H A E M O G L O B I N U R I A

FROM THE HAEMOLYTIC ASPECT.

A T H E S I S

SUBMITTED FOR THE DEGREE OF DOCTOR OF MEDICINE

BY

HARRY EDWARD GIBBS

M.B.,Ch.B.; F.R.C.S.E.

March 1901.

I N T R O D U C T O R Y

Of the many conditions pertaining to Medicine that have commanded attention during the latter half of the 19th Century, and have emerged from a position of little interest and importance to a state of great moment and of vital significance and consequence, few have more claim upon our consideration than has that condition known as Haemoglobinuria. This condition, from being, if not quite unknown, at least unrecog - nised and unrecorded prior to 1850, immediately came into prominence as soon as a few cases had been re - corded and attention directed to the phenomenon. But inasmuch as the form of this trouble, so far as then known, was almost never fatal, being of the nature of that now called Paroxysmal Hb-uria, the interest which was aroused was rather of the nature of curios- ity about a peculiarity of nature than one having a vital significance.

For many years this was the only form dis - cussed and recorded, and it was not till some twenty years after that the condition was found to accom- pany the absorption of certain noxious substances. Closely following upon the recognition of this fact

came the records of various idiopathic cases, for the most part isolated ones, though in one classical in - stance, a disease occurred epidemically in infants in which the main and characteristic feature was Hb-uria.

Whilst these new facts were still engrossing the attention of many of the medical profession, and had stimulated a few to perform some experiments with drugs, with the view of elucidating the cause of this interesting condition, a new aspect was given to the subject when attention was drawn to the condition as it occurred in certain Tropical countries. It was found that certain large tracts of the earth's surface were rendered almost wholly uninhabitable by the white race, owing to the prevalence therein of a disease which had Hb-uria for its chief symptom. Con - sequently what previously had been a subject of scientific interest now attained a vital interest and beyond that an indirect commercial interest since until means are found to combat this evil, certain parts of the world are practically cut off as fields of enterprising traders and colonists.

Thus the interest attached to the study for this condition is very great whether viewed from the standpoint of the practical investigator, the practitioner or the commercial man not to mention the personal interest felt by the sufferer, and the

necessity and importance of solving the mystery connected with the Aetiology and Pathology of this disease can hardly be overestimated. For these reasons the subject appeared to me as eminently suitable for the special study for a thesis, as affording an abundant scope for new experimental work. As the work proceeded, the scope of the work enlarged to so great an extent that finally only a small branch bearing upon the main question was specially entered into and it is now my desire to lay before you the results obtained from the experiments and the conclusions to be drawn therefrom.

In the following pages the so-called Toxic Hb-uria, as distinct from that termed Paroxysmal Hb-uria has been mainly dealt with, the latter being only cursorily touched upon in the preliminary pages, in so far as it relates to or illustrates features in the former.

My best thanks are due to Professor Greenfield to whom in the first place I owe the choice of the subject and the privilege of his supervision and help while conducting my work in the Pathological Laboratory of the Edinburgh University. I am also indebted to him for the use of some of the specimens which were of much service and also for his guidance in the methods of procedure and in the matter of the literature to be consulted on the subject.

I regret that my work was interrupted by my being compelled to leave the country at a time when the study was becoming extremely interesting and that I was not able to carry my researches as far as I had intended. Still the subject is one of such wide range that it is only by working out each point by itself that we can hope to ultimately reach a full understanding and I trust that the conclusions drawn from the experiments upon the points in question will prove more than merely interesting but also factors towards a more complete knowledge of the subject of Haemoglobinuria.

PAROXYSMAL HAEMOGLOBINURIA

To Dressler is commonly ascribed the honour of having first definitely described and put on record a case of this nature. In 1854 he published a case with notes and observations in the Arch. f.Path. Anat. under the heading of Intermittent Albuminuria and Chromaturia which was undoubtedly, from the description, a case of what would now most generally be termed Paroxysmal Hb-uria.

Although this is unquestionably the first really authentic record of a case of this condition there is very little doubt that the disease was recognised to a certain degree previously. Purely as a matter of interest in regard to the history of the disease one notes that in 1794 Dr Charles Stewart, in 1831 Dr Elliotson[1], and in 1838 a French Physician - Gergerès[2], each published cases which are to be considered instances of the occurrence of this condition.

After Dressler had thus called attention to the main symptoms of the disease several cases were

reported, but not till ten years later, when Dr George Harley[3] described a case of "Intermittent Haematuria"; did the condition become recognised by the English Physicians. The interest of English observers seems to have been at once roused for very soon afterwards numerous cases were reported under various terms, chief of which were the reports of two cases by Hassal[4] and soon after by Dickinson[5]. To the cele - brated Dr Pavy[6] we owe the discovery of the true nature of the condition and to him we owe the term of Paroxysmal Hb-uria, which has found the most general favour among subsequent writers on the subject. Since then a vast amount of literature has appeared on the subject mainly from the French School but not incon - siderably from the Germans and our own nation. The most thorough and masterly of recent works on the subject is that of Choostek whose monograph on Hb - uria appeared in 1894.

The characteristic features of a case of Par- oxysmal Hb-uria consist in the presence from time to time, and irregularly, of Haemoglobin in the urine, the paroxysm being occasioned by various causes, of which cold and fatigue though they may be very moder- ate in themselves are the most common. The onset is usually acute, following closely upon the application of the inducing cause; is characterized by chills and rigors and the patient is utterly prostrated for the

time. The temperature is variable but usually rais - ed. There is pain about the loins and often gastro - intestinal symptoms of vomiting or diarrhoea. There is also some discolouration of the skin which is ap- parently not jaundice and lastly the tendency is to recovery after a longer or shorter affliction with the disease, notwithstanding the want of a specific treatment, or even the power to materially affect its course by the use of drugs. In examining the record- ed cases to try to eliminate those factors most com- mon to them all with a view to elucidating the Path - ology of the condition, one is met at the very outset with the fact that there are two most distinct groups among those factors. In that the conditions, which determine the onset of the attacks in those liable to them, are such as are met with by almost every person daily yet in whom they are not sufficient to cause Hb-uria, we recognise that there must be a pre- disposition in certain people in whom such common conditions are capable of inducing an attack of Hb - uria. Hence the natural division of the causal fact- ors into Predisposing and Exciting, and in this con - nection it may be noted that in no condition of Hb - uria occurring as a natural disease in man can there not be recognised to a less or greater degree a division of the aetiological factors into these two main groups. In other words that no cases of Hb-uria are

simple uncomplicated diseases but are usually the result of the action of two or more morbid influences.

Reviewing the results of the various obser - vers in regard to certain factors that seem to bear on the condition, we find that in regard to sex about 86% occur in males. This figure is obtained by examining the statistics of Van Roosen, Henock[6], and De Labrosse[5], each of whom studied the condition inde - pendently and their results accorded well with one another.

With regard to age nothing definite can be said as cases have been recorded as occurring at all ages. By far the majority of cases occur during middle life between thirty and forty-five though occurrences in early life including even infants have been recorded by Hirschsprung[9], Hirst[10], and Variot[11], among others, whilst Stevens and Herringham[12] have noted its occurrence in patients at the other extreme of life.

The relationship of preexisting disease to the condition is as interesting as it is important. Of such diseases as predispose to Hb-uria of the Paroxysmal type none stands in such a prominent position as does Syphilis. So much is this the case that all authorities are agreed that it bears a very significant relationship to the great majority of cases of Hb-uria, whilst many observers such as Voelcker[13] and Lepine insist that it is a factor in every case of Paroxysmal Hb-uria. Malaria is stated by some to be

an antecedent of common occurrence in cases of Hb - uria of Paroxysmal nature but the consensus of opinion is against this view. Calmette[14] in 1889 argued strongly in favour of the relationship but the position he maintained has not been supported by other observers.

De Labrosse in his monograph in 1889 laid stress upon the nervous factor as a precursor or accompaniment of the disease and considered the condition due to a highly nervous reflex excitability combined with a local exciting cause.

There seems to be a very close relationship between that obscure condition termed Raynaud's Disease and Paroxysmal Hb-uria, the former often allied with the latter, though the converse does not hold. Bristowe and Copeman[15] were the first to draw atten - tion to this relationship and Foulerton[16] confirmed the truth of their observations.

An apparently hereditary instance of Paroxysmal Hb-uria is mentioned by Saundby[17] in which a father, a daughter, and a son were all sufferers from this condition.

Robins of Paris analysing the predisposing factors of some forty cases could not find any one disease markedly predominating but demonstrated that all the diseases which had been antecedent to the attacks of Paroxysmal Hb-uria were characterized by marked deterioration of general bodily health and

nutrition such as occurs in Syphilis, Malaria, Rheumatism, Bright's disease and in Cardiac disease.

Of the second group of causal agencies exposure to cold, even if it be very slight provided it takes place relatively suddenly, is by far the most common, if indeed it can ever be wholly put out of count. That this is merely a secondary cause of the attack and not the primary is demonstrated by the circumstance that the degree of cold that will induce an attack in these patients may be so slight as to be inappreciable to persons who are free from this liability. But as indicating the definite and long recognised association between cold and Hb-uria, the French writers always speak of the condition as "L'Hb-urie à figore" and it is widely termed "winter Hb-uria" in this country. This relationship is borne out not only by clinical evidence but also by numerous experimental investigations, the most classical of which are those of Ehrlick, Rosenbach (Berl.Klin. Wosch.1880), Mackenzie (Lan.1/84/Feb.), Bristowe and Copeman (L.2/89/Aug.) and Prof.Fraser (Ed.Med.J.1897)

Another way in which an attack may be induced is by fatigue physical and even mental, but it is doubtful if in these cases some unnoticed chilling of the body or of a part of it has not also taken place whereby to account for the attack. However a case recorded by Robins[18] of Paris and also one by Dickinson[19] seem to be undoubtedly occasioned by great bodily exertion and

fatigue.

