Blackwater fever / by W. H. Crosse.

BLACKWATER FEVER

BLACKWATER FEVER.

BY

W. H. CROSSE,

CONSULTING MEDICAL OFFICER TO THE ROYAL NIGER COMPANY, CHARTERED AND LIMITED.

Reprinted from the TRANSACTIONS OF THE EPIDEMIOLOGICAL SOCIETY OF LONDON, *N.S., Vol. XLIII.*, 1898-99.

London:
JOHN BALE, SONS & DANIELSSON, LTD.,
OXFORD HOUSE,
83, 85, 87, 89, GREAT TITCHFIELD STREET, W.

BLACKWATER FEVER.

By W. H. CROSSE,
Consulting Medical Officer, The Royal Niger Company, Chartered and Limited.

(*Read: March 17th*, 1899.)

Mr. President,—In venturing this evening to bring before your notice the disease called blackwater fever or hæmoglobinuric fever, I would submit that we are dealing with a subject of vital importance as regards our colonies.

It is admitted that this complaint is the cause of more deaths and invaliding than all the other diseases from which Europeans suffer in West Africa, and the same remark applies to the opposite side of the continent.

Koch, for instance, states that this disease creates the greatest havoc amongst Europeans in German East Africa.*

The disease, however, is not confined only to Europeans, for on the Congo railway many of the Chinese labourers died from it.

It has been considered to be rare amongst Africans; however, I am told that many died from it while working on the Panama Canal; and recently, we are informed,† there has been a serious outbreak of it among the blacks in the Cameroons, the disease specially attacking those who had come to the coast from the interior.

When I first went to West Africa, in 1886, blackwater fever was a complaint about which very little had been written, and the ordinary English text-books did not even mention the existence of such a disease. Dr. C. H. Eyles had published a brochure on the fevers of the Gold Coast,‡ in which a considerable amount of information is given about the disease, and an interesting account of a case of

* Koch (R.) *Das Schwarzwasserfieber. Arbeiten aus dem Kaiserlichen Gesundheitsamte*, 1898. xiv, 304.

† Plehn (F.) *Die Kamerun-Küste. Studien zur Klimatologie, Physiologie und Pathologie in den Tropen*, 1898. (Preface, p. iii.)

‡ *Malarial Fevers as met with on the Gold Coast.*

blackwater fever was published by Dr. Easmon in the *Medical Times*, August 29th, 1885, p. 277.

In 1892 I published a small book on the malarial fevers of the Niger, of which a large portion was devoted to this subject.*

The study of this complaint received a considerable impetus when Dr. Patrick Manson, on March 15th, 1893, read before this Society an interesting paper on African hæmoglobinuric fever.†

Since that time more and more attention has been given to the disease; and more especially quite recently, on account of the statement made by Koch, that blackwater fever is due to quinine poisoning.‡

I have already attempted to answer Koch's contention that blackwater fever is simply quinine poisoning, in a paper read before the Guy's Hospital Physical Society in October last.§

I have also dealt to some extent with the pathology of the disease, as evidenced by a case which I saw in England with Dr. Wooldridge, of Camberley, in a paper which I read with Mr. Pakes before the Pathological Society on December 20th, 1898.

I hope to-night to review the subject, and to lay before you a definite statement as to the opinion which I hold with regard to its pathology, causation, and treatment.

I cannot let this occasion pass without mentioning how deeply I am indebted to Dr. Washbourn, who, years ago, urged me to write on this subject, and showed me the first malarial parasites I had seen.

I also take this opportunity of thanking Dr. Howard, who has just started for East Africa, to whom I am indebted for much help in this paper. On account of his special training, we may look to him in the near future for valuable information about the disease under consideration.

Definition.

By blackwater fever, or hæmoglobinuric fever, I mean a febrile disease of malarial type, characterised by hæmoglobinuria, jaundice, and vomiting.

* *Notes on the Malarial Fevers met with on the River Niger*, by W. H. Crosse.

† *Transactions of the Epidemiological Society of London*, vol. xii, 1892-3 p. 111.

‡ Koch (R.) *Das Schwarzwasserfieber. Arbieten aus dem Kaiserlichen Gesundheitsamte*, 1898. xiv, 307-8.

§ *Guy's Hospital Gazette*, October 8th, 1898.

The name, blackwater fever, was given on account of darkness of the urine, which could scarcely fail to attract the attention of the sufferers.

The colour of the urine is due to the presence of hæmoglobin or methæmoglobin and not of blood; although in some attacks nephritis may occur, and real hæmaturia result.

Blackwater fever should not be used to include those attacks of malaria in which nephritis is a primary symptom, and which are attributed to plugging of the renal capillaries by malarial parasites.

My clinical descriptions will be based on my observations of the fever on the West Coast of Africa during nine years' service in the Royal Niger Company, in which time I saw about 100 cases.

Distribution.

Since attention has been drawn to blackwater fever, the disease has been recognised in several parts where it was formerly considered to be unknown, or, at any rate, extremely rare. For instance, when I had one of my earliest attacks on the Niger, the medical man who attended me did not recognise my illness as blackwater fever, and mistook the colour of the urine for that due to bile.

Sometimes when hæmoglobin and albumen were recognised, they were thought to be due to a renal hæmorrhage complicating the malarial attack, and up till quite recently the disease was often spoken of as hæmaturic fever. Many cases have been called yellow fever.

I do not think the disease is a new one.

Manson states that it was first described by naval surgeons stationed at Nossi Bé, a French settlement off the North West coast of Madagascar.*

Plehn quotes Bérenger-Féraud as stating that the disease existed in West Africa in 1820. He further says that it can first be proved to have become prevalent about 1850.†

The first fatal case on the Gold Coast is believed to have taken place in 1832.

It is common throughout West Africa, including the Gold Coast, Sierra Leone, Nigeria, Cameroons, and the Congo and Gaboon regions; it is also common in East Africa: for

* *Tropical Diseases*, p. 61.

† Plehn (F.) *Die Kamerun-Küste. Studien zur Klimatologie, Physiologie und Pathologie in den Tropen*, 1898, p. 104.

example, in Uganda, German East Africa, and in the Zambesi districts.

I have seen one patient who seems to have suffered from the disease in Somaliland. It has been considered very rare in India, but it is probable that it has been overlooked; for recently eleven cases have been described by Mr. Arthur Powell as occurring in Assam, and which he states were "identical with the fevers I have seen in those returned from the Gold Coast."*

It is frequent in certain tropical parts of North and South America, and in Cuba. The disease is said by Manson to have been epidemic among the labourers employed in making the canal through the Isthmus of Corinth.

Cases are reported from China, and Plehn states that its existence has also been proved in Italy, and Sicily, New Guinea, and Java.

The disease is stated to be becoming more prevalent in Africa. This cannot be entirely accounted for by the increase in the white population. I attribute its increase in certain parts of West Africa partly to the fact that, as the country is becoming more opened up, the traders live more on shore than they formerly did; for in the old days trade was in parts of the Niger Delta carried on, on the hulks which were stationed near the mouths of the river for that purpose. Another reason appears to me to be the fact that stores, houses, factories and wharves have to be erected, which of course necessitates considerable disturbance of the soil; in addition to this, large plantations are being formed, now that it is recognised that West Africa is, amongst other things, a capital coffee-growing country.

It may not be out of place here to quote from my own lecture (*Guy's Hospital Gazette*, October, 1898) the following:—

"Some will ask: Why has blackwater fever become so common recently? The first case on record in the Niger Territories is, as far as I know, my own, some ten years ago. The first case in the Niger Delta is said by some old coasters to have occurred in 1882.

"It seems to me that since we have begun to turn up virgin soil for coffee and other plantations, that the disease has become common. When I went to the Niger in 1886, there was not a single plantation. Very soon large plantations were made. I believe I was the first to start them, for I took out with me a great many seeds of Eng-

* *Journal of Tropical Medicine*, vol. i, No. 5, p. 117.

lish fruit; and soon after these were planted, an experimental plantation was made, first at Asaba, then at Abutshi, some 150 miles up the river.

"It is significant that our first three gardeners died from blackwater fever, and that for some considerable time cases only occurred near the plantations; and as plantations became more common, so the disease spread to the other stations in the territories."

Outbreaks of blackwater fever have been specially noted when the dry season has been prolonged and very hot, and when, therefore, lagoons and ponds which have been long covered with water have been dried up; the same thing has been observed when the rainy season has been broken up by long spells of drought.

Easmon, in 1881, had four cases of blackwater fever under observation, and attributes these attacks in some degree to the extreme drought of the season, drying up the extensive Quettah lagoon which had been covered with with water for twelve years.*

Climate and Conditions of Life.

The river Niger, near the sea, forms an enormous delta, and opens by many mouths into the Gulf of Guinea; this delta, which consists of mud and sand, is covered with mangrove forest and jungle; it is divided and subdivided in every direction by creeks, and, as the tide goes out, the shore shows itself as a foul mass of mud through which pour turbid streams on their way to the sea.

The level of the land is so slightly above that of the water that it is being constantly washed away, and where Europeans settle the ground is protected by pegging it round with sticks, and constantly backing them up with heavy clay, in order to prevent the sea from washing it away; to act as a further protection, old hulks and lighters are run close to the shore, and left there till they sink or fall to pieces.

The earth is constantly damp, for the subsoil water is close below its surface, and the ground is itself frequently drenched with heavy rains. The average temperature is about 80 deg. F., and the difference in 24 hours is often less than 10 degrees; the air is highly saturated with moisture, for the rainfall is very heavy, being between 125 and

* Easmon (J. Farrell). *The Nature and Treatment of Blackwater Fever*, 1884. p. 2.

150 ins. in the year. Sometimes in one day it is enormous: for instance, on turning to one of the meteorological reports of the Royal Niger Company, kindly lent to me by Sir George Goldie, the Governor, I find that at Akassa (the port of the Niger) on May 22, 1887, it was 4.080 ins.; on May 27, 1888, it was 5.905 ins.

Owing to the great amount of moisture, a mist frequently hangs over the land like a pall; whilst keys rust in one's pocket, and boots, put away for a day or two, become covered with a heavy mildew.

Periods of rain are interrupted by times of excessive drought, during which the ground splits and cracks in all directions, exhaling a peculiar stench from the decaying vegetable matter with which it is so largely impregnated. When to the above is added the fact that in the delta regions it is often difficult to obtain fresh meat, and always impossible to get a supply of fresh vegetables, it will be seen that the conditions of life are not favourable to Europeans. Finally, when we consider that mosquitoes and other blood-sucking insects abound, it will be conceded that malarial germs here find a congenial home, and in the debilitated Europeans a soil suitable for their growth; and it will not cause us surprise when we find that these regions are prolific in cases of malignant malaria.

Farther inland, say 150 miles up the river, the same conditions largely prevail; for the land, alternately drenched and scorched, is covered with a rank jungle. In the wet season the Niger is a splendid rolling river, in parts a mile broad, and capable of bearing sea-going vessels of deep draught; but in the dry season it diminishes so much that its bed is exposed in many parts, and it is with difficulty that a small vessel drawing 4 ft. or 5 ft. of water can be navigated through its narrow channels.

At the height of the wet season the land is in many parts inundated with water; native huts are flooded, and are frequently swept away. I have often seen a native fishing from a canoe in his own house. As the river falls, its banks are exposed to the fierce sun, and at low water they may be 26 ft. or 30 ft. high.

Away from the river, large ponds, lakes, and lagoons are found, and these wholly or partially dry up in the hot weather. The natives live in mud houses, under the floors of which they frequently bury their dead. To build their houses it is necessary to dig huge pits, in order to obtain the clay suitable for the purpose; these pits are not filled up, therefore they are found all about their towns; the

rain partially fills them with water, which stagnates, and low forms of vegetation luxuriate within them; in these pits all kinds of filth are thrown, and here snakes, mosquitoes, and other abominations find a pleasant retreat and a quiet breeding-ground.

I have said enough to show why malaria runs riot in these regions; one other factor, however, must not be omitted: I refer to the "conscientious objector"—and he is also in evidence here—for many of the Europeans have an abiding faith in the pernicious effects of quinine in all malarial cases, whether slight or severe.

I have a patient of this class now under my care. Recently he was invalided home on account of repeated attacks of malaria; his medical adviser supplied him with the quinine necessary for the voyage; but a fellow passenger knew better than the medical man, and he and some others persuaded the sufferer to take five grains of quinine every third day instead of twice a day as had been ordered. When I saw the man he was in apparently a hopeless condition, and ring-shaped parasites and crescents were plentiful in his blood. He took quinine in full doses, and in four days he was able to sit up in his front room. The poor fellow was very grateful; and as he shook hands with me, he said that he knew I had had to try the quinine kill-or-cure remedy, and he was glad I had not given him blackwater fever.

Of course it will be understood that in the higher lands of Nigeria, the conditions of life are much more favourable to Europeans.

Diagnosis and Symptoms.

Besides the hæmoglobinuria which gives the name to this disease, there are three other symptoms which are constantly present. Reports of cases are now frequent in which one or other of these symptoms is absent; such must be accepted with the greatest caution. However, it must not be forgotten that the same disease often varies in its intensity and symptoms in different parts of the world and in different patients, and that it is modified by the patient's condition of health, his food, his surroundings, and many other things.

There are, in fact, four cardinal symptoms, viz.:—

1. Fever.
2. Hæmoglobinuria.
3. Jaundice.
4. Nausea and vomiting of bile.

We will now consider these symptoms in detail.

Fever.—I contend that the hæmoglobinuria comes on during an attack of fever clinically resembling an ordinary malarial fever.

Often the temperature is not taken before the hæmoglobinuria has been observed; the patient feels, perhaps, that he has on him a more or less severe attack of fever, but does not trouble much about it, expecting that he will pull through all right as he has frequently done before.

