# CONTRIBUTION TO THE PATHOLOGICAL ANATOMY OF MALARIAL FEVER.

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## INTRODUCTION.

As with many other infectious diseases, the pathological anatomy of malarial fever had been thoroughly studied long before the discovery of the parasitic cause of the disease. Of the early studies it may be said, from the standpoint of our present knowledge, that they had nearly exhausted the subject of the more evident pathological changes in the viscera, and were essential, indeed, to the final discovery of the parasite, but that in the absence of a knowledge of *Plasmodium malariæ* their numerous misconceptions greatly detract from their value for present purposes. Of current writers,

Laveran is probably most familiar with the value of these studies, and in the last edition of his work properly honors them with abundant reference. Since the discovery of the parasite the entire field has been extensively reviewed, principally in Italy and France, and to some extent in America, Germany and England.

Nevertheless the records of close microscopic study of the lesions of ordinary malarial infection are by no means excessively numerous; much yet remains to be learned, possibly from a microscopic study of the visceral lesions, concerning the parasitology of the disease, while its numerous irregular forms still offer one of the most inviting fields for pathological research. An increased value still attaches to such records from the fact that malaria is seldom fatal in localities where a full clinical history can be supplemented by a complete microscopic examination of the viscera.

Considerations of this nature seem to justify the detailed character of the present contribution, which consists of the available clinical histories and the records of the gross and microscopic changes in the viscera of several cases of malaria, together with a discussion of any important features that the cases may present and their bearing on previous studies.

Most of the material was collected at Camp Wikoff, Montauk Point, Long Island, and the remainder was secured at Roosevelt Hospital or elsewhere in New York City. For the clinical records and notes of some autopsies of the Montauk cases, I am greatly indebted to Dr. Delafield of New York, and to Drs. Cotton, Allen, and Mosher of Boston. Case I, at Roosevelt Hospital, was under the care of Dr. W. H. Thomson, who kindly placed the clinical records at my disposal. Dr. Eugene Hodenpyl and Dr. John H. Larkin have each kindly contributed material and autopsy notes of one case.

## PART I.

### REPORTS OF CASES.

CASE I.—*Æstivo-Autumnal Malaria. Sub-Acute Course. Blood Containing only Crescents for two weeks before death. Prolonged Coma. Absence of Parasites in the Brain. Peculiar Deposits of Pigment in Renal Epithelium.*

F. H., 64 years. No important previous illness. Spent some time in Long Island City, N. Y., shortly before illness, which developed in New York City.

September 25, had a chill followed by fever and sweat. Chills recurred every other day till October 2-3, when they became irregular and less marked. Admitted to Roosevelt Hospital, service of Dr. W. H. Thomson, Oct. 6, 1896. Diagnosis, malaria. Treatment, quinine and ginger, aa. grs. XXV-XL daily. Arsenic later, Fowler's solution, gt. XV. daily.

The patient seemed to improve slightly, the temperature falling gradually, reaching 99° F. on Oct. 10, and remaining at about that point until Oct. 20. There was from the first marked insomnia and tendency toward mild delirium at night, partly controlled by sedatives, until Oct. 11, when the delirium increased, and periods of mild coma supervened. About Oct. 16, the coma deepened and became continuous till death. There were no evidences of uræmia, and the coma was clearly of the malarial type. There was one slight paroxysm of fever on Oct. 20-21 (101.4°), and on the 23rd the temperature began to rise steadily, reaching 108° on the 25th, just before death.

The *urine* was passed in considerable quantity, of acid reaction, 1020 sp. g., and in the last two weeks of the disease contained a trace of albumin and a few hyaline and granular casts. No mention was made of pigment in the urine.

I had no opportunity to examine the *blood* until Oct. 12, when it was found to contain an enormous number of spheroidal, ovoidal, and young crescentic bodies, as many as ten appearing in one field of the immersion lens. Prolonged and repeated search (4-5 hours) failed to show any rings. There were the changes of secondary anæmia with marked loss of Hb. and moderate variation in the size of the red cells. The leucocytes were slightly reduced in numbers. Mononuclears 35%; polynuclears 60%; eosins 5%. A few richly pigmented mononuclear cells were seen. Oct. 13. The parasites were as numerous as before but there were now some elongated and apparently full grown crescents, while the spheroidal bodies were less numerous. No rings seen. Oct. 15. The adult crescents now outnumbered the smaller forms, which were however still rather abundant. No rings could be found. The anæmia appeared rather more pronounced. There was no leucocytosis, but the eosins were still increased. Oct. 21. The numbers of parasites were still large and the forms were about equally divided among elliptical bodies and adult crescents. Oct. 25. Eight hours before death the blood was found to contain very few parasites. In the course of this search 8-10 young crescents and spheroidal bodies were encountered, but no rings. There was a moderate polynuclear leucocytosis.

*Autopsy.*—12 hours after death. The anæmia appeared slight. No œdema. No jaundice. *Lungs*, moderately congested and œdematous. *Spleen*, slightly enlarged, very soft, of characteristic slate color. *Liver*, slightly enlarged, of characteristic slate color. *Stomach and intestine*, negative. *Serous membranes*, slightly discolored in places. *Kidneys*, size about normal; capsules adherent in places, elsewhere surface is smooth; cortex slightly irregular; markings distorted in places. The cortex is light red in color, the medulla and papillæ very dark red, or rusty. The *marrow* of ribs and vertebræ is hyperæmic, and of slight chocolate tinge. *Brain*, moderately œdematous; not discolored; shows no petechiæ; the basal vessels appear normal.

*Microscopic Examination.—Liver.*—There is a very extensive deposit of pigment, in the form of discrete and conglomerate grains and masses, in the endothelial cells, macrophages, and occasionally in the liver cells. Much of this pigment is very compact and dark, and is evidently of rather old formation. The numbers of pigmented spheroidal or ovoid bodies are considerable, and many of these lie free in the capillaries, but all stages of the ingestion and destruction of parasites by phagocytic cells can be followed. Some peculiar bodies, possibly derived from malarial organisms, are to be seen. One of those rather frequently seen is spheroidal, a little larger than a red cell, with a thick shiny hyaline outer border, and showing a central mass of yellowish pigment granules. In some of the larger vessels there are several spheroidal bodies twice as large as a red cell, hyaline and faintly bluish stained throughout, and exhibiting a moderate number of central pigment granules. A good many small pigmented parasites were seen.

*Spleen.*—The deposit of pigment is extreme. Much of this is old pigment in compact masses within phagocytes, but there is a considerable number of free pigmented parasites, and all stages of their ingestion and destruction can be seen. Neither rings nor rosettes are seen. There is the usual cellular hyperplasia of the pulp cords.

*Marrow.*—The marrow of the ribs and vertebræ contains a moderately rich deposit of pigment which is usually limited to the phagocytes. Very little pigment is seen in the vessels, and very few parasites were identified either in smears or sections. The eosinophile cells and giant cells are increased. The nucleated red cells are abundant and some are slightly increased in size.

*Kidney.*—There is a moderate chronic diffuse nephritis with growth of new connective tissue in small wedge-shaped masses in the cortex. The glomeruli are apparently normal. The tubules show swelling of the lining cells, and in a few places the cells of the convoluted tubules are necrotic. They all contain much granular yellowish pigment giving the reaction of hæmosiderin. Very few parasites could be identified. The deposit of pigment, however, is very abundant and of peculiar distribution. The glomeruli contain more than the usual number of pigmented cells of the usual character. The larger vessels of the cortex are sometimes injected with blood in which are considerable deposits of brown granular or crystalline pigment. In the neighborhood of these vessels there are often many clumps of similar pigment and these are sometimes found in the lining cells of the convoluted tubules which are elsewhere entirely free from brown pigment. The limitation of this pigment in the cortex to the vicinity of vessels, strongly indicates that the crystalline deposits have resulted from the diffusion of dissolved Hb. or of escaped red cells.

Throughout Henle's loops, and especially in the ascending arms and in the collecting and discharging tubules the number of clumps of pigment is enormous. The vessels here, while injected with blood, are nearly free from pigment, which lies exclusively *in the lining epithelial cells of* the tubules, some cells containing 40-50, or more, clumps in a single section (Plate XI, Fig. 9). These cells, moreover, fail to show marked evidences of granular or fatty degeneration, or of fragmentation, but their protoplasm is uniformly finely granular, their edges are unbroken, and their nu-

clei unchanged. On close inspection these pigment clumps are found to be composed usually of small blunt-pointed crystals, sometimes of granules, of dark brown color, arranged usually in a rather compact circle or sphere. Some of the pigment is more diffuse. Occasionally a clear space surrounds the pigment clump, but the great majority of the pigment circles lie bare in the cell.

*Brain.*—Throughout the medulla, cerebrum, and cerebellum, the vessels are nearly free from pigment and parasites. In some sections from the frontal cortex there are a few pigmented endothelial cells and an occasional pigmented parasite, but most capillaries, though considerably injected, are free from all traces of parasites or their derivatives. In many of the pericellular lymph spaces throughout the cortex there were peculiar structures, the nature of which I have been unable to determine. These bodies consisted mostly of elongated fibrils or rods with tapering ends, about 0.5 to 1 $\mu$ in thickness, and 5-15 $\mu$ in length. They were sometimes single, more often multiple, and arranged in rosettes, or spirals, or in concentric layers, or irregularly clumped. They stained densely with methylene blue, faintly with hæmatoxylin. Similar deposits were found in other cases of malaria, and in one case of tuberculous meningitis. They may for the present be classed with the artifacts of nervous tissue.

EPICRITICAL:—In the above somewhat anomalous case there are several features of interest. The development of a case of fatal malaria in a patient who for twenty-five years had not been away from the vicinity of New York City is unusual. While autopsies on cases of malaria are not extremely rare in this locality, they are usually cases which were infected in southern latitudes.

While quinine in moderately large doses, with arsenic, controlled the active sporulation of the parasite and reduced the temperature, the treatment failed as usual to have any effect upon the crescentic forms, which persisted in enormous numbers until, rather suddenly in the last few days of the disease, they disappeared almost entirely, although the patient died in hyperpyrexia. This pyrexia is no indication of a failure of quinine to control the infection, as none of the young forms were seen after Oct. 12, and the terminal fever must be referred to other causes.

The prolonged delirium and coma are the chief clinical features of the case. There seemed little ground for doubting that the mental condition was referable to the malarial infection, because the coma was established before the urine contained casts and albumin; the changes in the urine were never marked; there were none of the usual concomitant signs of chronic uræmia, such as œdema, muscular twitchings, etc. The general condition of the patient was typically that of malaria; microscopic evidences of extreme malarial infection were

found in the blood, liver, spleen, marrow, and kidneys, while the evidences of nephritis were very much less marked than those usually found in cases dying in chronic uræmia. Neither can the coma be referred to the presence of organisms in the cerebral vessels, as none were found there, and it becomes necessary to regard the cerebral symptoms as dependent upon other conditions, probably toxic, associated with the severe malarial infection. This conclusion is in accord with the evidence furnished by other cases of the present series, which fails to support the view that malarial coma is always dependent on the presence of parasites or embolic processes in the cerebral vessels. (See especially Case VII.)

The most striking pathological feature of the case is the massing of pigment in the kidneys, especially in the cells of Henle's loops. A careful review of the microscopic studies of the viscera in malarial infection, which is believed to be fairly complete, fails to show the report of any similar condition in uncomplicated malarial fever. In the studies of Bignami,[1] Guarnieri,[2] Marchiafava and Celli (1887),[3] Kelsch and Kiener,[4] Stieda,[5] Bastianelli (1894),[6] Barker,[7] Benvenuti, Thin,[8] and others, the number of parasites and deposit of pigment in the kidneys are described as moderate. This general rule is explained by Bignami by the rapid renal circulation. The condition in the present case appears to resemble that found in the kidneys in hæmoglobinuric malarial fever, in some cases of which large deposits of pigment have been found, but differs from them in the peculiar distribution of the pigment, and in the absence of hæmaturia.

On first observing the pigment deposits in the epithelial cells I was inclined to regard them as the remnants of recent parasites, on account of the close resemblance of many of the pigment circles to those of the crescentic bodies, and from the presence of vacuoles about some clumps. Further observations on this and other cases, notably Case VII, led to the conclusion, however, that most of such pigment wreaths here and elsewhere have never been associated with parasites, but are derived from altered red cells. In the present instance this conclusion

[1] *Atti d. R. Accad. med. di Roma*, 1890; 1893.
[2] Ibid., 1887.
[3] Ibid., 1887.
[4] Maladies des pays chauds, Paris, 1889.
[5] *Centralbl. f. allg. Path. u. path. Anat.*, 1893, iv, p. 321.
[6] *Bull. d. R. Accad. med. di Roma*, 1893; 1894.
[7] *Johns Hopkins Hosp. Rep.*, 1895, v.
[8] *Lancet*, 1896, i, p. 1414.

is based upon the absence of any trace of the body of a parasite about the pigment clumps, the abundance of the clumps about the injected vessels of the medulla, and the crystalline form and peculiar arrangement of the grains of pigment in many of the clumps.

CASE II.—*Æstivo-Autumnal Malaria. Extreme Malarial Infection. Very large numbers of Parasites in Viscera, especially in the Heart Muscle. Rosettes in the Peripheral Blood. Extensive Pigmentation of Serous Membranes.*

J. B., 40 years. Went to Santiago in June, 1898, and remained about five weeks. During the last two weeks he felt feverish in the afternoon and complained of abdominal pain and diarrhœa. Never had a chill. The same symptoms continued during four weeks after his return to New York, when he took no medicine. Lately his chief complaints have been weakness and increasing pallor, but he has noticed no recent paroxysms. On August 15, he felt much worse and walked to the hospital with difficulty. When first seen he was apparently moribund but could answer a few questions as above. He soon became comatose. The pulse was very feeble, 124 per minute; temperature 101.6°; respiration 40. Extreme pallor and slight jaundice were noted. On physical examination the heart sounds were very feeble. The spleen was not palpable but the area of splenic dullness was enlarged. The *urine* was alkaline, sp. g. 1014; it contained a little albumin, but no casts were seen. During the night he vomited occasionally; delirium alternated with stupor; the pulse failed steadily; the temperature rose to 103.8° F., and he died 14 hours after admission.

*Autopsy.*—10 hours after death. *Externally*, extreme pallor, slight jaundice, no œdema. Subcutaneous tissues show a peculiar brownish yellow discoloration. *Lungs*, moderately congested and œdematous. *Heart*, size normal; muscle very flabby and pale; valves normal; chambers slightly dilated. *Liver*, surface and section of dark slaty color; outlines of lobules indistinct; size and consistence normal. *Spleen*, 1½ lbs., uniformly enlarged, of very dark chocolate color, pulp diffluent. *Kidneys* show signs of acute degeneration. *Gastro-intestinal tract* shows throughout a moderate catarrhal inflammation, but no hæmorrhages or erosions. *Serous membranes* all show small areas of black pigmentation. Peritoneum is of a dark slaty color and in the parietal pleura there are some large irregular patches of dense black pigmentation. Marrow of ribs and vertebræ is very hyperæmic and of dark chocolate brown color. The *blood* is very anæmic and of distinct chocolate tinge. The *brain* could not be examined.

*Microscopic Examination.—Blood.*—Smears taken on admission showed a large number of æstivo-autumnal parasites. Most were of the signet-ring form, without pigment, and all except the earliest stages were about equally represented. In a few of the larger rings one or two fine pigment grains were noted. Besides the rings there were a good many older forms with clumps of pigment. A few rosettes were found in the blood. The red cells showed the changes of a severe secondary chlorotic anæmia.

*Heart Muscle.*—The number of parasites in the red cells filling most of the capillaries is enormous. At many points nearly every red cell contains one or more organisms and the vessel appears to be distended with masses of infected red cells and pigmented leucocytes (Plate X, Fig. 7).

The forms of the parasites are about equally divided between non-pigmented rings, pigmented spheroidal bodies, and rosettes; but no crescents or distinct ovoids could be found. There are in the vessels a few pigmented endothelial cells of the usual appearance, and many richly pigmented leucocytes.

Most of the muscle cells contain a moderate deposit of large greenish yellow granules. There are no evidences of fatty or other form of degeneration of the muscle cells.

*Lungs* contain a great many richly pigmented phagocytes with parasites in all stages of degeneration. The capillaries are frequently distended and sometimes apparently occluded by masses of red cells, pigmented endothelial cells, leucocytes, and macrophages. The vesicles contain a few large pigmented cells. Parasites are not more numerous than in the peripheral blood.

*Kidney.*—The capillaries everywhere contain a moderate number of red cells harboring parasites. Most of these are the non-pigmented, ring-shaped organisms. A great many richly pigmented spheroidal parasites were seen in the same situation as the rings, and a few segmenting bodies were noted. In no place were the capillaries distended or occluded by masses of infected red cells and pigmented leucocytes, as was noted in the heart muscle. Evidences of phagocytosis are moderately abundant and extremely distinct, especially in the glomeruli. The phagocytic cells are always either mononuclear leucocytes or endothelial cells, the tubule cells being free from pigment. The observed phases of the process included the inclosure of an entire red cell infected with an unpigmented ring; the inclosure of one or many pigmented spheroidal bodies; all stages of the destruction of the bodies of inclosed parasites; and finally the circles and clumps of fine pigment grains, which remain after the destruction of parasites and red cells. From one to twenty circles were counted in large macrophages lying free in the capillaries. The glomeruli and the capillaries of the medulla contain more pigmented cells and parasites than do the cortical vessels. There is a marked acute degeneration of the lining cells of the convoluted tubules, but no signs of chronic nephritis. The tubules are slightly dilated, and contain either casts, or coagulum, or fragments of epithelial cells.

*Marrow.*—The deposit of pigment is very marked but much less than in the liver and spleen. The pigment is found in the endothelial cells, and especially in the large and giant mononuclear cells of the pulp cords. In these cells all stages of the ingestion and destruction of parasites could be followed. The number of parasites within red cells is considerable and larger than in the liver and spleen.

In sections of ribs and vertebral bodies very few fat cells are present, the marrow being excessively cellular. Nucleated red cells are abundant and some are of slightly increased size. The eosins and giant cells are distinctly increased.

In smears of the expressed marrow the same conditions were seen distinctly. Minute intracellular rings are very abundant, many cells containing two, and some three, or four, such parasites. Twin parasites were found in the cells, also, in the form of large vesicular bodies, one-third the diameter of the cell, and sometimes showing one or two very minute

pigment grains, but beyond this size, no twin parasites could be found. Well pigmented parasites were always single, and no cell was found containing two well developed spheroidal bodies.

A few minute rings and a great many pigmented spheroidal bodies were found apparently extracellular, a position which I am inclined to refer principally to post-mortem and artificial processes. Rosettes were abundant, and in several which were considerably flattened 18 spores could be accurately counted. A moderate number of young and middle-sized crescents were seen.

The phases of phagocytosis were quite distinct. The great majority of pigmented cells, and the only ones containing excessive pigment deposits, were the large mononuclear cells of the pulp cords. The pigment was found in the form of discrete grains, or often in compact clumps, or circles. From one to thirty or more of these pigment-clumps were seen in the larger cells. In many instances the circle of pigment surrounded a vacuole somewhat larger than the body of a parasite. In heavily pigmented cells irregular masses of granular pigment were usually found in the perinuclear region and elsewhere. The parasites seen within phagocytes included a few non-pigmented rings and many faintly staining pigmented spheroidal bodies. Many stages of the degeneration of parasites were seen in the bodies of these cells.

The frequent appearance of a circle of pigment grains around a small vacuole is probably referable to the complete destruction of the red cell (Plate X, Figs. 1 and 4). Many of these large circles of pigment grains surrounded a central compact clump, as though the englobed cell had contained a pigmented parasite. A great many small spherical masses of fine pigment grains, identical in appearance with the pigment clumps of full grown parasites or rosettes, were seen, and traces of the bodies of the parasites were often detected about the clumps. Many discrete coarser grains and clumps without vacuoles or surrounding granules seemed to represent that pigment which had been absorbed from the plasma after its discharge from the parasite. Larger conglomerate masses of older pigment were abundant, but even in these masses a granular structure was usually visible.

