

The types of anæmia in malarial cachexia and anchylostomiasis / by Leonard Rogers.

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Rogers, Leonard, 1868-1962.

Publication/Creation

[Place of publication not identified] : [publisher not identified], 1898.

Persistent URL

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AND ANCHYLOSTOMIASIS

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Journal of Pathology & Bacteriology,
1898, 5.



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THE TYPES OF ANÆMIA IN MALARIAL CACHEXIA AND ANCHYLOSTOMIASIS.

By LEONARD ROGERS, M.D., M.R.C.P., F.R.C.S.,
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DURING a recent investigation of the epidemic malarial fever of Assam, locally known under the name of kala azar, I had occasion to study closely the anæmia met with in malarial cachexia and in anchylostomiasis, with the result that I found the type in the two diseases differed so widely as to be of diagnostic importance in differentiating the two diseases, which, in that province, had formerly been confused.

The exact changes in the blood in the two affections are somewhat differently described by various writers. Thus in the case of anæmia of malarial origin, Kelsch and Kiener¹ say that the red corpuscles are reduced in numbers, while the hæmoglobin in each corpuscle is also reduced to five-sixths or one-half. Andrew Davidson² says that they are both reduced in numbers and deficient in hæmoglobin, the blood being paler than normal. On the other hand, Waddell³ gives the figures obtained in cases of malarial cachexia in Calcutta, which show that while the red corpuscles are reduced in number the average amount of hæmoglobin in them is relatively slightly higher than normal, while Cabot⁴ states that, as a rule the red corpuscles and hæmoglobin are diminished proportionally (colour index being 1). Most observers are agreed that in the absence of fever the white corpuscles are considerably reduced in numbers, but their proportion relatively to the red is not stated. I have not been able to find any estimations of the specific gravity of the blood in this disease.

In the case of anchylostomiasis still less definite statements are to be found. Thus Sonsino⁵ writes: "The observations respecting the microscopic alterations of the blood have not hitherto given uniform results. Generally it appears that the alterations consist more in a deficiency in the number of the red corpuscles than in want of colouring matter." Lutz⁶ records that he found the red corpuscles constantly and greatly

¹ "Maladies des pays chauds."

² "Hygiene and Diseases of Warm Climates."

³ *Indian Med. Gaz.*, 1883.

⁴ "Clinical Examination of the Blood."

⁵ Davidson's "Hygiene and Diseases of Warm Climates," art. "Intestinal Parasites."

⁶ Translation of Sotz's paper on "Anchylostomiasis," in Kynsey's "Beriberi of Ceylon."

reduced in number, and continues: "The hæmoglobin, as far as I can learn from the literature of the subject, seems to diminish in the same ratio." Neither of these writers gives any figures on this head. On the other hand, Sandwith¹ gives the number of the red corpuscles and the percentage of hæmoglobin in 173 cases, from which it appears that the hæmoglobin is reduced about twice as much as are the red corpuscles, so that the colour index or hæmoglobin value is reduced to one-half the normal.

Lutz² mentions that the white corpuscles in long-standing cases, although actually reduced, are relatively more numerous than the red. Again, I have not been able to find any records of the specific gravity of the blood in this disease.

Coming to my own observations, I will first take up the subject of the blood changes in malarial cachexia. The proof that the cases of kala azar, which furnished most of the material for the study of the subject, were really malarial in their nature is set forth at length in my book on the disease,³ but it may be mentioned that all the symptoms of the disease are entirely malarial from first to last, while the *Plasmodium malariae* is constantly present in the disease, cases of which are indistinguishable from ordinary malarial fever. Moreover, both the clinical symptoms and the blood changes in cases of ordinary malarial fever in the Sylhet district, which has always been quite free from the epidemic fever, were found by me to be precisely similar to those of kala azar.

The investigation included the following points—namely, the number of red corpuscles per cubic millimetre, estimated by means of Gowers' hæmacytometer; the percentage of hæmoglobin, estimated by means of the instrument of the same author; the number of the white corpuscles per cubic millimetre, calculated in the same way as the red corpuscles; and, finally, the specific gravity of the blood estimated by means of the instrument of Lloyd Jones. In a few cases, also, the coagulability of the blood was estimated by means of the instrument designed by A. E. Wright of Netley.