Concerning the Pathology of this form of Hb-uria, the views held and the theories put forth are as numerous as the present indefinite state of our knowledge would lead us to expect. Passing over such obviously incorrect views as that held by Van Roosen that the condition is a Haematuria where the cellular elements have been dissolved in the urine, we find in the first place a well marked difference in the views held by what are termed the French and the German Schools. The basis of this difference consists in whether during any part of the paroxysm the circulating blood is rich in free Hb or not. In other words the German observers insist on a state of Hb-aemia preceding and during the passage of Hb in the urine. The French School on the other hand deny this. Küssner[20] was the originator of the theory of Hb-aemia and his investigations have been repeated and confirmed by various observers since including Ponfick and Ehrlick. The view held by most French Pathologists on this subject was that the destruction took place in the kidney since they could demonstrate no Hb-aemia at any time during the attack. Hence they were forced to the view maintained most forcibly by Prof. Hayem[21], that the organ which was most active in the process whereby Hb-uria was produced was the kidney, and that in this organ very acute congestion ensued after exposure to cold and that in some way unexplained by

him the resulting action on the kidney tissue induced it to destroy the red cells and excrete the Hb in the urine. In this view the blood cell plays an absol - utely passive part and is actively destroyed by contact with the kidney capillaries but beyond this the explanation does not go. However, many observers since then have demonstrated both a preceding Hb- aemia and also a general want of resistance to injury on the part of the red cells in these patients and recently the French School have acknowledged these facts. Copeman[27] and Bristowe examined serum from blisters as well as blood plasma and clearly demon - strated the presence of Hb in the blood stream in a free form, even half an hour previous to its appear- ance in the urine. This observation is confirmed by the results of Ponfick[28] who found that in injecting Hb into the circulation a large quantity estimated at 1/60 of the total quantity naturally in any animal used, could be introduced without any subsequent ap- pearance of it in the urine. Above this quantity it could immediately be demonstrated in the urine and not only the excess but practically the whole amount that had been injected. Copeman also demonstrated a want of rouleaux formation, a marked poikilocytosis and general liability to injury of the red cells dur- ing the attacks, and also that within a variable time corresponding with the acuteness of the paroxysm,

there was a complete regeneration of the red cells which was always rapid, and hence he considered that the destruction which took place was an exaggeration of the normal physiological destruction that is always occurring in the blood. Ehrlick[22] confirmed these observations in the main and demonstrated the liability that the red cells of these patients possess of being destroyed by relatively slight lowering of the temperature in the surrounding medium, a fact refuted by Hayem and also by Rodet.

Murri[23], supported by Barlow and others, lays great stress upon "the inherent weakness of the corpuscle" to which he attributes the main cause of the disease. He considers that the cell is especially impaired in its combination of the Haemoglobin with the other constituents of the cell and that this is due to defective action of the bloodforming organs, the result of syphilis and other allied constitutional disorders. Robins[18] also holds similar views regarding the defectiveness of the individual red cell but in addition argues a renal factor apparently of the nature of an active congestion. Rosenbach[24] held the same view but Ehrlick propounded the view which has gained in favour recently, that the main factor in inducing the solution of the Hb from the red cells is the endothelium of the capillaries either by the production of a toxin under the influence of cold or by a direct phagocytic action

on them.

An interesting fact was noted by several observers, Johnson, Mahomet, and especially Ralfe that attacks of paroxysmal Albuminuria or more properly Globulinuria may occur from time to time in patients suffering from Haemoglobinuric attacks, accompanied with the malaise and modified symptoms of an attack of paroxysmal Hb-uria. In this phenomenon we probably have the explanation of the ultimate end of the Hb liberated in minute quantities which is not sufficient in itself to cause Hb-uria. Here probably the Hb when liberated in these small quantities, is broken up into at least two main constituents, the proteid portion of which is excreted by the kidneys and the pigmentary portion by the liver. Experimental evidence, where slight attacks have been induced in patients confirms this explanation of the condition. (Copeman. Allbutt Syst.Med.) As will be brought out later when dealing with toxic Hb-uria there are two other factors occurring in this form of Hb-uria which it is well first to mention here. One is the nature and form of the Hb as it is liberated from the cell into the blood plasma and the other is the seat of this liberation. All evidence shows that in this condition the Hb is in a simple form, probably pure and not combined with other proteid molecules or if so at least in a more soluble form. It will be seen how with even more excessive

destruction of the red cells than occurs in this condition no Hb-uria ensues, a fact to be explained on the nature of the Hb that is liberated. Secondly it is to be noted that there is every reason to believe that the destruction of the red cells occurs in the general circulation as distinct from the Portal circulation, namely in the part of the body exposed to the cold and in this fact we shall afterwards see how many of the phenomena of Hb-uria are to be explained.

The form of Hb-uria found affecting cattle and horses does not seem to be of this paroxysmal type but more allied to the toxic form to be dealt with later. It is nearly always rapidly fatal, usually in two or three days, and is associated with marked malaise, febrile excitement and often paralysis of hind limbs. In horses alone it appears to be due to changes in temperature and mainly affects stable horses which have been suddenly exposed to cold night air. In cattle and sheep it is nearly always found to be due to the feeding, certain districts and certain vegetables being closely associated with the onset of the symptoms.

TOXIC HAEMOGLOBINURIA

The term toxic in this relationship is used to differentiate certain forms of the disease from that which has just been discussed. In this sense it is a fairly definite term, yet when one looks at the forms comprised under the heading , one soon perceives that the term is less definite and that there are one or two varieties included in it. Three varieties of toxic Hb-uria stand out fairly distinctly in our present knowledge and it remains to be seen whether these three become further subdivided or rolled into one as more knowledge of the subject is obtained.

The first variety is that which might be termed definitely the toxic one as in it we can recognise the cause of the symptoms and can produce them at will. This includes the Hb-uria due to chemicals such as Potassium Chlorate, Pyrogallic acid, Arseniuretted Hydrogen; the toxins of the exanthemata chiefly scarlet fever and other allied agents.

Another form of toxic Hb-uria is that known as Black water fever. This seems to be associated in some definite way with malaria but our present

knowledge is tending to make it a distinct variety rather than to include it among the above definitely toxic group as being a sequela of Malaria and due to the toxins of Malaria.

A third variety includes certain anomalous cases in which absolutely no definite cause can be found and are apparently idiopathic. To such a class belongs the remarkable epidemic reported by Winklers occurring in the Dresden Foundling Hospital as well as many cases of individuals attacked with the disease in whom no cause for the illness can be found.

These three forms vary in certain important particulars but yet have certain factors in common and are better studied together. It is most probable that, as our knowledge extends, these divisions will be broken down and we shall find a definite natural physiological law the basis upon which the apparently different forms of Hb-uria stand. For after all we are confronted with only one symptom, the elucidation of which seems to be the key to understanding the disease, and whose solution would appear easy when one considers the relationship between the Hb in the blood stream and the excretory apparatus of the kidney, and how easily any free Hb could be excreted in the urine, thus constituting Hb-uria.

In looking into the literature of this form of Hb-uria which has been termed toxic one is met

with great difficulties. From an experimental aspect there seems to be no one who has studied the subject from the view of the presence of Hb in the urine. All the knowledge one can obtain can only be gleaned from experiments performed in elucidation of the origin of jaundice, a subject which caused a somewhat heated controversy between the leading pathologists of the period about 1880. Many facts then brought out throw light upon our present question, but as the object of those experiments was regarding bile formation and absorption, what facts bear upon Hb-uria are often left in an unfinished and indefinite state. But it will be necessary to hurriedly revise a great deal of the work of these investigators in order to appreciate the value of our present knowledge on the subject of Hb-uria.

Naunym[26] in 1868 seems to be the first to inject pure Hb into an animal and in each case he induced Hb-uria. His object was to verify a recent statement by Kuhner[28] to the effect that Hbaemia per se could cause jaundice and having disproved this he did not pay any attention to the Hb-uria he induced.

Tarchanoff[29] repeated these and other experiments in 1874 but came to erroneous conclusions which Stadelman[30] pointed out and demonstrated by experiment in 1878. Having elucidated the point in question the latter observer set about experimenting with a substance Toluylendiamin at the advice of his professor Schmiedeberg who had been struck with

the discolouration of the skin it produced when ad - ministered in some of his experiments . The exper - iments that followed were of great importance and mark the commencement of the study of the process of haemolysis occurring in the body. At the outset Stadelman found that he was apparently dealing with a substance that was not constant in its action, for he found that whereas in dogs it produced very in - tense jaundice, in cats it caused only transient jaundice but very profuse Hb-uria and further that the drug was almost inactive in producing either effect in rabbits except in very much larger doses. In investigating further the action of the drug on cats he recognised that the onset of Hb-uria and the period of the earliest recognisable trace of bile acids in the urine were identical, and was led to believe that the bile acids were mainly instrumental in the production of this phenomenon. Further exper- iments in order to prove or disprove this theory re- sulted in a negative conclusion and he acknowledged that he could not explain the occurrence. He failed to recognise the fact that Toluylendiamin produces very marked haemolysis, and thus, while his obser - vations were correct, he missed the link that was to make the results of his experiments uniform though still not quite intelligible.

Ponfick[61] in 1875 whilst investigating the practical utility of using the blood of animals for transfusion into man brought out a number of facts that bear ~~fruit~~ directly on our subject. His experiments lead him to two definite results, first that foreign blood is toxic and causes fatal results in relatively small quantities, and secondly the constant occurrence of Hb-uria when foreign blood is used. He recognised that the quantity of foreign blood necessary to produce either of these symptoms, though varying widely with various animals, were remarkably constant in successive experiments where the same set of different animals was used. He proved that it was not merely due to the extra fluid being injected for he injected pure foreign serum only, without result and yet on the further injection of but 1/40 part of what would otherwise be a minimal dose of foreign blood the result was a profuse Hb-uria, though again a similar injection of allied blood caused no Hb-uria under similar circumstances. He also bled an animal previous to injecting foreign blood and induced Hb-uria before the quantity of foreign blood injected had equalled the quantity abstracted. Hence it is to be concluded that the results are caused by the properties of the blood itself and not by any mechanical physical factor.

With regard to the origin of the Hb liber-

ated after injecting foreign blood many observers have held opposite views. Panum[32] and after him Mittler[33] and also Landois held that it was liberated from the recipients blood by a process of solution. Oscar Hasse considered that the transfused foreign blood immediately took up its physiological action in the system and that the cells of the recipient most prone to decay broke down and the Hb was liberated. Ponfick disproved all these views and proved that it was the donors blood that became disintegrated, a fact easily demonstrated in the case of fowls and mammals where the shape of the cells differs.

The question arises what becomes of the Hb that must necessarily be set free when a dose of foreign blood is injected which is too small to induce Hb-uria. That the vessels can hold Hb in solution without it appearing in the urine can be demonstrated by injecting Hb in a pure state directly into the vessels when, if small in amount, none appears in the urine. This form of the experiment when pursued further demonstrates another fact, namely that the results produced by the injection of foreign blood are directly referable to the Hb itself that is retained in the foreign blood. For it is found that pure foreign Hb produces Hb-uria or death according to the dose and that the dose corresponds in all cases with the amount of Hb in the blood of the

foreign animal , and varies between the same limits in regard to its effects. And further, what is most striking of all, is that the same law holds good for Hb prepared from an allied animal except that the limits for the production of Hb-uria or death are very much raised.

Other interesting facts that came out during these investigations were that if a certain interval were allowed to elapse between the injections, quantities of foreign blood could be transfused far exceeding the usual limits yet without producing any result. If this interval were not observed a Hb-uria resulted which corresponded with the sum total of the injections and lastly if a profuse Hb-uria had been produced in any way and had passed off it required a much smaller dose to start it again than was necessary to initiate an attack.

Regarding the cause of the toxicity Ponfick could only state that animals most unlike in habits &c. were most toxic to each other in this respect, and considered that there is an indefinable relationship between the Hb and protoplasm in various corpuscles which may account for the solution and destruction under new conditions or that the co-efficients of Hb or the concentration of the plasma may all have some bearing in the haemolysis that takes place. He estimated that if the liberation of Hb

within the body exceeded one-sixtieth part of the sum total of the Hb of the system, Hb-uria always resulted. Under that quantity it did not appear in the urine but was latent.

