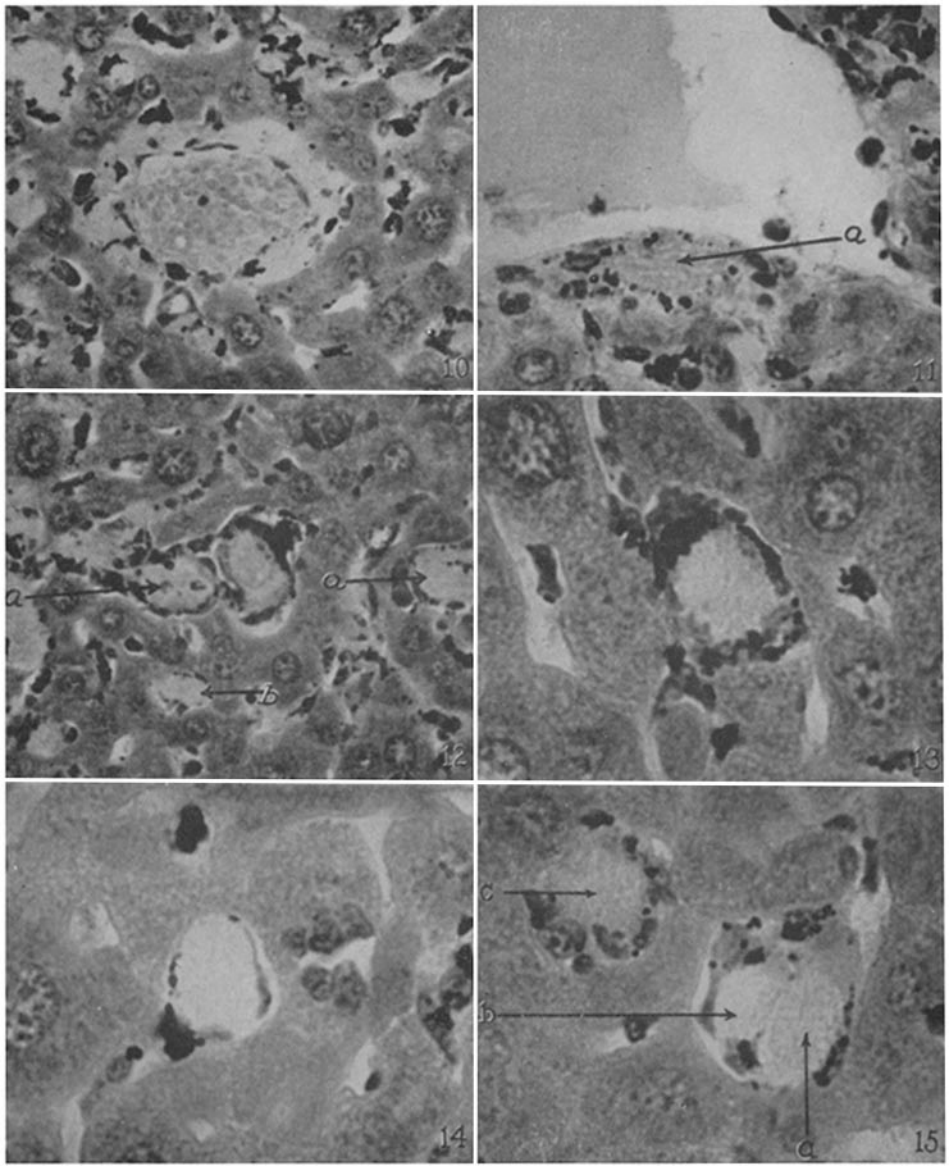

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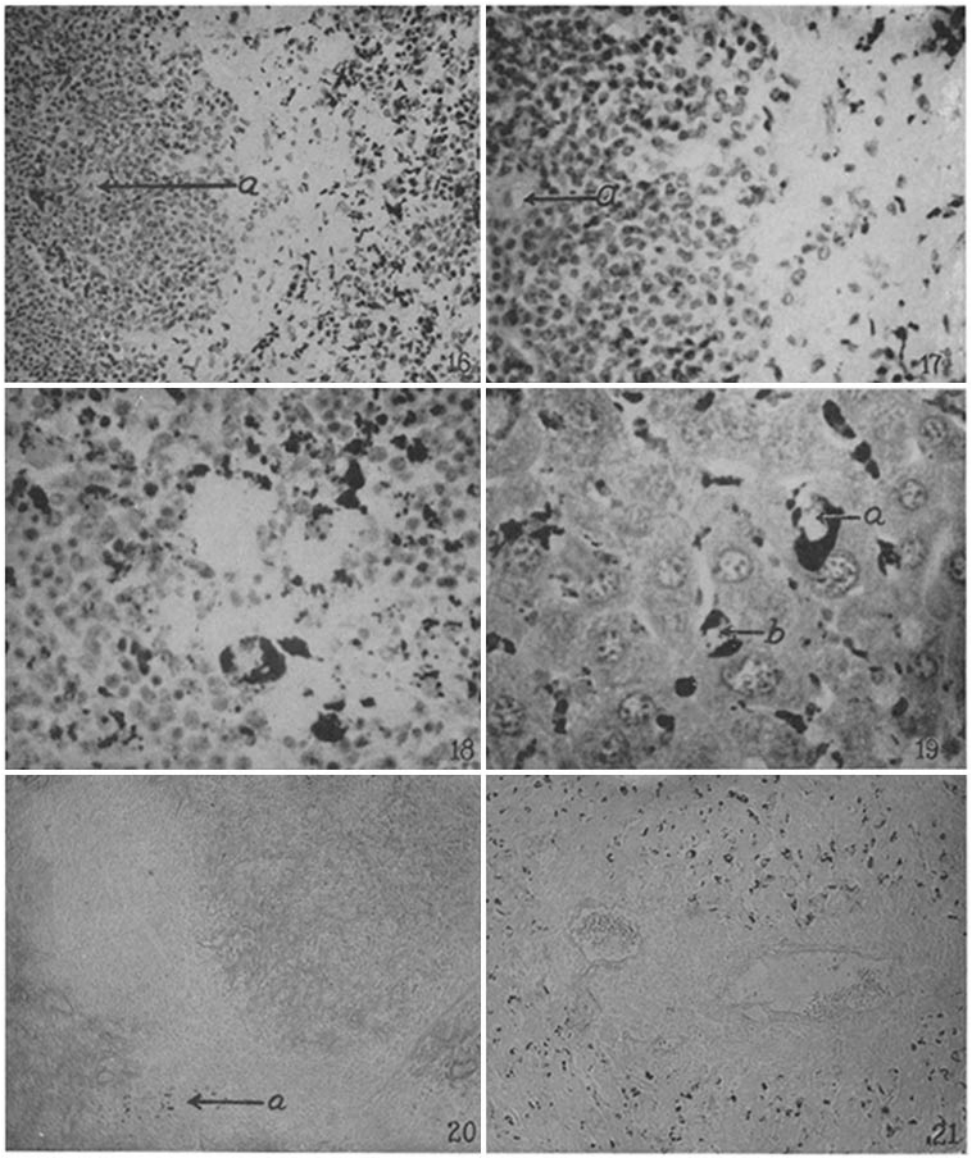

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