Malarial fever as met with on the Gold Coast / by C. H. Eyles.

MALARIAL FEVER

AS MET WITH ON THE

GOLD COAST.

BY

C. H. EYLES, L.R.C.P. & S. Edin.,

ASSISTANT SURGEON, GOLD COAST COLONY.

PRINTED FOR THE GOVERNMENT OF THE GOLD COAST COLONY.

LONDON:
WATERLOW & SONS LIMITED, PRINTERS, LONDON WALL.
1886.

D. Martin

with the Kind regards of

Sir Richard Griffiths

Stapleford

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PREFACE.

ON my first arrival in the Gold Coast, Sir Samuel Rowe, the then Governor, suggested that at the end of a year I should summarise in a paper such differences as I might observe between the fevers met with in India and those of the Coast. For various reasons I did not act on this suggestion.

When I say that the only "fevers" I have met on the Gold Coast are malarial, it will be readily understood why I do not attempt any systematic description. Indeed, I pre-suppose an acquaintance with Professor Maclean's articles in Quain's *Dictionary of Medicine* and in Reynolds' *System of Medicine*.

After drawing attention to the irregular forms of intermittent fever which seem to represent a transition stage between intermittents and

remittents, I pass on to consider the *bilious remittent* of the older writers, which has been divided and sub-divided, and described during the past thirty years under a variety of names. In doing this I have been necessarily led into the topics of icterus, hæmoglobinuria, and the ætiology of malaria. In this connection it is only fair to say that these sections were written for another purpose in the fall of last year, and that I have not been able to consult the text of Marchiava and Celli's communications.

C. H. E.

New Hampton,
22*nd June*, 1886.

MALARIAL FEVER,

AS MET WITH ON THE GOLD COAST.

"When a climate is called *unhealthy*," says Parkes, "in many instances it is simply meant that it is malarious."[1] This is emphatically so of the Gold Coast; *fever* here means malarial fever, and the one word *malaria* covers all but a trifling portion of the illness of Europeans in this climate, and is met with in all forms pyrexial and apyrexial. I have met with instances of fever here, which elsewhere I would have termed *febricula*, but it is impossible to eliminate the malarial element.[2]

INTERMITTENTS.

Intermittent fevers are divided in all text books into *quotidian*, *tertian* and *quartian*; and other forms are spoken of as the *double*, *triple* and *duplicated tertian* and *double quartian*, and these are said to be irregular. In these regular forms the periodicity is

[1] *Manual of Practical Hygiene*—3rd Ed., p. 483.
[2] Easmon: *The Nature and Treatment of Blackwater Fever*. Chart No. 6.

expressed in terms of days, any departure from this being considered irregular, *i.e.*, the irregularity is one of periodicity. In the Gold Coast, however, the most common forms in which intermittents are seen are irregular, not in periodicity, but in paroxysm, *i.e.*, the cycle of events recurs at tolerably regular intervals of time, but the events themselves do not conform to the classical descriptions of ague.

At first I was at a loss to classify the form of fever most frequently met with here; but felt inclined to believe I was dealing with a very mild form of remittent. It was not till I observed in the case of an official living in the same house as myself that there was a distinct period of intermission, lasting for two hours, that my suspicions were roused; and as a result of observations made on myself and confirmed in others I have called it *irregular quotidian*, *i.e.*, it is quotidian in periodicity, but irregular in paroxysm.

One of the most marked features about this irregular quotidian is the almost total absence of the cold stage,[1] at most it is represented by a passing sense of chillness on exposure to breeze, which may last for about ten minutes. The cold stage, usually the most striking and prominent feature, and the most distressing part of the affection to the patient, has furnished the name *ague*, and is the basis of popular nosology, in which the term *fever* is usually reserved for remittents. Thus in the malarial districts of India intermittents are spoken of as "fever

[1] Grant: *West African Hygiene*, p. 15.

and ague," or simply "ague." Dow, in recounting his difficulties, tells the stranger that—

> "The bar petered out
> And the boys wouldn't stay,
> And *the chills* came about
> And his wife fell away."

And dear old Jack Falstaff "is so *shaked* of a *burning* quotidian tertian that it is most lamentable to behold,"[1] and thus he does really "die of a sweat."[2] In this colony, however, it is not the cold, nor yet the sweating stage that affords the popular name; here it is always "*fever*," a term reserved in other parts of the world for remittents as *Walcheren fever*, *Mediterranean fever*, etc., and this fact sufficiently indicates the absence of the cold stage.

As a rule the fever is preceded by signs more or less generally understood; there is at first some amount of unusual exhilaration, then follows general lassitude and disinclination for work, dull pains in the muscle and joints, a sensation of chillness down the back, and an inclination to sleep; indeed persistent yawning enjoys a special reputation as a forerunner of fever. The thermometer will now indicate a slight rise of temperature (0.5° to 1·0° Fahr.), in about two hours the temperature rises to 100° Fahr., at the end of the third hour it will usually be 102° Fahr., and at the end of the fourth hour it reaches the maximum, about 104° Fahr., and at this point it may remain for six, ten and more hours. The

[1] *King Henry the Fifth*, II. i., 124. (Globe Edit.)
[2] *King Henry the Fourth*, part 2, Epilogue.

sweating stage is by no means well marked. At most there are occasional bursts of perspiration, but as a rule there is gentle, intermittent perspiration, accompanied by a gradual fall of the temperature, till a fever free interval, varying between two and four hours, is left. Two hours is the smallest I have observed, but perhaps more careful observations will show that there are even shorter intervals. In short, I believe that what is true of an individual attack of remittent is true of malarial poisoning as a whole. That is, as in remittents, the temperature in successive remissions is lower and lower; so in regular cases, this is carried out in each successive attack, till ultimately there is a period of actual intermission lasting it may be only a few minutes; and that this period of intermission gradually encroaches on the febrile stage.

In my own case, I at first suffered from mild remittents; these were followed by irregular quotidian, but in each successive attack of these latter the intermission was longer and longer, and side by side with this the cold stage became more marked, till ultimately I had an attack of regular intermittent. But a return to the Coast after eight months' absence brought about pretty much the same order of events, *i.e.*, the case did not start from where it had previously stopped.

Regular intermittents are to be met with, but chiefly among those who reside in the Coast for long (continuous) periods, *i.e.*, among the non-official population. The natives suffer largely, chiefly from

regular quotidian, and the stages are well marked, but of short duration. Among Government officials the irregular intermittents are the rule. The leave regulations no doubt are an important factor in bringing about these differences. Officials reside on the Coast for about a year at a time, and proceed on leave for six months; thus they have every opportunity of recruiting their health, and chronic malarial poisoning is less likely to arise; the members of the non-official community, however, reside on the Coast for periods of three, five, or even more years, and the consequent deterioration of health tends to modify the type of fever. Thus confirming what Sir Joseph Fayrer says in speaking about irregularities in intermittent fevers :—

"Determinate periods are not of much pathological importance, I think. When a man contracts ague, the type will depend on himself, his antecedents, and his surroundings, not on difference in the nature of the disease."[1]

Dr. Grant[2] recommends in these cases that quinine should be taken when the temperature is first observed to rise, and adds that an attack may thus be cut short. This advice being contrary to what is usually given, I determined to try it on myself first. For this purpose I took observations every half hour, and with each successive attack took quinine at a different time; and I find that if ten grains be taken in solution before the temperature rises to 102°, the result is satisfactory, *i.e.*, if taken early the

[1] *The Climate and Fevers of India*, p. 69.
[2] *Loc. cit.*

attack may be completely cut short, if taken later the subsequent fever is modified, but when the temperature is allowed to rise beyond this, the drug produces no appreciable result.

Like all popular traditions, the old Coast tradition "Fever you must have, and the sooner the better," seems to be based on a germ of truth; and the tendency for first attacks to be remittent, and the fact that the deterioration of health which follows long residence tends to modify the type of fever, while it leaves the patient in a condition less able to bear a remittent, account I think sufficiently for the popular belief.

REMITTENTS.

Remittents from the mildest—barely distinguishable from intermittents on the one hand and febricula on the other—to the severest and most fatal forms, are met with as a matter of course, and Professor Maclean's descriptions cover the field. But during the past five-and-twenty years one form of remittent has attracted particular attention and has been described under the names *fièvre bilieuse hématurique*, *hæmorrhagic malarial fever*, *febris remittens hæmorrhagica*, etc.,[1] and on the Gold Coast is known as Blackwater fever.[2]

[1] Hirsch: *Handbuch der Historischgeographischen Pathologie.* Bd. I., s. 164.

[2] And as the "very pernicious so-called Bile fever (Gallenfieber) of the Gold Coast described by Mähly."—Hertz: *Ziemssen's Handbuch der Speciellen Pathologie und Therapie.* 3rd Ed. II. i., p. 45.

Speaking of this form of fever Hirsch[1] says :—

"Undoubtedly this disease, characterised by hæmaturia the result of renal affection and by more or less intense icterus arising from hepatic disorder, has been observed by the older physicians ; accounts of it are to be found in the descriptions of the 'fièvre bilieuse grave' of the French, and the 'bilious remittent fever' of the English and North American writers ; the disease has, however, been frequently confounded with Yellow Fever."

From the terms of this description we observe that there is yellowness of the skin, with black urine, and renal and hepatic mischief. Now, to the physician who observed the clinical phenomena of disease up to within a few yeas ago, black urine, accompanying yellowness of the skin could mean but one thing, and that was *jaundice*, and when these symptoms accompanied a remittent fever, and he wished to draw a distinction between the cases in which this *jaundice* occurred, and those in which it did not occur, he naturally made this the basis of classification ; and he spoke of the affection either as yellow remittent, or if he wished to use a term conveying his inference (the word jaundice not lending itself to euphonious adjectival formation), he called it *bilous remittent*, and his inference was that the colour of the skin and urine was due to bile. Thus MacDonald, speaking of the tints of Specific Yellow Fever says :—

"They should not be confounded with the much darker and more greenish hue of yellow remittent fever depending

[1] *Loc. cit.*

altogether upon jaundice, and therefore of a very different nature."[1]

But in remittent fever, while completely developed jaundice is rare, yellow tinging of the skin, and vomiting of bile, are the rule, hence the term *bilious* was extended to cover all these cases, and is frequently used as absolutely synonymous with *malarial remittent*, a circumstance which calls forth a protest from Heinemann of Vera Cruz[2]:—

"The term *bilious fever*," says he, "has been employed by writers on tropical disease in so ill-restricted a manner that it seems necessary to define it here. If in the course of a simple malarial fever there occurs gastro-intestinal catarrh, in consequence of which there arises icterus, or if there be copious vomiting of bile, this should not, in my estimation, be erected into a special category of fevers; at most one may speak of an *icteric* form of malarial fever. In another form, however, the liver directly participates in the disease process, and the symptoms of an active flux follow icterus; it would be more correct to speak in these cases of a *hepatic* form of malarial fever, and to reserve the term *bilious* to those cases in which the symptoms of icterus gravis accompany the fever, in which we have grounds to believe that owing to increased destruction of red blood cells, there is an abnormal amount of icteric pigment in the blood, in short in which there is hæmatogenous icterus."

