II

Blackwater Fever
with
notes of a case, and some observations on the etiology of the disease.

Being a thesis for the degree of Doctor of Medicine of the University of Glasgow,
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Of late years very much has been done in the study of Tropical diseases, with the result that we now know the definite cause of many of them. For example, Elephantiasis has been shewn to be due to the presence of the Filaria in the Lymphatic system, Malaria has the Plasmodium malariæ as its specific cause, while ~~in~~ ~~both~~ the parasite in each case passes a portion of its life cycle in the body of the mosquito, and the infection is conveyed to the human subject by the bite of the insect. On the other hand, although much has been written regarding Blackwater fever, there is still a wide difference of opinion in the minds of Authors as to the true cause of this disease. Every case that can be reported may be of assistance in elucidating the problem which as yet

remains unsolved. For that reason I wish to bring before the notice of the Profession, a case that came under my care in Stirling in 1896, and to make some observations on the views which have been advanced by several writers on the etiology of Blackwater fever -

I propose therefore to divide my paper into two parts: —

I. Clinical notes of the case.
II Observations on the etiology.

Clinical notes of a case of Blackwater fever.

Y. M. aged 28, a missionary of the Congo Bolobo mission of the East London missionary Training Institute, had been working on a Station on the Upper Congo river, for a little over three years, and his health had been for the most part excellent, with the exception of periodical attacks of malarial fever of a benign character.

Towards the close of the above named period however, he suffered from one or two awkward attacks of Haemoglobinuric fever, a form of disease that is very prevalent in those regions. The extraordinary prostration that succeeds this malady, rendered it desirable that he should have an immediate change of climate, and he therefore left for Europe on furlough. He accomplished the trying journey down country, without further mishap, and reached London on 15th January 1896. Very soon after his arrival, he had a sharp attack of malarial fever, (not blackwater) the temperature rising to 105°7. Under treatment with Quinine the fever speedily abated, and at the end of two days the temperature was normal. He spent a few days in the South convalescing, & then came north to Stirling, to visit his relatives. Although he was still suffering from weakness, he spoke at several meetings, and underwent a considerable amount of fatigue, with the result that another relapse occurred, exactly a fortnight after

his attack in London. On this occasion however the fever assumed the hæmoglobinuric type.

1st day of disease.

About midnight on Saturday 1st February, he was seized with a violent shivering. He went to bed, and was well covered up with blankets, and a hot drink was administered. Having had some experience of this trouble before, he had a knowledge of the routine line of treatment generally adopted in such cases, and he took a purgative, consisting of Calomel ℈ V, and Compound jalap powder ℈ XV. That was not long retained by the Stomach, so the dose was repeated some time after. He spent a restless, and sleepless night, and at noon on Sunday 2nd Feb, his temperature, taken by himself, was 102°7. He had then a strong desire to pass water, and about ten ounces of urine were voided, of a dark port wine colour - Forty minutes later he vomited bilious matter. I saw him for the first time at 2 P.M., and the temperature was then

105°7. taken in the mouth. The pulse was 100 per minute, soft & compressible. The skin was perspiring freely. He was somewhat nervous and irritable, but his mind was perfectly clear, and he suffered no pain. He had a jaundiced appearance, the skin and sclerae were of a deep saffron yellow colour.

The purgative he had taken had not acted well, so I administered an enema, which moved the bowels freely. I then gave him X gr of sulphate of quinine by the mouth, and it was retained by the Stomach.

At 4.30 pm, the temperature was 104.2°7, pulse 100. I recorded the temperature every four hours, as nearly as possible.

At 8 P.M. Temperature was 104.4°7 pulse 100, & he was taking nourishment freely, at short intervals, e.g. Brand's essence of beef, Valentine's meat juice, Champagne, brandy etc.

At 10 P.M, he again passed water of a Port wine colour.

At 12 midnight Temperature was 104.1°7 and the bilious vomiting was very

troublesome.

2nd day of disease.

At 4 A.M. monday 3rd Feb. temperature was 103.3°F, bilious vomiting still continued.

8. AM. Temperature 103.3°F.

11-30 AM. Temperature 102.3°F.

I may here note that shortly after midnight on Sunday, a most distressing hiccough began, and continued throughout the night, only abating at intervals for a short period of about twenty minutes or so, until 7. AM on monday morning. From that hour on during the day, he was almost free from hiccough, & the vomiting was also less.

3-30 P.M. Temperature was 101.9°F. The hiccough again became troublesome during the afternoon, but he still was able to take nourishment well.