Usually the first warning is a sharp rigor on the second or third day of the fever; the patient's temperature will rapidly rise to 103° F. or higher, and the next specimen of urine which he passes will be found to be hæmoglobinous.

Coincident with this the temperature frequently falls, often to normal; this drop I regard as probably due to the virtual hæmorrhage, and wholly analagous to the fall that accompanies hæmorrhage in typhoid fever. It has not the importance which is often given to it, and certainly does not justify the argument used by some that blackwater fever is never malarial because the temperature is not maintained for two or three days, as is often the case in ordinary African malaria. Subsequent to the drop the temperature may rise, but not as a rule very high.

In fatal cases, in which collapse is present, the temperature is often subnormal, unless it rises owing to complications. In some cases, though, there is a daily remission, yet the temperature continues to rise till death closes the scene.

Hæmoglobinuria.—The colour of the urine may be any shade between light red and that of porter, depending partly on the amount of urine passed and partly on the quantity of colouring matter present.

This is undoubtedly in most cases either oxyhæmoglobin, or methæmoglobin, or both. Thayer, however, states that the colouring matter is always present in the form of methæmoglobin.*

Albumen is, of course, always present; as a rule, bile is absent, though it is somewhat difficult to recognise in the presence of hæmoglobin; and many observers, *e.g.*, Plehn, state that they have noted it.

On shaking up the urine the froth is pink in colour. I note that Thayer mentions the greenish froth of the urine of patients suffering from hæmoglobinuric fever; if there is one thing of which I am certain, it is that the froth of

* Thayer (William Sidney). *Lectures on the Malarial Fevers*, 1898, p. 155.

the urine of blackwater fever is, in West Africa, always, as far as I have seen it, of some shade of red.

On microscopical examination none, or only very few, red discs are to be found, but hæmoglobin casts of the renal tubules are plentiful. Nothing else abnormal is constantly found; of course, as in all albuminous urine, bacteria and torulæ grow freely if it has been allowed to stand for any length of time.

Blood discs may be present after a day or so, as a result of nephritis set up by the hæmoglobinuria.

Jaundice.—It is to be noted that although jaundice is present, bile is usually absent from the urine. Copeman states that bile is either entirely absent from the urine, or is present in an insignificant amount;* at the same time there is plentiful elimination of it in the vomit and the motions.

There are none of the usual accompaniments of jaundice, such as slow pulse, itching skin, etc.

The jaundice appears to me always to precede the hæmoglobinuria. Bérenger-Féraud says that icterus appears at the outset of the attack.†

Easmon, in one of his cases (*Medical Times*, August 29th, 1885, p. 277), notes at 9 a.m. that the urine was only highly coloured, and that there was slight jaundice, and that about 3 p.m. the urine was black; and in his paper on the Nature and Treatment of Blackwater Fever (p. 2), he says that the jaundice which is uniform is seen from the very first onset of the disease.

Now we hear of cases in which jaundice appears only after the hæmoglobinuria. Up to the present, I agree with Easmon on this point; but the study of the disease is so recent, and the reported cases are so few, that I am quite willing to admit that on this, as on many other points in this interesting complaint, further knowledge may cause the older observers to make some modifications of their opinions.

The jaundice, as a rule, deepens while hæmoglobinuria is present, and gives to the patient a greenish-yellow appearance.

Nausea and Vomiting.—These are the most distressing symptoms: they are usually very persistent, and hence give much trouble in the administration of drugs and nourish-

* Allbutt's *System of Medicine*, vol. ii, p. 747.

† Bérenger-Féraud (L. J. B.), *De la fièvre bilieuse mélanurique des pays chauds comparée avec la fièvre jaune; étude clinique faite au Sénégal*, 1874, p. 118.

ment. The colour of the vomit is usually characteristic, it being of a bright or olive-green colour. Cases are reported without any mention of green vomiting; but I can only say that I have found it to be an almost constant symptom in bad attacks, and something of a guide as to the severity of the complaint; I have recorded a case (Case 12) in which there was little or no vomiting.*

This symptom is regarded as constant by Bérenger-Féraud. He says: "the vomiting is bilious, of a decided green colour; it is a constant symptom at the outset of an attack. It stains the linen of a bright green, and when collected in a basin is of a beautiful green or olive colour."†

In Easmon's case, before referred to, he states that the patient vomited a clear green fluid which contained particles like chopped spinach.

Fisher (*Guy's Hospital Gazette*, 1897) states that vomiting does not appear if the patient has an empty stomach, or if he has, some hours previously to the hæmoglobinuria, been put on a milk diet; I cannot say that this has been my experience.

Other Symptoms.—Amongst the other symptoms that go to make up an attack of blackwater fever, the following may be mentioned. Frequently there is severe headache, also pain in the loins and limbs. Patients often complain of numbness of the extremities.

Usually, there is also pain in the liver and spleen; both these organs are often enlarged.

Constipation is usual at the outset of the complaint, but later, there is danger of severe diarrhœa, especially if too active purgation has been employed; when this occurs, it will of course increase the patient's exhaustion, and cause special symptoms of its own, such as colic, straining and smarting at the anus. In one of my cases, the motions were frequent, and towards the end they became reddish in colour—due, I take it, to hæmorrhage in the bowel; melaena is said occasionally to have occurred. Often there are oppression at the chest, sighing and shallow breathing, due, I think, to the patient's anæmia.

The persistent vomiting at times causes severe gastralgia and general discomfort; and to it, no doubt, is due the excessive thirst which is so frequent. Finally, in many of the worst cases, continuous hiccough is present.

Having enumerated the symptoms of blackwater fever,

* *Notes on the Malarial Fevers met with on the River Niger*, p. 84.

† Bérenger-Féraud (L. J. B.), *De la fièvre bilieuse mélanurique des pays chauds comparée avec la fièvre jaune; étude clinique faite au Sénégal*, p. 123.

I do not think I can do better than put before you a clinical picture, describing a typical first attack as I have experienced it.

The patient, usually an adult male, is passed in England as being sound. He is sent out to Africa, and possibly goes ashore for an hour or two at Sierra Leone; some fortnight later he arrives at his destination, usually quite well, but not infrequently feeling rather heavy and bilious on account of the discomfort of the voyage, and the want of exercise on board ship; another cause of his malaise may be over-eating, or taking too much alcohol.

At first, the climate—to the new-comer—feels exhilarating, and the complete change of mode of life and surroundings is agreeable. Within a few weeks, an attack of fever supervenes; the patient may have a rigor, then a hot stage and profuse sweating. Sometimes the first attack is so severe that the sufferer loses heart, becomes useless, and has to be invalided home.

If not, he soon feels better and gets about; probably leaves off his quinine, and long before health is thoroughly re-established, returns to duty which necessitates exposure to the sun and the night air. In a few weeks he becomes ill, and is treated successfully only to fall ill again; perhaps he suffers from "bilious remittent fever," as it is called, *i.e.*, he has a severe malarial attack, with vomiting and some jaundice, and the urine contains bile.

After four or five attacks of fever, either ordinary or bilious, remittent in character, with perhaps several days when he has felt out of sorts and chilly, but has not taken his temperature, and has kept about his work, he becomes cachectic, irritable and thin, his spleen is perhaps enlarged, he is constipated, and he often feels "liverish" and out of sorts.

Later on, you get a message that he has blackwater fever. On arriving, you find him lying in bed looking pinched, jaundiced, and ill; his tongue is broad, flabby and furred, and perhaps stained green from his vomit; he complains of headache, shortness of breath, nausea, and frequent vomiting, pains in his back, and in his abdomen, especially about his liver and spleen; he is much alarmed at the colour of his urine, which in bulk looks nearly black, and which in a test-tube is seen to be dark red in colour, and when boiled is found to be loaded with albumen.

He gives the following history: he felt unwell for a few days, but did not take much notice of it, and took little or no quinine. Two days ago he felt worse—had a rigor,

perhaps—and went to bed recognising that he had a severe fever. Next day he was somewhat better, but still feverish. That night there was a row in camp, and he got up to see what it was, and felt chilled, and took some quinine which he promptly vomited. This morning he had a severe rigor, followed by a rise in temperature to about 104 F., and he noticed he was jaundiced, and that the next urine passed was deep red in colour or almost black; that his vomiting was severe, and that the vomited matter was of a decided green colour.

The patient is obviously ill, and something must be done.

He is possibly constipated, and so an enema and cholagogue purge is given. Quinine is given very freely by the mouth, for the constant vomiting makes treatment very difficult; and even when the drugs are retained, one feels doubtful whether the inflamed mucous membrane absorbs the whole of them. However, the treatment is persevered with, and with the aid of bicarbonate of soda and morphia, eventually the vomiting is relieved and some food is kept down. The temperature drops to about normal within six hours of the blackwater symptoms; on the two following days it rises to about 102 F. The urine, which never gets scanty, in the course of twenty-four or thirty-six hours clears, the jaundice which deepened at first rapidly disappears, and soon the patient gets better.

Now let me shortly describe a case ending fatally:—

The patient had been up country for four days; but feeling very unwell he came down the river in an open canoe, and was much exposed to the sun; he had a severe rigor followed by fever, jaundice, vomiting, and dark urine.

When seen he is greenish-yellow in appearance, is dulled and apathetic, the urine is scanty and dark red in colour, and rather thick, and it is passed with some difficulty.

Frequent nausea is complained of, which is only relieved for a few moments by copious vomiting. There are pain and numbness in the calves and back, the abdomen is somewhat distended; pressure over the liver and spleen—which do not appear to be greatly enlarged—gives severe pain and causes fresh vomiting.

There is considerable difficulty in breathing, and the pulse is frequent and small, and there is intense thirst.

The case gradually gets worse and worse, in spite of treatment; the urine becoming more and more scanty, till at last only a few drops can be drawn off by the catheter;

hiccough is severe, and in about a week patient dies in a comatose condition.

There are some further points connected with the clinical aspect of the question to which I would direct your attention.

Cases occurring before six months have been spent in Africa are very rare, and first attacks are uncommon—though by no means unknown—after the third year spent in Africa.

Bérenger-Féraud states that out of 100 cases of this disease in the hospitals of Senegambia, the percentage of first-year cases was 5.4; of second-year cases 22.5; of third-year cases 42.5; there being after the third year a gradual decrease.*

Hence it appears to be the rule that before an attack of hæmoglobinuria supervenes on an ordinary malarial attack, the patient must have become more or less broken down or debilitated by previous fevers. Malarial patients, who are also cachectic from other causes, *e.g.*, dysentery, are also predisposed to the disease.

I have not come across a single case in which people who have taken quinine regularly as a preventive of fever have been attacked with blackwater fever. As a rule, it will be found that the patient neglected the early stages of his attack; and there is often some special aggravating cause also to be noted, *e.g.*, exposure to the direct rays of the sun, or to chilling breezes while suffering from slight fever; but this is not always present, and occasionally a fever beginning like an ordinary one may develop blackwater symptoms without any apparent cause; in these patients there is usually marked cachexia previously.

In many of the most virulent cases the patients have resided on or near a plantation, or have been employed upon works which have necessitated excavation of the soil.

Plehn cites a fatal case—Case 7—in which the patient, a young missionary, who had lived for two years in the Cameroons, latterly suffered from several slight attacks of fever, but had never before had blackwater fever. During the last days before his attack he had been gardening a good deal; the onset of the attack the patient attributed to violent mental agitation caused by a dispute with another

* Bérenger-Féraud (L.J.B.) *De la fièvre bilieuse mélanurique des pays chauds comparée avec la fièvre jaune; étude clinique faite au Sénegal*, 1874, p. 109 (not p. 107, as stated in *Plehn, Kamerun-Küste*, p. 106.)

missionary* (I would myself attribute the attack to the disturbance of the soil rather than to that of his mind).

A rigor usually precedes the onset of the blackwater symptoms; this is not, however, as is often stated, the true beginning of the disease; the patient has almost invariably more or less fever for at least a day or two previously.

The hæmoglobinuria usually passes off gradually in two or three days, and rarely returns during the attack. Occasionally, however, a succession of rigors occur, and the urine is only hæmoglobinous for a short time after each rigor. Davidson gives an account of such a case.†

Cause of Death. — There are two main causes of death:—

1. Suppression of the urine from secondary nephritis set up by the passage of hæmoglobin through the kidneys; the urine is scanty, and there is hæmaturia followed by suppression and uræmia; this has been put down to quinine poisoning, but the patients are often only first seen by the medical man when this condition is already established, and not infrequently before they have taken any quinine. Frequently also they are able to retain very little quinine when it is administered.

2. Exhaustion. Anuria may be present, but it is due to the collapse. In these cases the urine becomes clear, but there is profuse perspiration; the pulse becomes feeble, and the patient gradually sinks. The urine is scanty, as in all cases of collapse, and it may be almost suppressed, but it does not contain blood.

In certain cases, patients are stated to have died from shock due to the enormous destruction of the red discs.

The mortality in Nigeria due to blackwater fever appears to be about 20 per cent. of those attacked.

That the death-rate is high is hardly surprising, when we consider that in opening up a savage country like Nigeria, many men are necessarily cut off for days or weeks from their medical officers, and that proper hospitals and nursing are often absent. In addition to this, the well-known prejudice against quinine, and the folly and excesses of some men, must be taken into account.

* Plehn (F.) *Die Kamerun-Küste. Studien zur Klimatologie, Physiologie und Pathologie in den Tropen*, 1898. pp. 112, 113.

† *Hygiene and Diseases of Warm Climates*, p. 181.

Subsequent Attacks.

