BLACKWATER FEVER.

AN ESSAY.

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By:

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BLACKWATER FEVER.

Definition. A fever characterised by Nausea, vomiting, Pyrexia, more or less pronounced, jaundice, and the passage of dark porter coloured urine containing albumen, from which the disease has obtained its name.

Synonyms. (1) Haemoglobinuric Fever. This term is actually the most scientific and descriptive of the actual disease. (2) Malarial Haematuria (3) Bilious Haematuric Fever. There are many others used in the nomenclature of the language of the describer e.g. Fievre Ictro hemorragique of the French, Schwarzwaser Fieber of the Germans. Dr. John Gordon Thomson has given a number of these in his excellent account of Researches in Blackwater Fever in Southern Rhodesia. (Chap 3). To my mind however, the term Haemoglobinuric Fever is the most accurate and also the most scientific one that can be used in speaking of the disease, and most clearly descriptive of the condition.

Occurrence. Blackwater Fever was formerly associated with Tropical Africa. This I think has been brought about mainly because the majority of cases then seen and reported came either from the East or West Coasts of Africa, and the high mortality associated with it caused the disease to assume a significance which it has not yet lost.

We know however, from the account of the disease given by Castellani and Chalmers in their excellent work that the publications of many observers have clearly shown its occurrence in many parts of the world. It occurs in certain parts of India, in certain parts of Southern Europe, and South Russia. It assumed a most fatal form in Salonika during the War. It occurs in East, West, and Central Africa, and in Southern and Northern Rhodesia; it occurs in the tropical Malarious areas of South America and in the Southern States of North America also. Many cases are seen in Great Britain among those who have been resident in tropical countries, and who have come to reside in Great Britain for any length of time. Thus it is seen that it is a world-wide disease but one which does not, however, occur per se in areas which are non-malarious.

Immunity. All races are liable to it, but it is rare in the Negro races who are indigenous to the country they live in, and who can be termed immunes for the purposes of classification.
Causation. In writing of the cause of Blackwater Fever, and coming to a conclusion as to the true nature of the disease, several factors have to be borne in mind and studied in their various aspects. What then is the cause of Blackwater Fever? What factors attribute to its occurrence and why?

I know of no important disease to ascribe a definite cause to which is more difficult.

Castellani and Chalmers in their work on tropical disease specify distinctly:

(1) Malarial Haemoglobinuria
(2) Quinine Haemoglobinuria
(3) Specific Blackwater Fever.

With great diffidence I submit that this classification, speaking from the point of Blackwater Fever only, is erroneous and apt to mislead. I cannot accept the term Specific Blackwater Fever as distinct from Haemoglobinuric. About the term Quinine Haemoglobinuria I shall have more to say, and the relations of quinine to Haemoglobinuria will have to be fully considered.

If by the term Specific they mean a febrile condition attributable to a specific cause, a symptom of which is the passage of dark porter urine, we know that there are many agents which will cause it and which have a haemolytic action e.g. Pyrogallic Acid. Dr. Gordon Thomson remarks in Ch. 6 of his valuable work that Haemolysis is the laking of red cells and as a Corpuscle is an envelope containing Haemoglobin the bursting of this sets free the contents. He gives an account of the various agents which are known to produce Haemolysis e.g. The Saponins, Bile Salts, fatty acids, glycerine, ammonium chloride, etc.,

There are also certain febrile conditions in which Haemoglobinuria has been described as occurring e.g. Typhoid Fever, Typhus, Scarlet Fever, Pneumonia, Acute Rheumatism, etc., and it appears it may follow a transfusion of blood.

It may also occur in Sunstroke, Exposure to X Rays, Influenza, Scurvy, Syphilis, Yellow Fever, Leucocythaemia and Pernicious Anaemia.

I regard it of importance in putting forward any theory as regard to the cause of Haemoglobinuric Fever, the fact that Haemoglobinuria occurs in Scurvy,
Yellow Fever, Leucocythaemia and Pernicious Anaemia, especially in the latter two diseases I have enumerated. I think it will be conceded that in such diseases as Leucocythaemia and Pernicious Anaemia there is a want of the normal proportion between the various constituents of the blood, and further that the presence of the want of this proportion gives rise to the Haemolysis with its resulting Anaemia, and further that treatment on the correct lines tends to restore the balance with a resulting amelioration of the symptoms.

Further Dr. Gordon Thomson makes some references which I regard of supreme importance. He says in page 50 that we have in Paroxysmal Haemoglobinuria a condition which seems to be closely related to Haemoglobinuric Fever. In that there is a production of Haemoglobinuria accompanied by Haemoglobinuria, and remarks that this condition is associated with a previous attack of Syphilis, and that the most competent observers agree on this. Further, he quotes Yankani as stating that about 25 to 30% of Syphilitic patients both tertiary and congenital have the cold haemolysin in their blood and that no difference can be seen in this condition namely Haemoglobinuric Fever, from that of Paroxysmal Haemoglobinuria of which the primary causal factor is Spirochaeta Pallidum. Here then is a condition of Haemoglobinuria produced by a definite causal agent namely the Spirochaeta Pallidum, and it is therefore quite conceivable that the causation of Tropical Haemoglobinuria could be a parasite such as that of Malaria, and further that the failure of the parasite of the one, namely this Spirochaeta Pallidum always to produce the condition rather tends to emphasise the fact that there should be a causal parasitic agent in the other, namely, in Tropical Haemoglobinuria, possibly the Malarial Parasite since Haemoglobinuria does not occur in every case infected with Malaria.

Dr. Gordon Thomson also says that though the autolysin is easily demonstrable in Paroxysmal Haemoglobinuria, attempts to demonstrate it in cases of Blackwater Fever have failed, and further that though they failed and indeed in no case using Malarial Blood, Malarial cultures and Blackwater Fever blood was any definite Haemolysis caused, yet the resemblance was very striking between the action of specific Haemolytic Serum and Blackwater Fever.

He further remarks that though such observers as Celli, Cassagrani, and Cardamatis in 1802 failed to demonstrate the presence of a Haemolysis in
experiments with dogs, and later in 1906 also failed to detect a Haemolytic substance in Malarial Serum when treated with normal corpuscles, this offered no proof that the Haemolytic substance did not exist. Again in 1912 Archard and Girous found no Haemolytic power in the Serum and Plasma of Blackwater Fever either for the patients' corpuscles or those of normal individuals.

I regard Dr. Thomson's remarks in Ch. 6 of his researches so important that I make no apology for quoting them in full.

He quotes Gaspirini (1915) who said he was able to demonstrate constantly an autolysin in the red cells but not in the Serum in Blackwater Fever cases and that the Donath-Landsternier test only gave a positive result when the Serum was mixed with 0.02% of Hydrochloride of Quinine.

Dr. Thomson says that this experiment was complicated by using quinine solution. Again he quotes Bijou (1915) who states that there is a diminished resistance in the red blood cells and that there is in the blood an autolysin and this lysin comes into action owing to the failure of the body to produce the necessary Antilysin. Again he quotes Fletcher (1915) and Porak (1918) who failed to obtain positive results in trying to demonstrate the Autolysin. Dudgeon also in 1921 also failed in testing the Serum and red cells of Blackwater Fever cases for Haemolysin and Agglutinin. Now Ameuille Sourdel and Marcouelle (1918) in examining the resistance of washed red cells against immunised rabbits Serum found that it took 8 times less Haemolysin in Haemoglobinuric Fever to lave these cells than an equal quantity of cells from the blood of an normal person and further five times more haemolysin was required to haemolyse a patients red cells in the presence of his own inactivated Serum. It was therefore concluded that an antilysin was present in the patients' own Serum, I regard this as most important because I believe that the Antilysin which should be present in the Serum, becomes temporarily in abeyance.

Dr. Gordon Thomson, however, correctly points out the inconclusive nature of these experiments and quotes Browning (1915) as drawing attention to the fact that failure to produce a Haemolytic effect in vitro does not afford any evidence that a Haemolytic mechanism is absent in vivo.

Again after quoting experiments by Muir and McNe in 1911 and 1912 and by Dudgeon in 1921, who, in investigating the effect of Haemolytic Sera on animals showed that the pathological effects were the same
as those produced in Blackwater, one can I think legitimately come to this same conclusion, with a reservation, as Dr. Gordon Thomson does, that "There is a marked similarity between the action of a true Serum Haemolysin and an attack of Haemoglobulinuric Fever and that there can be little doubt that the mechanism is the same, and, if we can produce the same condition by continual attacks of Malaria, to the exclusion of all other parasites, the problem is solved."

I must express myself as wholly in agreement with the able remarks of Dr. Thomson, but I must point out that in the preceding page I remarked, that in coming to the same conclusion as Dr. Thomson that there was a reservation and there is, and I hope to produce evidence that there is a reservation. Dr. Thomson further comes to the conclusion that it is not altered osmotic tension which causes Haemolysis. The experiments of Christopher and also Bentley and Stevens tends to prove this and though it is conceivable that it might be due to this cause, experimental evidence is against it, and it can be for the present dismissed, but I am rather of the opinion that clinical evidence rather tends to show that it is.