7. P.M. Temperature 101°8 F. Vomiting again started, and in the vomited matter was a full-grown round worm. At this hour he again passed water, which had changed in character from the port wine

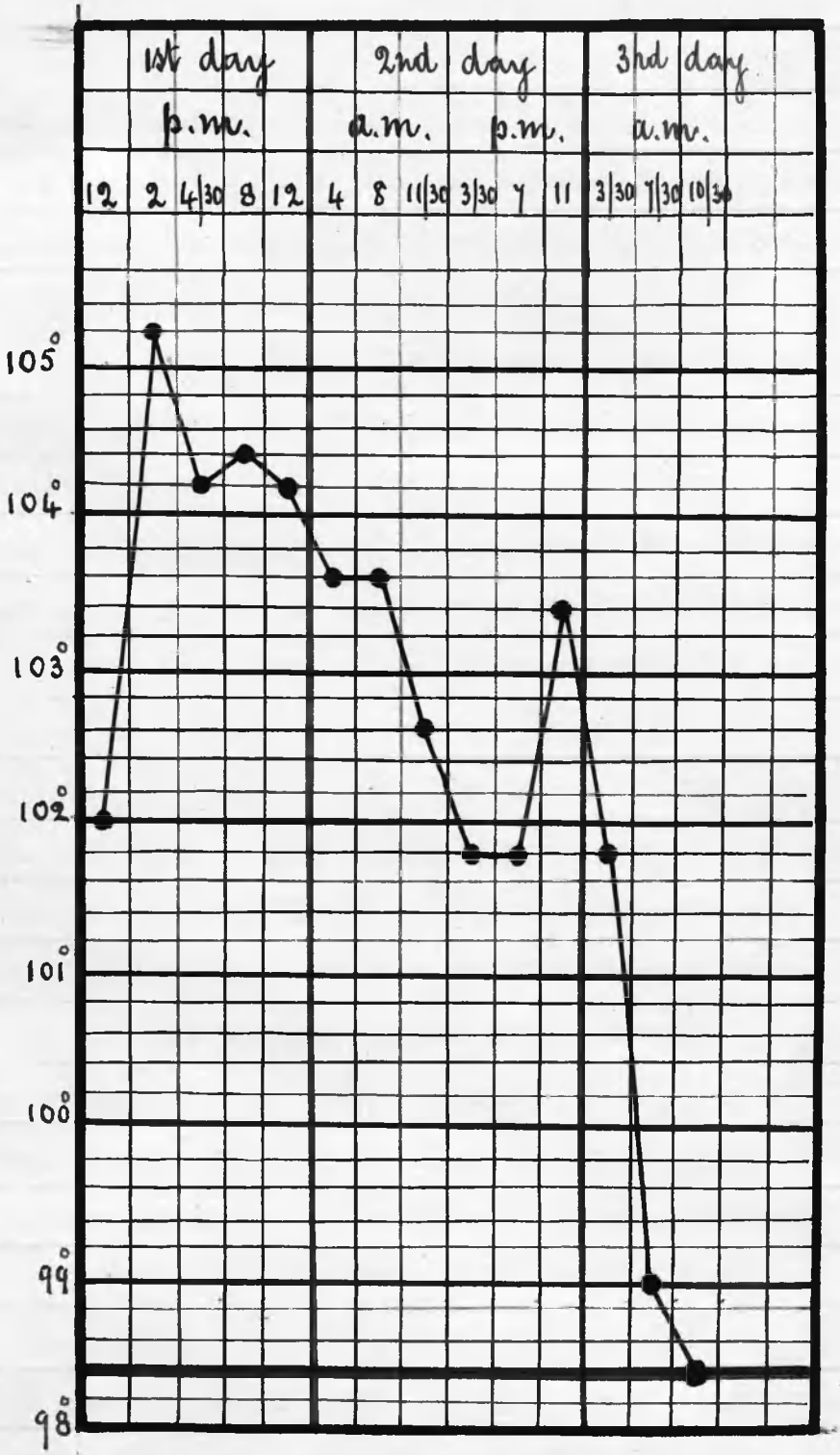

Chart of the temperature in case reported.

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colour to that of a dark mossy brown.

At 10 P.M, as the patient was very restless, I gave him a hypodermic injection of morphia gr 1/4, and he slept for an hour.

11.10 P.M Temperature showed a slight rise 103.4°F, pulse 112. The hiccough again became exceedingly troublesome, but was controlled for nearly four hours, by inhalation of nitrite of Amyl Capsules.

