H A E M O G L O B I N U R I C
F E V E R.

A STUDY BASED ON CASES SEEN IN PALESTINE.

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by

CHARLES AVERILL.

Haemoglobin is the most important and most abundant constituent of the red blood corpuscles and is a complex compound of the proteid globin, or globulin, with another nitrogeneous derivative called haematin, an iron containing pigment. (1). It is a crystalline substance but forms an exception to the law of diffusion, in that it behaves like a colloid in not passing through a membrane without decomposition. (2). Haemoglobin is found in the blood in two forms: in arterial blood it is loosely combined with oxygen to form the compound called oxyhaemoglobin and is of a scarlet colour: the other form is the deoxygenated or reduced haemoglobin, the condition in which it is seen in venous blood where it is purple in colour. (1). Normally this substance is not found in the blood serum.

Haemoglobinuria is essentially a condition in which haemoglobin appears in the urine, the degree of darkness of the urine depending upon the amount of haemoglobin present. Haemoglobinuria may arise from a variety of causes which may be classified as follows:-

(1) Paroxysmal haemoglobinuria, a disease sui generis.

(2) Fatigue haemoglobinuria, occurring in men and horses after exertion.

(3) Haemoglobinuria occurring as a symptom in the course of other diseases.

(4) Haemoglobinuria as the effect of toxic influences from without the body (as opposed to an auto-intoxication).

(5) Infantile haemoglobinuria, occurring in young children, and apparently differing from the other varieties. (2).

I have chosen this method of classification of the haemoglobinurias from Charpentier, because it allows me to place Haemoglobinuric or Blackwater Fever in group 3. This I do, because I/

I consider that Blackwater Fever is merely a manifestation of previous infection of the individual from Malignant Tertian Malaria. This hypothesis, however, is by no means universally accepted, and much dubiety still exists with regard to its etiology. During recent years and particularly as a result of the late war, the study of the disease has received a fresh impetus. In various fields of operation it exacted no inconsiderable toll of life among the troops there occupied. Prior to the outset of the war the chief places where Blackwater Fever was to be found were West Africa, Assam, certain parts of India, East Africa, certain parts of Southern Europe, and certain of the Southern States of America. With the advent of war, large bodies of men were congregated together in certain of these areas under conditions of hardship natural to campaigning. Together with the prevalence of malignant malaria and the fact that great numbers of these men were unacclimatised to these regions, a great many of them, as a result, fell victims to Blackwater Fever. (3). Particularly was this the case amongst the troops operating in German East Africa, Macedonia, Mesopotamia, and to a lesser degree in Palestine and the Jordan Valley.

As previously stated much dubiety exists amongst medical men as to what is the actual cause of blackwater fever and from time to time different theories have been advanced in an endeavour to explain its origin. Still the etiology is looked upon as being obscure, in spite of the much excellent work done upon the subject. In deference to the opinions of the many excellent authorities on the subject, a brief resumé of the most important theories may not be out of place. These are as follows: (i) that it is a disease sui generis. This theory was first promulgated by the late Sir P. Manson in 1893, in a paper which he read/

read before the Epidemiological Society. He thought, because of its peculiar symptoms and distinct geographical distribution, that it might prove to be a disease by itself. (4). In 1898 Sambon suggested that, from its similarity to Texas Fever in cattle, it might be a form of babesiasis. (5). More recently, Leishman has described the presence of structures which he terms inclusion bodies, from the fact that he encountered them inside other cells. The latter cells were principally of the large mononuclear type of endothelial origin: possibly cells disrupted from the walls of small blood vessels or lymphatics. He describes them as usually assuming one of two forms, - namely, a structureless homogeneous form and a ring form; the former is the commoner and is usually of a faint chromatin colour. The ring forms, which are rare, are almost always coloured a deep pink, not unlike the chromatin material found in protozoa. As regards their frequency in any particular case they are never abundant. (6). Balfour also mentions a case in which he found these chlamydozoal like bodies described by Leishman. (7). Leishman suggests as an explanation of the frequent association of this disease with malaria that the two conditions may possibly be transmitted by the same insect harbouring within itself two different species of organisms, each one giving rise to its corresponding pathological disease in the human subject. (6). On the other hand, we have opposed to this view the statements of various authorities who state that these inclusion bodies can be demonstrated by different methods of staining, the peculiarity being merely one of technique. Moreover, these peculiarities of staining can be obtained not only in blood films from blackwater fever patients but also can be seen in films from almost any case of malaria. (8). Other observers go further, and state that they can be demonstrated in many conditions, viz. small-pox and pellagra, and are to be looked upon merely as endothelial cells which have been taken up by these large mononuclear cells. (ii) that the condition is due to administration of/

of quinine. The idea that blackwater fever was the result of taking quinine arose in Greece and was first suggested by Veretas in 1858. This theory was further substantiated by Tomaselli, in Sicily, who first published a series of cases of haemoglobinuria in which he came to the conclusion that this symptom of the disease was entirely due to the previous administration of quinine, and that the condition was merely one of quinine intoxication. (10). In more recent times, further attention has been given to this view from the fact that Koch has again brought the theory into the lime light from his observations on cases in Africa and from his coming to the same conclusion as Tomaselli. (16). This possibility has been vehemently denied by certain authorities but one has to admit that a form of quinine haemoglobinuria does exist, just as we may get haemoglobinuria arising after the administration of other drugs, viz. potassium chlorate, quinine haemoglobinuria, however, appears to me to be quite a distinct condition apart from blackwater fever, and would seem to occur only in those people who have a special idiosyncrasy towards the drug; otherwise, considering the amount of quinine that is consumed all the world over, haemoglobinuria would be one of the commonest pathological conditions known, whereas it is very rare. Consequently, to account for the appearance of haemoglobinuria due to quinine, in such a country as Africa, one is driven to seek help in the idea of idiosyncrasy. [redacted] toxic doses quinine seldom causes haemoglobinuria, and in addition [redacted]water has been known to exist for a very long time and for a considerable period was confused with Yellow Fever, even in the days before quinine had been introduced into certain parts of the world as a therapeutic agent. Moreover, we are at present aware of numerous conditions in which the drug may be taken in considerable doses and over a long period without any ulterior effects/

effects resulting. Furthermore, from the experimental work done with regard to the action of the various quinine salts upon the red blood corpuscles, it has been shown that, owing to the toxicity of quinine itself, its concentration in the blood cannot reach an amount sufficient to allow of its direct haemolytic action on the red blood corpuscles taking place during life; and moreover, the red blood cells from a case of blackwater fever are not more readily haemolysed by quinine bihydrochloride than are the red blood cells from a healthy individual. (11). In addition, cases of blackwater have been recorded amongst Europeans living in the tropics who have been known never to have taken quinine at any time, as also there are cases on record where the onset of haemoglobinuria has occurred quite independently of the intake of quinine. Another point that requires elucidation is the fact that the haemoglobinuria apparently bears no direct relationship to the actual amount of quinine taken. (12). Castellani considers that there is a condition of pure quinine haemoglobinuria and adds that it is common in cases of chronic malaria and malarial cachexia. He thinks, however, that some other factor is essential for the production of the condition, otherwise it would be very much commoner than it is. He remarks that administration of a dose of calcium chloride before giving the quinine will prevent the onset of haemoglobinuria in an individual otherwise susceptible. (5). Incidentally, Ponfick found that haemoglobinuria only occurred when the haemoglobinaemia exceeded $\frac{1}{60}$th of the total amount of haemoglobin contained in the red blood corpuscles. If the amount liberated were less than this, then the liver, if healthy, would be able to cope with the haemoglobin and to convert it into the bile constituents. Experimentally in the living rabbit, the dissolved haemoglobin disappeared from the blood plasma at approximately the/

the same rate as a monomolecular chemical reaction. (11). By others it has been stated that haemolysis has two groups, a combining and a destructive one. The first group must unite with the red blood cell before the second group can act upon the cell. The existing factors which give rise to this condition are; (1) renewed malarial paroxysms to produce sufficient toxins to overwhelm the blood cells. (2) then a lowering of the resistence of the body to extraneous conditions. (3) the administration of quinine which may act in one of two ways, first, by depressing the vitality of the body or secondly, by acting as the toxophore radicle of the haemolytic process. No definite result can be predicted from the ingestion of quinine. Haemoglobinuria has occurred after the taking of quinine gr. I. while in others it has not occurred after gr. XXX taken over a long period.(13). (iii) that it is the result of malaria. At the present time, this appears to be the most prevalent view and it is with regard to this view that I am chiefly interested, in the writing of this paper.