Is it a Haemolysin elaborated from the tissues? He quotes Browning as saying that the conception of the formation of a Haemolysin from the tissues as a secondary consequence of damage by an infected agent or its toxins appears to be worthy of more extensive investigation and again saying that it is possible that a fatty liver acts as a source of the Haemolysin, and again, that Dudgeon made alcoholic and acetone extracts from the organs of Blackwater Fever patients and found Haemolytic substances in the kidney and spleen which were not present in the same degree in cases of Malaria. However, I gather from his remarks that he does not think that the Haemolytic agent is elaborated from the tissues and I am in agreement with him. Again he discusses the important aspect of an Haemolytic action of the Urine and says, if the Haemolytic power of the Urine is sufficiently strong at any time a Haemorrhage into the Urinary passages would produce Haemoglobin in the Urine, which it does not. My own opinion is that the Haemolytic action of the Urine requires most careful study, as we know that Urea is one of the most Toxic substances known, and the experiments of Dudgeon (1920) in particular, who showed that he was able to abstract a Haemolytic substance from the Urine in Blackwater Fever although the sterilized Urine injected into Rabbits has no effect on them, and again it seems to be certain that Haemolysis does not take place within the Urinary tract as no Haemoglobinaemia occurs but it is possible that there may be a Haemolytic substance in the Urine resulting

(5)
from the cachetic anaemic condition of the patient who
developes Blackwater Fever, or released by this specific
action of a Toxic agent in the blood. In this connection
Flehn draws attention to the low specific gravity of the
Urine in Blackwater Fever. He has noted this specific
gravity to be as low as 1,005 to 1,001. I have not found
this to be so. Again that Deaderick, and Barrat and
Yorke, have found in two cases of suppression the
specific gravity to be very low. My own observations
show that though this specific gravity varies, it has
not been as low as 1,001 in my cases it has been always
about 1,010 to 1,015.

Mierenstein (1913) claims to have isolated a
substance from the Urine in cases of Malaria and Black-
water Fever he called Haemoquinic Acid. It was de-
tected in 12 out of 13 cases of Blackwater Fever in
larger quantities than in ordinary Malarial attacks.
This substance had pronounced Haemolytic properties.
If this is so it must be of the first importance, but
I am unable to find any confirmation of his experiments
in the literature. Finally during his experimental
work in Southern Rhodesia Dr. Gordon Thomson states
that while unable to demonstrate Autolysins in Black-
water Fever he was able to confirm the work of
previous observers. He states positively that there
is no detectable Autolyasin comparable to that which
occurs in paroxysmal Haemoglobinuria but that success-
ful cultures were obtained of the asexual cycle of
the plasmodium falciparum, and on five occasions in
which no development took place he detected Haemolysis,
and again if blood was drawn at a period corresponding
to schizogony in the body Haemolysis invariably occurs.

Simpson (1912) had previously found evidence of
Haemolysis in Malaria in a period of schizogony. But
Dr. Gordon Thomson goes on to say that the numbers he
tested were too few to state positively as to the
results. Again he says (page 56) that we were unable
to detect any Haemolysis in the Serum of Blackwater
Fever cases at any period of the disease, but as we
have previously pointed out this by no means proves
that it does not exist. Careful reasoning must bring
one to the conclusion that it does exist.

Other Specific Causes. Such an authority as
Balfour (1913) has suggested that the Haemolysis
might be due to the injection of a highly viru-
ulent Haemolytic agent by some insect. It is well
worth consideration although I do not think this
to be the case. In a report compiled for the Colonial
Office in 1913 on the occurrence of Blackwater Fever
in Tropical African dependencies one Medical man said
Dr. Howard Cook of the Church Missionary Society Hospital
Kampala, suggests that a pre-disposing cause of Black
Blackwater Fever may be a spirochaete, though he does not put it forward as a common pre-disposing cause. His series of 5 cases reported are very suggestive, and indeed one case had a relapse of the Haemoglobinuria concurrently with his relapse of relapsing Fever. However, quite as recently as 1922 there was an epidemic of relapsing Fever among some natives in Accra on the Gold Coast but no occurrence of Haemoglobinuria as far as I know. Again the possibility of a Causal Agent resulting from the bites of insects and particularly by the bed bug has been advanced by Graham. I must confess that I cannot agree with him and can state that at the time of the advancement of this theory all cases of Blackwater Fever were investigated with a view to its support, but in no case as far as I know was any history of a patient being bitten by bugs or fleas ever obtained. No possible cause however is to be discounted in the absence of any specific cause being found but if these theories advanced by Graham and Balfour were possible, is it not within reason to say that there would be many more cases of Blackwater than there are?

Other Causes. Such as light Hintz (1916) has been stated to have a Haemolytic action which is increased by sensitizing substances particularly quininesalts and bile pigments and Hewetson (1922) in Southern Rhodesia thought of this theory and suggested that Blackwater Fever tended to occur in those houses where there was imperfect protection from the sun and condemned the corrugated iron roof. There is no question that the corrugated iron roof does not afford the same adequate protection from the sun as does a grass thatch but, it must be admitted that Blackwater Fever in former days occurred in West Africa in houses which had grass roofs. Again, certain foods and particularly alcohol throw an unnecessary strain on the liver. It is certain that residents in tropical countries do partake of highly seasoned and hot dishes such as curry, largely, and have done so from time immemorial, and also indulged in alcohol to a far greater extent than is the case with residents in non-tropical countries, but if India can be reasonably cited as a country in which hot dishes particularly are eaten Blackwater Fever should be much more common there than it is.

Connection between Malaria and Blackwater Fever. I regard the connection between Malaria and Blackwater Fever as so intimate as to be certain that the former combined with another factor must be looked upon as being the agent, if not the chief agent, of its causation in tropical countries. Dr. Gordon Thomson says that the whole evidence of his researches incriminates repeated infection with the plasmodium falciparum and I must confess that I am in entire agreement with him, with, as I shall endeavour to show, another factor which has not
been taken into account or at least its effect not sufficiently laid stress on as a causal agent. I allude to quinine.

I am now approaching a highly debatable subject and I am not attempting to be dogmatic but simply to advance a theory which can be supported only on clinical grounds. In ch. 4 of his researches Dr. Gordon Thomson discusses the co-relation between Malaria and Blackwater Fever and I regard it as proved beyond question that as far as Haemoglobinuric Fever in the Tropics, is concerned, this relationship is absolute. Clinical experience shows how many cases of illness undoubtedly Malarial in origin recover their health entirely under the proper administration of Quinine without a single parasite being found in the patient’s blood even under repeated examination. Practically every case of Fever, failing any absolute contraindication, is treated with Quinine and be it remarked recovers its health in a few days. Again analyses of the reports of cases of Blackwater Fever from the Colonial Office I find that in only about 2/3 of cases where parasites have been actually found. But Dr. Gordon Thomson’s researches proved conclusively that the evidence of Malaria and particularly the malignant type of Malaria caused by the Plasmodium Falciparum was found after post mortem examination in all the cases of Blackwater Fever he examined. I think there is no need, and that it is a waste of time to elaborate the argument of Dr. Thomson on this point, and that it is not possible to adduce any argument which will, in any way, disprove his conclusions.

Now what can be the agent which produces what seems to be, clinically speaking, a Haemolytic explosion or in the words of the late Sir Patrick Manson "What pulls the trigger," I believe it to be Quinine and by Quinine I mean an over-dose of quinine taken at the wrong moment.

In the first place I do not believe that any patients develop Blackwater Fever until they have suffered from repeated attacks of "Fever" almost certainly malignant Malaria, in fact have become thoroughly infected with the Plasmodium Falciparum. In the cases of Blackwater Fever that have come under my observation, how many time has a history such as this been elucidated. The patient has been having slight attacks of "Fever" at irregular intervals for some weeks. He has not been able to report himself sick or perhaps does not wish to. On the day in question he awoke feeling seedy, took a dose of quinine and went to his work; after a time he felt more unwell and returned home, took a dose of quinine say 10 grains and a few hours after this passed dark coloured urine. I am not wrong in stating that this is the most usual history, again I have known a colleague
say that he gave a patient an attack of Black-
water Fever with a dose of five grains of quinine.
The patient in question was under my care in
hospital in Kumasi and recovered after a very
severe attack with relapses. Again I could quote
another case, occurring so recently as 1924 in
which the patient had been suffering from inter-
mittent attacks of Malaria for which he had not
received proper treatment. He was ordered a dose
of quinine by myself in the early morning and four
hours after contracted a severe attack of Black-
water Fever from which he eventually recovered.
There are many cases in my mind presenting exactly
the same features and in all these cases the precipi-
tating agent must have been a dose of quinine taken
at the wrong moment. That is the point upon which
I wish to lay stress on. Haemoglobinuric Fever
in my experience has generally occurred in subjects who
have been unable to avail themselves of proper medical
advice as to the method in which they should take
their quinine, or in subjects in which quinine has
been administered to them without a proper appreciation
of all the concomitant circumstances. I am strong-
ly of opinion that failing absolute knowledge of the
Haemolytic agent in these cases, and it would appear
from Dr. Gordon Thomson's researches that the absolute
agent has not yet been discovered, that the agent
may possibly be and very possibly is, this dose of
quinine taken, I wish to urge, at the wrong moment
and one which is an overdose for the individual in
question. Of course, be it understood, there can be
no true tropical blackwater fever without Malarial
saturation necessitating the use of quinine to begin
with, by which I mean saturation for the individual
in question; it may be possible that in certain cases
there may not have been so many attacks of Malaria
previously as I have indicated but I think that if
this is so the number of attacks of Malaria were
sufficient to produce the necessary change in the
blood in the individual quoted. Again what is the
difference between Blackwater Fever and an attack of
Haemoglobinuric Fever precipitated by quinine? I
must confess that I do not know, though it is admitted
that quinine can and has precipitated an attack in
certain individuals and though it be wrong to say
that it has been the precipitant in all cases my
opinion is that in the vast majority of cases it has.
MacGilchrist (1913) has carried out a series of experiments in order to test the Haemolytic action of various salts of quinine. In his report on his experiment he says "Judging from the scanty literature on the subject, very little work has been done, although previous work has been done by Leveran and also by Han whose results differ widely, and also by H. Vincent who as long ago as 1905 reported the strong Haemolytic action of quinine and antipyrin in dilutions of 1 in 500 and 1 in 1,000 on red blood corpuscles suspended in normal saline which were Haemolysed in a few hours; note that this was with defibrinated blood.