III day of disease.

3.30 Am, Tuesday 4th Feb Temperature was 101.8°F.

7.30 AM. Temperature was 99°F. and as the feet were somewhat cold, hot-water bottles were applied.

10.30 Am, The temperature became normal, but the pulse which was 120 per minute, was exceedingly soft and feeble. Although the temperature had fallen, the Vomiting and hiccough still continued. At noon he was extremely weak, and he could not take nourishment or stimulant.

An hour later he had the desire to make water, but was too weak to do so. I passed a catheter and drew off about two ounces of very concentrated urine, almost resembling tar in colour. From that time on, the pulse became very feeble, and almost imperceptible, and it was evident that the patient was sinking fast.

I injected Strychnia and digitalis hypodermically, but without any beneficial result. He was perfectly clear mentally, and died of sheer exhaustion at 2-45 P.M.

Post Mortem Appearances:—

I was granted permission by the relatives to hold a post-mortem examination, & I did so twenty hours after death. The body was fairly well nourished, and rigor mortis was well marked. The Skin & conjunctivae were of a saffron yellow colour, somewhat deeper in shade than it was in life. The head was not examined, so that I cannot speak

of the condition of the brain in this case.

Thorax:—

The lungs appeared to be normal, and quite healthy. The heart weighed only 7½ ounces, & when compared with the normal heart-weight of 10 to 11 ounces, appeared to me to be small, but possibly it might be part of a general atrophy, the result of repeated attacks of malarial fever, & recurring attacks of haemoglobinuric fever; otherwise the organ was healthy. The pericardial surface had on it what at first sight I took for a deposition of yellow-ish fat, but on washing, and closer inspection, it was seen to be only staining, caused by the ~~the~~ yellow fluid. In the sac of the pericardium there was about two ounces of this yellow fluid.

Abdomen:—

The liver weighed 45½ ounces as compared with the average of 48 to 58 ounces in the male,

thus again pointing to a considerable general atrophy. It was dark on section, greatly congested, and from the cut surface the same yellowish fluid could be expressed.
The Spleen weighed 17 ounces, and was very much congested. When cut open it was seen to be extremely soft, pulpy, and friable.
Kidneys:— The right kidney weighed 4½ ounces, and the left weighed nearly as much.
I sent portions of these organs to Dr. Manson of London, to whom I am indebted for the few following notes.
"The Spleen is unfortunately quite "
" useless for histological purposes "
" as it is quite diffluent. "
" The presence of pigment (melanin) "
" in the Capillaries of the liver "
" gives evidence of a recent malarial "
" infection. The organ is much con- "
" gested, and the cells of the parenchyma "
" show abundance of pigment (melanin) "
" Characteristic of rapid Haemolysis "
" The renal tubules contain infarcts "
" of haemoglobin, and there are small "

" necrotic foci in the tissue of "
" the organ -
Nothing peculiar need be noted by me in this case - It is a typical example of the acute, fatal form of the malady, & is similar in most respects to cases reported by obser - vers of experience, such as will be briefly described later on.

Part II.

Observations on etiology of Blackwater fever -

Before going on to details of etiology pure & simple, it will be well to clear the ground by considering the Geographical distribution of the disease. It is very prevalent in intertropical Africa; and in parts of the West Coast. In British Central Africa it is very severe - It is found in Sicily, Sardinia, East Africa, tropic - al America, New Guinea, and in the Indian Terai. Although I have not read of its being reported as occuring in Siam, my brother Dr. H. Campbell Highet, who practises in Bangkok, informs me that he has met with two cases in which

complete recovery took place, and one case which ended fatally. The same observer in four and a half years, spent in Singapore, never saw a case of Blackwater fever, nor does he remember having heard from any of his Colleagues in the Straits Settlements, that the disease had been seen there.

Symptoms of Blackwater fever.

In blackwater fever the attack begins with an initial rigor, and these rigors recur at intervals during the course of the fever. The temperature may rise rapidly to 105°7 ushering in the haemoglobinuria. There is early manifestation of jaundice, the skin and conjunctivae are of a saffron tint; but there is no itching of the skin as in biliary jaundice. There is great restlessness, headache, & general feeling of malaise, pains in the loins, vomiting of a bilious or greenish character, & a feeling of extreme weakness. The urine may vary from a port-wine colour to that of porter, and

it contains tube casts, granular or pigmented, but not blood-corpuscles, albumen is abundant.