One point is definitely conceded by all and that is that haemoglobinuria consists in the alteration or destruction of the red blood cells to such an extent that an amount of haemoglobin is liberated beyond the capacity of the body to cope with. As a result it has to be got rid of somehow and in consequence it appears in the urine and gives rise to the condition known as Haemoglobinuria or Blackwater Fever. The essential termination of haemoglobin is its conversion by the liver cells into bile pigments, but owing to the excessive amount liberated, the liver hasn't time to reconvert it or possibly, the liver may be unable to do so from some other associated pathological condition in its own structure. Some authorities regard the condition of the liver as of great importance in the production of blackwater fever. All cases of severe malarial/

malarial infection do not give rise to haemoglobinuria. It is recognised, however, that if the liver is slightly congested from recurrent attacks of fever or from a drinking bout, the next attack of fever is often accompanied by an increase in the darkness of the urine passed; and the more congested the liver, the darker is the colour of the urine; so that, with some forms of malaria, it is difficult to say where the malaria stops and the blackwater fever commences. When, in such an infection as subtertian malaria, which requires that the liver above all other organs should be in good working order to deal with the excessive destruction of red blood cells, there happens to be congestion of the liver, which renders it incapable of dealing with the excessive amount of liberated haemoglobin, then the haemoglobin becomes a foreign substance in the plasma, and the kidneys are irritated and forced to try and get rid of it. (14). With regard to the excessive liberation of the haemoglobin from the red blood cells it is now generally agreed upon, that the liberation is due to the presence in the blood of a haemolytic agent, but what the nature of this agent is, still remains the baffling part in the study of the disease. Along with the bursting of the spores, most probably other substances are liberated along with the spores from the ruptured blood cells. (15). Any excess of bile salts that may be present in the blood serum do not appear to have any haemolytic qualities, as experimental injection of such salts into the blood stream appears to be quite innocuous towards the red cells and, moreover, the blood serum itself has strong inhibitive properties towards the bile salts. (17). The theory of immunity has thrown some light upon the subjects of haemolysis. The blood serum of one animal has the power of dissolving the blood corpuscles of another species. Bordet showed that if one animal were repeatedly treated with injections of corpuscles from another animal of a different species, the serum of the former animal acquired a marked haemolytic property towards the blood cells of the latter animal,

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so that if the serum of the former animal were added to a solution of blood corpuscles from the second animal the corpuscles become laked or haemolysed, i.e. their pigment was liberated. He also noted that if this haemolytic serum were heated to 55° C. it lost its haemolytic property but that this property was immediately restored to it by adding fresh serum from another animal altogether. Ehrlich and Morgenroth found, on examining the re-action further, that the heat-resisting substance, "immune body", combined with the red blood corpuscles at a comparatively low temperature, whereas the complement did not. They also come to the conclusion that immune-body and complement linked up with each other at 37° C. but that the combination was less firm. They decided, as a result of their observations, that the immune-body acts as a connecting link between complement and corpuscle, and was in consequence, called by Ehrlich the amboceptor. Such a haemolytic serum acts in the same way as bactericidal toxin, and furthermore, if a small dose of haemolytic serum be injected into an animal, no ill effects follow; and the dose can be gradually increased to such a degree, that the animal can be brought to a point of resisting such a quantity which, if given initially, would have killed it outright. Moreover, if from this animal a small quantity of serum be taken and added to the haemolytic serum, it will be found that the haemolytic serum has lost its haemolytic qualities. In other words, an antihaemolysin has been formed. (18). In proceeding to utilise this theory to explain the haemoglobinuria in blackwater fever, Bignami lays great stress upon the virulence of the aestivo-autumnal type of malarial parasites and emphasises the alteration that takes place in the red blood cells as the result of their invasion by this form of parasite. He notes that the corpuscle tends to shrivel up and to lose its contour and that its colouring matter is altered quite independently

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of the size of the contained amoeba. He states that the colouring matter goes through the same transformation as it does when actually contained within the body of the parasite and before it is there converted into black pigment. Seeing that this rapid necrosis of the red cell is not brought about by the actual increase in the size of the parasite only, it is probably due to the production of some poison by the amoeba contained in the corpuscle. This change is not noted in quartan and rarely in tertian infections. These facts seem to point to the production during its endoglobular existence of some substance which acts adversely upon the red blood cells. In consequence there is a corresponding change in the plasma, which change proceeds pari passu with, and as a result of the change which is taking place in the red blood cells. He considers that the red blood cells behave towards the organism much in the same way as the corpuscles of one animal do towards another. He considers, on the theory of immunity noted above, that there is formed in the plasma a substance which is haemolytic towards the red cells. (19). Proceeding along somewhat similar lines, Deaderick has further elaborated Bignami's theory. He considers the initial destruction of the blood cells to be due to the malarial infection, the sporulation of the parasites, and possibly also to the production and eventual liberation of toxins. The liberated haemoglobin is carried to the liver and there converted into bile pigments. Possibly the actual breaking down of the corpuscles due to the parasites is insufficient to account for the degree of haemoglobinuria present and he suggests that the liver cells themselves may possibly have taken on special haemolytic properties towards the corpuscles. In every malarial process there is probably a more or less continuous escape of haemoglobin into the blood plasma giving rise to haemoglobinaemia, which, however, it is within the power of the liver to cope with. It is this condition which gives rise to polycholia, a feature which is so characteristic of/

of malarial cachexia and chronic malaria generally. An infection so extensive that the decolorization of the corpuscles alone gives rise to haemoglobinuria probably never takes place in nature. Consequently, we are compelled to seek a further explanation of the process and to imagine the production of some substance which renders the corpuscles more vulnerable than usual. (20). When the haemoglobin reaches the liver it is acted upon by certain constituents of the hepatic cells which have a special affinity for it. When all these sunstances have been used up, which may frequently happen when the liver is not in a very healthy condition or has only recently been in action, or when the amount of haemoglobin for disposal is excessive, then we may suppose that the liver is stimulated to produce more of these substances. We may even go further and imagine the possibility of an over production of these substances with their consequent escape into the blood stream, where they may take on the function of ambo-ceptors with a special affinity for haemoglobin. That the liver is specially active at such a period can be proved microscopically when we see marked karyokinesis proceeding amongst the liver cells, as if they were in some way responding to the extra work demanded of them. Once the ambo-ceptor, according to Ehrlich's side chain theory, enters the blood, it meets the complement of the serum and the union of the two substances forms a haemolysin . If the union of these two substances to form a haemolysin is not counter-acted by the production of an anti-haemolysin, then the haemolysin acts upon the corpuscles to cause a haemolysis with a corresponding haemoglobinuria. If the production of the haemolysin does not proceed too rapidly and in too great quantity, then the body may have time to form an anti-haemolysin which may, in consequence, balance the haemolysin without destroying it. Probably as long as this state of equilibrium exists between the/

the haemolysin and anti-haemolysin, nothing happens. If, however, anything happens to disturb it in any way, viz. a chill, fatigue, exposure, a fresh attack of malaria, or even a dose of quinine, haemolysis takes place and haemoglobinuria is the result. (12). Under these circumstances the individual may be looked upon as being in a state of idiosyncrasy not unlike that of paroxysmal haemoglobinuria, where the serum contains a large amount of ambo-ceptor which readily unites with the erythrocytes at 0° C. In other words, the serum of both conditions has marked haemolytic properties. (21). The erythrocytes have a lessened degree of resistance and a state of haemoglobinaemia is always present, a state of affairs similar to that found in blackwater fever. (2). It has been shown that in the blood of haemoglobinurics, there is a dissolution of the patient's corpuscles in fresh human serum (fixation of the ambo-ceptor to the corpuscles) and also that the separated fresh serum (free ambo-ceptor and complement) has a solvent power on corpuscles. (2). Casagrandi has described the presence of a haemolysin in malaria which is almost completely masked by an anti-haemolysin. (12). Possibly the equilibrium may only require to be very slightly upset to give rise to a haemoglobinaemia, and possibly the presence of this haemoglobinaemia without haemoglobinuria might serve to explain the anaemia which is so marked a feature of malaria, and also the frequent relapses of the malaria itself when the number of parasites found are not in accordance with the severity of the symptoms. (12). Granting that the subtertian parasites appear to be the usual precursors of this grave condition, some authorities consider that the parasites or their toxins act upon the endothelial lining cells of the capillaries in such a way as to stimulate them to take on a phagocytic action towards the red blood corpuscles. Again, the theory of immunity is brought into play and this excessive phagocytic action is supposed to result in the formation of an anti-haemolysin within/