Soon after this McCoy (B.M.J. 1908) advanced the hypothesis that the sulphate salt of quinine were responsible for the precipitation of an attack of Haemoglobinuria in Malaria, and stated that it brings about this complication by lowering the salt concentration of the blood plasma thus causing Haemolysis by Osmosis. MacGilchrist's experiments were consequent on this. In the course of his experiments on quinine Haemolysis in vitro he ascertained that it was probable that all the red cells of a sample of blood were not equally resistant to Haemolysis, meaning I take it, that all the red cells in a sample say of loc. of blood did not re-act in the same moment and in the same degree. He ascertained also the important fact that blood Serum retarded autolysis or Haemolysis, and that to accelerate Autolysis or Haemolysis it was necessary both to wash corpuscles free of Serum and to incubate them also, and that then Haemolysis rarely begins before 36 to 40 hours. The acid salts of quinine were found to be powerfully Haemolytic in solutions of 1 in 1,000 in normal Saline. In perusing the details of his experiment I find that in the case of acid salts of quinine, that is, the bihydrochloride or the bisulphate or the bihydrobromide Haemolysis began in 13 minutes in the washed corpuscles. He further states that no increase in the size of the corpuscles takes place, and that the type of Haemolysis is very different to that which takes places in the process of Osmosis and that it occurs by the destruction of the Stroma. He concludes that it would appear that under ordinary conditions very large doses of an acid mixture of quinine can be given to rabbits without Haemolysis of any kind, but at the same time there is a Haemolytic tendency which becomes manifest in two ways, first, if the acid mixture is kept in contact in the blood of the rabbit in a vein from 3 to 4 hours Haemolysis takes place, and secondly the blood drawn from a rabbit injected with these large doses of quinine.
undergoes Haemolysis when withdrawn much quicker than blood drawn from the same rabbit before injection. It appears to me that these experiments prove that salts of quinine have a Haemolytic action but the fact remains that blood which has been drawn from subjects in which the Haemolytic action had been in process and injected into others had not been proved to have a Haemolytic action itself. MacGilchrist in publishing his conclusions says that he considers Haemoglobinuria to be caused by (1) Malaria, (2) Quinine and (3) A third factor which must be the most important factor of the three. He quotes Christopher and Chalmers who sum up as follows:— that Haemoglobinuria results from a condition induced by frequent attacks of Malaria especially under conditions associated with the administration of quinine, and arising within the body as a result of the conditions present. They state that it is due to changes in Osmotic Tension. Haemolytic Chemic-Toxic bodies cannot be definitely excluded as most of these produced oxy and not meth-Haemoglobin. In quoting the above from Christopher and Chalmers, Dr. MacGilchrist adds what appears to me to be an exceedingly pertinent remark. He says, “May not the third factor be an alteration in the blood plasma, in the form of a diminution of its alkalinity, thus favouring the formation of acids or double salts of quinine all of which have been found to be powerfully Haemolytic,” and for myself I regard this possibility as having a bearing of the most supreme importance in the cause of Haemoglobinuria. MacGilchrist further states that Haemoglobinuria can occur in infections with benign and quartan parasites but my experience is an agreement with Dr. Thomson who says that all his investigations show that only the parasites of malignant Malaria, Plasmodium falciparum, is implicated, and I cannot say that in my experience any case of Blackwater Fever has occurred in which either the benign or quartan parasites have been found.

Proceeding still further with his remarks MacGilchrist says that the peculiar symptoms of Haemoglobinuric Fever are all due to diminished alkalinity namely (1) Nausea and vomiting and epigastric pain.

Now diminished alkalinity can be caused by:—
(1) Starvation.
(2) Fevers.
(3) Improper Diet.
(4) Toxic Drug. such as Chloroform, Salicylates, Aspirin, and also by Syphilis. He further compares quinine and Chloroform in that both habit oxidation and both are proto-plasmic poisons.

Clinically, What do we know of the actions of Quinine?
We know for certain that it produces alarming symptoms in some normal individual, many, and with good reasons complain that they cannot take quinine, that it produces in them, even in small doses, buzzing in the head, and singing in the ears. The administration of it in cases of fever often produces deafness. I recently had a patient who passed through a very severe attack of malignant Malaria and could not take quinine because it produced in him besides deafness, a most irritating rash, and his statement was certainly true. We know that the drug has acquired a reputation as an ecbolic and that it has an action on the non-stripped muscle of the uterus. To quote one case of mine, a native African lady required curettage after abortion. The operation was performed, and the same evening she had a very severe malarial rigor, malignant parasites being found in the blood, for which an intra-muscular injection of six grains of quinine was given, within a few hours the whole of the contents of the uterus was forcibly ejaculated. I had no opportunity of ascertaining if subinvolution followed, but I consider it quite likely that it did. We know also that quinine is a powerful antiseptic, and all antiseptics are toxic.

It must be apparent therefore, that quinine is an exceedingly powerful drug and this powerful toxicity must be borne in mind when the question of its relationship to the etiology of Haemoglobinuria is under discussion. To affirm absolutely its relationship to Haemoglobinuria is to dogmatise without adequate premises, but I do regard it as most likely that it can induce a subtle change in an organism whose metabolism has undergone a metamorphosis, the result of repeated attacks of malignant Malaria. The most prominent symptom of this metamorphosis is to my mind hyperacidity and I do think that the addition of a drug, when improperly administered, must increase the hyperacidity and may induce this subtle change in the blood constituents which result in the exhibition of Haemoglobinuria.

It may be quite legitimately urged in criticism of the above that it seems clear that the direct action of quinine alone in the circulating blood plays no part in the Haemolysin, and its action, if action there is, must be in combination with some other factor. Barrat and Yorke (1909) have made careful experiments which show that in the presence of serum quinine has no action, and Dudgeon also in 1921 showed that rabbits rendered intensely anaemic by injecting immune serum did not develop Haemoglobinuria when treated with various quinine preparations either intravenously or intramuscularly.

Ramsden and Lipkin (1915) have found that 90% of a dose of quinine injected in the blood disappeared from the blood in one minute. This I think may be
taken to convey the impression that there is a sudden projection of the drug into the blood to account for the fact of its sudden withdrawal, and if this is a fact would more than account for the apparently sudden appearance of an attack of Haemoglobinuria.

Kliger (1923) found that it required a concentration of 0.2% of quinine bichloride to cause laking of the red cells, and say that this would necessitate the injection of seven grammes of quinine and its continuance for some time to produce Haemoglobinuria and although this certainly is a massive dose, but it must not be forgotten that the peculiar circumstances of the change of metabolism in the blood which occur in the Malarial subjects do not obtain in the case of his experiments. Again Kliger also found that a dilution of 1 in 50 of bile and 0.02 to 0.03% of quinine invariably brought about laking. Again it may be asked, Why does not the blood of a patient suffering from Haemoglobinuria produce the corresponding condition in another subject? And more important still, Why does the drug, when administered to a patient suffering from Haemoglobinuria, not adversely influence the course of the disease? as one can only admit that the observation of many recent observers indicate that it does not. In other words quinine does no harm to a patient suffering from Haemoglobinuria. That I admit is the most difficult question to answer, but I think it is not unreasonable to ask on the other hand why quinine had been associated in the minds of many competent observers both clinical and research as for instance the late Professor Koch, as a possible cause, and I think there is no reasonable doubt that it has. To my mind its action is associated with a sudden explosion which indicates a sudden rapid action and it is possible that the findings of Ramsden and Lipkin in relation to its sudden disappearance from the blood alluded to above may have an important bearing.