In mild cases the yellow discolour-ation is less marked, the urine contains less albumen, and becomes lighter in colour. On the other hand, if the case progresses unfavour-ably, the urine becomes scanty, darker in colour, and more con-centrated, until it resembles tar, and may be entirely suppressed. The bilious vomiting continues, there is intractable hiccough, and death may ensue from Syncope, Coma, hyperpyrexia, uraemia or exhaustion.

Pathological appearances

I Macroscopical:—

The Kidneys are usually large and congested in cases which have ended fatally at an early stage of the disease. "If the case survive for three or four weeks," as Manson shows, "and then die of uraemia," "the appearances are those of large white" "Kidney."

The liver as a rule is greatly enlarged, congested, and deeply stained with the yellow pigment.
The Spleen also is enlarged, congested, almost diffluent and deeply stained.
II The microscopical appearances have been specially studied by Thin who describes the conditions of the various organs as follows—
" Spleen:— White corpuscles containing malarial pigment in minute granules, and very small spheres were found in the tissues of the Spleen. They were comparatively most numerous in the malpighian bodies, and were present in the large white corpuscles in the splenic pulp. They were also found in white corpuscles lying external to the walls of the small veins, & in the lumen of the veins; the number associated with the veins being larger than those found scattered sparsely through the pulp.
" Liver:—
In the liver white corpuscles containing pigment were found in the capillaries, and in small

" numbers in the veins. most of the "
" pigment was found in the endo- "
" thelium of the Capillaries, the "
" course of many of the Capillaries "
" being marked out by the pigment "
" accumulated in the swollen and "
" degenerated endothelial cells. Occasion- "
" ally small particles of pigment were "
" found between the capillary vessel "
" and the contiguous liver cells. "
" In many of the liver cells the pig- "
" ment was found in minute granules "
" in the substance of the cells. "
" <u>Kidney</u>:— "
" The epithelial cells first "
" become swollen and granular, "
" then are detached from the base "
" - ment membrane and block "
" the tubule. The epithelial blocks "
" gradually disintegrate until the "
" final stage is reached, when the "
" lumen of the tubule is found fill- "
" - ed with a mass of minute round- "
" - ed granules not unlike groups "
" of large cocci. Every stage between "
" the first and last change in the "
" epithelial cell can be observed. "
" ..... "

"In the liver and Spleen the dark "
" colour of the pigment was accompan"
"-ied with a distinct greenish yellow"
"tinge, and nowhere was it accumulat-"
"ed in large blocks- "

Differential diagnosis:-

Blackwater fever may be mistaken for (1) Paroxysmal hæmaturia.
(2) Yellow fever.
(3) Bilious-remittent fever.
(4) Cases of severe malarial fever with renal hæmorrhages.

The distinguishing points may be thus noted-

Paroxysmal hæmaturia is mostly a disease of temperate climates, and is usually the result of exposure to cold- It is like Blackwater fever in that it is usually ushered in abruptly with severe rigors, but unlike the latter, the temperature is lower than normal- The appearance of the urine is very similar to that in blackwater fever, but chrystals of Oxalate of lime are often noted. It does not as in severe blackwater fever assume a tarry consistency; Suppression has not be noted, and

a rapid return to the normal condition is the usual course of events. In contrast with blackwater fever & its initial jaundice, high temperature and early prostration, we have this paroxysmal hæmaturia recurring at frequent & even regular intervals, once or twice in a day, once or oftener in a week or less frequently, without marked deterioration of the general health of the patient - finally paroxysmal hæmaturia is not a purely endemic disease. Yellow fever which may be confounded with blackwater fever, differs from it however in many important features. At the outset it is marked by violent headache, congested conjunctivæ, flushed face and in fact is sthenic in type whilst blackwater fever from the start is distinctly asthenic. In yellow fever the bilious vomiting & the icterus of the skin are late manifestations when they do occur, whereas in blackwater fever the jaundice, bilious vomiting and hæmoglobinuria are constant and early symptoms. In yellow fever enlargement and tenderness of liver