within the endothelial cells themselves, which is retained there until some exciting cause such as a chill, fatigue, fever, or quinine, causes its liberation. Once it is set free in the blood, it immediately attacks the erythrocytes, causing them to liberate their haemoglobin, principally in the liver, kidneys, and spleen. The first stage in the process is haemoglobinaemia; but immediately the liver becomes unable to utilise the haemoglobin, haemoglobinuria quickly appears. (22). In certain heavily infected areas where the individual is severely attacked by malaria, and is in a condition of chronic paludism, there is more or less a continuous destruction of his red blood cells going on. In consequence of the excessive demands made upon his blood forming organs, these organs are no longer able to produce healthy disease-resisting corpuscles and so as a result we get red blood cells of low resistence. Consequently a new invasion of parasites, even of the benign tertian type, with the toxins they produce, alone, or in conjunction with another poison introduced, viz: quinine, causes an extensive destruction of corpuscles, both infected and non-infected, with the result that haemoglobinuria appears. (22). A. Plehn states that, as the most vulnerable corpuscles succumb first, these patients are frequently able to tolerate quite large doses of quinine soon after the attack of haemoglobinuria has subsided, even in spite of the fact that it may have been the quinine which originally precipitated the onset of haemoglobinuria. (22). This theory of the formation of a haemolysin, according to Deaderick, serves to explain the occurrence of blackwater fever during and after malarial infection and possibly also accounts for the occurrence of the affection months after either the malarial infection itself has subsided or after the person has been removed from the blackwater area. Possibly also it may serve to explain the part played by quinine as a supposed cause of haemoglobinuria and also the independence between the latter and the sporulation

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of the parasites. (12). Certain authorities maintain that there is no real difference between quinine haemoglobinuria and blackwater fever and that the latter is practically never seen unless there has been a previous administration of quinine. They admit, however, that quinine per se cannot cause the disease but that soemthing else is required to render the individual susceptible to an attack of haemoglobinuria. This appears to me to be a candid admission that, after all, the two conditions are quite distinct. They go on to state, in support of their theory, that this idea is strengthened by the fact that the natives of endemic malarial districts rarely, if ever, suffer from haemoglobinuria, whereas in Europeans who are subjected to unnatural climatic conditions the condition is common. (23). The consensus of opinion appears to be in favor of the malarial theory. It is evident from statistics that those who take proper precautionary steps to escape malarial infection run a very good chance of never developing blackwater fever. Craig, (24) however, states that cases are on record where blackwater fever has occurred in individuals who have never had an attack of malaria. A series of observations carried out by A. Plehn in the Cameroons brings out the efficacy of the use of quinine as a prophylactic against malaria and its consequent bearing upon the incidence of blackwater fever. During 1897-99 he made observations on two series of colonists. The figures in the first row are of those who did not take quinine, and the second row of those who systematically did take quinine, i.e. gr. 7½ every fifth day.

Attacks of malaria.	Intervals between attacks in months.	Blackwater fever attacks.	Intervals between attacks in months.	Deaths from Blackwater Fever.
287.	2.	31.	18.5.	10% (about)
90.	5.	6.	74.0.	0.

Patients themselves have frequently been conscious of the fact that the taking of a dose of quinine has induced the passing of/

of black coloured urine soon after and cases are on record where such patients have submitted themselves for experimental purposes, and the point has been indubitably verified. In spite of these isolated cases, however, it is a matter of common experience that something else is required to explain the phenomenon. Some observers think that a distinction can be drawn between quinine haemoglobinuria and blackwater fever from their respective symptoms. They maintain that the condition of the latter is usually severe compared with the former and at the same time point out that fever is seldom, if ever, present in quinine poisoning; but I very much doubt this. Still, in view of the fact that all degrees from the mildest to the severest, may be encountered, it might be quite possible to distinguish at times between a case of quinine haemoglobinuria and true blackwater fever. The quinine, however, may simply play the same part as a chill does, and, consequently, more really depends upon the actual condition of the organism itself than the drug introduced. Consequently, the state of the blood at the time of the attack is of importance. It is quite possible, as A. Plehn states, that the haemolysis of the blood does not occur in the general circulation at all but possibly in the kidneys, a lesion of which is probably necessary for the precipitation of the condition. With regard to this suggestion, which will be discussed later on, it is interesting to note an observation that was made by Marchouse. He stated that, during the actual attack of haemoglobinuria, quinine could not be detected in the urine, but that immediately the haemoglobinuria subsided the kidneys began to secrete again and quinine once more made its appearance in the urine. (10). In view of the dubiety surrounding the etiology of this condition and the part that quinine plays in its production, some authorities divide the cases of blackwater fever into two groups - those which we are unable to associate with quinine, and this group is further sub-divided into those cases in which we get parasites present and those cases/

cases in which the malarial infection has run its course - the other group in which we definitely get the onset of the haemoglobinuria associated with the ingestion of quinine. But here again we have to remember that we may get in the same individual not only malarial relapses with haemoglobinuria and without it, but also haemoglobinuria following the administration of quinine and quinine given without haemoglobinuria following. In other words, neither malaria per se nor quinine per se can produce blackwater fever. The intermittent type of haemoglobinuria which occurs in malaria when the presence of parasites is demonstrated is generally the simplest form to explain, not only from the presence of parasites in the blood but also because it invariably reacts readily to the use of quinine. In a series of 55 cases studied by F. Plehn in Tropical Africa 24 cases were found to follow definitely with haemoglobinuria after quinine had been taken and for the most part the attack took place when the action of drug in the body was at its height. (19). Others state that frequently the attack of haemoglobinuria breaks out at the very time that the ague attack is expected. Possibly then it is not only a question of the quinine because from the previous remark it appears that the onset of haemoglobinuria was not unlikely even if quinine had not been taken. The taking of the quinine in view of the expected malarial paroxysm may be to a large extent a matter of coincidence with regard to the attack of blackwater. (25). As stated already, the experimental proof that quinine by itself dissolves the red blood corpuscles in those subjects in whom quinine haemoglobinuria occurs is wanting. Admitting a haemolytic action on the part of the quinine towards red blood corpuscles it is rather difficult to explain why it is that under apparently identical conditions we do not always get haemoglobinuria. Murri (19) who also investigated the/

the pathogenesis of a case of quinine haemoglobinuria in an undoubted case of this condition was unable to prove that the blood of his patient mixed with hydrochlorate of quinine dissolved in various quantities of physiological salt solution, and kept for several days, acted in any other way than the blood taken from a healthy individual. Bignami supposes the formation of a haemolysin and thinks that it is probably formed within the abdominal viscera, chiefly the liver and kidneys; and he assumes that there is an alteration in the plasma which is effected gradually as a consequence of a specific change in the blood corpuscles through which a certain number of them come to behave to the remainder much in the same way that the blood of one animal acts within that of another. In consequence of this change a substance is formed in the blood which under certain circumstances takes on haemolytic properties. (19).

From an earlier remark, it will have been noted that the geographical distribution of blackwater fever is very wide indeed. Although not co-endemic with malaria, it is nevertheless usually found in districts that are highly malarious. Still there are districts severely malarious in which blackwater fever has not been known to occur. Although haemoglobinuria is widely spread over the world's surface, it is very noticeable that, on the whole, it is more prevalent in lowlying districts, frequently of a swampy nature; a feature which serves to bring blackwater fever and malaria into close relationship. Again, it has to be remembered that cases have developed at high altitudes. Possibly this may be explained on the ground that the person may have been infected with malaria while stationed at a lower level and before proceeding to a higher area. A point, frequently very noticeable, is that change of district often brings on an attack of blackwater fever. More than likely, however, the circumstances necessary for an attack of blackwater fever had/

had been implanted in the person before his removal. Amongst Europeans, say in Central Africa, such changes of district, frequently precede the onset of haemoglobinuria, possibly because of the hardships associated with travelling. Like malaria, this disease is always present in the tropics, although epidemics, doubtful in character, have been described from time to time. On the whole the curve of blackwater fever shews no definite seasonal prevalence. In temperate climates it appears to follow closely on the outbreaks of malaria and is consequently more prevalent in these regions during the second half of the year. In Macedonia, during the war, it was commonest during November.

