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HAEMOGLOBINURIC MALARIAL FEVER

or

BLACKWATER FEVER.

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by

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HAEMOGLOBINURIC MALARIAL FEVER.

OR

BLACKWATER FEVER.

Blackwater fever is a febrile disease of which the most characteristic feature is the secretion of haemoglobinous urine. Haemoglobinuria in itself, however, does not constitute blackwater fever, for as is well known, it may be produced under other conditions. Thus there is what is called paroxysmal haemoglobinuria, the exciting cause of which is supposed to be cold, though it may follow muscular exertion or trauma. Then there is the definitely toxic haemoglobinuria which may complicate scarlet fever and typhus fever, or may follow the administration of various substances such as carbolic acid, arseniuretted hydrogen, chlorate of potash, and glycerine, or which may occur after transfusion of blood. Finally, there is the so-called epidemic infantile haemoglobinuria, an outbreak of which has been described by Winckel¹ as occurring in Dresden in 1879.

It would be satisfactory if a suitable name could be found which would serve to distinguish blackwater fever from the above mentioned varieties of haemoglobinuria, but in the absence of exact

knowledge as to its cause and pathology there is some difficulty in fixing upon a name which is not based upon a preconceived theory as to causation, and many of the terms which have been used to describe the disease* are based upon manifestly erroneous views. Personally, I regard blackwater fever as a manifestation of malaria, and for this reason consider that the name "Haemoglobinuric malarial fever" is a correct and scientific one, but as the designation "blackwater fever" is non-controversial and descriptive it is perhaps less open to objection. It has, however, one disadvantage, in that many people labour under the idea that the disease is so-called because it is brought on by drinking bad water. Hence arises the curious anomaly, that individuals of either sex who would be the last to mention the word 'urine' in polite society, have no hesitation in discussing blackwater fever at their dinner tables over their soup.

*

Scheube gives the following synonyms:-
"Bilious fever, Malaria biliosa haemoglobinurica, Febris intermittens perniciosa haemoglobinurica, Febris remittens haemorrhagica, Febris biliosa, Schwarzwasser Fieber, Bilious haemoglobinuric fever, Icteroide pernicious fever, Haematonic remittent, Yellow remittent, Black jaundice, Haemorrhagic malarial fever, Fièvre bilieuse hématurique, Fièvre bilieuse mélanurique, Fièvre ictéro-hématurique, Fièvre ictéro-hémorrhagique, Fièvre hémosphénurique, Fièvre ictéro-hémosphénurique, Fièvre pernicieuse ictérique, Accès jaune, Fièvre jaune des Crées ou des acclimatés, Fièvre bilieuse grave, Fièvre rémittente bilieuse.

There is no II. HISTORY.

According to Scheube² the first mention of blackwater fever can be traced to "the twenties of the nineteenth century", in reports of the French Colonial Medical Officers, and Plehn³ quotes Béranger-Féraud as stating that the disease existed in West Africa in 1820, and that it became prevalent in 1850. According to Easmon,⁴ Tidlie described the urine in the endemic fevers of Cape Coast as having the appearance of bloody water. Easmon himself first came across the disease on the Gold Coast in 1881. Crosse⁵ says that the first fatal case in the Gold Coast occurred in 1832, but he believed that it was not known on the Niger till 1888, though according to popular report a case occurred on the Niger Delta in 1882. Manson⁶ says that it was described first by French naval surgeons at Nossi-Bé in Madagascar. Sambon⁷ affirms that there was an epidemic in Sardinia in 1885, and also in Greece during the construction of the Canal through the Isthmus of Corinth, and that in America it is reported to have first appeared in Texas in 1866.

There is no doubt that it is only during the last twenty-five years that the disease has been distinctly recognised and described. My own impression is that it corresponds really to the malarial hæmaturia of the older writers, and that it has been endemic in tropical Africa ever since the first white man went there. In my experience malarial hæmaturia is an unknown condition, but as it is frequently referred to by the earlier travellers and writers, it seems probable that what they described was nothing more than hæmoglobinuria. With the opening up and colonisation of endemic malarial areas, blackwater fever has been definitely recognised as a distinct entity, and its differentiation from malarial hæmaturia has given rise to the mistaken belief that in some places it is of recent importation. This idea probably arose merely from the fact that what in former times was called malarial hæmaturia is now diagnosed as blackwater fever.

III. GEOGRAPHICAL DISTRIBUTION.⁸

The disease has a wide distribution, and is endemic in many more or less localised areas in both the old and the new worlds. The irregularity of this distribution will be referred to later, for it constitutes one of the very puzzling features of the disease, and one which has given rise to many speculations as to its cause. Probably the worst endemic regions of blackwater fever are to be found in the continent of Africa, more especially in that section of it which lies between the Tropics.

As regards British East Africa and Uganda, it is noteworthy that the disease is less prevalent along the coast line than in the immediate hinterland. In the intermediate zone between the coast and the central plateau - an area ranging in height up to 4,000 feet - malaria and blackwater fever are exceedingly common. On the high uplands, 5,000-6000 feet in altitude, malaria is not endemic, though both it and blackwater fever not infrequently develop among those who have contracted the infection elsewhere. On descending to the level of the Victoria Lake (4,000 feet) the malarial zone is again entered,

and blackwater fever becomes a common disease, and it occurs throughout Uganda, and along the whole valley of the White Nile.

As to the islands on the eastern coast of Africa, blackwater fever is not common as an indigenous disease in Zanzibar, whereas it frequently occurs on the neighbouring island of Pemba. It is very common in Madagascar, and it has been reported in Mauritius.

It is endemic throughout German East Africa, British Central Africa, the Zambesi Valley, and the Portuguese territories as far as Delagoa.

On the West Coast it occurs throughout the whole region lying between the tropics, more especially along the great rivers.

In North Africa blackwater fever is not common, but it is met with in Sicily, Sardinia, Greece, and Asia Minor.

Until recent years it was thought to be unknown in India, but it has been reported from Assam, Jeypore, and the Terai, also from Siam, Cochin China, Java, Borneo, and New Guinea.

It occurs in the southern states of America, and in some of the West Indian Islands, also in Central America, Venezuela, and Guiana, and in some parts of Brazil and Uruguay.

IV. SEASONAL INCIDENCE.

In Uganda malaria occurs with almost equal frequency at all seasons of the year, though a slight increase may sometimes be noted during the period between the approaching cessation of the rains and the beginning of the dry weather.

As regards blackwater fever, however, there is practically no definite seasonal variation. This is not surprising when we remember that the degree of malarial poisoning which, in my opinion, alone predisposes to the disease, develops as a rule slowly, and may not supervene until long after the initial attack of malaria. Hence it follows that there is often no correspondence between the seasonal incidence of the two diseases. As a matter of fact a bad malarial year is generally associated with an increase in the amount of blackwater fever, but owing to the possible action of disturbing factors this sequence cannot be considered an essential one. Thus, as often occurs, if a number of old residents are absent from their station and many newcomers have arrived, it is likely that malaria may be very rife and blackwater fever very scarce. These circumstances

explain the somewhat contradictory evidence that is sometimes produced with regard to the seasonal prevalence of the disease. Thus Thompson and Bennett state that in Southern Nigeria blackwater fever is more common in the dry season, whereas Plehn, speaking of the Cameroons where the climate is practically the same, says that it is more prevalent in the wet season.⁹ Other things being equal, it is, however, a practical certainty that in places where malaria shows a marked seasonal variation there will be a tendency to the production of a corresponding variation in the prevalence of blackwater fever.

V. RACIAL INCIDENCE AND IMMUNITY.

Black races seldom suffer from blackwater fever, but this implies no inherent racial immunity to the disease except that which results from an immunity to the malaria which causes it. In speaking of the immunity of natives to malaria, it must be understood that this indicates nothing more than that such people can harbour the malarial parasite without showing malarial symptoms. An analogous condition exists in the case of *Trypanosoma Brucei*, which affects wild game but little though it is rapidly fatal to domestic animals. It is certainly not to the advantage of a parasite that its presence should kill off its host, and consequently there is nothing surprising in Nature's arrangement that the inhabitants of endemic malarial areas should acquire a degree of tolerance which allows of the parasite living, as it were, on good terms with them. In the case of native children it is well-known that parasites are constantly found, even though there may be no symptoms beyond possibly some splenic enlargement. During infancy and early childhood the children do however occasionally exhibit the ordinary symptoms of malarial infection, but owing probably to a certain

degree of inherited immunity the disease is not as serious nor as fatal as it would be in European children. As they grow older the liability to such attacks diminishes, until by the time maturity is reached it ceases almost entirely, and speaking from my own experience I should say that adults rarely, if ever, suffer from malarial fever though the malarial parasites still remain. Great stress has been laid upon the fact that native children harbour the parasite, but so far as I know attention has not been drawn to the same thing in adults, but this is merely owing to the fact that in children the parasites are much more numerous and easily found. As a rule, if the blood of a healthy adult native be examined it may be difficult, if not impossible to find malarial parasites, but on several occasions when examining the blood of patients for other reasons, I have discovered parasites, though there were no malarial symptoms febrile or otherwise. In such cases, although no anti-malarial treatment was adopted, I have watched the gradual disappearance of the parasite, and during the whole time not a single sign of malaria has manifested itself. The conclusion I have arrived at is, that in endemic malarial areas most do not all harbour the parasite in small numbers. If the general health

suffers, from some extraneous cause, there may be a temporary increase in the numbers, but the immunity is so pronounced that no actual symptoms develop.

In regard to immunity there is another point of some importance to which fuller reference will be made when discussing the etiology of the disease. This is, that the immunity enjoyed by the aboriginal inhabitant of one malarious district does not necessarily protect him in another. If there is a specific difference between the type of malaria in each district, this fact is especially noticeable. Thus a man coming from a place where the benign forms of malaria are endemic may be immune to them more or less, but he is not immune to the malignant type.

Moreover, immunity to the malignant type in one district does not entirely protect from the same type in another district.

These facts incline me to the belief that there may be local strains of the same type of parasite which, though apparently similar morphologically, yet differ in quality and in virulence. This differentiation may perhaps be the result of their continual propagation from one individual to another in a very limited community, the habits of whose members may possibly further modify the parasites which

batten on them. Whether this is so or not, there remains the practical point that natives belonging to districts where malaria is not endemic suffer severely if exposed to it, and that if a native is susceptible to the attack of the malarial parasite he is liable to develop blackwater fever. I have myself only seen one case in a native and it exemplified the above fact. The patient was a boy belonging to a tribe which inhabits the healthy East African uplands where malaria is not endemic. He went to Uganda as a servant, suffered severely from malaria, and finally developed blackwater fever. In Uganda, practically the only sufferers are people alien to the country, such as Europeans, Indians, and Goanese, but as I have pointed out it is not entirely a question of race, and the occurrence of blackwater fever among natives has been reported by several observers.¹⁰

... was not only in individuals in whom there is a history of previous malaria contracted from their country, for it is very likely to recur, and I give two examples of this in Uganda, both of which ended fatally. In one the patient had served for over a year on an expedition in Central Africa, but had spent some months in England (12) ... In the other case the patient had been

VI. PREDISPOSING CAUSES.

Debility, anxiety, exposure and overstrain are all regarded as predisposing causes, but in my opinion these are of no importance when the malarial infection is absent, though they may act as exciting causes when the predisposition is already present. It is admitted by most observers, whatever their opinions as to the exact cause of blackwater fever, that residence in a tropical climate predisposes to the disease, that it seldom attacks newcomers, and that it is rarely, if ever, a primary disease. Thus Sambon¹¹, who believes in a special organism, writes, "Blackwater fever is seldom a primary disease, and seldom comes on within the first year". Personally I do not call to mind ever having seen or heard of a case occurring in Uganda during the first six months of residence. This does not apply to individuals in whom there is a history of previous malarial infection from another country, for in such it is very likely to develop¹², and I know of two examples of this in Uganda, both of which ended fatally. In one the patient had served for over a year on an expedition in Central Africa, but had spent some months in England before coming to Uganda. In the other case the patient had been

invalided from British Central Africa on account of blackwater fever, and was subsequently sent to Uganda. In both these instances a fatal attack of blackwater fever occurred within six months. Rees,¹³ however, affirmed that on the West Coast he had seen cases two or three months after the patient's arrival in the country. My own opinion is that the occurrence of blackwater fever is dependent upon certain definite conditions which result from the action of malaria, and the length of time required to bring about these conditions depends upon at least two factors, viz: the prevalence of malaria and the resisting and reparative powers of the individual. I do not therefore deny the possibility of blackwater fever occurring very soon after arrival in a tropical country, but speaking from my own experience I should say that in Uganda this condition of predisposition is not as a rule brought about until after a residence in the country of about eighteen months, and in support of this I may quote the following instance. Three or four hundred volunteers were enlisted from the Indian Army for a term of three years service in Uganda. These men suffered severely from malaria, but not a single case of blackwater fever occurred amongst them during the first two years of their service. During their third and last year however, there were

over a dozen cases, and this in spite of the fact that they were then living under much better conditions of food and accommodation than during their first two years. Grosse¹⁴ (of West Africa) believed that the liability to blackwater fever gradually increased up to the third year, after which it diminishes. Kerr Cross¹⁵ (of British Central Africa) also thought that there is less liability to the disease after the second year, but I have seen it occur in patients who have been twelve years and more in the country. It is sometimes said that patients may get blackwater fever who have never had malaria, but this I doubt, for we must remember that it is not essential that patients should have previously suffered from obvious attacks of fever. The action of the malarial toxins and the resisting powers of different individuals vary considerably, and thus serious anæmia and other ill effects may be established without any marked pyrexia, so that patients may stoutly deny ever having had fever, although there is every indication that they are suffering from chronic malarial cachexia. Such people are especially liable to develop blackwater fever, for the simple reason that as they are not treated the predisposition soon manifests itself. Now what is this predisposition, and how is it produced? In the first place there can be little doubt

that it is chiefly associated with the presence of the malignant form of parasite, and that it is rarely, if ever, produced from infection with the benign forms alone. It is true that cases of blackwater fever have been described in which benign forms were present in the blood, but these probably exemplify the not uncommon condition of mixed infection, and in such cases the presence of benign parasites is no reason for regarding them as the primary cause of haemoglobinuria. Ziemann¹⁶ is of opinion that the predisposition exists chiefly in persons who have suffered from an infection of estivo-autumnal fever, and that cases where other forms have been found were probably of mixed infection. He does not deny, however, that benign tertian and quartan might predispose in some circumstances. Koch¹⁷ mentions a case in which benign tertian forms were present, but admits that the malignant parasite had been found three weeks before during a previous attack of blackwater fever. Most authorities are agreed that blackwater fever, and indeed most cases of pernicious malarial fever are associated with the malignant form of parasite. (cf. Scheube, Thayer, Marchiafava, Biglami, Bastianelli.¹⁸)

The fact that the benign forms are not complicated by haemoglobinuria is probably due to their slighter virulence, and to their greater tendency to range themselves in well-marked groups, so that the different members of a generation mature and sporulate about the same time. As a result, there are definite periods of apyrexia during which toxic products are eliminated, and the recuperative powers of the individual are enabled to have free play. It is conceivable, however, that severe and repeated infections with benign parasites might eventually produce a condition similar to that which so often attends infection with the malignant form.