As regards the ultimate end of this so-called latent haemoglobin a very plausible theory is at present held and is confirmed by both pathological and physiological facts. It is generally believed that a small quantity of Haemoglobin free in the plasma is mainly dealt with by the liver. Wherever the disorganization of the haemoglobin into its main constituents of a pigment and a globulin takes place, whether in the capillaries throughout the system or in the liver or other organs there is hardly any doubt that the liver takes upon itself the function of eliminating the pigmentary portion and leaves the kidney to deal with the globulin portion, to excrete it or to retain it for the further use by the tissues of the body. For physiology tells us that almost all the pigment of the bile is derived from the haemoglobin of the tissues of the body and that a destruction of red cells is associated with increase of the pigment of the bile. Also that the liver in common with other tissues has the power of breaking up the pigment as it occurs in haemoglobin in order to extract and retain a large percentage of the iron contained in it and to excrete the other portion of the

pigment now much reduced in iron. This fact argues that in normal healthy people there is a constant breaking down and regeneration of the red cells of the blood, just as occurs in any other organ of the body, especially those most actively engaged in physiological processes, and that the pigments of the bile are to a great extent an index to the degree that this takes place.

The pathological feature throwing light upon this ultimate end of the Hb has already been referred to when dealing with the Paroxysmal form. Ralfe, Mahomet and others have repeatedly met with cases of Paroxysmal Globulinuria in patients suffering from the allied form of Hb-uria. The same subjective symptoms of malaise and fever were associated but in a very much less degree and it was argued that there had been a limited destruction of blood cells, in - sufficient to cause Hb-uria but that the organs were dealing with the foreign material in the plasma by a method suited to the needs of the circumstances. In health it is probable that the minute quantities of Globulin set free with the daily waste of the tissue of the blood is retained and made use of and only when this quantity exceeds a certain limit does the urine contain the excess of Globulin.

Up to this point numerous facts had been gathered chiefly by Tarchanoff, Stadelman and Ponfick

besides others but no one had been able to allocate to each fact its proper station nor to find a law or basis that would satisfy the several conditions. The man destined to serve as an exponent in this re - spect was Afanassiew. He also began his investigations in regard to the question of hepatogenous versus haematogenous jaundice and being struck with the general uniformity yet startling discrepancies in the results of Stadelman's experiments, he set about repeating these experiments, and was able to deduce certain facts. He first recognised the intensely destructive action upon the blood corpuscles of the drug Toluylendiamin and hence was able to explain much that was obscure to Stadelman. This same in - vestigator was the first to study the action of the drug in producing Hb-uria and thus he experimented more with cats, whilst Stadelman had made use of dogs almost exclusively. Again Afanassiew also found that the difference of the action of the drug mentioned by Stadelman in respect to the dog, cat, and rabbit was one of degree only and not an absolute differ - ence. He asserted that the animals were susceptible to the drug in the order of the cat, dog, and rabbit but that either jaundice or Hb-uria can be induced at will in any by careful dosage. Thus he attributes the anomalous action of the drug to the factor of susceptibility only, but it will be found later

that another explanation can be given. Based on these observations he enunciated certain theories regarding the production of Jaundice and its relation to Hb-uria which he considered merely as different phases of one and the same condition, namely destruction of the red corpuscles, the determining cause being the degree of the haemolysis. If the destruction were moderate the liver managed to deal with the debris, and having to deal with the coloured element produced excess of the bile pigment constituting a polychromia rather than a polycholia. This necessarily resulted in a more viscid bile which was with difficulty excreted along the fine ducts under the usual low pressure of the biliary duct system. Hence was easily explained the reabsorption into the capillaries of the bile pigment which being deposited in the subcutaneous and submucous surfaces constituted the marked jaundice, and thus he was able to practically settle the dispute regarding the origin of jaundice which had been raging for several years among the then most eminent pathologists.

Regarding the production of Hb-uria he argued that this merely indicated a haemolysis greater than the liver could cope with and that therefore the kidney was called upon to aid in the elimination. With regard to the rabbit where it was difficult to induce either it was argued that the animal had a

tolerance for the drug but that dosage was the only question regarding the ultimate result. (Virchows Archives Bd.98)

These results are held to be quite satis - factory with regard to the question of the cause of Jaundice and Stadelman in a monograph in 1892 having again revised his work in the light of Afanassiew's new discoveries, confirmed his views regarding the occurrence of jaundice and his able work sealed the discussion, mainly though his further discovery that the bile acids and pigments were normally excreted in inverse ratio to each other and the acids usually much later, thus explaining the presence of bile pigment in the urine whilst bile acids were absent, a phenomenon the discovery of which had first raised a doubt as to the liver always being involved in cases of jaundice and hence the idea of a haematogenous form.

But in regard to the production of Hb-uria and of the almost non toxic effects of the drug upon the rabbit, the explanation given by Afanassiew is not sufficient except in a too broad sense. It is not intended to discuss the alternate theories here but at a later stage in this paper. Now it is only necessary to mention that in many cases, which con - stitute a majority, toxic doses of the drug, whilst killing a rabbit ultimately, never induce either a jaundice or a Hb-uria. Also that with dogs and cats

individual susceptibility is so variable that one cannot predict what the result will be except that in dogs the rule is to have jaundice even with relatively large doses and in cats just as constantly we have Hb-uria even when the doses are correspondingly minute. For an adequate explanation of these seeming inconsistencies in the action of the drug we have to investigate several obvious points of vital importance to the question. We must try to ascertain whether the drug acts in the same way in each animal or if by reason of any compounds made between it and the organic tissues of the body into which it is injected, new and different actions are induced. Again the physiological processes in the animals under consideration must necessarily differ in accordance with their habits of life and it is but just to assume that they would react to pathological conditions differently. This may be evidenced in many and various ways, such as the individual organs playing a major or subsidiary part in the process of dealing with the condition induced by the drug, assuming this to be identical in every instance, or conversely the form in which the complex body Hb is presented to be dealt with by the various organs may differ in each case and thus again afford an explanation. But our object at present is merely to indicate the unsatisfactory nature of the conclusions of Afanassiew and the need for more information before we can accept

them.

On the other hand we find the results of these experiments confirm both the results of, and many of the deductions from the experiments of Ponfick mentioned before. It explains the need of a definite interval of time between successive injections of pure Hb in order to prevent the occurrence of a Hb-uria and also why a small quantity following closely upon an induced Hb-uria is able to reinstate the condition of Hb-uria for in one case the liver has not had time to deal completely with the results of the first injection, and hence calls in the aid of the kidney to deal with the new quantity even though it may be in itself too small to induce Hb-uria. In the second instance the liver is probably overwrought and physiologically clogged with the results of its previous activity so that it throws the whole burden of excreting the new injection of foreign material upon the kidney. But this new light on the subject does not explain why successive small doses rapidly repeated, cause a Hb-uria equal to that which would be produced by a single injection of the sum total of the individual injections. Assuming a pardonable faulty observation on the part of Ponfick, since we have no accurate methods in estimating the exact degree of Hb-uria, this feature may be explained as a

combination of the two above conditions, a gradual clogging of the functions of the liver by the waste products of its activity and hence the throwing upon the kidney of the easier function of eliminating the sum total existing in the system when it had risen above the 1/60 part according to Ponfick. A profuse Hb-uria would result in spite of only small doses used at a time and hence the observation made by Ponfick that the resulting Hb-uria corresponded to the sum total injections and not to the amount of the immediately inducing dose.

It should be borne in mind how different are the actions of the liver and kidney in their method of getting rid of the Hb free in the plasma. The kidney acts in a passive way relatively to the liver, practically as a filter through which the Hb unaltered finds an exit. We know not why it acts as a barrier to small quantities of the material and only letting it pass when the quantity is excessive. In an accidental way, but in common with all forms of living body tissue, the kidney cells do partly break up the Hb on its passage through that organ and hence we find the lining epithelium more or less pigmented with iron-derivatives of Hb. But in the liver a very active process takes place when dealing with Hb brought to it free in the plasma. The liver cells act each as a vigilant sentry retaining parts of the constituents of Hb either for the economy

of the body as a whole or for elimination elsewhere and allowing other portions to be excreted in the bile almost wholly as pigment. Thus the liver cells break up the Hb and retain the iron probably in a combination with albumen and return it into the circulation for subsequent use by the young red cells. The pigment now free from iron is excreted as bilirubin and is the main pigment of the bile. With regard to the proteid constituent of the Hb it has been proved by Dr Noël Paton[35] that the excretion of urea by the urine is almost exactly proportional to the degree of haemolysis and thus it is concluded that the liver excretes part as the organic constituents of the bile acids, since it is undoubted that the Glycocol and taurin of the bile acids are derived from proteid molecules, and secondly returns a part into the blood stream to be excreted as urea by the kidney. It is thus easily understood how the kidneys act as a safety valve or overflow channel to the liver in regard to the ultimate end of free Hb, and how that a great strain is thrown upon the functions of the liver in these circumstances. We shall see that these facts may have a very important bearing upon the subject of the trouble Hb-uria as it occurs as a malady affecting the human race. These satisfactory experiments of Afanassiew and the new theories he deduced from the results had the effect of

inducing many old and new observers to turn their attention to the subject of Haemolysis. Hitherto numerous cases had been recorded where Hb-uria had followed the administration of various poisons whether accidentally or experimentally and these now became more interesting in the light of the new discoveries. Klebs[36], Ponfick[25], Lassar[37], and Trojanow[38] had all independently recorded cases of Hb-uria following extensive burns whilst Marchand[39], Hofmeister[40], Reiss[41], and others had noticed that Chlorate of Potash could induce severe attacks of Hb-uria as also could arsenic in fumes as noted by Fitner[42], and Wächter[43]. The substances found experimentally to have this action were pyrogallic acid (Neisser[44], Afanassiew[45]) certain fungi (Ponfick[46], Bostrom[47]) distilled water (Tarchanoff[29], Leichtheim[48]) Glycerine (Afanassiew[45]) blood altered by modified heating (Schutze[49] and Afanassiew[45]) blood of different animals (Ponfick[31] and Landois[50]) and pure Hb (Naunym[34], Hermann[51], and Tarchanoff[29]). When examined with regard to the liberation of free Hb into the plasma it was found that in all the above circumstances this was the case and one common factor was recognised. But it became evident that the mere fact of the condition of Hb-aemia was not sufficient to answer all the demands of the theory of Afanassiew. For his teaching hitherto had been that it was the degree alone of Hb-aemia that determined the predominance of the symptoms of

Jaundice and Hb-uria. It would take too long to even refer in brief to the numerous experiments and the results obtained by the observers mentioned above. But in as much as Afanassiew[45] himself conducted many subsequent experiments with various modifications which led him to somewhat modify his previous views it would be as well to mention the results of his work and the theories he deduced therefrom. The experiments were conducted mainly with the view of inducing successive attacks of Hb-uria in order if possible to study the pathological changes occurring under these conditions. After trying a number of different agents he at last restricted himself to three as being most characteristic of different actions of haemolytic agents. These three were pyrogallic acid, Glycerine, and Toluylendiamin. He tried $KClO_4$ but it had other constitutional effects that rendered accurate work difficult. In the three drugs mentioned Afanassiew recognised three different actions upon the red cells which he thought explained their different actions. Glycerine caused a solution or extraction of the Hb from the cells apparently unchanged in constitution, but there were no morphological remains of the cells to be found. In the next place came pyrogallic acid which while abstracting the Hb from the cells left numerous morphological remains of the corpuscles as "ghosts" or "schalten" besides broken up, crumpled particles. Thirdly came

Toluylendiamin which caused rupture of the cells into small fragments each of which appeared to retain the constituents of the corpuscle as a whole. Under one of these types can be placed almost all the a - gents known to cause haemolytic action in respect to the red corpuscle. He found that with glycerine, though the destructive action upon the haemocytes was unmistakeable he was not able to induce jaundice. In small doses merely Hb-aemia and increase of bile pigment and with larger doses Hb-uria immediately ensued, there being never an intermediate phase of Jaundice. This result he attributed to the nature and character of the Hb liberated being in a pure soluble form and was of opinion that in this respect the action of glycerine most closely resembles the conditions that maintain in Paroxysmal Hb-uria.