Finally, in the marrow smears, the formation of peculiar *vacuolated leucocytes* could be traced from the smaller and medium-sized mononuclear cells of the marrow. In these cells the nucleus gradually lost its affinity for methylene blue and became indistinguishable from the cell-body. At the same time, in the nucleus and cell-body, hyaline globules developed and gradually increased in size until the entire cell was reduced to a coarsely reticulated faintly staining mass, identical in appearance with the vacuolated leucocytes seen in the circulation (Plate XI, Fig. 8). This process affected both pigmented and non-pigmented cells.

On the other hand no resemblance could be traced between any of the stages of these degenerating cells and the various forms of parasites to be found in the marrow, none of which, when admitting of positive identification in stained specimens, exhibited similar degenerative changes. *In the fresh marrow juice these leucocytes very closely resembled the forms of large vacuolated parasites described by some writers.*

*Spleen.*—The black color of the spleen is found to be referable to very heavy deposits of pigment, lying in endothelial cells, large mononuclear cells of the pulp and sinuses, and leucocytes in the sinuses, and in parasites infecting red cells. The outlines of the sinuses are no longer visible, being choked by the influx of pigmented cells, or distended or ruptured thereby. The Malpighian bodies are much reduced in size. No foci of large cells free from pigment were to be seen in the pulp tissue.

The parasites are very numerous and of all forms except crescents, but the majority appear to be inclosed in various phagocytes.

*Liver.*—The pigment deposits are extremely rich and are found in the long swollen endothelial cells of the capillaries and in large mononuclear cells lying often apparently free in the capillaries, and some of which are probably leucocytes. The parenchyma cells are free from pigment. The number of parasites is very large. Most of them are inclosed within the above phagocytic cells, in which all stages of their degeneration are to be seen (Plate X, Figs. 1 and 2).

In the red cells a moderate number of rings, pigmented spheroidal bodies, and a few rosettes are seen. In the capillaries of Glisson's capsule the numbers of parasites within red cells are very much greater than in the intralobular capillaries. The chromatic network of the liver cells stains faintly with methylene blue and is very ragged and irregular. There are no signs of fatty degeneration. The cells usually contain a deposit of large greenish granules.

EPICRITICAL:—Among the features of this case, attention may be drawn to the rather sudden termination after a period of comparative freedom from severe symptoms, in which respect there is nothing very anomalous; to the prominence of the cardiac symptoms; to the acute degeneration of the kidneys; and to the activity and extent of the phagocytic process. These features may best be considered in connection with the pathological conditions found in the viscera.

As the patient's condition had not led him to seek medical assistance until a few hours before his death, it must be supposed that the paroxysms immediately preceding the fatal attack were mild, as is also indicated by the further history obtained. Such pronounced heart weakness occurring early in the first severe paroxysm of the relapse would seem to class the case with those of acute cardiac failure in pernicious malaria. It was noted in the physical examination on entrance that the first sound of the heart was barely audible, and the pulse extremely feeble. The microscopic examination showed the presence of unusually large numbers of parasites in the visceral capillaries, the heart muscle containing an excessive proportion of them. All the small vessels in this locality were filled or distended with blood containing a colossal number of parasites in all stages of development, with an abundant admixture of pigmented leucocytes. A considerable

mechanical effect of such a massing of parasites in obstructing the circulation can hardly be doubted, although no signs of complete thrombosis of small vessels could be found. On the other hand, no inflammatory reaction in or about the vessels or in the muscle fibres or supporting tissue, no hæmorrhages, or evidences of degeneration or necrosis of cells, could be found. Yet if the mere presence of the bodies of parasites in a tissue is capable of exciting any such inflammatory reaction or causing cellular degenerations, this was an unusually favorable situation to demonstrate these effects. No such changes existing, their absence appears to furnish some evidence that the bodies of malarial parasites do not exert any marked local toxic influence, but that their local action is largely mechanical. Granting that a considerable disturbance of the heart results from the general toxic condition, it seems probable that the extreme cardiac failure observed in the present case resulted from the mechanical obstruction of the circulation by the masses of parasites in the capillary vessels, but the evidence that such a relation existed can hardly be claimed as demonstrative.

In the kidneys, on the other hand, where the effects of a toxic agent were very marked, the number of parasites was comparatively small, hardly exceeding that found in the peripheral blood. In these organs there were distinct signs of severe acute degeneration, referable, not to the presence of parasites, but to the general toxæmia.

The phagocytic process was extremely active in the liver, spleen, and marrow, where the great majority of parasites were englobed in phagocytic cells. The leucocytes were everywhere actively engaged in the process. In the kidney the majority of phagocytic cells were leucocytes. In the heart muscle, and in the connective tissues generally, the parasites were very abundant and were multiplying rapidly, unrestrained by any phagocytic tendency in the endothelial cells.

CASE III.—*Æstivo-Autumnal Malaria. Marked Cerebral Symptoms and Concentration of Parasites in Capillaries of Central Nervous System. Infection with a single well defined group of Parasites. Developmental stages fully apparent throughout a 48 hr. cycle. Severe degenerative changes in the cells of the Convoluted Tubules, with absence of parasites in the renal vessels. Capillary Varicosities in the Liver, with atrophy of parenchyma.*

B. T., 32 years. While in Cuba he had attacks of chills, fever, and diarrhœa, but partly recovered under quinine. On the transport the same symptoms returned. After arrival at Camp Wikoff he suffered from nearly continuous fever without chills, and the diarrhœa became more profuse.

On admission to the General Hospital, September 6, he was considerably emaciated, slightly jaundiced, and completely prostrated. He was given 2½ gr. of bimuriate of urea and quinine, subcutaneously, t. i. d., and

opium. He passed a restless night and the temperature remained high. At 10 A. M., September 7, examination of the blood showed a recent sporulation of parasites. The temperature fell steadily during the day but the patient became delirious in the afternoon, and comatose by night, and never recovered consciousness. There was a moderate rise of temperature on Sept. 8, while the coma deepened and the pulse gradually failed. Death occurred at 3 A. M., Sept. 9.

*Blood Examination*, September 7, 10 A. M., showed a great many æstivo-autumnal ring-shaped parasites, 2-3 $\mu$ in diameter, lying in shrunken red cells. Most of them are entirely free from pigment, but rarely one or more fine pigment grains may be detected. A great many of the rings are less than 2 $\mu$ in diameter. Multiple infection of cells is not unusually frequent. In the fresh condition the parasites exhibit rapid changes in outline but few distinct pseudopodia.

The red cells show the changes of a severe secondary anæmia with beginning changes in the size of the cells. The leucocytes are reduced in number. No eosins seen. No pigmented leucocytes.

Sept. 8, 10 A. M., the parasites are much less numerous. They are nearly all of larger size, 4-5 $\mu$, and maintain the form of a ring with thickened irregular segments. A few show one or two fine pigment grains. The chromatin is variously subdivided and usually displaced from the periphery of the ring, being often found as a small group of very fine granules in the centre of the ring, or arranged in the form of a crescent or figure 8, or as an irregular mass or group of granules lying at some distance from the ring. No spheroidal bodies with compact pigment mass and no rosettes were seen in this case. Several hours were spent at various times in the study of these specimens and during that time two crescents were encountered. The unity of the group of parasites is to that extent imperfect.

In the fresh condition the formation of pseudopodia and the amœboid motion are very active, and the pigment grains show slight vibratory motion. The leucocytes are as before.

*Autopsy.*—4 hours after death. *Body* markedly emaciated, slightly jaundiced; no œdema. *Lungs* show old emphysema and hypostatic congestion. *Heart*, rather small; valves and muscle normal; pericardium distended with clear serum. *Spleen*, slightly enlarged, moderately pigmented, dark brown, rather soft. *Kidneys*, about normal in size, consistence reduced, capsules not adherent, surface smooth, cortex somewhat thickened, pale, markings regular but indistinct. *Stomach*, contains bile, otherwise negative. *Intestine*, normal. *Brain*, no increase of serum, no venous congestion, no dropsy of ventricles; cortex slightly brownish on section; no petechiæ.

*Microscopic Examination.—Liver.*—The liver cells are very fatty, and contain many coarse yellowish granules, some of which give the reaction of hæmosiderin. No necrotic foci were seen. In many lobules the cords of liver cells are partly or completely atrophic and the capillaries are much widened, forming a variety of cavernous tissue. These changes are of irregular distribution in the organ, being sometimes most marked about central veins, but more often affecting large irregular portions of lobules. Pigmentation of endothelial cells and of leucocytes is marked but not extreme. Parasites are very scarce, but a few small spheroidal bodies and minute rings could with difficulty be identified.

*Spleen.*—Appearances similar to those of Case II; but very few parasites could be identified.

*Marrow.*—The marrow of the vertebræ is very fatty. In the cellular cords, there is in places moderate proliferation, and the cells appear in compact masses. Generally, however, the cords appear normal or deficient in colorless cells. The pigment deposit is slight and no parasites could be identified. In smears of the marrow a few ring-shaped parasites within red cells were identified. The nucleated reds, eosins, and giant-cells are very deficient.

*Kidneys.*—The convoluted tubules are markedly dilated and filled with granular coagulum. The cells are flattened, or broken and degenerated, and nearly all contain great numbers of large and small light yellowish granules which give the Prussian blue reaction of hæmosiderin. The capsules of the glomeruli are considerably dilated. The capillary tufts contain a moderate number of pigmented cells and a few spheroidal parasites. In a few of the ascending limbs of Henle's loops there are a good many clumps of pigment lying within the lining cells, but this condition is not at all frequent.

*Brain.*—Throughout the cerebrum, cerebellum, medulla, and upper cervical cord, the capillaries contain a very large number of red blood cells harboring parasites. Most of these are small pigmented spheroidal bodies; some exhibit the large ring form with little pigment, and a very few rosettes were identified. The pigment deposit, outside of the parasites, is slight. A considerable number of capillaries were found completely filled and apparently occluded by masses of infected red cells, pigmented leucocytes, and swollen pigmented endothelial cells. In the same regions the small arterioles and all the larger vessels were almost entirely free from parasites. The ganglion cells everywhere show reduction in size, irregularity, splitting, or loss, of chromatic bodies. These changes are less marked in the large stichochromes of the bulbar nuclei than in the cerebrum and cerebellum.

EPICRITICAL:—Although further evidence is hardly required to demonstrate the fact that in many cases of pernicious malaria of the cerebral type the capillaries of the brain contain an excessive number of parasites, the present case is such a striking example of this condition as to be worthy of record.

The relation of the cerebral symptoms can apparently be closely connected with the development of the parasites as followed in the examinations of the blood. Sporulation occurred during the night of September 6, when the temperature was at its highest point, 104°. At 10 A. M., September 7, when the patient was extremely restless, the blood and presumably the brain contained a large number of small ring-shaped parasites. Delirium and partial stupor began on the same afternoon. At 10 A. M., September 8, when the patient was comatose, the parasites had markedly increased in size and many had retired from the general circulation. At this time it is reasonable to infer that the

increased size of the parasites and probably their increased numbers in the central nervous system had seriously impaired the capillary circulation. At death, 3 A. M., September 9, preceded for several hours by profound coma, the sections of the brain show that the majority of the parasites had reached their full development, some were segmenting, and many cerebral capillaries were occluded.

The presence of a single group of parasites, the development of which could be followed throughout the cycle, is one of the interesting features of the case. Sporulation appears to have been completed during the night of September 6, when the temperature reached its highest point, 104°. At 10 A. M., September 7, the blood contained a large number of rings nearly all under 3$\mu$ in diameter, with a single large chromatin body, and without pigment. These parasites appeared to have had at least 6-10 hours' growth. At 10 A. M., September 8, the parasites had increased in size, measuring about 4-5$\mu$ in diameter; numerous outgrowths had appeared on the circumference of the rings; the chromatin (Nocht's method) was invariably increased in quantity, subdivided, and irregularly placed, and a few parasites showed slight pigmentation. There were still no spheroidal bodies, with compact pigment, to be found, after 30 hours' growth. The patient died at 3 A. M., September 9, and the great majority of parasites found in the cerebral capillaries were of large size and abundantly pigmented, and a few rosettes were seen, indicating the approach of general segmentation at the end of 48-50 hours' growth. Judging from the appearance of the parasites found in the sections of the brain it would appear that about 6-10 hours' growth separated considerable numbers of the youngest from the oldest members of the group, although between a few individuals the intervals must have been much longer.

The severity of the renal lesion, with the absence of parasites in the renal vessels, also requires mention. The changes in the cells of the renal tubules were more advanced than in any other uncomplicated case of the series and appeared to be purely of the type of acute degeneration. The lining cells were markedly eroded and largely composed of a multitude of light yellow granules giving the reaction of hæmosiderin. This destruction of the lining cells caused the dilated tubules to be more or less filled with granular detritus, but there was no further evidence of an exudative process. The kidney was free from chronic changes. In the absence of parasites and of signs or causes of acute inflammation, this lesion must be referred to a toxic condition associated with the malarial infection.

The evidence of the present case, therefore, fully accords with the conclusion drawn from other cases of the series, that the usual renal lesions of pernicious malaria are referable to the effects of a toxic process and not to the direct action of parasites.

CASE IV.—*Æstivo-Autumnal Malaria. Extreme Malarial Infection. Localization of Parasites in Bone Marrow. Infection with only one group of Parasites. Pernicious Anæmia.*

F. J., 27 years, private, U. S. Army. No important details of the history of this case were obtainable. It was learned that the patient had suffered severely from malarial fever in Cuba and on the transport, and was received at the hospital at Montauk in a precarious condition, dying a few hours afterward in spite of stimulation and subcutaneous injections of quinine.

*Autopsy.*—6 hours after death. *Body* very much emaciated, markedly jaundiced. *Lungs*, lower lobes œdematous; commencing hepatization of lower part of right upper lobe. *Heart*, flabby, pale; valves normal; pericardium distended with clear serum. *Liver*, of moderate size, almost black; gall-bladder distended with bile. *Spleen*, moderately enlarged, soft, black. *Kidneys*, slightly enlarged, surface smooth, capsule not adherent, cortex thick, yellowish, markings regular, indistinct. *Gastro-intestinal tract*, negative. *Peritoneum*, slate colored. *Marrow* of ribs and vertebræ chocolate colored.

*Microscopic Examination.—Blood.*—The only specimens secured were squeezed from the incised finger-tip at the autopsy, six hours after death. The red cells are extremely deficient in number and usually fail to form rouleaux. The plasma stains slightly. There are extreme differences in the size of the red cells, which vary from small microcytes to very large megalocytes; most are larger than normal. Nearly all cells contain an increased quantity of Hb. and many are polychromatophilic. Nucleated red cells are abundant and nearly all fall in the class of megaloblasts or gigantoblasts. There is a pronounced polynuclear leucocytosis (antemortem?), but eosinophile cells are scarce. Many leucocytes, both mononuclear and polynuclear, are pigmented. Comparatively few parasites could be found, and these were all small rings, as seen in the smears of the marrow.

*Liver.*—There is slight fatty degeneration of the liver cells; the chromatic network is irregular and indistinct, and the cells all contain large greenish granules which give the reactions of bile pigment. There are no areas of necrosis. The deposits of malarial pigment are abundant and very similar to those described in Case II, but the evidences of inclosure and destruction of parasites are very much less marked. Very few parasites could be identified.

*Spleen* shows the usual changes of acute malarial infection.

*Marrow.*—That of the ribs and vertebral bodies is very cellular. The hyperplasia affects principally the myelocytes, many of which show mitotic figures, other small mononuclear cells, and giant-cells, of which there are many groups of five, six, or more. No fat cells were seen. The sinuses

are gorged with red cells and pigmented leucocytes. Nucleated red cells are very abundant but no "islands" of these cells could be found. The pulp cords contain a great many heavily pigmented endothelial and large mononuclear cells. A few parasites were identified in the sections with difficulty.

In smears of the marrow, all stages of the inclosure and destruction of parasites could be followed in the large mononuclear and endothelial cells. The number of parasites found in these smears is enormous, and nearly all are the small ring-shaped forms without pigment. They are much more numerous in the marrow than in the blood smears or in any other tissues of the case, and much more numerous than in the smears made from the marrow of any other case of the series. Examples of multiple infection of the same red cell are very numerous, three and four rings being very frequently seen; five and six were sometimes encountered, and one cell was found containing seven distinct young rings.[9] In spite of the enormous number of parasites and the abundance of nucleated red cells, none of the latter were found infected. No crescents were seen. Of the nucleated red cells many are of normal size and appearance, but a great many darkly staining megaloblasts and gigantoblasts are present. The eosinophile cells are about normal in numbers, while the giant-cells are distinctly increased.

The *kidneys* show the lesions of acute degeneration similar to those of Case II, but the number of parasites in the capillaries is small, and no rosettes were seen. Pigmentation is moderate.

In the *heart-muscle* a few ring-shaped and a very few small spheroidal parasites were found.

The *gastro-intestinal tract* exhibited no lesions of importance; its wall contained a moderate number of small parasites without pigment.

The brain was not examined.

EPICRITICAL:—In this case there are several isolated features of interest. The localization of an enormous number of parasites in the marrow of the ribs and vertebræ is a peculiarity not encountered in any other case of the series. It has appeared from smears and sections of the marrow of other cases that the activity of phagocytes in this tissue, as in the liver and the spleen, greatly reduces the numbers of parasites that can be demonstrated in smears of these tissues. This general rule, first formulated by Guarnieri and Bignami, has applied in all other cases of my series, but in the present instance no large number of parasites was demonstrated in any other tissue except the marrow, where the excessive pigmentation is further evidence of unusual activity of the parasites in this locality.

Attention may here be drawn to the necessity of relying only upon smears of the tissues and not upon the examination of sections to

[9] Shown in Plate XXX, Fig. 2, in *Journal of Experimental Medicine*, 1901, v.

determine the number of parasites present in tissues which are actively engaged in phagocytosis. Although formalin as used in fixing the tissues proved to be a very superior agent for this purpose, it has always seemed to me difficult and hazardous to attempt to identify parasites in stained sections of the liver, spleen, or marrow, and in many instances where none could be identified in sections, smears of the tissues revealed their presence in abundance. In the kidney, heart-muscle, brain, and all tissues where phagocytosis is less active, the results of examination of stained tissues appear to be fully reliable, especially if Nocht's method is used.

A further point of interest in the present case is the evidence pointing to the existence of a single very compact group of parasites in the blood and viscera. The forms found in the blood and in the smears of the viscera included only the smaller non-pigmented ring-shaped parasites. Neither pigmented spheroidal bodies, nor rosettes, nor crescents, were anywhere seen. This condition is the more remarkable since the pigmentation of the viscera, the grade of anæmia, and the general condition of the patient indicated a somewhat prolonged course of the infection.

The changes in the blood in this case are of special interest, illustrating the rapid development, as a result of malarial infection, of a condition identical in morphological character with that of primary pernicious anæmia. As the first cases of malaria among the troops at Santiago developed in the second week of July, this patient, dying on September 10, could not have been ill longer than eight, or possibly nine, weeks. Yet in this period a condition of the blood was established indistinguishable from that of primary pernicious anæmia, including the abundance of large megalocytes with excess of Hb. and the presence of many megaloblasts. Even the smaller red cells exhibited an apparent excess of Hb. Apart from the lesions directly referable to the growth of malarial parasites, the changes in the marrow included a well-marked cellular hyperplasia affecting principally the myelocytes and other small mononuclear cells, and giant cells; disappearance of fat cells; increase in size of the nucleated red cells, the majority of which were megaloblasts; and disappearance of "islands" of nucleated red cells.