As all my observations were made on natives of India, whose blood standard is not the same as that of Europeans, it was first necessary to examine some healthy natives, and so to obtain a standard for comparison. This was not quite so simple a matter as it appears at first sight, for malarial fever is very common in Assam, while the majority of the natives of this, as well as of most other parts of India, harbour the *Anchylostomum duodenale*, although in the great majority of cases only in very small numbers, too small indeed to affect their health in any way. In order to eliminate all error, thymol was given to a number of apparently healthy men in a jail, and the number of anchylostoma passed

¹ "Anchylostomiasis in Egypt," *Indian Med. Gaz.*, 1894, vol. ii. p. 249.

² Translation of Sotz's paper on "Anchylostomiasis," in Kynsey's "Beriberi of Ceylon."

³ "The Epidemic Malarial Fever of Assam, or Kala Azar."

reduced in number and sometimes. The hemoglobin, as far as I can learn from the literature of the subject, seems to diminish in the same ratio. Noyes of these writers gives very figures on this head. On the other hand, Noyes gives the number of the red corpuscles and the percentage of hemoglobin in 173 cases from which it appears that the hemoglobin is reduced about twice as much as are the red corpuscles, so that the color index or hemoglobin value is reduced to one-half the normal.

Later, I mention that the white corpuscles in long-standing cases, although actually reduced, are relatively more numerous than the red. Again, I have been able to find very records of the specific gravity of the blood in this disease.

Referring to my own observations, I will first take up the subject of the blood changes in malarial cachexia. The proof that the cases of malarial cachexia, which furnished most of the material for the study of the subject, were really malarial in their nature is set forth at length in my book on the disease, but it may be mentioned that all the specimens of the disease are malarial from that point of view, while the specimens of malarial cachexia are malarial from that point of view.

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The number of red corpuscles per cubic millimeter, estimated by means of the hemacytometer, the percentage of hemoglobin, estimated by means of the instrument of the same name, the number of the white corpuscles per cubic millimeter, estimated in the same way as the red corpuscles, and finally, the specific gravity of the blood, estimated by means of the instrument of Lloyd Jones, in a few cases, when the composition of the blood was estimated by means of the instrument designed by A. E. Wigglesworth.

In all my observations were made on natives of India, whose blood standard is not the same as that of Europeans, it was first necessary to examine some healthy natives and so to obtain a standard for comparison. This was not quite so simple a matter as it appears at first sight, for malarial fever is very common in India, while the majority of the natives of India, as well as of most other parts of India, harbor the malarial parasite, although in the great majority of cases only in very small numbers, too small indeed to affect their health in any way. In order to eliminate all error, I have given to a number of apparently healthy men a full and the malarial parasites were

after it were counted. At the same time the amount of fever that each man had suffered from during the last two years was noted, and the quality of the blood was tested in the ways above enumerated.

The result was somewhat surprising, for, taking the percentage of hæmoglobin as an indication of the quality of the blood, it appeared that the average amount in seven healthy men who had no anchylostomum was 57·3 per cent., while that of seventeen men who harboured this parasite in numbers, varying from one to twenty, was 57·7 per cent.; so that it is obvious that these small numbers have no effect on the quality of the blood. On the other hand, it was found that the average percentage of hæmoglobin in sixteen men who had not suffered from more than one week's fever during the previous two years was 60·8, while that of eight men who had had more than one week's fever during the same period was only 52·7. It is obvious, therefore, that comparatively slight malarial fever is a much more important factor in causing anæmia than is the presence of small numbers of anchylostoma. Only men who had not suffered from more than one week's fever during the last two years, and who had not harboured more than twenty anchylostoma, were taken as perfectly healthy men. The average blood of fourteen such natives in Assam was as follows:—Hæmoglobin, 62 per cent. (Gowers' standard); red corpuscles, per cubic millimetre, 4,734,000; white corpuscles, per cubic millimetre, 7325; specific gravity of the blood, 1·054. It will be noticed that while the number of red corpuscles differs little from the normal European standard of 5,000,000, the hæmoglobin is very low, so that the average amount of hæmoglobin in each corpuscle is only ·65 of the normal. On the other hand, the ratio of the white to red corpuscles is 1 to 684, which is within the normal limits.

