ON AFRICAN HÆMOGLOBINURIC FEVER.

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Mr. President,—During the last ten or fifteen years our ideas on the subject of the fevers of tropical climates have been gradually undergoing a change. Venerable fancies, which generation after generation of writers had faithfully copied from their predecessors, have at last been challenged, and many of them abandoned for good. In this matter, as in so many others, we have ceased to reverence authority unless backed by demonstrable and demonstrated fact. We no longer believe that because Lancisi, or anyone else, said so and so, it must be so and so. Not many years ago malaria was held to explain every obscure problem in tropical pathology. There is a scientific ring about the word "malaria" which cloaked our ignorance in a respectable kind of way; there was something of comfort in it, too, like that which to the devout soul lay in the blessed word "Mesopotamia". In tropical practice it took the place which the word "gout" does in English practice. Merely to utter it and to prescribe calomel and quinine explained everything, and satisfied both patient and physician. It suffices no longer however. Tropical pathology and therapeutics have advanced with the advance of pathology and therapeutics in other departments of medical science. Reverence for authority and medical shibboleths has given place to reverence for facts and to diligent search for them, and to scientific methods. Notable fruit of this is that we have been able in recent years to sift from the rubbish-heap called "malaria", on to which our ignorances had hitherto been thrown, many diseases which our predecessors were content to call malarial. We have separated from it such diseases as tropical typhoid, relapsing fever, elephantoid fever, Mediterranean fever, anchylostomiasis, beri-beri, dysentery, liver abscess, and other though less important diseases. Within the last few years our views about these have undergone a very great change. But although the change has been great, I question if it has even yet gone far

enough. I believe that we are still in the trammels of tradition in many ways, that there are important diseases which we are still content to throw on the "malaria" rubbish-heap, but which, could we but get at the facts, we would see have little or nothing to do with malaria, but are specifically distinct and independent. I believe there are fevers and certain other pathological conditions which are still looked on as malarial, and that solely for no better reason than that they occur in tropical climates and in individuals who may previously have had attacks of genuine malarial fever. But because a man is living in the tropics, in a malarious district, and has had malarial fever, it is poor logic to conclude from this alone that the broken leg we are called on to treat him for is also malarial. It is equally illogical to conclude that because a man is living in the tropics, in a malarious district, and has suffered from malarial fever, that the particular fever or other disease we are called on to treat him for, is also malarial. Yet this is the kind of logic which is but too often applied to the diagnosis of tropical diseases, more especially tropical fevers. Practically it amounts to this;—because a fever occurs in the tropics it must be malarial. The medical mind cannot apparently disabuse itself of the "malaria" fetish. As so often happens in medical reasoning, coincidences are interpreted as existing in the relationship of cause and effect.

Just as there are many more human beings in the tropics and subtropics than in the temperate zones, there is a presumption that there are also many more diseases there, although we may not as yet have learned to recognise them. Therefore, if the pyretology of Europe includes some five or six fevers, it is not improbable that the pyretology of the tropics includes as many, if not more. And yet we credit the tropics with only three—yellow fever, dengue, and malarial fever. The two former are well defined; not so the last. It is true that certain fevers may be justly relegated to it, but I hold that there is a vast residuum of febrile disease credited to malaria, and usually called malarial, which has nothing whatever to do with malaria. I have seen many such cases. I call them "unclassed fevers". It has often occurred to me that writers of text-books, and especially systematic writers on tropical disease, would do well to imitate the old cartographers, who, when they came to lay out the map of Africa, wrote across much of it "unexplored territory".

I propose to say something about one of these doubtfully

malarial diseases, viz., blackwater fever, or, as it is sometimes called, hæmaturic fever, or, better, hæmoglobinuric fever; a disease hitherto classed as malarial, but which I think has been so classed on insufficient grounds. I do not say that it is not malarial; but I do say that it has not been proved to be such, and that there are strong reasons for thinking that it is a disease *sui generis*, one of the "unclassed" fevers I have referred to; and in the following remarks I hope to bring forward adequate reasons for at least suspense of judgment in the matter.

Before proceeding it might be well if I state what I mean by "malaria" and "malarial disease". I disregard the etymology of the word altogether. *Mal aria* means simply bad or vitiated air. But when we speak of "malaria" we mean something of a much more definite nature than the etymology of the word would indicate; we mean something specific in the shape of a special air-borne germ or poison; and when we speak of malarial disease we mean a certain specific type of disease, produced by this specific air-borne germ or poison. It would be easy to say that malaria is the *plasmodium malariæ*, or Laveran's bodies, and that malarial disease is an outcome of the action of these on the human body. This may be a perfectly correct definition, and in time it may prove to be such; but as yet it is premature. As yet we can only define malaria by its effects. I would say, then, that malaria is that poison, or those poisons or germs which give rise to the intermittent fevers—quotidian, tertian, and quartan ague—and the remittent fevers which seem to spring out of or merge into these; which at the same time gives rise to forms of hypertrophy of the spleen, and to the deposit of a peculiar kind of pigment in certain organs—notably the spleen, bone-marrow, liver, and brain; and, further, that its effects are to a very great extent counteracted by quinine. With the exception, perhaps, of pigmentation, none of these things is in itself peculiar to malaria; but taken together they are sufficiently characteristic for us to recognise it by.

Unfortunately, owing to the paucity of well-made and well-recorded *post mortem* examinations, we are not in a position to apply the pigmentation test in the case of hæmoglobinuric fever. We are therefore obliged to fall back on the clinical and therapeutical tests. The verdict they give is at best very doubtful; and this doubt is further accentuated by certain epidemiological facts in the history and geographical distribution of this disease to which I propose specially to direct your attention.

Before proceeding in this, as it is of importance that the disease of which I am to speak should be distinctly defined, I shall try, as briefly as I can, to give a sketch of its leading clinical features. This I would not inflict upon you could I refer you to a good description by any of our standard English medical writers. And here I would remark, in parenthesis, that it is a singular thing that of our numerous systematic writers on tropical disease, not one of them describes hæmoglobinuric fever, although it is one of the commonest diseases among Europeans in Africa, as well as one of the most deadly. There is no excuse for this neglect by our writers, for there are good descriptions of it by English observers; but these our standard authorities have ignored, as they have also the extensive and most valuable French literature on the subject. Among English writers I might refer to Easmon, Eyles, Sullivan, Prout, and especially to the excellent monograph on the fevers of the Niger by Crosse. Among French writers I would specially refer to Dutrouleau, Bérenger-Féraud, Nielly, Leroy de Méricourt, Corre, Roux, Kelsch and Kiener, and many others; indeed, it is to French writers that we are indebted for the best as well as for the earliest accounts of this important disease.

On the evening of 26th March last year I saw a gentleman in London who had just returned from travelling on the Congo. He was thirty years of age. I knew him a year before as a very active man of sound constitution, and a total abstainer. Soon after his arrival out on the Congo, and off and on all through the nine months he spent there, he had attacks of fever. Only one of them was associated with hæmoglobinuria and of especial gravity. The others, though trying, were not of sufficient importance seriously to interfere with his work, or his moving about the country and penetrating far into the interior of Africa. He left the Congo on the 15th of February in company with a lady, his cousin, who had lived in Africa for three years, and who had just lost her husband there from hæmoglobinuric fever. On the voyage to England my patient enjoyed fair health, though he had a couple of slight fevers *en route*. He was in good health when he landed at Plymouth on the 27th March. He did not remain many hours there, but took the first train to London. The weather was unusually cold and bleak at the time. The next day he was feverish more or less all day, and at 5 P.M. he had a smart rigor, quickly followed by high fever. He took at once a dose of calomel and

quinine, and went to bed. On using the chamber-pot, he noticed that his urine was of the colour of port wine. I saw him five hours later, about 10 P.M. He was then in bed, his skin hot and perspiring freely, his pulse quick, temperature 104.2°; he had some headache, and was inclined to toss about a little; he had also lumbarache and general feverish distress, and his skin was yellow as a guinea. Next day when I saw him in the afternoon the fever had abated, and the urine, although still discoloured, was less dark. On the third day the patient was practically convalescent, although weak, anæmic, and yellow skinned. He gradually improved, and is now fairly well, although there was a slight break-down last autumn from overwork.