And further on in the same article we find that in addition to the *icteric*, *hepatic* and *bilious* forms, there is a fourth form, the *hæmorrhagic*, which as we have seen, Hirsch recognises as a form of bilious remittent. If it would serve any practical purpose it would not

[1] *Reynolds' Syst. of Medicine*, vol. i., p. 483.
[2] *Virchow's Archivs*, vol. 102.

be difficult to gather from the descriptions of tropical writers terms indicating sub-classes to such an extent as to more than satisfy the most fastidious clinical observer. But no practical end would be met by such a proceeding; on the other hand it will only tend to needless confusion.

Speaking of the phenomena of intermittent fever Sir Joseph Fayrer[1] says :—

"These are subject to so much variation that the exact types are exceptional."

This is still more the case in remittents, and practically Maclean recognises this, for he nowhere attempts divisions and sub-divisions. Each case is dealt with on its own merits; with him, the one central point is that the disease is *malarial remittent fever*; this, that, or the other symptom may attract attention by its prominence, or may be absent—thus the urine may be simply febrile, or, in rare cases, its colour may be such as to suggest *blood* at sight, or it may be black; as to the liver, while congestion is the rule, inflammation is rare, but hepatic complic was frequent in the remittent fevers met with in the Ashanti Expedition of 1873; and while yellow tinging of the skin is almost constant, completely developed jaundice is rare. Such a view of the affection is, I am certain, far better calculated to enable the beginner to appreciate and manage his case, than to make divisions and sub-divisions based on the occurrence of individual symptoms.

[1] *Op. cit.*, p. 66.

Whether described as such, or in terms of inference, two facts stand out prominently in all accounts of this *Blackwater fever*, viz., that the skin is yellow and the urine black, or, in some instances, a colour suggesting blood. In the present time we know that the colour of black urine accompanying yellowness of the skin may be due to the presence of either biliary pigment or hæmoglobin, and if, after determining that in the majority of instances it is due to the latter, we were to assert that the older physicians did not describe the disease, we would be surely doing them an injustice. On similar grounds we may assert that they did not describe *cholera*. I take it that in reading the descriptions of the older writers we should endeavour to find out what the facts were which they designated in terms of inference; and that we should not endeavour to erect new categories of disease because our inferences and theirs from the same facts differ, and, I may add, must differ.

We see, then, that in Professor Maclean's articles there is distinct evidence that he met with this affection, which has been described under a variety of names; further these names denote, in the majority of instances, inferences, and are found to vary in precisely the same manner as do the names applied to *paroxysmal hæmoglobinuria*. This latter affection is characterised by the suddenness of its onset, the occurrence of a "variable and disproportionate icterus," and the passage of porter-like urine, in which, though the red corpuscles are singularly

absent, hæmoglobin is found in solution; and as *paroxysmal hæmaturia*, *hæmatinuria*, and *hæmoglobinuria*, it finds a place in all students' manuals of the practice of medicine. If, as is asserted, it owns a malarial origin, it would indeed be strange if it were not met with on the Gold Coast. Whenever I have seen it here it has been superadded to remittent fever, and in such cases there was more or less hepatic disturbance as indicated by tenderness and enlargement in the right hypochondrium, and by pronounced hypercholia evidenced by the character of the stools and the vomit; which latter is copious and green in colour (biliverdin)[1] when the stomach is not very irritable and permits of accumulation; and scanty, tenacious, and golden yellow in colour when the stomach is very irritable. Further, the urine may be hæmoglobinous for two or even three days: and in three of my cases it was icteric, *i.e.*, it responded to Gmelin's test. In short, this is the view I take of *Blackwater fever*, that it is a malarial remittent fever to which is added another malarial manifestation, viz., hæmoglobinuria, and that when this occurs there is more marked hepatic disturbance than in ordinary remittents. To support this view, the question I propose is:—*When, in the course of a malarial fever, we meet with icterus more or less profound, hæmoglobinuria, and hepatic complication, are we to consider the complex of symptoms as purely malarial, or are we to consider the fever as malarial and the others as phenomena owning a different origin?*

[1] Foster: *A Text Book of Physiology*, 3rd Ed. p. 229.

Icterus and hæmoglobinuria.

"The pressure under which the bile is secreted is very small,[1] but the blood pressure also in the portal vein is very low. In consequence of this a very slight increase in the tension of the bile within the gall ducts, or diminution of the pressure of the blood in the vein causes the bile to be absorbed."[2]

And when this occurs the bile passes into the lymphatics, is carried into the thoracic duct,[3] and, entering the general circulation, is distributed to the tissues, which it stains yellow, such as the skin and conjunctivæ, and its presence in the urine is recognised by its response to Gmelin's test. Such jaundice is termed *hepatogenous* or *absorption* jaundice, because the discoloration is produced by pigmentary material, which, having been elaborated in the *hepatic* cells, is subsequently *absorbed.*

But in certain specific diseases, while icterus is more or less constant, furnishing in malaria the term *bilious*, giving to yellow fever its name, and sufficiently prominent to be enumerated among "the most characteristic features of pyæmia,"[4] jaundice is rare. Is there any explanation for this, at least in so far as malaria is concerned?

[1] The pressure in the bile duct necessary to produce absorption is found to be, in the dog, equivalent to that of a column of bile of 275 mm.—Landois: *A Text Book of Human Physiology* (Stirling), p. 362.

[2] Lauder Brunton: *A Text Book of Pharmacology, Therapeutics and Materia Medica*, 1st Ed., p. 356.

[3] Landois: *Op cit.*, p. 362.

[4] Bristowe: *Reynolds' Syst. of Med.*, vol. i., p. 554.

In a series of experiments, undertaken with a view to determining the relationship between icterus and hæmoglobinuria, Afanassiew[1] finds that solution of the colouring matter of the blood invariably precedes hæmoglobinuria; that without the former condition the latter does not occur; but that hæmoglobinæmia may exist without the colouring matter necessarily appearing in the urine. In other cases, where there was icterus also, the urine responded to Gmelin's test, *i.e.*, there was jaundice. In all cases there were histological changes observed in the kidney, viz., glomerulo nephritis, and coagulative necrosis of the epithelium of the convoluted tubules; the hæmoglobin, he concludes, passes through the glomeruli as a coloured solution of albumin, while the *debris* of the red corpuscles he traces through the tubular epithelium into the urine, where it forms the bulk of the granular, brownish sediment. As to the liver, while in simple hæmoglobinuria it was enlarged and congested, when icterus coexisted there were signs of fatty degeneration and coagulative necrosis of hepatic cells, especially in the centre of the lobules, and more or less of small celled infiltration around the central and sublobular veins, and into the interlobular spaces. In all instances there was evidence of hypercholia; but in the severer cases the bile in the gall bladder and bile ducts was of increased consistence, being in one instance *(Versuch No.* 10*)* a black, slimy, thick fluid, which showed crystals of bilirubin, and brown granules and

[1] *Virchow's Archivs*, vol. 98.

detritus, when examined microscopically; and to this increased consistence he attributes the absorption of bile; and terms the jaundice *hæmo-hepatogenous; i.e*, it is an absorption jaundice determined by pre-existing hæmic changes, in so far that these, by urging the liver to increased formation of biliary constituents, render the bile viscid, a circumstance favouring absorption.

Thus Afanassiew finds the icterus to be hepatogenous; and in the three cases of mine in which the urine was icteric there was persistent vomiting of viscid bile, with hepatic tenderness and enlargement. Here we might fairly assume that this hæmohepatogenous icterus accounted for the phenomena. But there are, undoubtedly, instances in which, though there might be hæmoglobinuria, and profound icterus, there is no jaundice. Leaving aside my own cases, Dr. Easmon[1] records one in which, among other points of interest, we observe that on his first visit he notes—"conjunctiva deeply yellow and so the buccal mucosa and nails and skin generally." Hæmoglobinuria continues in this case for at least thirty-six hours after this note, and it is not till twenty-four hours later that the skin is observed as being "much clearer." In this case if the icterus were hepatogenous the urine should have shown it, for the icterus was evidently profound; but both Wickham Legg and Ringer were unable "to detect bile; on the contrary, the microscope and spectroscope revealed the presence of reduced blood" in speci-

[1] *Op. cit.* Case of S., p. 18.

mens sent to them. We are bound to conclude then that, though the factors necessary to produce hæmo-hepatogenous jaundice may have been present, and more or less in operation, the icterus was not due to this.

But the fact that the icterus of specific disease is not of hepatic origin has been long recognised ; and since Galen's time[1] the idea that under pathological conditions icteric pigment may be formed in the blood has been more or less afloat.

"The close relationship of the colouring matter of the blood to that of the bile, and the facts that the one is derived from the other, and both yield parallel series of almost identical coloured derivatives, make the view which Virchow strongly advocates—namely, that in many of the latter cases jaundice is due, not to the agency of the liver, but to changes in the hæmatin effected in the general circulation—both highly probable and easy of acceptance,"[2]

and to such icterus the term *hæmatogenous* was applied. But however probable this may be, Quincke[3] emphatically denies the actual occurrence of such changes, thus :—

"The formation of icteric pigment in the blood, *i.e.*, in the living blood, with the active participation of the same, has not been authenticated ; and further, in the working up of the physiologically useless red blood cells in the spleen and bone marrow, icteric pigment has not been met with by me or by any other observer. Wherever it is formed, the

[1] Perls : *Lehrbuch der allgemeinen Pathologie*, vol. i., p. 227.
[2] Bristowe : *A Treatise on the Theory and Practice of Medicine*, 3rd Edit., p. 721.
[3] *Virchow's Archivs*, vol. 95.

process takes place outside the blood current, *e.g.*, in extravasations under the influence of the surrounding connective tissue. The blood is not the manufacturer of icteric pigment, it plays but a passive role, supplying in its hæmoglobin the raw material, as it does to the liver in the normal process of bile formation."