Two kinds must be recognised :—

I. *True Relapses.* —These may occur within about a week of the primary attack; it is well known that such relapses are liable to take place with ordinary African fevers, if the patient has got about too soon and has been inadequately treated. The same thing may occur in blackwater fever. These should not, in my opinion, be called second attacks, as they occur before the patients are well: sometimes, while they are still in bed; they are usually mild as to the amount of hæmoglobinuria, but on account of the great prostration of the patients are not without danger.

II. *True Second Attacks or Recurrences.*—A patient who has had blackwater fever is more liable to suffer from the disease than one who has not. This is especially true if he stays in tropical Africa after the attack, for he will probably remain in the cachectic condition which renders him liable to a recurrence; and even after restoration to health by a holiday in England, on his return to Africa, if he gets into the old condition of cachexia, he is very likely to suffer from a fresh attack.

Moreover, second attacks or recurrences may occur without fresh infection in a manner precisely similar to ordinary malaria; thus, such an attack may occur on the voyage home or in England. Second attacks are usually more fatal than primary, and third attacks are worse still; but in rare cases, after two or three attacks, some kind of tolerance seems to be developed.

It will now be seen that the distinction which I intend to convey by using the words "relapse" and "recurrence" is important: a relapse is usually slighter, and a recurrence more severe than the primary attack. Moreover, confusion between the two leads to fallacious statistics. Thus, a man may say that he has had four attacks of blackwater fever, three of which occurred in two weeks, and the other one and a-half years later. This I regard as only two distinct attacks, two relapses having occurred in the first blackwater fever.

Examination of the Blood.

The difficulties of obtaining reliable information are very great. A medical man is at a great disadvantage; he is frequently worn out with nursing or sickness, and has little

energy left for scientific inquiry. Owing to the difficulties of porterage, often he cannot carry a large microscope and outfit with him.

As an instance of his difficulties, I may mention that when the Brass men raided our port on the Niger in 1895, they annexed everything they could, and amongst other things, our microscope, which is now, I understand, decorating a Fetish temple; and no doubt my operating case—which was also carried off—has performed a not-unimportant part in the sacrifices which were said to take place almost every day.

Since Manson's ingenious device of spreading large films with the aid of cigarette paper, the examination of blood specimens has been rendered much more easy. The method has been elaborated by Pakes and Howard; and I strongly advise anyone interested in this subject to read the plain and definite rules for spreading and fixing and staining blood films, published by them in the *Journal of Tropical Medicine* for February 1899.

Even when the observer is competent, and his methods are good, and though he feels certain that the patient is malarious, yet in the peripheral blood it may be almost impossible, without prolonged observation, to find a single parasite.

Now it is well known that the parasites of the æstivo-autumnal group are only present in the peripheral circulation during their earlier unpigmented stage of development, and even then in comparatively small numbers; and that most of the reliable work on their morphology and development has been done in Italy, where opportunities of examining blood aspirated from the spleen, or fixed in sections of organs obtained from post-mortem examinations, are available. In Africa it is scarcely justifiable to aspirate the spleen for scientific purposes, and the number of properly worked out post-mortem examinations are few.

Still, in spite of these difficulties, parasites have been found in the peripheral blood in cases of blackwater fever, and the more constantly the more competent the observer; they resemble the æstivo-autumnal group in that, until now, only young unpigmented forms have been found in the peripheral circulation. Whether identical with one of the three varieties already described as occurring in Italy, or distinct from them, remains to be worked out, and this can only be done by finding older forms in the blood of internal organs.

F. Plehn, who has done so much good work in this

connection, has described an organism found in the blood, apparently identical with that found in ordinary malaria in Africa; and recently A. Plehn* has recognised the identity of the parasites so described with the æstivo-autumnal parasite.

Mannaberg, referring to blood examination in this disease, gives us the following warning:—"Regarding blackwater fevers in which the search for parasites proves negative, it is to be remarked that this proves little when the blood is not examined at the very beginning; less when the patient has already taken quinine."†

Manson says:—"Plasmodia have been found in the blood and organs; they are small, and rarely sporulate in the peripheral blood, belonging doubtless to some form of the crescent-forming malignant type."

In three slips which I recently took from a patient in England suffering from blackwater fever, we found nine small circular unpigmented parasites with vesicular nucleus about one-fourth the size of a red corpuscle. I think you will agree that, so far as microscopical examination of peripheral blood is concerned, they are indistinguishable from the unpigmented æstivo-autumnal parasites observed in Italy.

Pathology.—Having thus laid before you, to the best of my ability, the known facts relating to this disease, I think that we are in a position to discuss the vexed question of its true nature and epidemiology. Four main views have, from time to time, been propounded.

These views are as follows:—

1. That the disease is nothing more nor less than quinine poisoning.

2. That the disease is not malarial, but is a distinctive entity, and one which is especially liable to attack those who are debilitated from malarial and other causes.

3. As far as I can follow Sambon, he appears to believe that the disease is the same as paroxysmal hæmoglobinuria.‡

4. That the disease is a complication of malaria. This is the view which I have always advocated, and one which, I venture to think, is held by nearly all those who have had extensive clinical experience of it; especially, I would

* *Beiträge zur Kenntniss von Verlauf und Behandlung der tropischen Malaria in Kamerun.* Berlin, Hirschwald, 1896.

† *Die Malaria-Krankheiten,* 1899, p. 225.

‡ *British Medical Journal,* September 24th, 1898, p. 868.

mention Easmon, the first British subject, I believe, who described the disease.

1. Koch's theory is that the disease is not a malarial one at all, but that it is directly due to the administration of quinine; but he further says that, although no case came under his notice in which quinine poisoning could be discarded, yet that he would not go so far as to say that all cases are due to quinine poisoning.*

In answer to this, I can say confidently that I have seen cases of blackwater fever in which no quinine has been taken. Dr. Cargill has reported cases to me which bear out this statement. Recently in England I have seen a case of blackwater fever, in which the patient had taken no quinine before the blackwater symptoms set in. This case is of considerable interest, for the patient, though he had many attacks of ordinary fever in Africa, and for which he had taken large doses of quinine, never had blackwater fever till he developed it some days after he had arrived in England, in bitter weather, debilitated with fever and dysentery, and when he did not take quinine. A further point of interest is that while taking quinine by the mouth he had a slight relapse; the acid-hydrochloride of quinine was then administered in large doses hypodermically, and was continued for some days, and yet there was no further hæmoglobinuria, and the patient ultimately recovered from the subsequent anæmia as well as from his dysentery.

Again, Surgeon G. McGregor, writing to the *Guy's Hospital Gazette*, January 21st, 1899, from H.M.S. *Mosquito*, Zambesi River, after stating that he has had experience of malaria in the West Indies, in West Africa, and on the Zambesi and Shire rivers, remarks:—

"Of the so-called blackwater fever, which I regard as a pernicious form of malarial fever, I have had three cases under my care, and in all of them quinine was given in doses of 45-60 grains in twenty-four hours throughout the illness, and all recovered. And not only is quinine administered during an attack of fever, but the bluejackets here take five grains of quinine night and morning for several months at a time, and blackwater fever is rare amongst them, although they suffer from the ordinary remittent and intermittent types, but in a much less aggravated form than occurs amongst residents on shore."

Later on, he strongly asserts that bad drinking-water

* Koch (R.), *Das Schwarzwasserfieber. Arbeiten aus dem kaiserlichen Gesundheitsamte*, 1898, xiv, 308.

and the absence of regular doses of quinine account for very severe types of fever which occur on shore.

On the Niger all cases were treated with quinine, and a large percentage of these recovered; surely these cases should have got worse under quinine treatment if Koch's statement is correct.

I have personally had many attacks of the disease: in all I have taken quinine; and though in England I have taken large doses for severe fever, yet I have not again developed any blackwater symptoms. My experience is that blackwater fever comes on chiefly in those who have neglected to take quinine. I have certainly had a case in which a man who had had one attack of the disease escaped any further attacks, apparently on account of the quinine which he took regularly.

Again, many cases have been reported in which patients have recovered from the disease when heroic doses of the drug have been given; I would refer specially to the cases reported by Dr. Moffatt, Principal Medical Officer, Uganda Protectorate; out of nine cases treated two died: in both of these he says that quinine was neglected till too late; all the other cases were treated with quinine, six of them with doses of 60-120 grains in twenty-four hours (*British Medical Journal*, September 24th, 1898, p. 926).

Dr. Robson, of Birmingham, who was in West Africa for two years, writes to the *British Medical Journal*, October 22nd, 1898 (p. 1287), as follows:—

"Again, in the most severe cases of blackwater fever I have seen patients get well who have been heroically dosed. I have myself, on more than one occasion, administered 60 grains (of quinine) as a single dose with advantage. . . . . When the tropical physician has a better remedy supplied him, no doubt he will relinquish his old favourite, but assuredly not till then."

Battersby, who suffered from more than one attack on the Niger, regards this complaint as purely malarial.

Eyles gives his opinion of the disease in the following words:—

"In short, this is the view I take of blackwater fever that it is a malarial remittent fever, to which is added another malarial manifestation, viz., hæmoglobinuria; and that when this occurs there is more marked hepatic disturbance than in ordinary remittents.*

I have elsewhere referred to a case of hæmoglobinuric

* *Malarial Fevers as met with on the Gold Coast*, p. 11.

fever cited by Davidson in his book, *Hygiene and Diseases of Warm Climates* (p. 181), in which the disease was not cured till quinine had been given very freely.

I think that these quotations (and I could give many others) suffice to prove that in most cases blackwater fever is not quinine poisoning. Is it so in any cases? Cases have been recorded, chiefly in Italy and Greece, where, in certain patients, owing to some inherent susceptibility, even minute doses of quinine were able to excite an attack of hæmoglobinuria; and whenever a subsequent dose was given, whether during an attack of malaria or not, another attack took place. It is said that sometimes this has been observed in several members of the same family. It is to be noted, however, that these results are very few in number, and have only occurred where the patients lived in malarial districts and suffered from malarial cachexia; and that some have previously had blackwater fever apart from quinine, and that the result is apparently independent of the amount of quinine given, a very small dose sufficing. Also, it is to be remembered that hæmoglobinuria is never a symptom of quinine poisoning in non-malarious subjects.

These cases must be taken for what they are worth. It is possible that very occasionally quinine may cause hæmoglobinuria, but this is an idiosyncrasy, and cannot be regarded as the cause of blackwater fever in Africa, for no one would be found to assert that the African cases infallibly relapse every time a small dose of quinine is administered, as is the case with these.

2. The second theory is that blackwater fever is a distinctive entity. This view was put forward by Manson in his able paper,* the main arguments being based on the distribution of the disease. Since then, fresh facts have been brought to light; and in his recent work on tropical diseases, towards the end of his article on hæmoglobinuric fever, he speaks of it as being "the most important of the African forms of malarial poisoning." It has been pointed out that the distribution and relative prevalence of blackwater fever do not correspond with that of the æstivo-autumnal parasite; and that in some regions where the latter was very prevalent, blackwater fever was very rare or almost unknown. In answer to this I would urge two points: in the first place, since attention was drawn to the disease it has been described in regions where it was thought not to exist; thus, Dr. Arthur Powell writing

* *Transactions of the Epidemiological Society*, 1892-93, xii, p. 111.

on hæmoglobinuric fever in Assam, says: "The existence of this fever in India was denied some years ago, but whether justly so or not, it is now either undoubtedly on the increase or, perhaps, more accurately diagnosed, where formerly it was confounded with bilious remittents." After noting that Crombie says it is practically unknown in India, he goes on to say: "I now record eleven cases which occurred in this district, which were identical with the fever I have seen in those returned from the Gold Coast."*

Secondly, according to the Italian observers, æstivo-autumnal fever is by no means the entity which it is often assumed to be. No less than three distinct parasites are described, viz: malignant tertian, malignant pigmented quotidian, and malignant unpigmented quotidian. It is very possible that there may be one or more other varieties which occur in tropical Africa and which have a distribution similar to blackwater fever, and with which blackwater fever is associated. Evidence in support of this is scanty, but it will be remembered that the three kinds of Italian malignant parasites have been only quite recently differentiated; indeed, the conclusions of Italian observers are still *sub judice*, and the question can only be settled by careful examination of the blood in internal organs, where alone the later development of the malignant parasite occurs.

3. Sambon's view that blackwater fever is paroxysmal hæmoglobinuria is sufficiently demolished by the fact that parasites are found in the blood of blackwater fever.

4. We now come to the fourth alternative, viz., that blackwater fever is not a distinctive disease, but is a complication occurring in the course of malaria. I venture to think that there is a large amount of evidence in favour of this view. It is certainly the view held by most African practitioners; I will endeavour to prove that it is a reasonable and natural hypothesis. In the first place, I would assert that the one predisposing cause present in almost all cases, is that the patients are previously suffering from a pronounced malarial cachexia; this was very clearly brought out in a series of cases recorded by Dr. Arthur Powell in Assam; it is further borne out by my own nine years' experience, and by the statements of all the other West African medical men with whom I have been brought in contact; for instance, Mr. J. J. G. Whittindale, Dr. F. Cargill, and my successor, Mr. E. E. Craster.

* *The Journal of Tropical Medicine*, December 1898, p. 117.

I cannot agree with Dr. Sambon's statement, "We know of several cases now in which melanuric fever was contracted within a few weeks of landing and without any previous attack of malaria,"* and I would draw attention to the fact that this statement is apparently contradicted in another part of the paper, for I find it stated that "It is of the highest importance to note that blackwater fever is seldom a primary disease. Authors, from all parts, are unanimous in stating that the liability to infection is constantly associated with the occurrence of malaria."†

Dr. Easmon says: "It (blackwater fever) only attacks those whose healths have, for some reason or other, become deteriorated." Further, he says, "It is often preceded by simple attacks of intermittent fever, with progressive anæmia and sallowness of the countenance."‡

Charts 6-9 in my book show that between December 5th and January 30th four malarial attacks—one of which was decidedly remittent in type—preceded an attack of blackwater fever which was intermittent in character.

