THE
CHANGES IN THE BLOOD IN THE COURSE
OF RHEUMATIC ATTACKS.

BY

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PART I.—*The variations in the Number and Worth of the Red Corpuscles ; and the absence of any recognisable relation between these changes and the appearance of Uro-hæmatoporphyrin in the Urine.*

THAT attacks of acute rheumatism are attended by profound alterations in the quality of the blood is evidenced by the conspicuous anæmia which is so frequently observed in the course of this malady, and which in some instances persists for a considerable time after convalescence is established.

These changes have been studied by two or three observers, whose accounts, although agreeing in several essential points, exhibit nevertheless some rather remarkable differences.

M. Besnier¹ states that Malassez observed a notable

¹ 'Dict. Encyclop. des Sc. Méd.,' article "Rheumatism," p. 492.

diminution of red corpuscles in this disease, and quotes some observations which demonstrate a fall, followed by a rapid recovery, in the number of corpuscles. In one case the number was reduced to less than two and a half millions in the cubic millimetre.

In their papers on Clinical Hæmatology¹ Drs. Baxter and Willcocks class rheumatic fever with some other acute diseases in which they were unable to detect any noteworthy changes in the blood; but they only give the results of two observations of the blood of a single patient.

M. Hayem's account² is by far the most complete which has been given, and I may perhaps be allowed to quote it in full. He writes as follows:—"Acute articular rheumatism is one of the diseases most destructive to the corpuscles. Since salicylic acid has been employed as an efficacious treatment I have had opportunities of comparing cases of almost equal severity, treated, some with this drug and others with quinine, and I think that I may conclude from them that the degree of anæmia produced by the rheumatism is chiefly determined by the duration of the attack. The shorter the attack, and the more rapidly it is arrested by the salicylic acid, the less pronounced is the anæmia. Yet in really acute cases with multiple articular lesions the diminution of red corpuscles is rarely less than a million. In lingering cases or cases with frequent relapses it reaches one and a half to two millions.

"The blood crisis and the repair follow very exactly the course of the accidents of the attack, or rather of the temperature, and local lesions which persist after the fever has subsided retard but do not entirely prevent the repair.

"One finds, then, in acute articular rheumatism a definite blood crisis of rapid development, as in the simplest cases of pneumonia, or successive and subintra-

¹ 'Lancet,' 1880, vol. i, p. 398.

² 'Du Sang,' 1889, p. 916.

crises, or, again, a protracted crisis analogous to that which follows after continuous fevers.

“The variations in the worth of the corpuscles depend usually upon the form of the crisis. Here, as always, it is at the moment of the appearance of many new and incompletely developed corpuscles that the diminution of worth is greatest; but it is not uncommon to see, especially in young subjects, with perhaps a certain chlorotic tendency, a progressive diminution of worth during a tedious recovery, which brings about a condition of more or less persistent chronic anæmia.”

M. Hayem further directs special attention to the increase of white corpuscles in this disease.

The most recent contribution to the subject is that of Drs. Maragliano and Castellino,² who, without entering into any detail, give a brief epitome of the results obtained from the examination of the blood of fifteen patients suffering from rheumatic fever.

These observers state that there is a profound alteration of the red corpuscles in the course of rheumatic attacks, which alteration affects both the central and peripheral portions of the corpuscles, and is both chromatic and morphological. They found a diminution in the number of red corpuscles, but failed to detect any actual increase of white corpuscles; the apparent increase being ascribed by them to the relative diminution of red corpuscles. They found that the changes observed were proportional to the duration of the attack, to the height of the fever, and to the general condition of the patient; whilst the restoration of the corpuscles during convalescence was very slow and uncertain. They remark that when the heart is attacked the changes in the blood incident to such complications are superadded to those directly attributable to the rheumatic infection.

¹ The worth of the individual corpuscle is obtained by dividing the percentage of hæmoglobin by the percentage of red corpuscles (5,000,000 = 100 per cent.).

² ‘Gazzetta degli Ospitali,’ 22 Marzo, 1891, No. 23, p. 196.

Having thus given an epitome of the previous literature of my subject, I may proceed to the discussion of the results of my own observations, and shall confine myself in this part of my paper to the variations in number and worth of the red corpuscles, reserving for a future communication the consideration of the variations in the number of white corpuscles, and certain other phenomena. I may, however, remark that all the evidence which I have hitherto obtained points to the occurrence of a true leucocytosis in this disease, and I am convinced that the statement of the Italian observers upon this point is erroneous.

My conclusions are based upon more than eighty observations of the blood of twenty patients at the West London Hospital, and I may here express my great indebtedness to my colleagues on the staff of that hospital for allowing me every facility for observing the cases under their care.

In a few cases the blood was only examined on one occasion, but in others as many as six or eight examinations were made at intervals varying from two or three days to a week. The blood was in all cases obtained from the lobe of the ear, which I find preferable to the finger for this purpose.

The counting of the corpuscles was performed with a hæmocytometer manufactured by Zeiss after a model suggested by Thoma. This instrument has one important advantage over those usually employed in this country, in that the floor of the cell is divided into much smaller squares, by which the counting is greatly facilitated. The dilution is performed in an instrument after the pattern of Potain's mélangeur.

The graduated chamber has a depth of $\cdot 01$ of a millimetre, and upon its floor is a square divided into 400 lesser squares, each $\frac{1}{400}$ of a square millimetre in area. Each set of sixteen squares is bounded by a triple line. In each observation referred to in this paper sixteen sets of sixteen squares, or 256 in all, were counted, corre-

sponding to thirty-two squares of Gowers' hæmocytometer.

I have compared my instrument with two of Gowers' pattern, using in each comparison the same drop of blood, with the following results. It will be seen that my instrument gave somewhat higher readings than either of the other two.