Strange to say, a day or two after this patient began to mend, his cousin, the lady who had travelled home with him, was seized in exactly the same way, the disease running pretty much the same course. Her temperature was higher, and for a short time stood at 107°. Like the other patient, she had been feverish all day before definite rigor set in, and with the rigor the urine became dark. I believe this was her sixth attack of hæmoglobinuric fever.

As I have said, I saw the gentleman about five hours after the initial rigor. His temperature was then 104.2°; he was sweating freely; he was passing from time to time urine of a port-wine colour; and his skin was deeply stained. As the urine passed showed no sign of clearing it was evident that a process of blood-destruction was actively proceeding. I pricked his finger and placed some of his blood under the microscope. It was at once apparent that I was contemplating a ruin, an army, so to speak, in stress of battle, the regiments broken and scattered, the soldiers many of them wounded or dead. I noticed first that the rouleaux arrangement of the corpuscles was exceedingly imperfect, hardly existed, in fact, the corpuscles lying together in clusters, or floating about singly. I noticed also that the individual corpuscles varied between very wide limits in size, shape, and depth of colour. Many of them exhibited a marked disposition to buckle up, cup, or fold on themselves, as if from limpness and imperfect filling of the cell-wall. Some were absolutely colourless, just visible in the liquor sanguinis, but utterly devoid of colouring matter; others were full-coloured, and between these extremes there were discs with every grade of coloration. There were noticeable, also, numbers of microcytes, both full-coloured or pale, or almost colourless, and

varying in diameter from about the 1-10,000th of an inch up to the size of an ordinary blood-corpuscle. Some of the corpuscles were "tailed", and when two would part company the tendency to stick together and tail out at the point of contact was very marked.

I examined the patient's blood again on the following afternoon. The urine had now become much clearer, and the body temperature had fallen, and the blood, too, had become more natural in appearance. Rouleaux formation was more perfect, microcytes were fewer in number, and there was greater uniformity in the size and shape of the red discs, and less tendency to buckle up and to tail. Along with this improved appearance of the red corpuscles there was a very manifest increase in the number of white corpuscles.

The urine passed during the first hours of the attack, when seen in bulk, appeared quite as dark as port wine; when in a thin layer, or when diluted, it was of a reddish brown colour. On standing, a copious light brown sediment formed, which, under the microscope, was found to be made up of a variety of elements:—1st. Innumerable straight, very dark brown, large, granular casts, some short, others fairly long. 2nd. A large amount of a light brown granular material. 3rd. Small, unpigmented, oval or round, single or double nucleated epithelial cells. 4th. Oval bodies, single, in twos or threes, and in groups; about these I shall have more to say presently. 5th. Ragged pieces of black pigment. After decanting the supernatant fluid, and washing the sediment in two or three waters, I found that the latter was soluble for the most part both in nitric acid and in liquor potassæ. On adding cold water to the nitric acid solution a precipitate was thrown down which redissolved on the application of heat. Alcohol or chloroform did not dissolve the sediment. Applying liquor potassæ to a slide of the sediment, whilst viewed through the microscope, it was seen that the brown granular matter and the dark brown casts were rapidly dissolved, whilst the epithelial cells were rendered very clear; but there was no corresponding action on the particles of black pigment, or on the ovum-like bodies I have alluded to. On boiling a specimen of the urine of the 28th March, a coagulum of about one-third albumen formed, and, as it subsided in the test tube, carried down with it all the colouring matter dissolved in the urine, the upper layer of which was thus left a light straw colour, clear and transparent. The urine of the 29th behaved similarly, the deposit of albumen being

very much smaller—about a fifth or sixth only. This last urine was acid, and had a specific gravity of 1020. It was the colour of Malaga wine, and deposited a considerable sediment.

Such is a short account of a case of African hæmoglobinuric fever occurring in England.

In the countries in which this disease is endemic the ordinary forms of malarial fever are particularly rife; and it has been remarked also that the subjects of hæmoglobinuric fever have almost invariably suffered considerably from recurring attacks of fever assumed by them to be ordinary intermittent and remittent. As a consequence of these attacks, or simply of what is considered to be chronic malarial poisoning, such individuals—as, for example, the patient whose case I have just described—come to be in a more or less anæmic, cachectic condition. Once a week, or once a month, or perhaps not so often, such an individual has his day or two of fever which he treats with a purgative and quinine. The attacks are in themselves not severe, for in a day or two the patient can get about as usual and attend to his duties. But, after a year or so of this, a time comes when he has an attack which turns out to be one of perhaps exceptional severity and gravity. He has the accustomed preliminary febrile malaise leading up to rigor, pyrexia, and diaphoresis, with complete intermission, to be followed next day, or two days later, by a repetition of the same; or perhaps—and this is the most usual course—there may not be a complete intermission, but the fever assumes a remittent type of perhaps an irregular character. And it would seem that these irregular, ill-defined forms of fever are somewhat characteristic of the type of the disease tending to end in hæmoglobinuric fever. A gentleman, who not only had personal experience of the disease but had nursed members of his own family and many of his colleagues during their attacks, informed me that on the Congo old residents always regard a fever with a low maximum temperature and an imperfect intermission—say, for the one 102°, and for the other 99.5°—with a rise of a degree or half a degree daily, as much more serious and much more likely to be suddenly complicated with hæmoglobinuric symptoms than a frank intermittent with a high maximum temperature of 105° or 106°, but with complete apyrexia in the intermission. Be this as it may, on the second, third, or fourth day of what appears to be an obstinate or smart attack of one of his ordinary and familiar fevers—sometimes even on the first day,

sometimes again not until after a week of fever—the patient is seized with an unusually severe rigor, and generally, though not always, with severe bilious vomiting and headache. The attack progresses in the ordinary way with this exception, that when he passes water, sometimes during, or sometimes after, rarely before the initial rigor, he finds that his urine is very dark, and, should he look at himself in the glass, that his skin has rapidly become of a bright yellow colour. The urine becomes dark first, the skin yellow rather later; in either event the change in colour is rapidly brought about. Concurrently with the darkening of the urine the loins begin to ache excessively, and the liver and spleen may enlarge somewhat and be very tender on palpation. At first the urine is only slightly darker than normal, but it rapidly passes through shades of malaga colour, port-wine colour, to almost inky black; and as it becomes darker it becomes scantier, thicker, and, in severe cases, of a gummy consistence. Pyrexia succeeds the cold stage, bilious vomiting persists, and perhaps several loose bilious stools are passed; or, on the other hand, there may be constipation, or vomiting may be entirely absent. Meanwhile the fever progresses, and the hot stage sets in, to be followed in due time by a copious diaphoresis. With the establishment of this the more distressing symptoms gradually abate; the loins cease to ache, the liver and spleen become less tender, and the bilious vomiting, if present, gradually subsides. At the same time, in favourable cases, the urine becomes less dark in colour and more copious, passing through shades of dark brown, malaga, yellow, and, finally, becoming clear and limpid and often very copious. It may take a day or two, however, for the urine to clear completely, and even longer before the skin and sclera lose the yellow tint which they had so suddenly acquired. On the subsidence of the fever and the clearing of the urine the patient recovers for the time being, with the exception that he is left profoundly anæmic and weak as if he had had a severe hæmorrhage, and that he is henceforth very liable to a recurrence of hæmoglobinuric fever.