As further evidence, I may mention one case which came under my notice, of a new-comer who developed blackwater fever within a few months of his landing in West Africa; but in this case it was found that the patient had previously suffered from severe malaria in Burma.

This condition of cachexia may be brought about either by several definite attacks of severe malaria, or perhaps by frequent slight attacks which are at times not even severe enough to keep the patient in bed, and which are therefore neglected. In the latter case, though the patient feels a little out of sorts and chilly, he usually disregards it, and does not take his temperature; or he may take it and find it to be 100° F., swallow some antipyrin or quinine and go to bed, and then get up next day feeling rather better, and go about his work. I take it that though such a patient would tell you that he had been in good health and had had no fever, yet malarial parasites had been present in his blood the whole time; and that though his power of resistance was just sufficient to keep them from multiplying to any great extent, still, all this time they were manufacturing toxines, and thus contributing to that toxæmia to which malarial cachexia is due.

Such persons as these are the subjects who are most liable

* *British Medical Journal*, September 24th, 1898, p. 868.
† *British Medical Journal*, September 24th, 1898, p. 867.
‡ Easmon (J. Farrell), *The Nature and Treatment of Blackwater Fever*, 1884, p. 2.

to suffer from blackwater fever, and I will go further and say that I am certain that when it arises in such cachectics its occurrence is due either to excessive exposure, privation, great fatigue, to some special malignancy of the parasite, or to some indiscretion committed by the patient during an attack of ordinary malaria which might otherwise have passed off without this complication.

Cause of Hæmoglobinuria.—Before discussing the cause of the hæmoglobinuria in blackwater fever we must look at the process by which destruction of hæmoglobin in malaria ordinarily takes place. In benign tertian and quartan fevers the parasite destroys the hæmoglobin and turns it into another pigment, and when it sporulates this pigment is set free and carried to liver, spleen and brain, causing the well-known malarial pigmentation. In the æstivo-autumnal fevers the same thing occurs, but the parasites cause the rupture of the corpuscles before the hæmoglobin is completely destroyed, thus causing hæmoglobinæmia. In ordinary fevers this free hæmoglobin is taken up by the liver and changed into bile pigment, but none appears in the urine. In severe æstivo-autumnal fevers one-third of the total number of corpuscles may be destroyed in one paroxysm and yet no hæmoglobinuria occur, the result of the excessive bile formation being bilious remittent fever.

For hæmoglobinuria to occur there must be a large number of corpuscles destroyed and a large quantity of hæmoglobin set free in the blood; this is proved by the experimental hæmoglobinuria induced by certain poisons. Hence, in order to explain the occurrence of hæmoglobinuria in malaria we are compelled to assume that there is a sudden destruction of corpuscles, thus setting free the whole of their hæmoglobin. Evidence in favour of this is to be found in some of the descriptions of the result of examination of fresh blood films during an attack of hæmoglobinuria. Thus Manson speaks of the apparent ruin and wholesale solution of the red discs. What change can it be that brings about this destruction? A. Plehn suggested that it was some alteration in the specific gravity of the blood, causing solution of the red discs. I would rather suggest it was due to the accumulation of malarial toxines. As above stated, the patients are cachectic, *i.e.*, they are suffering from chronic toxæmia. Supposing anything, *e.g.*, chill, should check the excretion of toxines, they might accumulate until they were able to effect the direct destruction of the red discs. On this theory, blackwater fever is to be regarded as a special complication of malaria.

The hæmoglobinuric complication I regard as wholly analogous to chlorate of potash poisoning, and paroxysmal hæmoglobinuria. In blackwater fever the cause is probably the malarial toxine; in chlorate of potash poisoning it is sufficiently obvious; in paroxysmal hæmoglobinuria it is unknown, though it possibly is syphilitic in origin, as suggested by Copeman,* who says: "A definite specific history has been forthcoming in all the cases that have come under my own observation." The three cases are, however, only analogous. I do not for one moment suggest the identity of the causes of blackwater fever and paroxysmal hæmoglobinuria, any more than I should of blackwater fever and chlorate of potash poisoning. The hæmoglobinuria is simply the natural result of the preceding hæmoglobinæmia.

One other fact certainly is of importance in blackwater fever, as in all other poisoning cases, and that is idiosyncrasy. I believe that some persons get hæmoglobinuria with a much lower degree of malarial toxæmia than others. Some of these patients may account for the slight and frequently recurrent cases that are reported.

Another factor may come in, and that is degenerative changes in the liver, the result of malarial poisoning, which impair its bile-forming functions. It is clear that if the liver were to strike work, the hæmoglobin would not be changed into bile pigment, and that a hæmoglobinæmia, however slight, would cause hæmoglobinuria. That such, however, is not the main cause, is, I think, shown by the fact that there is much bile formed during blackwater fever, as shown by the profuse bilious vomiting and the not-infrequent bilious diarrhœa.

While not wishing to claim that the above is any more than a possible theory as to the cause of blackwater fever, yet I would submit that it is possible, and further, that it helps to emphasise what I believe to be undoubted facts—viz.: that blackwater fever is of malarial origin, and further, that it is a special complication occurring in malarial cachectics, and dependent on the destruction, by some means other than direct parasitic invasion, of the red discs and the solution of the contained hæmoglobin in the plasma.

* Allbutt's *System of Medicine*, vol. v, p. 627.

Treatment.

Having thus discussed the pathology of blackwater fever, and shown what I hold to be its connection with malaria, I come to the practical question of its treatment. In dealing with this, it will be well to remind ourselves that three distinct factors are present.

There is, in the first place, the attack of malaria during which the hæmoglobinuric paroxysm develops.

Secondly, there is the chronic malarial toxæmia which has predisposed the patient to the attack.

Thirdly, there is the sudden loss of hæmoglobin, which in its effect in no way differs from an ordinary severe hæmorrhage.

The above are present in all cases; sometimes there is another factor present in the subsequent nephritis.

It is clear that only the first of these, namely, the malaria, would yield to quinine. So far as is at present known, quinine has only a parasiticide and not an antitoxic function in malaria; and hence it cannot be relied upon for treatment of toxæmia, and obviously not for the hæmorrhage.

Quinine, therefore, should be given in blackwater fever, but with the express object of clearing the blood of the malarial parasites, and hence it should be given in full doses similar to those given in ordinary attacks of tropical malaria.

It must, however, be clearly understood that by the time a patient has reached the point of hæmoglobinuria, his tissues are probably much degenerated and his vital functions seriously lowered; hence, though we may cure his malaria by quinine, we must not be surprised should he succumb.

A cachectic patient may be unable to withstand a severe hæmorrhage; when to this is added the constant and distressing vomiting which often involves starvation, he is clearly liable to die from exhaustion, as many of the cases certainly do.

On the other hand, this is a very different thing from saying that quinine is of no use in blackwater fever. I hold that it should be always administered in doses sufficient to make it certain that the blood is freed from parasites: just as the first step in the treatment of a patient suffering from sapræmia due to retained placenta is to clear out the uterus, and so remove any danger of further infection.

As previously mentioned in this paper, it is frequently

difficult to efficiently administer quinine by the mouth on account of the persistent vomiting, and administration by the rectum is unsatisfactory. I am, myself, a strong advocate of the hypodermic administration of quinine under these circumstances; and in this practice I am supported by the profession in Italy and America—though, as far as I know, many English medical men hesitate to adopt it. The advantage of the hypodermic method is sufficiently obvious, for one can rest assured that the dose which we administer is actually absorbed.

The supposed difficulties are really hardly worth our consideration if we are thoroughly aseptic.

Sulphate of quinine is not suitable for hypodermic injection; perhaps the best salt is the acid-hydrochloride which is chiefly used in Italy: it is soluble in its own weight of water. The acid-hydrobromide which is soluble 1 in 6 of water may also be used, especially if the patient is liable to cinchonism.

Personally, when in Africa I used the lactate which is soluble (according to Squire, Seventeenth edition, 1899), 1 in 6 of water. I am inclined to think that 10 grains of quinine administered hypodermically every eight hours on the first and second day of the disease, and every twelve hours on the third day, would be a sufficient dose; after this, I suggest that five grains should be given twice a day till the end of the attack. I may mention that I always boil the solution of quinine, and inject it while it is still quite warm. When the drug cannot be administered hypodermically, larger amounts may be necessary.

In a case of blackwater fever which I recently saw in England, quinine was at first given by the mouth; the patient had a relapse; it was then given hypodermically, and the patient recovered without any further relapse.*

It is, of course, to be remembered that quinine will accumulate if the urine is either greatly reduced or suppressed, and therefore it must not be continued in the same doses should this contingency occur.

So much for the treatment of the malarial element; as regards the other two factors, the main indications are to maintain free excretion, with the view to liberating the body from the accumulated toxines, and to procure rest and nutrition which will enable recovery to take place from the anæmia.

If the bowels are not opened, a cholagogue purgative and

* Wooldridge (A. T.). A case of Blackwater fever complicated by dysentery. —*Lancet*, March 18th, 1899, p. 762.

enema should be given; but over-purgation should be avoided. I always myself administer sodium bicarbonate freely: this helps to allay vomiting and gastric pain, and makes the patient more comfortable; and, I think, does good by its diuretic action, and also helps to diminish the acidity of the urine.

Opium should be given without hesitation to procure rest. Nutrition must be maintained by rectal feeding if necessary.

Strychnine and digitalis may be necessary in cases of extreme asthenia; they will act beneficially by helping to maintain the renal blood pressure, and therefore the secretion of urine: for, doubtless, some of the cases of anuria occurring in blackwater fever are the result of collapse and not of nephritis.

If nephritis occurs, the usual remedies are to be adopted, but caution should be used in the administration of such depressing drugs as pilocarpine, from the use of which I have certainly seen disastrous results; if it is decided to administer this drug, not more than one-sixth of a grain should be given at one time.

After recovery, the patient ought to be advised to take a holiday, if possible, in England; and should not return, at any rate, until he has completely recovered from his anæmia and cachexia. Indeed, on general principles it is probably desirable that no one should return to Africa after an attack. This is particularly the case where the blackwater fever has developed in spite of precautions, but applies less to those cases where the attack can be traced to exceptional hardship and privations, which are not likely to be repeated.

Those who, from one cause or another, cannot stand quinine, and those who suffer from even slight albuminuria, should not be selected for malarious climates.

Finally, I urge that the prophylaxis of blackwater fever by habitual use of quinine will be found to be more hopeful than its treatment.

I have come to the definite conclusion that, besides adopting precautions in regard to exposure to chills, wet, and to the sun, and as to moderation in food, alcohol, and sexual matters, every resident in the more malarious parts of Africa should take at least five grains of quinine each day.

In the large majority of cases I believe that this would prevent the chronic malarial poisoning which is the predisposing cause of blackwater fever; and would do much to eliminate this scourge from our colonies.

History of Case.

A. B., 26 years of age, had resided for 14 months in Nigeria, and during that time he had had many attacks of malarial fever and three of dysentery; he also suffered from fever on the voyage home. On his arrival, on November 25th, he was suffering from dysentery and had taken a severe chill.

November 26th, went to bed; took no quinine till the morning of the 27th, when he swallowed and promptly vomited a five-grain tabloid. He had a severe rigor on the 27th, at 11 A.M., and the urine became hæmoglobinous at noon on the same day. There was a slighter rigor on the 28th. Jaundice and green vomiting were marked on the 27th, 28th and 29th.

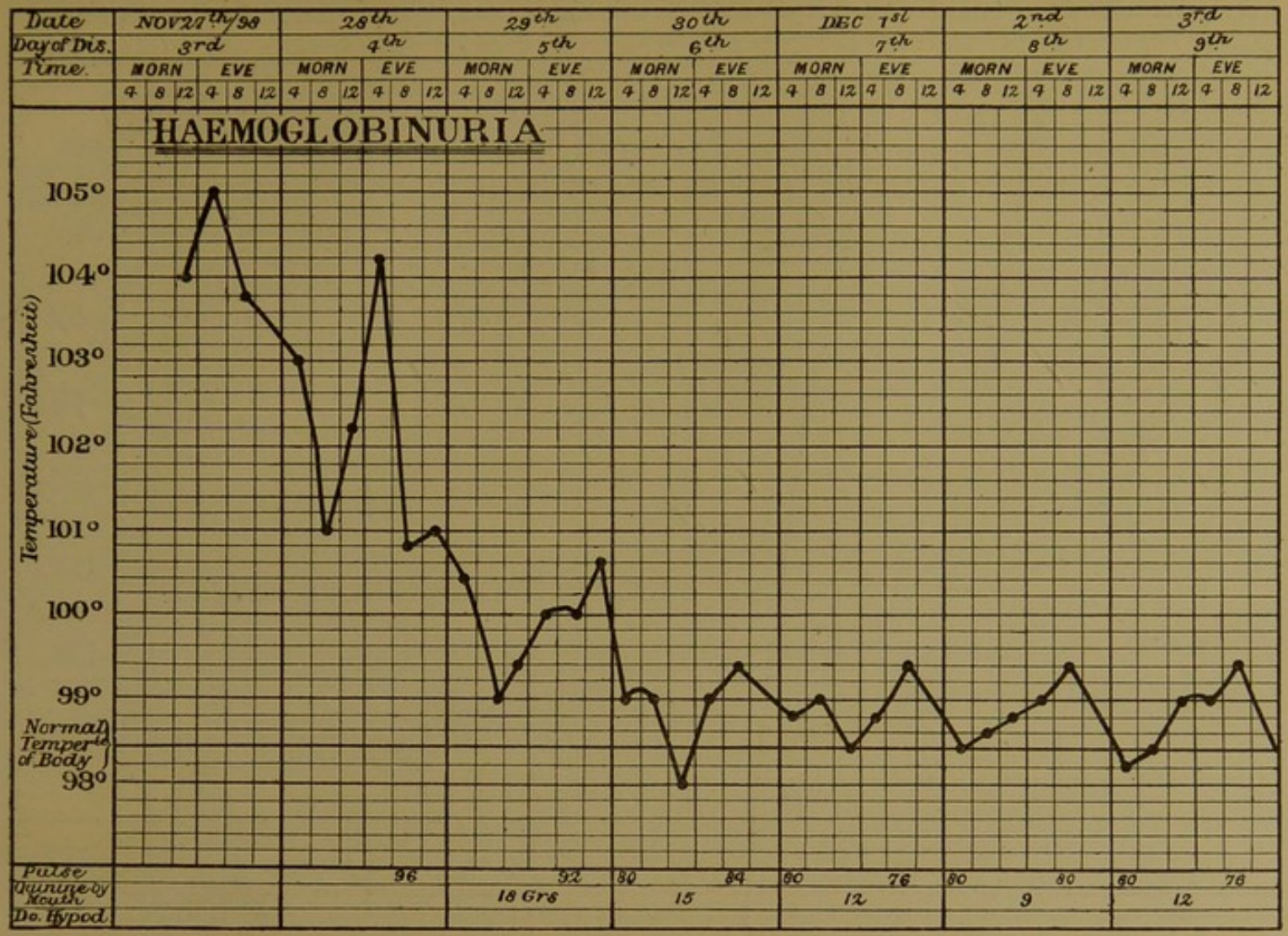
December 4th, patient became more sallow in appearance. December 5th, the urine passed between 4 P.M and 8 P.M. was hæmoglobinous.