Now MacGilchrist experiments (1913) clearly indicate the protective action of the Serum in preventing Haemolysis in vitro at any rate, and the fact that the exhibition of quinine as a curative agent even in large doses in many cases of Malaria must show that in normal individuals the protective action of the Serum is present and maintains the equillibrium necessary to prevent Haemolysis, which means that the necessary Antilysin is present. Now in Malaria, or rather chronic Malaria, the necessary Antilysin seems to be absent. When an attack of Haemoglobinuria occurs its protective action of the Serum is suddenly withdrawn or at any rate rendered in abeyance for the time being. It is therefore not illogical to infer that these recurrent attacks of Malaria tend to produce that change in the Serum which causes it to lose its protective
power, and further that it seems to be, also, that once having lost it the Serum quickly regains the protective power and the Haemolytic action is stopped. If I may be allowed to say so I think that the key-note of MacGilchrist's experiments lies in the fact that Haemolysis took place with such rapidity only in the case of washed blood corpuscles, and that those in the presence of Serum did not Haemolyse. This is what I inferred from a perusal of his article and I regard this fact of supreme importance and that it is conceivable that the Serum had a protective influence on the red blood corpuscles in vivo, which protective influence is suddenly withdrawn when actual Haemolysis occurs and that this protective influence is the third factor to be considered.

If 90% of quinine given intravenously can disappear from the blood in 1 minute as Ramsden and Simpkin tell us, quinine must be much more rapid in its action than is generally supposed, though how to account for this rapidity of action I do not know. Hele (1921) finds that quinine given orally, or by intramuscularly injection arrives at its maximum degree of secretion in the urine in its second hour in the first instance, and in the fourth hour in the latter. He also found that in one case where suppression was the symptom only traces were found in the urine and after death 40 milligrammes of quinine were found in the liver. This seems to indicate that the urine must be of supreme importance in the excretion of quinine.

The experiments and observations of Heirstein and Ramsden and Simpkin, indicate that the total percentage of quinine recoverable from the urine varies from 28% to 51% (Heirstein) to only 6% to 7% (Ramsden and Simpkin) in the case of large doses and to as much as 23% when the doses are much smaller. This seems to indicate that the secretion of quinine varies in an adverse ratio to the size of the dose, but why this should be I do not know.

The facts accumulated by various observers of the action of quinine vary so much and in my opinion point to the uncertainty of its action.

Having been convinced by clinical experience for some years now on the relationship between quinine and Haemoglobinuria I have been in the habit of withholding quinine to all patients if seen in the stage of ascending Pyrexia. I have made it a habit never to give quinine with a rising temperature, and I have come to regard the administration of quinine either at the onset or in the middle of a Rigor as most dangerous.

I do think it possible that the hyperacidity referred to by MacGilchrist as induced by the action of quinine may be a large factor in the production of
Haemoglobinuria but no experiments or observations have come to my knowledge which indicate the degree of hyperacidity induced in the blood, and I am of opinion that further experiments might be made on this point.

Another factor which requires further observation is the part played by Urobilin in the metabolism. Is Urobilin a product of Haemolysis or is it a factor in its production? Again, is the production of Urobilin increased to such an extent by quinine as to be dangerous? I think that these are pertinent questions which require an answer.

De Jonge (1904) states that quinine increases it.

Simpson (1910) states definitely that there can be little doubt that the excretion of Urobilin is increased more in malignant tertian Malaria than in any other disease accompanied by Pyrexia, and again, Simpson and Edie have found an increased secretion of Urobilin after quinine administration in 10 to 30 grain doses, and again Sorensen (1914) indicated an increased production of Urobilin before the onset of the Pyrexial stage. Personally, I am inclined to regard Urobilin as a product rather than a factor in our present state of knowledge.

I am well aware that no arguments as to the action of quinine in Haemoglobinuric Fever will explain all the fallacies which undoubtedly exist. It is a fact that very little separates that type of Fever known to West African practitioners as "bilious remittent" from Blackwater. In the former there is the same distressing vomiting, the same degree of thirst, and the same degree of epigastric tenderness and pain. This type of Malaria is the gastro-intestinal type, and due, I have always been taught, to the sporulation of the parasites in the arterials and venules of the intestine. There is the same manifestation of hyperacidity; I am speaking strictly clinically, but there is no albumen in the urine and which, though concentrated of high specific gravity and of a high red colour, in no way resembles that of Blackwater, but it has always seemed to me in observing these cases, that only some very insignificant additional factor is required to convert these cases into a true Haemoglobinuria, and this is the type of case in which I hold that on no account should quinine be given during a period of Pyrexia.

Of course it must be admitted that certainly in Africa and probably elsewhere also can neither alcohol or Syphilis always be excluded as a factor in the production of Haemoglobinuria, but whatever conditions may have obtained in the early days in West Africa, so to speak, conditions to-day are so changed that both alcohol
and Syphilis are a far less important factor in the production of any degree of illness than there used to be, and within my personal knowledge in only one of my patients could alcohol be a largely contributing factor and I know of only one other who had contracted Syphilis and who afterward and soon afterward died of Blackwater Fever, after having received a full course of treatment by N.A.B.

The very fact that so many observers have, as quoted by Dr. Thomson, such as Crosse on the Niger, A. Fehn, and E. Fehn, in Togoland, Thin and Moffat also on the Niger, cited so many cases where Blackwater Fever has occurred without the administration of quinine cannot be taken as absolutely contravening my argument, as, the possibility of these cases being caused by Yellow Fever, and not Blackwater Fever, must be borne in mind. In Asia, Hatori (1915) quotes cases as occurring among the Chinese in Formosa who never take quinine, but says they occurred after the administration of quack medicines and also thymol. I can only repeat that in West Africa, at any rate, quinine must be always a factor in its production.

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In describing the anatomy and pathology I make no apologies for following closely the observations of Dr. Gordon Thomson as quoted in his researches because he gives the very latest account available and his findings resemble so closely my observations on such cases as I have been able to examine.

The Spleen. The spleen is always markedly enlarged with a soft and friable consistence. In colour it is dark red, to reddish brown, and even black which Dudgeon points out is a similar appearance to that found in animals which have died of Haemolysis. Perispleenitis is generally present. The capsule may be thick and may or may not strip easily. The Malpighian corpuscles are enlarged from active endothelial proliferation (Dudgeon). Some of the larger veins may be thrombosed and the thrombi may be composed of much fibrine, polymorphous leucocytes, and a few red blood corpuscles. The venous spaces in the pulp are congested and the lining endothelial cells contain blood pigment. Dudgeon noticed localized patches of necrosis in the stroma. Pigment was noticed in five cases out of 13, in three pigment was entirely absent. Dr. Gordon Thomson states that there is ample proof that both parasites and pigment are rapidly destroyed during an attack of Blackwater. Crescents were found in 3 cases.

Free iron is easily demonstrable, but bile pigment in only one. Dr. Gordon Thomson summarises his results as follows:

(1) Increase in size up to three times the normal.
(2) Consistence soft and pulpy.
(3) A sago grain appearance, from enlargement of the malpighian corpuscles.
(4) Endothelial proliferation.
(5) Phagocytosis of red cells by endothelial cells.
(6) Thrombosis of larger vessels.
(7) Deposits of Haemosiderin.

The Liver. The liver is markedly enlarged in all cases, colour varies from light to dark yellow or brown, and in one case green. The colour varies according to the amount of jaundice. The capsule was not markedly thickened. Dudgeon found some Haemorrhages under the capsule varying in size. Bile capillaries choked with bile in all cases, and the gall bladder generally distended and full of thick bile. In all there was a Necrosis of the cells round the central vein of a lobule and generally accompanied by well-marked fatty degeneration in the cells adjacent. Dr. Gordon Thomson again Summarises as follows:
1. Severe degeneration and Nacrosis with Icterus.
2. Deposit of Bilirubin and Haemosiderin in the parenchyma cells.
3. No increase of fibro-blasts or Cologenous fibrils. Evidence of red cells destruction.
4. Malarial pigment varies, may be scarce or absent.
5. Marked distention of gall bladder and bile ducts.

The Kidneys. The condition of the kidneys vary enormously according to the degree of Haemoglobinuria. They are generally enlarged, and are congested; the colour varies from a pale brown to yellowish red or dark violet. There is generally intense engorgement of the Cortex and Medulla. On section the renal tubules show coagulated protein substance with granular debris and agglutinated red cells. The ducts of Bartini contain dark reddish brown blood of a granular nature, similar to the casts which appear in the urine. The basement membrane is left exposed. Epithelial cells are found in these plugs. The epithelial cells of the convoluted tubules especially show all stages of degeneration. Fatty degeneration does not seem to be marked. The glomeruli show all shades of congestion from slight to intense. The blood vessels of the kidneys were usually empty and no malarial pigment was found in the blood vessels or elsewhere. The convoluted tubules show a wide lumen with severe cloudy swellings and degeneration. The epithelial cells of the convoluted tubules was for the most part intact. There is no evidence that Haemolysis takes place in the Kidneys, and the pathological findings in the kidneys give no evidence that Haemorrhage and Haemolysis in that organ are the causal factors in the production of Haemoglobinuria. The actual site of the laking of the red cells cannot be determined but the evidence on this point is certainly in favour of a Serum Haemolysis similar to that which occurs in animals injected with Haemolytic amoebaeter.
The Alimentary Tract. Dr. Gordon Thomson reports that in all his cases there was an excess of bile in the intestine but the examination of the intestinal microscopically showed little changes. Other observers state that Black-water Fever is characterised by an acute gastro-enteritis.