and Spleen are by no means frequent, nor when present are they well defined, whereas in blackwater fever enlargement of liver and Spleen is usual, and pain and tenderness are often complained of.
The endemic areas of the two diseases do not Correspond, yellow fever is an epidemic disease, and is prone to attack newcomers to the district, whilst blackwater fever is more often a sporadic disease which affects old residents.
Bilious remittent fever:—
To an inexperienced observer a well marked case of bilious remittent fever, in its later stages, may simulate a case of black-water fever - In both there is the saffron yellow discolouration of the skin and Sclera, the vomited matter and the evacuations from the bladder and bowels are apparently bile-stained. On enquiry it will be found that the yellow discolouration of skin and discharges has been gradual in onset, whereas in blackwater fever it is an early and characteristic feature of the disease. Again rigors almost always

usher in the attack of blackwater fever, and may recur at frequent intervals throughout the malady, whereas in bilious remittent fever rigors are not a constant initial Symptom nor are they a common feature during the course of the disease. It is said moreover that the curve of incidence of malarial fevers does not correspond with that of haemoglobinuria.

(4) Severe malarial fever accompanied by haematuria may simulate blackwater fever. The resemblance may be rendered still more striking by the presence of haematemesis & melaena. In such cases there may be in addition epistaxis, purpura, sub-conjunctival and retinal haemorrhages. Microscopical examination of the discharges especially of the urine, will at once determine their true nature, and we shall find, instead of haemoglobinuria with a few stray blood-corpuscles, innumerable blood cells as in any haemorrhagic discharge.

Prognosis:—

The gravity of this disease renders the prognosis distinctly unfavourable - Manson states that one in every three or four cases proves fatal. Recovery as a rule leaves the patient extremely anaemic, and with damaged kidneys, and recurrence of the malady is prone to follow, even when the patient has removed from the endemic area to a temperate climate. Although the fever does sometimes arise within a few months after arrival in the endemic district, it is more generally found to attack individuals during their second or third year of residence. Freedom from attack beyond that period seems to confer a certain immunity upon Europeans, such as is said to obtain in natives of the district, although in neither is the protection absolute.

Prophylaxis:—

The maintainence of a general healthy condition of the system, avoidance of all excesses, and of undue exposure to the direct rays of the sun, guarding against

Chills, wettings and fatigue of all kinds, mental as well as physical, will materially assist in warding off this highly dangerous disease. Although the malarial parasite has not yet in my opinion been proven to be the specific cause of the disease, the fact that it occurs in highly malarious districts, & that repeated attacks of malaria are generally precursors of the malady, & according to many observers predispose to haemoglobinuria, it is incumbent upon all residents where the disease exists, to use every weapon with which modern science has furnished us, in order to combat this fell scourge of the tropics.

Etiology of blackwater fever –

Several theories have been advanced regarding the origin of this disease.

A That it is due to malarial infection
B. That it is due to quinine poisoning in malarial cachectics.
C. That it is a distinct disease.
D. That it arises from individual idiocyncrasy as to the kidneys in a person suffer-

ing from malarial fever.

E. That it is due to food substances ingested.

Considering the above views more in detail, we shall deal first with the theory that the malady is a phase of malaria - As arguments in favour of such a theory we find -

A (1) Blackwater fever is found in areas where severe malaria is present.

(2) On microscopical examination the blood very often reveals the presence of parasites of malaria.

(3) It usually attacks individuals who have suffered from repeated attacks of malaria.

(4) It affects the older residents who have presumably become saturated with the malarial poison -

When we examine the evidence against its being of malarial origin, as given below, the value of the affirmative evidence is considerably lessened.

Against -

(1) Malaria has a widely spread Geographic - al distribution, whereas blackwater fever has clearly defined endemic areas.

(2) The parasites of malaria which have

been found in haemoglobinuria were not of a uniform type, and even frequently the examination of the blood for parasites has proved to be negative-

(3) The mere fact of frequent attacks of "fever" having been said to occur in an individual prior to an attack of black-water fever, does not in the absence of a microscopical examination of the blood, necessarily imply that they were malarial - might these not have been as Manson points out, abortive attacks of true haemoglobinuric fever.

(4) The rule that it attacks only those who have been saturated with malaria does not hold good, for instances have been reported in which haemoglobinuria has attacked comparatively fresh arrivals.

(5) The curve of incidence of cases of black-water fever is not always conicident with that in malaria.

(6) Quinine has been found to be useless as a curative agent in blackwater fever.

With the evidence of such antagonistic nature before us, we may I think consider that the case for the malarial theory of blackwater fever has not been proven.