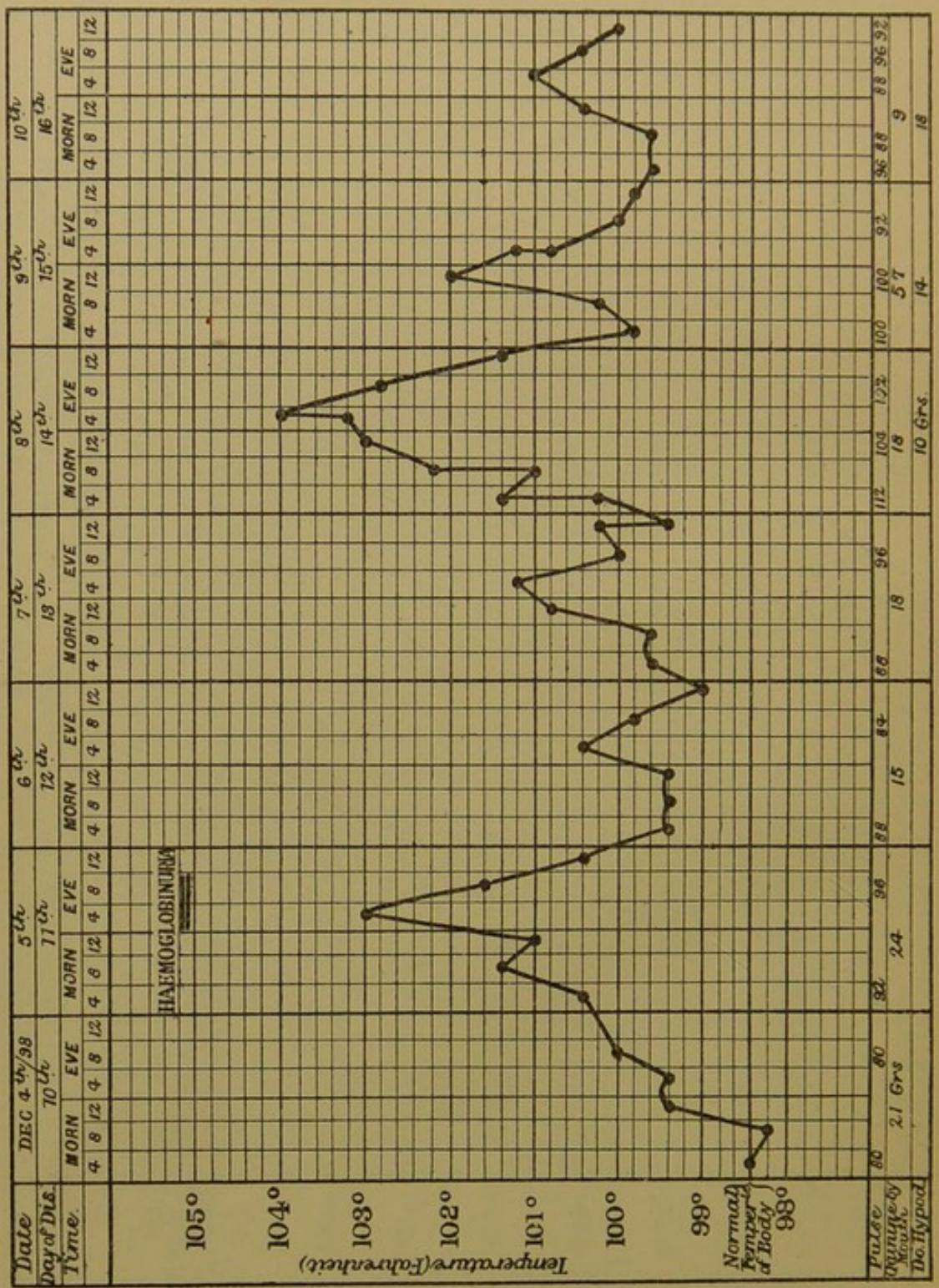
December 8th, as the temperature was rising, quinine was given hypodermically and by the mouth. After this there was no more hæmoglobinuria, and the patient gradually convalesced, his recovery being retarded by his dysentery and anæmia, and by a slough caused by one of the hypodermic injections of quinine, this being the only one out of fourteen which caused any trouble. There was no tendency to suppression of the urine except on November 29th, when only sixteen ounces were passed; bicarbonate of soda was then administered, and thirty-three ounces of urine were passed on the next day.

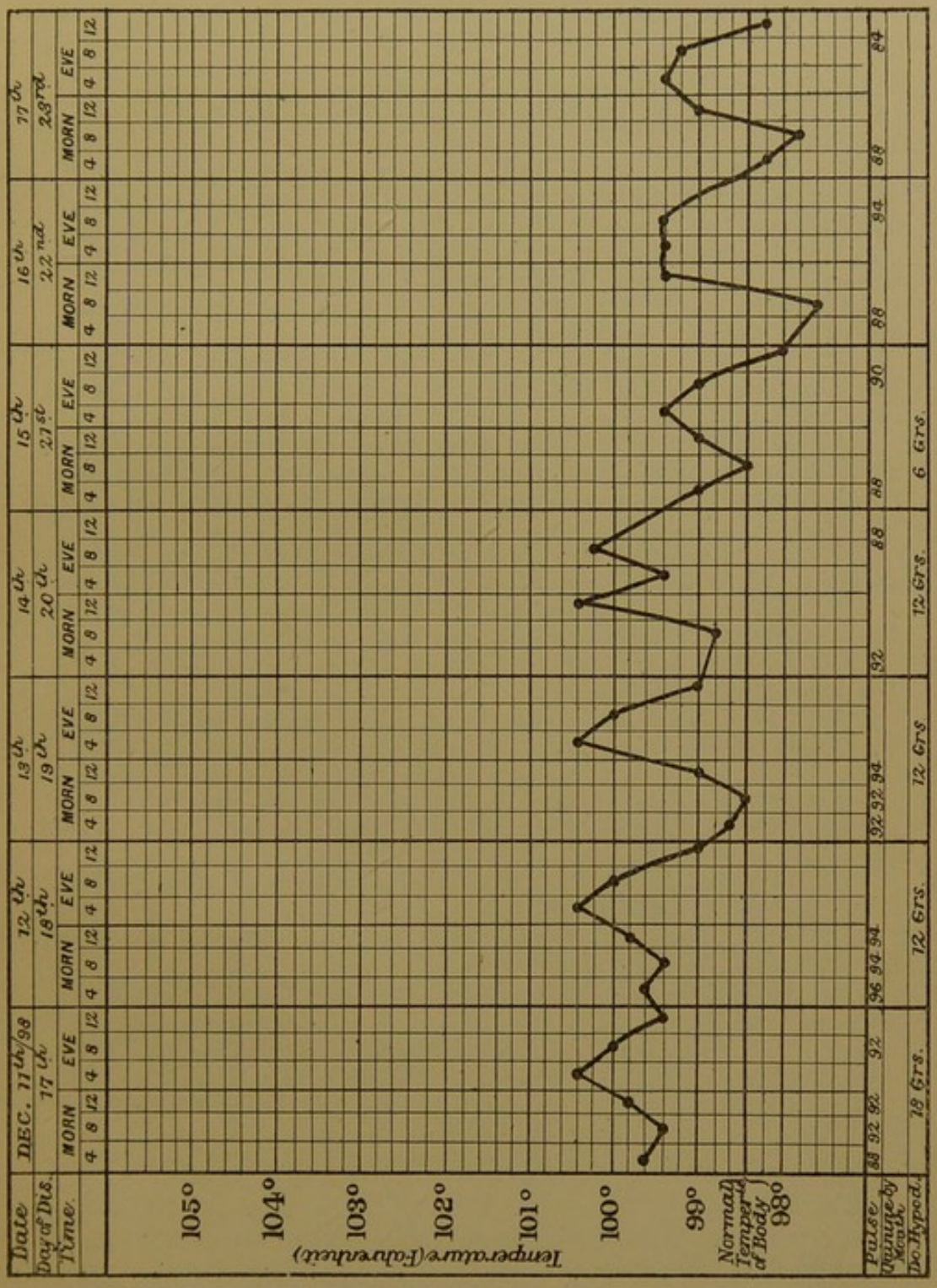
Quinine taken before the attack	...	None.
Quinine taken to end of December 5th, hypodermically	...	None.
„ „ „ by the mouth	...	111 grs.
Quinine taken from Dec. 6th to 15th, by the mouth	...	117 „
„ „ „ hypodermically	...	102 „

Total—by mouth 228 grs.; hypodermically, 102 grs. = 330 grs.

In this case it cannot be said that quinine caused the attack, nor is it likely that it had anything to do with the slight relapse.


HAEMOGLOBINURIA
Date
Day of Dis.
Time.
NOV 27th/98
3rd
28th
4th
29th
5th
30th
6th
DEC 1st
7th
2nd
8th
3rd
9th
MORN
EVE
4 8 12 4 8 12
Temperature (Fahrenheit)
105°
104°
103°
102°
101°
100°
99°
Normal Temperature of Body
98°
Pulse
Quinine by Mouth
Do. Hypod.
96
92
80 84
80 76
80 80
80 76
18 Grs
15
12
9
12


Date
Day of Dis.
Time.
DEC 4th/38
5th
6th
7th
8th
9th
10th
MORN
EVE
HAEMOGLOBINURIA
105°
104°
103°
102°
101°
100°
99°
98°
Temperature (Fahrenheit)
Normal Temperature of Body
Pulse
Urine
Do. Hypod.
2.1 Grs
24
15
18
10 Grs.
14
18


Date
DEC. 11th/98
12 Dr
13 Dr
14 Dr
15 Dr
16 Dr
17 Dr
Day of Dis.
17 Dr
18 Dr
19 Dr
20 Dr
27st
22nd
23rd
Time.
MORN
EVE
4 8 12 4 8 12
Temperature (Fahrenheit)
105°
104°
103°
102°
101°
100°
99°
98°
Normal Temper. of Body
Pulse
88 92 92 92
96 94 94
92 92 94
92
88
88
90
88
94
88
84
Quinine by Mouth
18 Grs.
12 Grs
12 Grs
12 Grs.
6 Grs
Do. Hypod.

BIBLIOGRAPHY.

1824. Isoard. "Dissertation on the Fever of Guinea, preceded by the Medical Topography of that country, *Lond. M. Reposit.*, 1824, xxii, 189-202.

1831. Boyle (J.). "A Practical Medico-Historical account of the Western Coast of Africa, together with the Causes, Symptoms, and Treatment of the Fevers of Western Africa," etc. 8vo. London, 1831.

1837. Macdiarmid (J.). "On Malignant Remittent Fever (West Coast of Africa)", *Lond. M. Gaz.*, 1837-8, xxi, 441.

1838. Labarre (J. M.). "Considérations sur les fièvres intermittentes d'Afrique." 4to. Paris, 1838.

1843. Pritchett (Morris). "Account of the African Remittent Fever on board H.M.S. *Wilberforce* in the river Niger, and Inquiry into the Causes of Disease in Tropical Climates." 8vo. London, 1843.

1846. Kellogg (S. W.). "An Account of the African Fever as it prevailed on board the U. S. ship *Preble* during her late Cruise, with an Abstract of Forty-three Cases," *N. York J. M.*, 1846, vi, 178, 377; vii, 51.

1847. Lugenbeel (J. W.). "The Acclimating Fever of Western Intertropical Africa," *Boston M. and S. J.*, 1847, xxxvii, 409-412.

1848. Kehoe (T.). "Observations on the Fever of the Western Coast of Africa," *Dublin Q. J. M. Sc.*, 1848, vi, 316-345.

1851. Landor (H.) "On the African Fever," *Prov. M. and S. J.*, London, 1851, 293-295.

1850-1852. Roe (P.). "Remarks on the Symptoms and Treatment of Gambia Remittent Fever (West Coast of Africa), from 1st of April, 1850, to 31st of March, 1852," *Dublin M. Press*, 1852, xxviii, 52, 67.