The average percentage of hæmoglobin in seven healthy Europeans in the rainy season in Assam was 71. The higher rate among Europeans is probably due to the much larger amount of animal food consumed by them, which contains more iron than the almost purely vegetable diet of the average native.

It is also worthy of note that I found several of the Europeans whom I examined had from 8 to 10 per cent. more hæmoglobin towards the end of the healthy cold weather than they had in the unhealthy rainy season, which shows the deteriorating effect on the blood of a hot damp climate such as that of Assam.

Taking the above as the standard of the blood of healthy Assamese, it may be compared with that found in cases of anæmia caused by malarial cachexia and anchylostomiasis respectively.

THE BLOOD CHANGES IN MALARIAL CACHEXIA.

The degree of anæmia in chronic malaria varies from a slight degree, which is not recognisable clinically, but is made evident by a

quantitative examination of the blood, to one of a high degree. Thus I have often found the hæmoglobin reduced to from 50 to 35 per cent. without any marked pallor of the mucous membranes in natives of India, but in all cases of malarial fever of any duration the hæmoglobinometer shows a definite and marked reduction, even when there is no clinical evidence of the presence of anæmia. On the other hand, I have several times found the hæmoglobin reduced to less than 20 per cent., while it is not uncommonly between 20 and 30 per cent.

The red corpuscles are also reduced in number in much the same proportion as the hæmoglobin, in which respect, as will be shown presently, the anæmia of malaria differs widely from that of anchylostomiasis. Thus in fifty cases of chronic malarial fever the red corpuscles averaged 2,462,000 per cubic millimetre, or 49·24 per cent. of the normal, while the hæmoglobin in 107 cases averaged 33·45 per cent., so that the proportion of hæmoglobin in each red corpuscle, or shortly the hæmoglobin value, works out to be ·65, or precisely the same figure which was found to be normal for healthy Assamese. It is evident, then, that the two are equally reduced in the anæmia of chronic malaria. That this feature is a constant one is shown by the fact that in uncomplicated cases of malarial disease, the hæmoglobin value was only four times found to be below ·5, and in three of these cases I found from my notes that the patients had suffered from severe bleeding from the nose, which would lower the hæmoglobin value in the way that I shall presently show occurs as a result of the steady loss of blood in anchylostomiasis.

The white corpuscles were also very markedly reduced, much more so in proportion than were the red. Thus the average number of thirty-six observations, made in the absence of fever, was only 2600 per cubic millimetre, while the proportion to the red corpuscles was only 1 to 1170, or about half the normal, and it was not rare to find only 1 white to over 2000 red. In these latter cases the prognosis was very bad, quinine seeming to have little or no influence in controlling the fever. During fever, especially if the temperature is over 102° F., a relative leucocytosis occurs, although the white corpuscles may still be below the normal number. Thus in one case, when the temperature was normal, there was only one white corpuscle to every 1225 red, but when it was 103·2° F. the proportion was 1 to 672. It is the multinuclear corpuscles which are chiefly reduced in numbers, while the lymphocytes are relatively increased.

The specific gravity of the blood is always reduced in anæmia, according to Lloyd Jones' observations.¹ This writer states that the reduction is in proportion to that of the hæmoglobin. In thirty-four observations in cases of anæmia due to chronic malaria I found the specific gravity of the blood to vary between 1·050 and 1·060 in fourteen cases, while in nineteen cases it was between 1·040 and

¹ "Clinical Examination of the Blood."

1·049, and in only one did it fall to 1·039, and this was a case in the last dropsical stage of malarial cachexia. The average of the observations was 1·048, which is only slightly below that of healthy natives, namely, 1·054; and in this respect again it will be seen presently the type of malarial anæmia differs widely from that which obtains in anchylostomiasis, even when the more severe degree of anæmia which is commonly met with in the latter disease is allowed for. Again, I found that the specific gravity of the blood falls as the red corpuscles and hæmoglobin become reduced, and rises as they increase again in cases of recovery; but there was no constant relationship between either the number of red corpuscles or hæmoglobin and the specific gravity of the blood, so that the composition of plasma must also influence its density.

