SOME POINTS REGARDING THE PATHOLOGY OF MALARIA.

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(With Discussion.)

Stenographic Report of Remarks made before the Johns Hopkins Hospital Medical Society.

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When the work of Drs. Thayer and Hewetson upon malaria was in course of preparation it was thought desirable that a study of the tissues from the fatal cases of the disease should be appended. The material at hand was comparatively limited, for very few cases of malaria come to autopsy under the quinine treatment. The patients that died were either pernicious cases or they suffered from some complication. Of the tissues studied, three cases were of æstivo-autumnal fever, and there was one case of double tertian malaria. I do not intend to discuss this evening in detail the findings in these autopsies, since a full account of them will be found in the Johns Hopkins Hospital Reports, under the title "A Study of Some Fatal Cases of Malaria." I have thought that it might be worth while to bring before you, freed from detail, some of the more general points concerning the pathology of malaria.

First, as to *the relation of malaria to cirrhotic processes*—the occurrence of focal necroses in the liver and spleen in malaria, and the bearing that these may have upon the etiology of cirrhosis. For a long time it has been disputed whether or not malaria has anything to do with the causation of fibroid processes. Many have claimed, for example Frerichs and Lanceraux, that there was a chronic paludal hepatitis of malarial origin. Chronic nephritis and cirrhosis of the brain and spinal cord are sometimes, it is said, due to malaria. Chronic interstitial pneumonia has also been traced to a malarial origin by Laveran.*

*The dispute as to whether cirrhosis of the liver can be a sequel to malaria or not has perhaps been warmest. Dr. Osler, in his Practice, points out the necessity of considering other etiological

If, as pathologists are inclined to think, cirrhotic processes as a rule have their starting-point in a degeneration of tissue elements, then it would not seem strange did malaria have sclerotic changes as a sequel, for we have in this disease multiple examples of cell-death. For instance, in the study of Case C of the series, multiple focal necroses were demonstrable in the liver and spleen, quite analogous to those described by Dr. Reed in typhoid fever and by Drs. Welch and Flexner in diphtheria, as produced experimentally by the bacilli which cause these diseases as well as by the introduction of the toxines which the bacteria produce. An interesting finding in association with these areas of necrosis was the occurrence of multiple capillary thromboses. It seems possible from a study of these cases that a direct relation can be traced from the capillary thromboses to some of the areas of necrosis, at least in the liver. It has been proven by Dr. Flexner, in his experimental work with blood-serum, that cirrhotic changes can result from focal necroses in an organ. It would not be surprising, therefore, that a disease like malaria, associated as it is sometimes with focal necroses, should occasionally be followed by cirrhotic changes.

Besides the focal necroses, which are probably due to toxines (although as a matter of fact the malarial toxines have not yet been isolated), we can think of other conditions in malaria which could be the starting-point of chronic changes. For example, the changes in the blood plasma which occur in malaria must be profound. A great many red blood corpuscles are broken up, a large number of leucocytes are altered, large numbers of malarial parasites are present, growing, mul-

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factors, *e. g.*, alcohol, syphilis, tuberculosis, even when malaria appears to stand in a direct relation to the disease. Of the many persons who have had malaria, very few of them have developed cirrhosis of the liver afterward. Dr. Welch states that in his autopsies in New York he met with only one case of cirrhosis of the liver that could be said to be due to malaria; that occurred in an Algerian. Bignami, the most important writer on the changes in the tissues in malaria, thinks that malaria may undoubtedly lead to subsequent proliferative processes, and he traces with great acumen the changes that gradually occur as a result of repeated attacks of malaria.

tiplying, dying. We know from experimental work that even slight changes in the character of the blood-plasma can lead to marked alterations in the cells of the tissues. The question of an alteration of the *isotonie* of the blood serum in malaria is an interesting one, particularly as regards malarial hæmoglobinæmia and hæmoglobinuria.

The relation of the melanæmia to the possible cirrhotic processes is to be considered. We know that very inert substances, like carbon or stone, in the lung, can give rise to chronic changes. Why could not the malarial pigment resulting from the destruction or from the segmentation of the parasites, give rise to chronic interstitial inflammation? Malarial pigment is deposited in the periphery of the hepatic lobules, and it is there that fibroid changes are most frequently located.