Idiosyncrasy does appear to play some part in this disease. It is fairly well recognised now that people who have once had an attack are liable to a recurrence. Racial susceptibility was at one time supposed to be an important factor as it was noticed that, after the advent of Europeans, Indians, and Chinese into Central Africa, the incidence of blackwater fever began to increase while the native population appeared to be immune to the condition. More than likely, however, this immunity is due to its having been conferred by previous infection during childhood, as it was noted that negroes, living in areas free from blackwater fever, were just as susceptible to haemoglobinuria when removed to a district where the disease was prevalent. (4). Amongst the conditions which predispose to the onset of this disease are ill health from any cause, poor food, hardships and, chief of all, previous malarial infection, particularly if this has been of the subtertion variety. Wherever the endemic index of malaria is high, there we get a large amount of blackwater fever. So far as is known, there is no active immunity to the disease and the only protection is that which is developed as a result of being a long time in an endemic area. (12). At times blackwater fever may appear in extensive epidemics/

epidemics in districts that have been free from the disease. Possibly, however, this may be due to an influx of susceptible persons into an endemic area just as happens in the case of Yellow Fever outbreaks. It is stated that 60% of the casualties in Von Lettow's force in German East Africa were due to an outbreak of blackwater fever. (4). Haemoglobinuric fever has been looked upon as a disease chiefly of white men but, as stated under the paragraph on idiosyncrasy, this is possibly explained by the fact that the natives have merely become immune through early infection and from living in an endemic area. All newcomers are alike susceptible if they have not come from a previous "blackwater" area. Males on the whole are more frequently attacked than females, but this is probably due to the fact that, as in other diseases, males are much more exposed as a rule to the various conditions that give rise to disease generally. Age does not appear to play a very important part as the disease has been observed in children as well as in adults. In America it appears to be more common before 30 (12).while in Africa 30 to 40 appear to be the favourite ages of onset, possibly because these are the commonest ages of the people who usually enter Africa. Some writers draw attention to a peculiar and occasional family susceptibility and one case is mentioned of a family of six children who all died of haemoglobinuric fever. (26).

Length of residence is more important and appears to play an active part in the causation of the disease. Most observers state that the disease is rare during the first six months of residence in the affected area. It becomes more prevalent during the second six months and during the second and third years it reaches its highest incidence. From this point it commences to decline in proportion to the length of residence in the "blackwater" area. Stephens gives the following figures to shew the effect/

effect that length of residence plays in the condition: (27)

First six months.	6.7%.
First year.	19.8%.
Second year.	30.7%.
Third year.	23.0%.
Fourth year.	9.5%.
Fifth year.	3.5%.
Sixth year.	6.6%.

The first six months' comparative freedom from infection may be accounted for by the fact that the individual is not generally badly exposed to infection during this period and possibly he may only have arrived at the end of the epidemic period. This, however, is lessened during the second six months, the second year, and the third year. The general diminution after the third year may be accounted for by a more marked resistence, actual or acquired, on the part of the individual and also to the weeding out of the more susceptible and weaker elements of the immigrants. As already stated haemoglobinuric fever is looked upon as a disease peculiar to low lying districts of swampy nature. Still, on examination of statistics, most cases are recorded as occurring in regions of high altitudes or even in districts quite distant and free from haemoglobinuric fever. This may be easily accounted for, as already stated. Most of these cases have usually previously resided in a heavily malarial infected area and for health reasons have had to remove. In the process of removal the hardships incidental to travel have not infrequently been the actual cause of bringing on the attack of the disease, the condition all the time merely having been latent, Anything, in fact, that lowers the resisting power of the body for the time being makes the person in consequence more susceptible to an attack/

attack of haemoglobinuria. Not much is known at present regarding the incubation period of this disease. Scott, in British Central Africa, noted that the onset of the disease often took place eight days after exposure to some lowering influence. Arkwright, on the other hand, from his record of cases states that the condition may appear as long as ten years after infection with malaria and, on the other hand, within fifteen days of infection with malaria. Be the incubation what it may, it is well known that the condition may remain latent for a long time, as the disease is occasionally seen in individuals in this country who have been home from the endemic area for some time. (12).

Symptoms. The onset of the disease is generally very sudden. After a chill or some severe form of fatigue, there is a marked rise in temperature which may be either irregular, intermittent, or remittent in type. Accompanying the sudden rise in temperature, there early appears the characteristic dark coloured urine, which may be copious in quantity and accompanied by pain during act of micturition. Frequently during this period of rigor the patient complains of pain and tenderness over the loins and back and, not infrequently, across the abdomen. On examination one may discover marked tenderness along the lower costal margins, together with enlargement of the liver and spleen. Tympanites is frequent and abdominal tenderness to palpation is common. Accompanying the above there is often nausea and vomiting, particularly of the bilious type. A few hours after the onset of the fever and accompanying the onset of the passing of dark coloured urine, the skin and conjunctivae begin to show an icteric tinge which usually goes on to a deep yellow colour as the disease progresses. During this stage the patient may feel/

feel restless and usually complains of considerable pain in various parts of the body. If the attack is a mild one, it may last no longer than an ordinary malarial paroxysm. If so, the patient may early break into a profuse sweat and begin to feel comfortable. With this stage of the disease, the urine gradually returns to its normal both in colour and amount. During the actual paroxysm the amount of urine passed may be either copious or very scanty in amount. Bile pigment may be occasionally found but more frequently it is haemoglobin that can be demonstrated spectroscopically. The colouration of the skin and conjunctivae usually lasts for a few days longer than the passing of the dark coloured urine. Patients usually recover very slowly and debility is pronounced for a considerable time after. During this period the fever may frequently recur and occasionally there may be a daily rise for some days. Often accompanying each rise of temperature there may be the passage of dark coloured urine; or again there may be only a single emission of dark urine. This phase of the disease is not common but, unfortunately, when present it may persist for weeks. In the severer and more common types, the temperature usually drops quite suddenly to normal and remains there. The vomiting is severe and sometimes continuous and is accompanied by the passing of dark coloured urine which may be also continuous, but at the same time tends to become gradually less and less in quantity until there is being passed merely a few drops of a dark, glairy, fluid at a time. During this stage of the disease the pains in the loins are extremely severe and rigors may be recurring at frequent intervals. If the complete or almost complete suppression of the urine is not averted then the prostration becomes pronounced and the typhoid state supervenes, usually with death following. Not infrequently the actual onset of/

of blackwater fever may be preceded by one or more attacks of malaria. The onset, however, may be entirely independent of any malarial attacks. The prodromata of this disease may, on the other hand, be so slight or gradual in developing and be accompanied by such a low temperature that the patient may be quite unconscious of the fact that he has ever had blackwater fever at all. In the majority of cases, however, the onset is with rigor and temperature, both as a rule being marked and accompanied by vomiting. Like certain types of malaria, the condition may set in with fever only and unaccompanied by any other of the classical symptoms of blackwater fever. Occasionally the rigor and the emission of the dark coloured urine have been noticed to accompany each other, the original temperature possibly having occurred 24 hours previously but being so slight escaped notice and so allowed the individual to be up and going about. (12). The characteristics of blackwater fever are Fever, Icterus, Vomiting and Haemoglobinuria.

The temperature usually ranges from about 101° F. to 105° F. It may be irregular, intermittent or remittent in character but, apart from this there is nothing noteworthy about it. Hyperpyrexia and sub-normal temperatures have been noted and described but they are unusual. The highest rise in the temperature takes place soon after the onset of the disease but from this point it early tends to fall progressively as the disease subsides. During the disease there may be frequently seen exacerbations of temperature, each invariably accompanied by a rigor and having every appearance of a septic process. Unlike a true malarial paroxysm the temperature in this condition shows no periodicity but tends to be maintained for a time after the passing of dark coloured urine has ceased, a period which may vary from a few hours to a few days. The type of temperature is quite independent of the severity of the disease but a marked peculiarity of this fever, although on the whole rare, is the subsequent rise

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in temperature that may occur after all the haemoglobinuric symptoms have subsided. The duration of this post-haemoglobinuric fever may be from 14 to 18 days. A recurrence of haemoglobinuria during this stage is not uncommon.