Such a description applies to a somewhat mild attack of the disease. Unfortunately, all do not terminate so favourably. A fatal issue is far from being uncommon, and appears to be brought about in one of the three following ways: First, the fever and the hæmoglobinuria may take on a continued or remitting type and bring about death by simple exhaustion; second, the fever and hæmo-

globinuria may cease after perhaps one or two relapses; yet though these finally cease the patient is left so weak that he may die after a few days of sheer anæmia and with symptoms such as follow a flooding. These two types are bad enough, but there is a third which is much worse and almost invariably fatal. In it death seems to be brought about by an uræmic condition, the result of plugging of the renal tubules by hæmoglobin or its derivatives, or of a consequent nephritis. There is the usual smart fever, the vomiting, and the dark urine; but instead of, as in favourable cases, the urine after a time becoming gradually lighter in colour and more copious, it becomes more scanty, of a thick, syrupy consistence, and finally completely suppressed. Recovery from this condition is quite exceptional. Death usually ensues after a few days—the secretion never becoming properly re-established, although there may be no recurrence of fever. In these cases the tongue becomes dry, the patient apathetic or delirious, and, finally, a convulsive seizure may end in coma and death.

If the dark urine characteristic of this disease is examined, it is found to deposit a copious sediment of a colour somewhat lighter than the blackish or brownish fluid in which it is suspended. Under the microscope this sediment is seen to consist of much dark brown, amorphous, granular matter; numerous tube-casts of a similar material embedded in a hyaline matrix; epithelium from different parts of the urinary tract; a few exudation corpuscles; and a very few—sometimes hardly any—red blood corpuscles. On boiling the urine a copious deposit of albumen, amounting to a half, or even more, sometimes not so much, is thrown down. If the chemical and spectroscopic tests for hæmoglobin are applied, the presence of this substance or of its derivatives is readily detected; and it is to these, and not to bile pigment, which is usually absent, that the dark colour of the urine is due. In fact, the physical characters of the urine are those of the hæmoglobinuria we are familiar enough with in this country.

If a slide of the patient's blood drawn during the acute stage of the fever and for a day or two thereafter is examined with the microscope, evidence of very active blood destruction is revealed. Rouleaux-formation hardly exists, and this is found to be combined with an extreme degree of poikilocytosis. The red corpuscles are much distorted, and vary not only in shape but also in size and in colour. Microcytes are abnormally abundant, much granular matter floats about in the liquor sanguinis, and in

every field absolutely colourless discs and rent and crenated corpuscles are to be found.

There are many other interesting points in the clinical tableau of hæmoglobinuric fever to which I have not alluded. In the foregoing brief description my object has been not so much to make a complete picture of the disease, but rather to call attention to its salient clinical features, so as to make plain what I mean by the term hæmoglobinuric fever. Nor do I propose to enter on a consideration of its pathology further than to say that hæmoglobinuric fever is regarded by most writers on the subject as being merely an extreme expression of ordinary malarial poisoning; the hæmoglobinuria being the result of an excessive and rapid development of that exaggerated hæmolysis which always accompanies, in greater or less degree, the malarial state, whether acute or chronic, and which, when moderate in amount, is generally believed to bring about, by a well-known physio-pathological process, the anæmia and policholia of malarial attacks. It is asserted that when this hæmolysis is very excessive, and is suddenly produced, and is in degree beyond the physiological powers of the liver to cope with, the liberated hæmoglobin is not all converted into bile pigment but floats about in the liquor sanguinis, or is deposited in the tissues until its excretion in a more or less unchanged condition can be overtaken by the kidneys. Hence the icteric tint of the skin, which is not produced by bile any more than is the dark colour of the urine, the colour in both instances being derived wholly from the hæmoglobin. There are theorists who even go a step further than this; they pretend to explain the exact mechanism by which the hæmoglobinuria is produced. They say—and in saying this they assume what, as far as I know, has not yet been proved, viz., the invariable presence in the blood in these cases of a prodigious swarm of Laveran's bodies,—they say that the plasmodia in the course of their evolution rupture the blood discs, and so liberate the contained hæmoglobin. I shall have something to say on this presently; meanwhile I would again point out that, with the majority of writers, hæmoglobinuric fever is only a severe form of ordinary malarial fever.

This brings me to the principal object of this paper, which is to suggest caution in adopting such an ætiology and pathology. The grounds on which I would base this caution are twofold—clinical and epidemiological. I shall not have much to say from the clinical standpoint; but,

before passing to the epidemiological side of the question, there are one or two points of a purely clinical character to which I would first briefly direct attention.

It is reasonable to think that high degrees of malarial poisoning are, unless in the algid type of pernicious fevers, accompanied by proportionate degrees of fever. Therefore, if we are to regard hæmoglobinuric fever as an expression of a high degree of malarial poisoning, we might expect that it would be accompanied by a corresponding amount of fever. But this is very far from being the case. Generally, of course, in hæmoglobinuric fever the fever is smart, sometimes amounting to hyperpyrexia; but not infrequently it is very slight or insignificant, and yet in such a case the associated hæmoglobinuria may be decided or even severe. Thus Corre narrates a case of a native woman at Nossi-be who refused to lie down during an attack of hæmoglobinuric fever; it is evident that in her case fever was absent or only trifling. Crosse, too, mentions a case in which during four attacks of hæmoglobinuria there were no marked constitutional symptoms or fever of importance. In conversing with several gentlemen, who had themselves suffered from the disease, I have been struck with the mild character of the constitutional symptoms they describe as accompanying some of their attacks.

Another clinical fact I may remark on is the abruptness with which the fever concludes, sometimes within a few hours, after the explosion of the hæmoglobinuria. Malarial fevers of severe type do not come to an end thus abruptly, and are not thus accompanied by low temperature and absence of constitutional symptoms.

Then, again, the peculiar cyclical character of the antecedent fevers which for months, or perhaps for years, precede the attack which is accompanied by hæmoglobinuria. These antecedent fevers seem, in some instances, to be very mild, and to recur with wonderful regularity once a month or once a fortnight, or at some more or less regular interval. This spacing of the cycle is not quite like that of an ordinary malarial fever, which is, as a general rule, either quotidian, tertian, or quartan.

The general employment of quinine in the treatment of hæmoglobinuric fever and of the recurring fevers which lead up to it—and which really seem to be hæmoglobinuric fever without the hæmoglobinuria, if I may so describe them—might be advanced as evidence for the malarial nature of the disease. But before concluding that this

popular employment of the drug is really founded on its curative powers and not simply on fashion, we ought to have some accurate knowledge of the natural evolution of the disease unmutilated by quinine. I have not come across the record of any such case; but we can see, if we refer to the published cases of hæmoglobinuric fever, that the fever has in many instances persisted for several days in spite of liberal dosing with quinine from the outset.

From a purely clinical stand-point I cannot see that there is sufficient evidence for regarding hæmoglobinuric fever as an ordinary malarial disease. Such evidence suggests rather, especially when taken along with the epidemiological facts I am about to detail, that in most instances we should regard the cases met with in practice as being of a compound character, resulting from two morbid influences: first, malaria proper; second, another poison, which determines a mild type of fever, but which also tends to produce hæmoglobinuria. But just as malaria may exist without this mild fever or its associated hæmoglobinuria, so hæmoglobinuric fever may exist without malarial complication. Clinical facts tend to show that the occurrence of the one type of disease favours the explosive manifestation of the other, and thus it is that so many of the cases appear to be of a dual character.

Looking at the question from an epidemiological point of view there are three things which particularly strike me:

First. Hæmoglobinuric fever, though not absolutely unknown in one or two places bordering on the Mediterranean, is practically confined to the tropical and subtropical regions of Africa and America. It is almost if not altogether unknown in India, the Eastern Peninsula, the islands of the Eastern Archipelago, North Australia, and China.

Second. Whereas hæmoglobinuric fever is by no means a rare occurrence in Europeans who have returned to Europe from the endemic area of the disease in Africa, there is no record of such an occurrence in malarials who have returned to Europe from the malarial countries of Asia and Australia.

Third. There is no distinct account of hæmoglobinuric fever in medical literature prior to 1850; and there is some evidence that of late years the endemic area of the disease has extended its borders.