Any condition which leads to intermittent hyperæmia of an organ has generally been looked upon as of importance as regards the etiology of chronic interstitial inflammation. In a single malarial infection, with every paroxysm there are changes in the vascularity of the organs, particularly in the liver and spleen, and in persons subjected to repeated attacks of this disease the varying size of these organs is a marked clinical feature.

Another possible etiological factor in the production of a cirrhosis is disturbance of digestion. In many cases of malaria associated with severe diarrhœa, there are thrombi of infected corpuscles filling up the capillaries in the surface of the intestine; as a result there must necessarily be marked disturbance in the processes of secretion into the alimentary canal and of absorption therefrom.

But given all these possible etiological factors for a primary degeneration of the cells in malaria, still individual predisposition or resistance must play an important part, for we know that the great majority of cases of malaria are not followed by extensive cirrhosis.

The second point I wish to refer to is *the occurrence of bacterial infections and protozoan invasions along with malaria.* Drs. Thayer and Hewetson in their article speak at length of the multiple infections in cases of malaria, an infection with two varieties of the malarial parasite or with different

generations of the same variety of parasite; but it is aside from that subject that I wish to speak.

As regards protozoan infections that may be concurrent with malaria, we know of at least one example. At the time these studies were made, the amœba coli had been found in the stools of one man who had dysentery synchronously with an attack of acute malarial fever. Since this work was done several cases of amœbic dysentery associated with malaria have been observed in this hospital. This is, it seems to me, of extreme interest, inasmuch as the writers in tropical countries have always laid great stress on the occurrence of malaria and dysentery together. Unfortunately, in neither of these protozoan diseases do we know as yet the mode of infection; the determination of this point for one disease may be of help in the study of the other.

As to the bacterial infections concurrent with malaria: many of the old text-books speak of a definite malarial pneumonia, and there is a tolerably wide polemic literature on the subject. The writings of Manson and Howard are worthy of particular mention in this connection. Dr. Osler tells me that he has found nothing peculiar to the pneumonia associated with malaria. There is as a matter of fact no proof that pneumonia in malaria is ever due directly to the malarial parasite. The cases that have been examined pathologically correspond with ordinary cases of pneumonia, and Bignami, Marchiafava and Guarnieri have had cases come to autopsy in which they have demonstrated in the lungs the micrococcus lanceolatus, the micro-organism practically always found in acute croupous pneumonia. As to bronchitis and broncho-pneumonia, which are often associated with malaria, particularly in children, it is now tolerably definitely settled that they are complicating infections due to bacteria, and apparently any one of the group of pyogenic organisms is capable of setting up a bronchitis or broncho-pneumonia in malaria.

The question of the concurrence of typhoid fever with malarial infection has been the subject of heated discussion. It is now definitely settled that a man may have typhoid fever and malaria at the same time. One such case has been reported by Dr. Osler and one by Dr. Gilman Thompson, of New York. But the great majority of cases in the literature and

in practice spoken of as typho-malarial fever or typho-intermittent fever are really cases of typhoid fever. Now that the diagnosis can be so easily made, there can be no excuse for a continuance of the old confusion.

The endocarditides often spoken of as complications of malaria will undoubtedly turn out to be due to bacteria, and not to the malarial parasite. As far as we as yet know, acute endocarditis is always bacterial in its origin, though a pure toxic endocarditis is not impossible.

Local streptococcus infection, *e. g.* erysipelas, is sometimes concurrent with malaria. We have met with one such case.

As to the concurrence of dysentery and malaria, I have already spoken of the protozoan (amœbic) form. Other forms are, as a rule, due primarily to disturbances in the capillary circulation of the gut (local accumulation of corpuscles infected with parasites), which result in alteration of nutrition, or even in necrosis of the surface; bacteria may then easily get in and lead to further changes.