Dr. Gordon Thomson summarises his findings as follows:

The organs most affected are the kidneys, liver, heart, and spleen.

Nearly the whole of the specialised epithelium of the kidney is destroyed. The liver is also severely damaged. There is free iron found everywhere. Generally speaking the pathological findings associated with Black-water Fever are such as would be found in a severe Toxic condition.

Professor Bartlett says that the changes are exactly of the degree and type one meets in a severe acidosis from any cause.

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SYMPTOMOLOGY.

Prodromata. The history of patients suffering from Blackwater Fever almost invariably indicates the presence of malignant Malaria, by which I mean he has become more or less heavily infected with the parasite plasmodium falciparum. He will almost invariably tell you that he has been having fever more or less severe, probably not sufficient to incapacitate him from his duties. It is a fact that many individuals who come under observation in the Tropics impress themselves upon the observer of experience as a likely subject for Blackwater. They have a peculiar facies, sallow, anaemic, drawn with often icteric conjunctivae. The urine does not contain albumen but is invariably very acid, high coloured, and of high specific gravity, and it is in these individuals that the explosion occurs which results in an attack of Blackwater Fever.

For this Fever he has taken quinine and generally a dose additional to his daily dose of say 5 grains.

When first seen the patient will be almost certainly distressed. He may be in the middle of a severe rigor, and he will have passed dark porter colour urine.

The most outstanding symptom and one which causes great distress are nausea and vomiting. The vomiting may be almost continuous and causes great exhaustion. The vomit after the latest meal has been rejected, consists as a rule of a few ounces of greenish, yellowish material of a bitter taste, and it is the violently expulsive nature of the effort to vomit being so out of proportion to the amount of material vomited which causes such great distress. I regard this as one of the most outstanding features in an attack of Blackwater Fever.

The Temperature may be as high as 103°F.

Rigor occurs in the majority of cases and the temperature will probably fall considerably after the onset of Haemoglobinuria.

The urine is generally of a dark porter colour like stout. Dr. Gordon Thomson mentions that Hiccough may be extremely persistent. I have not noticed Hiccough to be an outstanding feature in the Initial stages of the illness. In my experience it occurs later on, and in my opinion indicates a grave prognosis.

Headache is continuous and hard to relieve.

Pain. There is in the majority of cases severe
pain in the back over the region of the kidneys. Pain also will be complained of in the pit of the stomach and is due to the muscular effort caused by vomiting. There may be some bladder pain. Pain is also complained of in the long bones but this is not a symptom peculiar to Blackwater Fever. Pain also in the region of the liver and spleen is generally complained of.

The skin before the onset of Haemoglobinurimia is of a peculiar colour already alluded to. The icteric tinge is often very noticeable in the eye-ball and is as a rule wellmarked when the patient is first seen. A peculiar sallow tint associated with the oncoming profound anaemia is also noticeable and becomes more and more intense as the case progresses.

Jaundice. The skin also is of a peculiar lemon yellow colour associated with the presence of jaundice.

Dr. Gordon Thomson in his remarks says that this is not a true jaundice. Dudgeon, however, observed a true jaundice in 20 out of 49 cases. I find that this is not easy to determine whether or not the icteric tinge of Blackwater Fever is a true Jaundice. My interpretation of Dr. Gordon Thomson's remarks is to the effect that at the initial stage the tinge is not that of a true jaundice as it seems to be difficult to determine whether it is due to the presence of Bile pigment in the skin. This may possibly be true, but what else the tinge can be due to if not to bile pigment I do not know.

Later on, if the disease resumes a very grave and pernicious form, the Jaundice becomes as intense as in an obstructive Jaundice, and I have always found that a deepening Jaundice is always associated with a grave prognosis.

In addition to the icteric tinge more or less pronounced the skin also assumes a chalky appearance associated with the Anaemia produced by the destruction of blood corpuscles. The lips and other mucous membranes become almost chalky white very rapidly. An intense thirst is a very prominent feature.

The Pulse. The pulse is invariably quickened usually up to about a 100 per minute. In the first stage of the illness it is hard, not very compressible, and differs a little from the pulse of an ordinary febrile attack. Later on it naturally becomes weaker. Its rate increases and it may become dicrotic.

The tongue is invariably coated with a heavy white fur.

I have never noticed anything which could be
associated with cerebral changes in the initial stages of this illness.

Delirium is not a symptom as a general rule, neither is it noticeable in cases of suppression, in which the patient remains conscious and his mind clear up to the last. I have never seen convulsions, and I have never seen a violent delirium not associated with a high degree of Pyrexia.

The Urine. The urine is distinguished by its dark porter-like colour. When passed it should be poured into a urine glass and allowed to stand. The colour will be found to vary a great deal from a light red to a dark stout. Careful observation will show even that the urine even when of the darkest colour always has a distinctly red tinge, especially noticeable in the upper layer after standing.

Within a very short time after standing a sediment will be thrown down. This sediment I regard as important and as diagnostic of the disease. It varies very much in colour. Dr. Gordon Thomson says, it is brownish but it may vary from a pearl grey colour to a dark brown rather like that of mud.

Microscopically examined the deposit shows numerous amorphous granules which are the product of broken down red cells. Red blood cells are found very sparsely and are very often absent (Dr. Gordon Thomson).

Tube casts are always present and generally are abundant. These casts are both tubular and granular.

Bile is not always present. Dr. Gordon Thomson found it only in one severe case. My own impression is that bile is present in nearly every case, but Arkwright and Lepper (1918) report that the presence of bile is difficult to determine owing to the presence of Haemoglobin.

When examined spectroscopically the bands of both oxy and meth-Haemoglobin are shown. The reaction is generally acid (Dr. Gordon Thomson). My own experience is that the urine is nearly always acid. Deaderick states that it is slightly acid generally but may be neutral or alkaline. Dudgeon found acetone in six cases only out of 43. It is important to note that the urine of Haemoglobinuric patients does not undergo de-composition for a considerable time.

The specific gravity has been noted by competent observers to vary from a 1,001 to a 1,020. My own experience is that it is generally about a 1,015. Albumen in large quantities is always present. Dr.
Gordon Thomson says that it is present during the passage of Haemoglobin, but I have known a trace of albumen in the urine to persist for many weeks after all symptoms as regards the urine had cleared up. The amount passed in each 24 hours varies to a considerable extent. The amount may vary from a few drops to a 120 ounces.

The Haemoglobinuria may last from a few hours to a few days and then may disappear entirely. Again some cases show an extraordinary variation in the colour of their urine throughout the whole course of their illness. The urine may show the typical dark porter colour in one specimen passed, the next passed within an hour much lighter, the next after that again very dark, and so on for 48 hours or even longer. The amount of precipitate does not seem to vary much until the illness begins to make a definite turn to improvement; then it becomes noticeably less and of a much more pearly grey colour. The same may be said of the amount of albumen which varies greatly.

I have notes of a case occurring in 1907 in which the Haemoglobin persisted for 14 days, and again of another case in which it persisted for 28 days with intermissions.

Pyrexia. The height of the fever varies in each individual case during the initial rigor, and before the passage of the first Haemoglobinuric urine the temperature is high, rising to 104°F. After the passage of the first urine the temperature generally falls suddenly, sometimes to normal. As a rule the temperature rises again and reaches 101 to 102°F, and remains high as long as the Haemoglobinuric remains normal or even subnormal with a very persistent Haemoglobinuria, and conversely the temperature may remain high after all symptoms have passed away.
THE BLOOD.

The blood shows great macroscopic and microscopic changes of great importance. Macroscopically there is an intense Anaemia caused by the destruction of red cells. The Haemoglobin index is never less than 10% and may fall from 25% to 40%.

Dudgeon in 6 cases before death gives the following red cell counts.

(1) 992000 Per C.M.
(2) 1,330000 Per C.M.
(3) 1,000000 Per C.M.
(4) 9,00000 Per C.M.
(5) 824,000 Per C.M.
(6) 1,048000 Per C.M.

Deekes and James quote a case where the red cell count was only 8,00000 and the Haemoglobin index 10% and in which the patient recovered.

The clinical picture presented by the patient is that of an acute Anaemia such as can be caused by an intense Haemorrhage.

Microscopically Dr. Gordon Thomson remarks that in these cases it is extremely difficult even with the greatest care and skill in technique to obtain satisfactory blood films, and my experience teaches me that this is most certainly the case.

In addition the amount of time required to be spent on the preparation and examination of these films preclude any observer who is unable to give up his whole time to the examination of these films from examining them with such care and accuracy as is necessary.