With Toluylendiamin he found, as stated above, numerous particles of corpuscles in the blood but apparently no Hb-aemia as such, in the effects of smaller doses. The spleen was enlarged and en - gorged, significant of activity in dealing with this condition of the blood and preparing the particles for excretion. The capillaries of the liver and bone marrow were also congested in their activity in deal- ing with these particles which are disintegrated by the leucocytes and connective tissue cells of the whole organism and takes place more actively in these

areas. He also attributes the more constant occurrence of jaundice which was induced by this drug to this difference in its haemolytic action, and considers that Hb-uria supervenes when the destruction is greater and the haemoglobin from the particles becomes disseminated by solution in the plasma before the liver can deal with it at all.

The results of the experiments with pyrogallic acid were in keeping with what one would expect from its direct action on the red cells and the data obtained from the two above mentioned agents. With it one obtains usually both Hb-uria and a certain degree of jaundice and the animals seem to tolerate it worse than they do either Glycerine or Toluylendiamin.

The result of all these experiments was to indicate that Hb-uria was not so much dependent upon the haemolysis that took place as upon the process of that haemolysis and hence Afanassiew supplemented his previous assertion by saying that the nature of the haemoglobin set free in the blood was a second factor in the production of Hb-uria.

In the latter half of the eighties this study received an impetus from various sources be - sides that obtained from the interest evolved from the new discoveries. The most important of these new

factors which not only interested those who had been studying the phenomena from an experimental and scientific view but compelled the attention of the general profession and even of a certain part of the lay community was the recognition of a fatal disease almost endemic to parts of Africa whose main symptom was copious Hb-uria. Hitherto the paroxysmal form had been the most common and had received the most attention. But few cases of the so-called idiopathic disease had been recorded and now with the opening up of the West Coast of Africa this new disease was met with, a disease which unless conquered will render large and rich districts of Africa uninhabitable to the white race.

Another cause of increased interest was the increased study which had been devoted to the blood in health and disease and the new facts which that study elicited. Many new investigators were attracted to a subject which seemed to lend such promise of useful results. With this increase of interest directed to the subject, new methods of examining the effects of haemolysis upon the various organs were evolved which gave greater precision to the study. The chief of these was the discovery of the microchemical test demonstrating the iron pigment even in minute quantities in the different organs.

Engel and Kiener[52] in 1887 were the first to employ a strong solution of Ammonium Sulphide which caused the formation of a black sulphide of iron in the organs where the iron pigment of the blood had been deposited. By this method they were able more definitely to locate the positions in which the iron derivative was situated whereas practically no reaction was obtained upon a normal organ, e.g. the liver. On the other hand after poisoning with haemolytic agents especially with Toluylendiamin the parenchymatous cells of the liver lobules were found to show a great degree of deposition of iron in them appearing in the form of small black granules. The deposit was mainly at the periphery of the lobules and according to the chronicity of the poisoning extended deeper into the lobule and more completely filled the individual liver cells, crowding mainly about the bile duct capillaries which were usually distended with thick bile. The same reaction was obtained in various organs and tissues of the body of the animal mainly the spleen, bone marrow, and the kidney occupying the parenchymatous cells, leucocytes, and endothelial cells, the latter probably detached from capillaries.

The same processes, namely increased interest in the study of the physiology and pathology of

the blood together with improvement in the methods of study, caused the recognition of certain features as being common to conditions that were otherwise considered totally distinct and thus new light was thrown upon various allied conditions often very indirectly. It soon became clear that pernicious anaemia consisted mainly in a marked destruction of the red cells and that the process was chronic in nature. The same iron pigment was found in the characteristic seats for its deposit and with this knowledge the question as to the cause of this de - struction arose and many investigators put forth their energies in this direction. Of these the most notable was Dr W.Hunter[53] of London who made a special study of the pathology of Pernicious Anaemia and the result of his work on the subject which has been carried on for the last ten years has been interesting in many details that concern our present subject. Without going minutely into his experiments and reasoning we need only mention the results of his whole work. He maintains that instead of the character of the Hb liberated into the plasma determining its ultimate fate a more important factor in this respect is the seat at which the destruction takes place within the system. In this regard he differentiates very markedly between the Portal and the General

circulations. He considers that when the haemolysis takes place in the general circulation as distinct from the portal, Hb-uria is the rule and thus he accounted for the type called Paroxysmal. On the other hand he considers that in Pernicious Anaemia and in Malaria the seat of the destruction is in the portal circulation and the result of the haemolysis has to pass the liver to gain the general circulation and the kidneys and that here it is dealt with and that only when the destruction is excessive does Hb-uria occur. Feasible as this may seem and even tho' it may be correct, the data from which he drew his conclusions were incorrect. He asserts that the seat of the deposition of the pigment indicates the seat of the haemolysis, attributing to the organs the power of completing the breaking up of the corpuscles. In contradiction to most observers he does not consider that drugs like Toluylendiamin and Pyrogallic acid have direct action on the corpuscles in the vessels but that they act mainly in the circulation in the spleen. It is however generally accepted that the destruction takes place in the general circulation, being a direct action and that the spleen and allied organs merely collect the insoluble portions of such cells that are destroyed, the particles being mainly brought to the spleen by leucocytes

and other phagocytic cells. His theory does not account for the sudden and regular occurrence of Hb-uria in cats when Toluylendiamin is administered by mouth in which case the destruction would certainly occur in the portal system first if not entirely. One very interesting experiment he records where he excised the spleen in a rabbit on several occasions and found that the animal could then stand larger doses of Toluylendiamin though still without bad effects. In these cases he found a new factor namely very marked leucocytosis which especially affected the portal system, and he considered that the vast capillary system in the portal circulation had taken up the function of the spleen. The conclusion Dr Hunter came to regarding the pathology of the disease he was specially studying, namely Pernicious Anaemia was that it was due to the chronic absorption from a disordered digestive canal of a poison the most marked action of which was a slow chronic destruction of red cells in the portal capillaries, a theory which has been accepted by the majority of pathologists at the present time. Hence we see in Pernic - ious Anaemia a disease allied to Hb-uria the chief distinction being that in the former the haemolysis is a very chronic process whereas in Hb-uria it is a very acute rapid process but in both the essential feature is the breaking up of the red corpuscles.

All the foregoing discoveries and experiments, indicative of a vast amount of labour and energy on the part of the various investigators might have been still only of scientific interest and of general importance were it not that in recent years the disease known as Blackwater fever or Hb-uric fever has drawn so much attention to itself and made the solution of its aetiology and pathology a necessity if the white races are to develop certain large areas in Africa. The disease had been recognised by the French before, but in this country Dr W.H. Crosse appears to have been the first to publish cases and direct attention to the disease which he did in 1885. The disease occurs in greatest frequency in the tropical parts of Africa, attacking the white races especially and but rarely the natives. It usually attacks those who have been residing in the localities for at least several months, the average duration of freedom from the disease being about 18 - 24 months. During one of the many periodical attacks of malarial fever that all such residents are accustomed to, suddenly on this occasion the attack is prolonged, the temperature rises abnormally to 104° F. and higher, the patient at the same time experiencing severe aching pains in the back and loins, with headache and bilious vomiting. On making

water after or during such manifestations the urine is found to be any colour from red to almost black and the colouring matter is found to be Hb and the urine free from red corpuscles. The patient feels prostrated but usually recovers from the first at - tacks but can rarely withstand more than the fifth or sixth attack, death being due either to the direct effects of the modified haemorrhage as from exhaus- tion in prolonged cases or anaemia in more acutely fatal ones, or secondly from a form of uraemia. The attack is associated with a marked yellowish colour- ation of the skin and sclerotics which soon passes off and does not seem to be a true jaundice. Such are the main features of a typical case of Blackwater fever.

Though several cases had been recorded by practitioners in the tropics and a discussion took place upon the subject at the Paris Medical Congress of 1888, it was not till Dr Patrick Manson read a paper before the London Epidemiological Society in 1892 that the disease could be said to have been brought before the medical profession in this country in at all a definite and forcible way. Since then ever increasing interest has been displayed in the solution of this disease so formidable to all whose labour calls them to tropical Africa. As is always

the case with a new and obscure disease the theories put forward in regard to it in its several aspects are very numerous, in fact almost as numerous as the individual writers on the subject. Out of all these, three theories may be noted as containing the fundamental factors in almost all the views hitherto put forward. These are that

(i) Blackwater fever is merely a complication of malarial fever but in no sense a separate or new disease.

(ii) Blackwater fever is the result of two morbid processes one of which is malaria, the other being some poison which tends to produce a mild kind of fever and also determines the production of Hb-uria.

(iii) Blackwater fever is a distinct disease, its association with malaria being quite accidental.

Regarding the first theory that it is merely a complication of malaria, this was put forward by Dr W.H.Crosse[54] who had studied the disease in Africa as well as suffering from it personally. He considers that it bears to malaria the same relation that the symptom of Hyperpyrexia does to Rheumatic fever. Interesting as the analogy is, it however does not throw any further light on the subject. On the other hand one would expect in a country like India where malaria is so common and seen in all its variations and

complications, that this complication would also be common, whereas it may be said to be absolutely absent except of recent years. In Hb-uria also there are not other indications of an excessive exacerbation of an ordinary malarial attack, as in such a case one would look to find a more abundant sporulation of the plasmodia in the blood which is not in evidence.

Dr Washbourn[55] also considers Hb-uria as a complication of malaria pure and simple, attributing the symptom to a local renal condition due to the selection of the organisms for this organ in the same way as, he states, we have them selecting the intestine and brain in certain cases producing symptoms of Cholera and Apoplexy.