Case D of our series formed a most interesting exception to the general rule of mixed infections. The case was one which had been treated in the ward for a long time for acute nephritis and had all the clinical signs of acute nephritis. At autopsy the individual was found to have acute nephritis, and in addition an acute double tertian malarial fever and an acute general infection with the streptococcus pyogenes. The small capillaries all over the body, and particularly in the kidneys, were filled with thrombi, consisting often partly of fibrin, but mainly of cocci in chains. The number of malarial parasites in this case was simply enormous. In many of the blood-vessels the active recent parasites, that apparently had not undergone degeneration at all, exceeded in number the white corpuscles. In such a case we could think of counting the number of malarial parasites in a cubic millimeter of blood and would expect to find them standing in number somewhere between that of the red and that of the white corpuscles. No such case has ever come under the notice of the pathologists here before. Dr. Councilman, who has had a wide experience in malaria, and who made the autopsy in this case, expressed much astonishment at the tremendous number of organisms present.

From this brief review it will be seen that it is possible to have very different bacterial infections associated with malaria, and the infection may be local or general. Naturally many such cases would not be cured by quinine; the quinine would destroy the malarial parasites, but might have but little influence upon the concurrent infection. In malaria, therefore, as in diphtheria, one must not forget the possibility of a mixed infection, especially in making a prognosis.

The next point to which I wish to draw your attention is *the unequal distribution of the parasites in the body in malarial infection.* It was noticed long before the malarial parasite was discovered, that pigment could be found in different organs and inside of cells in various parts of the body at autopsies on malarial patients. In the earlier studies of malaria, after the discovery of the parasites, it was noticed that the parasites were most abundant in certain organs, for example, in the liver and spleen. Since the clinicians (French, Italians, Americans) have thoroughly studied the blood in malaria, we know that there are different types of the malarial organism, and that there are differences in the distribution of the parasites in the body in different infections, which correspond to these different types. In quartan fever the distribution of the parasites is most even throughout the blood and tissues, and one can form a tolerably accurate idea of the whole number by examining a drop of the peripheral blood anywhere. But even in quartan fever, especially during segmentation, there is a tendency to local accumulation. In the æstivo-autumnal fever the distribution is most unequal, and one can form little if any idea of the whole number of parasites present from the number he can find in the peripheral blood. In tertian fever the distribution of the parasites stands about half-way between the quartan and æstivo-autumnal as regards evenness of distribution. In the æstivo-autumnal form of malaria the pathologists, by their post-mortem observations, have been able to make important contributions to our knowledge of the disease. The general work on malaria is the result of brilliant clinical observations, but as regards inequality of distribution the pathologists have naturally been better able to make contributions. Even in the same organ there may be marked inequalities of distribu-

tion. While the spleen and liver usually contain in æstivo-autumnal malaria many more parasites than the other organs, yet different parts of the spleen or liver may contain more parasites than another part of the same organ. In the brain we may find here and there a capillary thrombosed with parasites or infected corpuscles, and then in large areas scarcely a parasite can be seen. The possible relation of this unevenness of distribution in the brain to the clinical phenomena sometimes manifested is worthy of note. The curious mental phenomena that are exhibited by certain malarial patients, particularly in the pernicious forms, can perhaps be explained by this mere mechanical blocking of capillaries in certain areas. This might explain, for example, the transitory aphasias, paralyses, and varieties of delirium.

When one thinks of the nuclei in the medulla, how small they are and how dependent they are upon oxygen for their well-working (for example, the respiratory centre and that governing the movements of the heart), it would not be difficult to understand how thromboses of their vessels might lead to severe symptoms and perhaps to sudden death. In one case of death with bulbar symptoms, Marchiafava found thrombi in the medulla. But it must not be forgotten that in such instances, and in the transitory aphasias, etc., mentioned before, we may have to deal simply with the toxic effects of the disease, rather than with disturbances of function dependent upon mechanical obstruction to this circulation.

Another form of malaria, *malaria perniciosa algida* or *cholerica*, is dependent upon this inequality of distribution of the parasites. In this form of the disease the capillaries of the mucous membrane of the intestines and stomach are blocked with a great number of infected red blood corpuscles or large phagocytic cells. The mucous membrane may become necrotic and be cast off, and one sees severe dysenteric symptoms or extreme vomiting. Of course such a dysentery is due almost directly to malaria and would scarcely come in the class of concurrent infections, although it is probable that even in such a case the advent of other micro-organisms would accentuate the dysenteric process.