His examination is generally conducted for parasites only, and I shall therefore make no apology for quoting as fully as I think necessary the findings of Dr. Gordon Thomson.

From my own experience I can speak to the variation in size, colour, etc., the occurrence of punctate, basophilia, and the appearance of ghost cells. Clinically it is of the first importance that the presence or absence of Malarial parasites or of Malarial infection, as manifested by the presence or absence of pigment noted, and the occurrence of leucopenia determined, but the with the ultra-microscopic the clinician can have nothing to do.
Dr. Gordon Thomson in quoting for the presence of parasites reports that Stevens (1915) clearly showed that parasites tend to disappear from the peripheral blood as the Haemoglobinuria develops.

The percentage of positive findings as given by him:

1. Before the onset 73%
2. On the day of onset 47.5%
3. On the day after 23%

Dr. Gordon Thomson himself found parasites in 23 cases examined before the onset.

It is only very occasionally that a heavy infection of malignant tertian parasites persists throughout the course of the illness, and in his experience of 100 cases, it was difficult to demonstrate Malaria even in those cases which showed a heavy infection immediately before onset, and that his results in films taken the day after the onset were universally negative. The above figures show that if a blood film is examined before the onset a high percentage of positive results will be obtained. Further, this percentage is so high that when we take into consideration the fact that even in untreated cases of malignant Malaria, parasites cannot always be detected, we have, in my mind, conclusive proof that that is the causal organism of this disease, and further that the P. Falciparum is the species incriminated in this condition.

Clinically, I have always been struck with the few instances in which parasites can be demonstrated in the peripheral blood in films from Blackwater Fever cases, but a previous history invariably points to an infection of malignant tertian Malaria caused by the parasite P. Falciparum, and it may be safely asserted that in the vast majority of cases Parasites will not be found, and indeed I can go further and say that in the majority of cases of all Malignant tertian Malaria, whether the onset of Haemoglobinimuria is possibly imminent or not Parasites in the peripheral circulation will not be demonstrated microscopically.

Of importance also is the presence or absence of Malarial pigment in the film or contained in the leucocytes. The large mononuclear leucocytes are increased in practically every cases to over 20% shortly before the commencement of the attack. (Christopher & Stevens 1900). Later Christopher and Bentley (1908) pointed out that this increase was largely due to large mononuclear leucocytes.
varying in size from 15m to 25m will be found and that sometimes only malarial pigment is found in these. These observers also state that large cells suggesting endothelial plaques from the capillaries will be found in size up to 20m or 30m, and often containing phagaclytosed red cells and debris.

Gordon Thomson states that though these large mononuclear cells are certainly increased in number in malarial attacks they are not found in blackwater and that in an examination of his films he only encountered a definitely pigmented leucocyte in one case. The remarks of so competent observer must carry weight, but I must say that I was under the impression that they were far more common.

Presence of other Parasites. Dr. Gordon Thomson further discusses the question of the possibility of the presence of other organisms and draws attention to the resemblance which has been noted in some forms of aspa falciparum to the organism of Babesia which is the organism of red water in cattle. He further remarks, however, that the cultivation of these on media make it clear that only the organism of malaria was present and says that he had never heard of Babesia in man. Again a spirochaete has been cited by Blanchard and Le Frou (1822). In their experiments about 10cc of blood was drawn off into a sterile centrifuge tube containing 1cc of a 20% sterile sodium citrate solution and centrifuged 3 times. The supernatant fluid being drawn off and subjected again to repeated centrifuging. In the last result of the process some spirochaetes were found and it is curious that in the course of the experiments was the deposit of the second case was inoculated into a guinea-pig which died, however, without jaundice or haemoglobinuria.

Dr. Gordon Thomson states that he employed the same technique in 15 cases. The blood for examination was obtained in different stages in the disease and on the 1st, 2nd and 3rd days after the onset, and in every case after the third centrifugalisation there were numerous pseudospirochaetes. These were of varying sizes and either comparatively thick or extremely fine.

In every case these filaments corresponded to filaments found in clotted blood from normal individuals, and further that though with dark ground illumination they appeared to be a actively mobile. No true spiral movement was exhibited. It seemed probable that these filaments were derived from degenerate or damaged red blood corpuscles and their apparent motility was due to causes such as changes in the surface tension of the containing fluid.
10 guinea-pigs were inoculated with centrifuged deposit from 10 distinct cases of Blackwater Fever, no spirochaetes were found and nor were there any abnormal symptoms.

No spirochaetes have ever been found in the urine of patients with Blackwater Fever.
DIFFERENTIAL DIAGNOSIS.

A word on the differential diagnosis of Haemoglobinuria may not be out of place and in Countries such as West Africa where Yellow Fever occurs it may be mistaken for in a patient who has been unable to give a history of his illness. As a rule in Yellow Fever the personal distress and anxiety of the patient is much greater. The headache is more intense and more frontal, and there is also a very pronounced photophobia. As a rule the conjunctivae are much more yellow and the skin has not that sallow tinge associated with Anaemia. As a rule the patient is more flushed. Epigastric pain and tenderness are greater in Yellow Fever also. Pain in the liver is more pronounced in Yellow Fever and the liver itself is more enlarged. The spleen on the other hand is more enlarged and more tender in Blackwater Fever as a rule. The pulse is slower in Yellow Fever. In Yellow Fever as the disease progresses, the Jaundice becomes more intense. There may be suppression of urine in both diseases, but if a specimen of urine were obtained, that of a Yellow Fever Case although it might be Haemorrhagic would not be the typical colour, and if obtained before the third day would not contain albumen. Examination of the blood would not show in Yellow Fever the predominence of large mononuclear leucocytes which would not also contain Malarial pigment.

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TREATMENT.

The treatment of Haemoglobinuric Fever resolves itself in my opinion to combating and alleviating the various symptoms which the case presents.

Clinically cases of Blackwater Fever are of two types.

1. Those with polyuria.
2. Those with Suppression.

Every symptom has to be carefully noted and its exact value appreciated. To begin with I will state my opinion that no drug can have any effect on the Haemolytic process itself, because, be it noted, the Haemolysis has already taken place when the disease manifests itself and though the process may suddenly cease, its effects as manifested by changes in the urine will not cease until the products of the Haemolysis have been entirely eliminated and thus it is in the treatment of these cases with the results of a Haemolysis that we have to deal.

Clinically its effects are manifested first by changes in the urine.

2. Vomiting.
3. Pyrexia.
4. Epigastric pain and tenderness.
5. Headache.
6. Anaemia (often very pronounced).
7. Either Anuria or Polyuria.

In the clinical estimation of these cases, therefore, the utmost attention should be paid to the urine. Each specimen passed should be kept in a separate urine glass and a full account noted of its colour, reaction, specific gravity, amount of deposit, and most important of all, the exact amount passed from time to time. By so doing, we estimate the type of case with which we have to deal and can ascertain whether Anuria or Polyuria will be the outstanding features.

Let me say at once, that no drug has been found to have any influence on the course of the Haemoglobinuria itself. Many have been tried at various times both by myself and many other observers and although highly recommended as specifics I am unable to agree that any of them are.

It must be noted that many cases undergo what would be looked upon as a spontaneous cure by which I mean that, without treatment of any kind, the urine

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cleared up rapidly, possibly after the passage of
the dark urine once only, and the sufferer rapidly
became convalescent, but we must remember that the
Haemolytic process must of necessity vary in its
severity and intensity, and in these cases which
cleared up so rapidly there was only a slight ex-
losion of the Haemolysis, and consequently less
of its effect to be eliminated. Clinically,
it has always appeared to me that the Haemolysis
happens suddenly and only once, so to speak, and
then as rapidly ceases. If I am correct, this
would account for so many features of these cases,
as, for instance, for its sudden onset.

I am not saying for one instant that the
Haemolysis may not be repeated; it most certainly
in many cases is, and in varying intensity, otherwise
it would be obvious that the urine would not vary
from time to time as it so often does. It cer-
tainly varies most noticeably in colour. A specimen may
be dark porter, the next light claret colour, the third
almost clear, or only smoky, and the fourth return to
the light claret or even dark porter colour again.
The amount of albumen and of the precipitate vary in
the same way, but, curiously enough, my observations do
not lead me to state that the specific gravity varies
also.

I think that these variations must be due to
exacerbations of the Haemolytic process, and the
remissions and variations must be associated with
its Malarial origin. As the variations are in
the urine, so are the variations in the degree of
Toxaemia, and in my opinion, the amount of Toxaemia
and the severity of the attack are manifested clinically
more by the intensity and deepening of the jaundice
than by the colour, always associated in my opinion
with a severe attack, and Dr. Gordon Thomson also
draws attention to the deepening Jaundice of those
cases which came under his observation, and which
proved fatal.