1851-1855. Ford (H.A.). "Some Observations on the Fevers prevalent on the West Coast of Africa, made at Gaboon, from 1851 to 1855," *N. York J. M.*, 1855, N. S., xv, 169-195.

1855. Hayne (L. J.). "On the Endemic Fevers of Africa," *Med. Times and Gaz.* London, 1855, N. S., x, 280-282.

1856. Ford (H. A.). "Observations on the Fevers of the West Coast of Africa." 8vo. New York, 1856.

1857. Baikie (W. B.). "On African Remittent Fever," *Edin. M. J.*, 1857, ii, 803-815.

1859. Clark (W. H.). "African Fevers, Intermittent and Remittent," *South M. and S. J.*, Augusta, 1859, N. S., xv, 172-176.

1859. Legrand (A.). "Un mot sur les Fièvres Intermittentes d'Afrique," *Gaz. d. Hôp.* Paris, 1859, xxxii, 2.

1861. Eames (W. J.). "Fever on the Niger," *Lancet.* London, 1861, ii, 604.

1865. Barthélemy-Benoit (P. E.). "De la fièvre bilieuse hématurique observée au Sénégal," *Arch. de Méd. Nav.* Paris, 1865, iv, 5, 105, 209, 298, 379.

1866. Chabbert (E. J. A.). "De la fièvre bilieuse hématurique observée au Sénégal." 4to. Montpellier, 1866.

1869. Ducroquet (L. F. T.). "Quelques considérations sur les fièvres intermittentes pernicieuses d'Afrique." 4to. Paris, 1869.

1869. Dudon (J. C.). "Notes et observations sur les affections paludéennes à la côte occidentale d'Afrique." 4to. Paris, 1869.

1873. Hunter (J. M.). "On the Remittent Fever of the West Coast of Africa," *Brit. M. J.* London, 1873, ii, 629.

1874. Bérenger-Féraud. "De la fièvre melanurique des pays chauds," etc. 8vo. Paris, 1874.

1874. Donnet (J. J. L.). "Notes and Practical Observations upon the Remittent Fever and Dysentery of the Gold Coast," *Lancet*, 1874, i, 227-230.

1878. Ritzzo-Matera (S.). "Intorno alla cura della febbre biliosa ematurica," *Osservatore Med.*, Palermo, 1878, 3. s., viii, 385-415.

1879. Meek (J. W.). "Malarial Hæmaturia," *Am. M. Bi-Weekly*, Louisville, 1879, x, 196

1879. O'Daniel (W.). "Malarial Hæmaturia," *Tr. M. Ass.*, Georgia, Atlanta, 1879, xxx, 183-186.

1879. Hammonds (J. D.). "Malarial Hæmaturia," *N. Orl. M. and S. J.*, 1879-80, N. S., vii, 169-172.

1879. Hand (D. H.). "Icterus: Hematurial Fever, or Malarial Hematurial Fever; History of its Rise, Symptoms, and Progress in South-west Georgia," *Eclect. M. J.* Atlanta, 1879-80, i, 87-90.

1880. Allan (W.). "Note on the Remittent Fever of the West Coast of Africa, with Remarks on Treatment," *Dublin J. M. Sc.*, 1880, 3 s., lxix, 404-406.

1880. Allan (W.). "Clinical Note on Eruptions occurring in the Febris Intermittens of West Africa," *Ibid.*, 1881, 3 s., lxxi, 89-91.

1880. Blancho (J.). "Fiebre intermitente complicada con ictericia," *Andalucia, Méd.* Cordoba, 1880, v, 27-29.

1880. Gist (J. M.). "Malarial Hematuria," *Arkansas M. Month.* Little Rock, 1880, i, 402.

1880. Greene (J. M.). "Malarial Hematuria," *Tr. Mississippi M. Ass.* Jackson, 1880, xiii, 106-115.

1880. Latière (Emile Victor Léon). "De la fièvre bilieuse mélanurique." Paris, 1880. 86 pp. 4to. No. 444.

1880. Malone (G. B.). "Malarial Hæmaturia," *Tr. M. Sc. Arkansas*, Little Rock, 1880, v, 74.

1880. M'Mahan (W. R.). "The Icteric Form of Pernicious Fever," *Tr. Indiana M. Soc.* Indianapolis, 1880, xxx, 26-34.

1881. Bradley (E. G.). "Malarial Hæmaturia, or Swamp Fever," *Mississippi Valley M. Month.* Memphis, 1881, i, 157-161.

1881. Brejon (Fernaud). "Du diagnostique differentiel de l'hématurie et de l'hémoglobinurie, principalement dans quelques maladies endémiques des pays chauds." 4to. Paris, 1881. 36 pp. No. 193.

1881. Corre (A.). "De l'hémoglobinurie paroxystique et de la fièvre bilieuse mélanurique ou hématurique des pays chauds," *Arch. de Med. Nav.* Paris, 1881, xxxv, 161-181. Also Reprint.

1881. Jacobs (J.). "Eenige Beschouwingen over Febris biliosa hæmaturica," *Geneesk. Tijdschr v. Nederl. Indie.* Batav., 1881, N. S., x, 669-678.

1881. Machado (A.). La Fiebre biliosa hematúrica en los Llanos de Venezuela," *Union Méd.* Carácas, 1881, i, 116, 124, 131, 139, 145, 166; 1882, ii, 16, 28, 29, 44.

1881. Malone (G. B.). "Malarial Hæmaturia" (a reply to E. G Bradley's Article in April number of this Journal), *Mississippi Valley M. Month.* Memphis, 1881, i, 253-259.

1881. Malone (G. B.). "Malarial Hæmaturia," *Mississippi Valley M. Month.* Memphis, 1881, i, 62-71.

1881. Sorel. "Note sur un cas de fièvre tellurique avec hématurie intermittente," *Union Méd.* Paris, 1881, 3 s., xxxii, 217-220.

1881. Thompson (J. E.). "Malarial Hæmaturia," *St. Louis Cour. Med.*, 1881, v, 277-282.

1882. Bérenger-Féraud. "Note sur deux cas de fièvre bilieuse mélanurique observés à l'Hôpital maritime de Cherbourg," *Arch. de Méd. Nav.* Paris, 1882, xxxviii, 297-302.

1882. Karamitas (G.). "Sur la fièvre hémosphérinurique palustre" (Abstr.), *Arch. de Med. Nav.* Paris, 1882, xxxviii, 153-156.

1882. Pineau (E.). "Un cas de fièvre mélanurique observé sur les côtes de Saintonge," *Union Méd.* Paris, 1882, 3 s., xxxiv, 409-414.

1882. Ritzzo-Matera (S.). "La chinina e la febbre itteroematurica," *Bull. d. Sc. Med. di Bologna*, 1882, 6 s., ix, 236-249, 289-310.

1883. Bland (J. J.). "Malarial Hæmaturia," *South Pract.* Nashville, 1883, v, 300-4.

1883. Helimenas Finol. "Un caso de fiebre ictero-hematurica," *Rev. Méd. Quir.* Maracaibo, 1883-4, i, No. 5, 10.

1883. Joiner (B. E.). Hæmaturic Fever," *South Pract.* Nashville, 1883, v, 62-67.

1883. Malone (G. B.). "Treatment of Malarial Hæmaturia," *Mississippi Valley M. Month.* Memphis, 1883, iii, 433-435.

1883. Moore (G. H.). "Malarial Hæmaturia," *Mississippi Valley M. Month.* Memphis, 1883, iii, 65-68.

1883. O'Daniel (W). "Malarial Poisoning, the Cause of Hæmaturia," *Tr. Georgia M. Ass.*, 1882. Augusta, 1883, xxxiii, 180-193.

1883. Tyson (J.). "Clinical Lecture on Remittent Fever complicated with Hæmaturia and Typhoid Symptoms," *Phila. M. Times*, 1883-4, xiv, 301-303.

1883. Tyson (J.). "Malarial Hæmaturia," *Med. News.* Philadelphia, 1883, xlii, 519-522.

1883. Tyson (J.) "Malarial Hæmaturia and Hæmoglobinuria," *Tr. M. Soc. Penn.* Philadelphia, 1883, xv, 69-77.

1884. Easmon (J. Farrell). "The Nature and Treatment of Blackwater Fever, with Bibliography, Notes and Temperature Charts of Cases Treated," *Bibliography*, p. 10, 8vo. London, 1884.

1884. Menger (R.). "Was it Malarial Hæmaturia?" *Texas Cour. Rec. Med.* Fort Worth, 1884-5, ii, 18.

1884. Vandein (Achille). "De la fièvre bilieuse mélanurique observée à Mayotte" (Mozambique). Paris, 1884, 85 pp., 2 pl., 4to, No. 210.

1885. De Sanctis (G.). "Casuistica sulla febre ittero-emoglobinurica," *Gaz. Med. di Torino*, 1885, xxxvi, 505, 539, 562, 577, 601.

1885. Dial (J. J.). "Report of a Case of Malarial Hematuria," *Texas Cour. Rec. Med.* Fort Worth, 1885-6, iii, 187-189.

1885. Easmon (J. F.). "Notes of a case of Blackwater Fever, with Remarks" ("Fièvre bilieuse mélanurique ou hématurique" of French writers), *Med. Times and Gaz.* London, 1885, ii, 277-280.

1885-1886. Fornét (E. K.). "Hämoglobinuria paroxysmalis" (Transl. from *Groosi Hetil.*, 1885, No. 52, Extr.), *Pest. Med. Chir. Presse.* Budapest, 1886, xxii, 255-257.

1885-1886. Furniss (J. P.). "Hæmorrhagic Malarial Fever or Intermittent Hæmoglobinuria (?) in an Infant," *Virginia M. Month.* Richmond, 1885-6, xii, 362.

1885-1886. Humphreys (B. F.). "The Prophylaxis of Malarial Hæmaturia," *Texas Cour. Rec. Med.* Fort Worth, 1885-6, iii, 487, 494.

1885. Landa (G. M.). "Reflexiones sobre un caso de fiebre biliosa mélanurica," *Enciclopedia.* Habana, 1885, i, 459-464.

1885. McHatton (H.). "Clinical History of a Case of (so-called) Malarial Hæmaturia," *Atlanta M. and S. J.*, 1885-6, N. S., ii, 412-415.

1885. Minella (F.). "Storia di un caso d'ematuria parossistica d'origine miasmatica," *Gazz. Méd. di Torino*, 1885, xxxvi, 35-38.

1885. O'Daniel (W.). "Malaria and its Toxic Influences. Malarial Hæmaturia." Atlanta, Ga. 1885, J. P. Harrison and Co. (Repr. from *Tr. Georgia M. Ass.*).

1885. Owen (W. G.). "Malarial Hæmaturia treated with Quinine Hypodermatically," *Med. News Phila.*, 1885, xlvi, 6.

1885. Perry (J. W.). "Malarial Hæmaturia," *Texas Cour. Rec. Med.* Fort Worth, 1885-6, iii, 244-250.

1885. Thompson (O. M.). "Malarial Hæmaturia, or Swamp Fever," *Nashville J. M. and S.*, 1885, N. S., xxxv, 113-117.

1885. Young (R. S.). "Malarial Hæmaturia," *North Car. M. J.* Wilmington, 1885, xv, 365-367.

1885. Abney (J. A.). "Malarial Hæmaturia; Its Cause, Pathology and Treatment," *Texas Cour. Rec. Med.* Dallas, 1886-7, iv, 255-262.

1886. Alexander (M. J.). "Malarial Hæmaturia," *Mississippi Valley M. Month.* Memphis, 1886, vi, 13-17.

1886. Brown (S. H.). "Malarial Hæmaturia," *Mississippi Valley M. Month.* Memphis, 1886, vi, 1-13.

1886. Calhoun (L. F.). "Malarial Hæmaturia," *Med. Herald.* Louisville, 1886-7, viii, 333-337.

1886. Catelli (G.). "Sopra alcuni casi d'ittero-emoglobinuria malarica e loro cura," *Gior. Med. d. r. esercito*, etc. Roma, 1886, xxxiv, 641-655.

1886. Chute (H. M.). "Intermittent Hæmaturia," *South African M. J.* East London, 1886-7, ii, 38.

1886. Day (R. H.). "Malarial Hæmaturia," *Med. Herald.* Louisville, 1886-7, viii, 557-566; *N. Orl. M. and S. J.*, 1886-7, N. S., xiv, 29-40.

1886. Duncan (H. S.) "Malarial Hæmaturia; Treatment, Speedy Recovery." *Nashville J. M. and S.*, 1886, N. S., xxxvii, 65.

1886. Gorron (G.). "Sulfate de quinine et fièvre bilieuse hématurique à la Guadeloupe." 4to. Paris, 1886, 71 pages, No. 231.

1886. Manson (Otis F.) "A Treatise on Malarial Hæmorrhage: embracing Epistaxis, Odontorrhagia, Stomatorrhagia, Hæmoptysis, Hæmatemesis, Enterrorrhagia, Metrorrhagia, and Hæmaturia." 8vo. Richmond, 1886, J. W. Ferguson and Son, 118 pages (Repr. from *Tr. M. Soc., Virg.*).