When an attempt is made to explain why the parasites and infected corpuscles are so unevenly distributed in the body, many difficulties are met with. Why, in quartan fever, are the parasites pretty evenly distributed, while in æstivo-autumnal fever they are unevenly distributed? Bignami has considered almost every point bearing on this subject, but comes to the conclusion that our knowledge at present is too limited to afford any satisfactory explanation. Phagocytosis may in part explain the inequality of distribution. A great many of the parasites are enclosed within phagocytes; but that would not account for all the phenomena concerned. Again, the parasites tend to accumulate where the circulation is slow; and it is probable that vaso-motor influences have something to do with the inequality of distribution. That would necessitate going back to the assumption of differences in the toxines in the quartan and æstivo-autumnal types.

We are not left without analogy as regards this inequality of distribution. For example, every pathologist is acquainted with the fact that in tumors there are most curious inequalities in the distribution of the metastases. In a general carcinosis or sarcomatosis, where the tumor cells arrive in the blood and are distributed by it, it is a well known fact that the secondary nodules develop sometimes in one organ, sometimes in another. Whether this is due to primary inequality in the distribution of cells, or whether it is due to differences in resistance against, or in opportunities afforded for the growth of the cells, or to both, is uncertain. Again, any one who has made systematic bacteriological examinations at autopsies will remember how unequal is the distribution of bacteria in acute general infections. In general streptococcus infections, for example, sometimes the organism will be present in the spleen in great numbers while only a few are obtained from the liver. In other cases the reverse may be so. Of course, in such instances one has to think whether or not he has introduced into his media as much fluid substance from one organ as from another. But even when the amount of fluid is the same the number of bacteria differs in the different organs. In acute miliary tuberculosis certain organs at times seem to be immune while other organs develop enormous numbers of tubercles. So these, then, are analogous conditions which are, as yet, not satisfactorily explained.

But in tumor metastases, bacterial infections and malarial invasions we have to do with crude mixtures of gross particles with the red and white blood corpuscles and blood plasma. A still more remarkable fact is that where soluble poisons are introduced into the blood there is an inequality in distribution. Of course, it is a physiological fact that substances that go to form the secretions are picked out by the glands, each gland choosing certain substances. Baumann has recently shown us how iodine, which must exist in the blood in extremely small amounts, can be picked out by the thyroid gland and built up into a body containing as much as 9 per cent. of iodine. Certain poisons—*e. g.* morphine and strychnine—we know are picked out preferably by certain organs. The toxines of bacteria in solution in the blood form focal necroses rather than diffuse necroses. If with soluble substances one meets with marked inequalities of distribution, it is not surprising that the distribution of gross particles in suspension should be anomalous. Besides it must be remembered that in malaria we are dealing with living parasites and living cells in the blood and tissues. In addition to the many and curious vital manifestations which cells are already known to be capable of exhibiting, there may be many with which we are as yet unacquainted.

The last point concerns *phagocytosis in malaria.* I shall speak of what we have seen in our fatal cases here. First, as to the cells concerned. Certain of the leucocytes are the main phagocytes; then the endothelial cells of the blood-vessels, the cells of Kupffer in the liver and the cells of the pulp-cords in the spleen play a part. The phagocytes may contain red blood corpuscles, some healthy, some injured, some infected, some fragmented; masses of blood pigment, malarial parasites, malarial pigment. Then again they may contain other phagocytes. The phagocytes have been named by various authors in accordance with the character of their contents as "pigmentiferous," "amœbiferous," "leucocytiferous," etc., although this, it seems to me, is an unnecessarily cumbersome terminology.