Thoma-Zeiss hæmocytometer	.	5,890,625	red corpuscles in the c.mm.	
Gowers' hæmocytometer, No. 1	.	5,753,125	„	„
Difference	.	137,500		
Thoma-Zeiss hæmocytometer	.	5,206,250	„	„
Gowers' hæmocytometer, No. 2	.	5,100,000	„	„
Difference	.	106,250		

For the estimation of the hæmoglobin a von Fleischl's hæmometer was employed. I have several times made repeated observations with this instrument, employing fresh specimens of blood from the same patient, and have obtained readings in some cases identical, in others differing by no more than 1 per cent. I believe that this form of hæmoglobinometer reaches as high a degree of accuracy as can be attained to in such instruments. The standard of hæmoglobin is, however, somewhat high, and I have never found any blood to attain to 100 per cent. with my instrument. I have compared the instrument with a Gowers' hæmoglobinometer, and found that on two separate occasions the von Fleischl's instrument gave readings which were 8 per cent. lower. Unquestionably errors will creep into determinations with any form of hæmocytometer or hæmoglobinometer, however carefully the manipulations be performed, and it would undoubtedly be a great mistake to argue anything from isolated results, which may always be incorrect; but I think that the charts appended will show that, as an ordinary rule, the errors do not materially affect the results, since the variations are sufficiently great to exceed their limits. A reference to the charts will show that the lines connecting a series of observations are frequently continuous, and that in

many instances the worth of the corpuscle remains practically constant in spite of great fluctuations in the percentages of corpuscles and of hæmoglobin. Again, the large number of squares counted in each observation must tend to reduce materially the errors of experiment.

In order to afford a standard of comparison I append the results of the examination of the blood of ten healthy persons, and also of ten chlorotic patients with the same hæmoglobinometer and hæmocytometer which were employed in the examinations of rheumatic blood.

<i>Healthy persons :</i>		No. of red corpuscles per cubic mm.		Per cent. of corpuscles.		Per cent. of hæmoglobin.		Worth.
1. Male, aged	34	5,056,250	...	101.125	...	82	...	81
2. Male "	22	5,240,625	...	104.81	...	80	...	76
3. Male "	23	6,665,625	...	133.3	...	82	...	61
4. Female "	28	5,175,000	...	103.5	...	80	...	76
5. Male "	24	4,690,625	...	93.81	...	81	...	86
6. Male "	15	4,821,875	...	96.42	...	77	...	79
7. Female "	27	5,453,125	...	109	...	66	...	60
8. Male "	23	5,468,750	...	109.3	...	90	...	82
9. Female "	21	5,028,125	...	100.5	...	72	...	71
10. Female "	40	4,990,625	...	99.8	...	86	...	86
<i>Chlorotic patients :</i>								
1. Female, aged	19	3,962,500	...	79.25	...	45	...	56
2. Female "	21	3,009,375	...	60.2	...	39	...	64
3. Female "	19	4,915,625	...	98.3	...	37	...	37
4. Female "	18	3,571,875	...	71.4	...	35	...	49
5. Female "	21	4,031,250	...	80.62	...	26	...	32
6. Female "	17	3,828,120	...	76.6	...	26	...	34
7. Female "	16	2,871,875	...	57.4	...	20	...	34
8. Female "	18	3,134,375	...	62.7	...	22	...	32
9. Female "	24	2,575,000	...	51.5	...	20	...	38
10. Female "	23	2,925,000	...	58.5	...	22	...	37

*Variations in the Number of Red Corpuscles during
Rheumatic Attacks.*

An attack of rheumatism is always attended with a considerable diminution of the number of red corpuscles. The fall commences very early in the attack, and is not

infrequently already at an end when the patient is admitted to a hospital. In ordinary cases, treated with salicylate, the fall usually comes to an end simultaneously with the defervescence and relief of the articular pains; in other words, with the subsidence of the attack. When the attack is at all acute the loss of corpuscles, as M. Hayem states, is usually about a million; as may be seen from the following table, which gives the maxima and minima of red corpuscles in the cubic millimetre observed in ten cases:

	Maximum.		Minimum.		Difference.
1. Male, aged 19 . .	5,106,250	...	3,815,610	...	1,290,640
2. Male „ 16 . .	5,684,375	...	3,909,300	...	1,775,075
3. Male „ 20 . .	5,618,750	...	4,721,875	...	896,875
4. Female „ 18 . .	4,871,000	...	3,832,000	...	1,039,000
5. Male „ 34 . .	4,918,750	...	3,859,375	...	1,059,375
6. Male „ 9 . .	5,140,625	...	4,221,875	...	918,750
7. Female „ 10 . .	4,675,000	...	3,906,190	...	768,810
8. Male „ 17 . .	6,200,000	...	4,978,125	...	1,221,875
9. Male „ 18 . .	5,109,000	...	4,136,000	...	973,000
10. Female „ 22 . .	5,578,000	...	5,267,000	...	311,000

The fall of corpuscles is usually extremely rapid, and I have several records showing the loss of about a million in as short a space of time as four or five days.

When the case runs a favorable course, and no serious visceral troubles supervene, the subsequent recovery of corpuscles is equally rapid, so that within ten or eleven days a million red corpuscles per cubic millimetre may be lost and recovered. For example, a patient (Chart I) was found to have 4,686,000 corpuscles on February 26th, and on March 10th the number was nearly the same, 4,871,000; yet in the interval between these two dates the number had been as low as 3,832,000. Here, as in other instances, the hæmoglobinometer confirmed the observations with the hæmocytometer, and throughout the period referred to the variations of worth obtained were very trifling (·57—·53).