1886. McIntosh (M. C.). "Malarial Hæmaturia," *Mississippi Valley M. Month.* Memphis, 1886, vi, 304-307.

1886. Stamps (J. A.). "Malarial Hæmaturia," *Med. and Surg. Reporter.* Philadelphia, 1886, lv, 1-6.

1886. Stubbert (J. E.). "Hæmaturia Miasmatica," *Med. and Surg. Reporter.* Philadelphia, 1886, lv, 263.

1886. Thornton (C. C.). "Malarial Hæmaturia," *Med. and Surg. Reporter.* Philadelphia, 1886, lv, 102-104.

1887. Baker (J. M.). "Malarial Hæmaturia," *North Car. M. J.* Wilmington, 1887, xx, 15-32.

1887. Brown (R. M.). "Malarial Hæmaturia," *Texas Cour. Rec. Med.* Dallas, 1887-8, v, 277-284.

1887. Day (R. H.). "Report of Case of Malarial Hæmaturia treated by Rectal Medication, with Remarks," *N. Orl. M. and S. J.*, 1887-8, N. S., xv, 616-623.

1887-8. Firth (R. H.). "On the Occurrence of Jaundice, Icteric Urine, and Hæmatinuria, in Remittent Fever," *Army M. Dep. Rep.*, 1885. London, 1887, xvii, 367-370, *B. M. J.*; London, 1886, ii, 762.

1887. Hart (W. P.). "The Etiology of Malarial Hæmaturia; the Pathological Condition of the Kidney that leads to the Hæmaturic Discharge; the Reason why Quinine should not, and Atropia should, be used in its Treatment," *Tr. M. Soc. Arkansas.* Little Rock, 1887, 36-45.

1887. Humphreys (B. F.). "The Prophylaxis and Treatment of Malarial Hematuria," *Texas Cour. Rec. Med.* Dallas, 1887-8, v, 125-132.

1887. Lehzen. "Ein Fall von paroxysmaler Hämoglobinurie," *Ztschr. f. klin. Med.* Berlin, 1887, xii, 307-320.

1887. O'Daniel (W.). "Malarial Hæmaturia," *Tr. Internat. M. Congr.* Washington, 1887, i, 226-231.

1887. Perkins (A. N.). "Remarks on Hæmaturia Miasmatica and its Treatment," *Daniel's Texas M. J.* Austin, 1887-8, iii, 216-218.

1887. Rousseau (Victor A.). "De la fièvre bilieuse hématurique au fort de Bammako." Campagne, 1885-1886. 4to. Bordeaux, 1887, 33 pp., 3 diag., No. 83.

1887. Stamps (J. A.). "Condition of the Kidneys in Malarial Hæmoglobinuria," *Tr. M. Soc. Arkansas.* Little Rock, 1887, 46-52.

1887. Wilson (I. J.). "Malarial Hæmaturia and its Treatment, as indicated by its Etiology and Pathology," *Mississippi Valley M. Month.* Memphis, 1887, vii, 249-256.

1888. Howard (W. A.). "Malarial Hæmaturia," *Texas Cour. Rec. Med.* Dallas, 1888-9, vi, 248, 277.

1888. Lépine. "Emoglobinuria parosistica da freddo" (Transl.), *Boll. d. Clin.* Milano, 1888, v, 235-239.

1888. Raymond (F. S.). "Quinine in Malarial Hæmaturia," *Memphis M. Month.*, 1888, viii, 209-212.

1888. Reilly. "Notes on African Fever," *Provincial Med. Journ.*, December 1888.

1888. Sanford (S. W.). "Malarial Hæmaturia in an Infant," *Memphis M. Month.*, 1888, viii, 49-64.

1888. Smith (W. T.). "Malarial Hæmaturia," *Tr. Louisiana M. Soc.* New Orleans, 1888, 225-229.

1888. Stamps (J. A.). "The Pathology and Treatment of Malarial Hæmoglobinuria," *Therap. Gaz.* Detroit, 1888, 3 s. iv, 675-678.

1889. Blanc (H.). "Essai sur les formes bilieuses du paludisme au Tonkin," *Arch. de Méd. et Pharm. mil.* Paris, 1889, xiii, 1, 101.

1889. Calmette (A.). "L'hémoglobinurie d'origine paludéenne; analyse et observations recueillies a la côte occidentale d'Afrique; processus anatomo-physiologique de cette affection," *Arch de Med. Nav.* Paris, 1889, lii, 81-106.

1889. Galvagno (P.). "Sulla febbre ittero-ematurica da chinino," *Riv. Gen. Ital. di Clin. Med.* Pisa, 1889-90, i, 61-63.

1889. Hamilton (J. W.). "Malarial Hematuria," *Texas Cour. Rec. Med.* Dallas, 1889-90, vii, 316-318.

1889. Kelsch (A.) u. Kiener (P. L.). "Maladies des pays chauds; région prétropicale." 8vo. Paris, 1889.

1889. Lipari (G.). "Contribuzione clinica all' esistenza della febbre ittero-ematurica chinica in individui malarici, Morgagni," Milano, 1889, xxxi, 529-569.

1889. M'Laughlin. "Hemorrhagic Malarial Fever," *New Orleans Med. and Surg. Journ.*, 1888-89, N. S., xvi, 645-662.

1889. Smith and Kilborne. "Redwater, or Texas Fever," *Annual Report M. S. Secretary of Agriculture*, 1889, pp. 87-91 ; 1890, pp. 92-93, 105-110.

1889. Tomaselli (S.). "La intossicazione chinica o febbre ittero-ematurica da chinino," *Lavori d. Cong. di Med. Int.*, 1888. Milano, 1889, i, 15-39.

1890. Barton (W. P.). "Hæmaturic Cinchonism, commonly called Malarial Hæmaturia," *Cincin. M. J.*, 1890, v, 109-114 ; *Memphis J. M. Sc.*, 1890-1, ii, 1-6.

1890. Tiraboschi (A.). "Emoglobinuria e malaria," *Gior. Internaz. d. Sc. Med.* Napoli, 1890, N. S., xii, 161-173.

1890. Magruder (E. G.). "Malarial Hematuria," *Texas Cour. Rec. Med.* Dallas, 1890-1, viii, 29.

1890. Martin. "Report of Eleven Cases of so-called Malarial Hematuria," *Atlanta M. and S. J.*, 1890-1, N. S., vii, 715-724.

1890. Tutwiler (H. A.). "Malarial Hæmaturia, Hemorrhagic Malarial Fever, Yellow Disease, etc., *Daniel's Texas M. J.* Austin, 1890-1, vi, 192-196.

1891. Brunelle. "Observation d'hémoglobinurie paroxystique (accès provoques)," *Bull. Méd. du Nord.* Lille, 1891, xxx, 209-223.

1891. Castle (R. F.). "Hæmaturia in East Central Africa," *Lancet.* London, 1891, i, 931.

1891. Coromilas. "Arrêt des vomissements par la pepsine chez les hématuriques de cause palustre," *Bull. Soc. de Méd. Prat. de Par.*, 1891, pp. 286-290.

1891. Crisafulli (G.). "Due casi di emoglobinuria parossistica da freddo," *Gior. Med. d. r. esercito*, etc. Roma, 1891, xxxix, 173-190.

1891. Darby (J. I.). "Treatment of Malarial Hæmaturia," *Alabama M. and S. Age.* Anniston, 1891-2, iv, 329-334.

1891. Evans (G.). "The Pathology of Malarial Hæmoglobinuria," *Memphis M. Month.*, 1891, xi, 1-7.

1891. Felkin. "Observations on Malaria and Enteric Fever (including the so-called Typho-malarial and Blackwater Fevers), and on the Possible Antagonism between Malaria and Phthisis," *Trans. Internat. Congress of Hygiene*, 1891, vol. i, p. 248.

1891. Freeland (J.). "Bilious Remittent Fever," *Leeward Islands M. J.* London, 1891, i, 23-58.

1891. Howard (W. R.). "Malarial Hæmaturia and Hæmoglobinuria ; Pernicious Malarial Fever," *Texas Cour. Rec. Med.* Dallas, 1891-2, ix, 283-286.

1891. Martin (E. H.). "Lipæmia or Malarial Hæmaturia," *N. Orl. M. and S. J.*, 1891-2, N. S., xix, 410-412.

1891. Mason (B. W.). "Treatment of Malarial Hæmaturia," *Atlanta M. and S. J.*, 1891-2, N. S., viii, 73.

1891. Meek (J. W.). "Malarial Hæmaturia," *N. Orl. M. and S. J.*, 1891-2, N. S., xix, 326-329.

1891. M'Cargo (W. H.). "A Case of Malarial Hematuria, reported for what it is worth," *Memphis M. Month.*, 1891, xi, 9-14.

1891. McVey (B.). "Malarial Hæmaturia," *N. Orl. M. and S. J.*, 1891-2, N. S., xix, 748-755.

1891. McHatton (H.). "Malarial Hemoglobinuria," *Times and Reg.* New York and Philadelphia, 1891, xxii, 491-494.

1891. McVey (B.). "Malarial Hæmaturia," *N. Orl. M. and S. J.*, 1891-2, N. S., xix, 167-171.

1891. Osherovski (L. J.). "Febris remittens perniciosa icterica s. biliosa. *Voyenno Med. J.* St. Petersburgh, 1891, clxxii, Pt. 1, 389-419.

1891. Parham (E. H. M.). "Malarial Hæmoglobinuria," *South M. Rec.* Atlanta, 1891, xxi, 365-367.

1891. Petty (G. E.). "Malarial Hematuria : Pathology and Treatment," *Memphis M. Month.*, 1891, xi, 496-500.

1891. Prout. "Malaria on the Gold Coast," *Lancet*, August 1st, 1891, pp. 226-228.

1891. Rançon. "Fièvre à forme rémittente bilieuse observée sur lui-même et traitée par le Kinkélibah (Combretum Raimbaultii Heckel), *Arch. de Med. Nav.* Paris, 1891, lvi, 465.

1891. Skipper (R. W.). "Malarial Hematuria," *Texas Cour. Rec. Med.* Dallas, 1891-2, ix, 146-148.

1892. Baccelli (G,). "Über einen Fall von nicht paroxysmaler Hämoglobinurie—Perniciöser, immanenter Zustand von Malaria-Infection. Vorläufige Nachricht über den klinisch-synthetischen Begriff dieser Infection, *Verhandl. d. Cong. f. innere Med.* Wiesb., 1892, xi, 523-531.

1892. Barton (W. P.). "Malarial Hæmaturia," *Med. Mirror.* St. Louis, 1892, iii, 103-109.

1892. Barton (W. P.). "Malarial Hæmaturia, the Old and New Theory," *Memphis M. Month.*, 1892, xii, 1-7.

1892. Hare (H. A.). "Malarial Hæmaturia, or Hæmoglobinuria, and the value of Quinine in this Affection," *Therap. Gaz.* Detroit, 1892, 3 s., viii, 448-455.

1892. Kohlstock (P.). "Ein Fall von tropischer, biliöser Malaria-Erkrankung mit Hæmoglobinurie," *Berl. Klin. Wchnschr.*, 1892, xxix, 427-430, 459-461.

1892. Manson (P.). "A Lecture on Benign and Pernicious Malarial Fevers," *Trans. Epidemiological Society*, xii, 1892-93; *Brit. Med. Journ.*, 1896, p. 257-260.

1892. Manson (P.). "On African Hæmoglobinuric Fever," *Trans. Epidemiol. Soc.* London, 1892-3, N. S., xii, 111-141.

1892. Marrs (M. C.). "Malarial Hæmaturia," *St. Louis Cour. Med.*, 1892, vii, 93-95.

1892. McHatton (H.). "Malarial Hæmoglobinuria : Answer to Dr. Parham," *South M. Rec.* Atlanta, 1892, xxii, 21-25.

1892. Le Nobel. "Über das Wesen der Gelbsucht bei perniciösem Sumpffieber," *Centralblatt f. Klin. Med.* Leipzig, 1892, xiii, 667.

1892. Parham (E. H. M.). "Malarial Hæmaturia," *South. M. Rec.* Atlanta, 1892, xxii, 119-121.

1892. Wheaton (S.). "Preparations from the Organs of a Case of West African 'Blackwater' Fever," *Trans. Path. Soc.* London, 1892-3, xliv, 168-170.

1892. Crosse (W. H.). "Notes on the Malarial Fevers met with on the River Niger (West Africa)," plate and diagrams, sm. 8vo. London, 1892.

1892. Davidson (Andrew). "Geographical Pathology : an Inquiry into the Geographical Distribution of Infective and Climatic Diseases." Edinburgh and London, 1892. 8vo. Two vols.

1893. Davidson. "Hygiene and Diseases of Warm Climates." 8vo. Edinburgh and London, 1893.

1894. Darby (J. I.). "Malarial Hæmaturia," *Charlotte (N. C.) M. J.*, 1894, v, 497-503.

1894. Draper (T. J.). "Malarial Hæmaturia," *Hot Springs M. J.*, 1894, iii, 195-198.

1894. Guice (N. L.). "Malarial Hæmaturia and its Successful Treatment without the Use of Quinine," *Ann. Med. Surg. Bull.* New York, 1894, vii, 1033-7.

1894. Hébrard. "Observations de fièvre bilieuse hémoglobinurique recueillies à Grand Bassam (Côte d'Ivoire)," *Arch. de Méd. Nav.*, 1894, lxiv, 446-450.

1894. Jones (F. A.). "Malarial Hæmaturia," *Amer. Practit. and News.* Louisville, 1894, xvii, 301-305.

1894. Marchiafava and Bignami. "On Summer-Autumn Malarial Fevers" (*New Syd. Soc.*, 1894). 8vo. London, 1894, p. 117.

1894. Oates (T. F.). "Some Remarks on the Ætiology, Pathology, and Treatment of Malarial Hæmatinuria," *Texas M. J.* Austin, 1894-5, x, 11-15.

1894. Parry (L. D.). "A Case of Paroxysmal Hæmoglobinuria," *Australas. M. Gaz.* Sydney, 1894, xiii, 76.

1895. Battersby (C. Harford). "West African Fever: Inaugural Thesis for Degree of M.D." Cambridge, 1895.

1895. Blalock (A. L.). "Report of a Case of Hemorrhagic Bilious Remittent Fever," *Coll. and Clin. Rec.* Philadelphia, 1895, xvi, 269-271.

