MALARIA AND MOSQUITOS IN ZEALAND.

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In the *Nederlandsch Tydschrift van Geneeskunde* of February 24th and July 14th, 1900, one of us published two articles about a little outbreak of malaria in Middleburg, the principal town of Zealand, where for thirty years this disease had never occurred.

Two remarkable peculiarities of this epidemic deserve to be mentioned: first, that it consisted only of cases of tertian fever (83 per cent. *F. tertiana simplex*, 17 per cent. *F. tertiana duplex*); secondly, that house epidemics were often observed. In the year 1899, 110 cases were divided between 45 different families; in some of them, consisting of 6 and 10 persons, none escaped the influence of the germs of the disease.

Although these facts could be explained very well with the aid of the malaria-mosquito-theory, the author of the articles quoted above was not at first much inclined to accept the view that these insects played an important rôle in the spreading of the disease, as they were not more abundant than in other years, and were even rare in spring-time, when the first cases made their appearance.

The progress of our knowledge on this subject was such, however, that the malaria houses were reinspected this year with accuracy; and it turned out that several *Culices* and *Anopheles (maculipennis)* were found. Further, it became

outer layer of the stomach wall. We found it impossible, however, to follow the development to a further stage, because no single mosquito survived the tenth day of captivity. The experiments were therefore repeated on July 25th and later, and the mosquitos kept in a wooden cage partly covered with mosquito gauze, whilst a rabbit was placed within every second or third night. The insects fed themselves regularly with its blood, and we thus succeeded in keeping them alive during more than thirty days. Our success now was complete. Of 22 mosquitos which had sucked blood with gametes, in the body of 18 we found one or another stage of development of the parasites.

No development, however, took place in 7 mosquitos which had sucked malarial blood in which febrigenous parasites only, and not gametes, could be detected. The same negative result was noticed in 20 cases, in which the insects had sucked the blood of persons who had suffered from malaria but who had recovered spontaneously or with the aid of quinine, and in whose blood the parasites were absent. When we add that, in all cases in which development took place the zygotes were of the proper stage of growth, the reader will be convinced that they resulted from the gametes present in the blood of the patients.

The first stage we could find was that of two days after infection. It appeared as a little egg-shaped body lying between the cells of the stomach wall. The third day it was found in the outer layer. It was 9 to 10 μ long, 7 to 8 μ broad; and consisted of two distinct parts—a yellow-tinged wall, at the poles a little thicker than in the middle; and within, a hyaline substance which seemed to be divided into spherical bodies.

Outside of these, immediately under, perhaps also within, the wall appeared little grains of a black pigment. On the following days (Fig. 2) the bodies increase in size, whilst the pigment disappears gradually; until on the sixth day, they have become round and of a diameter of 16 to 18 μ . The capsule has now become relatively thin; the number of spherical bodies has increased, and between them little round or oval bright drops are observed, just as Ross found them in zygotes from proteosoma, being considered by him to be oil drops.

Fig. 1.—*Anopheles* in the typical attitude in which it hangs from a ceiling.

evident that, as in Italy, *Anopheles* prefer to live in stables with rabbits, horses, and other quadrupeds. Within such stables as were situated in the neighbourhood of the infected houses whole colonies of them were found, so that it was not difficult to gather hundreds of them. In those parts of the town where *Anopheles* and these stables were nearly absent, hardly any cases of malaria were observed.

It will be unnecessary to insist here on the importance of this occurrence of *Anopheles* in a malarious country which is situated at a latitude so much more northern than those where until now all investigations on this subject have taken place. Of no less importance is it, we think, to answer the question whether the malarial parasites undergo here also a further development within the body of these insects, terminating with the accumulations of blasts (sporozoites) in the salivary glands.

As the examination of the stomach wall of 15 mosquitos caught in some houses and of more than 100 out of the stables furnished only a meagre result—only 1 zygote could be detected—and as 40 salivary glands also were examined with a negative result, we decided to try to infect *Anopheles* by keeping them under a mosquito net, together with a person who suffered from malaria, and whose blood contained not only the so-called febrigenous parasites but also gametocytes, which are destined to undertake sexual functions in the mosquito's stomach and to form vermicules (zygotes).

The insects which had sucked blood during the night were kept in a glass covered with gauze and were fed with bananas.

Our first preliminary experiments, beginning on July 9th, were immediately successful. From the fifth until the tenth day after infection several zygotes could be found in the

Fig. 2. Young coccidia in *Anopheles maculipennis* on the third day after infection with the tertian parasite ($\times 800$).

During the later days the increase in size took place much more rapidly than during the earlier days (Fig. 3). Still it

Fig. 3.—Coccidia eight days after infection ($\times 800$).

showed itself very dependent on the temperature of the air. Whilst during researches carried on at a daily temperature of 70° F. min., 84° F. max., the zygotes had reached a diameter of $36\ \mu$ on the tenth day, this size, during our researches at a temperature of min. 61° F., max. 70° F., was not reached until the fourteenth day. Meanwhile the spherical bodies became very numerous. The zygotes protruded beyond the tissues, and several of them could be seen nearly free in the cavity of the body, and only attached to the stomach wall by thin threads (Fig. 4).