Now, if any or all of these propositions can be established it is evident that we have in hæmoglobinuric fever

something different from ordinary malarial infection. For if hæmoglobinuric fever were only an expression of malaria why is it not frequently met with in India, China, and other highly malarious countries outside the African and American continents? Why, if it is a common expression of malaria in subjects returning from Africa, is it not at all events an occasional expression of malaria in malarials returning from other countries? And why is it that so striking a disease had not been described before 1850, and that it appears to be extending its area of late years, seeing that malaria has existed from time immemorial in many countries, and certainly in those in which hæmoglobinuric fever seems to have appeared but lately?

I shall examine several of these points in some detail.

First. With reference to the relative geographical areas of ordinary malaria and hæmoglobinuric fever.

In the tropical zone of Africa, especially on the western side of the continent, Blackwater fever, or Hæmaturic fever, as it is called there, is so common that every European frequenting these parts is familiar with it. In many districts nearly every European expects to get it sooner or later if he remains in the country long enough. There are reliable statistical data for this statement. The French writers have compiled valuable statistics on the subject, and these I am enabled, by the kindness of Dr. Grattan Guinness, to supplement by others of an interesting and convincing character.

According to Bérenger-Féraud 38 per cent. of Europeans residing at certain French settlements at Gaboon and on the Gold Coast, 28 per cent. of those residing on the Upper Senegal, about 15 per cent. of those at Cozamance and on the Rio Nunez, about 8 per cent. at Cayor, and from 1 to 3 per cent. of the European inhabitants of St. Louis and Gorée are annually attacked with hæmoglobinuric fever.

I have arranged in tabular form certain statistics showing the mortality among the *employés* of the Congo Free State from October, 1878, till the end of August, 1892. The figures deal with 938 Europeans. Including the time occupied on the voyages to and from Africa, the average duration of each man's service amounted to about 20.25 months. Of the 938 men, in the course of this very short service of considerably less than two years, 157, or nearly one-sixth, died. Of the 157 deaths, seventeen are attributed to hæmaturic fever. But as the returns of death were not very accurately made—as might be expected under the circumstances—we may be certain that while all those who

are stated to have died of hæmaturic fever did so die, it is highly probable that of the fifty-five deaths attributed to fever, and of the nine of whom the cause of death was not stated, not a few died of the disease we are considering. We are under the mark, therefore, when we conclude that 11 or 12 per cent. of the deaths of those Congo Free State *employés* were caused by hæmoglobinuric fever. Corre states that the mortality in this disease varies in different countries and at different seasons of the year, ranging from 11 per cent. to 50 per cent. of those attacked. Probably 25 per cent. may be taken as an average mortality. Applying this to the Congo State statistics, it would give us about seventy-eight cases of hæmoglobinuric fever in the total number of 938 men during the twenty months of their residence in Africa. This, however, does not represent quite faithfully the true position of the morbidity and mortality and risk to European life from the disease. Ordinary remittents and intermittents and other climatic diseases like dysentery, sunstroke, and tropical typhoid, are much more prone to attack the new-comer than the old resident. But the case is exactly the opposite with hæmoglobinuric fever. It may and does attack the new-comer, but in the majority of instances it is the disease of the acclimatised—of the old resident. Thus, of the fifty-five deaths from "fever" mentioned in the Congo State statistics the average duration of residence in Africa of the victims was only twelve months; whereas in the case of those who died of hæmoglobinuric fever it was 31.8 months. So that if the average duration of residence of the *employés* of the Congo Free State had been five years, instead of something less than two, the proportion of deaths from hæmoglobinuric fever would have been very much greater. Of the seventeen deaths actually registered as being from hæmoglobinuric fever, only two of them occurred under nine months' residence; the majority had been in the country over twenty months.

TABLE *showing the Mortality, the Causes of Death, and the Duration of Residence on the Congo of those who died of* 938 *employés of the Congo Free State with an average age of* 29 *years and an average residence there of* 20.25 *months. The statistics apply to the period between October*, 1878, *and August* 30*th*, 1892.

Disease.		Deaths.		Length of Residence.	
Fevers	Fever	42	55	$12\frac{3}{7}$	12 months.
	Bilious fever	6		$14\frac{1}{3}$	
	Brain fever	6		$6\frac{1}{3}$	
	Intermittent fever	1		4	
Hæmaturic fever		17		$31\frac{14}{17}$	„
Intestinal flux	Dysentery	14	17	9	$11\frac{8}{17}$ „
	Intestinal dyspepsia	1		28	
	Bowel complaint	1		13	
	Chronic diarrhœa	1		28	
Hepatic	Liver complaint	3	5	$16\frac{1}{3}$	$15\frac{4}{5}$
	Liver abscess	2		15	
Sunstroke		8		10	„
Nervous system	Brain disorder	1	5	1	$12\frac{2}{5}$ „
	Apoplexy	2		15	
	Delirium tremens	1		24	
	Meningitis	1		7	
Pulmonary	Pneumonia	1	2		$2\frac{1}{2}$ „
	Congestion of the lungs	1			
Miscellaneous	Diabetes	2	6	5	$9\frac{1}{3}$ „
	Anæmia	1		16	
	Heart disease	1		3	
	Blood poisoning	1		14	
	Congestion	1		13	
Violent deaths	Drowning	11	26		14 „
	Other accidents	2			
	Killed in fight	4			
	Suicide	4			
	Killed by buffalo	1			
	„ hippopotamus	2			
	„ crocodile	1			
	„ snake	1			
Fatigue and exhaustion		7		14	„
Not stated		9		$14\frac{6}{9}$	„
		157			

The statistics of several of the missionary societies on the Congo, with which Dr. Grattan Guinness and others have very kindly supplied me, tell, as far as they go, exactly the same story. Thus, of 161 missionaries who have lived in this region in recent years 43 have died in the country. The figures are as follows:—

	Numbers.	Invalided.	Died.
Congo Balolo Mission	26	... ...	2
Baptist Missionary Society	60	... 3 ...	23
Livingstone Inland Mission	44	... 4 ...	11
Swedish Missionary Society	31	... ...	7
	161	7	43

The returns as to the exact cause of death are complete

only as regards the Baptist Missionary Society. Of the 23 deaths in this mission six are attributed to hæmoglobinuric fever.

As regards other parts of the West Coast of Africa, we have the evidence of Easmon (*Med. Times and Gaz.*, Aug. 29th, 1885; and a special report made for the Government of the Gold Coast) and Prout (*Lancet*, 1st Aug., 1891) as to the frequency of the disease on the Gold Coast; of Crosse who in his recent work already referred to, on the *Malarial Fevers of the River Niger*, gives similar testimony as to that district; and of several of the Army Medical Reports in which allusion is made to the disease as it affects Sierra Leone, Cape Coast Castle, and other British settlements in that part of the world. There cannot, therefore, be the slightest doubt about the extreme frequency of hæmoglobinuric fever all along the western side of tropical Africa.

On the Eastern side of the continent it may not be quite so common, but still it is now well known to be far from rare in many districts. Thus it is well known and has often been described by the French naval medical officers stationed at Nossi-bé, Mayotte, and Madagascar. Dr. Castle (*Lancet*, 25th April, 1891) gives a short description of what undoubtedly is hæmoglobinuric fever at Usambara, East Central Africa. Our naval medical officers have frequently met with it on the Zambesi; and Dr. W. A. Scott (*Edin. Med. Journ.*, Nov., 1892) gives an admirable and unmistakable description of two cases occurring in the Shiré highlands, British Central Africa. Surgeon-Captain Parke describes his own attack of hæmoglobinuric fever when crossing the eastern part of the continent; and doubtless there are other allusions to this disease in periodicals which have escaped my notice. What I have said is, I trust, sufficient to establish the fact of the occurrence of the disease in many parts of tropical Africa, and its extreme prevalence in some.