CASE V.—*Æstivo-Autumnal Malaria. Massing of Parasites in Kidneys. Acute Hæmorrhagic Nephritis. Casts Entangling Infected Red Cells and Pigmented Leucocytes in Discharging Tubules. Infection with a single very compact Brood of Parasites.*

M. S., female, aged 17, contracted malaria on Long Island, and after a short period of mild paroxysms was completely prostrated on Sept. 12, 1900. On admission to hospital, Sept. 15, the chief symptoms were prostration, restlessness, vomiting, and moderate œdema of legs. Temperature 104.2° F. Urine, of high color, sp. g. 1018, contained many epithelial cells, detritus, and many red blood cells. Diazo-reaction marked. Widal's reaction absent. Bowels costive. Restlessness and vomiting were partly controlled by sedatives. The vomiting of a round worm led to the administration of three full doses of santonin on Sept. 19. Mild delirium developed into coma on Sept. 20, and with failing pulse and diminished, bloody urine the patient died on Sept. 20. There were two complete remissions of fever on Sept. 18 and 20, but no chill occurred. *Clinical diagnosis*, typhoid fever and acute hæmorrhagic nephritis.

*Autopsy.*—By Dr. Otto Schultze, 14 hours after death. Body well nourished, rigor firm, slight œdema of legs. *Heart*, *lungs*, *stomach*, and *pancreas* normal. There was one ounce of straw-colored serum in the pericardium, and a few ecchymoses in the visceral pleura and pericardium. *Intestine*, ileum congested, lymph-follicles slightly enlarged; colon normal. *Liver*, without gross indications of malarial infection, was pronounced normal. *Brain* normal. *Spleen*, 16 oz., firm, dark red, with prominent Malpighian bodies. *Kidneys* weighed together 16 oz.; cortex much thickened, capsule free, markings obscured, color very light; medulla intensely congested, in places rusty; in cortex of right kidney a superficial anæmic infarct with surrounding hæmorrhagic zone, measuring 3 x 2½ cm. in area, and 3 mm. in depth.

No gross evidences of malaria were detected.

*Anatomical diagnosis.*—Acute hæmorrhagic nephritis.

Cultures from liver and spleen yielded Bacillus coli communis, but no growth of Bacillus typhosus was obtained.

Through a misunderstanding all the viscera except the kidneys were thrown away. The kidneys were hardened in 5 per cent formalin.

*Microscopic Examination* (Plate XIII).—The lining cells of the convoluted tubules exhibited a very advanced stage of degeneration of a peculiar type. The cells were greatly swollen, their outlines obliterated, so that the distended tubules were filled with a coarsely reticulated mass of cell-detritus in which pyknotic nuclei were irregularly scattered. The degenerative process was principally hydropic, little fat or stainable protoplasm being present (Plate XIII, Fig. 13). There were many minute foci of necrosis, especially in the right kidney. The infarcted area was in an early stage of coagulative necrosis, and throughout this area, especially in the hæmorrhagic zone, the vessels were distended with blood containing enormous numbers of small pigmented parasites. Many small vessels leading to the infarct were distended to two or three times their normal calibre by thrombi of infected red cells. The capsules of the glomeruli were distended with granular coagulum (Plate XIII, Fig. 13). Most of the cortical capillaries were collapsed by the distended tubules and free from blood and parasites. Throughout the medulla were many miliary hæmorrhages, and most of the capillaries were distended with red cells, most of which contained parasites, or with thrombi of pigmented parasites which

had nearly destroyed the red cells. The parasites were remarkably uniform in size, being full grown æstivo-autumnal forms with abundant pigment. A very few rings and rosettes were seen. The discharging and many higher tubules were distended with granular, epithelial, or blood casts. Some of these casts had entangled leucocytes, often pigmented, and infected red cells, while some infected red cells lay free in the lowest discharging tubules. From their low position in the tubules all of these casts must have reached the urine in at least moderate numbers. The remarkable massing of parasites in the renal capillaries is shown in the photographs (Plate XIII, Figs. 14 and 15).

EPICRITICAL:—The absence of microscopic examination of the other viscera, while greatly to be deplored for the sake of completeness in the report of this case, cannot seriously detract from the importance of the findings in the kidneys. Doubtless there were many parasites in the other viscera, but in the absence of gross evidence of their presence it is safe to conclude that these viscera were not the seat of any special localization of parasites. This conclusion is rendered more trustworthy from the fact that the single compact brood in the kidney was composed of full-grown forms which were richly pigmented.

Moreover, numerous miliary hæmorrhages, and thrombosis of vessels with infarction, are the usual mechanical results of the presence of enormous numbers of parasites in a tissue, and the great extent of these lesions in the kidneys throws this case in the same class with the comatose and choleraic cases, with localization of parasites in the brain and gastro-intestinal mucosa respectively. The extreme degeneration of the tubule cells seems in part referable to the general toxæmia of the disease, but its extreme degree and peculiar character were not seen in any other case of the series, and may, with considerable certainty, be attributed to the obstruction of the circulation by the thrombi of infected red cells. Since the discharging tubules contained, among a large number of casts, some entangling infected red cells and pigmented leucocytes, while a few infected red cells were found free in the lumina of the tubules, it seems possible that a diagnosis of such a case might be established during life from the examination of the urine, which should show marked diminution in quantity, considerable albumin and blood, many granular, epithelial, some blood casts, and *infected red cells* and pigmented leucocytes, both free and adherent to casts.

CASE VI.—*Æstivo-Autumnal Malaria (?). No Parasites found in Blood. Few Parasites and unusually little evidence of malarial infection found in the Viscera.*

B., age 32. Served with regiment in Santiago campaign and contracted malarial fever in Cuba. Stated that he had four attacks in Cuba, marked

by chills and fever. The last and longest illness lasted three weeks. Was treated always by quinine with good results, but on omitting treatment the disease promptly relapsed. Recently he had suffered from mild chills daily, with more continued fever. On Sept. 4, the day of admission, he had a slight chill at 8 A. M. and that afternoon the temperature was 101.6°; pulse, 80.

Physical examination was negative, the spleen not being found notably enlarged. The patient was not markedly emaciated or anæmic. All symptoms pointing distinctly to malaria the patient was given quinine, but next morning, September 5, he had another chill and the temperature rose to 104°. Quinine was then increased, and given subcutaneously in large doses. On September 8, there was a moderate chill and rise of temperature. The stools were now diarrhœal, the abdomen moderately distended, the skin slightly jaundiced, and as the fever did not yield to quinine the blood was examined.

*Blood Examination.* Sept. 8.—The red cells showed the changes of well marked secondary chlorotic anæmia. The leucocytes were reduced in numbers. No eosinophiles. No distinct pigmented leucocytes, but a few contained single grains of pigment apparently malarial. In spite of prolonged search no parasites could be found. This result was confirmed by several subsequent examinations of the same and other specimens. The dissolved blood in the proportion of about 1 to 10 of water was mixed with a broth culture of B. typhosus, yielding prompt and typical clumping.

On the evidence of a temperature resisting quinine, of typhoidal stools and abdominal symptoms, absence of parasites from the blood, and presence of Widal's reaction, the administration of quinine was stopped from September 9 to 10 inclusive. The temperature declined, but the other symptoms persisted and the patient grew steadily weaker.

Blood examination, Sept. 9, gave the same result as before, but the Widal test was not repeated. Sept. 10, temperature fell to 99.6°, but the patient's condition was not improved. Quinine was again administered subcutaneously. Sept. 11, abdomen more distended; diarrhœa continues; no eruption; patient at times mildly delirious; pulse very weak. Blood examination, Sept. 11, showed no parasites, but a few characteristic pigmented leucocytes were seen. Sept. 12, patient died. The diagnosis was at this time regarded as probably typhoid fever.

*Autopsy.*—10 hours after death. Body moderately emaciated, slightly jaundiced. *Lungs*, moderately congested and œdematous. *Heart*, left ventricle slightly dilated, wall rather thin, flaccid; old thickening of mitral and aortic valves. *Liver*, moderately enlarged, moderately dark brownish in color, but not slaty. *Spleen*, moderately enlarged, firm, dark red in color. *Kidneys*, enlarged, capsule free, surface smooth, cortex thickened, pale; markings regular but indistinct. *Gastro-intestinal tract*, shows no lesions of importance; Peyer's patches are not enlarged or congested; mesenteric lymph nodes are not enlarged. The stomach contains blackish fluid but there are no evidences of gastro-duodenitis. *Brain*, in the absence of cerebral symptoms, was not examined. *Marrow*, hyperæmic, but shows no gross indications of malarial infection. *Blood*, moderately anæmic, but not otherwise changed in color.

*Microscopic Examination.—Spleen* shows the usual changes of acute malarial infection. The deposit of pigment, although considerable, is much less than usual in fatal cases of malaria. Smears of the splenic pulp made at the autopsy showed the presence of a very few ring-shaped parasites in red cells. The pigmented leucocytes and endothelial cells are of the usual character in acute malarial infection.

*Liver.*—The deposit of pigment is rather less abundant than in the spleen and is limited to the leucocytes and endothelial cells. The liver cells show destruction of chromatic network, and a moderate deposit of greenish granules; some contain fat globules. In the smears from the liver, no parasites could be identified, but some atypical intracellular pigmented spheroidal bodies were noted which may have been malarial parasites.

*Marrow.*—The deposit of pigment is scanty. Fat cells are moderately abundant in the ribs, but the evidences of cellular hyperplasia are distinct. In the smears some typical macrophages englobing parasites in all stages of digestion, are found. A few infected red cells are seen. The nucleated red cells, eosins, and giant cells, are deficient in number.

In the other viscera the deposit of pigment was much less abundant than in most cases of fatal malaria, and no parasites could be found.

EPICRITICAL:—While the data in this case must be regarded as inconclusive in important respects, the facts demonstrated render the case one of unusual interest and obscurity.

The most important feature is the absence of parasites from the blood, as repeatedly demonstrated, in a patient who nevertheless died with a typical temperature curve of fatal æstivo-autumnal malaria. The absence of parasites in this instance is not fully explained by the previous treatment with quinine, as in all other cases of my series in which all parasites disappeared promptly after quinine, the patient improved. Moreover, it is an almost invariable experience that cases of malaria that die without parasites demonstrable in the blood are more chronic cases complicated by severe anæmia or cachexia. All the other fatal cases of acute malaria seen at Montauk showed many parasites in the blood at death, although many of them had been treated with very large subcutaneous injections of quinine for as long a period as in the present case. Accordingly the absence of parasites from the blood, under the conditions existing, at once raised a doubt regarding the nature of the disease.

The possible existence of typhoid fever was completely set aside by the autopsy, unless one assumes an infection by B. typhosus without intestinal lesions.

Both the gross and the microscopic examinations of the viscera, however, as well as the clinical history, indicate as the cause of death an acute malarial infection in the fourth or fifth relapse, proving fatal

with very few parasites in the blood, which disappeared promptly on the administration of quinine. The present case therefore seems to fall properly in a rare and obscure class described by Marchiafava, Bignami, and Bastianelli[10] (1894), in which few parasites were found in the blood during an acute fatal attack of malaria, and in which no distinct gross signs of malarial infection were found at autopsy, the diagnosis requiring a microscopic examination of the viscera.

These cases occurred in July or late in the summer. They usually presented the rather typical clinical symptoms of pernicious malaria, especially the cerebral symptoms. On examination of the blood, however, even early in the disease, very few parasites (one or two in a single slide) or, later, none at all, were to be found, while the viscera showed no distinct gross lesions of a previous severe malarial infection. On microscopic examination of the viscera, pigment deposits were unusually scanty and few or no parasites were found.

These cases, according to the authors, are not to be classed with those in which the parasites gradually disappear in severe acute infections, none being found in the finger blood at death although the viscera exhibit abundant evidence of malarial infection; nor yet with those in which the parasites disappear after a long infection has spent itself. They believe that the fatal issue is rather to be referred to general debility of the patient, or to an unusually virulent infection, or to an occasional combination with sunstroke.

In my case the patient had not suffered from the campaign more than had many others, and although he had undoubtedly been living under very unfavorable conditions, this fact, though important, seems insufficient of itself to explain the unusual features of the disease. Neither was there any indication that the patient suffered unusually from the heat which prevailed at that time, even at Camp Wikoff. Finally, a virulent malarial infection usually produces very large numbers of parasites, severe anæmia, and heavy deposits of pigment, all of which were absent, at least in the fatal attack.

If the present case is to be accepted as one of pernicious malaria, and it is essentially similar to those of the Italian authors, the conclusions must then be drawn that æstivo-autumnal malaria may pass through four or five relapses without leaving marked deposits of pigment in the viscera and may end in a fatal attack in which very few parasites, which soon disappear under quinine, are to be found in the blcod or viscera.

After referring to their own cases of this character Marchiafava

[10] loc. cit.

and Bignami take pains to state that after years of experience they believe that fatal malaria does not exist without parasites in the finger blood. The present case cannot be regarded as an exception to this rigid rule, and I would particularly point out the fact that the patient's blood was not examined until 72 hours after the beginning of treatment by subcutaneous injections of quinine.

CASE VII.—*Fatal Malaria from Infection with Large Tertian Parasite (Golgi). Extreme Anæmia. Prolonged Coma without Parasites in Brain. Catarrhal Colitis. Hæmoglobinuric Malarial Fever.*

G. F., aged 32, private, U. S. Army, contracted malarial fever at Santiago in July, 1898, and had had repeated relapses with short intervals of improvement, when he had felt able to return to duty. Had often experienced severe shaking chills at somewhat irregular intervals. Had steadily lost flesh and become very anæmic. About Sept. 11, was again prostrated with severe chills and fever which failed to respond to quinine administered by the mouth or subcutaneously. On admission to General Hospital at Camp Wikoff, Sept. 13, the patient was comatose, and remained so until death at 3 A. M., Sept. 16. When seen by me, Sept. 15, the patient was comatose and moribund. The foregoing items of history were obtained from Dr. S. W. Allen, of Boston, who had seen the patient on admission, and to whom I am indebted for the opportunity of studying the case.

*Autopsy.*—8 hours after death. Body much emaciated, excessively anæmic, and slightly jaundiced. Chocolate-colored fluid exudes from mouth. *Lungs*, anterior portions anæmic, posterior much congested, moderately œdematous, and unusually dark in color. *Heart* muscle very flabby, of pale brownish tinge; valves normal. *Blood*, very watery, of slightly brownish tinge, coagulating feebly. *Liver*, not distinctly enlarged; of slaty color but not extremely dark; outlines of lobules very indistinct; gall-bladder distended with bile. *Spleen*, greatly enlarged, soft, but not diffluent; of typical chocolate brown color. *Pancreas*, small, dark salmon in color, rather soft. *Kidneys*, slightly enlarged, surface smooth, cortex thick, deep red, in places rusty, markings indistinct; organ very greatly congested. *Stomach*, partly digested in places, contains some dark bloody fluid. *Small intestine*, exhibits no abnormalities. *Colon*, lower third the seat of an intense catarrhal inflammation with superficial erosions, and swelling of solitary follicles. *Mesenteric lymph-nodes* are not enlarged. *Serous membranes*, slightly darkened and jaundiced, and contain slight serous effusions. *Marrow*, very hyperæmic, of chocolate brown color. *Brain*, white matter perhaps slightly darker than usual; dura and pia yellowish; no effusions, no petechiæ. Specimens preserved in 5% formalin.

*Microscopic Examination.—Blood*, Sept. 15. Smears contain a very large number of tertian parasites in all stages of development. These parasites are of large size, richly pigmented, except in the very young forms; their nuclei fail to stain by methylene blue, and the infected cells are much swollen and distinctly pale. A prolonged search, repeated on several subsequent occasions, failed to show the presence of any bodies that could be classed with the æstivo-autumnal parasite. All the ring forms were coarse,

usually pigmented, with a large achromatic spot (methylene blue), and the infected cells were swollen.

The red cells show the changes of a severe secondary chlorotic anæmia. There was no leucocytosis, but the eosinophile cells are not relatively numerous. A moderate number of pigmented leucocytes were seen.

At the autopsy, smears upon glass slides were made from the expressed marrow of the ribs, and from the splenic pulp.

*Smears from the marrow* contained an abundance of pigmented cells. The pigment is usually darker and finer than that seen in æstivo-autumnal infections. When occurring in clumps, the clumps are rather more compact, but most of the phagocytic cells contain more diffusely scattered pigment grains than are seen in æstivo-autumnal cases. Many rods and clumps, however, are indistinguishable from the æstivo-autumnal pigment. Very few infected red cells could be found, but there were a few small pigmented intracellular bodies staining faintly with methylene blue. Nucleated red cells, eosinophile cells, and giant-cells are distinctly deficient.

*Smears from the spleen* contain a great number of pigmented cells similar to those of the marrow. There are a large number of distinctly stained pigmented parasites of considerable size. Very few or none of the younger parasites seen in the blood could be identified in these smears. No vacuolated parasites could be found, but there was a considerable variety of small, vacuolated leucocytes, many of which were pigmented (Plate XI, Fig. 8).

*Spleen.*—There is extreme pigmentation of all the larger cells, the pigment showing the same characteristics as in the marrow and liver. No parasites could be identified. There is a well-marked cellular hyperplasia of the pulp tissue; the large and small sinuses are choked with pigmentiferous and other cells; the Malpighian bodies are reduced in size, and the blood content of the organ is increased.

*Abdominal lymph nodes* show moderate hyperplasia, slight pigmentation of endothelial cells, many mast-cells, but no parasites.

*Marrow* (rib).—The pigment deposit is very heavy, but few parasites could be identified. The cellular elements are very abundant and in places there seems to be some proliferation. There are marked congestion of all vessels and a few small hæmorrhages.

*Liver.*—There is extreme pigmentation of endothelial cells, macrophages, and leucocytes, but the parenchyma cells are almost entirely free from brownish pigment. The deposit of pigment in the former cells differs from that seen in æstivo-autumnal cases, in being finer and more diffuse (Plate X, Fig. 3). Although there are many cellular inclusions in the phagocytes, no parasites could be positively identified. The liver cells are not fatty, but the chromatic reticulum is faint and irregular, and many cells contain coarse greenish granules. A few small foci of necrosis were found, in the neighborhood of which dilated capillaries filled with large phagocytic cells were sometimes noted.

*Kidney.*—The blood content of the organ is enormously increased. All the large vessels are gorged with blood, the intertubular capillaries in numerous small areas are greatly dilated and distended with blood. The capillary walls are usually intact, but in many places there are small hæmorrhages into the tubules. Everywhere, especially in the medium-

sized and larger vessels, there are peculiar collections of pigment to be described later. The quantity of ordinary malarial pigment is not large.

The cells of the convoluted tubules show advanced stages of degeneration. In the less congested areas the cells are moderately eroded, and contain a large deposit of fine yellowish granules of hæmosiderin. Near the hæmorrhages and between markedly dilated capillaries, the tubule cells are often necrotic, the nuclei fail to stain, and the protoplasm is broken up into shiny opaque globules staining with eosin. Sometimes the entire cellular lining is fused into a homogeneous opaque mass entirely detached from the membrana propria. In some lining cells and in some tubules there are a few pigmented parasites, which are also to be seen in the capillaries.

*Lungs.*—All capillaries contain an enormous quantity of granular and crystalline pigment in leucocytes, endothelial and epithelial cells, and free in the vessels. No parasites were identified.

*Stomach* and *small intestine*, negative. The inflamed *colon* shows intense congestion of mucosa, exfoliation of epithelial lining in places, moderate pigmentation of leucocytes and of endothelial cells. No malarial parasites identified and no Amœbæ dysenteriæ found.

*Heart muscle.*—In the capillaries of the heart muscle there are a good many richly pigmented leucocytes, considerable deposits of crystalline pigment, but very few parasites could be found, either in the red cells or leucocytes, or in the plasma. There is considerable artificial separation of muscle cells in some places, but the tissue shows no evidence of inflammation nor the cells any marked signs of degeneration. Many of them show a deposit of greenish granules about the nucleus. There are a great many huge mast-cells in the endomysium.

*Brain.*—Throughout the cortex, medulla, and cerebellum, there is the usual hyperæmia, but the great majority of all vessels are entirely free from pigment and parasites. In a good many capillaries an isolated, pigmented, intracellular spheroidal body is found, of slightly larger size than those seen in æstivo-autumnal cases. The pigment in these bodies usually appears in coarse dark grains. In a very few capillaries, there are masses composed of a few pigmented spheroidal parasites, pigmented leucocytes and swollen pigmented endothelial cells, capable of partly obstructing the circulation in the capillary, but these obstructed vessels are so scarce that it seems hardly possible to refer the cerebral symptoms to this condition.