In another instance (Chart III) the red corpuscles

numbered 4,968,750 on July 2nd, and on July 14th, twelve days later, 5,106,250; yet on July 7th there were only 3,915,625, and on the 10th 3,873,437. Here, again, there was an equivalent fall in the percentage of hæmoglobin. Further instances might be quoted in illustration of the rapidity of the loss and recovery of red corpuscles.

The development of a fresh rheumatic manifestation during convalescence will be attended by a repetition of the fall, and the blood chart may thus show a series of such crises (Charts III and IV).

So far my observations agree entirely with those of M. Hayem, but there are other points in which they differ from his. I have not found that in protracted cases there is a continuous fall of corpuscles, but, on the contrary, that the number of corpuscles having reached a certain level tends to remain practically constant until recovery sets in. It must be borne in mind that although two consecutive countings give nearly the same number, there may nevertheless have been a further fall in the interval, and the observations may cut the falling and rising curves at about the same level. I have, however, charts to which no such explanation can possibly apply.

In one case (Chart II) there were no less than five consecutive countings, extending from April 7th to May 4th, in which the number of red corpuscles did not vary by so much as 216,000. During this period the patient was extremely ill with pericarditis with effusion, followed by pneumonia and effusion into both pleural cavities. In another case (Chart VIII) the numbers obtained on four successive occasions (September 28th to October 8th) only varied between 4,137,500 and 3,906,190.

Another point in which my results differ from those of M. Hayem is in the relation between the blood changes and the temperature curve. Undoubtedly in an ordinary typical attack of rheumatic fever the temperature curve affords a very clear indication of the activity of the morbid process, and when the temperature falls the blood-

corpuscles recover; but it sometimes happens that the number of corpuscles continues to fall after the temperature has reached the normal. Thus in one case the temperature became normal on October 30th, but between this day and November 2nd the corpuscles fell from 5,584,375 to 4,862,500, and there was a corresponding fall in the percentage of hæmoglobin. Still more convincing evidence that the blood-changes are independent of the temperature is afforded by Charts III and IV. The first patient was a young man whose rheumatic attacks were of the type so often seen in children. He had been in the hospital a year previously with the largest rheumatic nodules I have ever seen. He was readmitted with pericardial friction and slight arthritis of the shoulders. The temperature was normal. He had some subcutaneous nodules on the elbows. The blood-corpuscles were found to number only 3,843,700, and he was obviously anæmic. With the disappearance of the friction-sound the blood rapidly recovered, and over a million corpuscles were regained in nine days. He then developed a copious eruption of erythema marginatum, and again lost a million corpuscles. This fresh loss was attended by a corresponding fall of the hæmoglobin percentage, and was confirmed by a second observation three days later. During the erythematous attack the maximum temperature recorded was 100.6° , and that after the fall of corpuscles had already been observed.

Chart IV illustrates the same point. It is that of a young man who was in the hospital for his third rheumatic attack during the present year. The fall of corpuscles observed on August 28th corresponds to a fresh development of pleuritic friction, and that of September 19th to a return of pain in the ankles. Neither of these events was attended by any febrile disturbance whatever, the temperature never reaching 99° .

It will be gathered from these examples that, far from following the temperature curve, the blood curve affords a far more delicate indication of the activity of the rheu-

matic process. They show further that the changes in the blood are the same whatever the nature of the local manifestation with which they are associated, whether arthritis, pericarditis, pleurisy, or erythema; and point to a latency of the rheumatic process between the appearances of the successive manifestations in cases of this type.

The question presents itself whether the changes in the blood above described have any connection with the salicylic treatment, since Dr. Noel Paton has shown ('Journal of Anatomy and Physiology,' vol. xx, 1885-6, p. 667) that the salicylates have a hæmolytic action, reducing the number of red blood-corpuscles. The statement of M. Hayem that he has found the changes, alike in cases treated with quinine and with salicylate, at once disposes of this idea, and if any further evidence is required, it is to be found in the charts. In each of these a line is drawn along the top indicating the period during which the salicylate was given, the double line indicating frequent doses. In the case represented by Chart III salicylate was only given on two days, when the erythematous rash was at its fullest development; and this chart shows that the blood-changes may be perfectly well marked apart from this treatment. Again, the patient whose chart is numbered II only took salicylate during the first twelve days of his stay in the hospital.

Moreover the reduction in the number of corpuscles observed by Dr. Noel Paton was considerably less than that which occurs during rheumatic attacks.

In some cases there is a fall of corpuscles when the patient first leaves his bed, but the effect of getting up would seem to vary in different cases; for in some instances there is at this period a fall of hæmoglobin only (Chart I), and it is difficult to be certain whether such discordant results may be rightly attributed to this cause.

Variations in the Worth of the Red Corpuscles.

In many cases the variations in the percentage of hæmoglobin follow those of the corpuscles, and the worth of the individual corpuscle (obtained by dividing the percentage of hæmoglobin by the percentage of corpuscles) remains practically constant. When this rule is departed from there may be in some instances errors of observation; but it is so common to find variations of hæmoglobin independently of the corpuscles, that I am convinced that such variations cannot be all due to such errors. Indeed, there is, in rheumatic patients, a great tendency to more or less rapid falls of worth, which may occur during the acute stage, and be rapidly recovered from; or they may take place during convalescence, and be continuous unless interrupted by treatment. This latter event is that to which M. Hayem has directed particular attention, and it cannot be doubted that it is to such losses of hæmoglobin that the chronic anæmia which sometimes follows a rheumatic attack is due.

In illustration of this point I may refer to Charts V and VII. In Chart V the worth of the corpuscle fell rapidly whilst the number of corpuscles was increasing, but when the patient was put on iron, on March 10th, a recovery immediately commenced.