As regards America there is abundance of evidence of the existence of hæmoglobinuric fever both in North and South America, and in the West India Islands. The medical journals of the Southern States of the Union record numerous cases of local origin. Sullivan speaks of its frequency in Cuba. Many French writers testify to its prevalence in Martinique and other French possessions in the West Indies and in South America. Prof. Magalhães of Rio de Janeiro informs me that he has not met with the disease in Brazil; but further north, in Venezuela, it is well known, and Dr. Ackers of Caracas tells me that,

though not common in the highlands of that country, it is exceedingly prevalent in the plains and very deadly there.

The case is very different as regards Asia. By diligent search in such Anglo-Indian literature as seemed likely to yield the information I have done my best to procure reliable evidence for the existence of hæmoglobinuric fever in India; but I have completely failed to get anything like a description of cases at all corresponding to the African or American disease. Dr. Norman Chevers (*The Diseases of India*, 1886), a man of great erudition and experience, and also a keen and enthusiastic observer, makes no mention whatever of such a disease. He mentions the frequency of the various forms of hæmorrhage to which the victims of malaria are subject, and he shows that he was familiar with the literature of ordinary hæmoglobinuria—so that he was not likely to fail to observe and note so remarkable a disease as hæmoglobinuric fever had he encountered it—yet, in his elaborate work, he makes no allusion whatever to such a condition. Maclean (*Reynolds's System of Medicine*), Fayrer (*Climate and Fevers of India*, 1882), and Martin (*The Influence of Tropical Climates*, 1853) are equally silent on the subject. Morehead (*Researches on Disease in India*, 1860) makes no specific mention of hæmaturia or hæmoglobinuria in fever. He refers to jaundice as occurring in remittent fever, and he does mention one case in which the urine was of a deep brown colour, but he gives us no clue as to the cause of this colour, and we are left to infer that it arose from biliary staining, or possibly from ordinary hæmaturia. Morehead was a very close observer, and certainly would not have overlooked the occurrence of hæmoglobin in the urine had so striking an appearance been at all common in his field of observation. Moore (*Manual of Diseases of India*, 1882), speaking of the complications of fever, says: "The occurrence of jaundice during fevers has led to the term 'bilious remittent'. In this form of the malady jaundice often appears from the outset, and vomiting of dark-coloured matter is an early symptom. The urine is often coffee-coloured, owing not to bile, but to blood." But he does not state if this remark is founded on personal observation of what actually occurs in India, or if it is borrowed from others and possibly applicable only to disease in some other part of the world. And again, speaking of intermittent fever, he says, "albumen, renal casts, and blood will probably indicate some pre-existing tendency to kidney-disease". All this is some-

what indefinite, and may not refer to India. I do not think that either Morehead or Moore could have seen, or that they refer to genuine hæmoglobinuric fever. Hirsch cites Day (*Indian Ann. of Med. Sc.*, 1859) as authority for the existence of the disease in India; but, on turning to the article referred to, I find that what Day describes is simply "bilious remittent", and that there is no reference whatever in his article to anything which could be construed as hæmaturia or hæmoglobinuria.

The only allusions to a condition at all resembling African hæmoglobinuric fever which I can find in recent Indian medical literature are by Firth and Notter (both in the Appendix to the *Report for* 1885, *Army Med. Dep.*, pp. 367-377). The former, in 1,033 cases of intermittent fever, found that 25 were accompanied by jaundice simply—that is, 2.5 per cent.; none had icteric urine, and only 11 had hæmatinuria, or about 1 per cent.; but he does not say anything about the amount of hæmatin in these cases, and, from the context, we are led to infer it was merely a trace. Of 221 cases of remittent fever 4 had well-marked jaundice alone; 2 had jaundice together with hæmatinuria; and 2 had jaundice, hæmatinuria, and icteric urine. Two of the cases came under his own observation —one at Mian Mir, the other at Amritsar. The former had well-marked jaundice, and, on the day following the appearance of the jaundice, the urine became dark smoke-coloured and gave a biliary reaction. It contained hæmoglobin, a few blood-corpuscles, but, until two days before death, no albumen. The second case appears to have been similar, with the exception that the urine "was at no time albuminous". Notter says: "A form of malarial disease which I have seen in Meerut, and in no other station, is paroxysmal, congestive hepatic hæmaturia. The hæmaturia intermits—one day clear and without albumen, the next day chocolate-brown and containing much albumen, the *débris* of blood-cells, casts, and coloured granules, but no corpuscles." It is difficult, from the very meagre account we have of these cases, to come to a definite conclusion about their nature. In Firth's cases the absence of albumen and the small amount of hæmoglobin—only sufficient to make the urine smoky—is unlike African hæmoglobinuria. In Notter's cases the colour of the urine and the presence of a large quantity of albumen conform more to the African disease; but the absence of albumen on alternate days seems to negative this idea, as in African hæmoglobinuric

fever the albumen persists for a day or two after the hæmoglobin has disappeared from the urine.

The older Indian writers, with the majority of their modern successors, are equally silent on this subject. The reason for their silence is evident; they concerned themselves only with Indian disease; they did not write of hæmoglobinuric fever in India because it did not and does not, in its typical form, exist there. Certain French writers say that our English authors have overlooked this condition and confound hæmoglobinuric fever with ordinary bilious remittent. But this is not so. English writers, when they have the chance of seeing the disease in Africa, as some of them in recent years have had, and as Sullivan had in Cuba, recognise it, and regard it as a distinct form of fever—quite distinct from bilious remittent. We must conclude, therefore, that hæmoglobinuric fever does not occur in India, or is exceedingly rare there. Either this, or we must—contrary to all experience in other medical matters—indict the profession in India as being extremely careless and singularly deficient in the faculty of observation, and as having for all these years entirely overlooked a most striking, obtrusive, and important medical fact. This, of course, is absurd.

As regards the other parts of the Far East, I can find no good grounds for believing that hæmoglobinuric fever exists there any more than in India. If it does exist, it is found in very limited districts only. I have interrogated, either personally or by letter, many of my professional friends in the Straits of Malacca and in China, but, with one or two exceptions, one and all agree in saying that they have never seen a case of the disease, and several of them absolutely deny the existence of hæmoglobinuric fever in the districts with which they are familiar. Dr. Simon, of Singapore, says that, although he may have heard vague reports about such a disease he has never come across a case himself; and his experience has been a very large one, embracing patients from all parts of the Malay Archipelago as well as from China and India. Dr. Bentley, who has practised in Java as well as in Singapore, makes exactly the same statement. Dr. Walker, of Sandakan, Borneo, is not familiar with the disease; he can recall only one case, seen in the convalescent stage, which might have been of this nature. Dr. Atkinson, of the Civil Hospital, Hongkong—a great gathering place for sick people from all parts of the East, as well as for local patients,—and there is much and very severe malarial

disease in Hongkong, or rather in its outskirts—says: "Very frequently the urine contains albumen, and is darker than usual, but I have never met with hæmaturia occurring in a seemingly remittent fever case." Dr. T. Rennie has never met with it in South Formosa or in Foochow; Dr. A. Rennie has never seen it in Tamsui, North Formosa, where malarial fevers are particularly rife. Dr. Jamieson, Shanghai, says: "I have lately gone over my quarter of a century of voluminous observation of cases of malarial fever, and I have been surprised myself by the fact that I have never once noted the occurrence of hæmoglobinuria." As regards my own experience in Formosa, Amoy, and Hongkong, I have never seen what I could be sure was a case of hæmoglobinuric fever. I twice saw hæmoglobinuria in natives in Amoy. The patients were out-patients, and walked to the hospital; so that there could not have been much fever about them. As they only attended once they were lost sight of. I believe they were merely examples of ordinary hæmoglobinuria.