Fig. 4.—Coccidium containing sporozoites, sixteen days after infection, projecting from the stomach wall ($\times 800$).

On the sixteenth day the little spheres began to disappear. Instead of them we could now see thousands of thread-like bodies within the capsule. A few days later (the first time on the twenty-first day) these bodies could be found in the salivary glands, whilst empty capsules indicated whence they had taken their origin. We must add here that, until that day, the examination of the glands had always taken place without any result.

As we may conclude from this short description, and as may be shown still more clearly by some photographs (which we owe to the kindness and skill of Professor Beyerinck and Mr. van Deelden of the Polytechnical School at Delft), the development of malarial parasites takes place here in the body of *Anopheles* in the same way as is described by several Italian authors (Bignami, Bastianelli, and Grassi), and by the

members of the Malaria Expedition to Sierra Leone (Ross, Annett, and Austen).

It may be interesting to relate here at what temperature the development took place; we show, therefore, the graphical curves at the highest and lowest temperatures that were observed during the time of the experiments (July 25th to

Curve of the highest and lowest daily temperatures during development of malaria parasites in *Anopheles maculipennis*.

August 15th). They teach us that development has been possible whilst the weather was rather cold, and did not cease though the temperature fell once beneath 12° C. This may enlarge our view as to the conditions under which a spreading of the disease may be possible.

As nearly all the mosquitos that were caught in the stables were fertilised ones (our photograph shows this clearly enough) only these were used for the experiments, and it may be possible that we owe our immediate success partly to this fact, as we remember that in Sierra Leone a number of *Anopheles*, not fertilised, failed to show parasites after having sucked malarial blood.¹ As Koch noticed negative results in Java, too, this point deserves our full attention.

We were not able to detect sporozoites in other organs than in the salivary glands, neither in the fertilised eggs, nor in the apparently unfertilised ones (which can only be found by microscopical examination of the membranous ovaries, after having removed the others). Until now it is therefore not allowed us to accept that mosquitos may be infected in any other way than by biting animals which contain gametes in their blood. It is of course not impossible that different species can serve as intermediary host for their parasites. Man, however, is the only one yet known to us. As we have seen he is able to reinfect the definitive host, *Anopheles*, when gametocytes are found in his blood. Whilst in tropical malaria the gametocytes persist a long time after the paroxysms have ceased, in the tertian fever we could state that they disappear a short time after the last attack. Whether the fever ceased spontaneously or by the aid of quinine, they never could be found longer than one day after recovery. As it might be possible that, as in filaria, there exists a kind of periodicity in their appearance in the peripheral blood, preparations were made also during the night, but gametocytes could never be detected when their absence during the daytime was already determined. Control experiments by feeding mosquitos gave corresponding results. When *Anopheles* had sucked blood two days later than the last paroxysm no zygotes could be found. In several cases, however, when they had sucked on the day after the last attack of fever, development of parasites still took place. This was also the case when quinine was given in a large dose (1.5 gram d.d.). The presence of this drug in the blood seems, therefore, to be no obstacle against the forming of vermicules in the stomach of the mosquito.

A similar fact is shown for the semilunar parasites by Bastianelli and Bignami, and by Gualdi and Martirano.²

Compared with the tropical malaria (where, as already remarked, gametocytes persist a long time after the last attacks of fever) the state of things here related will assist to a high degree the success of the measures that must be taken against the spreading of the disease. Supposing that man is the only or principal intermediary host for the described parasites, jealously protecting him only during the periods of fever and one or two days afterwards against the bites of mosquitos, will diminish greatly the number of infected insects, and in consequence reduce the fever-rate to a minimum. With the aid of the other measures advised by the members of the Malaria Expedition of the Liverpool School, consisting in precautions to be taken by the inhabitants against the bites of the gnats, and in measures for reducing the numbers of the latter, we believe that it will be possible to make the disease disappear in our country altogether.

As to the latter measure (measures for reducing the numbers of mosquitos), here also it must be divided in two parts: First, destruction of adults or larvæ, and, secondly, measures to prevent the insects breeding. A large quantity of adults may be killed in the stables where hundreds of them are found together. To apply the necessary measures for destroying larvæ of course it is required to find the breeding pools. It took a long time before we succeeded in this. At last, however, one breeding place was detected in the shape of a drinking well of a surface of about 160 square metres, and situated at a distance of 100 metres from a stable with a large colony of *Anopheles*.

Further investigations will be required to learn more about the bionomics of adults and larvæ in our northern country. A full knowledge of the subject will show the best way to arrange measures by which we may finally rid ourselves of these dangerous carriers of disease.

REFERENCES.

¹ Vide Report of the Malarial Expedition of the Liverpool School of Tropical Medicine. ² Vide *La Malaria e le Zanzare*, 26 Oct., 1899. Roma.

PRELIMINARY NOTE ON AN UNCLASSIFIED
TYPE OF WEST AFRICAN FEVER.