The changes in the urine in this disease form one of the most outstanding features of the condition. Just prior to the attack the urine may be perfectly clear and then in a very short time shew all the characteristics peculiar to it in this disease. In favourable cases, the return to normal of the urine may be just as striking. The quantity of urine passed may be very variable. In very mild conditions, neither the quantity nor colour may be much altered. Prior to the onset of the condition, we may actually get an increase in the amount of urine passed, but as the disease becomes established the amount of urine tends to decrease and the condition may pass on to suppression. If improvement is going to be the rule then the urine early shews an increase in quantity, while, if suppression is to be the result, the urine is frequently diminished in quantity early on in the disease. The anuria may be due to the plugging of the uriniferous tubules with blood debris. Total suppression of urine is always a grave condition and frequently ends in death. In such cases death is usually brought about by sudden syncope, coma, or uraemic conditions. Plehn reports a case where life was prolonged for twelve days after the onset of anuria. The characteristic colour of the urine is usually dark brown although it may vary from almost black to a very light brown colour. It is nearly always acid in reaction and, if allowed to stand for some time, it separates into two very distinct layers, the upper of a clear port-wine colour, while the lower, composed of about half the total quantity in the glass tube, is of a darker colour and consists of sediment in which is found an enormous amount of brownish granular material, together with hyaline and haemoglobin casts. Renal epithelium and broken down red blood cells are

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not infrequently also present. The prescence of these broken down red blood cells might almost suggest the presence of a renal haemorrhage and indeed, in the early days of this disease, it was called haematuria, because it was supposed that the condition was one of haemorrhage somewhere in the urinary tract. Cases are recorded where the amount of red cells has been very great and where, after centrifugalizing the urine, the clear super-natent fluid failed to give, spectroscopically, the bands of oxyhaemoglobin. (12). If there were a renal haemorrhage in blackwater fever the red cells escaping into the urinary tract would almost certainly be laked on mixing with the urine, if the specific gravity of the latter were 1004 or less, because when blood cells are added to a urine of such a specific gravity laking of the cells takes place almost immediately. If renal haemorrhage were really the cause of the haemoglobinuria, then the most likely spot for the escape of the blood into the urinary tract would be the glomerulus, since here it would have the best opportunity for mixing thoroughly with the urine. (11). On this hypothesis, the haemoglobinaemia, which is a common feature of blackwater fever, would be secondary, from the fact that the blood, in passing along the uriniferous tubules, would have a certain amount of its haemoglobin taken up by the lining epithelium and passed on into the blood stream. From experimental work it appears to be the haemoglobinaemia which is the primary condition, while the haemoglobinuria is secondary, and, in addition, this haemoglobinaemia was always accompanied by the appearance of granular casts in the urine. The exact location of the formation of these casts is still uncertain and so also is the site of elimination of the haemoglobin. The presence of epithelial nuclei in the granular casts contained in the renal tubules and later on voided in the urine seems to support the hypothesis that the haemoglobin may be eliminated by the tubular epithelium, the latter suffering a certain amount of degeneration in/

in the process. In experimental haemoglobinuria upon rabbits, Barrett and Yorke found in the kidney substance large granules densely packed together. Obviously, they state, with large granules densely packed together, suppression would be more likely to occur and particularly if the amount of water in the urine were diminished as this passed along the uriniferous tubules. (11). On the other hand the presence of red blood cells in the urine in blackwater fever does not stand in any clinical relation to the haemoglobinaemia. The appearance of the red blood cells appears to be due to the separation from the basement membrane of the epithelial cells of the uriniferous tubules, which is frequently seen in cases of suppression of urine, and which is also indicated by the presence of epithelial casts in the urine of non-fatal cases of blackwater fever. When granular casts are not detached with separation of epithelium, the possibility of a few red blood cells passing from the blood capillaries adjacent to the exposed basement membrane is always present and presumably accounts for their occasional presence in small numbers in the urine in blackwater fever. (11). The froth of the urine may vary much in colour and frequently appears to have a greenish tinge as if bile stained. The colouring matter is probably methaemoglobin although on examination spectroscopically, both oxyhaemoglobin and acid haematin are found and occasionally the bands of urobilin may be noticed. (28). Probably the methaemoglobin is not in true solution since it is usually found in greater quantity in the centrifugalized sediment than in the clear supernatent fluid. Moreover, in cases that are progressing favourably, methaemoglobin disappears from the fluid part of the urine first. (12). When urine from blackwater fever is made alkaline with potash and then boiled, a purple colour is formed which, when spectroscopically examined, gives the bands of haemochromogen, shewing that the urine contains reducing bodies. (23). The specific gravity varies inversely with the amount passed./

passed. Albumin is always present, often to the extent of 1.6% and with the escape of haemoglobin there is always a certain amount of serum globulin present as well, so that when the urine is boiled it almost solidifies. Ordinarily the albuminuria continues for a few days after the attack, when it gradually disappears. In other cases it tends to persist, and then it indicates the development of nephritis. (28). As previously noted, it has been stated that quinine is not excreted during an attack of haemoglobinuria but that on the cessation of the latter the kidneys commence to secrete it again. Against this is the statement of Deaderick, who maintains that quinine is excreted in increased amount during the actual attack of haemoglobinuria and he looks upon this as an indication that the organism is incapable of protecting itself from the poisonous alkaloids by splitting the molecule as is usually the case. (12). Blackwater fever, therefore, from the above description, appears to bear a very close resemblance to a general toxaemia, affecting chiefly the kidneys. (29). A few hours after the onset of the disease jaundice begins to make its appearance, and the skin and conjunctivae become deeply yellow tinged. Pruritus is not common and petechiae and herpes are rare: by some the occurrence of the latter is looked upon as a grave omen in this disease. (12). Oedema may be present and depends upon the state of the kidneys. When the disease is going favourably we usually get a profuse sweating but, on the other hand, it may be the ushering in of a fatal termination. Certain authorities maintain that jaundice is not the proper term to use in discussing this disease, as the word implies the presence of bile pigment in the blood plasma and in the urine, a state of affairs which, as we have seen, rarely if ever occurs in blackwater fever. It has been asserted by Koch that after the administration of quinine, an attack of icterus may occur, the liberated haemoglobin being converted into bile pigment which appears in the urine. However, testing of either the urine proper or its deposit fails to show the presence of bile pigment. In experimental haemoglobinuria/

haemoglobinuria in rabbits, negative results were also obtained for bile pigments in the urine. Consequently, the tinging of the skin and conjunctivae is not a true jaundice due to the presence of bile pigments, although the causa causans is nevertheless derived as a result of the breaking down of the haemoglobin. (11).

Vomiting. This occurs usually very early in the disease and is a very distressing symptom. The stomach contents are completely evacuated at the beginning but in spite of this the vomiting continues. The ejected matter assumes a yellowish green colour due to the presence of bile but may even go on to develop a dark coffee ground colour not unlike that seen in the vomiting of Yellow Fever. The vomiting is quite independent of the intake of food and is probably of a nervous character. Nausea is invariably an accompaniment of the vomiting and in proportion to the severity of the latter. Occasionally the vomiting may be altogether absent or only very slight. The bowels may be constipated throughout or there may be a diarrhoea of a greenish material not unlike the urine that is passed. Dysenteric or haemorrhagic symptoms are rare although there is frequently meteorism or tympanites present. Pain, as already stated, is nearly always present and is chiefly located in the upper abdominal region just below the ribs. The pulse is very rapid, out of all proportion to the degree of fever present; it is full, however, and of good tension. As the disease progresses gradually the tension becomes lower and the pulse is easily compressible. As one would expect in a febrile condition of this severity very haemic murmurs are common and chiefly situated at the base of the heart. With the onset of recovery, both pulse and heart rapidly return to the normal. Respiratory symptoms are similar to those of any other acute febrile disease. Hiccough is almost always present in severe cases and at times forms a very distressing symptom. Manson saw a case in London where the fatal issue/

issue appeared to have been brought about by the persistent hiccough. (4).