There is a uniform reduction in the size and number of chromatic bodies in the ganglion cells and considerable post-mortem clouding.

EPICRITICAL:—While the statement of Italian authorities has long held true that no autopsy has been reported in a case of malaria with infection by the large tertian parasite, as the infection is never fatal, the present case requires a modification of this view, offering an instance of fatal uncomplicated malaria with infection by the large, and so-called "benign" tertian parasite, demonstrated in the blood during life in large numbers and without admixture with other varieties, and indicated further by the somewhat peculiar character of the pigment deposits in the viscera

The above claim of the Italian observers, although based on a very wide knowledge and experience, must be regarded as too sweeping, since almost any condition may occasionally prove fatal through accidental complications. Thus, Barker [11] has reported a case of tertian malaria with autopsy, in which death was referable to general infection with Streptococcus pyogenes.

In another case seen by me at Montauk, death occurred in the third relapse when the blood contained a great many large tertian parasites, and no other organisms were found after repeated and prolonged examinations. Death in this case was undoubtedly due to the growth of this usually benign parasite, but in a subsequent review of one of the specimens, a single crescent was encountered, necessarily throwing the case in the class of double infections, according to the present theory of malarial species, but not seriously vitiating its value as a proof that the large tertian parasite is occasionally malignant.

The severity of the anæmia in the present case also deserves mention, in view of the general rule that the large tertian parasite is less active in impoverishing the blood than the malignant tertian. Although the Hb. was not estimated nor the cells counted, the pallor of the patient, the anæmia of the viscera, and the watery condition of the blood in the large vessels indicated a state of anæmia which was not exceeded in any other case of the series.

The prolonged coma, with very few parasites and very little pigment in the brain, classes this case with others which indicate that profound cerebral disturbance in acute malaria is not necessarily connected with the localization of parasites or pigment in the cerebral capillaries.

The catarrhal colitis and its cause are a feature of interest in this case. The microscopic examination failed to reveal any evidence that the malarial infection was directly concerned in this lesion, as few parasites and little pigment were found in the wall of the colon.

The character of the pigment in the case deserves special attention. As already mentioned, its occurrence in finer and darker grains more diffusely scattered throughout most phagocytes, especially in the hepatic endothelium, appears as a feature which may serve to distinguish the deposits of tertian from those of most æstivo-autumnal infections. Throughout the viscera, in the small and medium-sized vessels and in some capillaries there were deposits of a peculiar form of pigment somewhat similar in color to, but different in form from, that elabor-

[11] Op. cit.

ated by the malarial parasite. Sections of some of the injected vessels appeared almost black from deposits of this material. On examination this pigment appeared in the form of fine or coarse grains, or short rods, or short acicular crystals of dark brown color. It was usually attached to the surface of the red cells, but much was free in the plasma. Various stages of its formation could be followed in the blood vessels of the kidney, pia mater, and heart-muscle. In the earliest stage noted the red cells were found to be fringed with a row of small dark granules, while the body of the cell exhibited a faint yellowish-brown tinge. This appearance was often limited to the central portions of the mass of blood in the vessels, while adherent to the walls were leucocytes containing malarial pigment of the ordinary character (Plate XII, Fig. 11).

When more abundant, the pigment grains were usually of larger size and in quantity sufficient to fill the interspaces between the red cells. In this case the section of the injected vessel sometimes appeared opaque and brownish. Usually the deposit was very abundant and the red cells were covered with rod-shaped granules or short acicular crystals lying in or on the cell, or in the plasma (Plate XII, Fig. 12). Such cells sometimes exhibited a diffuse dark-brown color. Radiating groups of finer acicular crystals were commonly found in the richer deposits. In the kidney and heart muscle many arterioles were almost black with the deposits. No parasites were found in any of the red cells affected by the process. The bodies of the leucocytes were usually free from pigment grains of this character, but many were surrounded by numerous crystals, especially in the capillaries.

The distribution of the deposits was peculiar. They were found most abundantly in the heart muscle and kidney; the earlier stages were noted in the lungs, pia mater, and abdominal fat and lymph nodes; a few crystals were seen in the marrow; while the liver and spleen, containing an unusual quantity of ordinary malarial pigment, failed to show any trace of this crystalline variety.

These extensive deposits of pigment which were found in nearly all parts of the general circulation seem, without doubt, to be referable to a greatly increased globulicidal action of the plasma, and taken in connection with the renal lesions, indicate that the patient was suffering from that extreme form of destruction of blood which characterizes hæmoglobinuric malarial fever.

CASE VIII.—*Æstivo-Autumnal Malaria. Amœbic Colitis. Extreme Malarial Infection. Absence of Pigment and Parasites from the Wall of the Colon. Extensive Growth of Amœbæ.*

J., aged 21, private, U. S. Army. When received at the General Hospital, Sept. 9, on his return from Santiago, the patient was too ill to give an account of himself. He was then in a typhoid state, extremely emaciated, with incontinence of fæces, and mild delirium. Temperature 103°, pulse feeble. The temperature fell to 97° in the course of 48 hours, but the patient showed no tendency to improve. He was given moderate doses of quinine by mouth, and the diarrhœa was imperfectly controlled by astringents. The condition was at all times hopeless and he died Sept. 19.

*Autopsy.*—Two hours after death. Body extremely emaciated and anæmic. *Lungs*, show areas of œdema and hepatization. *Heart*, no gross changes. *Liver*, not enlarged; color very dark brownish, slaty; outlines of lobules indistinct; gall-bladder distended with bile. *Spleen*, very large, rather firm, of very dark chocolate color. *Stomach*, small, contracted. *Small intestine*, negative. *Colon*, lower third the seat of numerous ulcers of moderately large dimensions; bases and edges necrotic and undermined, covered with bloody necrotic material; vicinity in some areas covered with fibrin. Fæces greenish gray in color; semi-solid; contain little mucus; microscopically, they contain a little pus and epithelium, many bacteria, many fat crystals, no pigmented leucocytes, a little food detritus. No amœbæ could be found. *Mesenteric lymph nodes*, much enlarged, hyperæmic, very slightly pigmented. *Marrow*, hyperæmic, of chocolate tinge. *Blood*, watery; shows a chocolate tinge.

*Microscopic Examination.—Spleen.* Shows the usual lesions of active malaria.

*Liver.*—There are advanced degenerative changes in the liver cells. The deposit of pigment in various cells is extremely abundant. A moderate number of pigmented spheroidal parasites in the red cells, free in the capillaries, and englobed in macrophages were identified.

*Marrow.*—In the marrow of the ribs there is an abundant deposit of fresh pigment and several pigmented parasites were identified. Nucleated red cells, eosins, and giant-cells, are deficient.

*Blood.*—At autopsy found to contain a moderate number of ring-shaped æstivo-autumnal parasites. Red cells showed the changes of severe chlorotic anæmia. There was a moderate polynuclear leucocytosis.

*Colon.*—The ulcers extend through the mucosa, often to the muscularis, and are floored by a partly necrotic tissue infiltrated with pus and blood. Muscularis is often infiltrated with rows of large round cells. There is very little attempt at healing, and the process seems everywhere to be advancing.

Amœba dysenteriæ is found in considerable numbers in the submucosa. The amœbæ are most abundant beyond the edges of the inflamed areas, groups of them being found where there are no signs of exudative inflammation. In the bases of the ulcers and in the necrosing portions they are absent or very scarce. Evidences of the malarial infection here are very scanty, most of the vessels being entirely free from parasites and pigment. Rarely an isolated slightly pigmented leucocyte is encountered, but no parasites could be found.

There is an extensive growth of bacilli, apparently post-mortem, in and on the ulcerating areas. No cocci could be found in the sections. The complete preservation of the amœbæ, and the absence of post-mortem

changes beyond the walls of the ulcers, as well as the absence of pigment, precludes the possibility that malarial parasites could have been present in the ulcers during life and disappeared very shortly after death (2 hours).

EPICRITICAL:—The present case illustrates a condition rather commonly encountered among the sick at Camp Wikoff on their arrival from Santiago. In the present instance the two protozoan infections appear to have limited themselves strictly to their natural situations and to have had little influence upon each other.

The wall of the colon contained large numbers of amœbæ, while exhibiting almost no indications whatever of the coincident malaria. The liver, spleen, marrow, and peripheral blood, on the other hand, showed the changes referable to an extreme malarial infection quite as severe as that demonstrated in some cases of fatal uncomplicated malaria. If there is any special tendency of an inflamed and ulcerated colon to gather malarial parasites or pigment from the blood, it failed entirely to show itself in this case.

It may be specially noted that while amœbæ were very abundant in the wall of the colon, none whatever were found in the fæces although they were carefully examined under favorable conditions at the autopsy. It should be said that there was very scant mucus, though considerable bloody necrotic material attached to the fæcal matter.

CASE IX.—*Tertian Malaria. Chronic Endocarditis. Disposition of pigment three months after subsidence of the active infection.*

J. H., aged 48 years. Had suffered considerably for two years past from dyspnœa on exertion, palpitation, attacks of bronchitis, and transitory œdema of extremities. In June 1897 he had a sharp attack of chills and fever, but recovered under quinine. These attacks were repeated at intervals during the summer but no acute attacks occurred during the winter of 1897-98. In June, 1898, the attacks recurred and the patient was admitted to hospital in a very debilitated condition. The spleen was much enlarged, the anæmia marked, and many tertian parasites were found in the blood. The last acute attack occurred early in July, 1898. Quinine was administered constantly and no further relapses occurred. Meanwhile the symptoms of endocarditis had steadily progressed and on October 11, the patient died.

*Autopsy.*—One hour after death, by Dr. John H. Larkin, to whom I am indebted for the material from the case.

*Heart*, much enlarged, chambers dilated, and the mitral and aortic valves markedly stenosed. *Lungs*, very emphysematous. *Liver* showed chronic congestion and fatty degeneration, but no gross indications of malarial infection. *Spleen*, much enlarged, firm, and unusually dark in color. *Kidneys*, the seat of chronic congestion and slight chronic diffuse nephritis.

*Microscopic Examination.—Spleen.* The Spleen shows moderate evidences of

chronic congestion, in the widening of the pulp sinuses. The Malpighian bodies are distinctly outlined. Most of the pigment is gathered in large conglomerate masses of dark coarse grains lying in and distending the endothelial cells and macrophages about the Malpighian bodies, or in the walls of the splenic arterioles, or in the septa and walls of the veins (Plate XV, Fig. 18). A moderate number of endothelial cells and macrophages in the pulp tissue contain a scanty deposit of yellowish discrete grains. The red cells in both liver and spleen are well preserved, and some contain pigment grains and bluish stained spheroidal bodies which cannot be certainly identified as malarial parasites.

*Liver.*—There are well-marked lesions of chronic congestion with dilatation of the capillaries in the centres of lobules, with atrophy of the adjoining cells, and fatty degeneration of central and peripheral cells. Most of the pigment is collected in very large intracellular masses either in the portal canals or in the centres of lobules (Plate XV, Fig. 19). A few endothelial cells throughout most lobules contain scattered grains of apparently fresh pigment. The liver cells appear to be entirely free from malarial pigment which is confined to the endothelial cells and large macrophages lying loose in the capillaries, or between the connective-tissue fibres of the portal canals. The pigment grains are usually coarse, dark, and thickly conglomerate, but less often are small, yellowish and discrete.

*Marrow.*—A few endothelial cells containing coarse black pigment grains were found.

*Lungs.*—Any malarial pigment present could not be distinguished from the anthracotic pigment of the septa and the fresh blood detritus in the epithelium of the vesicles, belonging to the chronic congestion of the organ.

EPICRITICAL:—The present case is reported to illustrate the condition of the malarial pigment three months after the subsidence of the acute infection. It will be seen that this period had sufficed to remove the traces of malarial infection from most of the viscera, while in the chief depots of pigment, the spleen and liver, the pigment had been largely transferred from the parenchyma to the connective tissue structures, giving sections of these organs a very characteristic appearance (Plate XV, Figs. 18 and 19).

It is to be noted that the above period was not sufficient to enable all the endothelial cells of the liver and spleen to become entirely free from pigment, some of them still presenting the usual appearance of the phagocytes of acute malarial infection. It is possible, however, that these cells were further signs of a partly-suppressed growth of the parasite, uncertain indications of which were also noted in the presence of bluish-staining pigmented bodies found in a few red cells. In appearance the old pigment was considerably blacker than the fresh deposits. It was usually gathered in more compact and somewhat larger spheroidal masses. About the clumps the outlines of an enclos-

ing cell, often enormously distended, could nearly always be discovered, but some of the pigment appeared to be lying free in the lymphatic spaces of the connective tissue.

Most forms of pigment deposited in tissues undergo gradual solution in their inclosing cells, yielding, in the case of iron-holding pigment, a diffuse reaction of hæmosiderin (Ziegler, Thoma, Neelsen). When submitted to the test for hæmosiderin, the cells in the neighborhood of the pigment clumps often gave a more intense blue reaction than was found in the other portions of the liver and spleen. On the outskirts of the clumps the granules appeared very fine, translucent, and of a yellowish tint, but none of these granules gave the blue reaction.

CASE X.—*Acute metritis. Purulent peritonitis, from infection with Streptococcus pyogenes. Extreme deposits of pigment in all viscera, closely resembling those of malaria.*

B. D., aged 25. There was no previous history of malarial infection. The patient had always enjoyed good health since childhood. Jan. 2, 1899, the patient was delivered of a healthy infant. She felt well until Jan. 6, when she was suddenly seized with a chill and fever, while the lochial discharge increased in quantity. The physician in charge regarded the condition as referable to malaria and administered quinine by mouth in large doses. The fever persisted and the chills were repeated, but there was no distinct periodicity in their occurrence. A digital exploration of the uterus was made on Jan. 7, and its cavity was found to be free from placental remains. A severe diarrhœa developed but yielded to opium, and was succeeded by constipation on Jan. 12. Jan. 13, another physician was called in, who found signs of general peritonitis, advising removal to hospital. He gave no quinine on Jan. 13 and 14, and it could not be learned how long this treatment had been continued. No local treatment had been used at any time. On admission to Roosevelt Hospital, Jan. 15, the patient was in collapse, with signs of general peritonitis and a moderate discharge from the uterus of chocolate-colored fluid of slight odor. The symptoms were entirely those of peritonitis from puerperal infection. Temp., 104°; pulse, 160; respiration, 38. The urine was acid, sp. g. 1024, contained a trace of albumin, pus, blood, many vesical and renal epithelial cells, but no casts. Death followed a few hours after admission.

*Autopsy.*—By Dr. Eugene Hodenpyl, 20 hours after death. Body of fairly nourished anæmic and jaundiced subject. No œdema. *Lungs*, much congested, œdematous, with a few small areas of hepatization. *Heart*, muscle pale, flabby, valves normal, chambers slightly dilated. *Liver*, size slightly increased, section smooth, rather darker than usual, outlines of lobules indistinct. Gall-bladder contains 2 oz. of dark bile. *Spleen*, moderately enlarged, very soft, of well-marked slate color. *Kidneys*, slightly enlarged and softened, markings swollen, indistinct; cortex irregularly congested and mottled. *Peritoneal cavity* contains a half-pint of sero-purulent fluid and is everywhere highly inflamed and granular. *Gastro-intestinal tract*, no lesions. *Marrow* of ribs and vertebræ, very hyperæmic, and of dark brown color.

*Brain*, pia slightly œdematous, vessels gorged with blood, brain tissue jaundiced; no ecchymoses or other abnormalities noted. *Uterus*, slightly involuted, wall rather friable, pale; mucosa deeply congested, of dark red color, covered with a thin chocolate-colored layer of mucus, blood and pus. No remnants of placental tissue to be seen in the cavity of the uterus. Cervix moderately lacerated. No thrombi or pus in vessels of broad ligament.

No cultures were made from the peritoneum or uterus. In smears of the pus from the peritoneum and from the uterine discharge large numbers of cocci in short chains were found. In sections of the wall of the uterus large numbers of cocci in short chains were found, but only on the surface or superficial portions of the mucosa. These cocci were identical in morphology with the ordinary form of Streptococcus pyogenes seen in pus.

*Microscopic Examination.—Spleen.* There is a very abundant deposit of pigment in the endothelial cells and macrophages of the pulp. In the sinuses there are many richly pigmented leucocytes. The pigment is mostly in the form of grains, short rods, or longer acicular masses. It is very frequently arranged in the form of a small mass of fine brownish grains or crystals. In some places it is more compact and darker. About some of the masses there are minute vacuoles. No malarial parasites could be seen within the red cells, but many contain one or more coarse pigment grains.

Smears of the spleen show abundant pigment, principally in the large mononuclear cells. The pigment is principally granular, but many short crystals are seen. No malarial parasites could be identified.

*Liver.*—The pigment in the liver is very abundant, occurring in the same form as in the spleen. The liver cells contain considerable pigment in the form of granules, spheroidal or wreath-shaped masses, or elongated rods. Many of the elongated, rod-shaped collections lie in small clear spaces within the liver cells, which contain also much greenish granular bile pigment and show moderate fatty degeneration. No malarial parasites were seen.

*Kidney.*—There are evidences of acute degeneration of the tubule cells. The convoluted tubules and adjoining capillaries are nearly free from pigment. In the glomeruli are a few pigmented endothelial cells and leucocytes. In the medulla and medullary rays, many of the lining cells contain numbers of wreath-like masses of granular and crystalline pigment. The adjoining vessels are injected with blood containing many pigmented leucocytes, apparently free pigment granules, and a few pigment wreaths, but no parasites.

*Heart-muscle.*—A considerable number of pigmented leucocytes are present in the capillaries but no parasites could be found.

*Lungs* contain a rich deposit of pigment lying principally in the capillary endothelium and outlining the vesicles in a pigment network. Some of these endothelial cells or macrophages are of extreme length and contain small wreaths of brownish pigment granules and crystals. Other cells show larger, denser clumps of pigment. In the pneumonic areas the exudate is composed largely of polynuclear leucocytes among which lie many pigmented cells.

*Uterus.*—The large superficial uterine sinuses contain blood-clots in many stages of organization. Over the inner surface of the uterus there is a thin

layer of pus and granular detritus entangling many pigmented leucocytes and a great many cocci in short chains. The evidences of exudative inflammation are limited to the superficial tissues. In the deeper tissue there is an extremely abundant deposit of wreath-shaped masses of pigment within capillaries, endothelial, large and small mononuclear, and connective-tissue cells. In many foci, especially in the neighborhood of large vessels, the pigment is quite as abundant as in the spleen. The sinuses and capillaries are injected with blood containing a large amount of free pigment and many pigmented leucocytes (Plate XI, Fig. 10). No malarial organisms could be identified. No smears were made from this organ.

*Marrow.*—The marrow sections and smears contain a moderate number of pigmented macrophages and endothelial cells. No infected red cells could be found. Nucleated red cells are abundant; the myelocytes are in excess; the giant cells are slightly increased; there are very few eosinophile cells.

*Brain and Medulla.*—A few pigmented endothelial cells and leucocytes were found, but no parasites.

*Blood smears* were made at the autopsy from the finger tip, mesenteric veins, and cerebral sinuses. The red cells exhibited the changes of a severe chlorotic anæmia with leucocytosis. A few pigmented leucocytes were seen. In spite of prolonged and repeated search no parasites could be identified in the blood smears.

The *blood-vessels* throughout many of the viscera contain an abundant deposit of pigment in granular and crystalline form, lying outside of and adherent to the red cells. Many of the red cells have a peculiar brownish tinge. Much pigment lies within leucocytes and endothelial cells, and the tissues in the neighborhood of such vessels sometimes contain a moderate deposit of pigment granules and crystals.

EPICRITICAL:—The present case is inserted in this connection for the purpose of illustrating the great similarity which the pigment deposits of septic conditions may show to those of malaria.