In favour of the view that it is only a complication of malaria is the fact agreed to by nearly everybody that the symptom only attacks people who have suffered from malaria and become somewhat cachectic on account of it. It rarely affects newcomers and then only if they have been previously malarial subjects. This fact is refuted by Sambon who states that he has seen it occur within the first few months of residence in an affected area. Dr W.H. Crosse considers that the complication is due to the toxaemic nature of the blood due to prolonged

saturation with malaria and that just as it is thought that syphilis predisposes to Paroxysmal Hb-uria so Crosse thinks that malaria predisposes to Blackwater fever, and their relationship is on a par.

The view that the disease is a manifestation of the working of two factors one malaria and the other a specific "poison" is that held and put forward by Patrick Manson.[56] He considers that its connection with malaria is indisputable as it only affects those that have suffered from malaria but on the other hand he brings forward many arguments to show that another factor must be present. The clinical facts in favour of the symptom not being purely of malarial origin are (a) the occasional absence of any febrile condition which is incompatible with the view that it is an acute malarial attack. (b) The abruptness of the conclusion of an attack is unlike malarial fever in an acute form. (c) The prolonged intervals of a week, fortnight, and month are unlike any periods known in true malaria where the intervals are usually one to four days. (d) The often uselessness of quinine in treatment.

Facts of an Epidemiological nature also favouring this view are (1) It occurs almost only in the Tropical parts of Africa and America and is almost unknown in India, Eastern Peninsula and Archipelago, Australia and China. (2) It occurs for the

first time in certain instances in people returning to Europe from the recognised affected quarters and not in those from elsewhere. (3) There is no record of the disease prior to 1850 and recently it has become frequent. This last fact could not be due to carelessness in former observers and the symptom is so prominent that the writers on diseases in those parts could not have failed to refer to it.

In favour of it being a distinct disease and its association with malaria merely an accident, (since in these districts it is rare for anyone to reside without soon contracting malaria) is the fact of its apparently recent origin and its very localized endemic area. Further, it is the view of the oldest Indian observers that what cases they now meet with have been introduced, as they deny having met similar cases in their previous long study of diseases in India. Again if a patient who has contracted the disease, immediately leaves the district for Europe, if he is not cured, he may suffer from subsequent attacks up to five months after being in a non-malarious country. Also that ~~these~~ patients coming from such endemic countries though never having experienced an attack while residing there, may have their first attack after they have left the

district, looking as if a parasite had developed in them meanwhile. In contradistinction no such case of a first attack beginning in a malaria-free country has ever been observed in patients returning from residence in other countries where malaria is very rife but Hb-uria is rare or absent. The uselessness of quinine in this disease lends colour to the view that it is not malarial in nature since this drug not only has a specific effect on malarial fever itself but also upon all symptoms secondary to malarial toxaemia. The fact noted by W.H.Crosse that the disease has become prevalent pari passu with the turning up of the soil in these districts in the developing of the countries with plantations affords a possible explanation as to the source of the new organism if such it turns out to be.

In respect to the organismal nature of the disease nothing definite can be stated. Assuming that it is related to some form of malaria it is found that the organism most usually found in the blood of such cases is one more closely related to the organism said to produce the Aestivo-Autumnal type of Malaria than to any other. However, as Manson states, the presence of any organism is not conclusive of it being the causal agent as the blood may show organisms in malarial patients months after

the last febrile attack and even during continued administration of quinine. The fact that in the Aestivo-Autumnal type there is practically no rigor whereas in Hb-uric fever it is well marked, militates against the view that this is only a malignant form of Aestivo-Autumnal malaria. Also the Geographical distribution of the two diseases varies, Hb-uric fever being more limited than is the fever usually attributed to the organism in question. And further where both diseases do occur in the same locality, though they seem to be affected by similar conditions their seasonal maximal prevalence bears no relation to one another. Also the relative prevalence of the two diseases varies in places where both occur.

The great feature in regard to the action of the Aestivo-Autumnal parasite upon the blood of the patient and which is strongly in favour of it being in someway the cause of Hb-uric fever is that no pigment is formed from the Haemoglobin, a marked distinction from the actions of the organisms associated with tertian and quartan fevers which always form a mass of pigment in the red cell they inhabit. For this formation of pigment which seems insoluble is an evident reason why tho' malaria is always associated with marked blood destruction, Hb-uria is

so rare. The Hb is liberated in a form that cannot be excreted by the urine and is probably dealt with in a way peculiar to itself. Since the parasite in Aestivo-Autumnal fever does not form a pigment a very great step towards the possibility of the production of Hb-uria is made and it seems that one needs very little in addition to determine that it should occur, and possibly it is in this way that cold, exposure or fatigue may be sufficient to induce an attack as is generally stated to be the case.

Other views have been advanced such as Sambon's[57] that it is merely paroxysmal Hb-uria occur - ring in warm climates and affected in some points thereby. He accounts for the high mortality in Hb-uric fever as compared with the non-mortality in Paroxysmal fever by the fact that the former attacks wrecks of malaria. He is of opinion that both forms of the disease are due to one of the varieties of an organism that Babes found in cattle affected with the symptom of Hb-uria in Roumania.

Another view was that put forward by Profes- sor Koch[59] in 1898 namely that all cases of Hb-uric fever were quinine poisoning and nothing else. Owing to the high position in the medical world of the

observer making this statement it received a great deal of attention but was universally condemned and bitterly so by practitioners who were fighting the disease and who from personal experience could vouch for the usefulness of the drug as a remedy in many cases but who found their patients objecting to following their advice or having followed it and not having been cured complained of having been overdrugged on the strength of the statement of a person with the authority of Professor Koch. Tomaselli in Italy was the first to suggest the idea and in many cases there seem to be grounds for its veracity. But the fact that the disease may occur in people who have never taken quinine, its geographical distribution and the undoubted success in treatment of cases with it, all negative the view very emphatically and no one but the originator now has any faith in it. However the fact that quinine is useful in many cases may be an argument that the disease is a combination of two factors as enunciated by Manson and that when the malarial factor predominates it has definite anti-malarial action and so restores the patient. A reverse condition of the factors would no doubt account for the want of success in other instances, or even be the inducing factor for the onset of Black - water fever.

P A R T II.

The chief feature,which has characterized the recent marked advancement in all branches of science, has been the recognition of general laws governing a series of principles which hitherto had appeared as separate identities, having nothing in common. A similar process is now in progress in regard to our conception of the blood and its functions and the recent vast amount of work upon this subject is accountable for this advancement.

Till very recently it has been usual to consider the blood and its functions rather in the light of one of the connective tissues with a definite limited use, than as a complex organ of the body, to look upon it as being more in the category of bone and muscle than of, for example, liver or kidney. But now, with the more general knowledge that has arisen and with the recognition of the more complex composition and the wider range of functions, the position of the blood in the relaive importance of organic tissues has advanced to one of great prominence. Complex as we must consider the cells of the

liver, which can perform so exactly the two distinct functions, the glycogenic and the biliary, this action would appear very simple when we examine the numerous and varied functions demanded of and performed by the blood. If we think for a minute of all the forms of tissue occurring in the body, each with its dif - ferent structure and functions and each requiring a pabulum, not only for its own nourishment but to af- ford as well material for its own particular function in the body, whether it be in the form of a secretion as of a gland or force as of muscle, or exhibited in the more complex functions of the brain, it seems in- conceivable that a single medium should be able to perfectly satisfy these so numerous and varied needs. Moreover to this same nourishing medium is destined the function of removal of waste products due to the metabolism of the various organs and tissues, acting, for sake of analogy, as water pipe and sewer in one. Upon this last feature we must not insist too strong- ly, since in the light of recent discoveries in re - gard to extracts of certain glands and tissues, and the deductions obtained from these as to the rôle played by the internal secretions, it becomes more and more doubtful if there is as much metabolic waste product as had been supposed, but whether each so -

called "waste product" does not form a necessary component of the blood for the healthy action of some other tissue or organ; whether, in other words, the organs of the body do not so mutually depend on the internal products of each other as to form, when acting perfectly healthily, a true example of Symbiosis. But in spite of this qualifying view, the blood must become to a certain extent deteriorated as shewn by the various constituents of the urine and faeces besides the less marked evidence in the sweat and the respirations from the lungs, so that the powers of adaptability of the blood appear all the more wonderful.

Further evidence of the very complex nature of the functions of the blood and hence of its constitution is seen when we consider the larger phys - iological acts in which the blood takes a prominent part. The phenomena in the act of respiration are very wonderful and demand powers on the part of the blood of a very delicate nature yet of absolute stability, and the varying relationships existing between the Oxygen, Haemoglobin and the Carbon dioxide have never seemed so very remarkable partly because they are better understood than any other of the functions of the blood and partly, because for a long time, in

these relationships nearly all the functions of the blood were thought to be expressed.

And in the matter of digestion and assimilation, it is mainly through the action of the blood that the dead inert substances we take as food are so changed that they form the living protoplasm of our bodies, whether by affording the juices for the coarse digestion of these substances, or by the absorption of these products and the subsequent submission of them to the various organs and thence the carriage of them in a form capable of being assimilated by the various tissues of the body, one and all.

Again we see in the processes associated with gestation and reproduction, which in the main, depend upon the reflex vascular changes set up, the extreme manifestation of the functions of this complex substance and perhaps its strongest claim to be regarded in the nature of an organ in itself. When we look to its functions in pathological states of the body especially in relation to that condition termed inflammation we see a differentiation of its various elements according to their function, the marvellous complexity of which has not yet been fully determined.

The survey of all these features enables us to conclude that there exists in the body no tissue

or organ possessing such multiplicity and variety of functions as does the blood: that besides performing the complex functions of oxygen - and nourish - carrier to the cells it possesses other functions, till lately not thought of and which as investigations proceed are becoming more and more important in their bearings. Yet notwithstanding these very numerous and complicated functions which one would think required special protection we find that the blood is really more exposed to deterioration and damage than almost any other organ of the body. As one instance we have already called attention to the fact that the blood is normally deteriorated to a certain degree by the discharge into it of the various metabolic products that are to be excreted through their special channels. That such is the case is demonstrated by the occasion of disease when the excretory apparatus is faulty and these waste products are retained and accumulate in the system. Then the blood may be damaged in quality by a faulty chemical change in the function of any of the tissues of the body, evidenced very markedly in the case of two glandular structures the supra-renals and the thyroid, but how far also affected by any or all the rest of the tissues of the body is at present not measureable.

Looking again at the pathological states, especially those associated with the fevers and acute inflammations we find that the blood generally has to bear the brunt of the fight and we constantly recognise how severe a strain this may be. The action of all the various toxins is by means of the blood and being foreign and hurtful to the system must also interfere with the proper functions of the blood itself.

Finally when we consider the nature of the substances taken as food, their great complexity and their frquent potentiality for harm by reason of their quantity, quality or combination we must admit that blood must need very great powers of adaptability to enable it to encounter this danger so well as it does. Yet the fact remains that this highly complex and important fluid is only separated from frequent sources of contamination by the absorptive membrane of the alimentary tract, whose selective powers are relatively feeble in regard to protection for the organism as is seen by the numerous cases of poisoning in the widest sense of the term.