Secondly I believe that the predisposition to haemoglobinuria indicates a pathological condition of the blood resulting from the deleterious effects of the struggle between the host and its parasite, and one which also indicates an exaggeration of the normal process by which the former endeavours to rid itself of the latter. It must be remembered that some degree of haemoglobinaemia must be physiological. "In the body the blood corpuscles are continually decomposed during the metamorphosis of the tissues, and haematoglobin is thereby set free." (cf. Neubauer and Vogel¹⁹). Under normal conditions

however, these substances never pass into the urine, but as a result of metabolism are excreted in other forms, either as urea and uric acid, or as biliary and urinary pigment. This destruction of red cells is thought to occur chiefly in the spleen, where large phagocytic corpuscles may be found enclosing them, and the blood in the splenic vein is said to be tinged with haemoglobin. Now, as this decomposition of red cells is continually proceeding, it follows that some normal destructive element must be concerned in the process either directly, or indirectly by rendering the corpuscles susceptible to the phagocytes, and there also exists doubtless its complement, an anti-body, to ensure that its action shall be kept within proper physiological limits. It has been suggested that a definite deficiency of such an anti-body may be the initial cause of some curious cases of paroxysmal haemoglobinuria. Thus Vidal and Rostaine²⁰, as a result of their researches, conclude that paroxysmal haemoglobinuria brought about by cold is due to an insufficiency of a certain anti-body.

Now if this theory of the cause of normal blood disintegration be correct, it will be readily understood that the physiological equilibrium might be upset in one of three ways or by combinations of them, viz: (a) by an increase in the normal destruc-

tive agent or (b) by a deficiency in the restraining influence or anti-body, or (c) by diminished vitality on the part of the corpuscle. I would therefore hazard the theory that as a result of malarial infection there is either an increase in the normal physiological hæmolytic elements of the blood, or else that a definite hæmolytic substance is evolved as an anti-toxin, and that in either case this results from an attempt on the part of the individual to eradicate the parasites by destroying the cells which they inhabit.

It has been accepted as a hypothesis supported by clinical observation and study of the parasite, that the febrile manifestations of malaria are the result of toxins set free at the time of sporulation. This may be a correct assumption, but I would submit what appears to me an equally tenable one, viz: that the febrile and other symptoms of malaria are in part also due to the production of anti-toxins, hæmolytic in character, the function of which is to act upon the parasitiferous cells, and to render them more easily accessible to the protective phagocytic elements. In other words, that there is an opsonic action in malaria similar to that which is now known to exist in cases of bacterial disease, the only difference being that in malaria the anti-toxin has to act primarily upon the red cells in

order to reach the parasite. In discussing this view, we must first consider the ordinary course of a malarial infection, and the attempts made by the individual to eradicate it.

When the malarial parasite is first introduced into the human host it propagates itself by sporulation, and after a certain number of generations it may have become so numerous that it is readily found in the blood. By this time, if not before, a susceptible person will begin to react to the toxins produced, and the usual febrile symptoms may appear. If however, the resisting powers of the individual are highly developed, these symptoms may be long delayed. In such instances we must either conclude that the parasite took on a resting stage as a result of finding itself in unsuitable surroundings, or that it had maintained a precarious existence, only overcoming the resisting forces with difficulty and loss to itself. Even when it has become sufficiently master of the situation to produce what we call malarial fever, there must be an enormous destruction of parasites or their spores, for otherwise they would become so numerous as to make the life of the host impossible. Instead of this, they are kept somewhat under control, and, moreover, after a certain lapse of time they decrease

rapidly, and an apparent cure is effected spontaneously. It is a well known clinical fact that very often malarial attacks tend to cure themselves, at any rate temporarily. There can be no doubt therefore, that whatever the cause, the malarial parasite cannot indefinitely continue to propagate itself successfully in the blood of the human host, though it may survive in sufficient numbers to allow of recrudescence when circumstances render it necessary or advantageous. This fact is, I believe, intimately associated with provision for the extra-corporeal stage of its existence, and with the production of gametes. It is a curious but well known phenomenon that the crescentic bodies are not produced, at any rate in great numbers, until some time after the first infection, and indeed if the disease is energetically treated at the beginning they may not appear at all. In an untreated case they are not usually found before the seventh or eighth day, when the acute symptoms of malarial fever may be subsiding, and when the sporulating forms are only present in small numbers. This seems to show that it is only after some generations of the latter have run their course and when they are, so to speak, losing ground, that the gametes are produced, and I think we may reasonably suppose that it is the unfavourable condition of the medium which supplies

the stimulus necessary for their production. In this connection it is interesting to note the statement of Marchiafava and Bignami²¹ that if quinine be given when there are pigmented parasites nearing maturity in the blood, crescents appear, and that if already present they suddenly increase. This observation confirms my theory that it is adversity which prompts the parasite to abandon the sporulating phase in favour of the sexual one by means of which it stands a chance of being transferred to fresh surroundings. It is important to mark however, that the sporulating forms from which the gametes originate may still continue in the blood, though in very reduced numbers. This is what might be expected, for if all the parasites were destroyed, or developed into gametes, there would be no further source from which the latter could be derived, and the infection would die out. This may in time occur, but an attempt is always made by the parasite to preserve a small number of its sporulating forms from which to derive a constant supply of gametes. This state of things may be very protracted, and is well illustrated by cases in which patients are invalided out of the country with gametes in their blood. Such individuals may continue to show crescents for a long

while though the sporulating forms may not be obvious, but it is certain that these still exist because they may sometimes be found, and if a sharp recrudescence of fever occurs they may reappear in large numbers. This fact tends to show that during the apyretic periods the blood medium is for some reason unsuitable for their successful development. In other words there is an attempt at immunization, which however is very imperfect, and never becomes complete as happens with the natives of endemic malarial areas. Not only is the individual subject to the continued action of the malarial toxins, but there is a constant drain on his blood-forming glands which may eventually result in the production of corpuscles deficient in vitality. Moreover, there is a continued elaboration of the malarial anti-toxin though it may be only in small quantities. In this respect there is a marked difference between the immunity of the native and the attempted production of it in a susceptible subject. In the former, a definite equilibrium is reached between the forces of the parasite and those of its host, and thus crescents may be found in the blood of an individual who is to all intents and purposes absolutely healthy. Such a condition is never found in the

susceptible white man, though in his case the occurrence of crescents unaccompanied by febrile symptoms represents an endeavour in that direction, but perfect and lasting correspondence between host and parasite is never attained, and the attempt to reach it may result in irregularities leading to further pathological processes.

In the present state of our knowledge it is not possible to indicate exactly by what method the protective forces of the individual overcome the parasite, but this much is certain, that the wholesale destruction of parasites is brought about by phagocytosis in two ways. Either the freed spores fall victims to the phagocytes, or else there is a large mortality from the same cause among the parasitiferous cells, and this results in the destruction of the contained parasites before sporulation has taken place. It is undoubtedly true that the parasites are destroyed by phagocytosis, for in the internal organs phagocytes and endothelial cells are found enclosing spores and parasites in all stages of their development. ²² Marchiafava and Bignami considered that phagocytosis is only exercised upon forms contained in profoundly modified red cells, and in this connection they drew attention to the

"brassy" or shrivelled parasitiferous corpuscles which are so characteristic of the malignant forms of malaria. Complete discolouration of the red cells may be noticed sometimes when the parasite is still immature, but at other times the corpuscle shrivels and the pigmented substance assumes an 'old gold' colour. Marchiafava and Bignami suggest that these changes may be attributed to an acute necrosis. They point out also that "smaller forms of fission" may be found in shrunken red cells, from which it would appear that fission is not completed in all the pigmented corpuscles, and they say also that in summer-autumn fevers the red cell is altered very early, that it shrivels and undergoes pigmentary modifications even when only one fifth of its mass is filled by the parasite.²³ Regarding these changes as the result of toxic action, they conclude that even during its endoglobular life the amoeba evolves a substance which fatally affects the red cell. In regard to this, however, I submit that it is contrary to what we should reasonably expect, for the parasite is compassing its own destruction if it produces a substance toxic to the red cell. Moreover, in pernicious fevers even non-infected corpuscles frequently show signs of damage and degeneration. I infer, therefore, from the above

easily verified observations, that a haemolytic anti-toxin is developed, by the action of which red cells and their contained parasites may be rendered more susceptible to the attacks of the phagocytes. If my theory be correct, the elaboration of this anti-toxin would probably increase *pari passu* with the growth of the parasite. It would culminate at or near the time of sporulation, when it would either destroy the red cells or perhaps induce a premature and sterile sporulation. In either case the phagocytes would then fulfil their functions.

We may note here that in the benign tertian and quartan forms the phagocytes apparently engulf large mature parasites only and rarely touch the endoglobular forms, whereas in the malignant type the latter are attacked as frequently as the former. This may possibly be due to the irregularity of the malignant type, for its parasites seldom appear in well-defined groups. Consequently elaboration of the anti-toxin will continue, in large amount during the whole course of an attack, whereas in the benign forms it will only reach its maximum at or about the sporulating period. In a chronic infection there would be every chance of an accumulation and intensification of this anti-toxin which might

lead to a dangerous disturbance of the usual equilibrium. When this unstable condition is imminent or has already been produced, I consider that the predisposition to blackwater fever is present.

VII. ETIOLOGY.

There are several theories in regard to the actual causation of blackwater fever.

- (1) That it is a bacterial disease.
- (2) That it is a disease caused by a specific organism, possibly of the protozoal type.
- (3) That it is merely a manifestation of quinine poisoning.
- (4) That it is due to the action of quinine in conjunction with malaria.
- (5) That it is a pernicious or severe form of malaria.

1) Yersin,²⁴ in two cases in Madagascar, found no malarial parasites, but discovered a fine bacillus which he was able to cultivate in gelatine, and which had a toxic effect on rabbits and mice. This observation has not been confirmed, and the view that blackwater fever is due to a bacterial infection cannot at the present time be entertained.

2) The somewhat defined geographical distribution of blackwater fever has led to the idea that it may be a distinct disease caused by a special protozoal organism. In this connection much stress has been laid upon the similarity between blackwater fever

and the so-called Texas fever of cattle, which latter is caused by a definite specific parasite, but up to the present no positive evidence of the existence of such a parasite has been forthcoming, and the belief in one rests entirely on theoretical grounds. An argument based on analogy carries but little weight unless supported by other evidence. As will be shown later, the peculiar distribution of the disease does not necessarily exclude a malarial causation.

(3) THE THEORY OF QUININE INTOXICATION.

In spite of the fact that pharmacologists affirm from experimental proof that quinine has hæmolytic properties,²⁶ it is doubtful whether any observers would agree with the theory that it is quinine per se which causes the hæmoglobinuria met with in malarial countries.

If we assume this hæmolytic tendency of the drug, we must also assume that it is exercised upon normal blood extremely seldom. Otherwise it is difficult to explain the rarity of hæmoglobinuria, for quinine is largely used all over the world in temperate as well as in tropical countries. Possibly there do exist individuals whose blood is in such an unstable condition - either naturally, or as a result of morbid processes - that quinine is capable unassisted of exerting its hæmolytic properties. The published accounts of certain cases do undoubtedly tend to prove this, but it must be remembered that hæmoglobinuria can be produced by other causes, some of which are obscure and suggest an entirely neurotic origin. An example of this was discussed at a meeting of the Royal Medical and Chirurgical Society, where Mr C. W. Ensor and Dr. Wakelin-Barratt²⁷ drew attention to the case of a lunatic in whom hæmoglobinuric

symptoms were always associated with maniacal attacks during which the patient beat his forehead with his hands for half an hour at a time. It is quite possible, therefore, that in some cases in which hæmoglobinuria occurs presumably as a result of quinine administration, that the real cause is of a nervous character. If a person is firmly convinced that quinine will bring on hæmoglobinuria, it is conceivable that it will have this effect merely as a result of suggestion. This explanation of course does not hold good in all such cases, for notes are given by Ketchen²⁸ of a case in which hæmoglobinuria supervened in a patient who took some quinine by mistake and without knowledge. In this instance the patient's blood must have been in an extremely unstable condition, for it is stated that hæmoglobinuria could be induced invariably by small doses. Ziemann,²⁹ also, quotes a case in which hæmoglobinuria was brought on by $\frac{1}{6}$ of a grain of quinine.

Hæmoglobinuria has also been induced experimentally, as was done with a patient under Sir Patrick Manson at the Seaman's Branch Hospital, Royal Albert Docks.³⁰

These cases of obvious quinine hæmoglobinuria are however, extremely rare - personally I have

never come across one - and moreover, when induced without relation to malarial attack they are apparently mild, and resemble the ordinary toxic paroxysmal form of the malady. They are lacking in the more severe symptoms which characterize blackwater fever, and are rarely fatal.

Even if it be admitted that under certain *exceptional* conditions quinine will cause hæmoglobinuria, this would not constitute an argument in favour of the theory that it is the usual cause of typical blackwater fever.

The idea that there might be some causal relation between quinine and blackwater fever seems to have been first put forward by a Greek physician S. Verétas in 1858, and later Tomaselli in 1874 expressed the same views as a result of observations on cases in Catalonia.³¹ Owing to the rarity of the condition these statements, however, did not attract much attention. In 1898 Koch,³² after a short visit to East Africa, published a paper in which he stated that he considered blackwater fever to be merely quinine intoxication, and by many he was wrongly credited with having originated the idea. Subsequently he appears to have modified his views, and he now agrees with those who regard quinine as being only one of the factors necessary for the production of hæmoglobinuria.³³

(4) There is a certain number of observers who hold this theory that blackwater fever is caused by quinine plus something else, and the great majority of these believe this second factor to be a malarial infection. Among those holding this opinion are Christophers and Stevens, the Plehns, Koch and Ziemann all of whom have expressed the view that quinine is the usual exciting cause of blackwater fever.³⁴ As the utterances of such authorities must necessarily carry great weight, their opinions have been accepted by many who have not had the opportunity of forming an independent judgment, though on the other hand they have not found favour among many of those who have had practical experience of blackwater fever and malaria. Thus Crosse, who had seen a great deal of both diseases on the Niger, entirely repudiated the idea that blackwater fever had anything to do with quinine.³⁵

Strachan, (Chief Medical Officer, Lagos) says, "I find it hard to believe that the disease is caused by quinine."³⁶

Stubbart states his belief that quinine has nothing whatever to do with the production of hæmoglobinuria, which he thinks more often antedates the administration of the drug. Clinical experience, he says, is against the quinine theory, and he quotes a large number of American authorities who agree with this.³⁷

For myself, after over fourteen years in an endemic area of malaria and blackwater fever, I am firmly convinced that quinine has nothing whatever to do with the onset of blackwater fever.

There are serious and obvious objections to the quinine theory. In the first place there is the difficulty of the geographical distribution of blackwater fever. If it is caused by quinine acting on a malarious person, why does the drug have this baleful effect in some places, and not in others which may be equally malarious?

Secondly, blackwater fever patients are frequently treated with quinine, and the mortality among those so treated is not greater than among those who do not get quinine. If the hæmoglobinuria is caused by the drug, why does it so often cease even if more quinine be given? Plehn attempts to explain this difficulty by assuming that the blood must be in a certain pathological condition before quinine will have this effect upon it, and he believes that this peculiar state is a transient one which may disappear very quickly, so that quinine, though causing hæmoglobinuria at one moment may be given with impunity a short time after.³⁸ This, after all, is very hypothetical, and it is contrary to all experience and probability that a drug could have

such a marked influence on the blood at one moment, and be innocuous perhaps an hour later.

