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Preliminary Report on the Results of Blood Examinations at Camp Wikoff,

AUGUST AND SEPTEMBER, 1898.

BY

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PRELIMINARY REPORT ON

THE RESULTS OF BLOOD EXAMINATIONS AT CAMP WIKOFF,

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By JAMES EWING, M. D.

During the five weeks, August 21 to September 24, 1898, the writer was detailed by Surgeon-General Sternberg to render what assistance blood examinations might give in the diagnosis of tropical and other fevers among the troops from Santiago arriving at Camp Wikoff. A preliminary report of the results of this work has been prepared as follows:

I. Statistical.—The report covers 782 examinations made at Camp Wikoff, seven cases kindly furnished by Dr. Charles Norris, from Swinburne Island, New York city, and eleven cases from miscellaneous sources in New York city. These 800 examinations are all, for the writer's convenience in the subsequent treatment of the material, here considered together.

Of these cases, 605 proved to be of malarial nature. To these may be added 40 cases of typhoid fever developing in malarious subjects, and in which the presence in the blood of pigmented leucocytes and severe anæmia were evidences of recent malarial infection, which was also distinctly indicated by the clinical history.

In the 605 cases of malaria, the plasmodia were found in the blood in 335 cases, while in 270 cases the diagnosis was based upon the clinical history and the

discovery in the blood of evidences of malarial infection. These evidences of malarial infection in the blood consisted (1) usually in the presence of intracellular bodies so much affected by quinine that their exact type could not be positively determined; or (2) in the presence of typical pigmented leucocytes; or (3), in chronic cases of distinct clinical character, in the presence of marked anæmia.

In 335 cases in which organisms were seen, the signet-ring form only of the æstivo-autumnal parasite was found in 88 cases; crescentic bodies only in 134 cases; and both rings and crescents in 27 cases. The æstivo-autumnal parasite was associated with the tertian parasite in 12 cases. The cases in which the æstivo-autumnal parasite was found number in all 261.

The tertian parasite alone was found in 74 cases, associated with the æstivo-autumnal parasite in 12 cases, or in all in 86 cases.

Four cases, which were probably of the quartan type, were encountered, but no rosettes were seen in the blood, and the diagnosis was not certain. They were classed as cases showing no organisms.

The blood was examined in 159 cases of typhoid fever, in 40 of which there were evidences of recent malaria, as above explained.

Table of Cases.

Typhoid Fever.		Malaria.					
		Æstivo-autumnal.			Tertian.	Double infection.	No distinct organisms.
		Rings.	Crescents.	Both.			
159 In recently malarious subjects with evidence of malaria in the blood.	40	88	134	27	74	12	270
		261			74	12	
		335					270
		605					
	645						
Total classified,	764						

From the above summary, it appears that about eighty per cent. of the cases of Cuban malarial fever are of the æstivo-autumnal variety, twenty per cent. of the tertian type, and of these about four per cent. show double infection with both parasites, while quartan fever would seem to be very rare.

II. ÆTIOLOGY.—It is probable that ninety-five per cent. of the patients in the Montauk General Hospital suffered in some form from malaria. A very large proportion of those who slept on the ground in the trenches and swamps about Santiago suffered from some form of fever. It appeared distinctly from the stories of patients that the greater the exposure in this respect, the more certain and virulent the infection. It was reported that every one of a group of men who slept on the ground at a certain particularly noxious spot died in Cuba of pernicious malaria.

Several patients who were early located on the higher ground claimed to have suffered only from "mountain fever," but their blood at Montauk contained crescents.

The earliest dates of beginning illness, as noted in the Montauk cases, were July 10th to 12th (in one case, July 5th), so that a week or ten days seemed necessary for the development of the disease in any large number of men.

Many of the most intelligent patients were closely questioned about the prevalence of mosquitoes, but the evidence obtained was unsatisfactory, as some admitted that the mosquito was to them a constant pest, while others claimed never to have noticed its presence. Every one, however, noticed and complained about the putrid exhalation of the soil, and seemed to regard this as the dangerous element.

It was a very evident fact that the negro troops not only contracted the disease in fewer numbers, but also withstood the infection much better than the white men. The writer did not see a single fatal case of uncomplicated malaria in a negro, and, as a rule, the fresh and

untreated cases showed a very moderate number of organisms in the blood.

III. Symptomatology.—Most cases described their illness as beginning with a chill of moderate severity, often preceded for a few hours by headache or general pains. Severe chills were nearly always referable to the tertian parasite.