In this case the possibility of malarial infection may be ruled out on the previous history, the distinct onset and course of ordinary septic metritis and peritonitis, by the failure of quinine to control the disease, and by the absence of parasites from the blood and viscera. On the other hand, the gross appearance of the spleen was identical with that of acute malarial infection, the liver and marrow exhibited a distinct brownish tinge, while the microscopic appearance of the pigment deposits was in many respects identical with that of malarial pigmentation.

On comparing these deposits with those of malaria some differences were to be noted. In the case of septicæmia the pigment grains were more often distinctly crystalline, and large, spheroidal, homogeneous black grains were more abundant than in acute malarial cases, while the fresh, yellowish, finely-granular pigment was much less abundant. The concentration of pigment deposits in the tissue about blood-vessels

was a somewhat characteristic feature. The wall of the uterus contained nearly as much pigment as the spleen. The pulmonary exudate contained an abundance of pigment, but in malaria pulmonary exudates have always been found nearly free from pigmented leucocytes. In the present case a considerable number of liver cells contained large and small vacuoles partly filled with brownish acicular crystals. In malaria this condition of the liver cells is rather rarely, though occasionally, encountered. In both cases the crystals fail to give Gmelin's test, they dissolve in ammonium sulphide, but not in ether, chloroform, or carbon bisulphide. The condition of the blood in sections of vessels showed that extensive destruction of blood cells was in progress throughout the viscera in the present case, and offers an ample source for the visceral deposits.

Nevertheless it would be impossible from a study of the pigment deposits alone to deny the coexistence of malarial infection, for as is shown in the description of other cases a similar destruction of blood may and in some degree frequently does accompany malarial infection. In Case VII the pigment deposit resulting from solution of blood cells completely overshadowed that derived from the malarial parasite.

The destruction of blood cells in various septic conditions may be confidently referred to the increased globulicidal action of the plasma which has long been known to characterize these conditions.

From the examination of this and many other cases I have become convinced that it is frequently impossible to distinguish between the pigment deposits of malaria and those resulting from increased globulicidal activity of the serum in other diseases. It follows that it is rarely, if ever, possible to establish the diagnosis of malaria from the presence of pigment deposits in the viscera. For in various other diseases there may be a deposition of pigment which is practically indistinguishable from that of malaria in color, form, intracellular position, general distribution, and chemical reactions. Moreover the slate color of the spleen in this case and the dark brownish tinge of the liver indicate that these are by no means pathognomonic gross signs of malarial infection. A further important inquiry concerns the extent to which the solution of blood cells in septic conditions is referable to post-mortem action of the globulicidal serum.

## PART II.

### I. TECHNICS.

*Fixation:*—The majority of investigators have preferred alcohol as a fixative agent in the study of tissues in malaria, placing small pieces in weak solutions for preliminary fixation, or using strong or absolute alcohol from the first. There seems to be nearly complete agreement that this is the best method to employ in this particular field. In addition to alcohol, a great variety of metallic solutions have been used with varying success, but none of them has been urgently recommended over alcohol.

In the present cases the fixatives used were alcohol, 80%, Lang's fluid, 1%, aqueous bichloride, and formalin 5-10%. The bichloride solutions may at once be discarded for the present purpose, on account of their tendency to leave metallic precipitates. In other respects they yielded good but not superior results. The tissues fixed in alcohol 80% gave satisfactory preservation of red cells and parasites, but less successful results as regards the tissues, which suffered the usual shrinkage. Hardening in formalin, 5-10%, proved most satisfactory. Shrinkage did not disturb the sections, the preservation of red cells and parasites was even better than that by alcohol, while the proved excellence of formalin as a fixative for general cytological study was very constantly apparent. Formalin seems to have a distinct advantage over some other fixatives in precipitating and rendering insoluble the pigments derived from dissolving red blood cells.

*Staining:*—Malarial parasites and their derivatives are well demonstrated in thin sections by staining 5 min. in 1% aqueous methylene blue, gently warmed, followed by moderate decolorization in strong alcohol, and clearing in oil of cajeput. This staining fluid may perhaps be slightly improved by adding a trace of alkali (.01% caustic potash), as used by Guarnieri. This method is practically that of Nissl and gives excellent demonstrations of changes in visceral as well as in ganglion cells.

Intracellular parasites are somewhat more deeply stained if the sections are previously treated for one hour with a moderately strong solution of hæmatoxylin, which also intensifies the nuclei of tissue cells. The use of hæmatoxylin clearly demonstrates the nuclei of the young and the segmenting parasites which are faintly or not at all stained in sections by methylene blue. *Amœba dysenteriæ* in sections stained by hæmatoxylin and methylene blue is very clearly demon-

strated, and may readily be identified by low magnification (Leitz No. 3). The nucleus of this protozoon fails to stain by methylene blue, but is sharply developed by hæmatoxylin. On several grounds, therefore, the combination of hæmatoxylin and methylene blue may be strongly recommended for the present purposes.

Attempts were made to stain the nucleus of the malarial parasite in tissues by the methods of Romanowsky, Ziemann, and Nocht. The results were not successful in demonstrating the chromatin, but Nocht's method brought out the body of the parasite very much better than any other method employed.

Very striking demonstrations of *Amœba dysenteriæ* were obtained by the application of this method to thin sections of the colon. These sections were stained for 24 hours and slightly decolorized 10-15 min. in 95% alcohol. The nucleus of the amœba then appears deep red, the body blue, the vacuoles are distinct and their contents variously stained.

In the study of pigment deposits in the viscera hæmosiderin was demonstrated by the common method, that of Perls. Sections were placed for one hour in 1% watery solution of potassium ferrocyanide and mounted in glycerine containing 1% hydrochloric acid. A useful procedure may sometimes be found in dissolving the malarial pigment by ammonium sulphide, which at the same time blackens the granular or diffuse hæmosiderin.

Formalin-fixation is a reliable means of identifying bilirubin, which is converted to the green biliverdin, but under the microscope the green tinge is not marked and the biliary derivatives may be mistaken for the yellow hæmosiderin granules.

I would strongly recommend the employment of smear preparations of the viscera, treated as blood specimens,[12] for the study of minute cellular changes, phagocytosis, and the demonstration of parasites. In the actively phagocytic viscera—liver, spleen, and marrow—it is often hazardous to attempt the identification of parasites in sections, whereas the examination of a smear made from these tissues furnishes convincing evidence of the number and type of parasites present.

## II. THE VISCERAL LESIONS.

### LIVER.

The *gross lesions* of the liver were usually but not always indicative of malarial infection. The organ was generally slightly swollen, but

[12] For the methods of staining smear specimens, see Ewing, Malarial parasitology, *Journal of Experimental Medicine*, 1901, v, p. 429.

this fact was not distinctly apparent at the autopsies, and in one case (III), with marked atrophy of liver cords and development of cavernous tissue, the liver was reduced in size. The consistence of the organ was usually slightly reduced. Fatty changes were seldom apparent to the naked eye. The pigment deposits were in the present cases always sufficient to give to the section of the organ a slightly brownish tint, but this change was sometimes far from characteristic and failed to be noted. In other cases the liver was slaty or black. The outlines of lobules were generally indistinct. Distension of the gall-bladder was commonly seen. That fatal malaria may leave inappreciable changes in the gross appearance of the liver is evident from Case VI, and especially from the cases of Marchiafava and Bignami in which very few or no parasites were found in the blood at death, and in which no microscopic evidences of a previous severe infection were found. It appears also that the pigmentation of the liver may be very slight when the parasites are massed in the intestinal mucosa.

The *microscopic examination* of the liver in the foregoing cases showed that the lesions varied but little from those described in acute malarial infection by Guarnieri in 1887, and Bignami in 1890.

Parasites, in the majority of cases, were comparatively scarce. They were usually englobed by phagocytic macrophages and endothelial cells, together with red cells, leucocytes, and pigment, and in these situations they almost invariably presented evidences of degeneration and solution. They were not positively identified in the liver cells. In Case II, dying just after sporulation of one of two or more very numerous broods of parasites, very large numbers of parasites were found in the liver, mostly within phagocytes and degenerating. In the other cases the hepatic phagocytes contained only scanty traces of the bodies of parasites, but many vacuoles and fresh pigment clumps. It is difficult to explain this difference except on the ground that the englobement of parasites in the liver is more active at certain periods of the cycle, or occurs intermittently, and that the destruction of englobed parasites may be completed very rapidly, i. e. within a few hours. Otherwise the livers of all acute cases with rich infection, ought to show abundant traces of the bodies of englobed parasites, which they did not show, with one exception, in this series of cases. It is to be noted that the exception was the only case of the series in which numerous rosettes were found in the tissues. There are several observations pointing to an increased phagocytic activity in the blood at the height of the paroxysm. Possibly the same rule holds in the liver.

However that may be, it is certain that the livers of acute cases with rich infection, exhibiting about an equal quantity of recent pigment, contain a very variable number of parasites in the early stages of destruction by phagocytes.

Among the active phagocytes could be identified the large mononuclear cells of the capillaries, endothelial cells, and leucocytes (Plate X, Figs. 1-6). There were often evidences of a fusion of large mononuclear cells, endothelial cells and leucocytes into large protoplasmic masses inclosing several infected red cells. Occlusion of capillaries by these masses or by many discrete cells was often observed, in the neighborhood of which the capillaries were sometimes found dilated.

Various lesions of the liver cells were observed. The normal liver cell stained by methylene blue, in sections and especially in smears, exhibits a coarse but regular and distinct chromatic reticulum. This reticulum was often found to be indistinct, its meshes uneven, and sometimes obliterated or displaced by various granules, indicating the changes of acute degeneration. Necrotic cells were rarely discovered in the present cases. I found many cells in advanced stages of degeneration, but few in which the nucleus was not demonstrable by hæmatoxylin or methylene blue, although the staining reaction was often faint.

Fatty infiltration of the liver cells was remarkably slight. In one case there were large areas in which the capillaries of irregular portions of lobules or of entire lobules were greatly dilated at the expense of the liver cords, which were markedly atrophic or had disappeared. The resulting appearance was that of cavernous tissue, as described in a few cases by Guarnieri, Bignami, Nepveu,[13] Lodigiani,[14] and Monti.[15] These dilated capillaries do not radiate from a central vein, as in the nutmeg liver of ordinary chronic congestion. Guarnieri refers this lesion to the disordered nutrition of liver and endothelial cells resulting from the obstructed circulation, partly also to direct pressure, conditions which existed prominently in my case. Bignami connects it especially with a previous necrosis of the liver cells. In the present cases these cells were not necrotic.

The liver cells usually contained many large and small greenish granules of bile pigment. They were most abudant in Case VII, which exhibited externally the most intense jaundice, but were abundant in

[13] *Marseille médical*, 1894, xxxi, p. 649.

[14-15] Cited by Barbacci in *Centralbl. f. allg. Path. u path. Anat.*, 1899, x, p. 64.

Case II, in which the jaundice was slight. That the intercellular bile capillaries were extensively occluded by pressure of swollen endothelial cells and macrophages in distended capillaries was evident, and to this condition the biliary pigmentation of the liver cells may be referred.

In all cases the liver cells presented a variable number of fine, light yellow granules which gave the reactions of *hæmosiderin*, while a diffuse reaction for hæmosiderin was obtained in some endothelial cells and in the connective tissue of the portal canals.

I was unable to find evidences of the hyaline transformation of the nuclei of liver cells described by Guarnieri, except in a few isolated instances. A variety of nuclear changes were observed in the liver cells which did not differ from those seen in other infectious diseases. Many nuclei were found in the process of direct division, while mitotic figures were rare. In some cases the evidences of regeneration on the part of the liver cells seemed to justify the use of the term "diffuse vicarious hypertrophy," employed by Guarnieri.

The portal canals were sometimes markedly infiltrated with round cells. Mast-cells were rather numerous in some areas, and sometimes these cells were pigmented.

While the present cases do not bear directly upon the question of cirrhotic processes in the liver following malaria, it was strikingly apparent that the infection had exhausted itself in producing vascular and cellular alterations, while there was an entire absence of the changes of beginning fibrosis.

### SPLEEN.

The spleen was increased in size in all cases, the change being generally proportionate with the length and, to a less extent, with the severity of the infection. It was noted at Montauk that the spleens of the malarial cases were as a rule much smaller than those of the typhoid cases. The organ was usually much softened and sometimes diffluent. The capsule was tense. In one case (VII) the spleen was rather firm and dark red. In the color there was usually distinct evidence of malarial infection, but this was sometimes slight, and the spleens of cases of typhoid fever in malarious subjects often gave no gross evidence of considerable pigment deposits demonstrable microscopically. In all the frank acute malarial cases the spleen was moderately enlarged, soft, and of dark brown, chocolate, or slate color.

The most prominent *microscopic* features were the pigment deposits and the cellular hyperplasia and distension of the pulp cords.

It was always difficult to identify positively parasites in the sections whereas they were always found in larger numbers in smears of the pulp tissue. They appeared to be more abundant than in the liver, and the same description of their inclosure and destruction in phagocytes applies to both liver and spleen. The macrophages were much more numerous and of larger size in the spleen than in the liver.

In all cases the sinuses and cords contained an excessive number of cells. The evidence of proliferation of splenic cells was most apparent in the frequent presence of islands of 8 to 10 cells of small size, compact grouping, deeply staining nuclei, and free from pigment. The Malpighian bodies participate largely in this process, as their dimensions were sometimes increased, and their outlines often irregular, and fringed at times with these islands of young cells.

Marked obstruction to the circulation in the spleen must have existed from the distension of sinuses by macrophages, swollen endothelial cells, leucocytes, and infected red cells. A pronounced condition of œdema was therefore nearly always present, and a few interstitial hæmorrhages, with necrosis of cells were found.

The deposit of pigment was usually more abundant in the spleen than in any other situation, and in acute cases was uniformly distributed in the macrophages, endothelial cells, and leucocytes of the pulp, while the Malpighian bodies were almost invariably free (Plate XIV, Fig. 16).

In the acute cases, the distribution of pigment was very uniform throughout the pulp. In a case of fatal typhoid fever which had been free from malarial paroxysms for three weeks, the pigment had been gathered in a network, with rather coarse meshes, throughout the pulp (Plate XIV, Fig. 17); while in another case of chronic malaria three months after the last acute seizure, the pulp was nearly free from pigment, which was gathered in large black intra- or extra-cellular blocks in the septa and walls of arterioles, and about the follicles (Plate XV, Fig. 18).

### MARROW.

A chocolate tinge of the marrow expressed from ribs and vertebræ was a characteristic change observed in the acute cases, and, in general, this change in the marrow kept pace with the similar alteration of the spleen. In Cases I and II there was chocolate-colored marrow in the middle third of the humerus and clavicle, indicating an extensive increase in the natural limits of red marrow. Bignami demonstrated such a hyperplasia throughout the femur.

Of the changes in the marrow referable to the growth of parasites,

cellular hyperplasia, obstruction to the circulation, and deposit of pigment, it may be said that they are very similar to and of equal extent with those of the spleen. In Case IV there was an excessive accumulation of parasites in the marrow, the majority of red cells being infected with one or more rings, and multiple infection being very frequent. No infected nucleated red cells could be found.

Usually the number of parasites demonstrable in smears was moderate, though larger, as a rule, than in the liver or spleen. Crescents were not abundant in the tissues of any of the fatal cases, and when present they were not seen in unusual numbers in the marrow, as found by Councilman,[16] Marchiafava, Bastianelli and Bignami ('94), nor in the spleen, as stated by Bignami. In Case I, in which enormous numbers of crescents were found in the blood for two weeks, largely disappearing before death, there were very few crescents to be found in the marrow smears, and the pigment deposits in the marrow were comparatively scanty. This condition is not entirely in accord with the observations of the authors mentioned. In one case (VII) there were numerous small capillary hæmorrhages in the marrow.

*Relation of lesions in marrow to malarial anæmia.*—The chief interest in the lesions of the marrow in malaria lies in their relation to malarial anæmia, and in this field the studies of Bignami and Dionisi[17] are most complete. The changes in the blood and marrow in the writer's cases accord in a considerable degree with the classification given by these observers.

The most striking of the series in this regard is Case IV, in which there were the lesions of pernicious anæmia in the blood and marrow, and an excessive accumulation of parasites in the marrow. Besides the changes referable to the presence of many parasites and much pigment, the marrow showed well-marked cellular hyperplasia, leading to atrophy and disappearance of fat cells, which are normally present in the marrow of the vertebral bodies. In sections, this hyperplasia seemed to affect principally the large and small mononuclear cells, while in smears the new cells could be divided among the neutrophile myelocytes and the lymphocytes. These cells, together with macrophages and swollen endothelial cells, appeared to cause more than the usual obstruction to the circulation of the marrow, yet no necroses were discovered. The islands of nucleated red cells commonly seen in normal marrow were, in this case, entirely lacking in sections and smears.

[16] *Amer. Journ. Med. Sciences*, 1885, lxxxix, p. 416.

[17] Atti d. XI. Congr. med. internaz., Roma, 1894, ii, p. 235.

In their place there was a considerable number of megaloblasts with increased Hb. A peculiar abnormality, first noted in sections and fully verified in the smears, was the superabundance of giant cells, which occurred in groups of eight or ten. Bignami and Dionisi found this peculiarity in their fourth type of anæmia as occurring in malarial cachexia, and which was marked also by a condition termed by them sclerosis of the marrow. No changes to which the term sclerosis could be applied were found in the marrow in any of the present cases. The examination of the blood, showing the presence of a majority of megalocytes with increased Hb., and of many megaloblasts, together with the condition demonstrated by smears and sections of the marrow, indicates that the fetal type of blood formation had been established in this case, and warrants its classification as pernicious anæmia.

That such changes in the marrow are rather frequently initiated by malarial infection there can be no doubt, as shown by the pathological studies of Bignami and others. In my series of blood-examinations in malaria at Montauk and elsewhere there are no less than 19 cases in which pronounced features of primary pernicious anæmia were observed.

Some regard such evidence as demonstrating the lack of specific quality in the changes commonly regarded as pathognomonic of primary pernicious anæmia. Bignami, however, believes that these cases are still to be regarded as true examples of primary pernicious anæmia, claiming that the reversion of the marrow to the embryonal type of blood-formation, as seen in some cases of malarial anæmia, is not referable exclusively to the infection, but partly results from other associated causes not definitely understood. With this view I am in accord. The majority of cases of pernicious malaria develop the changes of secondary chlorotic or pernicious anæmia, but some show those of the primary pernicious anæmia. The essential difference is not in the cause but in the character of the anatomical changes in the bone marrow. In each instance the changes are initiated by malarial infection. In one case they are maintained almost exclusively by that infection, with which they are more or less proportionate, but in the other they are maintained by the peculiar changes in the marrow which when once initiated may progress independently. This view of the pathology of malarial anæmia, instead of weakening the evidence in favor of the specific nature of the changes in primary pernicious anæmia, furnishes, on the contrary, very strong proof of the specific quality of this condition of the blood.

The lesions found in the present cases, and in some others not reported in this series, indicate that the changes in the marrow in fatal cases of acute malaria follow one of two types:

(1) The cellular hyperplasia is pronounced, the nucleated red cells are abundant and tend to increase in size, the eosinophile cells, giant cells, and lymphocytes are over-abundant, while the fat cells are compressed and atrophic. With these changes, the blood shows moderate or severe anæmia of the chlorotic type, with a marked tendency to develop the signs of pernicious anæmia, which not infrequently become distinct. Pigment deposits and parasites are often unusually abundant as in Cases II and VI.

(2) The cellular hyperplasia is moderate, fat cells being abundant in the vertebræ and persisting in the ribs. Nucleated red blood cells, eosinophile cells, and giant-cells are deficient. The blood shows severe anæmia of chlorotic type. There may be considerable differences in the size of the red cells, but the Hb. is very deficient. The leucocytes are usually diminished, and eosinophile cells are scarce. Pigment deposits and parasites are usually not very abundant (Cases III and VI).

In attempting to draw these general distinctions it must be admitted that the present observations are too limited to fully establish general rules.