Thirdly, it cannot be denied that haemoglobinuria sometimes occurs when no quinine has been taken. I have experienced this myself more than once, and have also seen it in patients under my charge. Other undeniable cases have also been reported. That it is a fact has been admitted even by those who believe in the theory of quinine causation. Ziemann, for instance, notes that "Blackwater fever attacks Togos who have never taken quinine,"³⁹ while Stevens says, "There are undoubtedly cases of blackwater fever in which the influence of quinine as the exciting cause can be excluded," though he adds that in his opinion "they are few in number and they cannot suffice to contradict positive experimental evidence."⁴⁰

If now we examine the evidence on which the quinine theory is based, it resolves itself into this, - that in the greater number of blackwater fever cases there is a history of quinine having been taken before the attack, and that in some rare instances haemoglobinuria can be produced at will by its administration. This latter sequence, being exceptional, carries but little weight, even granting that it is a case of cause and effect, while the former circumstance need occasion no surprise when

it is remembered that in a malarious climate everyone takes quinine on the slightest provocation. It becomes a routine practice which is a source of great trouble to an observer who, like myself, endeavours to defer the administration of quinine until the discovery of the parasite has confirmed the diagnosis. In Uganda, where there are endemic febrile diseases such as Sleeping Sickness and trypanosomiasis, the initial clinical symptoms of which closely resemble malaria, the question of a correct diagnosis is most important; yet it was rarely indeed that I was able to make one at my first blood-examination, thanks to this general habit of quinine-taking. Unless previous warnings from myself had taken effect, I invariably found that patients had dosed themselves with quinine before sending for me, and in consequence I frequently had to suspend all specific treatment for twenty-four hours or more until the parasites reappeared in the peripheral circulation as the effect of the quinine was wearing off. This being the case, I see no occasion for surprise if, when hæmoglobinuria occurs, there is in most cases a similar history of quinine. To attribute the hæmoglobinuria to the drug is illogical, for any other symptom which follows malaria might as reasonably be ascribed to it. Moreover, it must be borne in mind that though it

may be granted - for the reasons stated above - that in a given number of blackwater fever cases there will be a large preponderance of those in which there is a history of antecedent quinine administration, yet the actual ratio of the cases occurring among those who have not taken quinine, is greater than the ratio among those who have.

Taking everything into consideration, and judging from my experience in Uganda and East Africa, I can confidently say that, as a factor in the production of blackwater fever, quinine may be disregarded.

(5) THE MALARIAL THEORY OF BLACKWATER FEVER.

Most observers are convinced of the fact that blackwater fever is in some way connected with malaria. Thus Christopher, Stevens, the Plehn brothers, Ziemann, Thayer, Scheube, Easmon, Crosse,⁴¹ and many others are entirely of this opinion, although some of them incriminate quinine as the actual exciting cause. It is admitted even by the advocates of a special organism that the latter in all probability acts chiefly upon constitutions already undermined by malaria. We have, therefore, a very general consensus of opinion to the effect that the two diseases are frequently, if not invariably, associated with each other. For my own part I am convinced that the relation between them is a causal one.

Several objections have been put forward against the view that blackwater fever is essentially a manifestation of malaria:-

(a) The geographical distribution of the two diseases does not appear to correspond, though it is significant that, so far as is known, blackwater fever never originates in a non-malarious region. It must, however, be admitted that malaria is prevalent in many places where blackwater fever is rare or unknown. To explain this fact various theories

have been advanced. Manson surmised that the passage of the parasite through a particular species of mosquito might in some way add to its virulence.⁴² Others again have suggested that there may be local strains of the parasite varying in malignancy.⁴³ Either of these explanations may be correct, and if so, would account for the limited distribution of the disease. In my opinion, however, the above assumptions are unnecessary, for let it be conceded that blackwater fever is only associated with malarial infections of the malignant type, and the lack of geographical correspondence between it and malaria is no longer evident. On this hypothesis it naturally follows that the more prevalent the malignant type of malaria, the more frequent are those conditions which lead to haemoglobinuria. Thus, in distribution blackwater fever will correspond more closely not with malaria as a whole, but with the malignant form alone. In support of this view I cite the undeniable facts that the worst endemic areas of blackwater fever coincide with the worst endemic areas of malignant malaria. while in regions where the benign forms alone are found blackwater fever is either rare or entirely absent. Against this view it may be said that there are places in which there is malignant malaria but no blackwater fever. In such places, if they do exist, the

malignant parasite is infrequent and not the prevailing type, and consequently the occurrence of blackwater fever, though possible, is so rare that it may be overlooked. It is my belief that wherever the malignant parasite is found, there blackwater fever is potential, even though it may seldom or never be seen. It is interesting to note in illustration of this theory, that blackwater fever is comparatively rare in Greece, Sicily, or India, regions where the benign forms of malaria are chiefly found. In tropical Africa, on the other hand, blackwater fever is rife, and here the benign forms of malaria no longer predominate, but give place to the malignant type. In Northern and Southern Africa outside the Tropics the conditions are reversed, the benign forms becoming common, and the malignant parasite and blackwater fever relatively rare. The same thing is also seen on the continents of America and Asia. There is another factor, the exact significance of which I shall explain later, - which has some bearing on the distribution of the disease. I refer to the influence of chill as an exciting cause. In highly malarious places where there are sudden and, for the tropics, extreme variations in temperature, blackwater fever is especially liable to occur. I think this fact explains some confusing anomalies with regard to

distribution. Take the case of two localities equally malarious, one of which perhaps has a higher altitude. This, though not enough to decrease the amount of malaria, may be sufficient to cause an appreciably lower night and shade temperature, and if the chance of malarial infection be equal in the two places, blackwater fever will certainly be more prevalent in the one with the higher altitude. In other places it is not the altitude which alters the incidence of the disease, but some local physical or meteorological conditions which give rise to sudden and severe variations in temperature. All these facts are of some importance when considering the question of the distribution of blackwater fever.

(b) A second objection sometimes advanced against the malarial theory of blackwater fever is the fact that in so many cases parasites cannot be found. But it has been admitted that in most cases of the disease there is a history of antecedent quinine administration, and anyone with much experience of tropical malaria knows that it is often waste of time to look for parasites in a patient who is under the influence of quinine. In such cases I have had to wait for a week before parasites appeared in the peripheral blood, and with blackwater fever the patient would be either convalescent or

dead after such a lapse of time. Moreover, in some cases of malaria the parasites may be so sparse as to necessitate a most prolonged and exhaustive search before they can be found. Thus I have more than once had cases of acute malaria in which no parasites could be found until the third or fourth day, and even then the diagnosis had to be based upon the finding of one single parasite after a search of two hours. This occurrence of malaria without any sign of parasites in the peripheral blood has been noted by many observers. It would seem from this that the number of parasites present bears no relation to the severity of the symptoms, but it must not be forgotten that while the parasites may be very scarce in the peripheral blood, they may at the same time be very plentiful in the internal organs. This fact has been proved by the examination of splenic blood during life, and also by post-mortem examination of the organs.

As a matter of fact, however, parasites are found in a fair proportion of blackwater fever cases, especially if they are examined at the outset - Christopher and Stevens found the parasite in only three of a series of sixteen cases, though from other evidence (i.e. pigmented leucocytes and increased large mononuclear count) they judged that 93 per cent

were of malarial origin. In Koch's series of forty-one cases parasites were found in eighteen, while Plehn examined the blood in thirty-two out of forty cases, and found parasites in twenty-one. The Plehns insist on the fact that, if the blood be examined before the onset of hæmoglobinuria, parasites will always be found, though as a rule they disappear quickly. Christophers and Stevens also lay stress on the evidence from a class of case in which, although no parasites were found during the actual attack of blackwater fever, yet they appeared during subsequent relapses which occurred in Europe under conditions excluding the possibility of re-infection.

I have myself only once had the opportunity of examining the blood of a patient immediately before the onset of hæmoglobinuria, and I have rarely seen a more intense malarial infection than was present in this case. The patient was a native house-servant who presented himself at the Dispensary one morning with a temperature of 104°. It was noticed that his conjunctivæ were slightly yellow, and on examining his blood it was found to be simply swarming with malarial parasites. As he was a native, the likelihood of an attack of blackwater did not suggest itself to me. He was given a dose of colomel and some quinine, and was instructed to go to bed. However, feeling better in the afternoon,

he got up and went about his duties as usual, but was taken worse that night, and well-marked hæmoglobinuria developed. The following morning his blood was re-examined, and not a single parasite could be found. This case made a deep impression on me as showing that a negative blood-examination obtained after the appearance of hæmoglobinuria is an untrustworthy index as to the presence of parasites, for as in malaria these may be absent from the peripheral blood, though subsequent examination of the organs after death may reveal their presence in large numbers. An instance of this is given by Smith,⁴⁵ who quotes the results of a necropsy performed by Boisson on a soldier invalided from Madagascar. In this case the malarial parasite was present in extraordinary numbers - both free and associated with red corpuscles - seven out of ten red cells containing it.

Finally, if my view be correct of the pathological process which leads to hæmoglobinuria, we should not expect invariably to find parasites, while their absence tends to support the theory of causation to be explained further on.

(c) The supposed differences in the onset and clinical course of blackwater fever from those of an ordinary malarial attack are adduced by some observers as reasons for denying its malarial origin.

Thus, the initial rigor which is such a characteristic feature of blackwater fever may in the malignant type of malaria be hardly appreciable or perhaps entirely wanting. But as a matter of fact it is sometimes absent in blackwater fever, and on the other hand I have seen it in its most marked form in an ordinary malignant malaria, and this has usually been the case with patients who have been subjected to exposure or to the chance of chill during the early stage of an impending malarial attack.

As regards the course of malignant malaria it may be said that variability is the rule, a fact which has led to the classification of a bewildering number of clinical types the distinction between which I consider of very little practical utility. One of these, the so-called bilious remittent malaria, closely resembles a typical case of blackwater fever in every particular except in the absence of hæmoglobinuria. Thayer says of this form of malaria, "There is high fever, vomiting of bile-stained fluid, urine deep red colour. There may be obstinate epistaxis and hæmorrhage from other mucous membranes, and grave anæmia. The temperature remains elevated, there is profound prostration. The patient is dull and apathetic, face sunken, respirations feeble, pulse almost impalpable. Delirium or coma may follow." ⁴⁶ Now, this description

would apply almost word for word to many severe attacks of blackwater fever if there be merely added the additional symptoms of hæmoglobinuria. It cannot be said, therefore, that there is anything sufficiently distinctive about the onset and course of blackwater fever which can serve to differentiate it from an ordinary severe attack of malaria, excepting only the presence of hæmoglobinuria. A consideration of these facts proves that there are no valid reasons for denying the malarial origin of blackwater fever, and I propose now to submit a theory as to their exact relation to each other.

Blackwater fever has been regarded by some observers as merely an intense or malignant malarial infection, but expressed in this way the theory is not tenable, for blackwater fever often supervenes in what appears to be a mild malarial attack, and on the other hand a malarial fever so virulent as to cause death may run its whole course without producing any hæmoglobinuria.

The clinical symptoms of a malarial attack depend to a certain extent upon the idiosyncrasy and susceptibility of the patient, or upon some accidental circumstance such as the blocking of a blood-vessel in the brain. An old malarial subject may perhaps show few symptoms even though parasites are numerous

in his blood, whilst in a recent infection the symptoms may be acute even when no parasites are to be found. In my opinion blackwater fever should be regarded more in the light of an accidental complication of malaria, but one which only occurs under certain definite conditions. These have been fully described when dealing with the predisposition to the disease. When these conditions are established the blood of the affected individual is in an unstable state, and contains an accumulation of hæmolytic elements. In such circumstances any very slight adverse influence would be sufficient to bring about a sudden and wholesale hæmolysis, affecting not only parasitiferous cells, but even some unoccupied ones. I am inclined to think that in the milder forms of blackwater fever the former cells are the ones chiefly affected. This is, indeed, only what we should expect, for in the ordinary course of physiological blood-disintegration, the weaker cells will be those which are first attacked. Similarly, when pathological blood decomposition takes place, as in blackwater fever, the weaker cells will go first, and the mere presence of a parasite in its substance must necessarily reduce the vitality of a blood-corpuscle. If the amount of hæmolytic substance present be not excessive it is conceivable that the unoccupied red cells might have sufficient

resistance to escape. Most observers state that the amount of hæmoglobin excreted is too great to admit of the theory that it is only ^{derived} from parasitiferous cells, and they point out that in an ordinary malarial attack the red cells may be reduced by one-third of their total number without hæmoglobinuria showing itself. Their contention is that in this case the liver is enabled to deal with all the hæmoglobin so set free. It is obvious however, that the actual amount of hæmoglobin set free by the destruction of parasitiferous corpuscles will depend upon the age of the parasite at the time of the necrosis, for the destruction of a corpuscle containing a minute young parasite will result in the release of a much greater amount of hæmoglobin than would be the case if the parasite were approaching maturity, by which time but little of the original corpuscle remains. Now, the hæmolytic anti-toxin, the existence of which I postulate, must in the ordinary course act upon the mature rather than upon the immature forms, otherwise the latter would be but rarely seen. Therefore, the amount of hæmoglobin set free in a malarial attack may be excessively small, even if one third of the corpuscles were infected with parasites. When, however, the predisposition to blackwater fever is developed, the hæmolytic influences are greater,

and I believe there is a gradual tendency to the destruction of parasitiferous corpuscles at an early stage, resulting in a much larger quantity of free haemoglobin. If the red cells are more than usually deficient in vitality, and if an excessive amount of haemolytic substance is present, then the destructive action of the latter probably extends even to cells which do not contain parasites. It is likely that this is what happens in the severer forms of blackwater fever.

The theory that the haemoglobin in the urine originates from the destruction of parasitiferous corpuscles is severely criticized by Koch, but his arguments are neither logical nor convincing. He says, ⁴⁷ "These two facts, the lack of parasites in more than half the cases, and the omission of the relapses would alone suffice to prove that blackwater fever itself cannot be malaria, but that it is frequently associated with malaria." The fallacy of reasoning from the absence of parasites has already been dealt with. In regard to the absence of relapses on which Koch lays such stress, are we to understand from him that malaria always relapses even when treated with quinine? That the patients in his cases had had quinine is certain, for he would have us believe that the blackwater fever resulted

therefrom. Yet surely there comes a time in the history of every malarial infection when the last attack occurs? On examination, therefore, it does not appear that these two "facts" prove anything more than the similarity of the conditions which are present in blackwater fever and malaria. Koch goes on to say that if the haemoglobinuria resulted from the destruction of infected corpuscles, "it would follow that the parasites collectively must disappear from the blood in every case. This by no means occurs. Amongst my cases there were four in which the parasites were to be seen during and directly after the attack. In one case indeed, they were present in great numbers. Furthermore, in nine cases relapses occurred later on, which proves that the parasites did not perish regularly in the blackwater fever attack." But why should it follow that the parasites should "collectively" disappear? We know from practical experience that in an ordinary malarial attack there may be a great destruction of parasites, and yet that enough of them may survive to carry on the infection either without obvious interruption, or else later in a relapse. Why should not the same happen in malaria when blackwater fever is present? As a matter of fact, I am of opinion that the parasites often do "collectively" disappear. This point, however, will be referred to later.