The initial chill of relapses was sometimes described as more severe or as less severe than the first chill, or as wanting altogether. Many relapses in æstivo-autumnal fever at Montauk occurred without chills, but short chills were rarely absent in the tertian cases. In a moderate number of cases, instead of a chill, the patient was seized with violent vomiting, sometimes of blood.

In some fatal cases, æstivo-autumnal, the discharge of a new brood of parasites was marked by no symptoms, except a slowly rising temperature and general collapse. Some cases died during the discharge of a new brood with a falling temperature.

With tertian cases the temperature usually reached its highest point in six to twelve hours; in the æstivo-autumnal cases usually not before the middle or end of the second day.

In the tertian cases no specially peculiar symptoms were noted during the rise of temperature. In the æstivo-autumnal cases the rise of temperature was often marked by a slowly progressing nervous disturbance, often reaching coma. This coma differed in onset and character from the sudden coma occurring in many other cases.

The sweating and fall of temperature were profuse and rapid in the tertian cases; but in the others the sweat was often slight, or occurred only after the administration of quinine in large doses, and the temperature often required several days for full defervescence. On the other hand, some severe paroxysms of æstivo-autumnal infection were promptly aborted by large doses of quinine, and the temperature became normal and the blood free from parasites in twenty-four to thir-

ty-six hours. Such cases were indistinguishable clinically from tertian infection with moderate initial chill.

The histories in many severe cases indicated that the first attack lasted about a week, the temperature reaching its highest point on the second or third day, thereafter rapidly declining till the seventh or eighth day. Often a second paroxysm, of greater severity, followed almost immediately, and continued for a similar period. At Montauk there were rather numerous examples of these typical weekly recurring attacks. In the blood such cases usually showed the signet-ring forms for the first two or three days, young crescents on the third or fourth day, and adult crescents from the fifth to seventh days. A period covering the second to fourth days, with or without fever, was sometimes seen, during which no organisms could be found in the blood. These cases were actively treated with quinine.

It was a common impression that severe or untreated Cuban malaria is fatal in the third of these recurring attacks. Several fatal cases in the third attack were seen at Montauk.

The administration of quinine shortened many of the longer attacks to four or five days, and, treatment being continued, relapses were absent or mild, or exhibited an irregular remittent or intermittent fever.

The course of the fever in these fresh or old æstivo-autumnal infections exhibited the types of tertian, quotidian, remittent, and irregular fevers. Most of the cases of remittent fever of the present series were the result of disturbed paroxysms of the æstivo-autumnal infection.

A striking characteristic of the æstivo-autumnal fever, observed also in some cases of grave tertian infection, was the completeness of the patients' improvement, as judged by their subjective symptoms, during the intervals between attacks. In several fatal cases (130, 285, 295, 793) it appeared that the patient had avoided taking quinine after the subsidence of the fever, in Cuba or on the transport or at Montauk, to be

seized shortly by a paroxysm of greater severity than usual, and which was fatal. The failure in these cases to continue treatment with considerable doses of quinine for some weeks after the apparent cure was undoubtedly responsible for many unnecessary fatalities, and the essential importance of this precaution can not be too positively urged.

In none of these fatal cases was the blood examined during the quiescent interval, but in many cases in which crescents were found during afebrile periods the patient suffered later very severe paroxysms, and it can not be doubted that similar signs persisted in the blood of the others. It follows, therefore, that as long as crescents persist in the blood, active treatment should be continued, and indeed for some time thereafter.

The *cerebral type* of the disease was the most frequent form of the severe seizures.

In sixty-four cases the blood was examined during or shortly after a period of coma. In the blood of these cases crescents alone were found in thirty-three instances, rings alone in eleven, both rings and crescents in two, tertian parasites in five, both æstivo-autumnal and tertian parasites in two, and no parasites fully identified in eleven.

Most of the cases in which no organisms are reported were belated cases of mild and transient coma in patients who had been receiving large doses of quinine. The negative finding in other instances of this group, however, indicates beyond a doubt that *the parasites are occasionally very scarce and very difficult to find in the blood during periods of deep coma.* In many of the cases in which crescents were finally found the search was successful only after one and two hours.

Of the eleven cases of coma in which rings alone were found, ten died, and the surviving case was only saved by the most heroic treatment. On the other hand, among thirty-three cases showing crescents only, there were but three fatalities. This comparison indicates a striking difference in the prognosis in cases of coma. The appearance of the early forms of the parasite in

large numbers indicates a recent sporulation, and when coma results from the development of a new brood of parasites, it appears to be a very unfavorable condition. When coma supervenes at other periods of the cycle, it appears from the above data that the prognosis is very much more favorable.