1895. Cappellari (L.). "Un caso di ematuria intermittente," *Gazz. di Osp.* Milano, 1895, xvi, 1285.

1895. Catchings (C. E.). "Malarial Hæmaturia," *Med. and Surg. Reporter.* Philadelphia, 1895, lxxii, 885-887.

1895. Doering. "Ein Beitrag zur Kenntniss des Schwarzwasserfiebers," *Deutsche Med. Wchschr.* Leipzig u. Berlin, 1895, xxi, 761-763.

1895. Hare (H. A.) and Krusen (W.). "The Treatment of Malarial Hæmaturia," *Therap. Gaz.* Detroit, 1895, 3 s., xi, 291-293.

1895. Harrison (L. H.). "Malarial Hæmaturia," *Louisville M. Month.*, 1895-6, ii, 380.

1895. Kilpatrick (J. J.). "Malarial Hematuria," *Atlanta M. and S. J.*, 1895-6, N. S., xii, 608-610.

1895. Kohlstock. Zur Chininbehandlung des Schwarzwasserfiebers. Entgegnung. *Deutsche Med. Wchnschr.* Leipzig u. Berlin, 1895, xxi, 763.

1895. Küchel (B.). "Über das Schwarzwasserfieber, insbesondere seine Behandlung mit grossen Chiningaben," *Deutsche Med. Wchnschr.* Leipzig u. Berlin, 1895, xxi, 446-450.

1895. Long (J. B.). "Malarial Hæmaturia," *Louisville M. Month.*, 1895-6, ii, 453.

1895. Maclaud. "Un cas de fièvre bilieuse hématurique observé a Conakry (Guinée Française)," *Arch. de Méd. Nav.* Paris, 1895, lxiii, 338-341.

1895. Menville (C.). "Malarial Hæmaturia," *Louisville M. Month.*, 1895-6, ii, 421-423.

1895. Nepveu (G.). Contribution à la fièvre bilieuse hématurique," *Marseille Méd.*, 1895. xxxii, 396-404.

1895. Newton (I. J.). "Malarial Hæmaturia," *J. Arkansas M. Soc.* Little Rock, 1895-6, vi, 289-295.

1895. Peck (Elisabeth L.). "Bilious Remittent Fever, with Report of a Case," *Codex Med.* Philadelphia, 1895-6, ii, 108-111.

1895. Plehn (F.). "Über das Schwarzwasserfieber an der africanischen Westküste," *Deutsche Med. Wchnschr.* Leipzig u. Berlin, xxi, 397, 416, 434.

1895. Quennec. "Notice sur la fièvre bilieuse hémoglobinurique et sur son traitement par le chloroforme," *Arch. de Méd. Nav.* Paris, 1895, lxiv, 419-427.

1895. Rigney (J.). "Malarial Hæmaturia, or Creole Yellow Fever," *Med. and Surg. Reporter.* Philadelphia, 1895, lxxiii, 666-669.

1895. Shoaf (J. N.). "Malarial Hæmaturia," *Louisville M. Month.*, 1895-6, ii, 470-472.

1895. Steudel. "Zur Chinin-Behandlung des Schwarzwasserfiebers," *München. Med. Wchnschr.*, 1895, xlii, 1003-1006.

1895. Torres Homen (J. V.). "Bilious Remittent Fever of the Tropics" (Transl.), *Med. Age.* Detroit, 1895, xiii, 321, 363.

1895. Torres Homen (J. V.). "Treatment of Malarial Hematuria," *Med. News.* Philadelphia, 1895, lxvii, 271-273.

1895. Woldert (E. A.). "A Case of Malarial Hæmaturia, with a Study of the Plasmodium," *N. York M. J.*, 1895, lxi, 229.

1895. Vernazza (G.). "Febbre ittero-ematurica da malaria o da intossicazione chinica," *Gazz. d. Osp.* Milano, 1895, xvi, 235-237.

1895. Yersin. "Note sur la fièvre bilieuse hématurique," *Compt. Rend. Soc. de Biol.* Paris, 1895, 10 s., ii, 447-449.

1896. Bastianelli (D. G.). "Le emoglobinurie da malaria secondo i recenti studi," *Ann. di Med. Nav.* Roma, 1896, ii, 847-890.

1896. Battle (L. L.). "Malarial Hæmaturia: its Nature and Treatment," *Nashville J. M. and S.*, 1896, lxxix, 14.

1896. Bense (C. L.). "Nogeens Schwarzwasserfieber," *Nederl. Tijdschr. v. Geneesk.* Amsterdam, 1896, 2 R., xxxii, Pt. 1, 126-129.

1896. Berthier (A.). "Pathogénie et traitement de l'hémoglobinurie paludéenne," *Arch. de Méd. Expér. et d'Anat. Path.*, 1896, viii, 628-686.

1896. Bonnivento (G.). "Contributo allo studio della patogenesi della febbre biliosa emoglobinurica da chinino," *Raccoglitore Med.* Forli, 1896, 5 s., xxii, 225, 249.

1896. Breundat (L.). "Contribution à l'étude bactériologique de la fièvre bilieuse hématurique au Tonkin," *Archives de Méd. Navale*, 1896, lxv, 457-63.

1896. Bush (W. D.). "Malarial Hæmaturia, or Hemorrhagic Fever," *Med. Record.* New York, 1896, l, 209.

1896. Eschle. "Ueber das sogenannte Schwarzwasserfieber," *Aerztl. Prakt.* Dresden, 1896, ix, 676-693.

1896. Evans (W. A.). "Malarial Hematuria," *Memphis M. Monthly*, 1896, xvi, 632-637.

1896. Ferrier. "Fièvre bilieuse hémoglobinurique," *Lyon Médicale*, 1896, lxxxii, 323, 455, 497, 529.

1896. Fisch. Ueber Schwarzwasserfieber," *Correspondenz-Blatt für schweizer Aerzte.* Basel, 1896, xxvi, 271-76.

1896. Fleming (L.). "Malarial Hæmaturia," [in London Letter] *Med. Record.* New York, 1896, l, 426.

1896. Kanellis. "Quelques réflexions sur la fièvre hémoglobinurique bilieuse," *Progrès Médicale*, 1896, 3rd sér., iii, 227.

1896. Martin (E. H.). "Lysæmia, or Malarial Hæmaturia," *Memphis M. Month.*, 1896, xvi, 1-9.

1896. Moscato (P.). "Infezione palustre cronica:—Febbre ittero ematurica che riconosce per momenti etiologica nelle sue fasi evulotive ora la malaria, ed ora l'azione tossica della chinina," *Gazz. Méd. Lomb.* Milano, 1896, lv, 191-193, 211-213, 221-223, 231-233.

1896. Vaysse. "Un cas de fièvre bilieuse hématurique observée a Mayotte," *Archives de Méd. Navale*, 1896, lxv, 234.

1896. Woldert (E. A.). "A Case of Malarial Hæmatinuria, with a Study of the Plasmodium," *N. York M. J.*, 1896, lxiii, 1-3.

1897. Antony. "Fièvre bilieuse hématurique," *Journal de Méd. de Bordeaux*, 1897, xviii, 31-33.

1897. Baccelli (G.). "Emoglobinuria da malaria," *Gazz. d. Osp.* Milano, 1897, xviii, 193-197.

1897. Catrin. "Paludisme," [Debove et Achard, *Manuel de Médecine*, 1897, viii, p. 427].

1897. Fisher (W.). "The Malarial Fevers of Angola, West Coast of Africa," *Guy's Hospital Gazette.* London, 1897, xi, 54.

1897. Grocco. "Sull' emoglobinuria da chinino nei malaria," *Settimana Med. d. Sperimentale.* Firenze, 1897, li, 1-4.

1897. Woodson (R. S.) "The Fevers of South-West Texas: a Third Fever of the South," *Journ. Amer. Med. Assoc.*, 1897, xxviii, 534-537.

1898. Botescu (H.). "Notă a supra unuĭ caz de ematurie palustra," *Scitalul.* Bucurescĭ, 1898, xviii, 315.

1898. Tsakyroglon (M.). "Zwei Fälle von Febris hæmoglobinurica palustris," *Allg. Wien. Med. Ztg.*, 1898, xliii, 246.

1898. Konstantinoff (M. V.). "Febris biliosa hæmoglobinurica" (after observations in the territory beyond the Caspian Sea), *Russk. Arch. Patol. Klin. Med. i Backteriol.* St. Petersburg, 1898, v, 311-344.

1898. Murdock (L. A.). "Malarial Hæmaturia," *J. Mississippi M. Assoc.* Biloxi, 1898-9, ii, 144-147.

1898. Sims (A.). "The Use of Quinine in the Fevers of the Congo." Treatise for Aberdeen M.D.

1898. Loomis (Alfred Lee) and Thompson (William Gilman). "A System of Practical Medicine by American Authors." Vol. iv. (Articles on Malarial Diseases). 8vo. New York and Philadelphia.

1898. Connolly (R. M.). "African Hæmoglobinuric Fever, commonly called Blackwater Fever," *Brit. Med. Journ.*, ii, 1898. 882-85.

1898. Copeman (S. Monckton). "Hæmoglobinuric Fever" (*Allbutt's System of Medicine*, vol. ii), 1897, pp. 742-53.

1898. Crosse (W. H.). "The Treatment of Malaria and Blackwater Fever," *Guy's Hospital Gazette*, Oct. 8th, 1898.

1898. Crosse (W. H.) and Pakes (W. C.). "Blackwater Fever" (read before Pathol. Soc., Lond.), *Brit. Med. Journ.*, 1898, ii, 1875; also *Lancet*, 1898, ii, 1704.

1898. Battersby (Charles F. Harford). "Blackwater Fever" (Letter), *Brit. Med. Journ.*, ii, 1898, 1199.

1898. Koch (R.). "Das Schwarzwasserfieber," *Arbeiten aus dem Kaiserlichen Gesundheitsamte*, 1898, xiv, 304-308.

1898. (Koch (R.). "Reise-Berichte über Rinderpest, Bubonenpest in Indien und Afrika, Tsetse oder Surrakrankheit, Texasfieber, tropische Malaria, Schwarzwasser-fieber." 8vo. Berlin. 1898.

1898. Mackie (F. P.). "Notes on a Case of Blackwater Fever," *Lancet*, 1898, ii, 1470.

1898. Manson (Patrick). "Tropical Diseases: a Manual of the Diseases of Warm Climates." 8vo. London, 1898.

1898. Moffat (R. U.). "Blackwater Fever and Hæmoglobinuria." (Letter) *Brit. Med. Journ.*, 1898, ii, 926.

1898. Plehn (F.). "Die Kamerun-Küste," Studien zur Klimatologie, Physiologie, und Pathologie in den Tropen. 8vo. Berlin, 1898.

1898. Powell (Arthur). "Hæmoglobinuric Fever in Assam," *Journ. of Trop. Med.*, 1898, i, 117-119.

1898. Robson (Alfred W.). "Blackwater Fever and Quinine," *Brit. Med. Journ.*, 1898, ii, 1287.

1898. Sambon (L. Westenra). "Blackwater Fever," *Brit. Med. Journ.*, 1898, ii, 866-869.

1898. Sambon (L. Westenra). "Blackwater Fever," *Journ. of Trop. Med.*, 1898, i, 70-74.

1898. Thayer (William Sidney). "Lectures on the Malarial Fevers." 8vo. London, 1898.

1898. Ziemann (Hans). "Ueber Malaria und andere Blutparasiten: nebst Anhang: Eine wirksame Methode der Chromatin-und Blutfärbung. la 8vo. Jena, 1898.

1899. Bertrand (L. E.). "Sur un cas de fièvre dite bilieuse hémoglobinurique," *Bull. Acad. de Med.*, 1899. 3me sér, xli, 76-82.

1899. Du Bose (F. G.). "Malarial Hematuria," *Journ. Amer. Med. Assoc.*, 1899, xxxii, 539.

1899. Mannaberg. "Die Malaria-krankheiten." 8vo. Jena, 1899.

1899. Wooldridge (A. T.). "A Case of Blackwater Fever, complicated with Dysentery," *The Lancet*, March 18th, 1899, p. 762.

1899. Colomb (B.). "Quinine in Malarial Hemoglobinuria," *Med. News*, New York, 1899, lxxiv, 343.

1899. Lewis (H. W.). "Malarial Hæmoglobinuria; its Treatment by Injection of Normal Salt Solution," *North Car. M. J.* Charlotte, 1899, xliii, 180-190.

1899. Sambon (L. W.). "The Etiology and Treatment of Blackwater Fever," *Journ. of Trop. Med.*, 1899, i, 243-246, 262-264, 295-296.

1899. Hughes (M. Louis). "Group of Cases of Malarial Fever from West Africa, including a Case of Blackwater Fever," *Journ. of Trop. Med.*, 1899, i, 292-293.

1899. Koch (R.) "Blackwater Fever (Hæmoglobinuria)," (translated by P. Falcke), *Journ. of Trop. Med.*, 1899, i, 333-335.

1899. Seal (Chas. E. Baldwin). "Notes on a few Cases of Hæmoglobinuria in India," *Journ. of Trop. Med.*, 1899, i, 179-180.

1898-9. Da Silva Garcia (F.). "A febre biliosa hematurica em Angola e a prophylaxia da malaria pelos saes de quinina," *Med. Contemp.* Lisbon, 1898, xvi, 415, 425; 1899, xvii, 48.

1899. Thin (George). "The Parasite of Malaria in the Tissues in a Fatal Case of Blackwater Fever," *Brit. Med. Journ.* London, 1899, i, 1325-1327.