It does not take a great deal of imagination to
understand that if the Haemolytic process did not
for some reason or other spontaneously and instantly
cease, the mortality in this disease, since the attack
is directed against that most vital fluid, the blood,
would be of the very heaviest; indeed, few would escape.
I think it can be argued that if the Haemolytic
process continued for any time at all death must ensue
in all cases within 24 hours, but fortunately for those
attacked, the Serum seems quickly to assume again that
protective power which causes the Haemolytic process
to cease only to temporarily lose it again if
exacerbation of the disease occurs, and I think it
may not be an illegitimate argument to quote in

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in referring to the fact that 90% of quinine administered has been found to disappear from the blood in 1 minute as Ramsden and Simpkin tell us, and to which previous reference has been made, which may possibly have an important bearing on the protective power of the Serum and stand in favour of the contention that an over-dose, for the individual, of quinine taken at the moment when the protective power of the Serum has been temporarily placed in abeyance is a causative agent.

Of drugs which have been cited as having a favourable influence on the course of this disease the most common have been a decoction made from the roots of (a) Cassea Bereana and (b) Cassea Exfoliativa. These drugs have been given a thorough trial but no reports that they favourably influence the disease have been brought to my notice, nor have they given any special signs of having any effect when used by me in my practice. They certainly do not exercise any influence in preventing a further Haemolytic process.

Dr. Gordon Thomson states that many native drugs were brought to his notice in Rhodesia, but I agree with him when he says that they only have possibly diuretic properties. In 1913 Boye advocated the use of Calmette's anti-venom and quoted instances in which the Haemolymphuria rapidly cleared up under its use. Clinical experience teaches us that cases clear up just as rapidly without the use of any such dangerous drug as this must be, and Dr. Gordon Thomson quotes a case in which Burroughes and Welcomes Polyvalent anti-venom Serum was used with results which appear to have been disastrous. No arguments for their use have, in my opinion, been made out and I should certainly hesitate to use them myself.

N.A.B. Salvarsan and Galyl have all been used but I should hesitate to use any drug containing a heavy arsenic content in an acute stage of this disease, and I can only say that one case has occurred in which a full course of N.A.B. had been given for specific disease who contracted Blackwater Fever and died. Dr. Gordon Thomson says in his admirable essay that he is quite unable, from his observations of the different forms of treatment applied by different practitioners to form any conclusion as to the value of any one of them.

As regards treatment, therefore, I am of opinion that by far the better plan is to counteract such symptoms as present themselves with the remedies that are most suitable.
Acidosis or hyperacidity being always present alkaline remedies in large doses should be given freely, the most popular of these is known as Sternberg's formula and has been in use for many years and which has undoubted Palliative effects and is a great help in relieving the distressing vomiting. We can use either Sternberg mixture which is as follows:—

\[ \text{R} \]

Soda Bicarb 3\text{f}.
Hyd Perchlor 8\text{f}.
Aq ad 3\text{c}. every hour.

or Hearsey's modification which is even better.

\[ \text{R} \]

Soda Bicarb 8\text{f}.
Liq. Hyd Perchlor m 20\text{c}. every 2-3 hours.

One of the best remedies for combatting the exhausting and distressing vomiting is certainly copious drafts of hot water as hot as the patient can sip it and with say 20 grains of bi-carbonate of soda added to each tumblerful. Not only does the alkali counteract the hyperacidity, but what is as important in my opinion is that it gives the patient something to vomit. I have always found that it is the effort of reaching with nothing except a very little acid, and very bitter bilious fluid to bring up which is so distressing and trying to the patient. This is one of the best routine treatments and highly successful.

I cannot recommend the early intravenous injections of cyanide of mercury in doses of 0.05 grammes as recommended by Munoz (1920). I think these are more likely to do more harm than good and in addition so many pricks with a needle will be too distressing to the patient.

Treatment should always be commenced with an initial dose of at least 5 grains of calomel followed by an effervescing saline purge.

Epigastric pain and tenderness and also vomiting are specially relieved by hot applications to the abdomen.

I do not recommend the early exhibition of either sedatives or hypnotics, or of drugs to keep up the blood pressure. Morphia should be kept in reserve to combat the restlessness and insomnia when the patient is becoming exhausted, and I have found hypodermic injections of digitalis and strychnine of great value when the blood pressure begins to become low. Of the
two although digitalis certainly increased the blood pressure. Strychnine appears to me of greater value on account of its more lasting effect in directly stimulating the heart muscle.

Dr. Patrick Mansion in his days of teaching did not recommend the use of diuretics. If there is any tendency to suppression it is certain that diuretics will throw more work on an already over-worked kidney and by increasing the distention in the tubules do more harm than good. If the patient is passing plenty of urine diuretics will not be required.

The most important part of the treatment of any case of Blackwater Fever is the free use of saline rectal injections. Special tabloids are prepared by Burroughes and Welcome for use, and are most valuable. Formerly I have found the simple rectal injection not so efficacious on account of the fact that it was so frequently returned, and my invariable custom is now to attempt to throw the injection high up into the colon. For this purpose a douche can with at least six feet of tubing is used and a number twelve plain rubber catheter is passed up the rectum as far as it will go. The patient should be semi-prone, the most convenient is on the left side with the right thigh well flexed. No difficulty is experienced in passing the catheter well up and at least a pint or more of fluid can be passed into the colon and is well retained. I have found that this has a most stimulating effect particularly on the kidneys and there is as a rule passage of urine a short time after the injection has been given.

In the event of there being any tendency to suppression the injection should be of the greatest volume and as hot as the patient can bear it. I am quite certain I have successfully combated a tendency to suppression by this method. By using this method also I have had occasion to give salines intravenously but if these injections were not successful I should not hesitate to do so, but I must admit that all my patients have done well on their administration per rectum.

Stimulants are not required in the early stages of Blackwater Fever, in fact by throwing more work on organs already over-taxed, such as the liver and kidney, they do much more harm than good.

Especially bad, is the use of champagne which is acid and will do much more harm than good, in addition to which its stimulant effect is so transient as to be negligible in value. If the stimulant effect of carbonic acid on the gastric mucous membrane is required a little plain soda water will fulfil every indication.
The administration of bland fluids such as soda water, barley water, milk and water, or soda water, albumen water, whey, should be given and the patient made to partake of them as freely as possible. They are more palatable if given ice-cold.

If the patient is restless and excited I think morphia is the best drug to use in doses of not more than 1 tenth to 1 sixth of a grain. Other hypnotics have a tendency to upset the gastric functions already badly disarranged. If there is any tendency to alcoholism spirits may be given as freely as necessary. Glucose intravenously has been highly recommended and certainly does good. I can see no reason why ice-cream taken in very small quantities at a time should not be of great benefit. I have used X.A.B. in post-Haemoglobinuria Pyrexia with great benefit. Very small doses should be given.

Suppression. Warrington and Yorke (1921) in discussing the mechanism of suppression come to the conclusion that it is evident that under certain conditions the mere passage of Haemoglobin through the kidney of a healthy animal is sufficient to cause suppression owing to the occlusion of the lumen of the renal tubules by plugs of granular material derived from the Haemoglobin. The process is considerably facilitated by any factor which tends to lower the blood pressure of the animal and as a result the secretion of water by the malpighian capsules ceases. On the contrary when the blood pressure is sustained by the injection of saline solution and by feeding the animal on moist foods a large amount of Haemoglobin may be injected without any tendency to suppression. It would appear then that suppression is due not so much to inflammation of the tubules of the kidney as to mechanical blocking of the tubules by plugs etc. The treatment of suppression should be preventative as far as possible, by which I mean that the amount of urine passed should be most carefully watched and any symptom that the kidney is not acting freely should be combated at once.

Intense pain in the loins will give an idea that all is not well with the functions of the kidney.

Suppression can be warded off by stimulating the kidney by irrigation of the colon with hot saline douches given as hot as the patient can bear them and by hot applications applied freely to the kidneys themselves.

Boiling hot fomentations, hot poultices, and mustard if necessary, are clearly indicated. I have used cupping to the kidneys with success. By the free use of saline injections, however, I have found that all indications have been met.
Many years ago I saw an article by a French practitioner recording his success in cases of suppression with small doses of chloroform given very frequently, freely diluted. I should think this treatment was worthy of trial.

**Cases of acute cardiac failure during an attack of Blackwater Fever particularly in cases with Polyuria are by no means uncommon.**

**Treatment with quinine.** This is freely discussed by Dr. Gordon Thomson in his researches. He comes to the conclusion that he is unable to find that the treatment with quinine prolongs the disease, but is quite certain that it has no beneficial effect on the fever. He quotes Arkwright and Lepper (1918) who in a careful study of 16 cases stated that there is no evidence that this drug has a share in the production of Blackwater Fever, nor has it any effect on prolonging or reproducing the Blackwater.

He also quotes Dudgeon to the same effect.

But it seems that on the other hand Deaderick and Cardamatis collected 1,931 cases treated with quinine with a mortality of 25% and 998 cases treated without it with a mortality of 10.3%. There is also another list compiled by Cardamatis of 2,127 cases, 1,692 of which were treated with quinine with a mortality of 26.7%, and 524 treated without it with a mortality of 6.8%. It would appear from these figures that the mortality with treatment without quinine is a good deal lessened.