Koch further tries to prove his point by comparing blackwater fever with Texas fever, in which disease the hæmoglobinuria is caused by malaria-like parasites. Speaking of Texas fever he says, "the appearance of the hæmoglobinuria was in direct ratio to the number of parasites."... "But even in these cases and in which very many blood-corpuscles had perished, I never remarked that the parasites were influenced in the least by the attack. They were present in such myriads that considerable masses of the same could not disappear. Besides, in just such cases I have seen shoals of parasites free in the serum, and I am of the opinion that these parasites which after the disintegration of the corpuscles they had formerly denized had become free without in any way having been damaged by the disintegration of the blood-corpuscles." Now an argument from analogy is not always a reliable one. Because certain phenomena attend the life and development of the piroplasma of Texas fever, is that any reason why the same phenomena should manifest themselves in the case of the malarial parasite? One striking difference between the two parasites is at once apparent. Koch is of opinion that the piroplasma set free by the destruction of a red cell suffers no damage, whereas it is quite certain that when malarial parasites are driven from the shelter

of their protecting corpuscles, they are at once destroyed. This fact would in itself explain why they are not seen. Directly they are extruded from the corpuscles - or even before this if the latter have lost their vitality - they become foreign bodies, and are at once treated as such. Probably they are enmeshed in the capillary network of the internal organs and there disintegrated. As we have already seen, in many attacks of ordinary malaria there must be an enormous destruction of parasites and red cells, and yet these extruded parasites are seldom found in the blood. There seems no reason why it should not be the same in blackwater fever, if we grant the latter to be of malarial origin. Occasionally there may be observed corpuscles containing parasites which are in an obvious state of necrosis and disintegration, and the presence of such has been demonstrated in the organs of patients who have succumbed to blackwater fever. The opportunities for making such post-mortem examinations are not frequent and in several cases where post-mortems have been done, enough time has elapsed between the onset of hæmoglobinuria and the death of the patient to allow for the elimination from the body of many of these products of disintegration. I believe myself that splenic puncture at the very beginning of an attack of blackwater

fever might afford strong proof of the theory now advanced in regard to the etiology of this disease. According to this theory blackwater fever is merely an expression of the fact that a normal process has been intensified, with the result that all or many of the red cells containing immature parasites have been destroyed, and if there is still further intensification there may in addition be destruction even of corpuscles which are free from parasites.

If this theory be correct it explains why parasites are so often sought in vain when blackwater fever has developed, though they may have been plentiful before. It explains also why an attack of blackwater fever occasionally cures a malarial infection, for in such a case the destruction of the parasitiferous corpuscles has been complete. In this manner a chronic malarial infection may be completely eradicated. Sometimes, however, this destruction is only partial, and consequently a number of parasites may escape. These may not be numerous enough to show in the peripheral circulation, though they may serve to cause either a continuation of the febrile symptoms or a relapse later. If we remember that in the malignant type of malaria, parasites may be found in the blood at all stages of development, it is by no means unlikely that some may be affected by the anti-toxin, while others escape.

Presuming that a correct explanation has been given of the conditions which lead up to and attend the onset of hæmoglobinuria, it now remains to discuss the factors which serve as exciting causes.

The exciting causes of hæmoglobinuria are, in my opinion, chill, exposure, or exertion acting upon an individual in whom the predisposition is present. I have myself in fourteen years tropical experience never seen or heard of a case of blackwater fever in which one or other of these could be excluded. This is a practical point upon which I have no doubt whatever, nor is it dependent upon the truth or falsity of the theory which I have advanced as to the pathology of the condition.

The broad fact that chill and exposure are often associated with the onset of blackwater fever has been noted by many observers, but the essential importance of these factors and the primary rôle played by them have never been fully realized, and to my knowledge no explanation has been offered as to how they act. Ziemann says, "The breaking out of blackwater fever is favoured if at any time the body of the patient has been weakened by chill."⁴⁸

Wheaton noted that "blackwater fever was excited by a chill, and depended upon chill causing the breaking up of the red corpuscles in a patient in

whom the vitality had already been lowered by a previous attack of malaria.⁴⁹ Again Thompstone and Bennett remark that "exposure is often the exciting cause,"⁵⁰ and Powell observed in Assam that "chill apparently was the cause in seven out of eleven cases" seen by him.⁵¹

In regard to the action of a chill, it is conceivable that its injurious effects are produced by its direct or indirect influence upon the blood or upon the parasites themselves. In dealing with its action upon the blood it is worth while to refer once more to the disease known as paroxysmal hæmoglobinuria. The exact cause and pathology of that condition is unknown, but it has been accepted as an established fact based on experience that chill in susceptible subjects is one of the most common and potent causes in its production, and many cases have been reported in which the effects of chill could be definitely traced. Carpenter, at a meeting of the Society for the Study of Diseases of Children⁵² showed a case in which application of cold could produce hæmoglobinuria, and another in which, though hæmoglobinuria was not actually present, the red corpuscles were reduced to the extent of 20%. Other cases have been known in which the mere acts of getting out of bed, or of plunging the hands in cold water, were sufficient to produce

hæmoglobinuria. As already pointed out it has been suggested that in these cases there is a deficiency of some anti-body, the absence of which causes the blood to be susceptible to the influence of cold. Now, according to the views I have here put forward, blackwater fever implies a similar unstable condition of the blood produced as a result of malaria, which latter acts either positively by causing the elaboration of a hæmolytic substance, or negatively by reducing the normal anti-body and thereby lessening the resisting powers of the corpuscle. In either case the blood is brought into the same state as that which obtains in an individual who is subject to ordinary paroxysmal hæmoglobinuria and as in the latter a chill will precipitate an attack, there is no reason why it should not do so when the predisposition is the result of malaria. An example of the effect of chill on a susceptible *person* ~~occurrence~~ is afforded by one of my cases. The patient was an Egyptian soldier who had a severe attack of blackwater fever. (Vide Case 5) On the third day his urine had become perfectly clear, but febrile symptoms still persisted. Unknown to me the patient got up and sat for some time with his feet in cold water, "in order to make himself more comfortable," as he afterwards informed me. The next time he passed urine it was found to be very dark, though it cleared again quickly within a few

hours. It is, of course, impossible to prove that the return of the haemoglobinuria was in any way connected with the cold water episode, but the sequence of events is sufficiently striking. There is, further, the possibility that a chill might under certain conditions act upon the parasites themselves, more especially when other inimical influences are present. This may seem somewhat fanciful, but Loeb has drawn attention to the "tropisms" which "dominate the movements of many lowly-organized creatures,"⁵⁴ and by virtue of which the latter are enabled, if parasitic, to select a site advantageous for their future development. If this be so, it is conceivable that the malarial parasite may be affected favourably or adversely by outside influences. It has been accepted as a matter of practical experience, that exposure to heat or cold exercises a most potent influence in the production of an attack of malaria in an infected individual. This is generally regarded as being the result of depressed vitality on the part of the individual, whereby the resisting powers are reduced. This may be so, but on the other hand it may be that the parasite is in some obscure way susceptible to external influences, either favourable or unfavourable. Possibly, therefore, a chill acting at a certain stage of a

parasite's existence might in some way lead to an arrest of development, or to the reverse, a premature sporulation, thereby assisting in the production of an early necrosis among the parasitiferous corpuscles.

In addition to chill I have mentioned exposure and exertion as exciting causes of blackwater fever, and by this is meant any bodily or mental activity such as is likely to be undertaken by a patient who does not consider himself ill enough to be in bed. Here I must again draw attention to the matter of normal physiological blood-disintegration. There is no doubt that this proceeds more rapidly with increased tissue metabolism, and this being so, the effect of exercise and exertion must be to produce either an increase of normal hæmolytic elements or a loss of resistance on the part of the corpuscles. Now, if the blood be already overcharged with hæmolytic elements, or already deficient in the usual anti-body, it follows that as a result of exertion, some slight increase of the former or decrease of the latter may be enough to upset the equilibrium and precipitate a general hæmolysis. It is noteworthy that physical exertion alone is recognised as one of the exciting causes of paroxysmal hæmoglobinuria in those susceptible to it.

To sum up my conclusions:- Blackwater fever is a complication of malaria caused by a chill or exposure acting upon an individual whose blood is in an unstable condition as a result of the continued action and reaction upon each other of the malignant malarial parasite and the protective powers of its host.

... follows:-

... (59) ...

VIII. ONSET AND CLINICAL TYPES OF BLACKWATER FEVER.

The manner in which the disease usually begins contributes strong evidence to the truth of the theory which has been enunciated in regard to its causation. In my own practice the early history of every case of blackwater fever has shown a painful similarity, and has invariably been somewhat as follows:-

The day before the appearance of haemoglobinuric symptoms the patient has had fever, on account of which he may or may not have kept quiet at home. On the day of the attack he gets up, and though not feeling exactly well goes to work, or perhaps sits about on the verandah or elsewhere. Later, he begins to feel very ill and cold, and on passing urine finds it is black. In other instances the patient has been up and about all day though feeling 'seedy.' Possibly he tried to eat some dinner and then goes to bed. Shortly after, or perhaps not till towards morning, he has a severe rigor, after which he notes the colour of his urine. In many of these latter cases the condition was probably established early in the night, but was overlooked, for unless patients are on the look-out for it they may fail to notice the alteration in the urine,

especially when passed at night. In every case in Uganda which I have seen personally, or of which I have had reports, there has been a history of this kind. In reading the accounts of published cases, it frequently happens that nothing is said about the movements of the patient prior to the onset of the haemoglobinuria, but whenever his doings are recorded it will be found that a like history is given. The following are typical examples:- Smith and Taylor⁵⁵ reporting a case state that the patient was "a robust energetic man; he had not been on the sick-list during his tour, but said he had had a couple of hours fever occasionally. On the morning of the first day of his illness, (blackwater fever) he was seen looking well, smoking, and getting about his work."

⁵⁶ Crispin, relating the history of one of his cases, says:- "patient had had repeated attacks of malaria which he did not trouble much about."

⁵⁷ Bennett, reporting a case in Trinidad, writes:- "patient had been having attacks of fever for two or three months; got rather accustomed to them and treated them lightly. Within a few hours of the onset of haemoglobinuria he had been at work."

⁵⁸ Crosse, speaking of this aspect of the question says; "The haemoglobinuria comes on during an attack of fever clinically resembling an ordinary attack."

Often the temperature is not taken before the hæmoglobinuria is observed.....As a rule it will be found that the patient neglected the early attack.... the patient has almost invariably had more or less fever for at least a day or two previously."

Easmon⁸⁹ wrote, "It (blackwater fever) is often preceded by simple attacks of intermittent fever."

If accurate and full notes were given in regard to the early history of all blackwater fever cases, I am convinced that it would be found, as in my experience, that the onset was invariably preceded by an attack of malaria which was neglected, either knowingly, or through failure to recognise its character.

CLINICAL TYPES.

I recognise three fairly distinct types of blackwater fever, to which may be added a fourth, which though not specifically distinct, includes cases which can be conveniently grouped together.

Type I. The short and paroxysmal form in which both the hæmoglobinuria and the fever subside quickly and simultaneously.

Type II. A longer attack in which the hæmoglobinuria and the fever persist for some days, both gradually diminishing.

Type III.

An attack in which the hæmoglobinuria disappears, but the fever and other symptoms continue.

Finally, there are the cases in which suppression of urine takes place, but the occurrence of this latter does not constitute a distinct variety of the disease. It is to be regarded more as an accidental complication which may follow upon one or other of the preceding types.

IX. INITIAL SYMPTOMS.

The gravity and ultimate course of an attack of blackwater fever cannot be judged from the character of the initial symptoms, which as a rule are very similar in all cases. A very acute onset does not necessarily imply a dangerous clinical type, and on the other hand, a case which ultimately proves fatal may begin in a mild way. The premonitory symptoms are much the same, whatever the type, and consist in a sense of intense depression and illness, aching in the limbs, back and joints, and a feeling of cold. The nails are blanched, and the skin shows a well-marked goose-flesh type; the most extraordinary retraction of the penis is often present, and may persist throughout the whole attack. The chilly feelings gradually increase, and culminate in a severe rigor. Following this, or even before it has begun, the temperature quickly rises, probably to 103° or 104° . The state of the urine may perhaps not be discovered until after the rigor, but in a fair number of cases it was noted first. My own impression is that the urine is always hæmoglobinous before the rigor comes on, but of course unless a patient happens to pass urine this

will not be noticed until later. With the rise of temperature there is often severe headache and back-ache, and some vomiting. Slight jaundice is nearly always present, and may become intense. A second or even a third rigor may occur a few hours later, followed perhaps by a fresh rise of temperature, but during the first twenty-four hours it is not possible to make any forecast as to the manner in which the attack is likely to develop. Thereafter the course of the disease will vary according to the type, but before going on to describe these in detail, it is desirable to consider some of the general symptoms more minutely, and also the condition of the blood and urine.

(a) The Vomiting. The early vomiting of blackwater fever in no way differs from that seen in ordinary malaria. If the patient has lately eaten or drunk, the ejected material will simply consist of the last meal. If the stomach be empty the vomit will probably be merely mucus tinged with bile. The initial vomiting of blackwater fever is not usually severe, especially if no food has been taken for some hours previously. Indeed, for the first twelve hours there may be little or no vomiting, a very happy circumstance, for it allows of medicine being retained. In the severer forms of the disease,

however, the vomiting may become uncontrollable after the first twelve hours or more. Anything and everything taken by the mouth is immediately ejected, and there is violent and persistent retching which tends to exhaust the patient. At this stage the vomit often consists of a green slimy material resembling chewed grass; it is acrid and irritating, leading to intense soreness of the oesophagus and fauces. At times it becomes blood-stained, but I have never myself seen definite haematemesis. When, however, there is general bleeding from all the mucous membranes, it is quite probable that there may be haemorrhage from the stomach-walls. Hearsey⁶⁰ says that when there is bleeding from the fauces there may be haematemesis from the blood being swallowed. In the worst cases the vomiting continues to the end, and is followed by persistent hiccough, which is a sign of grave import. The vomiting may persist even when the acute symptoms are subsiding, and when recovery is taking place. I had one case in which it continued for seven days after the urine had cleared, and the temperature had fallen to normal. The patient ultimately recovered, but very nearly died from exhaustion and inanition. I have seen other less prolonged examples of this post-haemoglobinuric vomiting, and in nearly all cases it has a tendency to persist for two or three days

after the other symptoms have subsided. My own impression is that the vomiting of blackwater fever is merely a symptom of a general toxaemia due to the non-elimination by the liver of the large amount of waste products which have been thrown into the general circulation. Liver failure is in fact the main cause of many of the worst features of the disease. As long as that organ can continue its functions the evil results of malarial poisoning are not manifest. The predisposition to blackwater fever however indicates the arrival of a stage when the liver can no longer respond to the calls made upon it and when the hepatic cells themselves are beginning to show evidence of degeneration.

As a result the poisonous products of blood disintegration are no longer elaborated and excreted by the liver. Instead they are allowed to pass through again into the general circulation giving rise to symptoms of ~~or~~^{auto}-intoxication similar to those seen in other cases where the liver is at fault.

(b) JAUNDICE: This is nearly always present to some extent, and I agree with Crosse⁶¹ in saying that it is a symptom which occurs very early. I go even further, for I believe that the slight jaundice which is sometimes seen in chronic cases of malaria

is a symptom which indicates that the predisposition to blackwater fever has been established, so that the occurrence of such in an old malarial subject should always suggest the possibility of blackwater fever. It is a true haematogenous, and not a hepatogenous jaundice, although it may lead secondarily to a certain degree of hypercholia. It arises, no doubt, from the fact that the amount of haemoglobin set free is too great for the liver to deal with at once, and hence it is deposited in the tissues for future reference. If this process be repeated indefinitely, the liver in time becomes quite unable to cope with the condition, and if a sudden and extensive haemolysis takes place, it comes about that the possible and natural reservoirs being already to some extent filled, any further addition leads to a very rapidly produced jaundice at the very outset of the disease. It does not develop later because by that time a large amount of the free haemoglobin has been excreted by the kidneys, or has been dealt with by the liver, and the latter organ, being stimulated to fresh activity, may soon begin to relieve the tissues of the excess which caused the deep colouration. Thus, in a very bad case of blackwater fever,

Why?

the patient may be bright yellow from the first to the third day, but after that the colour begins to fade even if the course of the disease be unfavourable. Even with cases in which suppression of urine occurs, I have generally found that the deepest jaundice is to be seen at the beginning.