One point which has interested me much in the study of phagocytosis in malaria is that there is a division of labor amongst the phagocytes. Not every phagocyte takes up these

substances in the same degree. While almost any phagocyte seems to be capable of taking up any one of the table of contents mentioned above, yet as a rule certain phagocytes tend to contain one set of the substances, others to contain another set. In Case D, for example, of the series, the mononuclear leucocytes contained the majority of well preserved parasites, while the polymorphonuclear leucocytes contained a preponderance of the segmental pigment. Then again in the liver and spleen the large macrophages take up particularly the red blood corpuscles along with parasites and pigment, while the endothelial cells of the liver take up chiefly the blood pigment. I was very much interested in this phagocytosis in the mononuclear leucocytes in Case D, inasmuch as in the report of Thayer and Hewetson it is stated that it is exceedingly rare to notice any phagocytic tendencies on the part of the mononuclear elements in the fresh blood-slide, although the polymorphonuclear leucocytes are frequently observed to enclose the flagellating bodies. But in Case D in all the tissues we find parasites inside the large mononuclear leucocytes. It is just possible that they have taken up these parasites post-mortem, Dock and others having pointed out that the malarial parasites cease their development soon after the death of the host. It is unfortunate that in this case no blood examination was made during life. Had this phagocytosis on the part of the mononuclear elements occurred during life they could not have failed being detected in the fresh blood.

The physiological question of the relation of phagocytosis in malaria to bile production is of much interest, though for lack of time I must be content with merely referring to it. The phagocytes can be seen passing from the spleen, which seems to be the main cemetery of red blood corpuscles, laden with broken-up capsules and with pigment; then the blood pigment is seen in the endothelial cells of the liver, next in the Kupffer cells, and finally in the liver cells themselves, as though this were a method of transportation of raw material from the spleen to the liver for purposes of bile manufacture.

With reference to the relation of phagocytosis to natural resistance and to spontaneous cure I will say nothing, except that the strife is still going on between those who favor the

doctrine of phagocytosis and those who see in the blood-serum the main protecting mechanism.

As regards the form the parasites assume inside the phagocyte, it is easy to make out that a great many of the parasites rupture after inclusion, and one can see the lines of pigment running from the parasite out into the protoplasm of the phagocyte. Golgi thought that the parasites could multiply within the phagocytes, and Bignami still believes that latent infection is to be explained in many cases by the long continued life of the parasite within the phagocyte. Certainly forms of bacterial infection are described which have analogies with this view.

Then, finally, as to the inclusion of some phagocytes by other phagocytes. It makes a very interesting picture to see a huge phagocyte containing within it one, two or several of the cells of the body. Sometimes phagocytes are included along with non-phagocytic cells, and sometimes a phagocyte is seen inside of a phagocyte, which in turn is within a third larger phagocyte. Sometimes the huge phagocytes look degenerated; in such a case we can conceive of a young phagocyte going into the large phagocyte after its contents or even to eat up the dying protoplasm. On the other hand sometimes the included phagocyte looks degenerated, in which case we can think of the large active phagocyte taking up the small one into its substance—eating up its neighbor. These curious phenomena, which I have perhaps too fancifully spoken of as the cannibalistic and thieving tendencies of phagocytes, are among the many attractive problems connected with the sociology of cells which the future has to solve.

I have placed under the microscopes specimens which show (1) focal necrosis in the liver; (2) capillary thromboses in the liver, in Case D; (3) periportal infiltration with round cells; (4) vein in lung containing enormous numbers of malarial parasites; (5) makrophages in spleen; (6) malarial parasites enclosed in mononuclear leucocytes; (7) thrombi of infected corpuscles in mucous membrane of stomach. The beautiful plates which I pass around are from drawings made by Mr. Max Brödel from the microscope. I have never seen a more accurate reproduction in drawing, of what can be seen through the microscope.

Dr. Osler: Malarial cirrhosis seems to be remarkably rare in this country. No well marked instance of it has ever fallen under my observation. I have frequently looked for it at the Philadelphia Hospital, where we had a very large malarial material, and I think, with the exception of the one case mentioned by Dr. Welch, I do not know of any instance in the North in which the condition has been found. We have had only one case here in which clinically we suspected that the cirrhosis might be malarial.

With reference to the irritation of the malarial pigment as a cause of fibrosis, it is interesting to call to mind the observation which Dr. Welch brought before us here a few years ago, namely, a form of anthracotic cirrhosis in which the fibrosis in the liver seemed to be due to the amount of pulmonary carbon which had reached the liver in roundabout ways.