And similarly Ziegler[1] says :—

"The formation of pigment in the blood which is actually circulating is not carried beyond the first stage (the breaking up of the red blood corpuscles) within the vessels ; the completion of the process is effected outside the vessels."

So that a hæmatogenous icterus, meaning by that term icteric discoloration produced by the elaboration within the circulation of pigmentary material capable of tinging the skin and tissues, appears to be untenable. It is, however, interesting to find that without attributing the icterus to chemical changes occurring in hæmoglobin, other observers have suggested that, in yellow fever at least, it may be due to solution and effusion of the colouring matter of the blood ; thus MacDonald writes :—[2]

"It is highly probable that the greenish yellow hue is often due to the presence of bile. But, as I believe was first suggested by Warren, and subsequently by Sir G. Blane and others, the lemon yellow and orange tints are unquestionably owing to the solution and effusion of the colouring matter of the blood. M. Guyon regarded it as nothing more than the tinge of contusion."

This tinge of contusion is due to changes occurring

[1] *A Text Book of Pathological Anatomy, and Pathogenesis.* (MacAlister), pt. i., p. 101.
[2] *Loc. cit.*

in effused blood;[1] and to the crystals occurring in old ecchymoses Virchow gave the name *hæmatoidin;* but,

"These crystals appear to be identical in form with those of bilirubin, the chief colouring matter of human bile; and, when treated with fuming nitric acid, give the same colour reaction (Gmelin's reaction)";[2]

And further,

"The majority of physiological chemists are now of opinion that hæmatoidin and bilirubin are identical."[3]

So that practically the tinge of contusion and the hue of jaundice are due to one and the same material, which is termed bilirubin when manufactured by the liver, and hæmatoidin when manufactured at the seat of contusion. But for convenience we might term it *icteric pigment;* and as it is derived from hæmoglobin, in the one instance through the medium of the liver cells, and in the other without such intervention, we may speak of it as being hepatogenous or anhepatogenous; and to the discolorations produced, we extend these terms, provided the method of origin of the pigment be decided in each instance.

In following out the fate of effused blood, Quincke[4] observes that when the red blood corpuscles are

[1] Taylor: *The Principles and Practice of Medical Jurisprudence.* 3rd Ed., vol. I., p. 492.
[2] Gamgee: *A Text Book of the Physiological Chemistry of the Animal Body.* Vol. I., p. 120.
[3] *Ibid.* p. 121.
[4] *Loc. cit.*

taken up entire by the connective tissue cells, instead of icteric pigment, a brownish granular pigment, the iron of which undergoes further changes in the cell, is formed; when, however, changes are set up in this effused blood, so as to set the hæmoglobin free from the blood cells, the connective tissue converts it into icteric pigment, in which case the iron of the hæmoglobin[1] is carried away and excreted, chiefly by the kidney; and after objecting to the term *hæmatogenous icterus*, as involving the theory that icteric pigment is formed in and by the blood, continues :—

"It may even be that, under certain circumstances, icteric pigment may not only be formed in tissues other than the liver, but may be formed so extensively, and under such conditions that general icteric discoloration of the skin results: the formation of this pigment in the connective tissue after extravasations for example, permits us to speak of an *inogenous*[2] icterus as possible; this would be a special form of an-hepatogenous icterus; another special form would be the hæmatogenous—if it were known."

A necessary antecedent, then, for producing this *inogenous* icterus is solution of the hæmoglobin into the blood plasma; which is also a necessary antecedent for the production of hæmoglobinuria. And if it can be shown that in hæmoglobinuria, the connective tissue generally (*i.e.*, as a whole) is bathed in

[1] The formula for hæmoglobin is given as C_{600} H_{960} N_{154} FeS_3 O_{179}, and for both hæmatoidin and bilirubin, *i.e.* for icteric pigment, as C_{32} H_{36} N_4 O_6, Landois: *op cit.*, pp. 24, 35, and 357.

[2] From ἶς plur ἶνες connective tissue.

fluid holding hæmoglobin in solution, the possibility of the icterus being inogenous is brought reasonably with the compass of certainty; and there is both experimental and clinical observation to show that the lymph and tissue serum are hæmoglobinous. Thus Adami,[1] rendering the blood laky by injecting distilled water at 37°C. into the circulation, observes that both lymph and urine are hæmoglobinous.

"Thus then," says he, "when the blood has been rendered laky, the urine becomes richer in hæmoglobin than the blood plasma (as represented by the serum) and this again is much richer than the lymph.

"The great difference possible between the amount of hæmoglobin in the respective fluids is most instructive. We find that the lymph contains always much less hæmoglobin than the blood serum, and that the urine may contain 13·8 times as much as does the lymph, and 3·4 times as much as the serum, or may during the experiment, under the influence of a diuretic, become weaker in hæmoglobin than the serum."

And in one of Dr. Easmon's[2] cases we read:—

"The blister of last night which was taken off at 7 a.m. before it rose, has now risen, *and the serum is bloody*."

Up to this point I might provisionally formulate the result of the inquiry as follows:—Given a case of hæmoglobinuria, we may conclude that there is hæmoglobinæmia, on which will follow inogenous icterus. Further this condition of hæmoglobinæmia urges the liver to increased action, inducing

[1] *Journal of Physiology*, vol. VI.
[2] *Op. cit.*, p. 31.

hypercholia, and if this be carried to excess for any reason, it is possible hæmohepatogenous icterus may arise ; and in this way icterus, hæmoglobinuria and hepatic complication, are connected with one another.

But the question with which we started out was, not whether these were allied phenomena, but whether when they occurred in the course of a malarial fever, the complex of symptoms was explainable on a purely malarial hypothesis ; and if this is to be so, we ought to meet with the only common necessary antecedent to the other phenomena, viz., hæmoglobinæmia, in malaria. For this purpose it will be necessary to enter into the

Ætiology of Malaria.

As a result of his investigations into the ætiology of specific infective diseases, Koch found one fact so prominent that he regarded it as constant, and looked upon it as the most important result of his work :—

"I refer," says he, "to the differences which exist between pathogenic bacteria, and to the constancy of their characters. A distinct bacteric form corresponds, as we have seen, to each disease ; and this form always remains the same, however often the disease is transmitted from one animal to another." [1]

And further on he adds :—

"The greatest stress in investigations on bacteria is justly

[1] *Investigations into the Etiology of Traumatic Infective Diseases* (Syd. Soc. transl.), p. 65.

laid on the so-called pure cultivations in which only one definite form of bacterium is present."[1]

Everything that has been done in this branch of pathology since then tends to confirm these assertions; and these ideas lie at the root of all investigations into the ætiology of specific disease; so that

(*a.*) If a particular organism is invariably present in the blood or tissues of an individual suffering from a well-defined type of disease;

(*b.*) If a pure cultivation of this organism can be obtained; and

(*c.*) If a portion of such pure cultivation, on being injected into the tissues or circulation of a healthy individual liable to the disease, produces the symptoms and other phenomena of the original disease, inclusive of a like distribution of the organism;

(*d.*) The disease is said to be caused by that organism.[2]

As early as A.D. 1717 Lancisi[3] supposed that malaria was a disease due to parasitic animalcules which found their way into the blood; and since then there have not been wanting numerous

[1] *Ibid.* p. 68.

[2] Woodhead and Hare: *Pathological Mycology*, I. § 20.

[3] Except when otherwise stated, the information in this section is derived from Cornil et Babes: *Les Bactéries, et leur rôle dans l'Anatomie et l'Histologie Pathologiques des Maladies Infectieuses*, p. 457 et seq.

observers, who have, from time to time, put forward one form or another of organism as the cause of the disease. These, however, did not attract much attention, till in 1879 Klebs and Tomassi Crudelli found, in the air and soil of the Pontine marshes, an organism, which, on being injected into the circulation of rabbits, produced phenomena which they believed to be not unlike intermittent fever; and to this organism, the former of these observers gave the name *Bacillus malariæ*. But various objections have been raised against the claims of this organism; Laveran does not recognise in the chart an intermittent fever; the quantities injected were so large that any other organism, in similar amount, may have produced the phenomena; and apart from these, there are grave objections impugning the validity of the experiments; thus:—

(1.) The organism was obtained, not from the blood or tissues of an individual suffering from the affection, but from the soil and air of marshes.

(2.) It is not established that the animals experimented on are liable to the disease; or if liable, that the phenomena of the disease as naturally occurring in them correspond to those produced by the inoculation of the bacillus.

(3.) It is doubtful whether the cultivations were absolutely pure.

In the early part of 1882 Laveran found in the blood of patients, during paroxysms of intermittent

fever, an organism entirely different. It consisted of a fine, transparent, oscillating filament about 21 to 28μ in length and 1μ in thickness ;[1] in addition he found crescentic and cystic bodies, which, however, appear to be the remains of corpuscles on the one hand, and pigmented corpuscles on the other.[2] Later on Richard confirmed these observations.[3]

At the International Medical Congress held in Copenhagen, Rosenstein, of Leyden, said that, in cases of malarial fever, he had met with the bacillus of Klebs, as well as with the microbe of Laveran.

"Recently MM. Marchiafava and Celli have succeeded in finding filaments identical with those described by M. Laveran in the blood of patients affected with malarial fever. The Italian observers also state that they have caused quotidian attacks of intermittent fever by an injection of these elements into the veins of human beings. The spleen became enlarged, and the micro-organisms were discovered in the blood of those who had been inoculated. It appears, according to M. Debove, that Gerhardt, of Wurzburg, had recorded similar observations anterior to the above-named observers. In

[1] Diameter of red blood cell about 7·9μ, thickness about 1·8μ. Gamgee, *op. cit.*, p. 71.