In itself the symptom is not a grave one, except that in my opinion it indicates either a chronic infection or a more extensive haemolysis. If the predisposition to blackwater fever has been brought about by a long and persistent malarial infection, there is a far greater likelihood that the tissues are already more or less charged with the products of blood disintegration, so that when blackwater fever occurs jaundice is easily and rapidly produced. On the other hand, if the predisposition is the result of a more acute process, the haemoglobinuria may terminate before the pigment has been deposited in sufficient quantity to produce any striking discolouration of the tissues.

(c). THE URINE: In a typical case the urine is quite black and resembles stout. There may, however, be all gradations of colour, and at times it is more like port or claret. The depth of colour is no index as to the severity of the

attack, for I have seen very serious cases in which the urine remained throughout comparatively light. The first urine voided may be as dark as any subsequently passed, but in other cases each succeeding specimen shows a deepening colour until the maximum for the attack is reached. The pain over the bladder and the urgent desire to pass water described by some observers I have never noted. The amount passed is extremely variable and depends to a great extent upon the amount of fluid ingested. So long as plenty of urine is passed, (50 oz, or more, in twenty four hours) the exact colour is of little importance except when it shows no sign of becoming lighter by the third day. The specific gravity is as a rule above normal, the less urine passed the higher it will be. The reaction as a rule is slightly acid. Albumen is always plentiful; on boiling, the urine may turn almost solid. If a portion be allowed to stand, a thick reddish brown deposit forms, which may comprise half the entire bulk. On shaking, a copious froth forms which has a pink tinge. In this I am entirely in agreement with Crosse,⁶² who questioned the statement made by some authorities to the effect that the froth of blackwater fever urine has a yellowish or green tint. Examination of the sediment shows that

the latter is composed of amorphous masses of pigment, epithelial cells from both bladder and kidney, and many granular casts. Hyaline and blood casts I have never seen. As a rule blood corpuscles are entirely absent, but occasionally an odd one may be found. With the gradual clearing of the urine the albumen disappears, but a slight trace generally remains for two or three days after the final disappearance of the haemoglobinuria. It is said that in some instances there is reaction for the bile colouring matters (Thayer)⁶³ but I have never noted it in any of the cases in which I looked for it.

(d) THE BLOOD: In many cases of blackwater fever there is really nothing distinctive about the blood. As has already been pointed out, malarial parasites may be found, especially if the examination is conducted before the onset of haemoglobinuria, or very shortly after. Manson⁶⁴ states that "the most striking display of blood destruction by the malarial poison is to be seen in cases of haemoglobinuric fever." He says of one such case which he examined, "There did not seem to be a sound corpuscle in the patients body." Such a condition, however, is not peculiar to blackwater fever, for I

have seen an exactly similar state of things in patients suffering from malarial cachexia with no blackwater fever; and on the other hand, in some blackwater fever cases the blood shows no very striking anaemia. I believe, myself, that the anaemic condition of the blood sometimes so markedly seen in blackwater fever, precedes the attack, and is indirectly the cause but not the result of it. The usual large mono-nuclear increase so characteristic of malaria is also found in blackwater fever. It has been stated that there is at times in the latter a distinct ^{leu}~~leu~~cytosis, but this has been observed also in other pernicious forms of malaria unaccompanied by haemoglobinuria.

X. COURSE OF THE DISEASE.

Having now discussed the initial symptoms which are common to all attacks of blackwater fever, it ~~now~~ remains to consider the different course followed by the several types of the disease.

Type 1. The initial symptoms may be quite as severe as in the other forms, but after a few hours the temperature falls, the urine clears rapidly, and the patient is to all intents and purposes convalescent. This class of case is not at all uncommon, and is well illustrated by the following case:-

D. S; Goanese; Tailor. (Case 1.)

First seen on the evening of June 28th. History of having had fever off and on for the last eight days, but had not lain up for it. In the morning had felt attack of fever coming on, and took a small dose of quinine; then worked all day in the shop. In the afternoon had a severe shivering fit, and went to bed about five o'clock. In the evening noticed urine coloured. At 7 p.m., when seen, temperature was 102° , urine very dark. Blood examined with negative result as regards parasites; no marked changes in the red cells. XX Gr. Quinine were at once given intra-muscularly. On the morning

of the 29th the urine was quite clear and the temperature normal. During the night, the patient had passed urine three times; at midnight, when it was a little darker than that of the evening; about four o'clock, when it was lighter, and again in the morning when it was only just tinged. There was no further rise of temperature, and patient made an uninterrupted recovery and had no more fever.

Another example slightly more severe is shown in the following:-

H.T; English; (Case 2, vide chart).

Had served in the country for over ten years, had been home on leave two and a half years ago, and since then had had no definite attacks of fever. On June 4th he had fever, and malignant parasites were found in his blood. He objected to intra-muscular injection of quinine, so it was given by the mouth. His attack only lasted two days, and he resumed work on the 8th. On June 19th he felt very 'seedy', and took X Gr. of Quinine, but was at work in his office all day. On June 20th he felt worse, but went to work; took X Gr. Quinine with his breakfast, and again at lunch. In the evening was dressing to go out, but had a severe rigor, and went to bed instead; took a little Bovril for supper, but vomited it; had a very bad night, but his temperature was not taken. The next morning was going to get up about eight

o'clock, but had a severe rigor, so took XV Gr. Quinine, and remained in bed. First seen by me at 10 a.m. Temperature was 101.8, P.90; sweating profusely and vomiting; had not noticed anything wrong with his early morning urine. I took a smear of blood, and while examining it was informed that at 10.30 a.m. he had passed some dark-coloured urine. The blood-examination proved negative. He had kept down the quinine taken in the morning, and as he had very strong objections to intra-muscular injection. I decided to watch the course of the disease before insisting on it. The hydrarg.perchlor-alkaline mixture was ordered. At mid-day the temperature was 101.8°, but by four p.m. it had come down to 99°, and he was again sweating profusely. At 9.30 p.m. temperature was 101.8°, and an enema of hot water was given. During the day he had passed about 20 oz. of urine, the last specimen being distinctly lighter in colour.

June 22nd: Temperature 99. Had a severe rigor at 6 a.m. and the urine passed after it was a little darker than that of the previous evening. Blood examination proved negative. At 4 p.m. temperature normal, pulse 72, urine practically clear, bowels moved.

June 23rd: Temperature normal, urine quite clear, no albumen.

Patient made an uninterrupted recovery, and left for England a month later, having had no return of malaria. His case was interesting in that he suffered from chronic nephritis, and his urine was seldom free from albumen. For the week following the blackwater fever there was, however, no trace of albumen, and this I ascribed to the fact that he was kept entirely on a milk diet.

In this class of case there is seldom marked jaundice to a greater degree than may be seen in an ordinary attack of malaria. The vomiting also, is not as a rule severe, for the patient is beginning to recover before the time when this symptom usually becomes aggravated. In regard to the urine, a slight persistence of the hæmoglobinuria after the temperature has fallen to normal need not cause alarm, nor need it necessarily suggest the possibility of impending suppression. As illustrating this the following case may be quoted: The patient had had hæmoglobinuria for thirty-six hours; the second night he slept well, and woke in the morning feeling much better and with a normal temperature. The urine passed about 8 a.m. was, however, still quite black, and caused me some anxiety. At 10 a.m. however, about ten ounces of perfectly clear urine ^{were} ~~was~~ passed and no further symptoms febrile or otherwise, developed. In this instance the attack had expended itself early in the night, but as the patient had slept for some hours, the bladder still contained some hæmoglobinous

urine which was voided when he first woke, and the subsequent specimen was quite clear.

Type ii. In this the fever and hæmoglobinuria continue for several days, and subside gradually and simultaneously. The urine may perhaps begin to clear on the second or third day, and slowly resumes its normal colour. I have myself never seen the hæmoglobinuria persist in this class of case later than the fifth day, but in a case which was reported to me, both it and the fever continued for nine days, the patient ultimately recovering. These cases are more serious than those of the first type, and may early prove fatal, either from the virulence of the toxins, or from the slight resisting powers of the individual. However, so long as there is a plentiful secretion of urine, recovery can be looked for. The following illustrates this class of case:-

R.T: English; (Case 3, vide chart.)

Patient had been two years in the country, and recently had had repeated attacks of fever, but "not of a serious kind", and he "had not paid much attention to them." Had been taking quinine every day of late in small doses. During the week previous to his blackwater fever he had two attacks of fever whilst travelling, but did not keep his bed, and on one occasion marched with a temperature of 102°. On August 3rd he arrived at a station feeling quite well;

in the afternoon had a bad headache, and took X Gr. of Quinine; temperature not taken. He ate his dinner, but went to bed about ten, feeling "rather seedy." Woke up an hour or so later with a severe pain in the region of the heart, and a feeling of oppression. Found that his urine was black; a severe rigor followed. He was at once seen by an Indian assistant. As shown by the chart, five X Gr. injections of quinine were given between midnight of the 3rd and 6 a.m. of the 5th. During this time the urine remained black, and the temperature ranged from 99° to 103.4°. After the injection on the morning of the 5th the patient refused to have any more, though he took two IV Gr. doses of Quinine by the mouth on the 6th. He was first seen by me at 5 a.m. on the 7th. The urine was still dark, but lighter than it had been; there was slight jaundice; vomiting had not been severe; the temperature was 100°. Injections of Quinine were resumed, X Gr. being given at noon, and another at 7 p.m. when the temperature had risen to 103.6°. The following day, the 8th, urine was much lighter, but the temperature showing a disposition to rise again, another twenty grains of Quinine were injected at mid-day, and at 9 p.m. fifteen grains. On the 9th the urine was clear; the temperature, however, being 99° at 9 a.m. twenty grains of Quinine were given as a precaution. The temperature rose later to 100°, but the next day it was normal in the

morning, and only rose to 99° in the evening. After that the patient made an uninterrupted recovery, but about a fortnight later when he had resumed his duties, he had another severe attack of malarial fever. He was kept in bed, and treated with Quinine, and when convalescent invalided home. Having no microscope with me I was unfortunately unable to examine the blood in this case. It is perhaps not a perfect example of a simultaneous disappearance of the hæmoglobinuria and the febrile symptoms, for the temperature showed a disposition to rise again even after the urine had cleared. I believe that had a large dose of Quinine not been given on the 9th, the febrile symptoms would have recurred with great intensity; for if the gradual clearing of the urine is not accompanied by a corresponding lowering of the temperature, and a gradual improvement in the other symptoms, there is some cause for anxiety, as the case may develop into the next type to be described.

Type iii. In this the hæmoglobinuria disappears but the temperature may continue, and the vomiting may persist. These cases are very dangerous, and not infrequently prove fatal. On the second or third day, perhaps, the urine begins to clear, but there is no amelioration in the symptoms. The vomiting is incessant, it being impossible to give either food or medicine; the heart becomes dilated,

and a loud systolic bruit may be heard. The temperature, after showing a tendency to fall, rises again and assumes a remittent type; hyperpyrexia may ensue, in which case death usually follows. An example of this class of case may be shown here:-

S: Indian; (Case 4, vide chart). First seen on January 17th. Owing to the difficulty of working through an interpreter, a clear history was not obtained. Apparently about 10 a.m. whilst up and about, he had a severe rigor, after which he noted that his urine was black. His temperature, when seen, was 102.40. Owing to unavoidable causes, quinine could not be given intramuscularly, so it was administered by the mouth. A blood-examination was made with a negative result. On the 19th the urine was clear, and as will be seen from the chart, the temperature was only ranging between 99° and 100°. On the 20th and 21st I unfortunately could not see the patient, as I was myself laid up with fever. His temperature was, however, taken regularly, and on hearing that it showed a tendency to rise, I gave instructions that quinine administration should be continued. On the 22nd I saw him again at 1 p.m.; the temperature was then 104.60. His blood was examined, but no parasites were found. Quinine was given in large doses, but owing to the constant vomiting probably very little was retained. On the 23rd there was no improvement, and in spite of

cardiac stimulants, patient's strength was obviously failing. Death took place shortly after midnight, the temperature rising nearly two degrees after life was extinct. I have little doubt myself that if it had been possible to administer large doses of quinine intra-muscularly on the 19th and 20th, the patient's life might have been saved.

In the cases in which recovery takes place the temperature again becomes intermittent, being normal in the morning, and rising slightly in the evening. This may continue for a fortnight or more. It has been said that this post-hæmoglobinuric fever is not malarial, as it sometimes appears to be uninfluenced by quinine, but in my experience, if the quinine be given intra-muscularly and in sufficiently large doses, it will very often act as beneficially as it does in other forms of malaria.

In the less severe forms of this type ~~of malaria~~ the symptoms may be less violent, or the resisting powers of the individual may allow of recovery taking place, as is illustrated by the following case:-

Y.H.; Egyptian; (Case 5, vide chart). The patient was a soldier, and had been serving on the White Nile, where he had had a good deal of fever. On May 2nd he joined the steamer on which I was a passenger to Khartoum. The next day he had slight fever, but did not stay in bed. Similarly, on the 4th he found that his temperature was ranging from

99° - 100°, but he sat about the deck all day. Had been taking some pills of iron, arsenic, and quinine two or three times a day. On the afternoon of the 4th he felt very seedy, and in passing urine noticed that it was black, whereupon he went to bed and sent for me. When first seen at 5 p.m. he was shivering violently, temperature 99.8°; urine quite black. Twenty grains of quinine were immediately given intra-muscularly. At 9 p.m. temperature was 104°, and fifteen grains of phenacetin were given.

May 5th. Morning, temperature 101°; pulse 94; skin bright yellow; urine plentiful, but very black.

1 p.m. temperature 101.4°; pulse 103; last urine passed was a little lighter; vomiting good deal. Twenty grains of quinine given intra-muscularly.

5 p.m. temperature 102°; pulse 100.

May 6th. Morning, temperature 101°; pulse 100.

May 10 Vomiting incessantly. Improving.

May 11th. 12 mid-day, temperature 100.4°;

May 12 pulse 104. Temperature normal.

May 13th. 8 p.m. temperature 100.8°. Urine plentiful; colour much the same as after-noon before. Fifteen grains of quinine given intra-muscularly. Some days, but no fever.

May 7th. 9 a.m. temperature 99.8°. Pulse 110. Urine quite clear; vomiting a good deal. $\frac{1}{8}$ gr. morphia and $\frac{1}{30}$ Gr. strychnine given hypodermically.

12 mid-day. Temperature 100°, Pulse 100.
No vomiting since injection.

8 p.m. Temperature 100°. Pulse 104.
Morphia and strychnine repeated.

May 8th. 9 a.m. Temperature 101°. Pulse 110.

Slept well; no vomiting; took a little food, and said he felt quite well. Shortly after he got up and sat with his feet in cold water, for the weather being very hot he found the cabin oppressively warm.

