physician and mother at the bedside of a small boy, may be quoted in part as follows:

"HOW INNOCENT IS A 'STOMACH-ACHE'?"

A 'Stomach-ache' means *something's* wrong.

True, it may be nothing dangerous. But, because it *can* be very serious, no one should treat such a warning signal lightly. . . .

1. *Call a doctor.*
2. *Apply an ice-bag and remain quiet.*
3. *Do NOT take a laxative, food, or medicine.*

The importance of prompt medical attention is clearly indicated in a recent survey of appendicitis cases made by medical authorities. It reveals that the death toll, among those who delayed going to hospital from two to three days, was from *three to four times greater* than among patients admitted to a hospital within the first 24 hours. The survey further shows that fatalities among those who had taken a laxative after pain developed were *more than three times greater* than among those who had taken none. . . .

When in any doubt whatsoever about abdominal pain, call your physician for *safe* guidance—and call him *in time*. Then if serious disease is indicated an early diagnosis and treatment may speed recovery, reduce the cost of illness, and decrease the possibility of dangerous complications.

Send for Metropolitan's helpful free booklet, 'Appendicitis.'

The effect of such an advertisement on the casual reader is indicated by a copy of a letter in the company's possession, written by a Canadian traveller to the Pullman Company, which reads as follows:

"About three weeks ago I was travelling on one of your crack trains, and was stricken with a severe stomach-ache. The porter in one of your Pullman cars was most accommodating, and I asked him for, and he was glad to provide me with, some bicarbonate of soda in an endeavour to relieve my pain. He, however, brought me from the club car a bottle of a well-known cathartic, and told me that the conductor in charge suggested that I take a dose of the same.

Very fortunately, I had a recent institutional ad. of the Metropolitan Life Insurance Company that was running in the leading magazines. This ad. was headed, 'How innocent is a stomach-ache?' and advised that you do three things: '(1) call a doctor; (2) apply an ice-bag and remain quiet; (3) do not take a laxative, food, or medicine.'

Now I do believe that if I had not read this advertisement (I am not a medical man, and unfortunately have not been interested too much in physiology) I would have taken this strong cathartic and have had a ruptured appendix.

I decided to get off the train at 4.45 a.m. instead of going through to my destination. I was operated on around 6 a.m., and the surgeon told me that if I had taken the cathartic I would have had quite a gamble with my life."

The Druggists Step In

Posters have also been used—notably a poster for display in drug stores, with the co-operation of the druggists and pharmacists. The national organization representing the drug and pharmaceutical business was perhaps the second major national agency to participate in this effort in a consistent way. The public spirit and leadership of the druggists have met with wide and merited acclaim. The drug-store poster referred to carries an illustration of a man in some distress at the prescription counter evidently seeking medical aid, with the druggist indicating doubt and saying:

"It might be appendicitis—

You should see your doctor.

16,000 to 18,000 people in the United States die yearly from appendicitis. Many of these deaths could be prevented if the doctor were called at once.

Self-treatment for abdominal pain is dangerous!

Do not take a laxative, food, or medicine.

Remain quiet and call your doctor."

This organized effort to combat self-medication has been strengthened through other lines, for in Jan., 1940, the United States Federal Food and Drug Administration put into effect a ruling making it obligatory to print on the label of laxative drugs a warning statement regarding their injurious use.

The Press, the Radio, Lectures, etc.

The education effort included many other methods and instruments, such as the distribution of news releases, the

preparation of radio scripts and the use of radio stations, the furnishing of lecture outlines, with statistical data and case experience, and the encouragement of talks to lay groups of many kinds throughout the country. Here again there came in the active co-operation of the medical profession, as these talks were usually given by local physicians—often medical examiners of the company, urged to take an active part in the programme by the company's Medical Division. Groups addressed included women's clubs, parent-teacher associations, community and service clubs, employee groups, schools, churches, etc. In nearly 300 of the company's district offices, where groups of agents are employed, the agents were addressed by the company's medical examiners, stressing the vital points in the programme and urging active participation in this activity for the benefit of the policy-holders. At the same time special articles appeared periodically in the company's "Statistical Bulletin," which goes monthly to thousands of physicians, surgeons, educators, health authorities, public officials, and others.