According to the clinical character of the coma, these cases appeared to fall into two distinct classes:

1. The discharge of a new brood of parasites was often accompanied by a rise of temperature, gradual loss of consciousness, and slowly deepening coma. After a period of one to three hours the patients were usually in complete stupor and could not be roused. As already stated, most of them died, quinine proving ineffectual. The blood in these cases nearly always showed a large number of young rings.

2. Of the larger group of cases, many were brought to the hospital in coma, having been suddenly prostrated, with loss of consciousness, and with or without spasms or convulsions. Several such attacks developed suddenly in partly cinchonized patients in the wards. At the height of the coma the patient usually presented the typical appearance of "coma vigil," with nearly complete stupor, open eyes, pale sweating skin, stertorous breathing, a full pulse, fever, and pupils reacting to light. The blood in these cases contained crescents, sometimes tertian parasites, but few or no rings. Such conditions were nearly always relieved by large subcutaneous injections of quinine, or, if failing to respond, the stupor became complete, the reflexes were abolished, and the patient died. The result in cases of coma was seldom in doubt longer than twenty-four hours.

Some of these attacks of coma were mild and of short duration. In one case (335) the patient, while sitting up in bed smoking, three times in five days suddenly became unconscious, his pipe fell to the floor, and he remained stuporous for three or four hours. At the end of that period he would wake up, at once pick up his pipe, and resume smoking. Crescents only were found in the blood during these seizures. An embolic pro-

cess seems to be the only probable origin of such phenomena.

A considerable number of cases presented symptoms typical of meningitis, with marked rigidity of neck and limbs, and retarded pulse. The patients usually recovered promptly after the injection of quinine.

A great variety of milder nervous symptoms was observed, including localized neuralgias, spasms, aphasia, and mild hemiplegia; but these cases never failed to give a distinct history of a recent acute febrile attack.

Of the *algid type* no clear examples were seen, although many of the fatal cases died with low, but not subnormal, temperatures.

The *gastric type* of the disease was illustrated by many cases of violent and persistent vomiting, which occurred with or without fever. The response of many of these to subcutaneous injections of quinine was remarkable. In a few instances the initial paroxysm was marked by, or consisted in, considerable hæmatemesis. *In these cases, for some hours after the hæmorrhage, the parasites were usually scarce and difficult to find in the blood.*

In a few cases, showing crescents, the attacks of vomiting recurred every four days.

Intestinal symptoms were very common in the malarial cases at Montauk.

Simple diarrhœa was or had been a nearly universal complaint, and was usually referable to improper food.

Severe diarrhœa with mucous stools was a specially prominent complaint in sixty-seven patients who appeared to be suffering from *catarrhal colitis.*

Dysentery, or *ulcerative colitis,* was observed in thirty-six cases of malaria. It was probably much more frequent in occurrence than is indicated by these figures, for in the absence of prominent symptoms a previous colitis might have been overlooked in the history.

In the above cases of dysentery, crescents were found in the blood in nine cases, rings in six, tertian parasites in three, and both varieties of parasites in one case.

In seventeen cases the malarial element had been rendered quiescent by quinine, and no distinct parasites were found.

In nine of the active malarial cases the *Amœba dysenterica* was found in the stools. These amœbæ measured from forty to fifty-five micromillimetres in length while active, and fifteen to twenty-five micromillimetres in diameter when contracted to the spheroidal form after death. They were sometimes present in enormous abundance, especially in active untreated cases discharging much bloody mucus. In the more purulent stools they were less abundant, and in the entire absence of mucus the amœbæ could not be found at all. They were once identified in the aspirated fluid from a complicating perirenal abscess, but no hepatic abscesses were seen in the cases at Montauk. The amœbæ were usually associated with streptococci, and in several cases enormous numbers of infusoria, *Megastoma entericum*, were found.

There was no clinical or gross anatomical evidence that these inflammations of the colon were referable to the malaria.

In very few cases of dysentery was an active malarial element suspected before the examination of the blood, as the malarial symptoms were masked by, or mistaken for, the symptoms of colitis. Seven cases were fatal, in all of which the malarial infection was severe. Most of the other cases recovered or were transferred to other hospitals.

In forty cases of continued fever, with marked evidence of recent malaria, diarrhœa was referred to infection with typhoid fever.