All this activity on the part of the blood indicates a corresponding wear and tear upon the constituents and it is remarkable how little this is manifested in any marked way. Not only is there very little direct evidence of the metabolism taking

part in the blood under physiological conditions, the main evidence being the activity of the organs and tissues which make good any deficit, but even in disease when the chief feature has been a destruction of blood there is often no direct indication of the destruction in the form of characteristic products, but the evidence lies in an ascertained loss and a corresponding activity in the formative organs . The destruction thus constantly taking place even in health, and, judging from the activity of the blood-forming organs it must be considerable, being so obscured as almost to escape notice, it is not surprising that the symptom of Hb-uria should immediately arrest attention owing to the very definite evidence it affords of severe haemolysis. But when viewed plainly it is really more surprising that it is not a more common feature of blood disease or taking an extreme view, that it is not a constant feature indicative of the normal haemolysis consequent of the functional activity of the blood. From viewing its occurrence as a symptom of disease, or a phenomenon to cause surprise, it is rather the want of such occurrence and others, indicative of blood destruction, that should arrest attention and stimulate enquiry as to the ultimate end of the Hb

liberated in the normal and constant physiological processes. Hence it is to the physiological processes in regard to the destruction of blood that we need to turn our attention, and it is impossible to say what is abnormal process until we are assured of what is normal. We have mentioned that the production of bile in some of its consituents is closely associated with the destruction of the red cells, but we do not know the factors determining the selection of the liver or the kidney as the organ for the excretion of the blood pigment, for the normal way by means of the liver would appear to be an indirect way compared with the simple excretion by the kidney. So that the subject of Hb-uria assumes the character of an accident in a usually well regulated process. The actual presence of the Hb in the urine loses its importance in the consideration of the conditions which preceded its occurrence and rendered it possible, its presence being expected after a certain stage in the process of the haemolysis had been reached. It is these deeper physiological and chemical processes that must be first understood and the answer to the question as to the cause of Hb-uria and its allied conditions will be seen as a corollary to the more general proposition.

In the elucidation of certain of the points that have thus been raised I undertook certain studies and experiments, in the first place examining the action of various chemical and physical agents upon the red corpuscles themselves and secondly injecting various substances into animals under certain determined conditions with definite ends in view.

With regard to the experiments with the corpuscles themselves, to which I will first refer, the process I adopted was to use my own blood in almost all instances, usually pricking a finger through a drop of the solution which was being tested. The mixture was quickly transferred to a slide and examined under 1/7 inch objective. In some cases where the action seemed very rapid I had to make a fresh cover glass preparation of the blood and run the solution in under it. At first I tried to work with the warm stage and the high oil emersion lens, but need of frequent changes and additions caused more irregularities than would occur at ordinary temperatures and with a lower power. Moreover, with the

the extra care and time required when using the 1/12 emersion lens many phases in the changes had often occurred before they could be focussed and watched. My first experiments were to contrast groups of agents such as acids and alkalies in their relationship to the red cells. I soon, however, recognised certain features that made me test the physical properties of density and osmosis in their effects upon the cells. Finally I used certain well known haemolytic agents in order, if possible, to recognise some common feature in their working, which would help to throw light upon this very complex subject.

In regard to the first question regarding the difference in action of the acid and the alkaline salt solutions the most marked feature was the very slight reaction with even relatively strong alkaline solutions and the very marked reaction with very weak acid solutions. With solutions from 5% to 10% and a little stronger of such alkaline salts as Carbonate of Soda, Carbonate of Potash, Caustic Potash, Ammonium Chloride, except for a morphological change of little significance, very little destructive action ensued and never was there any marked degree of liberation of the haemoglobin. The cell was destroyed as a whole and in no way seemed to disintegrate into any of its constituents. One may take it that whatever

may be the relationship between the red cell and its colouring matter, it is not weakened by the alkalinity of the surrounding medium.

On the other hand with acids there is immediately a change in the shape and behaviour of the haemocyte, indicating much more activity due to the effects of an acid medium. A characteristic reaction is obtained with less than a 1% sol.of Acetic Acid. The cells whether quite normal in shape or crenated first of all, gradually assume a uniformly densely coloured spheroid shape. The centre shadow is first lost in which process the margin of the shadow be - comes wrinkled and crenated whilst the margins of the cells are quite uniform and regular. At the same time the whole cell seems to contract in size, be - comes more uniformly and densely coloured and easily rolls away in the current, all indicative of the spheroid shape that has been induced. This formation of a sphere from the normal disc of the red cell seems to be the first stage in all cases where the Hb is subsequently extracted or liberated. After this stage the process of decolouration proceeds according to the acid and the strength of the solution. The spheres merely become gradually blanched, leaving a perfect ring well defined but colourless indicating either the decolouration of the colouring matter or

its extraction from the cell. After a short time these pale rings become more indistinct and finally seem to collapse and shrivel like empty balloons into a small irregular mass. Pari passu with this shrivelling there is generally a marked deposition throughout the field of minute translucent refractile granules very similar to blood plates, but whether fibrin or precipitated Hb or its derivatives cannot be made out.

With citric acid the same changes ensue except that the colourless rings always retain a small mass of debris at one pole and hence have the appearance of signet rings. There is besides the mass of highly refractile granules throughout the fluid.

Other reagents act somewhat in the same way. A weak solution of $CHCl_3$ in water causes a very rapid decolorization of the cell the difference being that the decolorization and the disappearance of the cell body proceed uniformly so that no colourless ring results. A very similar result occurs with a .5% sol. of $KClO_4$ and in both cases the fluid medium appears to be colourless as if decolorization of the pigment occurred and not merely extraction of it from the cell. Very similar results are obtained with Gallic and Oxalic acids as also with Alum. With oxalic acid there is a true decolorization of the pigment so that

the resulting fluid is clear.

With Tannic acid an altogether different action takes place and one quite peculiar to itself as far as I can make out. Some of the cells influenced by a weak solution react as with any other acid fluid as described above. But the majority of the cells after first swelling up, then suddenly exude a coloured droplet which adheres to the side of the corpuscle, just as if the inside tension had been so great as to rupture the cell very slightly and allow a small oozing of the contents. This bud clinging to the cell is more highly coloured than the cell proper and is somewhat refractile. Moreover the original cell does not diminish in proportion to the mass extended but retains its original spheroid shape and size. Finally the corpuscle itself becomes pale and decolorized whilst the extended portion always retains its colour but gradually spreads out crescentically round the pale ring of the cell and then breaks up into very fine granules. Sooner or later the coherence of these granules breaks down and they are disseminated through the fluid, but in this case the colouring matter never seems to appear in solution but always precipitated in these granules.

With Toluylendiamin the results were very similar to those occurring with tannic acid except

the action was slower. With it also the Hb was not liberated in a soluble form but the cell protoplasm seemed to fragment, each piece retaining its colour apparently in a less soluble form than the normal Hb.

Recognizing the variety of results one obtained with the same cell various solutions of common salt were then tried to see what effect the action of fluids of varying density produced. The most striking feature of these experiments was the very great liability of the red cell to structural damage short of disintegration of its Hb or any other constituent, but demonstrated by the various forms of crenation and general poikilocytosis that ensued upon very slight alteration in the surrounding media. The percentage solution which least affected the shape of the red cell was .86. A stronger solution caused the red cells to apparently flatten out and lose all their elasticity. They become buckled up with broad irregular faces to the margins, appearing in miniature like flattened pieces of clay or mud baked in the sun. When in the stream they turn over and over like plates or roll on their edge like wheels, but have lost all the physical properties of the normal cells except in still retaining the colour.

With solutions of less density all the various phenomena of crenation become evident and with

very weak solutions the cells assume the spheroidal shape most constantly. These changes show how that, in transfusion of salines, it is necessary to make the solution very carefully and I have no doubt that in many cases the failure of this treatment is due to blood destruction in this manner, the mere bulk of added fluid has but immediate effect whereas the regeneration of red cells in proportion to the destruction needs a definite more or less prolonged period. Pure water certainly has a very deleterious action upon blood cells whilst distilled water is one of the most active pure liberators of Hb from the red cell we know. How far this is due to the physical property of its low specific gravity and how much to its other properties of solution &c. we cannot accurately gauge.

Besides several other chemical agents with which I experimented but whose results differed but little from those already mentioned, the results with the physical agents of heat and cold are of interest. Cold, up to a certain point seems to be a preservative of the red cells in that they retain their normal shape and size for longer periods in a cold than in a warm medium. But though the change must be very slow, cold has a deleterious effect also, as

after about two hours at 0°C the cells appear to swell up and then gradually to lose their colour which is seen to stain the medium immediately surrounding the individual cells. The cells in this colourless condition remain a very long time unaltered so that it would appear that this liberation of the Hb is the chief action of cold upon the cells.

In the case of heat at 45° the cells became very sticky and somewhat gelatinous, having first become spheroid and enlarged in size. They become uniformly densely coloured and then begin to exude droplets of their internal contents which adhere together with fine threads and go waving about in the fluid. Other cells gradually seem to burst wholly and then lose their shape becoming a mass of coloured protoplasm. Subsequently these masses may run together into one large mass of coloured protoplasm, uniform and homogeneous which finally will appear to dissolve leaving but a thickly coloured fluid.

These small experiments in themselves opened my eyes to the very great liability possessed by the haemocyte to undergo change in form and destruction. There seemed to be hardly any substance but which could destroy the cell and liberate its contents when applied under these conditions. The salt solution

at .86% appeared the only solution having what might be called a truly neutral action. To what extent this property is due to the presence of Sodium Chloride itself or to density of the water thereby produced or to other physical properties as osmotic power, cannot be properly estimated. But the main fact is that under these conditions the red cell is extraordinarily prone to damage and does not seem to have the same powers of resistance that other highly organized cells of the body seem to possess.

Making allowance for the altered conditions we can reasonably assume that these cells have a similar disposition to be damaged when in their natural medium the plasma and circulating in the vessels, but of course in a degree very much below that which we have recently been examining. We sometimes see very definite evidence that such a condition is present, and at other times we are aware that destruction takes place with but very little evidence and we may justly believe that the presence of this condition (the liability to change while in the blood stream) being confirmed by these two facts, there occur many instances of haemocytic destruction which by reason of their characters of size or quality, never give rise to any sign which is evidence of it to us in the present state of our knowledge.