Conclusion

This experience as a whole seems to stand out in support of the value of health education. It encourages the belief that organized effort to instruct the lay public, including those with comparatively little economic and educational advantage, can be productive of concrete results. Success depends on the use of a few simple facts, forcibly and dramatically presented. It involves the co-operation and co-ordination of many agencies and influences, and the use of a variety of approaches. Experience seems to demonstrate a degree of cause-and-effect relationship between an educational programme and a contemporary improvement in the fatality rate from appendicitis, augmented by therapeutic advances as well.

It may be added that this experience is another seemingly clear-cut demonstration that "public health is purchasable," and that purposeful, timely, and specifically "aimed" investments in this field produce definite, measurable, and substantial returns.

EFFECT OF THE pH OF THE BLOOD ON HAEMOLYSIS

WITH SPECIAL REFERENCE TO BLACKWATER FEVER

BY

FELIX SMITH, M.D.Birm., M.R.C.P.Lond.

Lieut.-Col., R.A.M.C.

AND

R. WINSTON EVANS

Captain (Pathologist), R.A.M.C.; Research Fellow in Haematology, Christie Hospital, Manchester

The Problem of Intravascular Haemolysis

In the course of observations on 16 subjects of blackwater fever, of whom 5 died and 11 recovered, we were naturally faced with the problem of the arrest of the haemolysis. This is of course the basic problem in all the acute haemolytic diseases, and very little is known about it. Many haemolytic toxins and poisons are known, but in no haemolytic disease has the haemolysin been isolated. In other diseases, notably paroxysmal haemoglobinuria and march haemoglobinuria, the factors which precipitate the breakdown are known (such as the influence of cold and syphilis in the former, and severe muscular strain in the erect position in the latter). We know, of course, that chronic malaria certainly, and big doses of quinine almost certainly, are the precipitating factors in blackwater fever, but we still do not know why in one case these factors produce the fever and in another do not.

Experimental Work

We have made a few observations which shed some light on the problem of the wide diurnal variation in the fragility of red blood corpuscles and the relation between the fragility and pH. We have shown that the fragility of red blood cells

is capable of changes within very wide limits and can vary from hour to hour. Furthermore, our experiments have proved that the red cell fragility is increased in blackwater fever at the onset, and that this is due, in part, to a lowering of the pH of the blood. It should be noted that Israël, working on paroxysmal haemoglobinuria, also observed that a low pH is connected with attacks of haemoglobinuria in that disease, but he does not connect this with alterations in the red cell fragility. The method used in these experiments on fragility was quantitative, the blood being diluted 1 in 200 in 0.4% saline in a haemocytometer pipette, and the number of cells remaining counted after half an hour in the counting chamber.

The first observation was that one subject showed wide variations if tested at different times on the same day. Counts were therefore done at close intervals throughout a 24-hour period, on both healthy and malarial subjects, and it was found that in all subjects there was a wide variation in red blood cell resistance. Examples are 600,000 at 8.30 a.m. and 2,850,000 at 2.30 p.m., 770,000 at 10.15 a.m. and 4,450,000 at 3 p.m., without change in the total red cell count. The period of increased resistance is from 11.30 a.m. to 8.30 p.m., with a peak at 3 p.m., and during the night the resistance remains low throughout. The red cell fragility is increased in blackwater fever—that is, the variations are below the limits observed in normal subjects.