Dr. Thayer: There is as yet no absolute proof that the malarial parasite produces a toxine, and yet there are observations which are rather suggestive, particularly those by Brousse and by Roque and Lemoine, who have shown an increased toxicity of the urine just following the attack; and by Queirolo, who has shown that the sweat during the sweating stage is much more toxic than that obtained under other circumstances. It must be said, however, that Botazzi and Pensuti have shown that much, if not all of this increased urinary toxicity may be accounted for by the increased excretion of certain potassium salts and urobilin, as well as by the presence of peptone. Taking into consideration, however, the various symptoms of malarial fever, there is, by analogy to the other similar conditions, every reason to believe in the existence of some soluble toxic substance. Particularly suggestive are the focal necroses of which Dr. Barker has spoken.

Another evidence of some grave alteration in the blood serum is shown in the hæmoglobinuria which occurs in some of the graver malarial infections.

With reference to the occasional paucity of parasites in the peripheral circulation, I have seen several very severe cases where, at certain times, but very few parasites could be found. I have never, however, seen a severe case where they could not be found on careful search. The fact that in certain severe

cases they were present in such small numbers in the peripheral circulation led Baccelli to think that in some instances a small number of parasites might produce the gravest symptoms owing to their excessive virulence. In their recent admirable article Bastianelli and Bignami rather dispute this and say that in no case of pernicious fever in which they have studied the tissues post-mortem have they failed to find a total very large number of parasites; very few perhaps in the peripheral circulation, but numerous in the spleen, brain, liver, or gastro-intestinal tract.

With regard to the localization of the parasites in the pernicious cases:—In a case of comatose pernicious malaria which recovered, there existed while the patient was entirely comatose a clonic spasm of the lower facial muscles on the left side, which disappeared entirely with the cessation of the paroxysm. We have had within the last six months one case of algid pernicious malaria. This man gave the history of having had quite an active diarrhœa for three or four days, slight attacks of fever and an occasional chill. Dr. Smith noticed the patient as he was led into the dispensary one morning at about 11 o'clock, and was impressed by the cyanosis and apparent prostration of the man; upon examination, he found him cold and pulseless. He was put to bed and was dead within two hours and a half. His mind was perfectly clear; he was excessively weak; voice husky; skin cold and clammy; cyanosis very marked; quite the picture of a man in the algid stage of Asiatic cholera. At the autopsy there was very marked injection of the mucous membrane of certain parts of the intestinal tract, particularly in the upper part of the large intestine, while on examination of fresh specimens the capillaries were seen to contain much pigment. The brain showed little or no melanosis. The specimens have not been thoroughly worked up as yet.

It is a very interesting fact with regard to phagocytosis that while, in fresh malarial blood, a large number of the phagocytes that one sees are mononuclear, yet I have never seen any active phagocytosis by mononuclear leucocytes. Occasionally one sees in the fresh specimen a fairly well preserved parasite in polymorphonuclear leucocyte. Occasionally, also, we may see pigment and some of the remains of the para-

site lying within a vacuole-like space within the leucocyte. Within a few days I have seen a fragment of parasite taken up, the mass of pigment becoming surrounded by an apparent vacuole and presenting an appearance which might well have suggested that the whole structure represented a complete engulfed parasite. Bignami makes the suggestion that some of the so-called "latent" cases and some of the relapses may be due to the preservation of certain forms of the parasite within leucocytes. In his last article he suggests that perhaps the best explanation that one can offer is the supposition that there is some encysted form of the parasite which has as yet escaped our observation.

Dr. Barker: I did not speak at all of the round-cell-infiltration of the liver in one case which we saw. It might have been accidental. Dock has described, however, a similar case of periportal infiltration with round cells.

It is rather depressing, in view of the immense amount of clinical and pathological work which has been done on malaria, and of the fact that the parasitic nature of the malady is settled beyond all reasonable doubt, to find a writer in one of our best medical weeklies describing certain changes, perfectly familiar to the modern hæmatologist, which are sometimes visible in the red blood corpuscles, and asking the question, "Is there a malarial parasite?" Then again a prominent army surgeon in India has recently, it is said, stated that there is no malarial parasite; that what has been described as the malarial organism is the stained nucleus of the leucocyte!