B. The theory that quinine is the causative agent of blackwater fever, does not in my opinion bear much weight. Were the theory correct, we should expect hæmoglobinuric fever to have an area of distribution as wide spread as that of malarial fever. The drug is administered as the antidote to malaria throughout the world, and yet we find the endemic areas of hæmoglobinuric fever comparatively restricted. Doubtless quinine, just as other drugs and various articles of diet, may produce a condition of hæmoglobinuria, but this must not be confounded with the true hæmoglobinuric fever. Finally well marked cases of hæmoglobinuric fever have been noted, where no quinine has been taken even for a considerable time prior to the attack.

C. That blackwater fever is a distinct disease, will I believe in time come to be an acknowledged fact.

" Dr. Sambon believes blackwater fever "
" to be a specific disease. He considers "
" that its peculiar geographical distribution "
" and seasonal prevalence, its character- "

" istic symptoms always constantly "
" the same in the mildest and gravest "
" cases, proves that the specific agent of "
" blackwater fever could not be any one "
" of the several malarial protozoa already "
" differentiated. The closest analogies are "
" found to be not between blackwater "
" fever and Summer Autumn fever, "
" but between blackwater fever and "
" Texas fever which is the hæmoglobinuric "
" fever of Cattle. The parasites of tertian "
" fever and of Summer-Autumn fever "
" have been found in cases of black- "
" water fever; but this per se does not "
" prove that they are the cause of "
" hæmoglobinuric fever. That they should "
" be found in a patient suffering from "
" blackwater fever was only what might- "
" be expected, because blackwater fever "
" was in many places co-endemic with "
" tertian and with summer-autumn "
" fever. A mixed infection of blackwater "
" fever and summer autumn fever was "
" therefore just as possible as a mixed "
" infection of tertian & quartan fevers. "
" Several Authors have observed a small "
" unpigmented parasite in cases of "
" blackwater fever, which so far as "

"description goes, seems to correspond"
"entirely with that found by Smith &"
"Kilborne in Texas fever. The morpho-"
"logical differences between the parasites"
"of Texas fever and those of the Summer-"
"Autumn group are so slight, and the"
"concurrence of some form or other of"
"malarial infection with that of black-"
"water fever is so frequent, that it is not"
"surprising that the specific parasite has"
"not been as yet definitely isolated-
"No multiple, rosette-like division has been"
"witnessed in the parasite of Texas fever, as"
"in those of other malarial fevers, but pro"-
"bably simple binary fission is the mode"
"of multiplication in the asexual phase of"
"Piroplasma bigeminum. Possibly in black"
"water fever there is the same mode of"
"division - In fact, the frequent association"
"of two parasites within the same cor-"
"puscle and their apparent connection"
"has been noticed by Woldert & others."
"This would be an important diagnostic"
"Character if it were confirmed."

D The theory that the disease arises from individual idiocyncrasy as to the kidneys in persons suffering from malarial, seems to me to be a far fetched one, &

may be dismissed in a word. If it were so, then it is difficult to understand why the disease arising from this idiosyncrasy should be confined to certain endemic areas, & not be found in other portions of the globe where malaria is known to be rife.

E With regard to the suggestion thrown out by Koch that, haemoglobinuric fever is due to the ingestion of certain articles of food or drink, further proof is wanting.

Treatment

The patient should be kept at rest in bed, in the recumbent position. The usual routine remedies are, a Saline; or jalap and calomel powder, or enema to clear out the bowels, diaphoretic mixtures, or pilocarpin hypodermically, anti-pyretics, careful cold sponging. Quinine in doses of 20 grains at least twice a day at first. If there is much vomiting, and the stomach rejects the dose, it may be given hypodermi-cally, or by the bowel. Draughts of hot water repeated at intervals clear

the stomach of bile, and ease the retching- Morphine hypodermically may relieve the retching and headache. Hypnotics such as Sulphonal will help to control the restlessness. For the persistent hiccough I found inhalation of Nitrite of Amyl useful. A stimulant is necessary to resist the marked prostration, and a good dry Champagne or brandy are the best. Bland drinks, such as milk and white of egg may be given, rice-water, barley water. Pig's bile has been administered with apparent benefit. Transfusion of normal Saline Solution might be advocated for the tendency to collapse, & Syncope may be met by hypodermic injection of Strychnia, digitalis, ether or brandy. Symptomatic treatment may be carried out as occasion requires. Removal to a healthy climate as soon as the strength of the patient will permit is essential to recovery, and it should be firmly impressed upon him that he ought not to return to a malarious part for at least six months or a year. He ought also to be warned against

fatigue, both mental and physical, chills, wettings & undue exposure to the Sun's rays. As a prophylactic quinine should be recommended.