The natural limits of red marrow in the normal subject are rather variable, and the quantity of fat in the ribs and vertebræ decidedly so. Moreover, in a series of routine cases coming to autopsy from various causes I have found great dissimilarity in the appearance of the marrow cords, and of smears therefrom, which it is difficult to connect with the various states of nutrition and disease in the subjects. There will be no harm in describing the above types of changes in the marrow of pernicious malaria, if it is understood that it presents a tentative classification which is to be readjusted on the evidence of future investigations.

## LEUCOCYTOSIS OF MALARIA.

Most observers have found very little change in the number of leucocytes in the finger blood during acute malarial attacks of average severity. This absence of leucocytosis with a rapidly rising temperature may be found of considerable corroborative value in the diagnosis of malarial fever.

A slight leucocytosis at the beginning of the paroxysm has been noted by Kelsch, Billings,[18] Vincent,[19] and others, but the numbers usually remain

[18] *Bulletin of the Johns Hopkins Hospital*, 1894, v, p. 89.

[19] *Annales de l'Institut Pasteur*, 1897, xi, p. 891.

below 10,000, while the percentage of polynuclear cells is increased. Vincent finds that quinine tends to increase the polynuclear leucocytes during the entire paroxysm. With the falling temperature and during apyrexia the leucocytes are usually distinctly diminished (2000-4000), especially the polynuclear forms, giving a relative lymphocytosis.

Except during the 3 to 4 hours immediately following the chill, therefore, malarial blood usually shows a diminished number of leucocytes, and a distinct relative lymphocytosis. The lymphocytes, small and large, may sometimes become quite numerous, especially in well-established cases. This fact accords with the increased cellular activity of the lymphoid tissues shown by microscopic examination of the viscera.

Bastianelli refers the loss of polynuclear leucocytes to the increased phagocytic activity of these cells. Vincent noted a periodical decrease in the number of large mononuclear cells, which he refered to the same process.

In the severer æstivo-autumnal paroxysms many observers have noted a distinct leucocytosis. Kelsch found that the leucocytosis of pernicious malarial attacks often consists in marked lymphocytosis. Bastianelli and Bignami find that in addition to various inflammatory complications, leucocytosis in pernicious malaria may result from rapidly progressive anæmia. They find it to be of frequent occurrence in hæmoglobinuric fever, and in cases attended with severe diarrhœa.

The presence of eosinophile cells may be noted in most cases of malarial fever, and these cells are usually increased in number during afebrile periods. Grawitz rightly regards this feature as of diagnostic importance, as in most diseases likely to be confused with malaria eosinophile cells are long absent or scarce. Bastianelli and Bignami found that eosinophile cells diminish during the paroxysm, and increase during apyrexia, while the blood is regenerating. In two cases of pernicious malaria, with many parasites, they found many mononuclear leucocytes and a very few eosinophile myelocytes, similar to those seen in myelogenous leukemia.

In the present cases the usual behavior of the leucocytes was noted in the majority of instances.

In some severe and prolonged cases the lymphocytosis was a marked feature, these cells being distinctly increased in number. Eosinophile cells were never found greatly increased, but their nearly constant appearance in patients who were suffering from continuous or intermittent fever furnished a somewhat peculiar feature of the blood of malarial infection.

In some pernicious cases moderate polynuclear leucocytosis was observed; and in a few cases complicated by pneumonia, colitis, or severe cachexia, a considerable leucocytosis was found. In two of the fatal cases reported in this study, and in others, ante-mortem leucocytosis was observed, but the majority of fatal cases failed to show distinct leucocytosis. These estimates were all based on the examination of dry specimens.

*Pigmented leucocytes* were seen in the majority of cases, most abundantly in the severe and long-established fevers. They were found in nearly all fatal cases, but were most abundant in a case which recovered (No. 238). It appeared that pigmented leucocytes were more closely related to the severity of the antecedent paroxysms than to the extent of the pigment deposits in the viscera.

They were most abundant during and shortly after the febrile period, but were repeatedly found in afebrile cases and after parasites had disappeared from the blood. The phagocytic cells seen in the blood included mononuclear and polynuclear leucocytes and endothelial cells. The large and small mononuclear cells were most often found to contain pigment or parasites (Plate X, Fig. 6), but in a few cases, for reasons not clear, large numbers of polynuclear leucocytes were found harboring rosettes, other forms of parasites, and pigment (Plate X, Fig. 5). In a few cases very large endothelial macrophages were found in the blood containing parasites in all stages of degeneration (Plate X, Fig. 4).

The objects englobed by phagocytes as seen in the circulation included: (1) Parasites, free or inclosed in red cells; (2) Pigment elaborated by parasites, usually in small clumps, sometimes in large masses; (3) Hæmatoidin derived from the destruction of red cells; (4) Hæmosiderin derived from the detritus of red cells; (5) Intact or broken red cells; (6) Other leucocytes. Crystalline pigment was often seen in leucocytes in sections of tissues but never in the circulating blood during life. The degenerative changes in phagocytic leucocytes mentioned by Bastianelli and Bignami, including vacuolation and diminished staining capacity of nuclei, were noted in many severe cases. The number of vacuolated leucocytes (Plate XI, Fig. 8) found in the blood was always considerable and sometimes very large.

### LYMPH NODES.

The abdominal lymph nodes were examined in all cases, and usually found moderately swollen, but always without signs of pigmentation. Microscopic examination was made in two cases only; in these the nodes were hyperplastic, the lymph sinuses were invisible, the stroma contained many mast-cells, and there was a scanty deposit of pigment, mostly in the endothelial cells.

### LUNGS.

In gross appearance the lungs in pernicious malaria, both in these and in other reported cases, presented little that is characteristic of

the disease. They commonly contain a considerable deposit of pigment and are often very dark colored, but this feature is usually not distinctly characteristic, owing to the simultaneous presence of anthracotic pigment, hypostatic congestion, and frequently of jaundice.

Somewhat peculiar areas of lobular pneumonia were found in two cases, and have been described by Bignami, but the exudate was composed of the ordinary elements, and the inflammation was not specially connected with the growth of parasites.

Microscopically, the lungs are usually found to contain a very large number of pigmented cells, sifted from the general circulation, and in some cases a moderate additional deposit elaborated by the parasites in the pulmonary capillaries. Some large pulmonary macrophages, probably derived from other viscera, were found, filling a considerable length of the capillary. Thrombi composed of such cells, with pigmented leucocytes, swollen endothelium, and infected red cells were not infrequently found in the pulmonary capillaries of Case II. The lungs were œdematous but free from hepatization.

There appear to be no recorded instances of an excessive growth of parasites in the lungs comparable with that found in other viscera. Bignami speaks of a rusty color of the sputum in some cases of bronchitis in pernicious malaria, which he regards as of little clinical import, and I can find no report of the microscopic examination of such sputum, or of the lungs and bronchi in such cases, to show that an excessive growth of parasites in the lungs may give this character to the sputum.

From what has been shown of the action of the lungs in sifting bacteria and leucocytes from the blood in infectious diseases, it might be expected that the lungs would suffer severely in malarial infection. Their comparative immunity in this instance may perhaps be referred to the rapidity of the capillary circulation and the abundance of oxygen.

### CARDIAC MUSCLE.

French writers especially (quoted by Laveran) have laid emphasis on the pallor and flaccidity of the myocardium in pernicious malaria. That condition was noted in nearly all the present cases at autopsy. In Case II nearly all tissues, including the heart muscle, were more or less discolored by malarial pigment. In Case VII, the heart muscle was generally light colored, but exhibited a slight brownish tinge referred at the time to the jaundice.

Microscopically, there were no pronounced changes found in the

muscle cells, but the perinuclear mass of large greenish granules was sometimes very abundant. Mast-cells were sometimes found in unusual numbers in the endomysium. Distinct fatty changes were not observed. With one exception, little pigment and few parasites were found in the capillaries. In Case II there was a notable exception to the usual rule and very large numbers of young parasites and pigmented cells were found completely filling distended capillaries throughout the heart wall (Plate X, Fig. 7). Although numerous parasites were found in other viscera and the brain was not examined, there was an excessive proportion in the heart muscle, while cerebral symptoms were late and cardiac failure was the most prominent clinical symptom.

Of similar cases, Benvenuti[20] has reported one in which the heart's capillaries were filled with infected red cells, the endothelium pigmented and degenerated, the muscle fibres swollen, their striation indistinct and the yellow pigment increased. In the brain it appears that there were as many parasites as in the heart, and many were also found in the kidney. Coma and cardiac dyspnœa were the principal symptoms. In another case Benvenuti found many parasites in brain, kidney, and heart, while the principal symptom was stupor. The clinical histories accompanying these reports are meagre for the present purpose, and it is difficult to judge of the relative number of parasites in the different viscera. I have been unable to find in the literature any other reports of such cases. Theobald Smith, however, finds that in Texas cattle fever very large numbers of parasites are commonly found in smears made from the heart muscle.

The available evidence, therefore, hardly seems to warrant a positive conclusion that acute cardiac failure in pernicious malaria may result from a massing of parasites in the cardiac muscle, and it would be safer to conclude from the present case merely that the condition of the cardiac and skeletal muscles demands more attention than is generally paid to these tissues in pathological studies of malaria.

### KIDNEY.

Grossly, the kidneys in pernicious malaria usually give evidence of acute degeneration in their slightly increased size, diminished consistence, rather pale cortex, and indistinct but regular markings. There are usually no characteristic signs of malarial infection. In Case I the medulla and papillæ exhibited a somewhat peculiar darkening of color, from the unusual deposits of pigment. In some cases of black-

[20] *Policlinico*, 1896, iii–M., p. 390.

water fever the presence of extra-vascular blood in cortex and medulla considerably alters the above description, as in Case VII. In Case V the cortex was very light colored, while the medulla and papillæ were deep rust-colored from the large numbers of parasites in the capillaries in these areas. In this case there was also a large superficial anæmic infarct.

Microscopically, the usual lesions, well illustrated in the present cases, consist in granular, hydropic, and fatty degeneration, pigmentation by hæmosiderin granules, and sometimes isolated or diffuse necrosis of convoluted-tubule cells. The intertubular capillaries usually contain moderate numbers of pigmented leucocytes, macrophages, and infected red cells, while the glomeruli gather a larger number of similar elements.

The kidney rarely suffers from the accumulation of growing parasites, as does the brain, the mucous membranes, etc., a fact referred by Bignami to the rapid circulation in the organ. In blackwater fever I can find no reports of excessive numbers of parasites in the kidney, and in other cases, as a rule, the numbers of parasites have not exceeded those in the peripheral blood.

On the other hand, the eliminative function of the kidney exposes it to the effects of the toxæmia of malaria, so that albuminous urine is a very common clinical sign in acute pernicious malaria, especially if protracted, while the condition of the renal cells in the present cases, and in most others reported, shows nearly constantly a considerable damage to the organ from this cause. The lesions, however, were, in most of the present cases, of a purely degenerative type, without evidence of exudation into the stroma or other changes in the connective tissue. In Case III the degenerative changes were very intense, many cells were extensively eroded, and some necrotic, and although the tubules were dilated, and casts and granular coagulum were present in considerable abundance, indicating a near approach to exudative nephritis, yet there were no leucocytes in the tubules and no leucocytes or serum in the stroma.

With the minor exception of a slight glomerulitis, described in one case by Bignami, no more serious lesions have been found in the kidney in uncomplicated acute malaria. That the lesions are entirely out of proportion to the number of parasites in the organ and are probably of toxic origin has been generally accepted. The peculiar very abundant deposit of hæmosiderin granules in the renal cells, as illustrated in extreme degree in Cases III and VII, is a somewhat characteristic feature of the malarial kidney, but is sometimes seen in other diseases.

The anomalous condition of the medullary tubules in Case I, the lining cells containing enormous numbers of pigment wreaths, has already been considered in the report of that case (p. 124). Changes characteristic of "blackwater fever" were found in Case VII, and consisted in extreme congestion, numerous small hæmorrhages, excessive deposits of granular and crystalline pigment, probably derived from dissolved hæmoglobin, and peculiar necrosis of tubule-cells. In Case V the intense and peculiar degeneration of the tubule cells seems referable in part to the obstructed circulation from thrombi of infected red cells, while the hæmorrhagic type of the nephritis was distinctly the result of localization of parasites in the renal capillaries.

GASTRO-INTESTINAL TRACT.

In six of the present cases no gross lesions in the gastro-intestinal mucosa were to be found. In one case (III) considerable diarrhœa of long standing failed to leave any traces of inflammation in the intestine or colon. In Case VII an intense catarrhal colitis was apparently not caused directly by the malarial infection, as only moderate traces of parasites and pigment were found in the intestinal wall.

In Case VIII amœbic dysentery of moderate extent was combined with intense general malarial infection, but sections of the ulcers, while showing large numbers of the amœbæ, exhibited very scanty traces of malarial infection, no parasites and few pigmented leucocytes being found.

These cases indicate that marked diarrhœa in pernicious malaria may occur without anatomical changes in the intestinal mucosa, or may result from a secondary catarrhal colitis not directly caused by the malarial parasite, or may result from amœbic colitis, in which the malarial infection is not directly concerned. It has already been shown also that hæmatemesis, severe diarrhœa, and paroxysms resembling Asiatic cholera occur as the result of the massing of parasites in the gastro-intestinal mucosa.

According to Marchiafava, in the choleriform malarial cases, the parasites are very abundant in the mucosa of the small intestine, but scarce or absent elsewhere. Infected red cells may be identified in the stools, which are often bloody. The intestine contains bloody fluid and flocculi of mucus. The mucosa is swollen, congested, and shows superficial hæmorrhages and erosions. It is often dark brown or chocolate colored, while the unaffected light solitary follicles project prominently. Microscopic examination shows: (1) injection of vessels of mucosa and especially of villi with blood containing many parasites; (2) necrosis of epithelium of villi and mucosa, in which areas neither nuclei nor parasites can be stained; (3) infiltration with

leucocytes beneath the necrotic areas; (4) bacterial invasion of necrotic tissue; (5) mitotic division of nuclei of sound epithelial cells; (6) freedom from parasites of vessels of submucosa, which contain many pigmented leucocytes.

In Case II, although a considerable number of parasites was found in the intestinal mucosa, there were no changes referable to their presence, and the patient did not suffer from diarrhœa.

There has apparently been little opportunity to ascertain the character of reparative processes which may follow the acute lesions in choleriform pernicious malaria, since such cases are usually fatal. Pensuti,[21] however, has furnished one observation of interest in this connection. A patient who had suffered in November, 1892, from severe malaria with vomiting and profuse diarrhœa, was treated actively by quinine, but the diarrhœa persisted and he died of broncho-pneumonia in February, 1893. In the intestine, especially in the ileum, the mucosa was hyperæmic, and showed some amyloid changes in the vessels. In many places there was complete disappearance of the glandular layer, which was replaced by young connective tissue. The remaining islands of glandular tissue showed marked hypertrophy of alveoli. A good deal of pigment (character not stated) was found in the mucosa. Pensuti regarded the lesion as referable to the toxic effects of malaria.

There seems to be little pathological evidence on which to discuss the relation to malaria of some forms of tropical colitis not amœbic, but often associated with pernicious malaria.

### CENTRAL NERVOUS SYSTEM.

*Gross appearances.*—In some cases of comatose malaria with rich infection the brain presents a characteristic brownish discoloration, most marked in the gray matter, which results from deposits of pigment. This condition has been found in a considerable number of cases, but by no means in all. In 40 cases Kelsch and Kiener found marked discoloration of the cortex in 9, and faint changes in 11 cases. When present it invariably indicates the presence of a very large number of parasites and much pigment in the brain tissue. Its absence, on the other hand, by no means excludes the presence of a large number of pigment-free parasites in the gray matter, a fact which was apparent in some of my cases not reported here, and which is referable to several causes. The æstivo-autumnal parasite is not always a very active pigment-producer, and Guarnieri and Bignami have depicted cerebral capillaries completely thrombosed by pigment-free rosettes. Very large

[21] *Gazz. med. di Roma*, 1893, xix, p. 121.

numbers of young parasites may therefore be present in a tissue which shows very little gross evidence of pigmentation. The discoloration resulting from jaundice, which frequently complicates fatal malaria, may obscure the effects of malarial pigmentation. Finally, as will subsequently be shown, the majority of cases of comatose malaria do not exhibit a massing of parasites and pigment in the brain, so that the characteristic discoloration of the gray matter sometimes found is not to be expected in these cases. Accordingly of eight cases of comatose pernicious malaria in which I was able to examine the brain a brownish discoloration, which could be regarded as absolutely characteristic of malaria, was not found in any. Most of the cases were jaundiced, but in two others showing many parasites the discoloration present was too faint to be regarded as pathognomonic of the disease.

Multiple hæmorrhages in the gray matter have been described in comatose malaria by Guarnieri, Bignami, Marchoux,[22] Monti, Bastianelli, Blanc, and Spiller.[23] These lesions were not discovered in any of my cases. In Bastianelli's case the hæmorrhages were limited to the cerebellum, while disturbances of equilibrium were said to have been prominent symptoms during life. In a case reported by Blanc, in addition to numerous capillary hæmorrhages, there was a large subcortical clot.

Pial œdema of moderate grade has been found in the majority of cases, but cannot be regarded as of special significance.

Blanc and Borrut claim to have observed true inflammatory exudative lesions in the brain in pernicious malaria, but their observations have not been confirmed. Maillot, in 1851, mentioned two cases of red softening of the lower dorsal cord.

*Microscopic changes.*—The microscopic appearances of the brain tissue in the typical cases of pernicious malaria of cerebral type are too well known to warrant minute description here. The principal feature is the massing of red cells infected with various forms of æstivo-autumnal parasites in the capillaries. Usually the parasites have been found uniformly distributed in the brain and cord, but Marchiafava[24] observed a case with bulbar symptoms, in which there was special localization in the medulla, and in a case of Bastianelli's the limitation of hæmorrhages to the cerebellum indicated a special massing of parasites in that region. The numbers of these parasites are sometimes

[22] *Annales de l'Institut Pasteur*, 1897, xi, p. 640.

[23] *Amer. Journ. Med. Sciences*, 1900, cxx, p. 629.

[24] *Lavori d. III. Congr. di med. int.*, Roma, 1890, p. 142.

enormous, often partly or completely occluding the lumen of the vessel. Complete thrombosis frequently results from the agglutination of infected red cells, pigmented leucocytes, and swollen endothelial cells. Capillary hæmorrhages result in the neighborhood of such thrombi, and are probably preceded by degenerative changes in the capillary endothelium. While most of the fixed pigment is found in the endothelium and in circumvascular lymph spaces, parasites are rarely seen in the endothelial cells. Monti, however, describes well preserved parasites in degenerating endothelia and believes that the parasites are sometimes capable of development in these cells. Such an occurrence is at least unusual.

To the general condition of obstructed circulation it is probably safe to refer the marked cerebral symptoms of such cases of acute pernicious malaria.

The infiltration of pericellular lymph spaces with small round cells, which is seen in many infectious diseases, was noted in some of the present cases, but not in excessive degree.

The deposit about the ganglion cells of peculiar masses of variously twisted threads and rods staining densely with methylene blue, was noted in the description of Case II.

Considerable attention has been paid in recent years to the condition of the *ganglion cells* in comatose cases of malaria. Monti studied the changes in the ganglion cells in several cases by means of Golgi's method. In some instances no important alterations of the ganglion cells were found. In others, with severe nervous symptoms, extensive changes were discovered, of focal distribution, affecting principally the dendrites. These processes were thinned in places and beset with many small swellings, and the changes affected either the finest twigs only, or the entire dendritic system, or the cell body itself was shrunken and irregular. Some dendrites showed the usual changes of varicose atrophy. The axis cylinder processes were sometimes found normal, but in the severe comatose cases extensive changes of the above types affected the axis cylinder as well as the dendritic processes. Monti referred the changes to occlusion of capillaries, finding them very similar to the lesions produced by multiple emboli produced by intravascular injection of lycopodium.