[2] In examining the blood of hæmoglobinuria patients, I have obtained the *schatten* of Afanassiew, *i.e.*, decolorised stromata of red corpuscles ; as also the pigmented corpuscles of Marchiafava and Celli. Want of apparatus has interfered with a systematic search being made for the oscillaria.

[3] In the meanwhile Marchand (*Virchow's Archivs*, vol. 88) communicated an observation made by him in 1876, in which he found in the blood during the cold stage an actively oscillating organism, which disappeared during the sweating stage. The organism shown in the wood cut accompanying his paper does not, however, bear any resemblance to that of Laveran (*Fig.* 116, *Les bactéries*).

reply to a question from M. Dujardin-Beaumetz, M. Laveran asserted that the administration of sulphate of quinine was followed by the disappearance of the animated filaments from the blood of the patients; only the pigmented granules persisted. M. Guyot urged that under these circumstances it was strange that quinine should fail to cure some cases of malarial fever. In answer to this criticism, M. Laveran said that sulphate of quinine only acted on the most active pathogenic elements, the mobile filaments."[1]

If we are to adhere to it as a fundamental principle, that one organism, and one only, is the cause of any given disease, it will be well to recollect that

"it cannot be too strongly insisted upon at the outset that the presence of a micro-organism in the body, or in one of the cavities of the body, may not have the slightest significance from an ætiological point of view."[2]

We have here a choice between two organisms, both of which have been found by an independent observer in malarial fever. Against one, grave objections have been raised impugning the validity of the experiments; as to the other, more than one observer claims to have successfully applied the crucial test of inoculating the human subject; while it is insisted that the mere presence of an organism may have no ætiological significance. Under these circumstances we must consider the former to be but an accidental concomitant of the disease, its presence in the blood and tissues being brought about by the fact that it exists in the surroundings of the patient, the air and soil of marshes; and, granting

[1] *Lancet*, 15th August, 1885.
[2] Woodhead and Hare: *op. cit.* § 3.

the purity of the cultivations, though injections of it in large quantities into the circulation of rabbits may give rise to febrile phenomena in those animals, nothing has been proved as to the type of the fever, nor of the part played by the organism in the economy of its human host. We are then restricted to one organism, the microbe of Laveran, and if this be the cause of malaria, we should find it bring about the one common circumstance which is antecedent and necessary to hæmoglobinuria and general inogenous icterus, viz., hæmoglobinæmia.

Remarking on the observations of Laveran and Richard, the *Lancet*[1] says:—

"The organism has a special habitat, the red corpuscles of the blood, in which it develops, and which it leaves when it has arrived at a perfect stage of development. During the attack of fever many globules are seen, which possess a small perfectly round spot, but they have otherwise the normal appearance, and possess normal elasticity. In other corpuscles the evolution of the parasite is farther advanced—the clear spot is enlarged, and is encircled by small black granules, while around it the hæmoglobin, recognisable by its greenish-yellow tint, forms a ring which becomes narrower and narrower as the parasite increases in size. *Ultimately the substance of the corpuscle is reduced to a narrow decolorised zone, from which the hæmoglobin has disappeared.*"

And this disappearance of the hæmoglobin from the corpuscle, and its consequent solution in the plasma, supplies the condition of hæmoglobinæmia, for which we have been seeking. And thus, if at the end of the last section we could have considered the

[1] 12th June, 1882.

phenomena on hæmoglobinuria being granted, we have now gone a step further, and can consider them on malaria being granted.

Continuing its remarks, the *Lancet* adds:—

"Many other phenomena of the disease—the remarkable anæmia,[1] the action of quinine, and the persistence of the infection—are all perfectly explained by these facts."

And among these explainable phenomena, icterus hæmoglobinuria, hepatic and splenic complication seem to claim a place as being produced by the hæmoglobinæmia produced by the parasite.

Having now found the answer to the first question, and being in a position to reply that when in the course of a malarial fever we meet with hepatic complication, hæmoglobinuria and icterus, either alone or in combination, we require nothing beyond a malarial hypothesis to account for the complex of symptoms, another question naturally suggests itself, viz.:—

What is the import of icterus and of hæmoglobinuria in malarial fevers?

It might be urged that icterus and hæmoglobinuria ought to supply us with a measure of the intensity of malarial poisoning.

[1] At the recent Congress of German Physicians and Naturalists, held at Strasburg, Virchow asks, to what we are to attribute tropical anæmia, "diminished blood formation, or increased corpuscular disintegration?" In malarial climates, at least, might not this hæmoglobinæmia induced by the parasite, account for the anæmic condition, the jaundiced hue, and even in a measure for hepatic disease?

Thus, it might be said, in intermittents the amount of hæmoglobin set free is such as can be dealt with by the liver, spleen, and bone-marrow. When, however, the amount set free exceeds this, the connective tissue disposes of the excess producing icterus, and the liver being urged to increased action, there are symptoms of hypercholia in these cases. When the poisoning is still more intense, and a greater amount of hæmoglobin is liberated, the surplus hæmoglobin is excreted by the kidney; and the appearance of jaundice indicates that the highest possible point in intensity of poisoning is reached.

At first sight, there appears to be some amount of probability in this, but on examining the question we find we can make no assertion as to intensity of poisoning from these phenomena; for hæmoglobinuria occurs not only as an apyrexial manifestation of malaria, but Heinemann records an instance in which it accompanied intermittent fever;[1] and I have met with it not only in the severest case of remittent fever I have yet seen (that of T), but also in a remittent so mild that the only cause for anxiety was the patient's panic at being attacked by "Blackwater Fever." But still the occurrence of these phenomena is not without interest, and a return to Afanassiew's experiments will at least lead us a step nearer the end.

Unfortunately, Afanassiew does not define the term *Icterus* as used by him; but his paper is confessedly devoted to considering the pathological

[1] *Loc. cit.*

changes in "the kidney and *liver* in certain intoxications accompanied by hæmoglobinuria and icterus," and when he says —"Wenn es bei einem gelbsuchtigen Thiere sich darum handelte, die Galle in den Harn- und Gallenkanälchen, den Leberzellen, Nierenepithelien und malpighischen Knäueln an Ort und Stellen zu fixiren, so haben wir die methode angewandt, welche," &c., we must conclude that the condition whose relationship with hæmoglobinuria he is investigating is jaundice.[1] But he also uses the term icterus to indicate yellowness of the skin and sclerotic, &c., so that in examining the records of his experiments and his conclusions, this dual application of the term has to be borne in mind.

When, in speaking of his glycerine injections, he says, in mild intoxication, though hæmoglobinæmia existed, the colouring matter of the blood was not excreted by the kidney; but the intoxication being further pushed, while the liver, spleen, and bone-marrow disposed of some part of the hæmoglobin, the remainder appeared in the urine; and offers as a sufficient explanation for the non-occurrence of "*icterus*," that the kidney rapidly excreted the hæmoglobin; I am able to follow him, if by the term icterus he means absorption jaundice, for it is quite conceivable that the stimulant to the liver being rapidly removed from the circulation, that organ, though urged to increased action, does not

[1] To avoid needless repetition and possible misconstruction, I use *icterus* to denote an-hepatogenous icterus and yellow tinging of the skin, and *jaundice* to denote hepatogenous icterus.

manufacture the biliary constituents to such an extent as would bring about a sufficiently high tension to favour absorption. If, however, the term *icterus* be taken to mean yellowness of the skin, which may indicate inogenous icterus, his conclusion that mere rapidity of excretion is sufficient to account for the absence of the symptom appears to me to be untenable; for, under these circumstances, the hæmoglobin would have to be excreted as rapidly as it is liberated, and his own cases do not bear this out.

In his third experiment, nine injections of glycerine are spread over a period of four weeks. On two occasions during this time the urine is hæmoglobinous for two successive days, yet no icterus was observed. Further, during the last three days the animal was alive, the urine was hæmoglobinous, yet the first note in the autopsy is "the dog is not icteric; the subcutaneous cellular tissue is somewhat œdematous"—from which the conclusion is that the first note was made from external appearances, and that the skin and sclerotic were not yellow.

If, now, the occurrence or non-occurrence of icterus were dependent solely upon the rate of excretion of hæmoglobin, in this case, at least, there should have been icterus. In cases of hæmoglobinuria, Adami observes that—"it would seem that into the lymph also small quantities of hæmoglobin passed almost directly."[1] Here, then, the lymph must have been hæmoglobinous for three days, but how rapidly the

[1] *Loc. cit.*

icterus accompanying hæmoglobinuria may develop is seen from Dr. Easmon's case of S, cited above. In one of my cases it developed in seven hours from the initial vigour; and Von Recklinghausen records a case in which death occurred, but without any special symptoms, fourteen hours after an injection of lamb's blood into the circulation of the human subject, and in which the autopsy showed well-developed icterus, due, as he says, undoubtedly to the injection of foreign blood.[1] Under these circumstances, not only are we bound to conclude that the length of time for which dissolved hæmoglobin remains in contact with the tissues (or, to express it otherwise, the rate of excretion) is not *per se* a sufficient factor determining the occurrence of icterus; but we are compelled to go a step further, and say with Von Recklinghausen,[2] that "mere solution of hæmoglobin alone is not sufficient to produce icterus (Blutikterus), there are other conditions (fermentation?) which require to be fulfilled."

Speaking of the icterus accompanying conditions in which there is destruction of the red blood cells and solution of the hæmoglobin into the plasma and lymph, Quincke [3] says:—"Since in hæmoglobinuria and allied conditions icterus is neither constant nor proportional, there must necessarily be other conditions for its production." And in his own account of the production of inogenous icterus, he says that

[1] *Handbuch der Allgemeinen Pathologie des Kreislaufs und der Ernährung*, p. 438.