One example of a physiological variation may be given in full:

Time	Cells Unhaemolysed	Time	Cells Unhaemolysed
8.30 a.m.	940,000	8.30 p.m.	1,280,000
9.30 ..	762,000	10.0 ..	920,000
10.30 ..	1,950,000	11.30* ..	1,740,000
11.30 ..	2,200,000	1.0* a.m.	1,055,000
1.0 p.m.	2,150,000	2.30* ..	920,000
2.30 ..	2,460,000	4.0* ..	980,000
4.0 ..	1,560,000	5.30* ..	923,000
5.15 ..	1,485,000	7.0 ..	1,500,000
6.30 ..	885,000	8.30 ..	1,300,000

*Sleeping.

All possible factors of experimental error were considered and excluded, and the experiment was repeated until we were satisfied of the constancy of the result. A rigid technique was observed throughout the series of experiments, which were carried out only with CO₂-free solutions. It was found that the variations in fragility were unaffected when the tests were made in the incubator at 37° C., at room temperature, and on ice.

Dacie, Israël, and Wilkinson (1938) have shown that the red blood cells in cases of haemoglobinuria are susceptible to a haemolysin of unknown nature, present in normal serum, which exerts its greatest effect between pH 7 and 7.2. They have also shown that during sleep the pH of the blood is decreased. It therefore occurred to us that the increase in fragility which had been observed during the night hours might be related to this lowering of the blood pH. Experiments *in vitro* were done, using a 0.433% solution of saline buffered to the pH levels of 6.8, 7.5, and 8.2. The results obtained were: (1) At the lowest pH the cells were more fragile, as judged not only by the number of cells surviving but also by the wide difference in size and shape. These cells were all markedly spherical and swollen, and their appearance suggested that they were almost at the point of haemolysis. (2) At pH 7.5 intermediate figures and appearances were observed, and (3) at pH 8.2 all the surviving cells were singularly healthy and normal in appearance. The actual numbers of surviving cells counted at these levels depended, of course, on the time of day that the experiment was performed. (This work is being continued.) The application of these results to the treatment of blackwater fever is discussed under "Treatment."

Certain Clinical Features of Blackwater Fever, based on Personal Experience

The remarks that follow are based entirely on personal observations, and we are quite aware that more extensive experience might well lead to a modification of some of the views expressed.

Blackwater fever can be considered as an intense haemolytic anaemia of sudden onset, occurring in association with malignant tertian malaria. The mechanism of the haemolytic process is not known, but it is thought by many that the

haemolysis results from some metabolic breakdown which is precipitated by the administration of quinine or synthetic quinine substitutes. Lysis of the corpuscles occurs, with liberation of oxyhaemoglobin into the plasma. This is converted into methaemoglobin and other pigments. Fairley and Bromfield (1937, 1939) have shown that the serum contains oxyhaemoglobin, methaemoglobin, and methaemalbumin. This last pigment has a large molecule, is impermeable to the kidney, and is never found in the urine.

The appearance of the urine in blackwater fever is characteristic. It is of a port-wine colour, with a pinkish froth on shaking. A heavy brownish sediment collects on standing. Albumin is present, and microscopy shows absence of cells. Later in the course of the disease, when some renal necrosis may have taken place, a few red and white cells may be present.

Clinically, blackwater fever in our experience presents certain differences from the disease described in the textbooks as occurring almost exclusively in "old coasters" with a long history of numerous attacks of self-treated subtertian malaria. Our cases have all been in unusually good types of soldier, which, from the Army point of view, made their recovery all the more important. In only one case was there reason to suspect carelessness in the taking of suppressive quinine, and this case also had the greatest number of attacks of malaria—five: the other patients were regular quinine-takers and were in good general condition. Alcoholism, venereal disease, dysentery, and lack of a reasonable standard of education were not factors in this group of cases. The "pre-blackwater" state as described in the textbooks was not present. The statement made in some books that the disease is almost confined to light-haired men was also found untrue for our cases. In fact, we think the majority of these cases—certainly the last five—were of the type with black hair, rather pale complexion, and brown eyes.