The lesions in the ganglion cells demonstrated by Nissl's method have appeared in the present cases not to differ essentially from those seen in other infectious diseases with marked cerebral symptoms. These changes consist principally in varying degrees of chromatolysis

affecting the cortical cells rather uniformly, but the cells of the bulbar nuclei more irregularly. The earlier stages of the lesions include reduction in size, irregularity and subdivision of the chromatic bodies, usually beginning in the dendrites, later involving the cell body. In more advanced stages the chromatic bodies are largely destroyed, and a moderate number of cells may be entirely bereft of chromatic substance. The more serious lesions of true acute degeneration, such as destruction of cyto-reticulum, shrinkage and cleavage of cell body, vacuolation, and nuclear changes, were seldom seen in my cases.

As to causation of these lesions, probably local disturbances of circulation are a more important factor in malaria than in most other diseases, but the comparative uniformity of the lesions noted indicates that a general toxæmia is, even in cerebral cases, the more important pathogenic agent.

A great variety of *nervous symptoms* referable to disturbances of the central nervous system have been attributed to malarial infection by early writers whose reports lack the evidence, now demanded, of a positive blood examination. The rather extensive literature of this subject has been fully considered by Mannaberg, and in a recent article by Bardellini.[25]

Since the discovery of the parasite, there is good clinical and in some cases anatomical evidence indicating that many of the nervous symptoms early referred to malaria may really be dependent on mechanical or toxic lesions resulting from this infection. Authentic cases have been reported showing hemiplegia (Marchiafava, Vespa); general convulsions (Marchiafava, Bignami, Baccelli); tetanic spasms after acute malaria (De Francesco); athetoid movements (Boinet and Salebert); disturbances of equilibrium (Bastianelli, Bignami); trismus, nystagmus, various toxic and clonic spasms (by many writers); post-malarial psychical disturbances (Pasmanik, Ségard, and many others); symptoms of disseminated sclerosis, paresis, increased reflexes, ataxia, bulbar paresis, in two cases (Angelini and Torti); electric chorea of Dubini (Bastianelli and Bignami); paralysis of the bladder from spinal lesions (Bardellini); hyperidrosis from affection of the sympathetic (Bardellini); and polyneuritis somewhat resembling Landry's paralysis (Bardellini, Torti, Mesnard). Bardellini concludes that when nervous lesions are transitory they are probably embolic, but when permanent they are probably complicated by multiple hæmorrhages. In a review of the recent literature he could find no satisfactory evidence that periodic neuralgias may be directly referable to malarial infection.

It must be admitted that while the etiology in most of the above cases was probably malarial, yet the evidence is generally unsatisfactory and, usually lacking anatomical support, is inconclusive, while in some instances the malarial infection was clearly secondary and had nothing to do with the chronic lesions.

[25] *Annali di medicina navale*, 1898, iv, p. 919.

*Coma in pernicious malaria.*—From the study of 64 cases of malarial coma at Montauk and in New York, some of which are included in the present series, it appears that this cerebral symptom in malaria occurs in three rather distinct clinical pictures and under three entirely different pathological conditions.

(1) *Malarial coma may be referable to massing of young amœboid parasites in the cerebral capillaries.*

This type of coma, which has long been recognized as a frequent form of pernicious malaria, is illustrated in Case III in which the cerebral symptoms were found to be associated with an extensive massing of parasites in the cerebral capillaries, while the deepening stages of coma could apparently be connected with the increase in size of the parasites and the gradual filling of the vessels with thrombi of infected red cells, pigmented leucocytes, and swollen endothelial cells. No capillary hæmorrhages were discovered.

Clinically, the coma resulting from this pathological condition is rather slowly established in the course of active infections, when many young parasites are found in the finger blood and when the temperature is elevated. The patient is usually first delirious, then mildly comatose, then deeply comatose, finally stuporous, with abolition of pupillary and other reflexes, and almost always dies within 48 hours after the beginning of marked cerebral symptoms. Of 11 such cases observed at Montauk 10 died, and very vigorous treatment succeeded in saving only one.

(2) *Malarial coma may be referable to embolic processes with temporary occlusion of vessels in small areas of the brain, and without uniform massing of parasites in cerebral capillaries.*

In these cases the coma develops suddenly and may be as suddenly recovered from. In a case previously reported the patient three times in five days fell back unconscious in bed, his pipe dropping from his mouth, but after a variable period he recovered consciousness, picked up his pipe and resumed smoking. From this very transient form the duration of the coma may be much more prolonged and serious, but it is seldom fatal. It may occur in febrile or afebrile cases and may exhibit distinct symptoms of focal irritation or meningitis. In the blood, few or many crescents, sometimes tertian parasites, but very few rings are usually found, and occasionally no parasites can be discovered. Emboli of parasites, pigmented leucocytes, and visceral macrophages, seems to be the only anatomical lesion which can explain such symptoms. They arise in established cases of the disease and

on microscopic examination extensive malarial lesions are found in the viscera but few or no parasites are to be found in the brain. Although crescents or tertian parasites may be abundant in the peripheral blood in these cases, I have not seen, nor been able to find in the literature report of any case in which large numbers of crescents or tertian parasites were found occluding cerebral vessels, and it appears that these parasites do not exhibit the tendency to unequal distribution in any degree comparable with the fertile æstivo-autumnal forms.

(3) *Malarial coma may be referable to the general toxæmia of the infection.*

In these cases the coma usually develops slowly but may in cachectic cases be ushered in suddenly, apparently by some embolic process. It is often of prolonged duration and not being caused by massing of young parasites in cerebral vessels it is unaffected by quinine. Occurring only in severe cases and being associated with serious toxic lesions in many viscera it is nearly always fatal.

Cases I and IV of the present series illustrate this type of coma. These patients were comatose, one at least three days and the other for two weeks before death. As no other cause for the coma was found it had to be referred to the malarial infection, which was very severe and long established. These cases differed radically from the classical type of comatose malaria, as in one only a few crescents, and in the other only tertian parasites, were present in the blood, and no parasites and comparatively little pigment were found in the brains. They show conclusively that the coma of pernicious malaria is not always referable to the presence of parasites in the cerebral capillaries. In the Montauk series [26] there were four other fatal cases of comatose æstivo-autumnal malaria in which crescents only were found in the blood, and one other fatal tertian case with prolonged coma. Jancsó and Rosenberger [27] also have reported a fatal comatose case in which the brain contained few parasites, which were abundant in the other viscera, the coma being referred by the authors to a toxic origin. It is possible that too little attention has been paid to the opinion of Guarnieri that malarial coma may sometimes be caused by obstruction to the portal circulation. This opinion was based upon the evident obstruction to the hepatic circulation commonly found in the liver of pernicious malaria, and upon the experimental production in dogs of coma without convulsions by ligature of the portal vein.

[26] Ewing, *N. Y. Med. Jour.*, 1899, lxix, pp. 114; 149.

[27] *Deutsches Arch. f. klin. Med.*, 1896, lvii, p. 449.

Uræmia may possibly be held partly responsible for some cases of this type but the clinical picture is not that of uræmia and the renal changes are not such as are commonly associated with uræmia.

Distinct differences in prognosis belong to these three varieties of coma.

Of eleven cases in which coma supervened during the development of a numerous brood of parasites, ten were fatal. Some of these, but not all, were of the classical cerebral type with massing of parasites in the brain. The energetic use of quinine has some influence in such cases.

When coma develops gradually in severe and long established cases, with few young parasites in the blood, it is usually of toxic origin, is unaffected by quinine, and is almost invariably fatal.

Of 33 cases of coma developing, often suddenly, in cases with crescents only in the blood, there were but three fatalities.

### THE MALARIAL PIGMENTS.

Two forms of malarial pigment have long been recognized. One of these, melanin, is granular, brownish, elaborated directly by the parasite, according to Sacharoff from the nuclear remnants in the red cell, and fails to give the Prussian blue reaction of hæmosiderin. It is not, on that account, necessarily free from iron. This pigment is dissolved by ammonium sulphide and readily by heat, but long resists the action of strong acids and alkalis, and I have found it to be insoluble in hardened tissues by chloroform, ether, or carbon bisulphide.

The other described form of malarial pigment occurs more abundantly in protracted cases, as small yellowish granules, located principally in the tissue cells, especially in the liver, kidney, spleen, and marrow. It yields, when fresh, the reaction of Prussian blue, but gradually loses this reaction. It is probably the hydrated oxide of iron (Thoma).

When the Hb. of red cells is dissolved in the plasma, as occurs in poisoning by potassium chlorate, arsenic, etc., and in diseases such as pernicious anæmia, scorbutic ailments, malaria, septicæmia, etc., it may be found in the tissues in granular or crystalline form and of dark brown or reddish color. Sometimes such Hb. granules are soluble in water, but more often they are altered in some way and become insoluble in water, when they have been called " parahæmoglobin " by Nencki. Parahæmoglobin is very nearly identical with hæmatoidin, which is frequently precipitated in granular or crystalline form from blood extra-

vasations, and both are soluble in chloroform and carbon bisulphide. Perls, Thoma, and Ziegler, on whose authority these statements are made, leave one to infer that since melanin, the black malarial pigment, is insoluble in chloroform, etc., this test furnishes a chemical reaction which may distinguish hæmatoidin from malarial pigment. On submitting formalin-hardened tissues containing old blood extravasations to the action of chloroform, I find that two weeks' exposure has no effect upon the granules and crystals of hæmatoidin. Possibly they had been altered by age, or by the action of formalin, but the same result was obtained in tissues hardened in alcohol. Both hæmatoidin and black malarial pigment were dissolved by ammonium sulphide. Accordingly I failed to find the described chemical reactions of hæmatoidin of practical value, at least in hardened tissues, in distinguishing between malarial pigment and the granular and crystalline deposits derived from destruction of red blood cells.

Another difficulty arises in the identification of malarial pigment in tissues. Many cases of pernicious malaria are attended with marked jaundice. In many cases of jaundice from other causes bilirubin, now regarded as identical with hæmatoidin, is deposited in granular or more often in crystalline form, and is identical in color with hæmatoidin and with much pigment found in the bodies of malarial parasites. In sections of two cases of marked jaundice following pneumonia, one in a young infant, the other in an adult, I found many crystals and granules of bilirubin (?) (Perls, Ziegler) in the hepatic endothelium. In the case of the infant, they were found in large masses in the liver cells also, as well as in many leucocytes in various organs, which very closely resembled the pigmented leucocytes of malaria. Now bilirubin in fresh bile is turned green by formalin and gives Gmelin's reaction, but the crystals in neither of these cases turned green in formalin nor gave Gmelin's reaction. There were, however, other greenish particles in the formalin-hardened sections of both livers. In both cases chloroform failed to alter the crystals in two weeks, and they failed to give the Prussian blue reaction. That the crystalline deposits in the liver cells of the new-born infant were derived from the bile there can be little doubt, and the failure of the reactions may be explained, as is done by Gerhardt and others (quoted by Perls), who find that in many forms of jaundice urobilin and not bilirubin is formed. Urobilin fails to give Gmelin's reaction. Formalin-hardened sections of these tissues were treated for 24 hours, also, in carbon bisulphide, and in ether, but no change in the pigment was observed. The same negative result was obtained with sections of malarial tissues.

These cases are briefly referred to in order to point out that the jaundice of infectious diseases may cause deposits of pigment which are indistinguishable morphologically, and by all ordinary chemical procedures, from much malarial pigment. Various reports of the finding of malarial pigment in the liver cells in pernicious malaria have possibly not been made with full recognition of this fact. The positive identification of malarial pigment therefore becomes a matter of great difficulty, for it appears from the above considerations that in malarial fever one may meet with granular, sometimes crystalline pigment particles, free in the vessels or englobed in various cells, not giving the Prussian blue reaction, nor dissolving in chloroform, ether, or carbon bisulphide, but dissolving in ammonium sulphide, which may have any one of the following origins:

(1) Pigment elaborated by the intracellular parasite.

(2) Hæmatoidin derived from the remnants of infected red cells.

(3) Hæmatoidin or altered hæmoglobin deposited in granular or crystalline form from red cells dissolved in the plasma. (Hæmoglobinuric fever, jaundice, extravasated blood, post-mortem processes.)

(4) Bilirubin or urobilin granules or crystals.

Throughout the study of the present cases, in addition to the dark brownish granular pigment inclosed in cells or parasites, larger dark brown particles exhibiting more or less crystalline forms were frequently found. When scanty they were usually limited to the spleen, but in Case VII there were excessive deposits in all viscera except the liver and spleen. Since the pigment in parasites is invariably granular and not crystalline—possibly there are rare exceptions in the crescentic bodies—the above considerations render it extremely probable that the strictly malarial pigment, i. e., that derived from parasites, is never found in crystalline form, and that all such crystals ought to be referred to some other origin. Moreover as the detritus from dissolved red cells may be found as brownish granules in the bodies of phagocytes, it cannot be claimed, even for the pigmented macrophages, that all granular pigment is derived from parasites.

When one follows the changes that occur in degenerating parasites and red cells within a macrophage, there are, however, certain long-retained characters which often serve to distinguish the pigment derived from parasites from that resulting from the destruction of red cells.

In sections of tissues, the pigment within parasites is invariably finely granular, first appearing as one or two fine grains, later as a

larger, more or less irregular clump, while in æstivo-autumnal rosettes the pigment appears in a rather compact spheroidal mass of fine granules. In sections, the pigment is usually less compact than in blood smears, in which it may often be found in a single large block with outlying grains. When these pigmented parasites are englobed in macrophages the body of the parasite rapidly disappears, in 4 to 5 hours according to Marchiafava, leaving a small vacuole about the pigment clump, and usually leaving the pigment undisturbed in arrangement of granules for some days. When the pigment clump is englobed after its discharge from the rosette into the plasma, it appears sometimes to retain its compact arrangement, in which case the englobed mass fails to show a surrounding vacuole. In the leucocytes of the peripheral blood, which appear to absorb most of their pigment from the plasma, it is seldom possible to detect any vacuole surrounding the clump. When a red cell is englobed in a macrophage, the Hb. is frequently reduced to brownish granules skirting the periphery of the space originally occupied by the red cell, or sometimes showing a less regular arrangement of fine granules within a large vacuole.

Finally, when a red cell infected by a pigmented parasite is englobed, the destruction of the red cells may leave a peripheral ring of granules, while the larger compact mass from the parasite occupies a central or peripheral position (Plate X, Figs. 1 and 4).

From a minute study of the appearances of intracellular pigment clumps in sections, and especially in smears of tissues, it is possible to follow degenerating parasites and red cells through all the stages just described, and to distinguish in many instances pigment derived from parasites from that resulting from the destruction of red cells. After a variable time all englobed pigment appears to concentrate in more compact perinuclear masses, and the above features can no longer be identified. Some of the larger masses appear to form by the coalescence of two or more vacuoles.

When one compares the deposits of hæmoglobin which occur in inflamed tissues infiltrated with blood, with deposits of malarial pigment, certain characters are often distinctly apparent which serve to distinguish the one from other. Chief among these is the crystalline form of much of the pigment in the inflammatory deposits. In many such cases the formation of intra- and extra-cellular circles of crystalline pigment may be traced from whole or subdivided red cells. Such features were noted especially in the renal tubules of Case I of the present series (Plate XI, Fig. 9). Sometimes the pigment circle repro-

duces the original size of the intact red cell, usually it is smaller, the red cell having been subdivided before its final alteration, while frequently the crystals are isolated and elongated, or of small size resembling granules. No spheroidal clumps of finely granular pigment like that of the æstivo-autumnal rosette were seen in several inflamed mucous membranes with disintegrating blood, examined for this purpose. In cases of pneumonia, septicæmia, and blood extravasations from various causes, along with the crystalline pigment there was much coarsely granular pigment in leucocytes and endothelial cells, but none or very few of the clumps exhibited the finely granular character of fresh malarial pigment.

Since malarial pigment as seen in the parasite is practically never found in crystalline form, and there seems to be no good reason to assume its transformation into crystals after englobement by phagocytes, crystalline pigment must be referred to other sources, principally the destruction of red cells.

According to Thoma, hæmosiderin probably results when the detritus of red cells is acted upon by living tissue cells, while hæmatoidin is produced in the bulk of a blood extravasation where living phagocytes are absent.

The study of hepatic macrophages in malaria shows, however, that englobed red cells may be reduced to hæmatoidin as well as to hæmosiderin. Not infrequently one finds in the bodies of such macrophages red cells which give the hæmosiderin reaction, but show in addition some black hæmatoidin grains. This fact has also been noted by Barker. The two pigments appear to form, in malaria, under nearly identical conditions, and in the large macrophages it appears certain that the majority of englobed red cells are reduced to hæmatoidin.

Not having found in chloroform, ether, carbon bisulphide, acidified potassium ferrocyanide, or ammonium sulphide, any chemical reagent that will distinguish malarial pigment from parahæmoglobin, hæmatoidin, bilirubin, or urobilin, etc., one must apparently rely upon morphology alone for its identification in hardened specimens.

In pernicious malaria, the formation of pigment by the parasite, the intracellular destruction of red cells, the solution of Hb. in the plasma, occurring most extensively in hæmoglobinuric fever, but seen to some extent probably in all fatal cases, the deposit of bilirubin or urobilin crystals or granules in jaundiced cases, all are processes which are variously intermingled in the disease, and in the study of the tissues it is of prime importance (see Cases I and VII) to distinguish as far as possible between them.

Case X has been reported here in order to illustrate the practical importance of the foregoing observations.

Certain alterations of interest were noted in the deposits of pigment in liver and spleen after subsidence of the infection. Throughout the periods of active infection the pigment was richly and uniformly distributed in all parts of the organs. In a case of typhoid fever in a malarious subject dying from perforation three weeks after the disappearance of parasites under quinine, the pigment in the liver was found in less numerous but larger and more compact clumps within the capillaries, but very little had yet reached the portal canals. In the spleen the beginning concentration of pigment had caused the appearance of a pigment network with large meshes, within which were newly-formed cells free from pigment (Plate XIV, Fig. 17).

In another case, dying three months after subsidence of the infection, the greater concentration of pigment is clearly indicated in the photograph (Plate XV, Fig. 18).

Ferrier,[28] in a case dying one month after cessation of fever, found a moderate amount of pigment in the cells of the pulp cords only. In another case, after a similar period, much pigment in nodular blocks 2-3 times the diameter of the splenic cells was found in the splenic cords. Rather less pigment was found in the arterial walls and peripheries of follicles. In a third case, six weeks after acute symptoms, most of the pigment was found in very large cells in the centres of the pulp cords.

## DESCRIPTION OF PLATES X-XV.

### Plate X.

Fig. 1. Appearance of hepatic macrophage in Case II. Various stages of destruction of infected and uninfected red cells and of parasites.

Fig. 2. Hepatic endothelial cell in established æstivo-autumnal fever, containing pigment.

Fig. 3. Hepatic macrophage in Case VII, fatal infection with large tertian parasite. The pigment is distributed in fine granules and in blocks.

Fig. 4. Endothelial macrophage of circulating blood, containing rings and masses of pigment and degenerating parasites. Red blood corpuscle at the side.

Fig. 5. Polynuclear leucocyte of circulating blood with englobed rosette and full grown parasite.

Fig. 6. The usual pigmented mononuclear leucocyte of the circulating blood.

Fig. 7. Capillary in muscle of the heart, showing numerous intra-corpuscular parasites. Case II.

### Plate XI.

Fig. 8. Appearance when stained of vacuolated, pigmented leucocyte, common in malarial blood.

[28] *Arch. de méd. expér.*, 1897, ix, p. 87.

Fig. 9. Pigmentary deposits in cells of renal tubule, from disintegrating red corpuscles. Case I.

Fig. 10. From section of uterine submucosa of Case X, puerperal septicæmia. Deposits of wreaths of granular and crystalline pigment, resembling malarial pigment, in tissue infiltrated with blood.

PLATE XII.

Fig. 11. Early stages of destruction of red corpuscles with deposit of peripheral rings of hæmatoidin. Pigmented leucocytes. Case VII and others.

Fig. 12. Later stages of destruction of red corpuscles with deposit of crystals of hæmatoidin. Case VII.

PLATE XIII.

Fig. 13. Photograph of section of kidney, Case V. Degeneration of renal epithelium and granular coagulum around glomerulus. × 250.