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In differentiating the fevers of the West Coast of Africa it is important to exclude the great malarial class from others, by defining malaria as that form of fever in which definite parasites are found in the red blood corpuscles and pigment occurs within leucocytes and in the substance of certain organs. Of such fevers, which through the absence of parasites and pigment may be excluded from the malaria group, is the fever we are about to describe. For reasons which will appear in our paper we propose to provisionally call this disease "hyperpyrexial fever."

CLINICAL FEATURES OF HYPERPYREXIAL FEVER.

This fever is generally ushered in by a slight rise of temperature followed by profuse perspiration and a fall in the temperature to about 99° F. After a period of apyrexia of perhaps twenty-four hours' duration the temperature begins again to rise, slowly at first, but when 105° is passed with alarming rapidity, one degree in 10 minutes having been frequently observed, and it may reach 107° on the second day. For 14 or even for 30 days subsequently there is absolutely no tendency for it to fall. The skin acts either very slightly or not at all, and all antipyretic drugs fail.

The tongue is at first furred on the dorsum and red at the edges and tip; late in the disease it becomes dry and shrivelled. There is no enlargement of the liver or spleen. The urine is of normal character and abundant; the bowels are regular or inclined to looseness. The conjunctivæ are injected and the pupils contracted. The mind remains remarkably clear in most cases, except when the temperature

is at its highest, but constant symptoms in the early days are great anxiety and restlessness.

With regard to the examination of the blood, no plasmodia or pigmented leucocytes have ever been discovered, but in two of the later cases it was noticed that the blood tended to coagulate the moment it was exposed to the air, so that it was only with great difficulty that satisfactory films could be obtained.

TYPICAL EXAMPLES OF THE DISEASE.

CASE I.—This patient had been on the coast for about five months, and had had no fever until the present attack. During the last month he had lived in a tent at a quarry some twenty miles up the Akwayafe river, and, feeling ill four days before admission, got into a canoe and found his way down to the mouth of the river, where he was picked up by a launch and brought to the hospital. On admission, his temperature was only 99.6° F., and he was apparently going on satisfactorily when, as in previous cases, his temperature began slowly to creep up—the beginning of a constant tendency towards hyperpyrexia. He was treated by baths, as will be subsequently described. After his fourth bath he was put into a cold pack, which was changed every hour for four days. The temperature then steadied, and eventually he left for home practically well.

CASE II.—This patient was sent from an out-station on the fourteenth day of his illness, and was still under treatment when the record was made. So marked was the tendency to hyperpyrexia that on two occasions no fewer than two cold baths were necessary in the twenty-four hours, and it was not until the twenty-second day of the disease that it was possible to substitute the continuous pack for the cold bath. From that time until now the temperature has averaged 102°. The patient lies helpless in bed, occasionally showing some glimmering of intelligence, but for the most part remaining unconscious of his surroundings, taking nourishment well, but passing urine and feces under him. This condition, as far as we could tell, may continue indefinitely. The temperature shows no tendency to assume alarming proportions, and the heart and lungs are acting well. (See Chart, p. 203.)

Treatment of the Condition.

This may be summed up in one word—baths. The patient is put into a cold bath, and his temperature brought down to 100° or 99°. He sleeps for about an hour, and then feels fairly comfortable, but the temperature at once begins to creep up again, and in eighteen or twenty-four hours it is back at 106°, or at the point at which it is considered advisable to check it. Quinine and other drugs have been systematically tried without influencing the course of the disease; the coal-tar antipyretics are absolutely useless. Cold sponging and packs are incapable by themselves of reducing the temperature, although in a recent case which recovered it was found that by reducing the temperature by means of the cold bath to 101° or 102° it was possible to keep it there by means of cold packs renewed at hourly intervals.

Progress of the Cases.

It has been observed that, if the patient is to recover at all, some change for the better is to be looked for about the end of the third week. The temperature, which up to this time would constantly rise at once after the bath, might remain at 102° or 103° for several hours, and perhaps in the course of the next week two or more days might pass without the necessity for a bath. Convalescence is gradual, and it may be six weeks after the onset of the fever before the temperature finally assumes its normal course. On the other hand, in 50 per cent. of the cases which have come under observation a fatal issue has occurred.

ADDENDUM BY DR. H. E. ANNETT.

Dr. Annett, who watched cases in the Calabar Hospital, has been good enough to write the following notes on the disease, with the results of his investigation of the blood condition of each case.

The microscopical examinations of the blood in these cases made by means of stained and fresh specimens, revealed neither parasites nor pigmented leucocytes. In the second case, about the end of the second week, an estimation of the number of blood corpuscles gave 4,384,000 red corpuscles, and 15,000 white, while the hæmoglobinometer showed 90 per cent. hæmoglobin. Attempts to cultivate micro-organisms from the blood failed. It was noted that the blood coagulated almost immediately after exuding from the punctures.

The following points in these and in similar cases differentiate this type of fever from others occurring on the West African Coast, and further negative its connection with true malarial fever:

1. These cases occur during the dry season, at a time when the number of typical cases of malarial fever is smallest.
2. The onset, symptoms, and course of the disease are quite