Pulmonary symptoms were rather infrequent. A few cases of bronchitis were seen, and two cases of pneumonia—one fatal—developed during the course of chronic malaria, and one case of pneumonia developed in the course of a tertian infection.

Nephritis of severe or moderately severe grade was observed in five cases, but no systematic examinations of the urine could be attempted, so that in the absence of

distinct external signs, such as œdema, this lesion might often have been overlooked.

Jaundice was noted in pronounced form in ten cases, most of which were fatal, while a slight jaundice or yellowish discoloration of the skin from this or other causes was seen in the majority of cases of severe malaria.

Anæmia was noted in all the cases examined, and proved to be the most constant of all the symptoms. In the great majority of the active infections, the changes in the blood were those of secondary chlorotic anæmia, but usually without leucocytosis. Usually, even in severe cases, this anæmia was of moderate grade. And it was often a matter of surprise that blood showing so few morphological changes should harbor enormous numbers of parasites. This apparent anomaly was specially evident in negroes. There was always, however, a distinct loss of Hb in the red cells, although the diminution in the number of cells was not always plainly evident in stained specimens. The anæmic character of the malarial blood was almost always apparent as the drop was expressed from the finger and spread on the slide, and *in this respect the difference between the malarial and the typhoid specimens was very striking and constant.* The condition of the blood was, of course, usually apparent in the facies of the malarial cases; much less frequently in the typhoid cases.

In the severer and more prolonged fevers the changes in the blood became more pronounced, but with the increasing anæmia the number of parasites in the blood became distinctly less. Many of these cases showed the *early* changes of pernicious anæmia, with extreme reduction of red cells, and poikilocytosis. A few such specimens showed a large number of parasites, which, with this type of anæmia, were usually scarce.

In many prolonged cases the blood showed the changes of secondary pernicious anæmia, with extreme reduction in number and marked variations in size of the red cells, and leucocytosis. It was extremely rare to

find any considerable number of parasites in such specimens.

In several chronic cases the changes in the blood were indistinguishable from those of primary pernicious anæmia, megalocytes with increased Hb constituting a large percentage of all red cells, and megaloblasts being abundant. These changes had been established within six or eight weeks. Lymphocytosis, relative or absolute, was often observed in these and milder cases, and the eosinophile cells were often distinctly increased.

The evidence derived from the observation of these cases strongly indicates that the anæmia of severe malarial infection progresses for some time after the blood has been freed from parasites, a conclusion that is further borne out by the comparatively large number of deaths (ten) from anæmia and cachexia that occurred in cases showing no parasites in the circulation. The bearing of this fact on prognoses was well illustrated in some of the fatal cases, in which recovery was expected when the blood was cleared of parasites, yet the patients went on to die of progressive anæmia.

No uniform difference could be seen in the progress of the anæmia in the cases of æstivo-autumnal and those of tertian infection. If any existed, it seemed that the tertian infection was more severe in this respect than was the æstivo-autumnal. The anæmia in two fatal tertian cases was exceptionally severe.

The Fatal Cases.—Of six hundred and five cases of malaria, thirty-nine were fatal, at the General Hospital, six and a half per cent.; but it was impossible to estimate the full mortality of the disease, as many patients were transferred to city hospitals during the intervals of improvement.

Of these thirty-nine cases, twenty-five showed æstivo-autumnal infection, two tertian, two double infection with both varieties, and in ten no distinct parasites were found. In the æstivo-autumnal cases, rings alone were found in twelve, crescents alone in nine, and both rings and crescents in four cases. In six of the æstivo-

autumnal cases there was dysentery, usually, but not always, amœbic. Four patients suffered from severe diarrhœa with catarrhal colitis. In eight cases there was intense jaundice, and the immediate cause of death in one case was pneumonia, and in another nephritis. The ten patients showing no organisms died from malarial cachexia, or from complications.

PARASITOLOGY. 1. *The Æstivo-autumnal Parasite.*—The earliest forms of this parasite seen in the circulation were small spheroidal, hyaline, moderately refractive, intracellular bodies, about one micromillimetre in diameter. In the fresh condition these bodies showed slight changes of shape and position. In stained specimens they nearly always appeared slightly vesicular. Small, evenly stained forms were seen in marrow smears only. At the same period, in the plasma, were regularly seen bodies of the same size, but with small projecting knobs, giving them the appearance of a star with blunt points. These bodies usually exhibited an active, rolling motion, but were sometimes sluggish, when they were seen to assume the form of the intracellular, spheroidal bodies.