Anaemia is usually very pronounced and becomes extreme in the majority of cases, as one would expect from the great destruction of red blood corpuscles. The number of erythrocytes may drop during an attack to 1.000.000 or even less. Examination of the blood shows it to be thinner than normal. Macrocytes, microcytes, poikilocytes, polychromatophilia and basophilia are usually all present, although any of them may be strikingly absent. Certain authorities lay great stress upon the condition of polychromatophilia which is present, and designate the cells so affected as polychromatocytes. Pathologically, these cells appear in the blood as a result of anaemia, and are an intermediate stage in the development of the red blood corpuscles. (3). Possibly they are the result of toxic substances acting on the bone marrow. In all cases of malaria which have been improperly treated and particularly in chronic malaria, these cells are always present and give signs of the state of the organism. In blackwater fever they disappear with the onset of an attack but rapidly appear again when the haemoglobinuria has subsided. (31). In spite of the marked haemolysis that is going on, a blood film may shew remarkably little departure from the normal. Nucleated red cells may be present but are chiefly found during convalescence. The colour index usually shews nothing very definite, although it tends to fall slightly during the course of the disease, but it rapidly recovers on the onset of convalescence. The percentage usually runs pari passu with the red cell count. During the height of the disease a leucocytosis is stated to be the rule, the polymorpho-nuclears preponderating. During the period when the temperature is falling and convalescence is setting in, there is a relative increase of the large mono-nuclear leucocytes, while/

while in reality a general leucopenia is present. (12). Certain observers noted in spleen films from a case of blackwater fever, phagocytosis of the red blood cells going on. In a differential count of 2,200 spleen cells 1.7% were large macrophages containing red blood corpuscles and 1.3% were small mononuclear cells also containing red corpuscles. In both kinds of cells were seen red blood corpuscles shewing no evidence of any alteration whatever, corpuscles which were more or less decolourised and clear spaces about the size of a red blood cell. Further examination of the enclosed cells failed to show any parasites or even evidence of parasitic invasion. (32). Deaderick considers this as important in point of view of the theory that the haemolytic substance may in large part be found in the patient's own body as a result of auto-immunization against his own blood corpuscles. (21). With regard to the presence of parasites in the red blood corpuscles, those cells which are infected with parasites are usually the first to be dissolved, so that plasmodia tend to disappear rapidly from the peripheral blood with the onset of haemoglobinuria. (33). Stephens has collected the following series of cases where the blood was examined before and after the onset of blackwater fever for the presence of parasites. (27).

Day before haemoglobinuria.		Day during haemoglobinuria.		Day after haemoglobinuria.	
Cases.	Positives.	Cases.	Positives.	Cases.	Positives.
67.	49.	162.	77.	160.	37.
	73%.		47.5%.		23%.

Seeing that the parasites rapidly disappear from the blood in blackwater fever, Stephens and Christophers applied two other tests for the detection of malaria, viz:- the presence of pigment, leucocytes, and an increase in the percentage of large mononuclear leucocytes. It has been said by certain authors that the latter is simply a sign of a protozoal infection. While the evidence is wanting that this is true as a general statement, yet, as/

as in some cases it may be true, attention will be chiefly given to the pigment. (27).

	First Day.		Second Day.		Fourth to sixth days.	
	Cases.	Positives.	Cases.	Positives.	Cases.	Positives.
Parasites only.	10.	6.	7.	0.	10.	1.
Pigment.	10.	8.	7.	6.	10.	4.

From the presence of pigment, pigmented leucocytes and the great increase in the large mononuclear leucocytes, the evidence appears fairly conclusive that there exists between blackwater fever and malaria a very close relationship indeed.

The degree of change which takes place in the plasma has been measured with the spectroscope in a number of cases of blackwater fever, in three of which the observations were made before, during and after an attack. This method showed a small amount of dissolved haemoglobin in oxalated blood plasma of a healthy man, but it rarely exceeded .15%. In blackwater fever occasionally only these same small amounts were found even during an attack, but in the considerable majority of cases the amount was greatly increased, rising from .40% to .95%. There was also a close relationship between the amount of colouring matter dissolved in the blood and the degree of haemoglobinuria present at the time. The same observers carried out a further series of experiments on rabbits to determine if the injection of a solution of haemoglobin into the veins would produce haemoglobinuria, and plotted out curves of the amount of this substance in the blood and the urine at different intervals after the injection. When the urine was obtained by continuous catheterization, they found that the rate of excretion continues to rise for some hours after the injection until the amount in the urine exceeds that in the blood, and later it slowly falls again. It is thus clear that the presence of excess of dissolved haemoglobin in the blood does not in itself produce haemoglobinuria, and that such excess is commonly present during the course of blackwater fever. (34).

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The blood platelets are numerous and of large size and the alkalinity of the blood is often diminished. Although the destruction of the red blood corpuscles may be very great, the specific gravity of the blood continues to remain high. (12). It has been remarked that there is occasionally a remarkably low tonicity of the blood in blackwater fever: in other cases it has the normal value or may even be slightly raised as in the case of malaria. The loss of normal value in blackwater fever may be due to the fact that the weak corpuscles, i.e. those of high tonicity, are destroyed; or again, it may be due to the fact that the tonicity of the corpuscles as a whole is completely changed after the liberation of their haemoglobin. (35). In itself blackwater fever may not be very painful, but the vomiting and thirst are usually sufficient to make the patient feel very ill and these, coupled with the passage of very dark urine, have frequently a very marked effect upon the patient's outlook with regard to the disease.

The causes of death are various. The most important is that of suppression of urine: next we might consider exhaustion and cardiac asthenia as the other commoner causes.

Suppression of Urine. This is by far the commonest cause of death in blackwater fever. It may come on at any stage in the disease and may occur when the patient is actually convalescing and the urine has almost returned to its normal. Although suppression of urine is common as a cause of death, uraemic symptoms are by no means so common as they are in other conditions where we get suppression of urine occurring. This may possibly be accounted for by the fact that the vomiting and diarrhoea are frequently very pronounced in this condition; and possibly also due to the diminished metabolism which results from the defective oxygenation. (12).

Exhaustion usually results from the extensive destruction of the/

the red blood cells, combined with the inability of the blood forming organs to make good the loss. Occasionally the hiccough, when present, increases the exhaustion.

Cardiac cases may result from asthenia brought about by the improper blood supply to the muscle of the heart: or perhaps may be due to actual thrombosis of the heart itself. Plehn regards this latter event as a not uncommon cause of death in blackwater fever. (12).

The Mortality varies very much in different epidemics. Numerous cases may be so slight as not to indispose the individual and so escape notice. In Southern Nigeria, in some years, and in Algeria, it has been as high as 50%. On an average the case mortality of blackwater fever may be put down at 25%. (4). In the light of our present knowledge, it is almost impossible to forecast an attack of blackwater fever. Observers with considerable knowledge of this disease state that people who have been resident in a blackwater area for six months and who have been subject during that period to recurrent attacks of malaria improperly treated with quinine should be looked upon with suspicion. The suspicion, they say, may be increased if these people show a tendency to drowsiness, mental apathy with physical restlessness and a slight yellow tinging of the skin and conjunctivae. The presence of albumin should always be looked upon with suspicion as its presence is usually absent in other tropical fevers. Koch designates as "Blackwater Candidates" those in whom, a few hours after taking quinine, the temperature rises to 38° C. or more, the urine turning dark in colour with the scleras showing a slight yellow tinge the following morning. (12). Young (31) considers, as already stated, that the presence of basophilia and polychromatophilia as very suggestive indeed.

Complications are rare in this disease. Nephritis is practically always present to some degree or other and as stated may frequently/

frequently cause death. The nephritis on the one hand, may be very rapidly recovered from, or on the other, it may resolve very slowly and so account for the prolonged convalescence and consequent ill heath which so frequently follows this disease. The changes in the kidneys may be considered as due to the action of the haemoglobin upon the tufts and tubules. Other complications are very rare although many have been described.

Morbid Anatomy. Symptoms vary greatly according to how recent and severe the attack of malaria has been. Practically all the pathological changes found in Malaria are also present in blackwater fever. The most pronounced changes depend upon the haemoglobinuria and the production of bile. Consequently, as is to be expected, the most marked morbid changes are to be found in the kidneys, spleen and liver.

The Kidneys are usually congested, consequently enlarged and softer, and weigh more than normal. On section the tubular areas may show up markedly owing to the deposition of pigment, the colouration being more pronounced towards the apices. (12). Frequently, however, they are pale and anaemic. On the surface of the organs are often scattered small brownish plaques, the result of diffuse pigmentation of the uriniferous tubules. The great majority of cases show wedge shaped, haemorrhagic foci with bases, which may be several cms., square, towards the surface and their apices towards the medulla of the kidneys. Pellerin observed these foci only in the cortex, and never in the columns of Bertini or in the pyramids. In addition, this observer called attention to older cystic cavities situated in the cortex and filled with a dark cloudy fluid. It is doubtful whether these areas, which Pellerin regarded as haemorrhages, are not, rather infarcts. Their form certainly suggests this last view, though positive haemorrhages do occur in the pyramids. (28). In certain recorded cases, in which/

which death took place on the day on which haemoglobinuria first appeared, it is possible, if not probable, that the condition of the kidneys would have led to suppression of urine if life had been prolonged. (11). These same observers divide the points for consideration with regard to the kidneys into four groups: (1) the presence of granular material in the lumen of the renal tubules: (2) degenerative and other changes in the renal epithelium: (3) fluid distension of the renal tubules: (4) interstitial changes. (11).