The onset of all our cases of blackwater fever was characterized by a rigor. This is worth mentioning because definite rigors occur in less than a third of our series of cases of subtertian malaria. The only unusual symptom preceding the rigor was a sense of intense general fatigue for two or three days. After the rigor vomiting was a constant feature, and these three symptoms—fatigue, rigor, and vomiting—should lead to careful examination of the next specimen of urine. It is essential to examine it microscopically before making the final diagnosis. Acute pyelitis, with an unusual degree of haematuria, associated with acute bacillary dysentery, imitated the onset of blackwater fever in one case, and illustrates the importance of microscopical examination. When blackwater fever occurs during quinine treatment of an attack of subtertian malaria it often does so on the third or fourth day. It is safer to give the quinine hydrochloride in six doses of 5 gr. than in three of 10 gr. Quinine must of course be stopped completely if blackwater fever occurs. Slight jaundice associated with albuminuria is also an indication for stopping quinine. In treating malaria the urine should be rendered alkaline as a routine and the patient kept in bed. Cases of blackwater fever should not be moved unless circumstances make this absolutely essential. It is tempting at the onset to send these patients to hospital, as their general condition is often quite good; but within 36 hours they become extremely pale and obviously too ill to move. Very deep jaundice did not occur in any of our cases, but a lemon-coloured tinge appeared on the first day and deepened as the haemolysis continued.

It has been calculated that a man may lose the equivalent of 4 to 6 pints of blood by intravascular haemolysis in 36 hours in this condition. The liver, like the reticulo-endothelial system generally, has an enormous capacity for dealing with liberated haemoglobin by splitting haematin into bilirubin and haemosiderin, the first being excreted in the bile and the second being stored, chiefly in the liver and spleen. The appearance of haemoglobin in the urine is therefore an indication more of the rapidity of the breakdown than of its extent. Nevertheless, at best it means the loss of several pints of blood, and the condition is comparable (but not exactly similar) to that of traumatic haemorrhage. The pallor and sweating and the thin running pulse are very similar to those of wound shock, and the general treatment has much in common with that of shock. The factor which is absent is that of the effects

of a wound—with the possibilities of sepsis, absorption of products of tissue breakdown, etc. The factor which is present in blackwater fever and absent in traumatic haemorrhage is that of the rapid accumulation of the breakdown products of intravascular haemolysis and the serious damage which can result to the kidneys from attempts to excrete these products.

The older theory that the chief, and likeliest, cause of kidney damage is the accumulation of crystals of acid haematin in the tubules is now largely discarded. Sections of the kidney show microscopically that the tubules are blocked, but it seems more probable that this material is a plug of methaemoglobin, with the debris of broken-down red blood cells and damaged renal-tubular cells, etc. It is possible that the first step in this process is the early degenerative change in the epithelial lining of the tubules due to the severe anaemia, with resulting nutritional deficiency of these cells. That the cells lining the glomeruli are much less and much later affected may be taken as supporting evidence of this theory, since these cells receive a more plentiful blood supply than do those lining the tubules. However this may be, the fact is that the tubules do tend to become blocked, and one of the most important points in treatment is to prevent this blocking. We therefore should consider the factors causing this renal obstruction, and how they can be avoided or minimized. These factors are: (A) the pigments and cellular debris resulting from continued haemolysis; (B) the tendency of these products to obstruct the renal tubules; (C) the severe degree of anaemia, damaging the kidneys' excretory function; (D) the production of acid haematin crystals in the kidney tubules; (E) the existence of living subtertian malarial parasites in the blood.