11 a.m. Felt rather 'seedy', and in passing urine noted that it was slightly darkened again. Twenty grains of quinine were immediately given intra-muscularly.

12 mid-day. Temperature 103°; pulse 110., but the next urine passed was quite clear again.

4 p.m. Temperature 101°; pulse 105.

May 9th. Slept well; temperature did not rise above 99°.

May 10th. Temperature 99°, improving.

May 11th. Temperature normal.

May 12th. Temperature normal.

May 13th. Patient was transferred from my care to hospital at Khartoum. That night had a severe rigor, and temperature rose to 104°. I learnt subsequently that febrile symptoms continued for some days, but no further hæmoglobinuria occurred. This relapse of fever I believe was due to the fact that the patient

did not have any quinine after the 8th, He did not want to have any more injections, and as his stomach was still irritable I hesitated to give it by the mouth, especially as he seemed so well. Unfortunately I was not able to examine the blood, as I had no microscope with me.

There now remain for consideration the cases in which suppression of urine occurs, either with or without continuance of the febrile symptoms. In the former the attack is in reality one of Type ii or Type iii, to which has been added the additional complication of suppression; whilst in the latter it is of Type i, the usual successful issue of which has been interfered with from the same cause.

Blackwater fever cases of this kind may begin in the usual way, and though at the outset there may be a free flow of urine, it later becomes scanty or ceases entirely. If the temperature persists - the attack being of Type ii or iii-death may follow quickly, for the patient has to withstand not only the effects of the suppression, but also the added strain of the continued malarial attack. If this latter is not violent, and if the patient is strong and vigorous, he may, however, live some days, and in the end die mainly as a result of the former. In one case under my care, the patient after the first day had suppression of urine for thirty-six hours, after which the flow was re-established. This is the only instance

I have ever seen of the kind, for as a rule the onset of ^{Su}ppression spells death. In this particular case the patient continued to have fever even after the flow of urine was re-established, and died from cardiac failure as the result of an indiscretion, just when he was thought to be convalescent.

If suppression of urine takes place, but the temperature falls to normal, I regard the case as belonging to Type i. The blackwater fever attack is really over, and the patient ought to be convalescent, but the kidneys are choked with hæmoglobin, and as a result their whole excreting functions are in abeyance. Life may be prolonged for some time even under these conditions. I have seen a patient linger on for seven or eight days without passing more than a few ounces of urine, and this is by no means exceptional. In such cases the vomiting continues, the heart dilates, and the patient gradually falls into a comatose state. Typical symptoms of uræmic poisoning may be entirely absent, or may only show themselves just before the end. This, no doubt, is due to the fact that up to the time of the blackwater fever attack, the kidneys have been working normally, and in consequence the blood and tissues are not already surcharged with toxic waste products, as is the case in a patient suffering from chronic kidney disease. Not only so but the condition of the patient, and the fact that little food is being ingested, have reduced tissue metabolism to its lowest limit.

It is worth pointing out, that in this class of case if the patient survives long enough, it may be found that any little urine which filters through is quite clear, showing that though the kidneys have struck work, elimination of the free hæmoglobin has been going on elsewhere. An example of a case of this kind is shown by the following:--

B; English. (Case 6.)

Patient was travelling by canoe on the Victoria Nyanza. On January 8th he spent the whole day in the canoe from sunrise to sunset. He camped on an island, and after dinner whilst sitting in front of his tent, began to feel very ill, and found that he had blackwater fever. He at once despatched a messenger for me by canoe, but I did not reach him till midnight on the 10th. He informed me that the fever had continued up till the morning of that day, the 10th, when his temperature fell to normal. When I reached him, his temperature was normal and his pulse 78, but he had passed no urine since the morning, and was vomiting incessantly.

January 11th. At 4 a.m. he passed 6 oz. of black urine, the first after an interval of twenty-four hours. Vomiting was incessant, and nourishment had to be given per rectum. Temperature normal during the early part of the day, but rose to 99.6° in the evening. At midnight he passed 4 oz. of very dark urine.

January 12th: About mid-day he passed 2 oz. of urine rather lighter in colour. Temperature remained throughout at 99°; but the heart was beginning to show signs of failure. 4.30 p.m. Passed 1 oz. of urine much lighter in colour.

January 13th: Temperature remained normal.

At 8.30 a.m. he passed 2 oz. of clear urine, which however contained a good deal of albumen. The vomiting continued, and the pulse was gradually getting weaker.

At 4.45 p.m. the bowels were freely moved, and he passed 2 oz. of straw-coloured urine.

Towards evening the heart began to fail rapidly and death took place at 2 a.m. on

January 14th. Patient was conscious up to within an hour of his death, and there were no uræmic symptoms.

In this case the patient only passed 17 oz. of urine altogether during the last four days of his illness. When first seen, his temperature was normal, though suppression had already set in, and he had a good strong pulse of 78. In my opinion his blackwater fever attack was over, and he should have been convalescent, and the accidental occurrence of the suppression was the cause of all the subsequent symptoms and fatal issue.

XI. CAUSE OF DEATH IN BLACKWATER FEVER.

MORTALITY and PROGNOSIS.

In my opinion the actual causes of death are as follows in order of frequency:-

- (a) Suppression of urine either by itself as happens when it is accompanied by a normal temperature ^{following} ~~in~~ Type i, or in conjunction with the malarial attack as in Types ii and iii.
- (b) The continuance of the malarial attack as is best illustrated by Type iii, when though the hæmoglobinuria disappears, the fever continues. It may however also occur in Type ii, in which the virulence of the attack may kill the patient even before the urine has cleared.
- (c) Toxaemia due to the retention of waste products in the blood resulting from liver failure.
- (d) Cardiac failure, or exhaustion before or after all symptoms have subsided.

Some authorities state that the cause of death in some cases is due to the large destruction of corpuscles, and the condition is likened to death from hæmorrhage. The cases in which the

hæmoglobinuria continues with a normal temperature are cited as examples of this, and the absence of fever is regarded as a sign of collapse due to the pseudo-hæmorrhage. Personally, I have never seen the hæmoglobinuria continue after the temperature falls to normal, except where suppression of urine is supervening, and there has been in consequence a delay in the excretion of the free hæmoglobin. Now in such cases, as has already been pointed out, the fatal termination is usually long delayed, and results eventually from the effects of the suppression. If it were due to the destruction of corpuscles we should expect death to occur quickly.

PROGNOSIS.

(a) Immediate. One undeniable feature about all cases of blackwater fever is that as regards the hæmoglobinuria, there is a strong tendency to spontaneous cure. The presence of hæmoglobin in the urine merely indicates an attempt on the part of the individual to excrete what is a foreign body in the blood stream. If the kidneys become blocked in the process recovery is impossible, even if eventually the supply of free hæmoglobin is exhausted

by excretion through other channels. In the absence of suppression the hæmoglobinuria will most surely cease although death may result from the other causes mentioned. Hence, as long as the kidneys perform their functions, the prognosis will depend entirely upon the virulence of the malarial attack, and the strength and resisting powers of the patient. In cachectic, weakly patients, especially if the subjects of cardiac or other organic diseases, the prognosis is always serious; otherwise it depends upon the type and course of the malady.

In Type i, recovery is the rule and convalescence may be quick and uninterrupted: the only complication to be feared is suppression of urine.

In Type ii, the majority of the cases recover unless suppression supervenes: occasionally however the severity of the attack may cause death even when that complication is absent.

In Type iii, the prognosis is very grave, for though the hæmoglobinuria has subsided, the continuance of the malarial infection throws a severe strain on resisting powers already weakened by the blackwater fever. As I have already indicated, the onset of suppression - whatever the type of the disease - almost invariably leads to a fatal result.

Taking all classes of cases together the mortality in my own experience has been about 20 per cent, of which the greater number have resulted from suppression of urine, or from virulent attacks of Type iii. It must be remembered, however, that in places where blackwater fever frequently occurs many cases are seen and treated under the worst possible conditions. Sometimes the hæmoglobinuria has already been established for a day or more before the patient is first seen by his medical attendant. At other times the patient and his doctor are so situated that proper treatment cannot be rendered. Often too, the ignorance and prejudices of race and caste make efficient care and nursing impossible. I am confident that if a patient is seen and treated from the outset under ordinary favourable conditions, recovery can be looked for in at least ninety five per cent of all cases seen.

(b) ULTIMATE PROGNOSIS.

There is always intense anæmia after blackwater fever, but it is wonderful how quickly patients recuperate, especially if they leave the country. The future prognosis will depend to a great extent upon the character of the attack.

There is one striking fact in regard to the disease, namely, that it so often appears to cure the malaria. A patient who has had a long succession of malarial attacks, may recover from blackwater fever quite a new man, and may have no more malarial fever for months. Even if he remain in the country he may enjoy a long period of freedom from malaria. This is especially so in the class of case described under Type i, and to a less extent among those of Type ii. In these it would appear that the destruction of parasites has been complete, and the whole system seems to be swept clear of them. If such patients are prepared to take the risk attending a re-infection, they may be allowed to complete their term of service, with a warning that most scrupulous care should be taken in all future malarial attacks, but if they have been more than eighteen months in the country they would be well advised to take leave.

In cases of Type iii the conditions are quite different. In these a large number of parasites may have perished, but some have escaped, and these are sufficient to continue the malarial infection, even though they may not be numerous enough to show

in the peripheral circulation. Such cases, unless energetically treated, are almost sure to have further relapses of malarial fever, and associated with these there will always be the risk of a recrudescence of blackwater fever. Patients who have had attacks of blackwater fever of this type should be invalided to a healthy climate at once.

In regard to the remote effects of blackwater fever I cannot speak from personal experience. It is stated that renal cirrhosis may result, but I have never seen evidence of this. Possibly it is a late sequela. A certain degree of cardiac dilatation occurs in nearly all forms of blackwater fever, and imprudent conduct during convalescence might possibly lead to permanent organic mischief. Speaking from my own observation I should say that a single attack of blackwater fever is not likely to be followed by any very serious results.

MORTALITY IN SECOND AND SUBSEQUENT ATTACKS.

There was formerly a very general idea that a second attack of blackwater fever might be successfully weathered, but that a third invariably proved fatal. This idea is quite unfounded. I have myself had blackwater fever on five different occasions

and I know of other similar instances. Crosse⁶⁶ thought that the mortality in second attacks was higher than in the first, but I cannot say that I have noticed this. I have seen and heard of cases in which the second attack proved fatal, but other things being equal, I do not consider that there is necessarily any special risk about second attacks unless they follow after a very short interval. In my opinion, if a patient survives a second attack he is not likely to die in any subsequent one. Possibly a certain degree of tolerance is cultivated, and more important still, the onset of the disease ceases to cause such great alarm. In malarial fever, and especially in blackwater fever, the mental attitude of the patient exercises a potent influence on his chances of recovery. I remember one case of malaria in which I am confident that pure fright contributed not a little to the fatal issue. Now blackwater fever is a disease of dread omen in tropical countries, and if a patient is suffering from 'funk' his chances of recovery are proportionately reduced. If twice before he has survived attacks of the kind, he naturally expects to do so again, and the probabilities are that he will do so.

XII. RELAPSES AND SECOND ATTACKS.

The distinction between a relapse and a second attack must necessarily be somewhat arbitrary. Personally, I regard the attack as a separate and distinct one if a definite period of freedom from hæmoglobinuria has elapsed: that is to say, if I consider a patient convalescent, a return of fever and hæmoglobinuria would be classed by me as a second attack. On the other hand, if, after the urine has partly cleared it again darkens, I regard this as a relapse: or if the urine has cleared but the febrile symptoms have continued, I look upon a reappearance of hæmoglobinuria as a relapse. In my experience relapses have not been common, which I attribute to the fact that I insist on the most scrupulous care during convalescence, the patient being kept in bed for some days. The only example of a relapse which has occurred in my own practice was that already referred to (vide ^{case} ~~about~~ 5). In this instance there was a very definite exciting cause. Second and subsequent attacks are not at all uncommon, in fact a patient who has once had blackwater fever appears to remain predisposed to

it for some time, especially if the malarial infection continues, or if a fresh one is contracted. This fact is readily explained by the theory put forward in regard to the cause and pathology of the disease. The unstable condition of the blood which has been described would appear to last a long time, so that under similar conditions and provocation hæmoglobinuria may be again induced. In this connection reference might be made to what has been described by Bastianelli⁶⁷ as post malarial hæmoglobinuria. He considers that it may occur in patients whose blood and organs are free from parasites, although there must always have been a recent infection. It is quite possible that this may be so, for if the blood has been left in an unstable condition a patient might be as liable to the influence of chill as a person who is subject to the ordinary paroxysmal form of hæmoglobinuria. Bearing in mind however the difficulty which attends the demonstration of the malarial parasite when hæmoglobinuria has supervened, I am myself inclined to suspect that in these cases of so-called post-malarial hæmoglobinuria, the initial factor has been a sudden though evanescent recrudescence of the malarial infection.

XIII. DIAGNOSIS.

The diagnosis will not as a rule present much difficulty, though in places where yellow fever occurs, it might possibly be mistaken for it. The jaundice of blackwater fever is, however, an early and not a late symptom as in yellow fever. The urine in yellow fever is albuminous and may contain blood, but not hæmoglobin: the vomit is not so distinctly bilious and in the later stages is black, whereas in blackwater fever it is but rarely bloody.

In blackwater fever there will invariably be a history of previous malarial fever or of indefinite ill-health, and malarial parasites may be found in the blood, but of course yellow fever might supervene in a malarial subject. Yellow fever is said to attack new comers much more frequently than old residents, whereas the reverse is the case with blackwater fever.

In regard to ordinary paroxysmal hæmoglobinuria, I fail to see how it could be distinguished from mild blackwater fever when it occurs in a malarious climate. The history of the case, and the presence

XIV. MORBID ANATOMY.

or absence of malarial symptoms can be our only guide. Whenever there are definite reasons for suspecting a malarial infection, I should regard the onset of hæmoglobinuria as a manifestation of blackwater fever, even if it occurred in a person who is subject to attacks of the paroxysmal form of the disease. In many cases of blackwater fever there is nothing very distinctive about the post-mortem appearances which would serve to differentiate it from a severe or chronic malarial infection.

The following macroscopical changes may be noted:-

THE SPLEEN is usually enlarged, and if the malarial infection has been a chronic one the capsula will be thickened. It is invariably congested: in consistence it may be firm and its colour rather brownish, or it may be very dark in colour, and almost fluid.

THE LIVER as a rule will be found slightly enlarged and on section shows a yellow brown colour. The gall-bladder is generally distended.

THE KIDNEYS show signs of hyperæmia, and the same brown colour may be noted as is seen in the liver and spleen.

XIV. MORBID ANATOMY.

following:-

THE SPLEEN: I have had no opportunities for performing extensive post-mortem examinations. The utmost that I have been allowed to do has been to remove portions of organs through a small opening. It would appear that in many cases of blackwater fever there is nothing very distinctive about the post-mortem appearances which would serve to differentiate it from a severe or chronic malarial infection.

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THE KIDNEYS show signs of hyperaemia, and the same brown colour may be noted as is seen in the liver and spleen.

Microscopic examinations may reveal the following:-

THE SPLEEN: A certain amount of pigment will almost certainly be found, the quantity and distribution varying to some extent according to the chronicity of the malarial infection.

THE LIVER: The hepatic cells may show degenerative changes. There is invariably some pigmentation which however is not always excessive.