The first condition was always present ina more or less marked degree. The state of the renal epithelium is not described alike by all observers, some finding the epithelium quite normal, others meeting with cloudy swelling, coagulation necrosis, or fatty degeneration, or again the epithelial cells were found loaded with coloured granules. Werner describes four cases in which this condition was present, but those are not improbably cases in which suppression of urine would have been observed if the patients had survived. Interstitial changes (presence of epithelioid cells and leucocytes) were usually met with. In any attempt to apply these points to explain the condition of the kidneys during simple haemoglobinuria, it is necessary to consider those changes which are necessarily present and those changes which occur as a secondary process in the disease. We can easily infer from examination of urine in blackwater fever that granular material is present in the tubules of the kidneys during the actual haemoglobinuria. If haemoglobin is eliminated by the renal epithelium, then in all probability these cells contain brown granules of haemoglobin during the haemoglobinuria. This, however, is very rarely seen experimentally. (11). Possibly the presence of granules in the lumen of the renal tubules is not the sole change which

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the kidneys present during haemoglobinuria. As regards the degenerative changes occasionally observed in the renal epithelium after death, the fact that the urine soon becomes normal after the attack of blackwater fever has ended, no trace of coagulable proteid remaining in the urine after haemoglobin has disappeared, tends to prove that as far as the haemoglobinuria is concerned, the renal epithelium is unaffected. Possibly haemoglobin is eliminated by healthy epithelium. No parenchymatous change of the epithelium necessarily attends the appearance of haemoglobinuria, nor does the constitutional disturbance accompanying blackwater fever seem to be usually accompanied with secondary affection of the renal epithelium. (11). Whether the granular material in the renal tubules ordinarily causes some obstruction is not definite. An increased flow took place in the experimental haemoglobinuria in rabbits. In blackwater fever, on the other hand, diminution in the quantity of urine passed is common. The fact that interstitial changes are usually absent after death from blackwater fever may be regarded as negativing the necessary association of nephritis and blackwater fever. (11). Consequently we may say that the production of haemoglobinuria in blackwater fever is quite consistent without there being any pathological condition of the kidneys being present. Barrett and Yorke state that from their observations, an attack of haemoglobinuria does not necessarily damage the kidneys. (11).

The Spleen, as in malarial infection proper, is always enlarged, and sometimes to a great extent, the enlargement being chiefly due to congestion. From the repeated attacks it may come to be so large that it eventually comes to occupy the greater part of the abdominal cavity. The capsule of the organ, particularly on its convex aspect, is greatly thickened and in parts adherent to the abdominal wall itself. The

substance/

substance of the organ is pulpy and very friable on being handled. Many of the trabeculae of the organ become greatly hypertrophied owing to the increase which takes place in the pulpy substance of the organ. (12). The malpighian bodies may be very prominent and necrosed to a greater or less extent. The necrosis is evidenced by the presence of fibrin, nuclear remains, leucocyte invasion, and oedema. Melanin may be scanty or abundant, occurring in the phagocytes. Haemosiderin may also be present. Large phagocytes, crowded with nuclear remains, cell debris, red cells and leucocytes, may be seen in the necrosed areas. Pigmented leucocytes and parasites may be found post morten, when absent from the blood during life. (27). The small vessels of the spleen are usually greatly hypertrophied and the hypertrophy, in many places, is so great as almost to obliterate the lumen of the vessels themselves. (12). The Liver is usually much enlarged and congested and on microscopic examination shews excess of pigment. The liver structure may vary considerably in colour. The capsule is usually slightly adherent and may shew thickening due to old inflamation. The pigmentation is invariably extensive, shewing evidence of the considerable blood destruction that has taken place. The cells themselves contain yellow pigment and haemosiderin and from the abundance of these substances contained in the lining cells of the arterioles, the course of the latter can be very easily traced. (3). Thrombi may occur in the arterioles due to blocking from the contained pigmented material and debris. Cloudy swelling and fatty degeneration of the hepatic cells is not infrequent. Biliary infection of the cells is common, more severe in the centre than towards the periphery. Karyokinesis of the liver cells is usually pronounced and, as already stated, this active process is looked upon as an attempt on the part of the liver to meet the extra demands made upon it to deal with the excess of liberated haemoglobin. The gall bladder is usually enlarged and full of very/

very dark inspissated bile. (3).

The stomach and intestines may show very few pathological changes, except that the coat may be bile stained. There may, however, be a degree of amyloid degeneration of the mucous membrane of both stomach and intestines; there may also be small haemorrhages into the coats of the tract.

The pleurae may show punctate haemorrhages and there may be a varying amount of serous fluid in the sacs.

The cut surface of the lung may be pale and frothy and exude a serous coloured fluid. Hypostatic congestion is not uncommon in severe cases. (12). As in other severe fevers, the heart is usually somewhat pale and flabby but the cells do not usually show any signs of degeneration. The capillaries sometimes show contained parasites. The brain is pale and as a rule unpigmented: the lateral ventricles may be distended with fluid.

Diagnosis. Dark coloured urine may be passed in a variety of conditions, and if, say, a case of paroxysmal haemoglobinuria were to occur in a blackwater area it would certainly be mistaken for blackwater fever. If, again, only methaemoglobin be found, the colour of the urine is then so like that in many other conditions, that the difficulty in diagnosis can be readily appreciated. In all cases of blackwater fever, if the urine be boiled the albumin coagulated will be of a dark brown colour. (36). With a previous history of malaria, the diagnosis is facilitated and together with vomiting and jaundice, this should be fairly easy. Examination of the blood may help by revealing the presence of large mononuclear leucocytes and pigmented leucocytes. The other conditions with which blackwater fever might be confused are Yellow Fever and Bilious Remittent Fever. In the former condition we usually find the new comers into a district attacked while blackwater fever usually attacks older residents and in addition, while one attack of Yellow Fever usually confers immunity, a patient who has once had an attack of blackwater/

blackwater is apt to have recurrences. Haemorrhages are common in Yellow Fever but rare in blackwater. The pulse in Yellow Fever is strikingly slow whereas in blackwater fever the reverse is the rule. In Bilious Remittent Fever the onset is slow and the jaundice develops gradually, while albuminuria is not constant and the urine is coloured by bile instead of haemoglobin.

Prognosis is bad and entirely depends upon the amount of urine passed. If the urine steadily decreases in amount, then the outlook, indeed, is grave. Anuria is always serious and is usually the sign of a fatal termination. Much can be learned from the amount of urine passed. If a patient survives a period of suppression, he not infrequently succumbs during convalescence from resultant nephritis or exhaustion. Severe and continuous vomiting is dangerous, while diarrhoea, on the other hand, is not infrequently useful in so far as it gets rid of some of the toxic elements and prevents any tendancy there may be to the onset of uraemic symptoms. Drowsiness with a gradual diminution in the quantity of urine passed, usually serves to warn one of the near approach of death. Deaderick (12). considers that the prognosis is better, the more quinine there has been taken before the onset of haemoglobinuria, and granting that the condition is not aggravated by more quinine.

Prophylaxis. If this disease is to be looked upon as a result of malarial infection, then the prevention of the one is the prevention of the other and this seems to apply with even greater force in blackwater fever than in malaria. A. Plehn in 1898-99 found that, amongst the officers of the Cameroons who used no prophylactic quinine, there occurred in 578 months of residence 287 cases of malaria and 31 of blackwater fever and that 10% of the blackwater fever cases terminated fatally. During the same period amongst those who used prophylactic quinine, there/

there were in 446 months of residence 90 cases of malaria and 6 of blackwater fever, of which none were fatal. Thus while malaria was reduced by half, blackwater fever was reduced by one quarter, (12). Even more striking figures are given by Fink, (37). with regard to the effect that quinine has in preventing malaria. In 1906-7 quinine was given irregularly amongst certain battalions of the Burma Police, the average strength of a battalion being 1400, while in 1908-9 it was given regularly. The admissions for malaria are as shown.

	Indoor cases.	Outdoor cases.	Total.
1906.	1602.	3372.	4974.
1907.	1695.	2714.	4409.
1908.	328.	200.	528.
1909.	340.	107.	447.