[2] *Loc. cit.* [3] *Loc. cit.*

when there is corpuscular disintegration, and consequent solution of hæmoglobin, the connective tissue converts the latter into icteric pigment; but that the process is not quite so simple we find from the fact that he speaks of it as a *necrosis*.[1] Are we to understand by this that the corpuscular disintegration is accompanied by a chemical alteration, and that it is some chemical derivative of hæmoglobin that the connective tissue converts into icteric pigment? I believe there are not wanting indications which point in this direction. In five out of the thirteen of Afanassiew's experiments there is no hepatogenous icterus. These are Nos. 1, 2 and 3 (Glycerine injections), No. 4 (Pyrogallic Acid) and No. 13 (transfusion). In four out of these five there is no icterus of any sort, the exception being No. 4, in which, for two days preceding death, the urine contained methæmoglobin, and the autopsy showed icteric tinging of the subcutaneous cellular tissue and sclerotic; but there was no evidence, either during life or after death, of bile pigment in the urine or kidneys. In the other four cases, concurrently with the absence of all traces of icterus, there is absence of methæmoglobin from the urine.[2] At this point I am compelled to stop, for other than Afanassiew's experiments I am not aware of any observations in which the presence or absence of

[1] Thus "Wo das extravasirte Blut zunächst der *Nekrose* verfällt und das Hämoglobin aus den rothen Blutkörpern austritt," &c.

[2] This is not absolutely correct, for in experiment No. 1, on one occasion, methæmoglobin was observed.

icterus is noted, together with the form in which hæmoglobin is excreted. As a rule, it has generally sufficed to say that there is hæmoglobinuria, and it is accepted that methæmoglobin is the form in which the colouring matter is excreted;[1] and that in the fresh state the urine contains methæmoglobin, which, on standing, is converted into hæmoglobin.[2]

Nevertheless, the facts that in more than one-third of Afanassiew's cases in which there was hæmoglobinuria there was no jaundice; and that among these there was icterus in the only instance in which there was prolonged methæmoglobinuria are very significant; and their significance, at least in malarial fever, is heightened by the fact that Von Mering finds that, *cæteris paribus*, the higher the temperature the more rapidly and abundantly is methæmoglobin formed.[3]

If, now, we accept that the conversion of the colouring matter to methæmoglobin is necessary for the production of inogenous icterus, *i.e.*, that one of the changes required to be undergone by hæmoglobin before it can be transformed into icteric pigment is its conversion into methæmoglobin, and that without this there will be no icterus, we may account for the occurrence of icterus as a more or less constant feature of remittent fever somewhat as follows:—

[1] Ralfe: *Clinical Chemistry*, p. 161.

[2] Hoppe Seyler, quoted in Neubauer und Vogel: *Analyse des Harns*, 8th edit., p. 145.

[3] *Das Chlorsaure Kali, seine physiologischen toxischen, und therapeutischen Wirkungen*, p. 84.

The parasite produces solution of the hæmoglobin into the blood plasma, and the febrile state brings about the rapid conversion of the colouring matter into methæmoglobin, which in its turn is converted into icteric pigment by the connective tissue; and the absence of hæmoglobinuria is due to the fact that colouring matter is liberated in quantities too small to appear in the urine. But this, however, will not hold good altogether for icterus, for in paroxysmal hæmoglobinuria there is no elevation of temperature; so here there are conditions other than febrile which bring about the change. What these conditions are, however, we do not know. Of this much, however, we may be certain—that, whatever the changes are which have to be undergone by hæmoglobin before it is finally converted into icteric pigment, the condition of the tissues concerned in bringing about these changes largely determine the result; and that, as hæmoglobin is convertible into icteric pigment by two such widely different tissues as the connective tissue corpuscles and the liver cells, any light thrown upon the steps of the process in the one instance will tend to elucidate the changes as occurring in the other; and further, in this connection it is not uninteresting to observe that urobilin occurs in the urine of fevers generally,[1] and in cases of extensive extravasation of blood.[2]

Turning now to the occurrence of hæmoglobinuria, we find that the usual account given is, that when

[1] Landois, *op. cit.*, p. 542.
[2] Ziegler, *op. cit.*, ii., p. 31.

the amount of free hæmoglobin in the circulation is in excess of the amount which can be dealt with by the liver, spleen, and bone marrow, the surplus is excreted by the kidney ;[1] in short, the part played by the kidney is altogether passive, being that of a safety valve. So long as the kidney structures were divided by physiologists into two groups, viz., the renal epithelium, the actively secreting part, and the glomeruli, the filtering part,[2] any observations made tending to show that hæmoglobin was excreted, not, as Nussbaum believed, by the renal epithelium, but through the glomeruli, without challenging the filtration hypothesis, only tended to emphasise the idea that the part played by the kidney was purely passive. In this manner, Afanassiew's observation that hæmoglobin is excreted through the malphighian bodies, lent countenance to the view that, when the amount of free hæmoglobin in the urine exceeded that which could be dealt with otherwise, the surplus only was excreted by the kidney ; but that, when from any reason (such as altered blood pressure) the filtering process was not sufficiently rapid, the liver was urged to increased action, which in the end resulted in the production of absorption jaundice.

More recently Adami,[3] after examining the whole question in Heidenhain's laboratory, sums up as follows :—

"Notwithstanding that in the ligatured frog the blood pressure in the kidney is reduced to a very low quantity,

[1] Neubauer und Vogel, *op. cit.*, p. 384.
[2] Foster, *op. cit.*, p. 371.
[3] *Loc. cit.*

being simply a venous pressure, we find that hæmoglobin is passed out through the glomeruli. This would prove that, in the batrachian kidney at least, the glomerular activity is dependent not so much upon the blood pressure as upon the renewal of the blood within the capillaries and the rate of flow. And as this passage of hæmoglobin out of the glomeruli is to be noted in cases where there was no apparent accompanying passage of water, it would seem that the glomerular epithelium has *properties of a definite secretory nature*, for the phenomenon does not admit being explained by a filtration hypothesis.

"This opinion is confirmed by the results of various experiments upon the dog.

"When in the dog, by section of the spinal cord in the cervical region, the blood pressure had been lowered below 40 mm. Hg., and the urinary flow brought to a standstill, injection of laky blood was succeeded by the appearance of *hæmoglobin in the capsule chambers of the glomeruli, although there was no visible contemporaneous excretion of water.*

"Hence, here, too, *the glomerular epithelium must be looked upon as possessing powers of a selective secretory nature.*"

Under these circumstances we are bound to conclude that the part played by the kidney is not as simple as is represented—that it does not merely "*allow* the hæmoglobin to pass out after the destruction of the corpuscles and its consequent solution in the plasma"; [1] but that the presence of hæmoglobin in solution beyond a certain amount stimulates the glomular epithelium to activity. Leaving the spleen, bone marrow, and connective tissue out of account, we might say that the presence in excess, and in an available condition—solution—of its normal stimu-

[1] Cornil et Ranvier: *Manuel d'Histologie Pathologique*. 2me Ed., T. ii., p. 563.

lant, hæmoglobin, the liver is urged to increased action. Hence, hepatic complication of some sort with more or less of hypercholia, is present in all malarial fevers, and that when the amount in solution reaches the saturation point necessary to stimulate the glomerular epithelium, hæmoglobinuria occurs, irrespective of the ability of the other tissues to dispose of the colouring matter. But that this cannot be accepted as final we see from the results of Afanassiew's experiments Nos. 4 and 5, in which, all else being equal, in the one instance the urine is simply hæmoglobinous, and the post mortem shows hypercholia, with hepatic congestion and fatty degeneration around the vena centralis; while in the other instance the urine is first icteric and then hæmoglobinous. These facts do not at all conform to what is given as the method by which hæmoglobinuria is brought about. What the explanation is I cannot say, unless it is to be sought in the spleen, which in the former instance is "enlarged and of a blackish brown colour," and in the latter is "*small* and nearly black." Possibly the want of congestion of the spleen in the latter case threw an increased amount of work on the liver, and absorption jaundice occurred before the "saturation point" for the kidney was reached.[1] Again, in the case of H

[1] Afanassiew endeavours to account for the variability of jaundice as being dependent upon the occurrence or non-occurrence of certain alterations in the red blood cells. This may hold good when the toxic agents employed are different. But in Experiments Nos. 4 and 5 the agent was the same, but the result different. And any such explanation is insufficient, for yet it would remain to be explained whence the difference?

(appended), the occurrence of jaundice appears to be attributable to renal disease. Viewed simply as a case of remittent fever, it was a mild one; and, but for renal complication, the result might have been otherwise. The case of T, on the other hand, was really severe, *without jaundice*, and with but slight hepatic disturbance.

We see, then, that these secondary phenomena—viz., icterus, hæmoglobinuria, hepatic and splenic complication, while all more or less due to solution of hæmoglobin in the plasma, are each and all dependent upon a variety of circumstances; and that they are determined to a large extent by the state of the patient's tissues at the time. Under these circumstances, the bald assertion that this or that symptom was observed in any given case does not call up in the mind any one definite idea. Thus jaundice may be due, as in some of Morchead's cases quoted by Maclean, to the impaction of a lumbricus, or it may arise from insufficient action of other organs, as the spleen, the kidney, or perhaps the bone marrow; or, again, it may be due to extensive corpuscular destruction. And the same may be said of hæmoglobinuria. But if these phenomena, when considered by themselves, are so very variable, and capable of so many interpretations that we can predicate nothing definite of them, how much less are we in a position to assert that their occurrence indicates *intensity* of poisoning.

In speaking of diseases produced by micro-organisms, by the term *intensity of poisoning* we

certainly do not mean amount of poison ; that is, the term bears no reference to the number of organisms concerned ; for, as first shown by Professor Greenfield in *Bacillus Anthracis*, and later by Pasteur in *fowl cholera,* by modifying the environment of an organism, such alterations are produced without any corresponding morphological variations, that large quantities of this *attenuated* virus may be introduced into the circulation of animals with the result that they reproduce the disease, but in a much milder form ; though the amount used might be much greater than the amount of unattenuated virus whose injection would lead to fatal results. While, however, *intensity of poisoning* might be looked upon as a term synonymous with *virulence of organism,* we would not be justified in asserting that the *severity of the disease* varies directly as *intensity of poisoning,* for there is yet another factor to be considered, and that is the tissues of the host ; for it is found that, once an animal suffers from a disease the result of the modified or unmodified organism, it is to a large extent protected from subsequent attacks, so that, if attacked at all, the disease will be mild—a fact amply proved in vaccination and small pox.

To a large extent this is true of malaria.