The patient whose chart is numbered VII left the hospital with falling hæmoglobin and rising corpuscles, in spite of the administration of iron; and during his sojourn in the hospital the worth of the individual corpuscle fell from $\cdot 69$ (1 equals normal) to $\cdot 59$.

Falls of worth during the acute period are illustrated by Charts III, VII, and VIII. They do not always occur at the period when large numbers of new corpuscles are being thrown into the circulation, but may take place while the number of corpuscles remains constant, or when the corpuscles are also falling, the percentage of hæmoglobin falling still more rapidly.

Nevertheless it is not very common, even in children,

for the patient to leave the hospital with a much lower worth than is obtained at the first examination of the blood, however striking the anæmia may have been during the acute stage.

The following table, which gives the worth at the time of the first and last observations in eleven cases, illustrates this point:

Name and age.	Worth at 1st obs.	At last obs.	Difference.
A. B., 10 . . .	·59 ...	·62 ...	+·03
C. T., 9 . . .	·65 ...	·64 ...	-·01
W. B., 18 . . .	·70 ...	·71 ...	+·01
H. G., 16 . . .	·59 ...	·65 ...	+·06
H. R., 20 . . .	·69 ...	·59 ...	-·10
F. H., 18 . . .	·90 ...	·76 ...	-·14
E. P., 18 . . .	·51 ...	·42 ...	-·09
W. F., 17 (1st attack) .	·65 ...	·69 ...	+·04
M. A., 22 . . .	·57 ...	·59 ...	+·02
E. C., 34 . . .	·74 ...	·68 ...	-·06
W. F., 17 (2nd attack) .	·65 ...	·64 ...	-·01

In a considerable number of cases the worth of the corpuscle was low at the time of the first observation, but I have had no opportunity of ascertaining whether there is apt to be a fall of worth during what may be called the incubative stage of the disease.

More remarkable even than the falls of worth during the attack is the rapid rise of hæmoglobin percentage independently of any increase in the number of corpuscles. This is a comparatively rare phenomenon, but I am convinced that it does sometimes occur. In the case of the boy whose chart is numbered II the hæmoglobin rose no less than 18 per cent. between April 21st and May 4th, whereas the percentage of corpuscles remained practically constant. This result was so striking that both observations were immediately repeated *de novo* with a fresh drop of blood, and the results of the second examination agreed closely with those of the first. Similar double observations were made on May 11th, when the worth of the individual corpuscles was found to be once more

falling rapidly. It should be noted that on May 2nd the patient's urine was bright pink, but limpid; it gave the guaiacum reaction and contained albumen. Such urine was passed on two or three occasions only, and there was pain in micturition when it was passed. Unfortunately I did not have an opportunity of seeing this urine, which was not examined for corpuscles. It seems probable that the rapid fall of worth which occurred soon after was connected with this event.

In the case of the child A. B., Chart VIII, the hæmoglobin estimation was also repeated with a fresh drop of blood on October 8th, when a rise of hæmoglobin was observed, and the two examinations gave identical percentages.

One or two of the charts suggest that possibly the salicylic treatment may have a share in the causation of the falls of worth (notably Chart VIII), but in other cases similar falls are seen which are quite independent of salicylic treatment, and I believe that this factor may be safely excluded.

Attempt to trace a Relation between the Changes in the Blood and the Appearance of Uro-hæmatoporphyrin in the Urine.

Uro-hæmatoporphyrin is an urinary pigment which was discovered and described by Dr. MacMunn, who has shown further that it is identical with one of the products of the action of reducing agents upon hæmatin, and is therefore almost certainly derived directly from hæmoglobin. I do not propose to enter here upon any lengthy discussion of the properties of uro-hæmatoporphyrin, nor of the morbid conditions under which it appears in the urine, for this would lead me far away from my present subject. I may, however, be allowed to call attention to certain points in connection with this substance. Uro-hæmatoporphyrin appears to be very closely related to hæmatoporphyrin, and it is permissible to doubt whether we are justified in

regarding these bodies as absolutely distinct on the ground of the spectroscopic differences alone. In acid solutions uro-hæmatoporphyrin yields a spectrum containing two dark bands and an intermediate shaded band, which I have failed to distinguish, by measurement, from those which constitute the spectrum of acid hæmatoporphyrin in dilute solution, as when some of this substance is added to normal urine. Under such conditions the broad shading, which in concentrated solutions is continuous with the second band of acid hæmatoporphyrin, is reduced to a faint but distinct narrow band which corresponds in position with the intermediate shaded band of uro-hæmatoporphyrin.

Dr. MacMunn is convinced that a third band near the F line forms an essential part of the spectrum of acid uro-hæmatoporphyrin, but Le Nobel maintains that this line is due to impurities; and I may remark that it has seemed to me that the intensity of the band in question diminishes as greater purity is arrived at, and in some of my specimens it has been reduced to a mere shading, too indistinct for accurate measurement.

When a solution of uro-hæmatoporphyrin is rendered alkaline with ammonia it sometimes yields a five-banded spectrum, chiefly differing from that of hæmatoporphyrin in the presence of two bands instead of a single narrow band in the red.

I may mention that I have repeatedly prepared a substance giving spectra identical with those of the urinary pigment, in the same way as Dr. MacMunn has done, namely, by acting upon an alcoholic solution of hæmatin with zinc and sulphuric acid, and also by the reduction of ordinary hæmatoporphyrin. My own observations also support Dr. MacMunn's statement that uro-hæmatoporphyrin is usually present in considerable quantities in the urine of patients suffering from acute rheumatism, and that the pigment present in such cases frequently yields the characteristic five-banded alkaline spectrum. In some of my cases, however, a four-banded spectrum was

obtained on the addition of ammonia. The chloroform extract from such a specimen was evaporated to dryness on a filter, and the residue dissolved in rectified spirit gave a five-banded spectrum, the readings of which agreed closely with those given by MacMunn for neutral uro-hæmatoporphyrin, and also with those of the spectrum of neutral hæmatoporphyrin, which also shows five bands. I am strongly inclined to think that in this case the pigment present was ordinary hæmatoporphyrin; and it is interesting to note that in this case alone did I succeed in obtaining an acid spectrum without any line at F.