During nearly all periods of the first two, or sometimes three, days after sporulation, the peculiar signet-ring form of the parasite was seen in the red cells. In the fresh condition this body appears indistinctly vesicular, is slightly amœboid, and, especially in virulent infections, was wont to extrude short globular pseudopodia. In stained specimens, in cells flatly spread and instantly dried, this typical body has the appearance of a signet-ring, a quarter to two thirds the diameter of the red cell, the thickened portion of the ring, or signet, being usually very prominent, and the bow of the ring being exceedingly thin. It may exhibit one or more minute achromatic points, and one small deeply staining granule. There seems little room for doubt that this form of the parasite is really of the form of a ring, and not, as is sometimes stated, spheroidal with an achromatic centre.

The growth of the signet-ring body in the circula-

tion appears to be slow, as they were usually seen of slightly increased size for two, and in six cases for three, days after sporulation (162, 500, 612, 646, 681, 782).

The largest signet-ring form seen in the present series were about four to five micromillimetres in diameter. They were almost invariably non-pigmented, but occasionally one or two fine pigment grains could be seen scattered along the periphery of the ring. Their position, projecting beyond the outline of the red cell, or apparently applied to the surface of the cell, is often characteristic.

The signet-ring form of the æstivo-autumnal parasite was readily distinguished from the early ring-shaped form of the tertian parasite on the following features:

(1) The tertian ring never shows a distinct signet on one side and an extremely fine, regular bow on the other, but is thicker and more irregular.

(2) The tertian ring very early exhibits a distinct spheroidal achromatic portion, which is absent or extremely minute in the æstivo-autumnal parasite. (Alcoholic eosin and methylene blue.)

(3) The tertian ring early produces many fine pigment grains, which are late and infrequent in the æstivo-autumnal ring.

(4) The red cell is usually shrunken when infected by the æstivo-autumnal ring, and nearly always swollen when harboring the tertian parasite.

The diagnostic value of a close scrutiny of these signet-ring forms was strikingly illustrated in a case of quotidian æstivo-autumnal fever (338) in which, in the same red cell, two rings were found; one, three micromillimetres and a half in diameter, developed in a paroxysm, occurring thirty hours previously, and a second ring, a micromillimetre and a half in diameter, coming from a paroxysm about six hours before the examination of the blood.

In another case (67) of double infection, young crescents were found with great difficulty, but rings of both types were abundant, and readily distinguished

on the above features. Later, adult forms of both varieties were seen.

After the second or third day, or in cinchonized cases often much earlier, the signet-rings usually disappear from the circulation, and their further development proceeds, if at all, in the viscera, especially in the brain, marrow, and spleen. In these situations the growth of the parasites may be followed in smears of the tissue made on glass slides and treated as blood specimens. In such specimens most of the later forms of the parasites can be seen simultaneously. Besides the rings, tissue smears usually contain many spheroidal, hyaline, pigmented, intracellular bodies, three to five micromillimetres in diameter. These bodies are probably the next developmental stage beyond the rings, but the gap between the ring form and the spheroidal pigmented body is very wide, and their supposed relation can not at present be claimed with certainty. From the pigmented spheroidal body all transition forms up to adult *crescents* are to be seen in abundance. Small pigmented spheroidal bodies were seen in the circulation in one fatal case of the present series (67), but are rare in the peripheral blood. From the third to the fifth day after sporulation *elliptical intracellular bodies* begin to make their appearance in the circulation. From the fourth to the sixth day crescentic forms are usually to be found, and thereafter in cinchonized cases, only adult or nearly adult crescents are usually to be seen. All these later forms are abundant in marrow smears.

The *segmenting forms* of the æstivo-autumnal parasite are almost never seen in the circulation, and were only once encountered there in the present cases. In the marrow smears from a fatal case (793), however, many æstivo-autumnal rosettes were seen. In eight of these the spores could be accurately counted, and their number was invariably eighteen. These rosettes were slightly smaller than the tertian rosette, a difference apparently due to the smaller size and lesser number of the spores. The pigment, composed of coarse, brownish-yel-

low grains, was usually centrally placed. Distinct remnants of the Hb of the red cell were usually seen surrounding the rosettes.

In regard to the time required for the fertile cycle of the æstivo-autumnal parasite, the writer secured no evidence that it can transpire in the period usually ascribed—viz., forty-eight to seventy-two hours. In cases of quotidian and tertian fever from this infection, there was no indication that the new brood of parasites had developed from the generation of one or two days preceding, the larger signet-ring forms of these generations being usually still present in the circulation. Moreover, the slow development of the ring forms, and the wide morphological gap between them and the rosettes, make it appear extremely improbable that the change from large signet-rings to rosettes could occur in less time than is required for the development of large rings from spores, which in six cases was found to extend over forty-eight hours.