Several French writers allude to the occurrence of hæmoglobinuric fever in Cochin-China; unfortunately, I have not had an opportunity of seeing the original thesis to which they all refer. That some such fever exists there is rendered very probable by the following remarks by Dr. Wenyon, of Fatshan, China: "The fever which ravaged like a plague the Chinese army on the Tonquin border of Kwangsi, in 1885, was frequently accompanied by hæmoglobinuric symptoms; but I was not allowed to deal with or examine medical cases there; the officials told me that I had only been sent up to treat surgical cases. Beyond the fact that some such fever was prevalent and very fatal then, I know little about it. I have seen two or three marked cases in this neighbourhood (Fatshan), but, with one exception, have seen none of these cases more than twice. The exception was a case which I had in hospital three months ago. He was a Hunan man, about 40 years of age, in a low typhoid condition when brought to hospital; temperature, 105°; daily remissions, but for six days never below 101°; urine, port-wine colour, contained both albumen and hæmoglobin, but the quantity of albumen was small. I did not venture to give antipyrin, the man was so weak, but gave quinine and tincture of bark. On the sixth day the temperature was normal, urine of a natural colour, and the man felt so much better that, in spite of persuasion, he left the hospital."

I think, therefore, that although hæmoglobinuric fever,

or a disease in some respects resembling it, may be found in one or two places in Asia, it is, to say the least, exceedingly rare in most of the highly malarious regions there, in fact, practically unknown.

Second. The second epidemiological circumstance pointing to specific differences between ordinary malaria and the poison causing hæmoglobinuric fever is this :—The number of Europeans in India, China, and the East generally is very considerable, and every year there are hundreds who return to England and to Europe suffering from different forms of fever and malarial disease. I have never heard of, read of, or seen an instance of hæmoglobinuric fever among these Anglo-Eastern invalids. In tropical Africa the number of Europeans is comparatively small, and the number of invalids returning to Europe from that country insignificant as compared to those returning from the East. Nevertheless, in my own very limited experience I have seen in England two cases of hæmoglobinuric fever in Anglo-Africans, and within the last few months I have heard of at least half-a-dozen other and similar cases; in fact, it would seem to be by no means an uncommon occurrence.

In France we note exactly the same thing. Every year multitudes of invalids return to that country from Cochin-China and Tonquin and other French possessions in the East—many of them highly malarious; but yet there is no record, as far as I know, of a single case of hæmoglobinuric fever developing in France among these Franco-Eastern invalids. But I can refer to at least five cases in recent French literature in which hæmoglobinuric fever developed in Frenchmen who had returned to France after passing some time in Africa. Bérenger-Féraud records two (*Arch. de Méd. Nav.*, Oct. 1882), one of the cases occurring six or seven months after the patient had returned to France from Mayotte; the other three months after return from Senegal. Rouvier (quoted by Corre) records a similar case;—a soldier who developed the disease in Toulon after serving four years in Senegal. Finally, Kelsch and Kiener detail a fifth case which they observed in Paris in the person of an African traveller who, returning to France in January 1883 developed a series of attacks of hæmoglobinuric fever the following May.

Besides the English cases of which I had personal cognizance, I can refer to four other instances of hæmoglobinuric fever of African origin developing in this country. One case is mentioned in Crosse's book. The

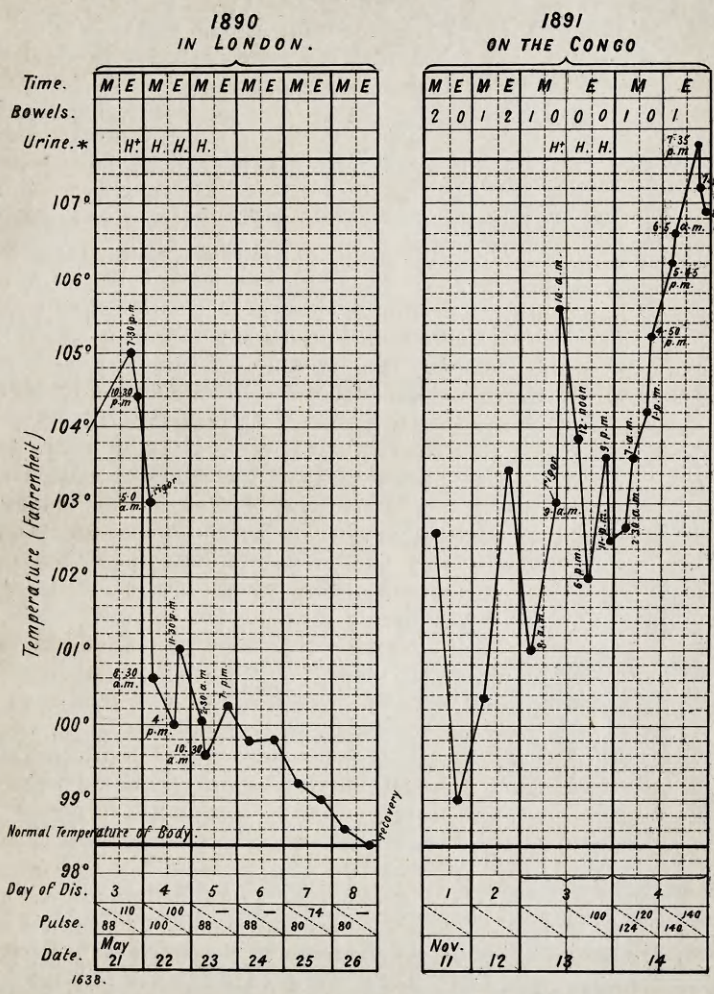
patient while in Africa had attacks of hæmoglobinuric fever in December 1890, and again in March 1891. He then returned to England, and in August of that year, while at Eastbourne, had another attack described as "simple hæmaturia". Another case was alluded to by Dr. Samuel West at the meeting of the Pathological Society on the 31st January last; the patient was under his care; the disease developed in London, and proved fatal.

The two cases which came under my own observation, and to which I have already alluded in some detail, occurred within a few days of landing in England, and about a month after the patients had left the African endemic area. They need not be further alluded to at present; but as the subject is one of some novelty, as well as of importance, I shall add a *précis* of the notes of two other cases which have come under my notice indirectly. For the notes of the first of these I am indebted to Dr. Grattan Guinness, and for those of the second to the patient himself, and to Dr. Hadden, of Dublin.

Mr. N. (Chart I), a missionary, three-and-a-half years on the Lower Congo, at a station some 180 miles up from the mouth of the river, about the end of March 1890 started for England on furlough. On his way down country he was very feverish and had to lay up *en route* at one of the mission-stations with a smart attack of what was considered to be ordinary malarial fever. No sooner had he recovered somewhat than he was called on to nurse a fellow-traveller, a lady, during a severe attack of hæmoglobinuric fever of which she died. On board steamer he was fairly well, only suffering from the cold weather experienced after passing Madeira. The night he landed at Southampton it was cold and raining, and to a chill caught then he attributes an attack of fever that evening. This was on the 19th of May. On the morning of the 20th he had so far recovered as to be able to move about a good deal in London. The weather was cold at the time, and he felt chilled. The same evening he had a severe rigor, lasting about three-quarters of an hour. Before and after the occurrence of the rigor he had taken quinine, and, also, after the rigor, fifteen grains of antipyrine. On the morning of the 21st May he felt fairly well, but during the course of the afternoon he had a recurrence of rigor, and when Dr. Guinness saw him at 7 P.M. he was passing into the hot stage of the fever. His pulse was 110, and his urine was high-coloured,

CHART Nº 1.

CHART Nº 2.



1638.

*H indicates the occurence of Hæmoglobinuria.

depositing an abundant sediment of urates, but no trace of blood or hæmoglobin was recognised. Quarter of an hour later urine was again voided, and now, for the first time, contained blood, or, rather, hæmoglobin. At this time his temperature was 105°, and his skin, though warm, was neither harsh, nor dry, nor perspiring. He complained of aching of the loins and heaviness of the head. At 9 P.M. he began to perspire freely, but his temperature still remained high—105°, his pulse hard and bounding, and his urine was dark from hæmoglobin. At 10.30 P.M. temperature had fallen slightly to 104.4°, and he was dull and heavy-looking. Shortly after midnight he had a copious motion after an enema; his temperature then fell to 103°, and he perspired freely. About 4 A.M. he had another rigor, but temperature did not rise, and perspiration became profuse. It was then noticed that his skin and scleræ were icteric. At this time the patient became very desponding and thought he was going to die. His urine was still very dark, and was passed with pain, and frequently. Temperature, however, steadily fell, and by the evening of that day he felt better. After a restless night, on May 23rd the urine was still dark and albuminous, and was passed with some discomfort; but towards evening it had cleared up in great measure, and the yellow colour of the skin was less decided. The temperature was then only 100°. The note on May 24th is to the effect that he had passed a good night, and that he improved further during the day. After this date there was no return of the fever, and the patient gradually regained his usual health. During the attack he was treated with liberal doses of quinine, to the amount of eleven grains on the 20th May, thirty grains on the 21st, and sixty grains on the 22nd. He had also several doses of gallic acid, besides purgatives.