"Malaria," says Maclean, "disappears before agriculture and subsoil drainage, but when the cultivating hand of man is withdrawn and the old conditions re-appear, malaria again resumes its sway."

And that agriculture has the effect of producing

such changes in the environment of the organism to such an extent that the *prevailing type* of malarial fever in a district is governed largely by the extent of agriculture, seems to be amply proved.

"It is a well-known fact," says Rush,[1] "that intermittent and bilious fevers have increased in Pennsylvania in proportion as the country has been cleared of its wood,[2] in many parts of the State. *It is equally certain that these fevers have lessened or disappeared in proportion as the country has been cultivated.*"

And again, Norcom,[3] speaking of the occurrence of *Febris remittens hæmorrhagica* in the Southern States of North America, says :—

"Before the war the Southern States were in a high state of cultivation, and the lands thoroughly drained. Hence the malignant forms of malarial disease, as a general rule, were not known, except in very low, badly drained swamp lands. Within the past eight years (*i.e.*, preceding 1874), owing to so much land lying waste, defective drainage, and the general unsanitary condition of the country, the malarial poison has acted with intense virulence, and caused the disease we are now considering."

In what manner micro-organisms produce disease is by no means settled. Whether the disease is due to their presence, or to some product of theirs, is a question which has still to be solved. But of this much, however, we may be certain—that in febrile

[1] Quoted in Hirsch, *op. cit.*, I., p. 192.

[2] "As a fact, it has been proved that the destruction of woods and forests has not led to an increase of malaria, but frequently to its mitigation, *in consequence of better drainage and improved cultivatiion.*" *Lancet*, 19th June, 1886, p. 1174.

[3] Quoted in Hirsch, *op. cit.*, I., p. 194.

diseases they, or some products of theirs, bring about some change which leads to increased metabolism of tissue, and to these initial changes, whatever may be their nature, we may apply the term *febrile factors*, which will always represent the resultant of the virulence of the organism and of the state of the tissue on which it acts.

The fact that the micro-organism is observed to attain maturity at the time of paroxysm favours the idea that these febrile factors are generated at about that time, and that they continue in operation for some time afterwards, and then become exhausted. Should they become exhausted before the lapse of twenty-four hours, the temperature falls to normal and the fever is spoken of as intermittent. Should it, however, happen that before the febrile factors are entirely exhausted, a second set are generated, the temperature again rises; there is no intermission of fever; at most there is a period of fall indicating exhaustion of the factors, and the fever is spoken of as remittent. This remission no more indicates an impending paroxysm, than does the period of intermission; and the gradual fall of the thermometer is not to be looked upon as the fall in the barometer indicating an approaching storm, but should be considered as the calm after a previous storm.

Looking upon the tissues as a constant factor, responding always in the same manner, the more virulent the micro-organism, the more abundantly are the febrile factors generated, and the longer

will they be in operation before they are exhausted; and, as in places where (as in the Gold Coast) there is no agriculture or subsoil drainage, the virulence of the micro-organism is unabated; the tendency is for fevers to be remittent in these localities.

The fact, however,that,as Maclean points out, newcomers in malarial countries suffer from remittents while the natives suffer from intermittents, prevents our looking upon the tissues of the individual as constant factors; they are modified in much the same manner as they are by small pox, &c., but not absolutely so; for even after one has passed through the "remittent stage," and intermittents are the general rule, one not unfrequently is attacked by a remittent. Further, it is within the experience of all who have had to deal with these fevers in essentially malarious climates, like that of the Gold Coast, that in a community of individuals similarly circumstanced as to length of residence and surroundings; at the time of the "rains" the one individual will suffer from an intermittent, and the other from a severe remittent. As the surroundings (including the poison) were the same, we are bound to conclude that the difference was produced by the state of the patient's tissues at the time of attack; in short, his general health largely determined the result, a fact of the highest importance in the hygiene of malaria. Thus we are bound to extend what Sir J. Fayrer says of remittent fevers to malarial fever as a whole :—

"The type of fever will depend a good deal on the

individual who suffers as well as in the circumstances under which he is attacked."[1]

In short, we cannot from individual cases predicate anything of the *intensity of the malarial poison* in any locality; though under certain restrictions we might do so from the prevailing type of fever.

In a measure, then, the virulence of the organism contributes to determining the type of fever; and it is quite conceivable that a very small amount of the organism may be capable of generating a large amount of febrile factors; while owing to the small number of red blood cells inhabited by the micro-organism, the amount of hæmoglobin set free would be small, and the consequent icterus and hepatic and splenic disorder would be slight; but that the greater the number of micro-organisms invading the body, the more pronounced will these phenomena be. So also it is quite conceivable that owing to prolonged modification in the environment, the organism might entirely lose all capability to generate febrile factors, and that the invasion of the individual by large numbers of such attenuated virus may be followed only by hæmoglobinuria, &c. And again any combination of virulence and amount of organism will be followed by a corresponding combination of the essential and secondary phenomena of malarial fever.

But as the production of the essential phenomena is dependent on two factors, the virulence of the organism, and the tissues of the patient; so the secondary phenomena arise from the action of a

[1] *Op. cit.*, p. 96.

large *amount* of the poison on tissues in some way altered. Thus in the passage quoted from Norcom above, in addition to want of agriculture and subsoil drainage "the general unsanitary condition of the country" brought about the occurrence of *Febris remittens hæmorrhagica;* and it might safely be granted that wherever there is general insanitation there is also deteriorated health. And again, Dr. Easmon, speaking of this same affection, says :—

"It only attacks those whose healths have for some reason or other become deteriorated. It is very often preceded by simple attacks of intermittent fever, with progressive anæmia and sallowness of countenance;"[1]

and my own observations are entirely in accord with this.[2] So that for the occurrence of the most unusual of the secondary phenomena deteriorated health is necessary.

It will be seen from the above that I divide into two categories the phenomena of malarial fever, viz., the essential and secondary. Under the essential I place the purely febrile phenomena, *i.e.*, those met with in fevers generally, viz., elevation of temperature, with gastro-intestinal, circulatory, cerebral, urinary and other disturbance, the distinguishing feature being that the fever is paroxysmal and periodic; so that in cases of remittent (single paroxysm) there will be diurnal variations of temperature, not necessarily at the times in which they occur in continued fevers, but determined by the

[1] *Op. cit.*, p. 2. [2] Cf. Hertz: *loc. cit.*

time of onset of paroxysm. And among the secondary phenomena I place those symptoms traceable to solution of hæmoglobin, viz., icterus and jaundice, hepatic and splenic complication and hæmoglobinuria.

CLASSIFICATION.

In the classification of malarial fevers, the time element is regarded as the basis; thus the duration of the paroxysm is employed to divide them into two large classes, viz., *intermittents and remittents;* in the former case the paroxysm lasts less than twenty-four hours; in the latter over that time, so that before one paroxysm terminates another begins. Further, in sub-dividing intermittents the time element is still preserved, and the varieties are spoken of in terms of days, as quotidian, tertian and quartian, any departure from these being considered irregular. But with remittents this is departed from; indeed it would be inconvenient to sub-divide them on any basis expressing the duration of any one stage in terms of hours; and cases of multiple paroxysm are comparatively rare. Nevertheless, the fact that remittents vary in severity seems to have created a want for terms expressing this variability; and attributing these variations to the occurrence of the secondary phenomena authors have proceeded to divide and define, and to make matters chaotic.

These secondary phenomena are not only very variable, but they may occur equally in a mild as in a severe

case. So that all that is needed is to make two lists of all the possible permutations and combinations of these phenomena, and head them "mild" and "severe" and the classification will be complete; not only so, but it will have this advantage, that while it will include all "forms" already described, there will be few "varieties" which will have to be struck out as "not met with." Palpably such a classification is valueless for clinical purposes; and as valueless have I found any classification which divides remittents into anything beyond *mild and severe*, or *simple and complicated.*

Returning to Heinemann's classification, we find that he tacitly divides his cases into simple and complicated, the complicated cases are the *icteric*, *hepatic*, *bilious*, and *hæmorrhagic.* The simple form then has to be arrived at by a process of exclusion; it must be a remittent fever without icterus, jaundice, hepatic complication including hypercholia, and hæmoglobinuria; this would be simple indeed, and when found should be noted. The term *bilious* he reserves for those cases "in which there is hæmatogenous icterus," the inference is that there are cases in which there is no hæmatogenous icterus; not only would these latter be very exceptional, but if his classification is not to overlap, in his *bilious* cases there must be no participation of the liver in the disease process, which would be rarer still. In the same way it may be shewn that each and all of his classifications would cover only exceptional cases; but that the great body of cases which have

afforded material for classical descriptions must pass for the present nameless.

It is, however, when we come to remittent fevers accompanied by hæmoglobinuria that there is a glut of names. It would seem that some recent authors fail to appreciate the fact that the older writers do precisely what we do, *i.e.*, describe clinical facts chiefly in terms of inference. They find that those terms of inference do not correspond with their own inference, hence the disease is new, and a new name is, of course, necessary. Others, again, recognising the description, object to the old names as misnomers, and give new names, but in terms of inference, and later these again are rejected and others coined. In this fashion the old *bilious remittent* is palmed off again and again under new names, and on the Gold Coast is known as *Blackwater fever*.[1]

There can really be no objection to using some of these names provided they conveyed some tolerably definite idea of the case as a whole, but this they fail to do; for, based chiefly on the occurrence of some one symptom, they convey the idea it is true that that symptom occurs, but they give no idea as to the case as a whole, whether it is severe or not. What is really objectionable is that the occurrence of this or that symptom should be made an excuse

[1] How this name came into existence, I know not. Whether Dr. Easmon, who uses it, found it ready made, and adopted it as being both euphonious and generally understood; or whether he first translated it from the French, I know not. It has, however, this decided advantage, that it implies no theory or inference.

to coin a new name, and that the vocabulary should be ransacked to heap upon this combination every epithet that will convey an idea that the disease is fatal.