Fig. 14. Photograph of section of kidney, Case V, showing massing of malarial parasites in renal capillaries. × 250.

Fig. 15. Photograph of section × 1000, same case, showing pigmented parasites in renal capillary.

PLATE XIV.

Fig. 16. Photograph of section of spleen, Case VII, showing distribution of pigment in acute pernicious malaria.

Fig. 17. Photograph showing reticular arrangement of pigment in the spleen, three weeks after subsidence of acute malarial infection.

PLATE XV.

Fig. 18. Photograph showing disposition of pigment in the spleen, three months after acute malarial infection. Case IX.

Fig. 19. Photograph showing distribution of pigment in the liver, three months after acute malarial infection. Case IX.

FIG. 1.

FIG. 2.

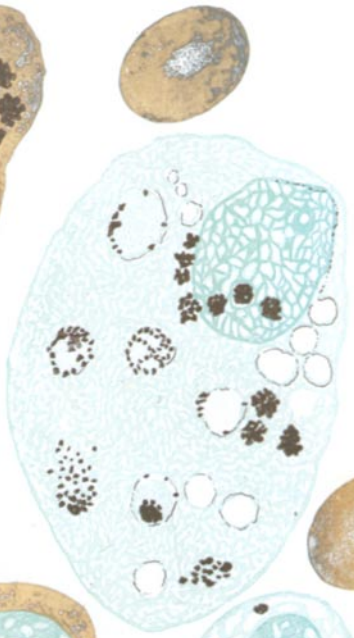


FIG. 4.

FIG. 3.

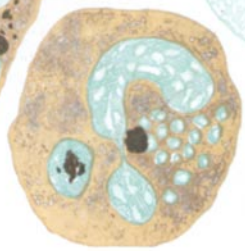
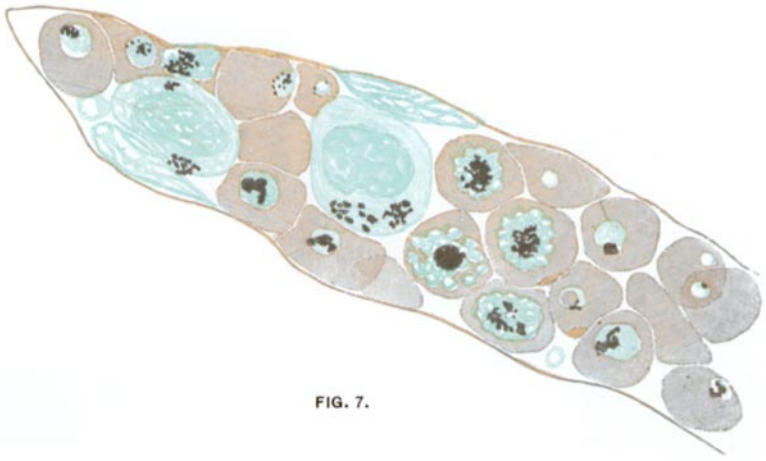


FIG. 5.

FIG. 6.



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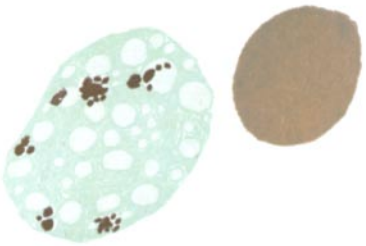

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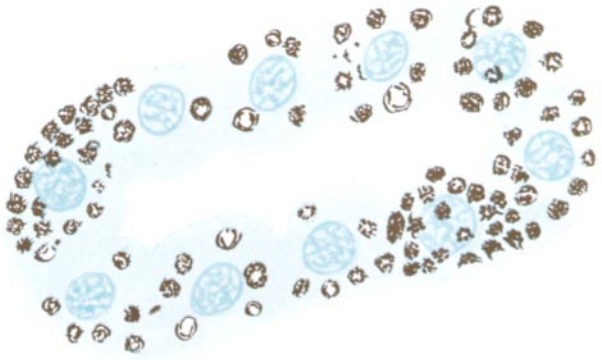

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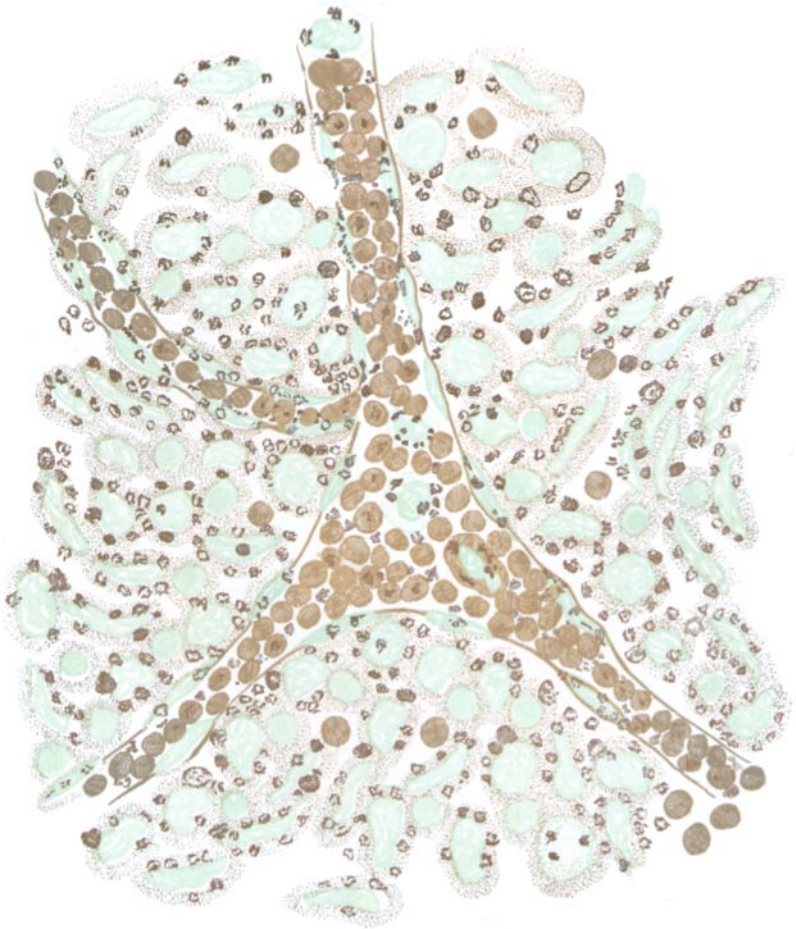
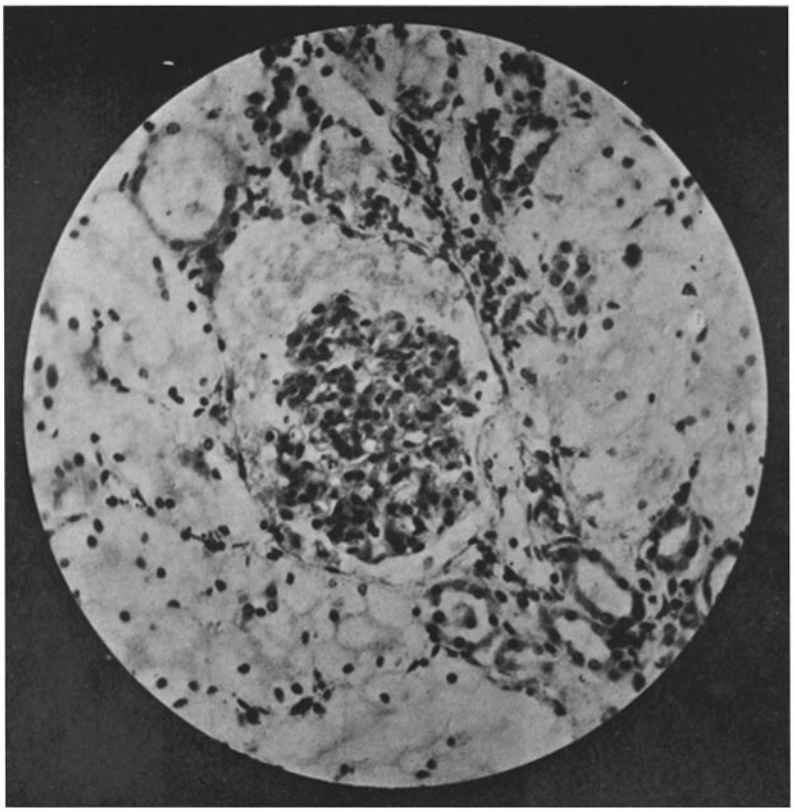


FIG. 10.

FIG. 11.

FIG. 12.



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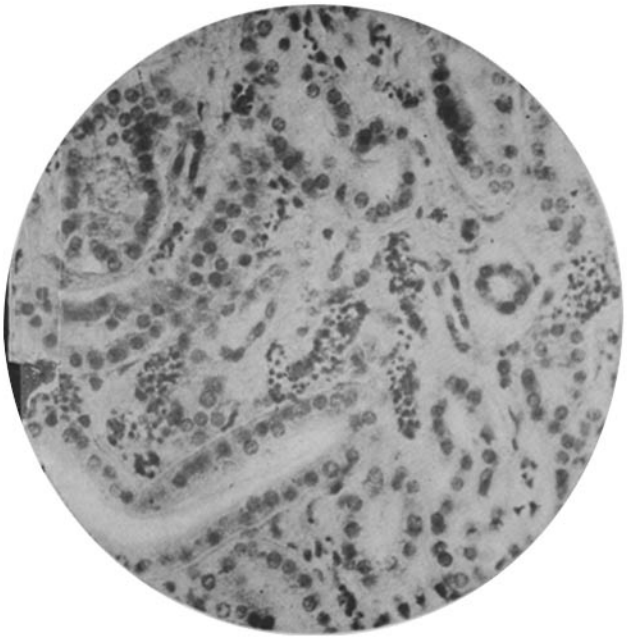

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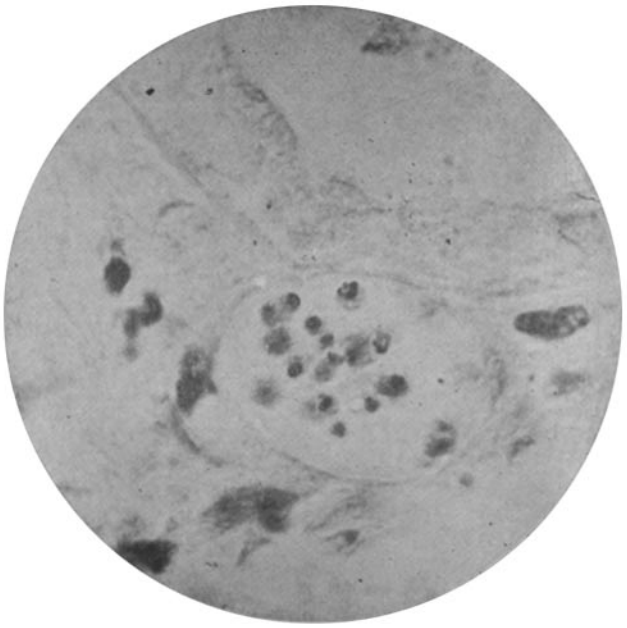

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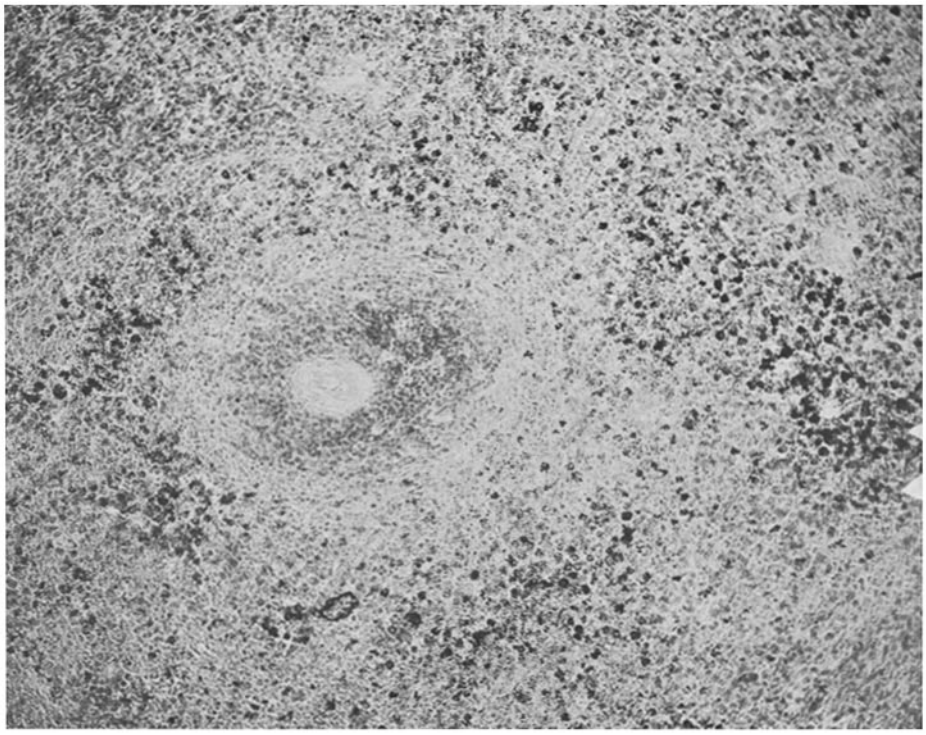


FIG. 16.

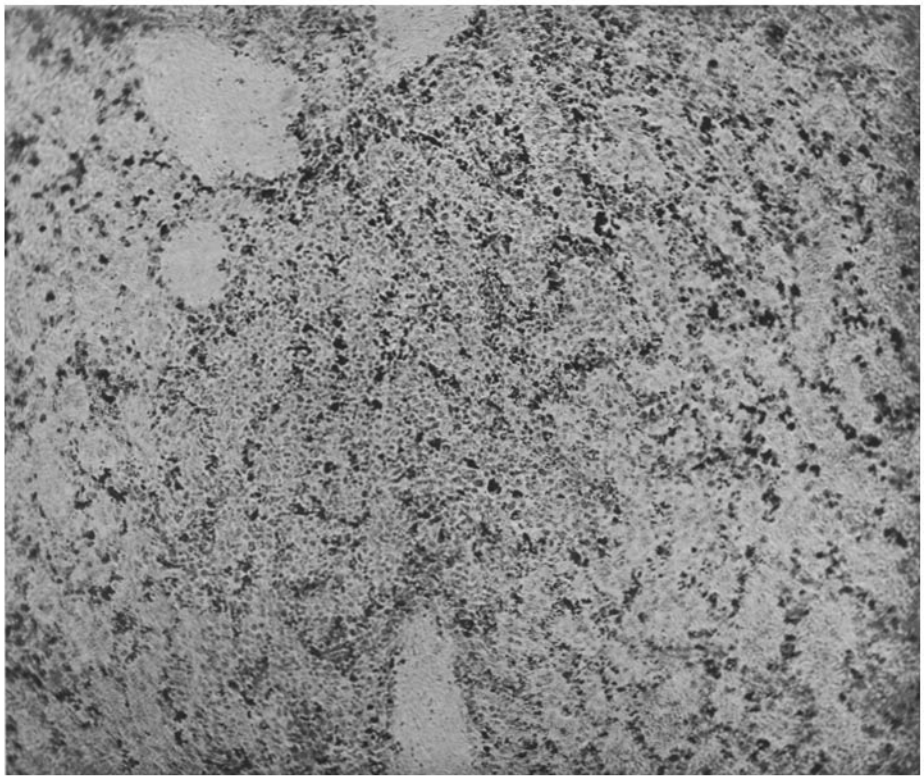
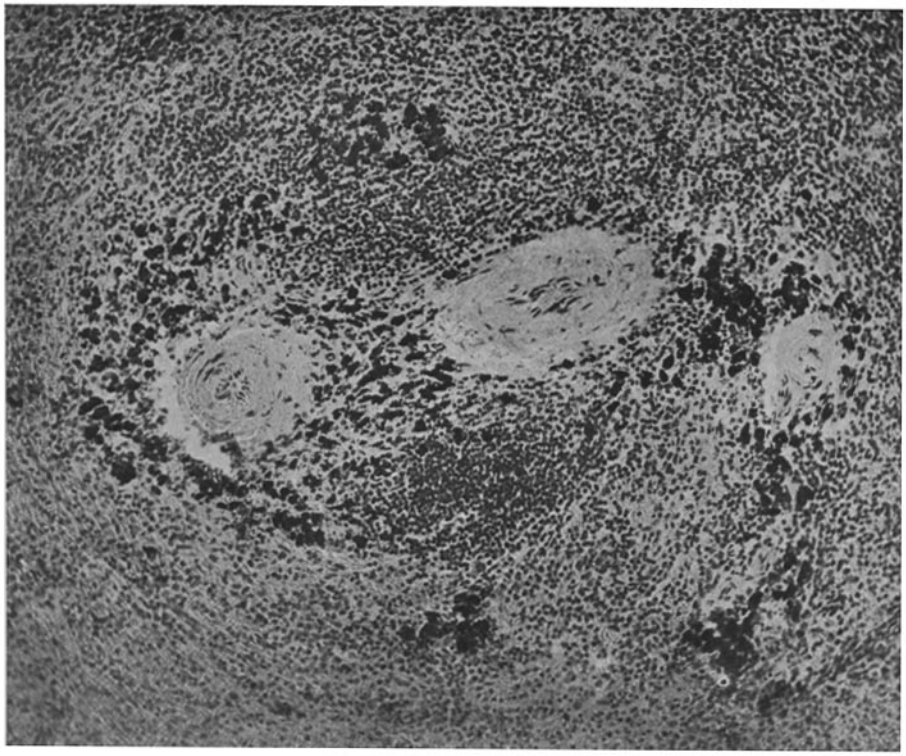


FIG. 17.



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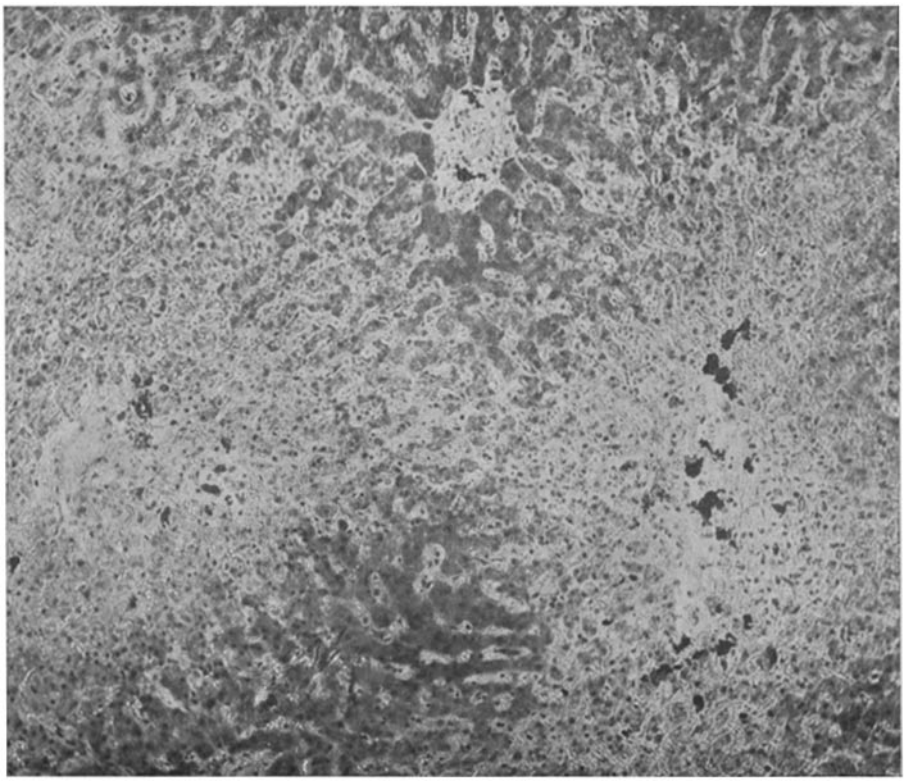

FIG. 19.