Treatment of Blackwater Fever

Factor A

The first problem in treatment, therefore, is how to check the haemolysis. The application of the results of the experimental work on fragility mentioned above is obvious. Alkalis must be given in such amounts as actually to increase the pH of the blood plasma. The value of this was most strikingly illustrated by two of our cases. In the first an attack of tetany, with a major convulsion, occurred after administration of 2% sodium bicarbonate in normal saline by slow intravenous drip. This patient passed clear urine immediately afterwards and the haemoglobinuria never recurred; his general condition also improved considerably and the attack of tetany appeared to be the turning-point to recovery. He was a young man whose acid-alkali balance was easily upset. During his attack of tetany the pH of the blood would be raised well over normal physiological limits, and the effect was presumably to raise the resistance of his corpuscles and cause the haemolysis to cease. In a second case the urine had become clear and remained so for 36 hours, when a recurrence of haemoglobinuria occurred in two specimens. Alkalis were given in concentrated form (3M sodium lactate 40 c.cm. intravenously and 60 g. each of sodium bicarbonate and sodium citrate by mouth). The next specimen was clear, and the proof of hyperalkalinization was to be seen in the production of Trousseau's sign when a sphygmomanometer was applied to the arm.

For the prevention of haemolysis and the rendering of its products as harmless as possible we have given alkalis by mouth as follows: Sod. bicarb. gr. 20, sod. citras gr. 20, aq. ad 1/2 oz.—two-hourly, or double that dose four-hourly. This is not a particularly high dosage, but there is another and most important means of alkalinization at our disposal—the use of 2M or 3M solutions of sodium lactate intravenously. As a routine 20 c.cm. of this solution has been given three times a day at equally spaced intervals, using a 20-c.cm. syringe and a fine hypodermic needle. In our opinion double this dose might easily be used with advantage. It can be made up in a saturated solution of sodium bicarbonate, but without the latter it has the inestimable advantage of being sterilizable by boiling, and since a saturated solution of sodium bicarbonate is only about 11%, the amount thus given is small, and we have discontinued its inclusion. Intravenous administration of concentrated solutions of sodium lactate is strikingly effective in producing rapid alkalinization and stopping haemolysis. It has, however, the disadvantage of causing thrombosis of veins, and one should therefore avoid the use of veins which may be needed later for blood transfusion.

Factor B

The problem of ridding the kidneys of the products of haemolysis is met by the intake-and-output balance of fluid. In the Tropics sweating is responsible for perhaps half of the excretion of the intake of fluid by mouth and thus tends to concentrate the urine. Sweating therefore is a danger in blackwater fever, and the nurses should be instructed to keep the patient's skin cool: we have always ordered tepid sponging to reduce temperatures surpassing 103° F.

At the onset nearly all the cases show an excretion of urine of two-thirds of the intake of fluid by mouth, and this is quite satisfactory. We have become concerned only when the output has fallen below half the intake. It is a point in prognosis that cases showing a poor excretion from the start have a poor chance of recovery; and, conversely, patients in whom the output of urine remains high in quantity still have a good chance of recovering even though the urine remains dark and bloody and the blood count falls below 2,000,000 cells.

The administration of fluid by mouth probably cannot be overdone, but, from the evidence of a fatal case, it can be easily overdone by intravenous drip administration. This case developed oedema of the dependent parts, and on performing the necropsy the tissues throughout the body were found to be saturated and swollen with water. The excretion of water is the function of the healthy kidney, and to pile up the "head" of water behind the kidney in the hope of "flushing out" that organ is unscientific. It is much more reasonable, in our opinion, to try to sustain the efficiency of the kidney by attending to its nutritional needs—i.e., by the judicious use of blood transfusions. This is referred to under the next heading. On this question of excretion a final word may be said on the subject of uraemia. One of our patients certainly died of acute kidney failure. We gave the orthodox treatment, which is really an attempt to make the kidney and bowel take over the excretory functions of the kidney; but it is probable that by so doing we only made bad worse, by concentrating the urine and increasing the already extensive blockage of the renal tubules.

Factor C

The blood picture at the onset is invariably characterized by a considerable degree of anaemia. A typical series of red cell counts is as follows: 3,500,000 at the onset, 2,800,000 after 24 hours, 2,200,000 after 48 hours (the urine is often clear by this time), 1,800,000 after 72 hours. The fall in haemoglobin percentage is parallel with that of the red cells, and a colour index of unity is maintained, using mean standards.