It is possible, however, that the inhibitory influence of quinine may so retard or disturb the cycle that no reliable observations on this point were possible in the Montauk cases. It is possible also, though improbable, that the cycle in secondary paroxysms differs from that in primary seizures, very few of which were seen at Montauk.

With these possible sources of fallacy, it is the conclusion of the present study that the fertile æstivo-autumnal cycle may require much longer than forty-eight hours, and that sterile forms are not fully developed until the end of six or seven days. Clinically, a great many cases showed characteristic attacks lasting seven days, followed immediately by relapses of equal duration. The periods given above for the appearance of various forms of crescentic bodies were verified by so many observations that the writer is convinced of their accuracy. Adult crescents appearing in the circulation before the end of the fourth day of the cycle are probably to be referred to a preceding generation of parasites.

2. *The Tertian Parasite.*—The earliest forms of the tertian parasite seen in the blood of the present cases were, as is usual, small, spheroidal, non-pigmented, intracellular bodies, slightly larger than the similar forms of the æstivo-autumnal parasite. In all cases in which such forms were seen, larger and typical tertian rings were also found. The spheroidal, achromatic portion, which characterizes the tertian ring, develops with the increasing bulk of the parasite until, in the adult forms, it measures two to three micromillimetres in diameter, and exhibits a faint reticulum.

In the tertian presegmenting forms, the reticulum of the body of the parasite becomes very distinct, staining deeply with methylene blue, and at this stage the single achromatic portion appears to subdivide, and is found in the meshes of the reticulum.

The usual development of the tertian parasite was followed in many cases. In one particular, the Cuban tertian parasite appears to differ from that seen in the New York cases. In two fatal cases (130, 559), and in several very severe tertian infections, the parasites were much more actively amœboid than the writer has ever seen in cases of New York malaria. On this account, in stained specimens, the pseudopodia of the larger parasites were extremely long and numerous, so that in some cells the body of the parasite was represented by a series of small blue grains between which no uniting threads could be distinguished.

3. *The Quartan Parasite.*—In only four cases of the series were organisms found which probably belonged to the quartan type. These cases responded promptly to quinine. The histories were not of typical quartan seizures, and, as the paroxysms were not repeated, the diagnosis could not rest on the clinical records. In these cases the organisms were highly refractive and slowly amœboid in the fresh condition; the cells were shrunken and the pigment unusually coarse in stained specimens. No chills were observed, and no rosettes seen in the blood. The cases were therefore classified as those showing no organism that could be positively identified.

4. *Atypical Organisms.*—In most of the cases classified as showing no parasites that could be positively identified, atypical, intracellular, pigmented bodies were found.

Such bodies are to be distinguished from (1) bluish staining masses, often seen in the red cells of any secondary anæmia; and (2) from blue-stained foreign bodies lying in or on the red cells, which often simulate the malarial organism. Aside from these possible sources of error, in well-established cases of malaria after much quinine has been taken, one frequently meets with shrunken atypical "quinine organisms" usually containing one or more pigment grains. They are usually irregularly spherical in outline, and the infected cell should always show some alteration in size, form, or hæmoglobin.

While such bodies do not constitute evidence on which the positive diagnosis of malaria may be based, the frequency of their occurrence in undoubted cases of malaria at Montauk leads the writer to believe that their significance is greater than the conservative blood-analyst would naturally admit.

Vacuolated, pigmented and non-pigmented, extra cellular bodies were seen in many cases. This group does not include the adult tertian parasite, which in the fresh condition usually appears to be free from the cellular remnant almost invariably demonstrable by staining, nor the large sterile homogeneous forms showing pigment in vibratory motion.

In the fresh condition the appearance of the cystic extracellular bodies strongly suggests an origin from malarial parasites.

In rare instances sluggish amœboid motion may be observed, in which case their malarial origin can not safely be denied, although pigmented leucocytes sometimes show amœboid motion.

On the other hand, cystic leucocytes are very common in malaria. They were noted in every case examined in the fresh condition at Montauk. When these cystic leucocytes contain pigment, as they not infre-

quently do, it appears to the writer impossible to distinguish them from the bodies described by some as extracelluar forms of the malarial parasite.