While it is certain that very many cases recover under its use, the evidence that it actually does good is by no means conclusive.

It is a fact that the parasites are enormously diminished, if not entirely killed off, either because of or certainly during an attack of Haemoglobinuria, and this fact alone should render one cautious in its administration, and further, again the fact that in most cases the history will elicit the fact that the Haemoglobinuria has been precipitated by a dose of quinine should make one more cautious still.

Again I think that it will be found that those cases recorded as having been treated during their illness with quinine have received it in such small quantities that the course of the disease could not have been influenced one way or the other though Crosse records cases treated with large doses on the Niger.

I am quite convinced that one cannot be dogmatic in discussing a question which is so controversial.
as this. Personally I have only treated one of my cases with quinine who developed suppression and died. On the other hand, I can quote cases who have developed suppression without quinine.

My results without quinine have been as satisfactory as one can expect, as I think that generally speaking the general practice on the Gold Coast at least has been to treat Haemoglobinuria without quinine. There is no doubt that Sir Patrick Manson's advice long ago given is sound. His advice was to administer quinine if Malarial parasites have been found in the blood. There is in these cases a clear indication for its use, and the advice must be sound. Again, in the event of a patient having daily rigors with the continuance of Haemoglobinuria I should certainly give small doses of quinine only when the temperature is at its lowest. One grain intramuscularly would be sufficient, which would be repeated daily and the results watched.

In the post Haemoglobinuric Pyrexia quinine is indicated, and I have never seen its administration in suitable doses of 1 to 2 grains intramuscularly do any harm or cause any exacerbation of the Haemoglobinuria.

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Prognosis.

Prognosis and Mortality. The prognosis in a case of Haemoglobinuric Fever must always be very guarded. My own experience teaches me that cases of Polyuria are less fatal than those with a tendency to suppression. I have no hesitation in saying that the death rate from Blackwater Fever has been appreciably lessened since 1911. In the report to the Colonial Office Dr. W.J. Grahame gives the mortality as having risen from 15.6% in 1905 to 36% in 1911. In my series of cases the mortality works out at about 18%.

My opinion is that a given case of Haemoglobinuric Fever in a normal individual whose constitution is sound and whose internal organs, particularly the kidney, is undamaged should recover. Though any latent weakness in the kidney leads to suppression.

Allowance should always be made for the damage caused by the Toxin of malignant Malaria to non-stripped muscle especially that of the heart. Dudgeon and Clark in 1919 showed fatty degeneration in the cardiac muscle in 23 out of 45 cases. It appears to me also that the non-stripped muscle, especially of the arterials, and venules of the kidney must suffer damage also.

It is difficult to think that there should be this great variation between cases from Anuria to Polyuria solely on account of the great amount of Haemoglobin liberated or amount of Toxins to be got rid of, and I think it within reason to suppose that a failure of the kidney mechanism manifested by Anuria is due to damage to the non-stripped muscle of the kidney from chronic malarial toxæmia.
PROPHYLAXIS.

Prophylaxis. I have not the slightest hesitation in saying that Haemoglobinuric Fever as applied to all tropical countries is an eminently preventable disease and one can reasonably look forward to the time when this disease, which next to Yellow Fever, has been most certainly one of the chief causes of the heavy mortality associated particularly with West Africa and, be it noted, without Yellow Fever, particularly in Rhodesia, also will not be known.

Prophylaxis of Blackwater, the same as the Prophylaxis of Malaria.

The prophylaxis of Blackwater Fever is the prophylaxis of Malaria and I have not the slightest hesitation in saying so. The prophylaxis of Malaria is the regular dose of quinine taken at the time when the Subject finds it most suitable for him to take it. I do not mind what hour in the 24 hours it is taken.

Whether or no the dose of 25 grains taken in divided doses twice weekly or the more general dose, I believe, of 5 grains daily, taken for 7 days in the week, I do not care, as long as the dose is taken regularly, and certainty exists that the full dose is absorbed and exercises its full function as a preventative.

Let me go further and say that this regular dose of quinine does no harm to any individual and if individuals exist who have an idiosyncrasy to the drug, and there are such individuals, these individuals must not live in Malarious districts. If their occupation renders it necessary that they must reside in districts where they are liable to contract Malaria every means must be tried whereby they can take their quinine without harm to themselves and I am certain that they can find the means if they take the proper measures.

I think that those individuals who in spite of their regular dose become so heavily infected with Malaria as to become subject to Blackwater Fever do so because this prophylactic dose is not being absorbed into the blood and therefore becomes, not only prophylactic, but even harmful. Quinine must not be blamed for failing in these cases, but it is the individuals' own methods that are at fault.
Now the usual way of taking quinine is in the handy practical tabloid form, and the salt taken is generally the bi-hydrochloride or bi-sulphate. The French I believe take their dose in Cachet, a very good method.

If an individual's digestion is in any way disorganised and in a tropical country frequently is, this salt of quinine will not be entirely absorbed and consequently does harm by rendering the gastric Mucous Membrane more irritable and increasing his Dyspepsia. This Dyspepsia takes the form of hyperacidity to which as a possible factor in the causation of Blackwater Fever I have endeavoured to draw attention.

My experience has taught me to regard this question of hyperacidity as the keynote of Malaria and therefore of Blackwater Fever prophylaxis.

My advice therefore is to watch the individual carefully as regards his quinine prophylaxis.

Again the irregularly taking of quinine or the habit of taking the drug only when the individual thinks he requires it or feels off colour is to be deprecated on all sides. Still more the habit of taking a big dose of quinine at the commencement of an attack of Malaria. I do not think an individual can have any idea what harm he can do himself by so doing.

If therefore it is found that the quinine prophylaxis is insufficient I have made it a habit of giving quinine with an alkali for many years past. Dr. Gordon Thomson quotes Sinton (1923) as having recommended this but I am not the only observer who has made a habit of it for many years past. In 1906 I was recommended to carry in my armentarium a bottle of tabloids each of citric acid, soda-bi-carbonate and five grains of quinine with excellent results, and the mixture containing 60 grains of magnesium sulphate combined with quinine has been a stock medicine in West African dispensaries for many years also. The method of giving quinine with magnesium sulphate is an excellent one and its value as a prophylactic in Malaria cannot be too highly spoken of and I can most thoroughly recommend its daily use for patients who to the eye of the experienced medical man are not absorbing their quinine properly. Not only does the magnesium sulphate act as a stimulant to the liver but its value in counteracting hyperacidity is of the very highest.

Of course the most certain method for the administration of quinine is intramuscularly and I should not hesitate to administer a prophylactic dose of 3
I find that a daily dose of as much as 15 grains of quinine in divided doses can be given as a prophylactic quite safely to individuals who require it and I have seen great benefit result even in these big doses. Many individuals, particularly those who have had Blackwater Fever, can take the daily dose of 10 grains for months at a time without any harmful effect being manifested at all.

I know that many will not take quinine as they are afraid of it, and again women seem to be particularly adverse to taking it regularly also. I can say with truth that I have never seen the daily dose ever yet to have done any harm even to women but I have always been in the habit of recommending that they not take it during the menstrual period. There is no reason why the suitable and proper dose should not be found for all residents in the tropics. The administration of arsenic and iron in convalescence is too obvious to be referenced to. A sea voyage, or at least a change of air is clearly indicated, but while I have known individuals entirely recover their health in West Africa after an attack, I know many others who have not.

Finally I hope that nothing I have written in this essay will be taken to mean that quinine is a harmful drug; on the other hand to the normal individual quinine is perfectly harmless but it is obvious, I think, that those who become heavily affected with malignant Malaria become abnormal and may become idiosynratics to a drug they should otherwise freely tolerate and therefore the drug loses that protective faculty that they have a right to expect.

Koch is reported to have said long ago that quinine precipitates Blackwater and his words have been misunderstood and misconstrued so as to convey the impression that quinine is harmful whereas it is by no means so and if properly administered is entirely the opposite.

All I wish to plead is that every medical man whose occupation takes him to a Malarial district and whose work lies among a population of Non-Immunes, should exercise the utmost vigilance and miss no opportunity of advising all and sundry of proper quinine prophylaxis, bearing in mind that quinine can produce an acidosis which may possibly be an important factor in precipitating that explosion which produces an attack of Blackwater Fever, and that therefore, his treatment should be directed on the lines of combating that acidosis by the administration of alkalies with his prophylactic dose of quinine.
CONCLUSIONS.

The conclusions to be arrived at in this small essay are as follows:-

1. That malignant Malaria and Blackwater Fever are inter-dependant on the other.

2. That the prophylaxis of one is the prophylaxis of the other.

3. That quinine may be undoubtedly the precipitant of Blackwater Fever, and is the principal factor to be borne in mind in consideration of this disease.

4. That no absolute causative agent has yet been found but the possibility of quinine by producing hyperacidity acts on the red blood corpuscles at a time when the Serum has temporarily lost its protective faculty.

5. That every effort should be made by practitioners in the tropics to educate the Non-Immune population into an appreciation of quinine and in what directions its use and dis-use lies.

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