Dr. MacMunn has also pointed out that in some cases the urinary pigment gives a four- instead of a five-band spectrum when rendered alkaline with ammonia.

The quantity of uro-hæmatoporphyrin present in the urine of rheumatic patients does not approach to the amount of hæmatoporphyrin or allied substances present in some cases which have been described by Stockvis,¹ Salkowski,² Ranking and Pardington,³ and MacMunn,⁴ in which the liquid had a deep red colour; indeed, the colour of the urine is not, as a rule, appreciably altered by the presence of the pigment, even after the addition of an acid. In some cases the acid spectrum may be seen after simple acidification, and in one instance I have seen some of the bands of neutral uro-hæmatoporphyrin without any preparation at all; in most cases, however, it is necessary to obtain a concentrated extract in order to observe the bands; and in some the quantity present is so small that it is not possible to obtain the alkaline spectrum. It must not be supposed that the presence of uro-hæmatoporphyrin in the urine is in any way pathognomonic of rheumatism; it is merely an unusually constant phenomenon in that disease, and the quantity present is often unusually large.

¹ 'Nederl. Tijdschrift voor Geneeskunde,' 1889, ii, p. 413.

² 'Lancet,' 1890, vol. ii, p. 607.

³ 'Zeitschrift für physiol. Chemie,' Bd. xv, p. 286, 1891.

⁴ 'Journal of Physiology,' 1890; 'Proc. Physiol. Soc.,' p. xiii.

The method employed for the detection of uro-hæmatoporphyrin in the cases referred to in this paper was that recommended by Dr. MacMunn.

Neutral and tribasic acetate of lead were added to the specimens of urine, and the precipitate formed was filtered off from the decolourised liquid. The precipitate was then treated with rectified spirit acidulated with sulphuric acid, and the extract so obtained was examined with the spectroscope.

It is unfortunately only possible to form a very rough estimate of the relative amounts of the pigment present in different specimens; but when equal quantities of urine are examined, and nearly equal quantities of acidulated alcoholic extract are prepared, it is possible to obtain some idea of the quantity present from the relative intensity of the absorption bands in different specimens.

It seemed probable that, since uro-hæmatoporphyrin is a reduction product of hæmatin, it might be possible to trace some relation between its appearance in the urine and the destruction of red corpuscles or of hæmoglobin. I accordingly made frequent examinations of the urine in seven cases, in which I was at the same time observing the changes in the blood, and I am obliged to acknowledge that I have failed to detect any obvious connection between the blood-changes and the excretion of this pigment.

In the first case examined from this point of view (Chart VII) it seemed as if the appearance of uro-hæmatoporphyrin in the urine was associated with falling worth, but the later observations lent no support to this view, for the pigment was present in some cases whilst the worth was rising, and the repair of the red corpuscles was going on rapidly.

Chart IV exhibits only very trifling variations of worth, but nevertheless uro-hæmatoporphyrin was found on no less than fourteen out of the seventeen occasions on which the urine was examined, sometimes in mere traces, at other times in considerable quantity.

Again, in the case represented by Chart VIII uro-hæmatoporphyrin was found repeatedly, in varying amounts, both during the period of deterioration of the blood and during that of repair.

Chart VI is less conclusive. In this case the excretion of uro-hæmatoporphyrin ceased when convalescence was fairly established, and only at the first two observations was any considerable quantity found.

In some cases in which the blood-changes are well marked no uro-hæmatoporphyrin is found in the urine.

Chart III illustrates this; here the variations in the number of red corpuscles are most conspicuous, but the urine was examined on five occasions, always with negative results.

Perhaps the absence of any relation between the two sets of phenomena was most strikingly demonstrated in the case of a patient whose chart I have not reproduced. He was a man, æt. 34, who on his admission to the hospital was passing urine which contained a large amount of uro-hæmatoporphyrin, or most probably ordinary hæmatoporphyrin. During his stay of twenty-one days nine examinations of the urine were made, and the pigment was found to be present on each occasion. He was discharged on August 31st, the corpuscles having increased 17 per cent. since his admission, and the hæmoglobin 6 per cent., whereas the worth of the individual corpuscle had fallen .06. On September 23rd he attended as an out-patient with some return of pain in the joints, and his urine was found still to contain hæmatoporphyrin. On September 26th the pigment was again present in large quantities, as also on October 10th, when the patient was readmitted with a moderately acute rheumatic attack. Hence it may be inferred that the patient was excreting hæmatoporphyrin during at least a considerable part of the interval between his discharge and readmission, but yet on October 12th the red corpuscles numbered 4,793,750 as against 4,918,750 at the time of his discharge; the percentage of hæmoglobin

had risen from 67 to 71, and the worth of the individual corpuscle from $\cdot 68$ to $\cdot 74$.

It may be that there is a relation between the changes in the blood and urine which the methods employed are not sufficiently exact to detect, but I do not think the observed phenomena can be in any way explained by supposing that just as drugs are excreted in the urine for some time after their administration is stopped, so uro-hæmatoporphyrin may appear in the urine after the process which leads to its formation has come to an end. In Case 8, for instance, the pigment was still found in the urine twelve days after the last evidence of excessive blood destruction was obtained; for the fall of worth between October 8th and 12th would seem to have been due rather to a deficiency of hæmoglobin in the freshly formed corpuscles than to any active destructive process.