KIDNEYS: In the glomeruli there may be slight melanosis of the endothelium, the convoluted tubules show marked degeneration of the epithelium, and according to Thin the granular masses found

in them are due to the products of the disintegration of the epithelial cells. Henle's loops

are usually filled with haemoglobin, while in the straight tubules there will be found many casts

composed of the same substance. The cells of these tubules and of Henle's loops are little affected.

In some cases malarial parasites may be found in the organs, though they may be confined to one part. Thus, in a case the organs of which were examined by Thin, parasites were found only in the brain.

XV. PROPHYLAXIS.

There are three main principles which should guide us in the prevention of blackwater fever.

(1) The condition results from malaria, hence the primary prophylaxis consists in avoiding malarial infection.

(2) A certain degree of malarial poisoning is necessary before hæmoglobinuria will supervene, and systematic and thorough treatment of a malarial attack will prevent the development of the predisposition.

(3) The final exciting cause of blackwater fever is chill and exposure at a time when there is active malaria present.

(1) In regard to the first it is unnecessary for me to recapitulate the usual and well-known methods which can now be so effectively employed as a result of our knowledge of the role played by the mosquito in the transmission of the disease.

However, reference should perhaps be made to the question of prophylactic dosing with quinine. In ordinary circumstances it is in my opinion not called for, but under certain conditions it may

be advisable: (a) if malaria is extremely prevalent and if for any reason it is impossible to avoid being bitten by mosquitos, especially at night, or (b) if an individual has a bad malarial history, and has shown a tendency to develop malignant symptoms, such as cerebral malaria or hamoglobinuria. Various methods of taking quinine prophylactically have been advocated. Personally I do not think it matters much about the exact dose taken at a time, provided that not less than thirty five grains are taken weekly - I have on more than one occasion proved the efficacy of a daily dose of five grains. Most people can take this amount without suffering any unpleasant results. I myself once took five grains a day regularly for nearly two years, and during that time had no malaria. A patient of mine took the same dose daily for two and a half years, and though stationed during the whole time in a very malarious district, he escaped without a single attack. One important fact to which attention must be drawn is, that small prophylactic doses taken in this manner will not prevent relapses of malaria when once infection has taken place, unless the initial attack has been thoroughly and energetically treated.

(2) If in spite of all precautions malaria is contracted, the second stop in the prevention of blackwater fever is to insure that the former be properly treated. If this is not done relapses are almost sure to occur, and the patient develops the condition of chronic malarial poisoning which predisposes to the onset of hæmoglobinuria. And here I may remark that there is no disease that I know of which is more persistently neglected and badly treated than malaria. This is in part due to the fact that in places where the disease is common people develop the habit of treating themselves, either from necessity or from choice. Familiarity robs it of its terrors, especially as the attacks tend so often to terminate spontaneously, and may be followed by quiescent periods. As a result of this people often neglect quinine, which is for many reasons an unpopular drug, and they will extol the virtues of a "good sweat" as a cure for malaria, oblivious of the fact that the mere termination of the attack does not indicate a permanent cure of the malarial infection. Whatever the cause, it is undeniable that there is a disposition among the laity - shared unfortunately by many medical men - to regard

malaria as a disease requiring no particular care or attention: hence very frequently no attempt is made to bring about a radical cure. As a result, relapses are the rule and cause no surprise, and the parasites perhaps linger on in the system for months. I consider that a recent infection of malaria can be and ought to be absolutely stamped out, and this can only be effected by systematic and careful treatment. Of late years I have adopted the following procedure with most successful results: Quinine is given intra muscularly (thirty grains a day or more, according to the severity of the case) as long as there are any febrile symptoms. When the temperature is normal, twenty to thirty grains are given by the mouth daily for a week. For the following fortnight ten to twenty grains are given daily, and after that time five grains daily for at least a month, and if desirable to be continued indefinitely. I can say with confidence that a recent malarial infection treated in this manner is radically cured. No relapses need be anticipated and the condition which predisposes to blackwater fever is avoided. Although in this way we diminish all risk of hæmoglobinuria, it is better to regard every case of tropical malaria as ^{one} of potential blackwater fever,

for it is never safe to assume that the condition of predisposition has not yet been established. This brings me to (3) the final prophylaxis against hæmoglobinuria, which is to avoid all chill and exposure at a time when there is active malaria present. To ensure against this, a patient with malaria - especially if an old malarial subject - should be sent to bed immediately on the first sign of an impending attack, and after it is over he should not be allowed to get up until he has had at least forty eight hours without the slightest rise of temperature. This would seem an easy rule to enforce, and yet nothing is more difficult than to persuade patients of the risk they run. I have already spoken of the hap-hazard way in which malaria is frequently treated, and associated with this there is the pernicious doctrine that a slight rise of temperature can be disregarded. This latter has, I believe, arisen in great measure from non-recognition of the essential difference which exists between the benign intermittent and the tropical forms of malaria. In the former the attack runs a definite course. After the initial rigor - which is so marked that it commonly drives the patient to bed - there is a rise of temperature which persists for some hours until a profuse perspiration indicates

that the attack is over: the temperature begins to fall, and unless there is a double infection it will not rise again until the next attack is due, thirty six or forty eight hours later. Now in this type of malaria, when once the temperature begins to fall it may be relied upon to go on doing so, and consequently the actions of the patient at this stage matter but little. As these intermittent forms are rarely accompanied by any malignant symptoms, it has become the habit to regard a slight temperature as of little importance.

Now in the tropical type the course of the disease is entirely different: the initial rigor is so slight that the patient may not even realise that he has malaria: the fact that the temperature falls to normal affords no guarantee that it will not rise again in a very short time, and it very rarely happens that there is an abrupt termination of the attack. The usual course is as follows: After a certain period - one to three days - the acute symptoms and high fever subside, and it will be found that the morning temperature is about 99° but in the evening of that day there will be perhaps quite a sharp rise. The following morning the temperature may be normal, but in the evening there

may be a slight rise of a degree or more. The next day the temperature may remain normal throughout, and then - and only then - can the infection be regarded as under control. Even then there may be a relapse unless systematic treatment is continued. After careful study of a very large number of malarial cases I can affirm that even under vigorous treatment there is almost invariably a slight evening temperature for two or three days after the acute symptoms of the initial attack have subsided. This fact is not appreciated by the laity, and it is a very general custom to disregard these slight rises of temperature, whereas chill or exposure at this very stage when there may be little or no temperature is, in my opinion, the one and only exciting cause of hæmoglobinuria in a predisposed subject. This is a practical conclusion about which I have no doubt whatever, and it is strongly supported by the fact that I have never seen a case of blackwater fever develop in a patient who was at the time under my charge except once, and in that solitary instance my orders with regard to going to bed were not obeyed. In every other case that I have seen, the condition was already established when first I saw the patient. Case 2 might be regarded

as contradicting this assertion, but the hæmo-
globinuria supervened within half an hour of my
first visit, and as the patient had manifestly
been going about for two days with fever upon him,
his case clearly exemplifies my argument. I can
confidently affirm that if a patient betakes him-
self to bed at the very first sign of an impending
malarial attack, and if he remains there until
he has had forty eight hours without any rise of
temperature whatever, there is but little risk
of hæmoglobinuria supervening, however much (Cp. Hanley whose experience
is similar) ⁶⁹ quinine he may take. I do not wish to deny the
possibility of blackwater fever occurring even
where this regime is followed; all I can say is
that I have never seen it do so myself. It must
be remembered that it is quite possible for a
patient to get a chill even when he is ostensibly
well-protected in his bed. This is especially
likely to occur in the well-ventilated houses of the
tropics. After a long and restless night the
patient may towards morning fall asleep and in the
"chill wind that comes before the dawn" the
mischief may be done.

XVI. TREATMENT.

It has already been pointed out that in a very large percentage of cases of blackwater fever the disease tends to spontaneous cure. If this be admitted, it is easy to see how readily some one treatment may establish for itself a fictitious reputation. It is my belief that of any given number of cases which recover from blackwater fever, the majority do so not as a result of the treatment, but independently of or perhaps even in spite of it. Hence in this disease, empirical therapeutics are particularly fallacious. It is difficult indeed to understand how any specific line of treatment can be advocated for the cure of hæmoglobinuria, since the latter is, after all, merely a symptom indicating the presence in the blood stream of free hæmoglobin which the kidneys are attempting to discharge. When the supply is exhausted then - and not till then - will the urine become clear.

In the absence of a theory as to what causes the condition it is manifestly impossible to indicate any rational specific treatment. I,

however, believe that the fons et origo mali is malaria, and therefore I advocate treatment with quinine. It must be clearly understood however, that I do not for a moment suppose that the quinine has any effect upon the existing condition of hæmoglobinuria. It is given not to combat a symptom, but with a view of attacking the original disease which led up to it. A patient who is suffering from blackwater fever or slowly recovering from it, is not in a fit condition to withstand an added malarial attack, and if such supervenes, as is the case in Type iii, there is great risk of its proving fatal.

The doctrine that quinine should be withheld unless parasites are found is a most dangerous one, for it has already been shown that the absence of parasites from the peripheral circulation in blackwater fever, affords no evidence that they may not be present in the organs. Precious time is thus lost, and the patient may die or sink into a hopeless condition before the parasites appear. There are some authors who deny the utility of quinine on the following grounds:-

That many cases of blackwater fever recover without quinine.

That a certain number die even if they are treated with it.

As to the first of these objections we have already noted that blackwater fever very often cures itself. In Types i and ii, especially (and they constitute the great majority) it seems as though the system had been entirely cleared of malarial parasites, and hence, in these cases, as soon as the kidneys have eliminated the hæmoglobin the patient is cured, and no quinine is necessary. Even in cases of Type iii, in which there is a continuance of the malarial infection, death does not necessarily follow even if quinine is not given, for the subsequent malarial manifestations may be slight or the resisting and recuperative powers of the individual may be good; but the fact that recovery may take place without quinine is no logical argument for withholding quinine. It is never safe to assume that the malaria has been exterminated or that its recrudescence will be mild.

With regard to the second objection, it is true that a certain number of cases of blackwater fever will prove fatal even if treated with quinine, but in many of these the actual cause of death is suppression of urine, and this may occur whether quinine has been given or not. In a small number of cases the drug will not avert a fatal

issue, for the same reason that it sometimes fails in cases of severe malaria unaccompanied by hæmoglobinuria. The toxins at work are perhaps too potent, or the resisting powers of the individual are too weak, or his debilitated condition is such that all his bodily functions are disorganised and perverted. A recent malarial infection can and ought to be cured at once if treated properly, but if it has been neglected the time may come when it will be too late for the saving grace of quinine to be of any avail. In a certain number of cases, the occurrences of blackwater fever indicates that this fatal stage of malarial intoxication has been reached and the failure of quinine is the natural result. The drug should not be condemned because it sometimes proves inefficacious, for if we exclude the risk resulting from suppression of urine, the chief danger to be apprehended in blackwater fever is a continuance of the malarial infection. Acting on this view I advise that blackwater fever should be treated on the same principle as an ordinary malarial attack, quinine being given as a routine practice, intramuscularly, as long as the febrile symptoms persist. I have seen it stated that in blackwater fever quinine given in this way is apt to cause abscesses and other troubles. Now, I have my

self used this method extensively for the last ten years, and only twice have I seen abscesses follow injections made by myself, and in both these cases there was a definite exciting cause. In not one single case of blackwater fever treated with quinine injections have I ever seen the slightest trouble follow, and it is perhaps worth while to indicate the method employed. When I first began the practice of intramuscular injection I used a large sized anti-toxin syringe. Sufficient water to fill the syringe was first boiled in a test tube, and from twenty to thirty grains of quinine were dissolved in it: the solution was then heated to boiling point, and injected whilst it was still warm. Of late years I have used a sterilized solution of bi-hydrochlorate of quinine which can be obtained in small sealed glass capsules each containing ten grains in 2 c.c. of water. I employ an all-glass syringe having a similar capacity, and if more than ten grains is to be given I fill two syringes. After employing one, it is detached from the needle still in situ, and the second quickly affixed. Ordinary aseptic methods should of course be observed, and it is my routine practice, when the syringe and needle are charged ready for use, to plunge the needle up to the hilt in pure carbolic. After keeping it there for a minute or so, it is taken out and at once inserted into the spot selected.

Not only does this ensure an aseptic track, but I believe the thin coating of carbolic exercises some anæsthetic effect. Not only so, but a minute drop spreads out over the site of the puncture and causes a slight superficial eschar which serves to mark the spot. This is not unimportant, for great care should be taken not to put a second injection in close proximity to a previous one. I regard the buttock as the seat of election for these injections, but if many have to be given it may be necessary to go to the scapular muscles or to the deltoid and triceps. The disadvantage about the arm muscles is that a patient will very likely use his upper limbs freely even when he is lying in bed, and there is no doubt that muscular exertion tends to assist inflammatory action. Another practical point is that the patient should keep the muscle as quiet as possible for a few minutes after the injection. Given in this manner and with these precautions the method has proved perfectly safe, and can be utilized even for babies of a fortnight old. The pain is not excessive, and soon passes off at the time: the next day or later there may be slight pain and stiffness and even some swelling and redness, but

these will subside unless the patient walks about, or in other ways irritates the part. If an abscess does form it should be opened as soon as possible, and as a rule gives little trouble. The worst cases of sloughing that I have seen were due to the injections having been given hypodermically in the forearm by inexperienced operators. For black-water fever then, quinine should be given in this manner, the amount and the frequency of the dose being dependent upon the patient's temperature. As a rule an initial dose of twenty grains should be given at the outset, followed perhaps by three or four more at twelve hour intervals. The important points are, to take the temperature chart as the measure of the amount of quinine necessary, and to administer it intramuscularly, for only in this way is it possible to ensure certain and prompt action. When there is excessive vomiting it is not possible to judge how much or how little has been retained if it is given by the mouth, and even if it is not obviously ejected, the condition of the patient may be such as to render complete absorption problematic. This applies to all mouth given remedies for black-water fever. In the severe forms of the disease, in which vomiting comes on early, and is perhaps almost

incessant, even a genuine specific would be of little avail, for it would not remain in the stomach. If a patient is well enough to retain medicine he will probably get well without it, and this fact increases my scepticism in regard to the so-called 'cures' for blackwater fever to which some reference must be made.

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Hearsey (Principal Medical Officer British Central Africa) has published accounts of a series of cases ending in recovery which were treated with a mixture containing Hydrarg., Perchlor. and Soda Bicarb. I believe that in cases of mild or medium severity, this combination does tend to allay the vomiting, but on the other hand these types of the disease frequently recover whatever treatment is adopted. In two cases in which I tried the above mentioned mixture, it failed to avert a fatal issue, though it is only fair to say that in one it was not administered until twenty four hours after the onset of hæmoglobinuria. In the other case it was given from the outset, and it failed to exercise the slightest influence upon the vomiting. As already stated, blackwater fever patients, if placed under favourable conditions and if carefully nursed and treated, stand a very

good chance of recovering, and it is not safe to assume that this happy result is due to any particular specific remedy. Dr Hearsey's suggested line of treatment should, I think, always be tried, but it must be remembered that it is merely a symptomatic treatment and not in any sense a specific.

Dr O'Sullivan Beare⁷¹ some years ago drew attention to what he called a "native remedy" for blackwater fever. This consisted of a preparation obtained from *Cassiana Beareiana*. I regret that I have not myself had an opportunity of experimenting with this substance, nor have I heard of any extended trials with it. To my mind it appears curious that the natives should possess a remedy for a disease which is admittedly so infrequent among them and I am inclined to think that there has been some confusion between blackwater fever and haematuria. This latter is very common in East Africa as a result of *Bilharzia*, and it would not be surprising if the natives professed to have a cure for it.