During the stage of haemolysis the leucocyte count was invariably found to rise, a relative and absolute increase in monocytes being responsible: in one case the monocyte count was 47.5% of the total leucocyte count of 18,000. They are presumably liberated to deal with cell debris, such as "ghost" red corpuscles. The bone-marrow picture is that of a normoblastic hyperplasia, the majority of the normoblasts being of a large variety showing early eosinophilic staining reactions. At a later stage in the disease—i.e., during the recovery period—these are replaced by a smaller form of normoblast with an intensely basophilic cytoplasm, probably indicating an acute iron deficiency. As the haemolysis abates there is a marked fall in the number of circulating leucocytes, and in three of our cases a leucopenia (in the region of 4,000) developed.

Treatment of the anaemia is therefore mainly the administration of iron, and the iron salt at our disposal was ferri et ammon. cit., which was given in a dose of 30 gr. t.d.s. This was started very soon after the urine had cleared. In order to make sure that no dietetic deficiency should slow up the response of the bone marrow it was our practice to give liver extract intramuscularly at the same time.

In some cases of blackwater fever there is a tendency for a slow marrow response, and the haemolytic toxin responsible for the disease may possibly exert a toxic effect on the marrow. In one case alarm was felt at the possibility of a marrow aplasia occurring. In all cases the total red cell count does not begin to rise until three clear days after haemolysis has ceased, and it may be as long as six days. It must not be forgotten that the fact that the urine has ceased to contain haemoglobin does not mean that haemolysis has ceased. It may be going steadily on—and when parasites persist and the temperature remains up, haemolysis certainly is going on, just as it does in any severe case of subtertian malaria.

A good deal of attention has recently been paid to blood transfusion in blackwater fever and many papers have been published on it. It is almost universally praised, and some authors advocate frequent transfusions of whole blood from the onset of the disease. Our own experience has caused us to modify this view; we now regard the problem as follows:

Blood transfusion would be of tremendous value if the normal plasma given contained any antihemolytic substances which would cause the intravascular haemolysis to cease. In fact, in our experience there is no evidence that it does so. This would not matter much if it were not that blackwater fever patients seem to be particularly liable to violent reactions during or after the transfusion—especially in the first two days. This may be connected with the tendency to acidemia, and is therefore a further reason for early and thorough alkalinization. The problem of compatibility is particularly acute in blackwater fever, and cross-matching—both ways—is essential. Moreover, the suspensions of cells should be tested not only at room temperature but also on ice in an ice-box for a full 24 hours. It often happens that out of a dozen donors, all of the same group as the patient, only one or two—and sometimes none at all—are really compatible when subjected to this stringent test. Even when one is found, unpleasant reactions have occurred during

transfusion, and the best method is probably to give minute quantities, and to give them slowly—e.g., 20 drops in the first ten minutes, after which the transfusion may be proceeded with more quickly.

For these reasons we have given up using blood transfusions in the first two days. We, however, acknowledge their great importance in preventing a profound anaemia from developing, and when the red cell count is steadily falling and is approaching 2,000,000 a pint of blood should be given. It is useful to remember that whenever a needle is safely fixed in the patient's vein, for either blood or sodium-bicarbonate-and-saline transfusion, the opportunity is present to add slowly 20 or 40 c.cm. of the concentrated sodium lactate solution mentioned above.

Transfused red blood cells undergo intravascular destruction just as do the patient's own cells, and for this reason alone it seems wise to avoid transfusions in the early stage of the disease, when, as previously noted, our efforts should be directed at checking—not increasing—intramuscular haemolysis.

Factors D and E

The question of preventing the formation of acid haematin crystals has already been mentioned, and it suffices to say that the high degree of alkalization advocated will certainly prevent this happening.