In stained specimens many such cystic leucocytes were seen in the present cases, but in the entire series the writer met with no structures of this type which could be regarded as extracellular forms of malarial parasites. All suspicious vacuolated, pigmented, extracellular bodies gave evidence of their origin from leucocytes, and the conclusion was reached that in the absence of typical amœboid motion, or vibratory motion of pigment, the identification of these bodies is extremely hazardous, and that the diagnosis of malarial parasites should not be based on their presence alone.

Pigmented leucocytes were noted in a large proportion of the specimens examined, and proved to be one of the most striking characters of the blood in nearly all forms of malaria. The pigmented leucocytes were usually of the large mononuclear variety. Some of them had englobed not only pigment, but the bodies of parasites, and were themselves often cystic. In one case (67) very large macrophages, thirty-five to forty micromillimetres in diameter, were found in the circulation.

The pigment was usually coarse and brownish-yellow in the æstivo-autumnal cases, and slightly finer and darker in the tertian cases. In old cases all pigment appears to assume a much darker color. It occurs in small rods or grains, either scattered through the body of the cell or gathered in masses of considerable size. In typical form these leucocytes were unmistakable, but when scanty in number and containing only one or more small black grains, they had to be distinguished with care from leucocytes contaminated during the preparation of the specimen.

Pigmented leucocytes were most abundant in well-established cases of æstivo-autumnal fever. The largest numbers were seen in a fatal case of double infection (67). Their recognition proved of great diagnostic value in (1) *chronic malarial fever*, when they were

often found after all trace of parasites had disappeared, and (2) in cinchonized cases of more acute fever, in which plasmodia could not be found. In the later stages of æstivo-autumnal fever pigmented leucocytes were many times found in five to ten minutes, while the discovery of a crescent required an hour or more.

Free pigment, probably of malarial origin, was seen in many cases, but never in the absence of pigmented leucocytes.

Occasionally red cells were found to contain pigment similar to that seen in the leucocytes, but no trace of a parasite.

The Occurrence of the Plasmodium in the Circulation.—The plasmodium was found in the blood in every case in which the blood was secured within eighteen hours after the chill. In only one case (456) was the organism not found twenty-four hours after the chill. Nearly all of the cases had taken heavy doses of quinine, many of them for several days before coming under observation. In the great majority of the cinchonized cases of acute æstivo-autumnal fever organisms were found if the blood was examined within a week after the beginning of the paroxysm, while crescents frequently persist for ten, or sometimes for fourteen days, or longer.

As previously stated, there was a period noted in several cases between the second and fourth days, when large doses of quinine had completely rid the blood of the signet-ring forms, and, in the absence of crescents, the examination proved negative.

On the other hand, a prolonged search was often required before the organisms could be detected. In three cases examined during the chill, thirty-five, forty-five, and fifty minutes were required before a single signet-ring form could be detected, and in nine other cases only crescents could be found (fifteen minutes' search) during the chill.

In four cases examined twelve to eighteen hours after the chill, the discovery in one of a single tertian parasite required thirty minutes, and in three, sixty and

seventy minutes were required for the detection of one signet-ring form.

In one case examined twenty-four hours after the chill one signet-ring form was found after a search of two hours and ten minutes. In another case (456) two hours' search was unsuccessful, although atypical pigmented intracellular bodies and pigmented leucocytes were seen. A second specimen could not be secured.

The conclusion is drawn from these data that the parasite can always be found if the blood is examined with care and persistence within twenty-four hours after the beginning of the chill, although quinine may have been administered in large doses.

In thirty cases of *remittent malarial fever*, selected as showing fairly continuous pyrexia, rings alone were found in eight; crescents alone in eleven; both rings and crescents in one; tertian parasites alone in one; double infection in one; and no distinct organisms in eight.

In many other cases a continuous pyrexia lasting three to seven days was noted, but these cases did not seem to fall properly within the class of remittent malarial fever.

In chronic cases, during febrile periods, organisms were usually found in the blood, but they were often missed during afebrile periods. In one case (507), exhibiting an irregular fever, crescents were found four weeks after the last chill, quinine having been constantly administered. In another case (310) young crescents were found three weeks after the last chill, in spite of the use of quinine. It is probable that mild seizures had been overlooked by these patients.

Typhoid Fever and Malaria.—In sixty-nine cases giving a distinct history of recent malarial fever and exhibiting similar evidence in the blood, in the form of severe anæmia, pigmented leucocytes, often atypical pigmented intracellular bodies, and in some cases a few plasmodia, the question of a double infection with typhoid fever and malaria had to be considered.