It takes a long while before names lose their connotation, and do what we will, if we make the occurrence of any individual symptom the basis of classification, and say of this or that form that it is malignant or fatal, the idea will, nay must, pass current that whenever that symptom occurs the case is malignant or fatal. To take an example, the term *Blackwater fever* may, as a term, cover two varieties of the old "bilious remittent," viz., those in which the urine is hæmoglobinous, and those in which it is icteric; now both these have been described under various names, and no matter by what name they are called, they are described as malignant. I have met with *Blackwater fever*, and I grant it is malignant; yes, very malignant; but the most malignant part of it is the name. A patient has an attack of what may be a mild remittent. At first he takes it, I had almost said as cheerfully as he has taken other attacks; but he passes water and it is black; he has "Blackwater fever" and is panic struck; and the medical attendant has to deal with a far more formidable complication than hæmoglobinuria or jaundice, viz., panic.

"That which we call a rose
By any other name would smell as sweet."

But there is such a thing as giving a dog a bad name.

If there is a want, and no doubt there is a want, of a short name by which to designate those severer forms of remittent fever in which all or almost all the secondary phenomena are present, *i.e.*, in which there is yellowness of the skin, hepatic complication, hypercholia, and blackness of urine (hæmoglobinuria, or jaundice, or both), the old term, *bilious remittent*, should be restricted to cover them; but it should be distinctly understood that the cases, so called, should be *severe*, and the test of severity should not be the mere occurrence of these symptoms; but that, in arriving at a conclusion as to whether the case is severe or not, it should be judged of on its own merits, and *as a whole*.

TREATMENT.

When malaria is mentioned, quinine naturally suggests itself. I say *naturally*, for there is perhaps no fact so well established in therapeutics as the efficacy of quinine in malaria; and this efficacy was said to be due to its "anti-periodic" action. This seems now to be explainable by the fact that quinine arrests the development of, or completely destroys an organism, successive crops of which attain maturity in more or less specific periods of time.

Any line of treatment, then, which lays claim to being rational, must be so directed that there will be in the circulation at the time when it is expected the organism will develop, a sufficiency of quinine to destroy the crop. With this object the drug is

administered a short while before the paroxysm is expected, and it is a mere accident whether the temperature of the patient is normal or not at the time of administration. In intermittents and mild remittents, where there is no particular cause for anxiety, I have usually administered twenty grains of quinine about two hours before the expected paroxysm, giving a second dose (of ten grains) if there has been any tendency of the temperature to rise. But in severe cases, as those of multiple paroxysm, or others in which there is extreme prostration, or previous deterioration of health, where I felt any anxiety at all as to what the result of a return of paroxysm would be, I have not waited; but have from the onset administered quinine in twenty grain doses, repeated every third, fourth, or sixth hour, according to the nature of the case, reducing the doses and lengthening the intervals according to the amount of progress made.[1]

The question has arisen, and I have been frequently asked by laymen[2] and others, whether one should or should not wait for remission. Professor Maclean's practical reply is one that cannot be improved upon :—

"In the adynamic forms of the disease, such as I have

[1] Whether it is a mere coincidence, or whether it is owing to this treatment by heroic doses of quinine, I know not; but certainly I have not met with any case of remittent in which the fever lasted over the fifth day. One lasted eight days, but the treatment began on the fourth.

[2] Laymen usually propose that the administration of quinine during fever is "adding fuel to fire."

described as coming from the malarial quarters of the city of Hyderabad, I never waited for a remission, but gave it (quinine) at once by mouth or rectum, or both, combining with it the assiduous use of support and stimulants at short intervals."

. . . . . .

"What I wrote on the treatment of the complications of ague I repeat here emphatically. Practitioners who relax in their efforts to stop the exacerbation, who pause in the use of quinine while they apply routine remedies for this or that symptom, now applying leeches to the head because delirium or headache is present, to the epigastrium because there is some tenderness there, will have little success in the worst forms of Indian remittents."

But the administration of quinine is not altogether plain sailing—

"It forms with the bile a salt which is sparingly soluble except in excess of bile."[1]

Hence the long-established rule of administering purgatives and emetics before exhibiting quinine; and few drugs have been more in repute than calomel. And in remittents, where there is more or less of hepatic complication, calomel serves other purposes.

"A certain quantity of bile is lost in the fæces, but a considerable portion of it seems to be utilised again and again, being formed by the liver, poured out into the intestine, re-absorbed, and again excreted. This circulation of the bile between the intestine and the liver has been called by Lussana the entro-hepatic circulation. It has been shewn

[1] Lauder Brunton, *op. cit.*, p. 860.

that the bile which is absorbed by the duodenum does not merely act as a stimulus to cause a greater formation, but it is actually re-excreted." [1]

And further—

"Recent experiments have shewn that one of the most marked cholagogues which we know, viz., calomel, appears rather to diminish than to increase the secretion of bile." [2]

Thus calomel not only tends to give the liver rest; but, acting as a cholagogue, it hurries the bile out of the intestine, and removes that which is both a precipitant of quinine and a stimulus to greater bile formation.

In such cases, where the state of the stomach would permit it, I have usually begun the treatment by administering five grains of calomel, with a similar amount of colocynth and hyoscyamus pill, followed if necessary by a draught of sulphate of soda. In my later cases, at least, where there has been persistent vomiting of bile, and where the stomach is very irritable, I have entirely given up administration of quinine *per oram*, and have resorted to enemata, a practice with which I have every reason to be satisfied. The bowel is first washed out with a tepid water enema, and then twenty grains of quinine introduced in solution, the same opportunity being taken to administer aliment if necessary. In such cases the exhibition of quinine *per rectum* certainly gives better results

[1] *Ibid.* p. 354. [2] *Ibid.* p. 350.

than administration *per oram;* the physiological effects are sooner developed, and smaller quantities suffice.

Acting under the belief that what I term the secondary phenomena of malarial fever are as much attributable to the action of the malarial poison as is the fever, I have looked upon the treatment by quinine as being as much directed against them as it is against the fever; hence I have done nothing special for them. Nevertheless, when the adoption of any measure is likely to afford the patient comfort or relief, I have employed it, *provided always that it will not interfere with the administration of quinine.*

From the fact that it is distressing to the patient and his attendants alike, and that it interferes largely with the administration of food and medicine, the persistent *bilious vomiting* is a prominent clinical feature in almost all severe remittents. It keeps pace with the fever, it increases with each paroxysm, and subsides more or less towards remission The administration of carminatives and hydrocyanic acid I have found not only valueless, but distressing to the patient. Sinapisms to the epigastrium and right hypochondrium, followed by warm fomentations, seem to soothe the patient and afford relief. Sometimes, when the patient is exhausted from the vomiting, and the retching still continues, weak whisky and water, or gin and water restore him and allay the retching. But, above all, what the patient most appreciates, and what seems

to do him most good, is "a little ice to suck;" but, unfortunately, ice is not always obtainable in the Gold Coast.

In some there is a tendency to *delirium*. To darken the room, avoid all noises, and it may be to apply a sinipism or blister to the nape of the neck, while an evaporating lotion is applied to the forehead, are the measures I have found sufficient.[1]

In some cases the exhaustion is extreme, and the patient restless and *sleepless;* "sleep would be a boon." In these cases I have found chloral especially valuable; it gives the patient six to eight hours of sleep, after which he awakes, "feeling quite another man."

None but those who have themselves had an attack of remittent can know the unspeakable relief which a free outburst of perspiration brings with it, and wherever practicable I have administered diaphoretics. *Warburg's tincture*, when it can be retained by the stomach, is all that can be desired.[2] Of course, when practicable, recourse should be had to "long drinks," which may be palatable; weak tea, warm lime juice, "soda with a dash of hock in it," oatmeal and water, toast water, and other

[1] To one of the officials who helped to nurse T. I am indebted for the following: Cut a lime in halves, rub the cut surface over the face and forehead, then gently fan the patient. Those with whom this has been tried are loud in its praises as being "quite soothing," and conducive to sleep.

[2] Dr. Ross, of Sierra Leone, speaks very highly of *Antipyrin* in this connection, and has shewn me some very instructive charts. I have, however, not had any practical experience of this drug.

drinks suit the fancies of different patients, and these fancies I have indulged.

A complication likely to become serious in cases of "Blackwater fever," particularly in those instances in which the urine, in addition to being hæmoglobinous, is likewise icteric, or where there is a copious deposit of granular sediment, is *suppression of urine*. It should be watched for in all cases. Sinapisms and dry cupping to the loins, with fomentations, serve the purpose in some cases. In others diuretics are necessary. When practicable I have given a mixture of Acetate of Potash with squill; in others again, where the irritability of the stomach will not permit the administration of drugs, a little gin and water, to which is added some Acetate of Potash, is retained much better.

The question of *stimulants* must be decided at the bedside of each individual patient, the decision being arrived at, not only from the nature of the case, but from the previous habits of the patient. I have myself had no occasion to employ alcoholic drinks as *stimulants*. As I said above I have sometimes used gin as a diuretic, or whisky and water to relieve retching, or hock and champagne for thirst; but these have been given in moderate amount just sufficient to meet the requirement. As a restorative to muscle I have largely used Liebig's Extractum Carnis, employing it as an adjunct to food. Cases will, however, arise in which the patient is one who had previously accustomed himself to the use of stimulants; and in such I believe it would

not be right to withhold the accustomed stimulant entirely.

Without at all wishing to enter into the complicated questions of *dietary* and assimilation in fever, I may say that the want of fresh milk is very much felt here. We are reduced to depending upon mutton or fowl soup. These are not foods, and in severe cases which last over the first day the question of food will arise. Benger's peptonized beef jelly I have found invaluable, for patients tolerate it where the stomach rejects almost everything else. On peptonised foods prepared with Benger's Liquor Pancreaticus, and administered either *per oram* or *per rectum*, I have largely relied. In mild cases, or during convalescence, whenever the stomach would tolerate them, egg flips are valuable, and these, if properly prepared and flavoured, are seldom unacceptable to patients.

The remainder of the treatment is largely one of nursing. Whatever skilled nursing can do ought to be done. In this connection I may mention one point. Usually, when a patient has an attack of fever he takes to bed, and immediately has the windows and doors closed. In a short while the air of the room becomes foul with respiratory impurity, and is charged with the odour of the vomit and evacuations, and the patient is supremely uncomfortable. It is difficult to persuade either the patient or his attendants that this is not as it should be—that what is really required is not to warm the air in the room, but to warm a layer of air around the

body, a blanket or two being sufficient. It goes without saying that, in the sick chamber there should be ample ventilation, and that all evacuations should be immediately removed. By throwing open the doors and windows a free current of air is established. It is only when the currents are fitful and partial that they are objectionable ; but on the Gold Coast the current is always rapid enough to be a breeze, and to this few patients object, provided they are well wrapped up.