Finally, there is one aspect of blackwater fever which tends to be forgotten. In the constant watch which must be kept over the intake and output, the reaction and appearance of the urine, the blood picture, and so on, we are apt to forget that the patient is suffering from a severe attack of subtertian malaria. It is an attack, moreover, which cannot be treated by quinine or quinine substitutes. High temperatures on the first, third, and fifth days are therefore not a matter for surprise, and an attack of typical malaria is common enough about 10 days after the blackwater has ceased. In one case parasites persisted in the blood from the onset of the disease; the urine cleared up, but the temperature persisted; and finally, 14 days after the onset, the patient died of cerebral malaria. Looking back on this case, it is now felt that we should have given quinine courageously instead of in the minute doses we used. Our present plan is to give a half-tablet of mepacrine 48 hours after haemoglobinuria has ceased. If no ill effect ensues we give a half-tablet twice a day for a week, and thereafter two tablets every Sunday and Wednesday in the approved "suppressive" manner.

Discussion

This paper claims that the fragility of red blood cells varies considerably throughout the 24-hour period. Further, it advances the theory that the pH of the blood plasma is the factor responsible for these alterations in fragility and claims that this is demonstrable *in vitro*, using solutions of saline varying in pH from 6.8 to 8.2. An immediate criticism is that the pH of the blood plasma never varies to anything like this degree; and a second criticism might be that pH estimations of the blood were not done at the same time as the fragilities were estimated. This latter procedure was not possible—to the necessary degree of accuracy—owing to the conditions under which the work was performed. The former objection is perhaps fairly met by the assumption that in cases which developed clinical tetany the plasma pH actually would approach 8.

Case reports have not been included in detail, and a short account of the series should therefore be given. The original 10 cases were seen by one of us (F. S.) and treated on the lines given by the textbooks. It is well known that blackwater fever varies in severity from place to place and in different years. Three consecutive deaths occurred early in the series, and it was realized that we were confronted by a particularly bad type of the disease. In the cases numbered 7 to 10, therefore, an attempt was made to improve this high mortality by using early and repeated blood transfusions—a method which has been advocated with enthusiasm in recent years. In only one case did we feel satisfied that this procedure saved the patient's life. In the other cases blood transfusion was clearly not without its dangers, even though the greatest care was exercised in matching.

Cases 11 to 16 occurred in a different colony, where laboratory conditions were considerably better. The second of these cases coincided with the observation of the variation of fragility of red cells. It is referred to earlier on in this paper as the case in which tetany occurred followed by cessation of haemolysis. The suggestion that alkalaemia was responsible for this was obvious, and led to the experimental work *in vitro* which confirmed this. Cases 13, 14, and 16 were treated successfully by the method described, enough alkali being given

to produce Trousseau's sign. Cases 10 and 15 both had suppression of urine from the onset and died of uraemia.

The final case illustrates the points which it is desired to bring out, and the following notes are therefore included:

Case Notes

B. H., British, aged 24; 14 months' service in Tropics. Blood group O. Admitted 9 p.m. Sept. 28, 1942.

Previous History.—In U.K., no serious illness. In the Tropics: General lassitude for three months; headaches for four weeks; no temperature, sweating, shivering attacks, or other symptoms to suggest malarial infection. He has been sleeping within a few hundred yards of a native village. He observes antimalarial precautions and takes a daily dose of quinine hydrochloride 5 gr. Occupation, indoor and sedentary. For three months has been on duty three nights each week, but does not remember being bitten by mosquitoes. Smokes 20 to 30 cigarettes and has one or two bottles of beer a day. Walks about two miles daily.