Boracic acid, given internally, has also been advocated as a remedy for blackwater fever, but it is difficult to see upon what grounds. No doubt the virtue of many so-called 'cures' lies in the fact that in all cases their administration involves

the ingestion at frequent intervals of a certain amount of fluid, and this tends to keep up the flow of urine which is so essential if recovery is to be looked for.

Apart from the administration of quinine the treatment of an attack of blackwater fever must be mainly symptomatic, and the chief and most important point of all is to promote free diuresis, especially in the early stages. The prevention of suppression is after all the main object to be aimed at, for its occurrence practically removes all hope of recovery, whereas if it is avoided the patient may survive even if he gets no medicine at all. Every effort therefore should be made to ensure a free flow of urine by encouraging the patient to drink copiously, it matters little of what, so long as the fluid imbibed is bland and non-irritating. Weak tea, soda and milk, barley water or rice water all are suitable. Fortunately the vomiting is not so troublesome in the early stages, and even when it becomes more marked the patient should still be encouraged to drink, for a certain amount may be retained. Not only so, but the presence of some fluid in the stomach tends to diminish the intense retching which ensues when the organ is empty. When dealing with ignorant and

unintelligent people who cannot appreciate the rationale of such simple treatment, the best way is to colour three or four pints of water with some harmless ingredient, and to tell them that if a successful issue is to be brought about, this must all be consumed within say twelve hours. They will conscientiously absorb it, thinking it is medicine. If the vomiting is so violent that nothing can be retained, large enemata of warm water may be given. If administered slowly these are often retained and absorbed. When suppression of urine is definitely established, nothing appears to be of any avail for the relief of the condition. I have tried large injections of saline solution into the cellular tissue under the skin, cupping, and other similar remedies, but have never seen any benefit accrue.

Quinine can be relied upon, as a rule, to control the temperature within reasonable bounds, so that vigorous antipyretic measures are seldom called for; but when there is great discomfort, headache, and delirium with a temperature of 104° or more, a dose of phenacetin does no harm and relieves the acute sufferings. Too free diaphoresis is however, to be deprecated, as tending to concentrate the urine.

The vomiting often constitutes the most distressing and exhausting symptom of the disease. I have tried all the usual remedies, but cannot speak with confidence of any. Small doses of morphia - one eighth of a grain hypodermically - seem at times to do more good than anything else, but in some cases nothing has the slightest effect. In such circumstances it may be necessary to feed the patient with nutrient enemata. The cardiac weakness is best met by hypodermic injections of strychnine.

To sum up:- If quinine be given in efficient doses; if a free flow of urine be maintained, and if the symptoms of blackwater fever be treated on ordinary general principles, a cure may confidently be expected in a very large proportion of cases. Occasionally, however, there will be met a class of case which baffles all treatment.

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4 HOUR CHART.

DISEASE.

B. wt
Type I

Name *H. T.*

Age *English*

Diet

Case Book No.

Notes of Case

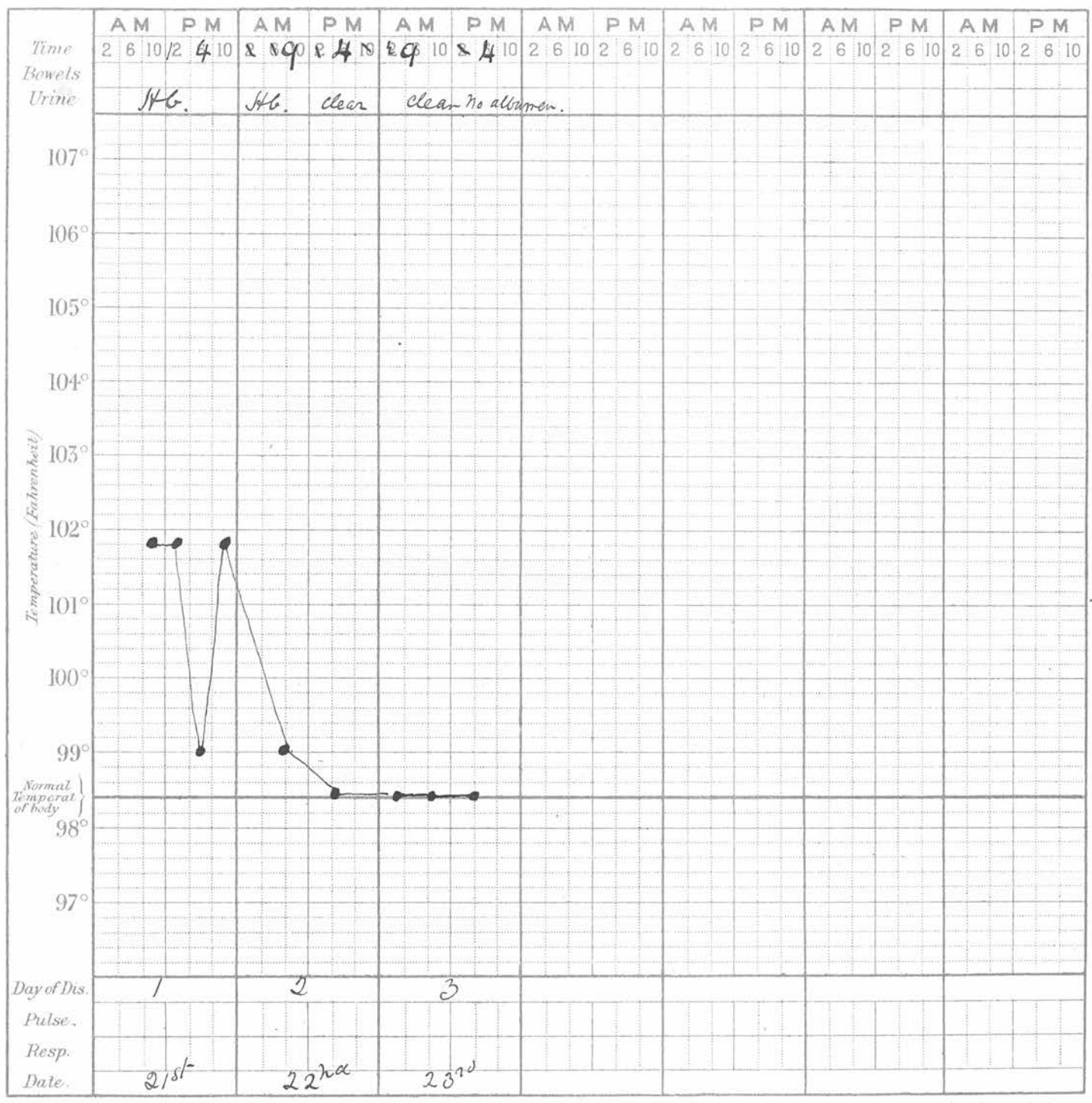
Chart of Case 2.

Haemoglobinuria
ceased on 2nd day.

Date of admission

June

Result *Recovery*



4 HOUR CHART.

DISEASE.

B.W. 4

Type II

Name R.V.

Age English

Diet

Case Book No.

Notes of Case

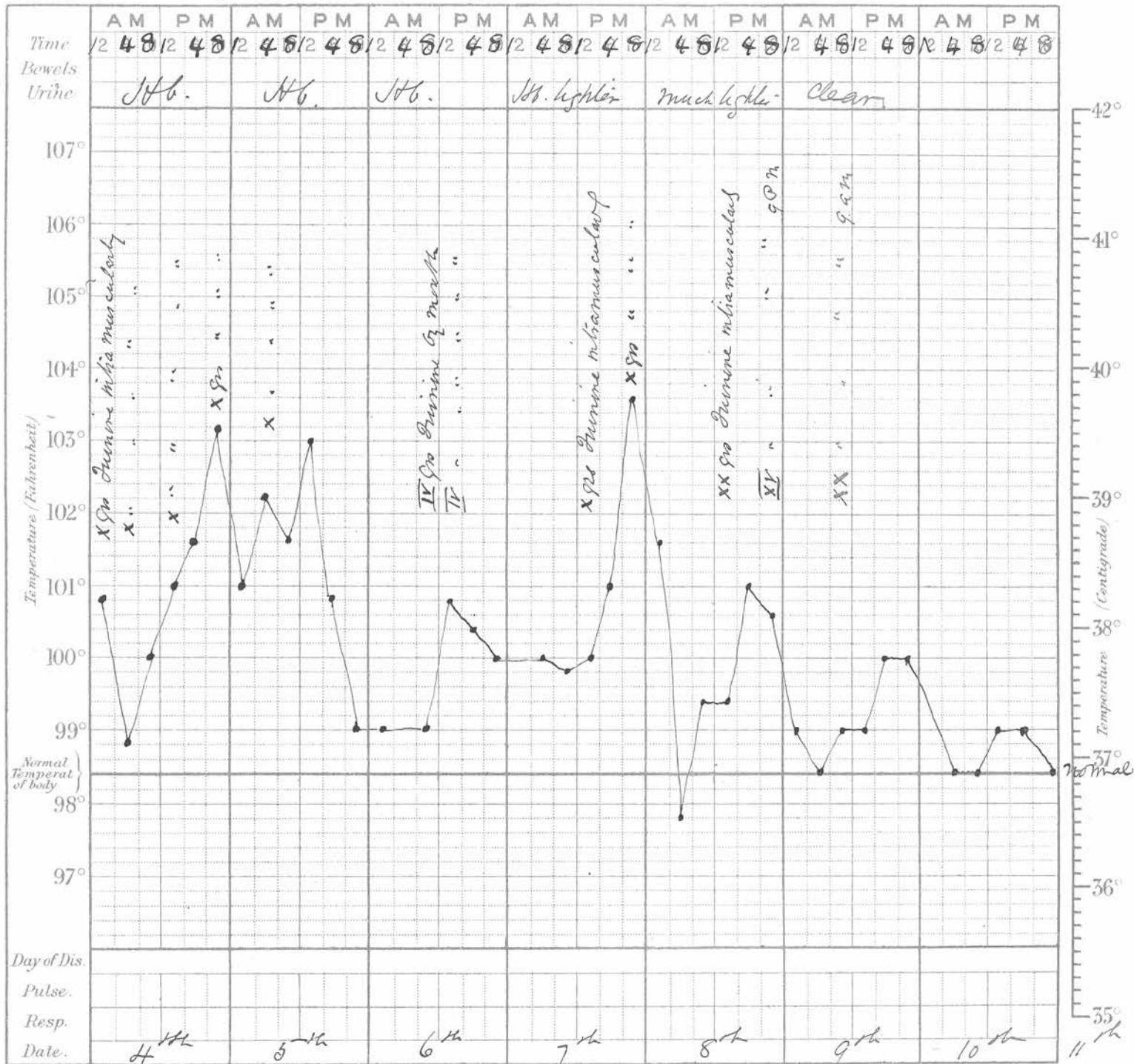
Chart of Case 3.

Haemoglobinuria ceased on 5th day.

Date of admission

August

Result Recovery



4 HOUR CHART.

DISEASE.

B. W. F.
Type III

Name *S.*

Age *Indian*

Diet

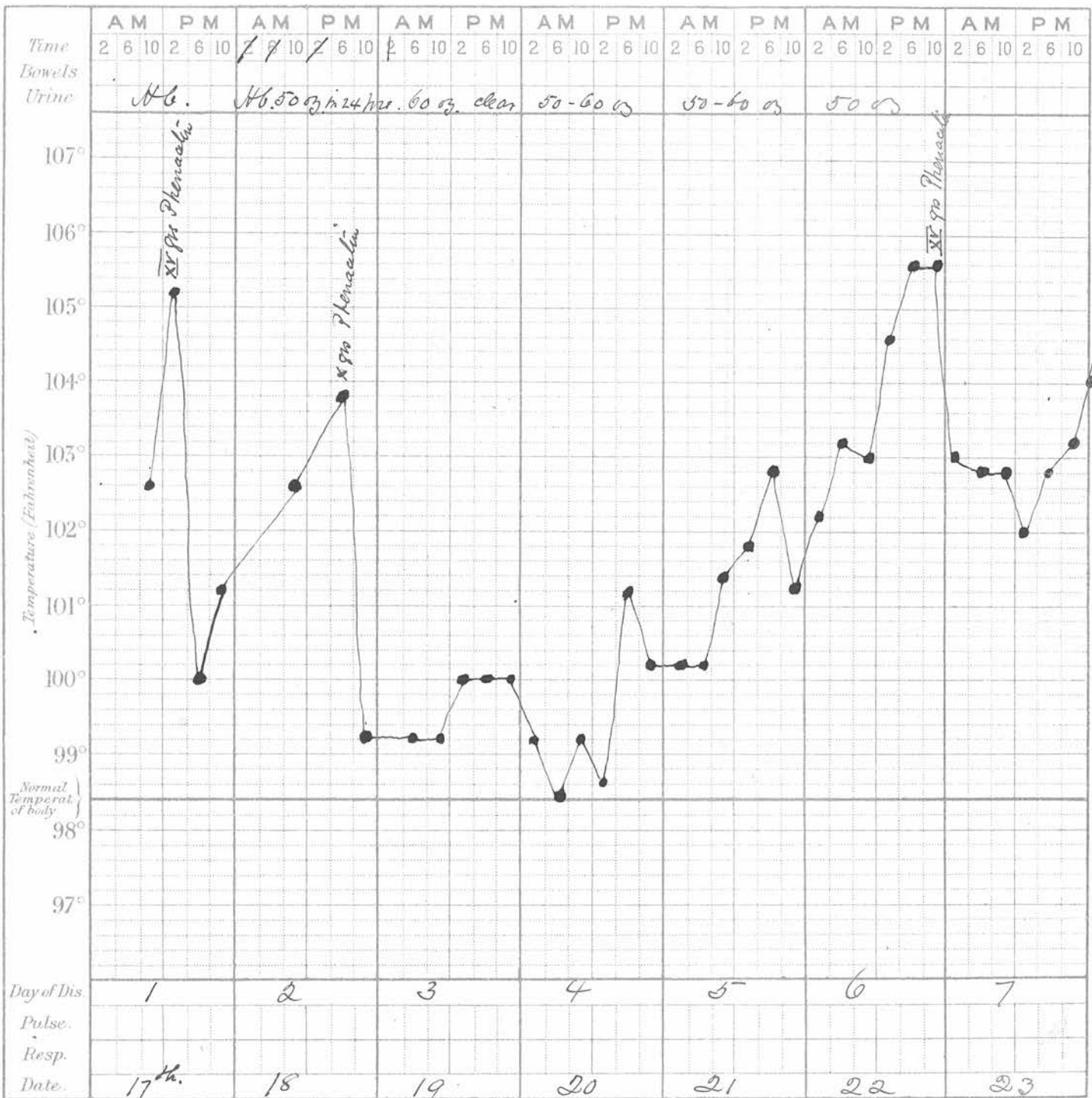
Case Book No.

Notes of Case

Chart of Case 4

Wound cleared on evening of 19th the 3rd day.

Date of admission *January 17*
Result *Death*



4 HOUR CHART.

DISEASE.

*Bowel
Type III.*

Name *J.H.*

Age *Egyptian*

Diet

Case Book No.

Notes of Case

Chart of
Case 5

*Wound cleaned on
4th day - slight
recurrence on 5th day.*

*After two days of normal
temperature patient had
a severe return of fever.*

Date of admission
June 4th

Result *Recovery*