Unfortunately, the history of this case does not stop here. In May of the following year Mr. N. returned to the Congo. During the first few months he kept well, and it was not until September that he began to get fever again, and then it was only a slight attack lasting a couple of days or so. He was careless in exposing himself to the sun and weather, and he worked very hard. About the beginning of November he complained of feeling tired, sleepless, and without appetite, but still he persisted in working and going about. On November 11th he began to get fever of a remittent character. On the 13th hæmoglobinuria set in, and on the evening of the following day

he died, urine having been suppressed for nearly twenty-four hours, and the temperature having risen to 107.8° (Chart II). During this attack, as on the previous occasion while in England, he was liberally dosed with quinine.

Another missionary who had suffered from hæmoglobinuric fever in Africa informed me that he had lived in the Congo country from April 1889 till the summer of 1892, when he returned to England. During his residence in Africa he had frequent attacks of fever. One attack, which may have been typhoid, was more severe than the others, as it laid him up for three or four weeks; the other attacks lasted only a day or two. Just before leaving for England he had two attacks of what he calls "intermittent", but on leaving the Congo on 10th June 1892, and for a fortnight afterwards, he was quite well. On his way up the African coast he contracted dysentery at Lagos, and during the remainder of the voyage he was very ill. For a week before arriving in England he had attacks of irregular feverishness, chills, and vomiting, but he saw no sign of blood in his urine. He arrived in England on 23rd July. On the evenings of the 25th, 26th, and 28th he had fever, but he was well enough to be about on the 29th. Three weeks later, on the 20th August, being then in Ireland, he believes he caught a chill. Next day, finding that his temperature at 1 P.M. had run up to 103°, he went to bed and took a purgative and a hot drink. By 7 or 8 in the evening he had perspired freely. He then took fifteen grains of quinine and fell asleep. About 9 o'clock he woke up feeling chilly and very ill. Vomiting and severe rigor then set in. Dr. Hadden of Dublin, who saw the patient, describes the shivering as "the most alarming and violent rigor he had ever witnessed". By midnight the patient appeared to Dr. Hadden to be dying, his pulse being scarcely perceptible at the wrist, and his temperature over 104°. The urine passed an hour before was of a brownish black colour, had a distinct sediment, and coagulated on boiling. Warm bottles were applied to the body, and gradually the violence of the rigor abated and the patient's condition improved. In the morning he himself noticed that his urine was dark-coloured, and Dr. Hadden ascertained that it still contained albumen. By evening, however, the fever had subsided, and in a few days the urine had quite cleared up, and the patient was about as usual. There has been no recurrence of the fever or of the hæmoglobinuria, and when I examined the urine a month ago it was perfectly normal.

Besides these six English cases I have heard of others, but cannot supply particulars. Disregarding them, but including the French cases already referred to, we have the record of eleven well-authenticated examples of hæmoglobinuric fever which have occurred comparatively recently in France and England in Europeans who had resided for some time in Africa. Although I have been on the outlook for such cases, I have not seen or heard of anything similar in anyone from India, China, or elsewhere in the East.

Third. With regard to the first part of the third proposition advanced, viz., that there is no distinct account of hæmoglobinuric fever in medical literature prior to 1850, I can only say that, with the exception of one short passage in Boyle's *Practical Medico-Historical Account of the Western Coast of Africa*, published in London in 1831, I can find no allusion in medical literature prior to the year mentioned which might be construed as referring to this affection. And even this possible allusion by Boyle is in a sense second-hand, for it is quoted from a report by Tidlie, written in 1822, on the *Epidemic Fever of the West Coast*, and all that it says on the subject is that sometimes "the urine has the appearance of bloody water". It is very strange that a condition so alarming, so unusual in ordinary fevers, and one so calculated to force itself on the attention, should have been systematically overlooked by generation after generation of medical men, had it been in former days at all common, or anything like so common as it is at present.

In a valuable thesis on the *West African Fever*, by Dr. Battersby, which I have had the privilege of reading, the following passage occurs: "It is hard for anyone who is familiar with the fever to believe that this prominent symptom" (referring to the hæmoglobinuria) "could have been overlooked, as its appearances are so characteristic, and the course of the disease so defined, that it is difficult to make a mistake in diagnosis." I think it very probable that this absence of allusion to Blackwater fever until recent years receives its explanation in the second part of my third proposition, which is to the effect that there is evidence that of late years the endemic area of this disease has extended. Positive evidence to this effect is wanting as regards Africa, but it is forthcoming as regards America, and can be found in the medical journals of the Southern States of the Union. I am sorry that, owing to difficulties of reference, I have been unable personally to

go over this evidence in detail, but it has been carefully studied by Hirsch, who distinctly says, in his *Geographical and Historical Pathology*, under the heading of "New Types", that hæmaturic fever is really a new disease, or, rather, according to his view, a new form of malarial disease. He is very positive about its recent extension in the United States, and quotes many American writers in support of his allegation. Hirsch is a most careful and critical writer, and one not likely to fall into error in such a matter. Now, if hæmoglobinuric fever has extended in America within recent times, is it not reasonable to explain the silence of the older writers on African disease by the supposition that the appearance of hæmoglobinuric fever on the West Coast of Africa is but a comparatively modern event. Dr. Battersby, who has seen much of the disease on the Niger, and, moreover, has had personal experience of it, tells me that he thinks this formidable affection is becoming year by year more prevalent in this part of Africa.

From these, and from other considerations, I think that there is good *primâ facie* evidence for the truth of my conjecture that hæmoglobinuric fever is not simply a form of ordinary malarial fever, but that it is dependent on a poison which, though resembling in some of its effects ordinary malaria, differs from it in other respects very materially. Whether this difference is, in a biological sense, a specific one, or only of the nature of a variety, I cannot say; nor shall we be able to pronounce on this until our knowledge of the malaria-germ itself has extended very considerably; but certain it is that there are strong clinical, historical, and epidemiological grounds for believing that these two morbid states are neither etiologically nor pathologically identical.

Thinking I might get some information on the subject from direct observation of any germ which might be present in the blood in hæmoglobinuric fever, I made two prolonged examinations of the blood of the patient whose case I describe at the beginning of this paper. I searched many slides of his blood on two occasions, each examination lasting perhaps for a couple of hours, and carried out in conformity with Laveran's directions. But I cannot say positively that on either occasion I saw unquestionable malaria plasmodia. There were certainly no crescents and no flagellated organisms present. I did see, however, three bodies which possibly were, and which answered in a rough way to the description of two of the forms of Laveran's bodies. In two of the instances they