I think, indeed, that the above-quoted cases afford sufficient evidence that the presence of uro-hæmatoporphyrin in the urine does not imply any excessive destruction of red corpuscles or of hæmoglobin, and that, unless it be derived from the histohæmatin of muscle, its excretion must be attributed to a perversion of the ordinary processes for the disposal of effete blood-pigment rather than to a destruction of larger quantities of hæmoglobin than the ordinary channels of elimination are capable of dealing with. At the same time it is a fact that the period of rheumatic fever, in which uro-hæmatoporphyrin is most apt to be present in the urine, is one during which the processes of blood destruction are very active at times.

Indications for the Treatment of the Anæmia of Rheumatism.

It will be seen from the observations which are embodied in the paper that the anæmia of rheumatism is of two kinds: 1st, an acute oligocythæmia developing during the acute stage of the disease, and rapidly recovered

from as soon as convalescence sets in ; and 2ndly, a pseudo-chlorotic condition which is developed as a sequela of the attack in a few cases, and which, unless it is appropriately treated, may last for a long period, the fall of worth continuing in spite of the amelioration of the patient's condition in other respects.

The acute oligocythæmia calls for no special treatment, but the fall of the number of corpuscles in some cases, and of the hæmoglobin percentage in others, which appears to be dependent upon the patient's first getting up, suggest the desirability of keeping the patient in bed for some time after the subsidence of the acute symptoms, even when it is not rendered especially desirable by an affection of the endocardium. Iron appears to be often extremely useful in combating the pseudo-chlorotic condition. Its effect was well shown in the little boy, aged eight, who was left conspicuously anæmic after an attack of articular rheumatism associated with chorea and extremely numerous subcutaneous nodules, and who had a loud præ systolic mitral murmur. On June 20th this boy's corpuscles numbered 5,012,500, but his hæmoglobin percentage was only 60, the worth of the individual corpuscle being $\cdot 59$. He was given two drachms of steel wine three times a day, and on July 4th the red corpuscles had increased to 5,634,670, the hæmoglobin to 75 per cent., and the worth to $\cdot 66$. On July 17th, another fortnight later, the corpuscles had again fallen to 4,968,750, but the hæmoglobin remained at 75 per cent., and the worth had further risen to $\cdot 75$, making an increase of $\cdot 16$ in four weeks.

It should be mentioned that even at the last-mentioned date the nodules had not all disappeared, and fresh ones occasionally developed for some time afterwards.

Again, it would appear that, in the case represented by Chart V, the substitution of fifteen grains of the ammonio-citrate of iron daily for sodium salicylate checked the fall of worth which was till then progressing rapidly ; but, on the other hand, Chart VII shows no

effect from the administration of similar doses of the same compound, at least during the period over which the observations extend.

Note.—Since the above was written further study of the properties of the urinary pigment referred to has convinced me that it is actually hæmatoporphyrin, and that its spectrum in acid solution free from urobilin is identical with that of hæmatoporphyrin prepared from blood, showing no band before the F line.

PART II.—*Variations in the Number of White Corpuscles.
The Character of the Fibrin Network in Simple Slide
Preparations of the Blood.*

Received March 3rd—Read May 24th, 1892.

Variations in the Number of White Corpuscles.

In the first part of this paper I have described in detail the changes which I observed in the number and worth of the red corpuscles in the course of rheumatic attacks; and I now propose to supplement that description by an account of the variations in the number of leucocytes which occur simultaneously with those changes.

M. Hayem¹ states that the white corpuscles are always increased in number during acute attacks, but Drs. Maragliano and Castellino² maintain that there is no real leucocytosis in these cases, and attribute the apparent increase of the white to the relative diminution of the red corpuscles.

Mr. Gostling,³ in his important paper on the increase

¹ 'Du Sang' (1889), p. 916.

² 'Gazzetta degli Ospitali,' 22 Marzo, 1891.

³ 'Medico-Chir. Trans.,' lxi, 1886, p. 206.

of white corpuscles in the blood in inflammation, communicated to this Society in 1886, quotes only the numbers counted in a single case of rheumatic fever, and contrasts the scanty fluctuations there observed with the far more conspicuous variations which are associated with suppurative diseases. Halla,¹ v. Limbeck,² Reinert,³ and Carl Sadler⁴ have also recorded cases in which some increase of the number of white corpuscles was observed.

My own observations tend, one and all, to confirm the accuracy of M. Hayem's statement upon this point. In every case of acute rheumatism in which I have examined the blood there has been evidence of a distinct increase of white corpuscles during the febrile stage, but at the same time the leucocytosis has been very moderate in degree.

For the counting of the white, as well as of the red corpuscles, a Thoma-Zeiss hæmocytometer was employed, with the special mixing pipette which is made for this purpose, giving a dilution of only ten or twenty instead of one or two hundred times.

The blood was diluted with a .03 per cent. solution of acetic acid, a liquid which is very convenient for the purpose, as it renders the leucocytes more conspicuous, and at the same time destroys the red corpuscles.

A microscopic field of known area was taken as the unit, and fifty such fields were counted at each observation. The area of the field taken was such that the cubic capacity of the portion of the hæmocytometer-cell included in fifty fields was equal to that over 490.8 squares of Gowers' hæmocytometer.

It appears to me to be the better plan to state the number of leucocytes per cubic millimetre of blood, rather than to give merely the relation between the numbers of white and red corpuscles as is usually done. The relative

¹ 'Zeitschr. f. Heilkunde,' 1883, Bd. iv, p. 348.

² Ibid., 1890, Bd. x, p. 422.