During the second two years only four cases of blackwater fever occurred. The preventive method is quinine in some form or other, administered at varying intervals. This prevents the onset of malaria and in the present state of our knowledge, while we look upon malaria as the forerunner of blackwater fever, then the prevention of the one is the prevention of the other. This drug may be administered as quinine sulphate gr. X. every four or five days. Another point of considerable importance is to continue the use of quinine, even though the individual may have been resident in an endemic area for a considerable time.

Treatment. Considering the diversity of opinion that exists as to the part that quinine plays in the production of haemoglobinuria, it would be strange if there were not a corresponding doubt with regard to whether quinine should be given or withheld. From various and reliable sources discussing the indiscriminate administration of quinine in all cases of blackwater fever, it appears that the death rate is much higher than in those cases where it is withheld altogether. Still, most authorities admit that it is going/

going too far to debar quinine altogether from the table of treatment. In any case of haemoglobinuria, quinine must be given cautiously, because there are times when it is well nigh impossible to decide whether quinine should be given or not. Hannaberg states that with regard to its administration; (1) if, without quinine preceding, haemoglobinuria appears and the blood film shews the presence of parasites, then give the drug. (2) if an attack of haemoglobinuria occurs after a dose of quinine but the patient was able to take it previously without any ill effects and parasites are still persisting in the blood, then continue the administration of the drug but with great caution. If the paroxysm of haemoglobinuria occurs within a few hours of the taking of quinine, then further administration depends upon the presence of parasites in the blood. (3) if the history of the case proves that the patient previously suffered from haemoglobinuria following the ingestion of quinine and the examination of the blood shows the absence of parasites, then do not give quinine. (12). From the above it will be seen that considerable stress is laid upon the presence or absence of parasites before deciding whether quinine should be given or withheld. Deaderick thinks, however, that this rule is not infallible as in the great majority of cases, if examined sufficiently early, parasites are present; whereas, if examined well on in the course of the disease, parasites are invariably absent from the peripheral blood. Consequently, it does not appear as if much benefit would be derived from the administration of quinine when the disease is well on its way. He further states that the cases in which quinine is indicated are: (1) those in which the parasites show no tendancy to disappear 48 hours from the onset of the condition. (2) those infrequent cases of intermittent haemoglobinuria where the outbreak of fever corresponds with the sporulation of the parasites. (38).

Quinine, in large or small doses, according to Lovelace, (38). was, in his series of 514 cases, an invariable antecedent of haemoglobinuria/

haemoglobinuria and under no circumstances at all should it be given to a blackwater fever patient during the period of haemoglobinuria, nor for several days after. The effect of the paroxysm of haemoglobinuria is itself that of a drastic, but temporary therapeutic agent, decimating the malarial parasites in the patient's blood much as a single intravenous dose of salvarsan decimates the spirochaetes of syphilis in the lesion of that disease. If it is decided to give quinine then it is probably best to give it either intravenously or subcutaneously, because, when given by the mouth, it is frequently retained with difficulty by the stomach and it is questionable if the amount of quinine absorbed through the stomach wall is sufficient or efficient for therapeutic purposes.

In the mildest cases even, the patient should be confined to bed from the very beginning. The cardiac condition should be remembered as a fruitful source of trouble and in addition the patient should be moved as little as possible because not only has movement caused heart failure but it has also been known to bring on anuria. Patients should be most carefully guarded against chill in view of the fact that we do not yet definitely know what part this plays in the production of haemoglobinuria. In view of the congested state of the liver that is invariably present, it is well to endeavour to increase hepatic action as much as possible. Some give ½ to 1 oz. of magnesium sulphate on the principle that it flushes out the stomach and duodenum and clears away any excess of bile that may be present and at the same time tends to relieve the hepatic congestion. It also, sometimes, helps to relieve the vomiting which is so marked a feature of this disease. If vomiting is not severe, then a light fluid diet may be given with good results. Unfortunately, there is no specific for this disease. Many things have been tried but none so far have proved very satisfactory. Methylene blue has been used but it is unsatisfactory owing/

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owing to its irritating action upon the kidneys and the fact that it masks the real colour of the urine. Salicylic acid has been tried but it is equally unsatisfactory. With a view to stopping what some call a haemorrhage, various astringents have been tried, all of which have proved useless. One point to remember is to refrain from the use of all drugs that in any way tend to irritate the kidneys. Other authorities advocate the use of chloroform on the principle that it (1) controls the vomiting, (2) increases the output of urine, (3) diminishes the albuminuria. Quennec used the following formula; Chloroform grm., 6 Gum arabic grm., 8. Sweetened water grms., 250. This amount is given daily, a small sip being taken every 10 minutes. In addition, he gave quinine grm. I. subcutaneously every day along with sulphate of soda and senna per rectum. Against this treatment is the argument that chloroform is a cardiac depressant, irritates the kidneys, and lowers the blood pressure. Cardamatis gives ether in every case, the dose being a teaspoonful every 3 hours, which he gradually increases if the amount of urine being passed tends to decrease. If suppression sets in, he gives one teaspoonful every hour, and at the same time injects 1 c.c. hypodermically every 2 or 3 hours. By this treatment, he maintains that the pulse is strengthened, praecordial anxiety along with the dyspnoea and vomiting are all diminished and, moreover, that a profuse diuresis is brought about by its administration. A popular form of treatment is Hearsey's modification of Sternberg's Yellow Fever treatment. Sternberg's original formula is: Soda Bicarbonate gr. 150. Mercury perchloride gr. $\frac{1}{3}$, Water 2 pints. Sig. $1\frac{1}{2}$ ozs. every hour. Hearsey modified this and gave in cases of haemoglobinuria Sod. Bicarb. gr. X. Liquor hydrarg. perchlor. m. XXX. every 2 to 3 hours. Calcium Chloride has also had its advocates, but its results appear uncertain. It is stated that, in people who are liable to an attack of haemoglobinuria following the administration of quinine, a dose of calcium chloride will prevent the onset. (5). In cases of suppression with symptoms of uraemia threatening, decapsulation of the/

the kidney has been done: but the results have not been strikingly successful. (39). Most of the recorded cases show the passage of a very small quantity of dark, thick, blood stained fluid for a short time and unfortunately, too often just preceding death. Cassia Beareana (13) has its advocates and they claim for it that it acts not only as a cardiac tonic but also as a diuretic and a diaphoretic. These three actions, they state, must be useful in this condition and that it certainly has a tendancy to break the fever, and, in cases of malignant tertian malaria, bordering on blackwater fever, it has acted in its antiperiodic effect just like quinine. Vitex Peduncularis, (4) a plant found in the Nagpur province of India, where it has been used in fever conditions by the natives for a long time, has been described as useful both in malaria and blackwater fever. The infusion is made with one, two or four ounces of the leaves in 40 ounces of boiling water, and is given in 8 to 10 ozs. of the 1 in 40 infusion in 24 hours, this being quite free from any toxicity. The fever on the whole does not run a sufficiently high course to call for any active interference in the way of antipyretic treatment. If the fever should be high, cold baths are certainly contraindicated, as it is known that cold may have a deleterious effect upon the red blood corpuscles. Morphia should be given unhesitatingly if required and may do considerable good in relieving the restlessness that is so frequently present. Diuretics probably do more harm than good and the only diuretic that is of any use and which may be used without any danger is water. The latter is a useful non-irritating diuretic and as the kidneys are often blocked up with debris it may possibly do good in helping to flush them out. The administration of plain water may be modified and given in form of saline solution, preferably as a hypertonic solution. Some maintain that it should be given early in the disease and continued with by every route possible, including rectal and subcutaneous. (41). The after treatment is mainly dietetic and should consist/

consist, chiefly of liquid and non-nitrogenous substances for a considerable time after the haemoglobinuria has passed away in view of the fact that the kidneys are usually damaged, to a slight degree at least. Tonics can be resorted to, to build up the strength during convalescence if desired. A point of considerable interest is, how soon after the subsidence of blackwater fever may quinine be given. It is difficult to decide at times what to do; but one must always remember that one is faced with two considerations: if quinine is given too soon after the disease, haemoglobinuria may be again precipitated while on the other hand, if postponed, it may expose the patient to a fresh attack of malaria and a subsequent attack of blackwater fever. On the assumption that most of the susceptible cells have succumbed during the disease and that the cells now present are composed of the more resistant and newly formed ones, quinine may be commenced with in very small doses and the result of administration carefully watched while the dose is being gradually increased.

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