Looking at it from another point of view we are again compelled to the conclusion that a certain degree of haemolysis may constantly take place, not only without the production of Hb-uria but without any definite evidence that it has occurred except by inference, which is another way of expressing our want of observation or want of ability to relegate to their proper places the facts that have been observed. For, to follow the same method of reasoning as we used above, we know that some substances such as for example Chlorate of Potash have very marked haemolytic action, Glycerine and Carbolic acid have the same action but to a lesse r degree. Next comes the substances which do not shew such marked evidence of haemolytic action and which only after more thorough pharmacological investigation have been found to be agents of this kind, viz. the phosphates, Ammonium Chloride and Sodium Salicylate. And from these facts may we not reasonably assume that there is a great variety of substances, even in the heterogenous foods that we are accustomed to consume, which may produce some degree of haemolysis, of which as such we are quite unaware and have no idea. The fact, that such a process as we here assume to take

place, does actually occur is demonstrated by the study of the disease Pernicious Anaemia which is now almost conclusively proved to be one due to absorption of some noxious material from the alimentary system. This we recognise because it takes place on a large scale and continuously and so constitutes the disease, but it is logical to suppose that a similar process may occur at intervals due to faulty ingestion or digestion, not so profound in degree, and which is passed unnoticed as such. We have therefore every reason, short of actual proof, for suspecting that this is relatively a frequent occurrence though its manifestation as Hb-uria is far from being so. For in addition we have numerous instances of slight general depression or malaise following on the taking of substances "which have not agreed" with the person and yet without any recognised reason. For want of other explanation may not this be a symptom of blood deterioration and even destruction? And, as another suggestion, may not the increase of bile formation following a hearty meal be due to the wear and tear upon the blood in its action in dealing with the ingesta in the portal system. For undoubtedly besides the main recognised functions of the Portal System and its organs, the function of controller, as

to what to let pass into the system generally whether for its benefit or harm, is a very important one. And in accordance with all agencies of this nature, there always exists an extra strain by reason of the character of its work, and consequently a corresponding wear and restoration, and evidence of all this is found in the physiological phenomena of the Portal vascular system and Liver.

As a point of interest of unknown significance up to the present, attention may be called to the variety of ways in which the damage to the cells is shewn. The apparent pure extraction of the colouring matter with little appreciable structural change of the cell as is seen with distilled water and cold, the more active liberation of the Hb and ultimate change of the cell as by weak acids, the exudation of droplet of the cell constituents due to tannic acid and gradual warming and lastly of the gross changes, the fragmentation of the cells as a whole due to Toluylendiamin, these differences all indicate a variability in the reactions of these cells which is as little expected as it is difficult to assign any reason for. Whether the determination of the form by which the cell undergoes destruction is due to vital forces or to physical or chemical, there can be little doubt that this character connotes a like

potential variability taking place within the circulation under the necessary circumstances and if this be granted it is very probable that the form of disintegration influences the phenomena by which we are accustomed to recognise the degree of haemolysis and determines the forms of the pathological states known as Pernicious Anaemia, Chlorosis, Hb-uria and a host of allied conditions.

With the knowledge of the actions of certain poisons upon the blood cells thus gained I then set about certain experiments upon animals. My aim was to try to induce Hb-uria, not so much with the recognised agents which produce it, but with agents known to produce haemolysis. I wished to find out why these substances which definitely cause haemocytic destruction do not also produce Hb-uria whereas certain others do so; thus seeking for the physiological factor determining the onset of Hb-uria or not in those recognised forms of Haemolysis. So that the question now before me is in some respects the converse of the one I set out with, the question as to "what prevents Hb-uria following upon every haemolysis" instead of "what is the cause of the Hb-uria which does sometimes occur", in this way premising that given a certain degree of Haemolysis the occurrence of Hb-uria would be the normal result under the circumstances, and the obscuring and prevention of this the more extraordinary phenomenon.

A method of procedure was suggested to me by the experiments and conclusions of former investigators. It will be remembered that Afanassiew and later

on Ehrlick laid great stress upon the seat of blood destruction without specifying clearly except between capillaries and blood vessels. Hunter more recently attached the same importance of the seat of haemolysis but he differentiated between the Portal system and the rest of the body. Afanassiew also called attention to the form of the Hb dealt with as being a factor of importance. And lastly the question of the use of Quinine in Blackwater fever, whether it is beneficial or the reverse, suggested the employment of this drug in combination with Haemolytic substances.

In my first experiments, therefore, I made use of Guines pigs and treated them with Toluylendiamin. The reason of this will be clear as I knew that I had here an haemolysis but without Hb-uria. My object was to try to induce the haemolysis to shew as Hb-uria by varying the different physiological processes of the animal by means of drugs having definite pharmacological actions. My theory was that I could somewhat confirm or refute Afanassiew's and Hunter's views regarding the significance of the seat of destruction in the circulation by dilating or contracting the vessels through which the altered blood would pass to get to the kidneys, and in this

way either exaggerating or diminishing the importance of the seat of destruction as the case might be.

I first treated an animal with Toluylendiamin alone in order to watch its effects and to find out the dosage required as well as to obtain knowledge of the pathological results of this drug when acting alone. The guinea pig used was about 600 grmms. and on the first day grm. .5 was given per os. This produced but little effect, merely making the animal a little quieter, the urine high coloured but no Hb. Next day another grm. .5 of the drug was administered and towards evening the animal shewed marked signs of poisoning but still no jaundice nor Hb-uria. The urine contained numerous small globular bodies possessing only negative characters being unaffected by eosin, osmic acid, soudan, or ether. They were colourless, very minute and very numerous and looked most like fat droplets. The blood examined fresh shewed a number of bodies very similar though in smaller and discrete quantities. There were no signs of Hb-aemia, though the red cells were very variable in shape and size and colour. The animal died on the fourth day and p.m. one found the liver very congested and with signs of marked biliary activity, the spleen was also large and of dull purplish colour,

but the kidney except for being deeply coloured and shewing slight apparent cloudy change, was unaffected.

Taking another animal I administered grm. .2 Toluylendiamin and an hour later grm. .3 of freshly prepared Sodium nitrite. My object here was to try to hurry the blood affected by the Toluylendiamin past the Portal system and into the general circulation so that the portal capillaries and the liver should have as little chance of affecting the broken down blood as possible. For unless, as we shall presently shew reason to think is the case, the cause of the difference in action of this drug on cats and rodents lies in a difference in the product formed by the interaction of the drug and the Haemoglobin, one would necessarily have to attribute the difference to some such physiological condition as in my premise has been attributed to the portal system of capillaries or the liver. But however I varied the doses and attempted in this way to increase the return of the portal blood into the general circulation the only effect seemed to be rather an increase of tolerance of the drug and with never a symptom or sign of Hb-uria or jaundice.

In view of the failure to obtain positive results by means of vaso-dilators and mindful of

possible
certain remarks of Professor Fraser regarding the
relationship between high vascular tension and the
recurrence of Hb-uria I tried some experiments in
this the opposite direction. Instead of vaso-dilators
I administered vaso-constrictors with the haemolytic
drug. Ergotinin, freshly prepared was used and minim
1 was given on two successive days with apparently no
bad effects upon the animal. On the third day the
dose was repeated together with grm. .2 Toluylendia-
min. Only a small quantity of urine was passed,
which was very concentrated, having a quantity of
colorless drpplets but no Hb-uria. The animal quickly
succumbed to even this small dose and died the next
evening. So that the Ergotinin seemed to increase
the activity of the drug without yet causing either
jaundice or Hb-uria. Besides Ergot. I also used
Supra-renal extract to increase the tension by con-
tracting the vessels. However, in spite of the al-
tered conditions and the longer period that any quant-
ity of blood must be in contact with the capillary
endothelium, there was no Hb-aemia produced and no
Hb liberated by the kidneys into the urine.

As a further investigation on the same lines
I saturated an animal with Sulphate of Atropine
thereby inducing as far as possible a cessation of

Glandular metabolism, including that of the liver. The rodents being peculiarly insusceptible to this drug very large doses were given. But in spite of this throwing of the liver, among other organs out of action I could obtain no Hb-aemia nor Hb-uria with Toluyleudiamin.

And lastly in this relationship may be mentioned the experiments with quinine, as being both important and interesting first because it has been credited with being the cause of Blackwater fever by a certain school and secondly because of its well known action of causing stasis of all metabolism to a very marked extent in which respect it is a useful adjunct to our experiments. It has been mentioned before that there are certain clinical reasons for supposing that there is some truth in the statement that Blackwater fever is sometimes induced by the administration of quinine and now we will see that there are other reasons as well. The statement of Professor Koch that all cases of this fever are due to Quinine produced such a storm of contradiction that the pendulum swung to the opposite extreme and people have come to believe that no such cases are attributable to quinine, and those holding either of

these extreme views are probably equally in error. As has been stated earlier in this paper, all forms of Hb-uria occurring as symptoms of disease are complicated in nature and have apparently variable determinants. A system lowered by prolonged exposure to malarial poisons seems to be one of these variable causative agents. From the pharmacological properties of Quinine one might similarly expect a priori that it would in some cases induce an attack of Hb-uria. Although , in dealing with animals I could not manage to demonstrate this action , it does not shake my belief that some such action does occur in regard to the disease in question as it occurs in man.

But in my experiments with Quinine I was surprised to find that besides its other pharmacological properties it also possessed a very marked haemolytic action towards guinea-pigs in itself. One of the animals died from the effects of an overdose of Quinine whilst I was trying to get its system well under the influence of the drug before using Toluylendiamin. On examining the internal organs I found the liver exceedingly fatty but in both liver and spleen, especially the latter, was found a marked quantity of iron pigment similar in every way to that found with other well known haemolytic substances and absent from the normal animal. This then lends an additional reason for believing that in some

cases of administration of quinine , it is the exciting cause of the onset of Hb-uria in people so predisposed. The very marked fatty degeneration of the liver, though due in this case to toxic lethal doses, indicates the kind of action that smaller doses would have. And these two actions are more than sufficient to warrant the statement on experimental grounds besides on clinical data, that quinine may in many cases be the actual exciting cause of an attack of Hb-uria. I would not, however, prohibit its use but would use it more carefully than is usually done. It is most probable that this fever is due to a specific organism allied to the malarial types and I would give the quinine in sufficient doses at first to destroy this organism and then avoid the drug as much as possible in the subsequent treatment of the case.

On the strength of these experiments, which though not sufficiently numerous and varied to be conclusive proof, nevertheless afford strong presumptive evidence, together with other clinical and physiological facts, it is clear that the significance attached to the seat of the haemolysis is unwarranted. In fact I am of opinion that the seat of the destruction has nothing to do with the presence or absence of Hb-uria consequent on a marked destruction of red cells.

The conclusion one must therefore come to after viewing all the facts is that though Hb-uria always indicates a corresponding destruction of red cells, yet it is only one of the signs and probably the least common one of Haemolysis. In other words that instead of being the usual sequel to an acute blood destruction, it is only a signal under certain conditions which are probably rarely present and that many if not the majority of instances of Haemolysis take place without any subsequent Hb-uria. The subject we commenced with has thus grown very much in scope and the question of Hb-uria becomes the question of haemolysis in all its physiological and pathological bearings. The question as to the exact cause of the Hb shewing as such in the urine on certain occasions would occupy but an insignificant position in the greater question of haemolysis before us, were it not that the disease known as Blackwater fever is so prevalent in certain districts and has such great mortality that the attention generally

has been directed to this special feature of haemolysis. But for any answers to the question to have any scientific basis, it is necessary that we should first understand the laws that govern Haemolysis in all its phases. Nor is it improbable that by tracing back the symptoms thus, by their different lines to a common centre, the fundamental principle will be found at length and a true dependent position ascribed to the various phenomena at present recognised but not understood. An interesting paper recently published by P.Ehrlick of Frankfort will be referred to later on which is noteworthy from the very different point from which he has approached the question and for the wide scope of its range.