³ 'Die Zählung der Blutkörperchen,' &c., 1891.

⁴ 'Fortschritte der Med.,' Bd. x, 1892, 4, Supplement Heft.

numbers have, of course, the advantage of being independent of changes in the total mass of blood, but they give but a very imperfect notion of the fluctuations of the white corpuscles, which may be almost completely masked if the numbers happen to be increasing or diminishing simultaneously with those of the red corpuscles.

The average number of white corpuscles contained in healthy blood has been very variously estimated; but my results agree most closely with those of more recent observers, who give, for the most part, a considerably lower figure than was formerly adopted.

M. Hayem considers that 6000 white corpuscles per cubic millimetre is about the normal; and Dr. Habershon, after making 80 examinations of the blood of forty healthy individuals between the ages of twenty and fifty, obtained an average of 6600 white corpuscles per cubic millimetre, or one white to 670 red corpuscles.¹

Dr. Habershon also found that when the blood was examined at a short interval after a meal the average was somewhat higher, viz. 8620 per cubic millimetre.

In order to exclude the effects of food as far as possible, my examinations were made at nearly the same hour on different days, usually between 3 and 4 o'clock in the afternoon, the chief meal having been taken at 1 p.m.

It is upon the fluctuations observed, rather than upon the actual number of white corpuscles present at any given period, that I rely for the proof of the statement that there is a true leucocytosis in acute rheumatic cases, for there are few readings of which I have records which would not be regarded by some as but little exceeding the numbers compatible with health.

For the sake of convenience I have taken 7000 per cubic millimetre as the normal number, and have called this 100 per cent., and have thus been able to represent the variations on the charts by making this number correspond with the zero line.

¹ "On the Variations in the Number of White Blood-corpuscles in Diabetic Patients," 'St. Barth. Hosp. Reports,' vol. xxvi, 1890, p. 153.

The conclusions here presented are drawn from a series of eight cases in which the special white corpuscle pipette was employed ; but I may add that in a number of other cases, in which the white corpuscles were counted with the red, results were obtained entirely in accordance with those arrived at by the more exact method.

M. Hayem mentions 25,000 per cubic millimetre as the number to which the leucocytes may attain in very acute cases, but none of the cases which I examined in this connection could be described as very acute, and the highest observed number was 19,882, or 284 per cent., the proportion of white to red corpuscles being as 1 to 209.

In the first part of this paper it was pointed out that the diminution of the number of red corpuscles had but little relation to the amount of the febrile disturbance, having a far more obvious association with the occurrence of local lesions. The increase of leucocytes, on the other hand, seems to have an intimate relation to the height of the fever, whereas local lesions attended with little rise of temperature may be accompanied by an increase of white corpuscles so slight as hardly to exceed the limits of health.

These points are well illustrated by the case of a patient whose chart is numbered III. In that instance a copious eruption of erythema marginatum, which appeared during convalescence from a slight attack of articular rheumatism, was attended by a loss of no less than 1,000,000 red corpuscles per cubic millimetre, whereas the maximum number of leucocytes counted, at a time when the red corpuscles were at their lowest, was only 8271 per cubic millimetre, or 118 per cent.

The increase of white corpuscles is a very early event in the rheumatic attack, so early, indeed, that it has usually reached its limit before the first observation is made ; and in hospital patients it is only possible to observe the fall which occurs as soon as convalescence commences.

When, however, a relapse or recrudescence occurs

under observation the leucocytosis may be satisfactorily studied; this is very well illustrated by Chart IX.

The patient in question was a young woman, *æt.* 21, who had been in the West London Hospital a year previously, suffering from acute articular rheumatism and valvular disease, and who then exhibited numerous subcutaneous rheumatic nodules.

She was admitted a second time on November 15th, 1891, under the care of my colleague Dr. Herringham, to whom I am greatly indebted for the opportunity of studying this and other cases.

The primary attack quickly subsided under treatment, and the white corpuscles, which on November 16th numbered 11,714 per cubic millimetre, or 167·5 per cent., had fallen by November 19th to 9160, or 133·3 per cent., whilst there had been a simultaneous recovery of red corpuscles.

On the morning of November 23rd the temperature, which had been normal, was found to have risen again to 100°, and in the afternoon of that day there was found to be a suspicious increase of white corpuscles, although the number of red corpuscles was also increased.

This rise of temperature marked the commencement of one of those remarkable relapses in which local manifestations are almost entirely wanting, although the febrile disturbance is considerable. There was, indeed, a slight return of articular pain, but this was unattended by any swelling, and there was no evidence of any rapid increase of the cardiac mischief, nor of the development of endocarditis; nevertheless it was, of course, impossible to exclude the possibility of fresh endocarditis.

On November 26th the white corpuscles had undergone a further increase to 15,217 per c.m., or 217 per cent., and there was a moderate loss of red corpuscles.

The temperature remained high, with occasional intermissions, until December 5th, but on November 29th the white corpuscles had already fallen to 11,041, or 157·7 per cent., and on December 3rd a further diminution to 10,369,

or 148·1 per cent., was recorded. On the 7th the number was 8780, or 125·4 per cent.; but on December 12th, although the temperature continued to be normal and subnormal, a fresh increase of white corpuscles to 9595 was found to have taken place, and this increase was the earliest warning of a second relapse, during which the blood was not further examined.