appeared to be intracorpuscular and were spherical or discoid in shape, occupying the whole of a corpuscle with the exception of a narrow rim of normally-coloured hæmoglobin. They were colourless except at the periphery, which was encircled by a corona of very minute dark pigment-granules. The third body observed had the appearance—obscurely indicated however—described as the "rosette" form of the plasmodium, and was considerably smaller than the other two, occupying perhaps about half only of the corpuscle it lay in. I saw no bodies having amœboid movements, either outside or inside the corpuscles, and no free bodies such as have been so frequently described as characteristic of malarial blood. As regards the intracorpuscular bodies I did see, I cannot avoid the impression that possibly they were the result of changes in the corpuscles of a degenerative character, and in some way a result, and not a cause of the hæmolysis which was in active progress at the time of my examination. It is possible that this absence of parasites, or, assuming that the three bodies I did see were parasites, that this comparative absence of parasites may have been owing to the circumstance that my examinations were made rather late in the fever, as it was not until after the sweating stage had set in, some five hours from the commencement of the initial rigor, that the first examination was made, and the second not until the afternoon of the following day, and, moreover, that the patient had been taking quinine freely. Still, I cannot but think that if hæmoglobinuric fever is caused by the germ reputed to be the cause of malarial fever, and especially if the extensive blood-destruction which I saw in progress was the result of the mechanical presence of the plasmodium malariæ in the blood-cells, as Laveran and others maintain, I ought to have seen the parasite in proportionate abundance, and many examples of them in every field of the microscope. I have come across no observations by others on the blood of hæmoglobinuric fever undertaken with special reference to the presence or absence in this disease of the malarial plasmodia. Such observations are much wanted; but I may remark that before they can be made with sufficient frequency, it will be necessary, in order that the observations and experience of the busy practitioner may be utilised, that the present methods of search be simplified, made more reliable, and, above all, more expeditious. A clinical method for diagnosis which requires one or two hours to apply is practically useless.

I might here remark that, as regards this hæmolysis which occurs both in hæmoglobinuric and in ordinary malarial fever, my view of the matter is that it is not a direct result of the mechanical presence of a plasmodium, or of other protozoal organism in the diseased corpuscles themselves. I have examined blood from cases of Asiatic malarial fever, as well as blood from this hæmoglobinuric fever case, in which not one corpuscle in ten could be considered healthy, and yet the most careful scrutiny with high powers and suitable illumination entirely failed to discover more than two or three bodies which could be interpreted as being Laveran's bodies, and that, too, in the course of examinations lasting not for minutes merely, but for hours. Consequently, I look on the poikilocytosis in these cases as the result of poisoning of the blood by some product, or secondary effect of a disease-germ, and not of the direct mechanical action of the germ itself on each individual distorted corpuscle. The black pigment found in the organs in malaria may be directly evolved from the hæmoglobin by and while the plasmodium is epi- or intra-corpuscular, and be subsequently deposited in the well-known seats of malarial pigmentation; but the prodigiously extensive and often sudden hæmolysis and hæmoglobinæmia and poikilocytosis in some cases of malarial fever are surely the result of chemical poisoning, the hæmoglobin being subsequently deposited in the tissues as the ochre pigment of Kelsch and Kiener, or eliminated by the liver as bile pigment, or by the kidneys as hæmoglobin or hæmoglobin derivatives.

I should like to allude to one other matter which may possibly contribute to throw light on the etiology of this very obscure disease.

Whilst examining the urine of the hæmoglobinuric fever case I have so frequently alluded to, I came across some curious bodies, the nature and signification of which I am at a loss to explain. These bodies I found in the lowest layer of the sediment of tube-casts and granular matter deposited from the porter-coloured urine. They resembled in shape and size the ova of a parasite; but they were evidently not of this nature, as, though frequently occurring singly, they were usually arranged in groups of twos and threes (Figs. 2, 3, 4), the elements lying side by side with their short axes approximated, and not—as they would have been had they come from the uterus of a parasite—with the long axes approximated; very often, too, they were arranged in large bunches or clusters (Fig. 1), looking very

much like the end of a head of Indian corn. The individual bodies were dark reddish brown in colour—harmonising in this respect with the tube-casts and granular pigment matter among which they lay. It is just possible that these bodies were something which had got accidentally mixed with the urine after it was passed; but the way in which their colour harmonised with the other urinary deposits present is against such a supposition. Unlike the tube-casts and brown pigment matter, the oval bodies were not soluble in nitric acid, or liquor potassæ, nor were they affected by alcohol or chloroform. They were fairly uniform in size, measuring about 1-800″ by 1-1000″, or thereabouts. They had a distinct double outline, and, in many of them, at one end indications of an operculum, or, rather, absence of outer wall, were faintly distinguishable. They could not be fractured readily by pressure on the cover-

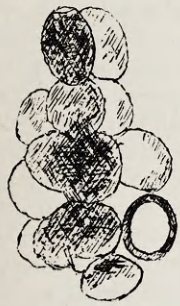


Fig. 1.

Fig. 2.

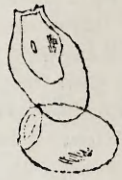


Fig. 3.

Fig. 4.

glass. I cannot say what was the nature of their contents, as the outer wall or shell was too opaque to admit of this being made out. On examining a specimen of the urine thirty-six hours after it was passed I found, in two examples (Fig. 3) at least, that the contents of these little bodies had escaped through a considerable and circular opening at one pole, and that the ova-like bodies were now hollow and filled with urine. That their original contents had escaped was evident, for I could make out the periphery of the cavity; and in the interior of one I saw a large bacterium moving about, showing that free communication existed between the interior of the body it lay in and the surrounding urine. The idea that they might have been some species of coccidium has occurred to me—perhaps because coccidia are coming into fashion just at present. Whatever their exact nature may have been, they were evidently an

organism of some sort, and not simply hæmoglobin or urinary crystals, and, as I have said, I do not think they were owing to accidental contamination of the urine. Future observers would do well to search for similar bodies in such cases; and when a search is undertaken it must be borne in mind that these bodies are of high specific gravity and rapidly sink to the bottom of the urine, and that therefore they will be present in the very lowest layers only.

Before concluding, there are two highly practical points I shall briefly allude to. The first has reference to the treatment of hæmoglobinuric fever; and I would ask what are the grounds for believing that this disease is amenable to quinine? In going over the literature of the subject, as well as in conversations with many individuals of African experience, I have been struck with the uniformity with which, so soon as fever shows itself in the endemic area of this disease, quinine is given, and generally in very large doses; and also that, notwithstanding this liberal dosing with quinine, how in many instances the fever goes on uninfluenced apparently, and perhaps increases in severity. It not infrequently happens that hæmoglobinuria occurs on the third or fourth day of this treatment, and while the patient is in a state of cinchonism. As regards this disease, as in many of the reputedly malarial fevers which I have read of and seen, I am often tempted to think that quinine, so far from being what it is so often called, our "sheet-anchor", is, on the contrary, a fashionable delusion. There is one thing which is very much wanted in therapeutics at the present day, and that is a scientific statement of the actual value of this drug in many tropical fevers, and a logical marshalling of the data on which much of its reputation is founded.

The other point I would refer to is the possibility of the extension of hæmoglobinuric fever to tropical regions of Asia hitherto exempt. It looks as if hæmoglobinuric fever had originated in Africa, and, like yaws, that it had been carried with the negro to America. That it has not as yet been carried to India and much of the Eastern world is possibly owing to the fact that the set of trade and communication with Africa has not been towards Asiatic countries; and because, when communication has taken place, it has been by slow and circuitous routes, affording time for infective individuals or materials to lose their specific disease-causing properties. But when communication becomes more rapid and more direct, I think it does not require much prescience to foretell that there will

ensue an infection of Asiatic soil with African hæmoglobinuric fever-germs, and that in time this disease will establish itself and spread on the Asiatic continent. If the hæmoglobinuric fever-germ is allied to the malarial fever-germ, as the latter has been so the former may be transported to virgin soil. Who can tell what will be the effect in the dissemination of such diseases of such a revolutionising influence on the trade routes of the world as the successful opening of the Panama Canal? A direct trade in fast steamers would immediately ensue between Panama and Hongkong, Manila, Singapore, and India. At present there is no direct trade between tropical America and these places. But the time will come when Panama and the West Indies will have direct communication with the great ports of Eastern Asia, when trade will no longer follow the circuitous route *viâ* San Francisco and Japan, but will proceed by the shorter and more direct route of a few days only across the Pacific. When this comes about the time may not be very far distant when African and American diseases will appear in Asia, and among them hæmoglobinuric fever, and also the somewhat similar but more formidable yellow fever.