INVALIDING.

For what is said on this subject in malaria I would refer the reader to Maclean's and Sir Joseph Fayrer's writings, and shall restrict my remarks to invaliding after an attack of bilious remittent in the restricted application of this term, *i.e.*, in "Blackwater fever." When we recollect that it is not the malarial poison alone, but likewise the state of the patient's tissues, which decides to a large extent the type of fever ; and that hæmoglobinuria, as a complication of malaria, almost invariably occurs only in those whose previous health has in some way deteriorated, there is ample justification in recommending a change. But when in addition to this we consider the state of the kidney, an early change to a better climate, so as to avoid the repeated congestions arising in all malarial fever, is imperative. So long as it was believed that the kidney merely *allowed* the hæmoglobin to pass through, one might have been sceptical

as to the occurrence of any real structural change in the organ; but it is otherwise—there is ample ground to believe that the process in hæmoglobinuria is not merely passive; and further the direct observations made in experimental hæmoglobinuria show that there are extensive and grave structural lesion.[1] Under these circumstances it is anything but desirable that a patient should be permitted to remain in a climate and in surroundings when he is likely to suffer from malarial fevers; in which repeated congestions only tend to intensify the mischief already set up.

With Government officials there is no difficulty. Should the medical officer deem a change necessary, and that the detention of the patient in the colony till Head-quarters can be communicated with is not likely to be in any way prejudicial to the patient, he is detained till the Governor's permission is obtained. Should it be otherwise, the necessary certificate is granted by the medical officer to the commissioner of the district, who engages a passage by the first vessel. In either case the result is the same. Thus the individual who virtually decides whether the patient is to be invalided or not is the medical officer, and *with him lies the entire responsibility.*

In the case of non-officials, however, this is not so; private considerations step in. All we can do is to advise, leaving the responsibility to the patient.

[1] I regret I have been unable to make any examination of the kidney in these cases. In both my fatal cases a *post mortem* examination was impracticable.

APPENDIX.

THE notes as given below do not indicate the general condition—they are jottings showing the occurrence of the phenomena as treated on above. The day is the *fever day*, *i.e.*, it is calculated from the ascertained hour of onset of symptoms. The case of T. is interesting as being one of multiple paroxysm attended with hæmoglobinuria, icterus, and but slight hepatic disorder; that of H. teaches a lesson as to the influence of renal disease in malarial climates, and is an instance of the manner in which rectal feeding may be continued for days.

1.—T.

Remittent Fever, Hæmoglobinuria. Recovery.

PREVIOUS HISTORY.—Has suffered frequently from malarial fever. After travelling fifty-five days *in the bush*, chiefly on foot, put in to Elmina to refit. From fourth to ninth day after arrival suffered from irregular quotidian ague; from eleventh to sixteenth from periodic supra-orbital neuralgia, which was simply deferred on treatment by daily doses of ten grains of quinine; on sixteenth day took to bed suddenly with fever, four hours after the time at which the neuralgia was expected.

FIRST DAY.—*Fever* remittent—105° to 102°—three paroxysms; cold stages distinctly marked; duration of each paroxysm, from onset of cold stage to first ascertained fall of temperature, five hours, two-and-a-half hours, and three-quarters of an hour respectively; interval between onset of

first and onset of second paroxysm nine hours; between second and third, four hours. *Urine* passed twice, viz., at 8th and 14th hours; first, *cafe noir;* second, "like defibrinated blood;" hæmoglobinous, non icteric. *Icterus* first observed 16th hour. *Bowels* moved, highly bilious; no *vomiting*.

Second Day.—*Fever* remittent—104° to 101°—slight rise of temperature corresponding to first paroxysm; two hours before time of second had a well-marked paroxysm; cold stage, ten minutes; hot stage two hours (really a deferred first); no third. *Urine* first half of day, thirty ounces, transparent, "bloody," hæmoglobinous, non-icteric; none during second half; *Icterus* marked; *Bowels* freely moved, bilious; *Vomiting* slight, bilious (green); *Liver*, slight tenderness, no appreciable enlargement.

Third Day.—*Fever* remittent—102° to 99·4°—slight rise for half an hour corresponding to first paroxysm, asleep during time of second and third (chloral). *Urine*, first half, one pint as yesterday; second half, not measured, reddish yellow, markedly albuminous (? hæmoglobin). *Icterus* profound in early part of day; but after six hours' sleep much diminished. *Vomiting* copious, green.

The turning point in this case was after the six hours' sleep from which the patient awoke, "feeling stronger;" and he steadily and rapidly rallied.

Fourth Day.—*Fever* still; slight rise at first paroxysm (100°); *icterus* diminishing, patient able to sit up; no vomitting; bowels moved.

Put on board ship for England at fifth hour.

Treatment.—A diaphoretic was first prescribed but not persisted in. Sinapisms and fomentations to epigastrium and loins. *Quinine*—first day, 120 grains; second day, 100 grains; third day, 80 grains; fourth day, took 20 grains before embarking; all in scruple doses, *per oram;* on some occasions the pills were rejected by the stomach.

On the voyage the patient rapidly convalesced, and six months after, on meeting him in London, he appeared none the worse for his acquaintance with African fever.

Remarks.—In this case there were three malarial manifestations, *first* irregular quotidian fever, followed after an interval by *second* neuralgia, which was in its turn followed after an interval of a day by *third* remittent fever, which latter is certainly the severest I have seen. Quinine was lavishly given, but how much was absorbed and how much passed through the intestine as an insoluble bile salt? No physiological effects of the drugs were observed; and even these large and repeated doses failed to bring the fever under, for, on the second day, there was at least one paroxysm; and on the third and fourth, though there was no paroxysm there was a temporary rise of temperature on each occasion corresponding to the time of onset of the first paroxysm of the first day.

H.

Remittent Fever: Hæmoglobinuria; Jaundice; Renal Complication; Death during Convalescence.

Previous History.—Has suffered frequently from malarial fever, which were latterly regular quotidian; ten months previous to present attack passed black urine during an attack of remittent fever; since then has been anæmic, and more or less out of health. After feeling out of sorts for the greater part of the day took to bed at 11 p.m., "with a smart attack of ague." Next morning finding his urine black, sent for me.

First Day.—*Fever* remittent—? to 102·2°—single paroxysm, *Icterus* marked. *Liver* tender, enlarged. *Vomit*, scanty, tenacious, yellow, intensely bitter; stomach very irritable. *Bowels* moved twice, highly bilious. *Urine*, eight ounces in early part of day; three ounces for the remainder; hæmoglobinous, icteric (?), copious granular sediment, abundant hyaline tube casts.

Second Day.—*Fever* remittent—103° to 100°—*Icterus* profound. *Vomit* as yesterday. *Urine*, after twenty-eight hours, suppression passed two ounces, total for the day five ounces; hæmoglobinous, icteric,[1] casts and sediment as yesterday.

Third Day.—*Fever* still; temperature fell to normal at tenth hour. *Icterus* diminished. *Vomit* as yesterday, but on two occasions copious and green. *Urine*, ten ounces for the day; no change.

Fourth Day.—*Fever*, slight rise at time of paroxysm, otherwise normal. *Icterus* slight. *Vomit* not so frequent, more copious and green. *Urine*, about a pint, reddish tinge, albuminous (? hæmoglobin); re-acts faintly to Gmelin's test; sediment white, hyaline tube casts still abundant.

Fifth and Sixth Days.—*No fever*. *Icterus* barely noticeable. *Urine* on fifth day highly coloured, albuminous, non-icteric, abundant tube casts; on sixth day on one occasion distinctly hæmaturic. *Vomiting* continues, but not nearly so frequent—is more copious and green.

Seventh Day.—No fever, hæmoglobinuria or icterus; stomach still weak and irritable. *Urine* scanty, markedly albuminous, and shows abundant casts.

Put on board ship for Europe (14th hour), but died a few hours afterwards.

Treatment.—Sinapisms and fomentations to loins and right hypochondrium. Gin, quinine and aliment for first five days entirely *per rectum;* for first two days *quinine*, sixty grains per diem in scruple doses; third day, forty grains; fourth and fifth days twenty grains, then discontinued.

Remarks.—In this case the renal mischief which had apparently been set up ten months previously, and been

[1] A translation from Afanassiew — *Versuch*, *No.* 10, 10*th March*—would accurately describe the urine and give the method for detecting the presence of bile pigment:—"The dark red urine is simultaneously hæmoglobinous and icteric. The albumin and hæmoglobin were precipated by heat, and the addition of dilute acetic acid; and the filtrate tested for bile pigment."

aggravated by repeated congestions accompanying intermittent fever, was a serious bar to recovery. The fever, it will be observed, was soon brought under way by the free administration of quinine, after which the icterus and hæmoglobinuria disappeared; but *uræmic* symptoms set in on the sixth day, or it may have been earlier but masked by the fever.

A short while after this case, one occurred in the practice of a friend, in which, after two days of mild remittent, the patient died; the autopsy showed a somewhat advanced contracted granular kidney, and marked cardiac hypertrophy. Here also, no doubt, the state of the kidney contributed to bringing about a fatal result.

THE END.

The following post mortem observations are of interest in connection with Afanassiew's experimental results :—

"In *fièvre bilieuse hématurique*, besides most marked hyperæmia, the autopsy shews *enlargement and softening of the spleen and liver; the latter may even be icteric and at times fatty;* the skin which is dusky is marked by petechiæ, ecchymozes, and pustules filled with blood; the brain and membranes are congested and icteric; the gall bladder is filled with dark viscid bile; the mucus membrane of the stomach and intestines is soft and congested; heart soft and flabby; kidneys markedly hyperæmic; bladder mostly empty, its lining membrane is nyecled and ecchymosed; the urine is bloody and albuminous, *as to the occurence of biliary pigment, there is as yet some doubt for while some observers have met with it, others, as Veillard, have not.*"
(Hertz op : cit. p.54.)