The decrease of the white corpuscles during the decline of the attack may be as rapid as their increase at its onset, as is shown by the following examples :

Date.		Number of white corpuscles per cm.		Percentage.
Case 1.—Oct. 29th	...	17,194	...	245·6
Nov. 2nd	...	7,700	...	110·0
Case 2.—Jan. 23rd	...	19,882	...	284·0
„ 27th	...	17,950	...	256·4
„ 30th	...	9,024	...	128·9

On the other hand, there are cases in which the fall is very gradual, and the number of white corpuscles may remain high for some time after the febrile disturbance, and all obvious local manifestations of the disease have come to an end. The following case illustrates this :

Date.		Maximum temp. of day.		Number of white corpuscles per cm.		Percentage.
Oct. 8th	...	100·8° F.	...	13,300	...	190·0
„ 12th	...	99°	...	12,691	...	181·3
„ 17th	...	98·4°	...	12,831	...	183·3

The Blood Platelets.

Since the blood platelets remain visible for a considerable time in the solution of sodium sulphate, they may be observed and counted on the hæmocytometer field. In some cases in which I have attempted to count them there has been a well-marked increase in their numbers during the period of convalescence, and in one instance the increase was very remarkable, the number of platelets reaching the very high total of 1,415,000 per cubic millimetre, or nearly one platelet to every three red corpuscles.

Halla¹ also observed a great increase of platelets after defervescence in some of his cases.

Form of the Red Corpuscle.

I have not observed any noteworthy change in the form of the red corpuscles, and in the cases in which they were measured with a micrometer scale no marked deviation from the normal size was noticed. In a few cases in which the degree of anæmia was conspicuous, some distortion of shape was apparent in some of the corpuscles.

Characters of the Fibrin Network.

When a drop of blood from a rheumatic patient is placed upon a slide and simply enclosed by a cover-glass, the corpuscles soon become massed together, and lose their natural shape, the masses of corpuscles being separated from each other by broad lakelets of clear serum, in which lie numerous leucocytes. In a short time filaments of fibrin, much coarser than the delicate fibrillæ which form in healthy blood, begin to traverse the clear spaces in all directions, and in this way a coarse fibrin network is gradually formed, which has a radiating structure, the radiant points being formed by groups of leucocytes or collections of blood platelets.

M. Hayem² considers that these appearances of the blood have a very important diagnostic value, since he has found that the fibrin network is more conspicuous in acute rheumatism than in any other disease except croupous pneumonia.

In order to test the diagnostic value of this indication, I have examined in the manner described the blood of a number of patients suffering from a variety of inflammatory disorders, and have been led to the opinion that the test has only a very limited application. Undoubtedly

¹ 'Zeitschr. f. Heilkunde,' 1883, Bd. iv, p. 349.

² 'Bull. et Mém. Soc. Méd. des Hôpitaux,' 1886, p. 18.

the above description agrees with what is observed in the great majority of cases of rheumatic fever, and in the patient whose chart is numbered IX the character of the fibrin network varied, as will be seen, with the intensity of the rheumatic manifestations, and especially with the degree of febrile disturbance, the network becoming much more delicate when the temperature fell, and much coarser again when the relapse set in. Yet it occasionally happens that the blood exhibits a different appearance, even in typical rheumatic cases, as is shown by the following example.

A young woman was admitted to the hospital suffering from acute arthritis of many joints, and having a loud pericardial friction-sound. The blood was examined on the day following her admission, and was found to present a quite unusual appearance. The corpuscles very rapidly became crenated, and did not show the slightest tendency to form rouleaux or to aggregate into masses; indeed, no one corpuscle adhered to any other. There were no masses of corpuscles and no lakelets of serum, nor could any fibrin network be seen with a quarter-inch power, even after an interval of half an hour. The morning temperature on the day in question was 99.8° , the evening reading 102.4° .

These unusual appearances suggested a doubt as to the accuracy of the diagnosis of rheumatic fever, but the subsequent course of the case, its behaviour under salicylic treatment, and the development of an endocardial murmur dispelled all question as to its nature. Four days later the blood of this patient presented an appearance more closely resembling that usually met with in rheumatic cases, but the temperature was falling, and the fibrin network, although conspicuous, was by no means coarse.

I do not doubt that the appearance of the blood may be of considerable value in cases in which febrile disturbance precedes any of the more characteristic rheumatic manifestations, by giving a useful hint as to the probable nature of the disease, and it is in such cases that

M. Hayem has found it of service ; but in afebrile cases, when the question arises whether or no local lesions which are sometimes rheumatic are in the particular instance manifestations of rheumatism, it is of no service, since the coarse network is wanting, even in attacks the rheumatic origin of which is almost beyond question, as long as the temperature exhibits no considerable elevation.

Again, in cases of acute gout the blood may exhibit appearances which only differ very slightly, if at all, from those met with in acute rheumatism ; and hence the test is of no service in distinguishing between these two forms of articular affection, which sometimes resemble each other so closely.

(For reports of the discussions on these papers, see 'Proceedings of the Royal Medical and Chirurgical Society,' Third Series, vol. iv, pp. 70 and 132.)

CHART I.—Emily P., æt. 18. Rheumatic fever ; arthritis ; pericarditis ; endocarditis ; erythema nodosum.

CHART II.—H. G.—, male, æt. 16. Rheumatic fever ; pericarditis ; pneumonia ; pleurisy.

CHART III.—W. B., male, æt. 18. Subacute rheumatism; pericarditis; erythema marginatum; nodules.

CHART IV.—W. F—, male, æt. 17. Subacute rheumatism; pleurisy.

CHART V.—F. H—, male, æt. 18. Rheumatic fever; pericarditis.

CHART VI.—C. T.—, male, æt. 9. Subacute rheumatism; arthritis; endocarditis.

CHART VII.—H. R.—, male. Rheumatic fever; arthritis; endocarditis.

CHART VIII.—A. B—, female, æt. 10. Rheumatic fever; endocarditis; bronchitis.

CHART IX.—F. C—, female, æt. 21. Rheumatic fever; relapse.