History and Progress.—An attack of shivering, followed by sweating, occurred on the evening before admission. On Sept. 28 he complained of headache and pains in the joints and muscles of legs and arms. Felt hot and sweated freely, and in the late afternoon vomited seven times in two hours. Bowels opened normally. Temperature 103.8°, pulse 124, respirations 18. Spleen enlarged 1 in. below left costal margin. The skin over the chest and back affected by prickly heat. No signs of anaemia, jaundice, or oedema. Herpes labialis not present. Conjunctivae suffused. Urine dark in colour but contained no albumin; reaction acid. Examination of all systems showed no sign of disease other than the splenic enlargement and the existence of an attack of subtertian malaria. On admission given potass. citras and sod. bicarb. aa 30 gr., and nursed in blankets.

Sept. 29.—Blood film positive for parasites. Quinine hydrochloride 10 gr. b.d. Alkalis as above t.d.s.

Sept. 30.—Felt well. Temperature 100° at 7 p.m. Treatment continued, with quinine increased to 30 gr.

Oct. 1.—Felt well. Bowels open twice. Urine alkaline to litmus. Temperature normal until 7 p.m., when it was 99.6°.

Oct. 2.—At 3 a.m. vomited. Got up and passed "dark-coloured" urine, which was not saved. Returned to bed without reporting this. Awakened at 5 a.m. feeling shivery. Urine again passed, and later reported as containing "haemoglobin, albumin, much debris, occasional epithelial cells, and very occasional erythrocytes." It was alkaline in reaction. Conjunctivae and skin showed slight jaundice. Liver and spleen tender on palpation. At 6 a.m. temperature 100.2°, pulse 86. Treatment by abundant fluids and alkalis started immediately. Quinine stopped. 8 a.m.: night urine was 7 oz. plus one lost specimen. Fluid taken by mouth, 31 oz. 8.15 a.m.: 3M sodium lactate 40 c.cm. intravenously. 11 a.m.: Hb 60%; R.B.C. 4,000,000; W.B.C. 6,000—polymorphs 62%, lymphocytes 28%, monocytes 10%. 12.45 p.m.: Complained of aching pain in lower abdomen, accentuated after passing urine. 1.50 p.m.: B.P. 120/80; 3M sodium lactate 20 c.cm. intravenously. 7.20 p.m.: 3M sodium lactate 40 c.cm. intravenously; carpal spasm present on application of pressure to arm. 8 p.m.: Intake of fluid since 8 a.m., 155 oz. by mouth plus 12 oz. alkaline mixture (360 gr. pot. citras, 360 gr. sod. bicarb.) plus 100 c.cm. sodium lactate solution intravenously; urinary output, 80 oz.; the urine remained "black" throughout the day. 8.45 p.m.: A slight rigor; complaint of cramps, and jaw felt stiff; Trousseau's sign easily elicited; specimen of urine definitely lighter in colour.

Oct. 3.—2.55 a.m.: Urine practically normal in appearance. 4.55 a.m.: A "black" specimen of urine. 8 a.m.: Urine again normal in appearance. Since 8 p.m. on Oct. 2 intake of fluid has been 128 oz.; output of urine, 58 oz.

Later details show a rapid improvement in urinary output and there was no further haemoglobinuria. Blood examinations on Oct. 3 showed Hb 50%, R.B.C. 2,500,000; and on Oct. 4 Hb 45%, R.B.C. 2,500,000—illustrating the rapidity with which a severe degree of anaemia may be reached. There was gradual improvement on the succeeding days.

Summary

Certain aspects of the pathology and treatment of blackwater fever are discussed. An account is given of experimental work which shows that the fragility of red blood corpuscles is increased at low pH levels and decreased at high levels. A new rationale for the treatment of intravascular haemolysis is therefore suggested, and the methods of giving alkalis are described. The value of intensive alkali therapy is illustrated by reference to cases. A discussion on the clinical and haematological features of blackwater fever is given, with an account of the treatment.

REFERENCES

- Dacie, J. V., Israëls, M. C. G., and Wilkinson, J. F. (1938). *Lancet*, 1, 479.
Fairley, N. H., and Bromfield, R. J. (1937). *Trans. roy. Soc. trop. Med. Hyg.*, 31, 139.
— (1939). *Ibid.*, 32, 431.