But as regards the feature of Hb being present in the urine under certain circumstances the one factor which struck me as being of great significance was the solubility or insolubility of the Hb liberated. For if we review the substances which are known to repeatedly and constantly produce Hb-uria and compare them with the list of substances which, under the microscope, are found to liberate the pigment of the cells into the surrounding fluid apparently unchanged, we find.that the substances are practically the same in each case. Conversely a

drug like Toluylendiamin which whether by combining with the pigment or causing it to combine with some proteid molecule causes the liberation of a product which is insoluble, we find that Hb-uria does not ensue. In confirmation of this I treated an animal with Tannic acid, a substance which I had proved to possess this property of liberating the Hb in a modified form, to a very marked degree. The result was eminently confirmatory of this view, in kind it was just what I had expected but in degree the features were very exaggerated. Large doses were given gradually increasing from grm. .2 to grm. 3 per diem. Soon some degree of jaundice was produced and the urine contained the same kind of non-descript bodies that were found after treatment with Toluylendiamin, but in very much greater quantities. On section of the various organs post mortem there was evidence of very excessive blood destruction so that many capillaries were blocked with altered blood pigment and such organs as the liver and spleen were loaded with iron derived from the broken down Hb. Yet in spite of this evidence of very marked destruction , the products of which caused death partly by mechanical effects of accumulation, there was never any sign of Hb in the urine, that is, unless these small bodies are derivatives

from this substance. That Toluylendiamin should induce Hb-uria in cats appears to be an exception, which after all need not cause surprise and in all probability many similar apparent contradictions in the actions of drugs in this connection would be forthcoming if we extended our experiments to different animals. For it is most likely that the vital reactions if not the very chemical composition of the protoplasm of two such animals as the cat - a carnivorous and the guinea pig - a graminivorous animal differ very widely. That this difference is very markedly present in the blood and its constituents is what might be anticipated from general reasoning as well as from experiments such as Ponfick's and that the same drug should liberate a soluble form of Hb in the one animal and an insoluble form in the other is interesting though not necessarily surprising.

Moreover what evidence we at present possess in regard to the cause and production of Blackwater fever bears out this theory. In most of the known types of Malaria if not in all true forms, there lies the power of producing a definite pigment from the red cell in which it develops, and this pigmented mass becomes scattered into the blood stream in an

insoluble form when the plasmodium bursts the cell. Thus it happens that true malaria is not accompanied with Hb-uria although there is marked haemolysis. But that form of malarial parasite which is most clearly associated with Blackwater fever, viz. the aestivo-autumnal form is peculiar in not forming any pigment whatever although breaking down the red cells in the same manner and it would therefore appear that in this case the Hb is liberated in a soluble form and so can appear in the urine as Hb. Whether this is always the causal organism or not we may be certain that whatever the organism may be, it is one which has not the power of forming an insoluble pigment with the Hb as is commonly the power with the well known Malarial organisms.

The attention of Professor P.Ehrlick of Frankfort, whilst engaged in the study of immunity, was called to the behaviour of the red cells under certain circumstances which was of interest to his special study. He thereupon took up the subject of Haemolysis and though mainly with the object of elucidating his theory of immunity he has obtained a great number of facts that are of interest to us.

From Ponfick we learnt the principles governing the action of the introduction of the blood of one animal into the vessels of another. But Bordet (Deuts.Med. Wochens. 1896) shewed that although a rabbit's blood and a guinea pig's are miscible without destruction of either, yet if a rabbit be injected with the blood of a guinea pig, then the serum of the rabbit thus treated has a lytic action upon the blood cells of the guinea pig. Ehrlick confirmed this experiment numerous times using the blood of sheep and goats in a similar way. Moreover he found that if the serum of the animal injected was warmed to 55° C for a short time 15 - 40 min. this lytic action was lost but was quickly regained on the addition of normal serum from either the sheep or the

goat or indeed of almost any animal. In accordance with the"Geiterketten theorie" which Ehrlick had enunciated in 1885, he recognised that this lytic action was due to the combined action of two bodies, one the "Intermediate Body" held in the treated serum and the other "the Complement" held in the normal serum, and maintained that the complement acted the part of a ferment and that it could only act by means of the Intermediate Body. He actually managed to separate these two bodies in a very definite way, proving the truth of his supposition. He also demonstrated that the intermediate body had a very strong affinity for the red cells on the one hand, and a weaker affinity for the complement on the other, and that by the action of cold he could separate the red cells, with the intermediate body adhering to them, from the free complement, and again could prove the presence of this complement in the supernatant fluid. By various experiments with these bodies he proved conclusively that the intermediate body af - fords the link which fastens the complement to the red cells and so brings them under its influence. Morgenroth had previously produced evidence, that a similar condition prevailed in the action of ferments, namely the combined action of two agents. On the basis of these experiments can be explained almost

all the physiological phenomena of digestion, of metabolism and of the actions of toxins.

Using goats and sheep, injecting the former with the defibrinated blood of the latter, besides confirming all previous work, he found the presence of other complements, some heat resisting and others not so. Moreover he found that the serum of the animal, whose blood was to be tested, could afford the complement to its own destruction. For instance the serum of a dog can actively break up the red cells of a guinea pig. But if the dog's serum be heated for a short time to 56° C, it loses this lytic action upon guinea pig's blood but regains it on the addition of almost any normal serum, the peculiar fact being that even the serum of a guinea pig itself will serve the purpose. Professor Ehrlick argues the presence in each and every serum of a number of lysins (intermediate body and complement) each acting differently and specifically in accordance with the species of animal, upon whose blood it is able to effect its action of lysis. For instance he holds that the dog's serum contains a great number of lysins and each peculiar to the blood of the rabbit, guinea pig, cat &c. that it is acting upon; upon this fact he bases the arguments for the existence of numerous anti-lysins which are allied to anti-toxins in his

study of immunity.

Besides dealing with animals of different kinds even though of the same species experiments were made by injecting the blood say of a guinea pig into another guinea pig. A most interesting and astonishing effect was the production of a lysin which could break up the cells of the animal from which the injected blood was taken. Thus we differentiate between the hetero-lysins (the product of injecting say rabbits with guinea pig's blood &c.) and iso-lysins (the product when the injection is from say guinea pig to guinea pig). This result apparently led us to a climax when we considered what, from analogy, would happen, when one bleeds an animal to a certain extent and after defibrinating the blood returns it to the vessels of the animal again; or what would come to the same thing, what are the effects of the absorption of large extravasations of blood within an animal. Investigations on these points revealed little except what our clinical knowledge would tell us by itself. It was found impossible ever to produce an auto-lysin (self-destroying agent) and Ehrlick attributed this failure to the non-production of intermediate bodies capable of allowing the ferment like complement formed to exert its action according to his side - claim theory.

These are the bare results of the experiments which Ehrlick describes in his paper. It is full of suggestive and interesting data and of course deals more particularly with the subject of immunity in which direction all his deductions are made. However there are many apparently unexplainable discrepancies in his results, whose significance he cannot himself account for yet and also there will be need of fuller and wider investigations and repeated confirmations before the generalizations and theories will have much weight.

B I B L I O G R A P H Y

1. Elliotson - Lancet 1/1831/500.
2. Gergerés - Med.Gazette. Paris 1838.
3. Harley - Med.Chir.Jrs. 1865.
4. Hassal - Lancet 1/65/568 - 2/65/368.
5. Dickinson - Med.Chir.Jrs. 1865.
6. Pavy - Lancet 2/66/33.
7. Henock - Dict.Encyclop.Med. Paris.
8. De Labrosse - Monograph 1889.
9. Hirschsprung - Congrès Internat.Period. d.Sc.Med.1884.
10. Hirst - Univers.Med.Mag.Philad. 1890.
11. Variot - Journ.de Clin.et de Therap.Inf. 1894.
12. Herringham - St.Bart's.Hosp.Rep. 1886. XXII.
13. Voelcker - B.M.J. 1/98/418.
14. Calmette - Monograph 1889.
15. Bristowe and Copeman - Lancet 1/89/260.
16. Foulerton - Lancet 2/90/710.
17. Ralfe - Lancet 1/88
18. Robins - Soc.Med.des Hôpit. 1888.
19. Dickinson - Jrs.Clin.Soc. London 1894.
20. Küssner - Deutsch.Med.Wochen. 1879.
21. Hayem - Gaz.hebd.de Med. 1889.
22. Ehrlick - Deutsch.Med.Wochen. 1881.
23. Murri - Centralbl.f.d.med.Wissensch.1885.

24. Rosenbach - Berl.Klin.Wochensch. 1888.

25. Ponfick - Berl.Klin.Wochensch. 1874.

27. Copeman - Allbutt's Syst.Med. 1898.

26. Naunym - Archives f.Anat.et Physiol.1868. 1868'

28. Kuhner - Lehrbruck der Physiol. Chemic.1868.

29. Tarchanoff - Pflüger's Archives. Bd.IX.

30. Stadelman - Archiv.f.Experim.Pathol. Bd.XV.

31. Ponfick - Virchow's Archives. Bd.62.

32. Panum - Virchow's Archives. Bd.27.

33. Mittler - Versuch. uber Trans.f.de Blutes 1874.

34. Afanassiew - Berliner Zeitschr f.Klin.Med. Bd.VI.

35. Paton - B.M.J. ii/86/July 31.

36. Klebs - Tagebl,de München.Naturf - vers 1879.

37. Lassar - Virchows Archives. Bd.79.

38. Trojanow - Monograph St.Petersburgh 1882.

39. Marchand - Virchows Archives. Bd 77.

40. Hofmeister - Deutsch.Med.Wochensch.1880.Bd 38.

41. Reiss - Berliner Klin.Wochensch. 1882. No 52.

42. Eitner - Berliner Klin.Wochensch. 1880. No 18.

43. Wächter - Berliner Klin.Wochensch. 1880 No 18.

44. Neisser - Zeitschr.f.Klin.Med. Bd.I.

45. Afanassiew - Virchows Archives. Bd 98.

46. Ponfick - Virchows Archives. Bd 88.

47. Boström - Deutsche Arch.f.Klin.Med. Bd.32.

48. Leichthiem - Volkmans Sammlung Klin.Vortrage No 46.

49. Schutze - Archiv.f.Mikroscop.Anat.Bd I. 1865

50. Landois - Monograph. Leipzig 1875.

51. Hermann - Monograph 1859.

52. Engel and Kiener - Compt.Rend.Acad.de Sc. cv/87/465.

53. Hunter - Lancet. ii/88/ 608.

54. Crosse - Epidemiolog.Soc.Lond.1899.

55. Washbourne - Lancet. ii/98/1774.

56. Manson - Jrs.Epidem.Soc.n.s.Vol.xii/92-93.

57. Sambon - B.M.J. ii/98/376.

58. Babes - Comp.Rend.Acad.d.Sc.Paris.1890. cx.

59. Koch - Monograph.Das Schwarzwasser fieber, 1898.