Of these, forty were reported as cases of *typhoid fever in anæmic and malarious subjects.* In some of

these cases the disease began with one or more short rigors repeated on successive days, after which the disease progressed with the usual symptoms of typhoid fever. In one such instance (791) tertian parasites were found during the first few days and before typhoid fever was suspected, but they disappeared rapidly under quinine, and were not again seen. The patient died from peritonitis in the fourth week.

In another case (514) the usual history of Cuban malaria was interrupted by the development of typhoid fever with all essential symptoms. Plasmodia could not be found in the blood, but in the second week of convalescence tertian chills and fever developed, and tertian parasites were found in the blood.

In a third case (683) the history indicated the slow onset of typhoid fever in Cuba, which was safely withstood without quinine, but in the second week of convalescence tertian chills and fever supervened and tertian parasites were found in the blood.

There were other cases (1, 3, 51, 115, etc.) illustrating the same behavior of the malarial infection during the course of typhoid fever.

Further evidence of the usual incompatibility of malarial and typhoid fevers was furnished by the two fatal cases of typhoid fever in malarious subjects that came to autopsy (523, 683). There no parasites could be found in the blood during life, but in smears from the spleen and marrow diligent search revealed the presence of a very few rings and crescents, with much old malarial pigment.

The reason why the blood was examined in a hundred and fifty-nine cases of typhoid fever was the intermittent character of the fever, which was exhibited in patients both with and without malarial antecedents. *In no case of undoubted and established typhoid fever were malarial parasites found in the blood in connection with any of these sudden rises of temperature, but only at the onset of the disease or during the convalescence.*

On the other hand, many patients whose blood con-

tained numerous parasites were seen in the "typhoid state," but there were always some essential symptoms lacking to confirm the diagnosis of typhoid fever, while the subsequent course of the disease, where observed, demonstrated the purely malarial character of the fever.

These patients might suffer from epistaxis, hæmatemesis, bloody stools, tympanites, a few rose spots, though oftener herpes, diarrhœa, and delirium, and in some a partial Widal's reaction was obtained. But the intestinal symptoms were inconstant or referable to dysentery or simple diarrhœa, from which many of the malarial cases suffered, and these patients never showed subsultus or cracked tongues, and they did not die, or, if they did, dysentery and malaria were demonstrated at or before the autopsy.

In another group of twenty-nine cases, the absence of any large number of parasites, and the presence of typhoidal symptoms, left a reasonable doubt regarding the diagnosis.

These cases seemed almost certainly malarial, on account of the previous history, the facies, the anæmia, and usually the sudden recovery at the turn of the disease, while in seven of them a few parasites were found in the blood.

On the other hand, the suspicion of typhoid fever was raised by the continued fever, abdominal symptoms, and general typhoidal state, although symptoms of typhoid fever were not present in distinct and convincing form. A moderate reaction with Widal's test was sometimes obtained in these case, but this evidence failed to be convincing after sharp reactions had occurred in a case of dysentery (269) and in a cinchonized case of pernicious malaria (328).

It is possible that some of these patients suffered from both active malaria and typhoid fever, but there were no positive indications that the latter infection was present. In the cases that came to autopsy there was never any doubt of the nature of the disease. It was either typhoid fever or malaria, but never both,

although microscopical evidence of dormant malarial infection was found in at least two cases of typhoid fever.

In short, in spite of very painstaking effort, the attempt to find a case of typhoid fever and active malaria progressing simultaneously was unsuccessful.

From the study of this group of cases it is concluded:

1. That typhoid fever is to a large extent incompatible with active malarial fever, and that during the course of the former the latter infection is usually suppressed.

2. That the presence of old malarial infection may alter the course of typhoid fever through the anæmia, but that active sporulation of the malarial parasite very rarely occurs during the course of established typhoid fever.

3. On the other hand, since malarial paroxysms often reappear during convalescence, a scanty growth of the parasite must often persist during the course of typhoid fever, and it is possible that some of the irregularities of temperature observed in these cases are referable to this partly suppressed growth.

4. That the anatomical evidence of a post-mortem examination is much needed to demonstrate the existence of typhoid fever in cases showing active malarial paroxysms.

Measles and Malaria.—During convalescence from measles, symptoms of malaria developed in two cases, and parasites were found in the blood, crescents in one case and tertian organisms in the other.

The eruption in these cases had been characteristic, but the course of the disease had not apparently been altered by the activity of the malarial infection.