The coagulability of the blood was tested by means of A. E. Wright's instrument in a few cases, but it was found to be within the normal limits, although as a rule somewhat lower than the average of healthy persons.

To sum up, the type of the anæmia in malarial cachexia is characterised by—(1) an equal or nearly equal reduction in the number of the red corpuscles and the hæmoglobin, and a consequently normally high hæmoglobin value of each red corpuscle; (2) the white corpuscles are greatly reduced in numbers, both absolutely and to a still greater degree relatively to the number of the red corpuscles; (3) the specific gravity of the blood is reduced, but only to a slight extent.

THE BLOOD CHANGES IN ANCHYLOSTOMIASIS.

Taking the observations in the same order as before, it was found that the percentage of hæmoglobin in twelve cases of anchylostomiasis averaged 15·16, showing a more marked degree of anæmia than the malarial cases presented.

The red corpuscles averaged 2,145,000 per cubic millimetre, or 42·9 per cent. The hæmoglobin value of each red corpuscle in nine cases averaged only ·31 as against ·65 both in healthy natives and in those suffering from malarial anæmia, so that the hæmoglobin was reduced more than twice as much as the red corpuscles in cases of anchylostomiasis. This was a constant feature of the disease, for the highest figure met with was ·39, which is much lower than the lowest found in any case of malarial cachexia. The anæmia of the two diseases can then be absolutely differentiated by this feature, and I find that the averages of the number of the red corpuscles, and of the percentage of hæmoglobin in 173 cases of anchylostomiasis given by Sandwith¹ of Cairo confirm my results on this head, for they also show that the percentage of hæmoglobin was reduced almost exactly twice as much as that of the red corpuscles.

The number of white corpuscles in ten cases averaged 5338, and

¹ "Anchylostomiasis in Egypt," *Indian Med. Gaz.*, 1894, vol. ii. p. 249.

their ratio to the red was as 1 to 524, so that, although they were absolutely reduced in number, yet relatively to the red they were increased as compared with the normal of natives of India. Here again it will be seen the anæmia of anchylostomiasis differs most materially from that of malarial cachexia.

The specific gravity of the blood is very greatly reduced in cases of anchylostomiasis, for it was found to vary between 1·038 and 1·030, while the average of eight cases was but 1·034. This was partly due to the greater average degree of anæmia present in these cases than in the malarial ones, but only partly so, for it was found that in cases of the two diseases which presented a similar degree of anæmia, as judged by the percentage of hæmoglobin, the specific gravity of the anchylostomiasis cases was still on the average eight points lower than of the malarial ones. This again is a simple and rapidly applied way of differentiating the two types of anæmia, although its value is scarcely so absolute as that of the hæmoglobin value.

It should also be mentioned that the average blood change found in four cases in which malarial cachexia was found to be complicated by the presence of large numbers (from 80 to 120) of anchylostoma, and the type of the anæmia was in all respects intermediate between those of the two primary conditions, while in some cases in which it was impossible from the history to determine which disease was the primary cause of the anæmia, an examination of the blood enabled a correct diagnosis to be arrived at.

To sum up, the type of anæmia in anchylostomiasis is characterised by—(1) a much greater reduction of the hæmoglobin than of the number of the red corpuscles, and consequently a very low hæmoglobin value or colour index; (2) the white corpuscles are absolutely reduced in numbers, but relatively to the red they are increased; and (3) the specific gravity of the blood is very greatly reduced, allowing for the amount of reduction of the hæmoglobin.

EXPLANATION OF THE DIFFERENCE IN THE TYPES OF ANÆMIA.

A little consideration will show that the blood changes that have been recorded above are just such as might have been expected, when we take into account the way in which the anæmia is produced in the two diseases under discussion. In the case of chronic malarial fever the red corpuscles are gradually destroyed by the action of the *Plasmodium malariae*; the hæmoglobin is not lost to the body, but is stored up in the form of an iron-containing pigment in the liver, spleen, and other organs. Now, I found the marrow in the shafts of the long bones, in twenty-five post-mortems on fatal cases of chronic malarial fever in Assam, to be constantly converted into red marrow, just as has been found by Robert Muir¹ to occur in cases of per-

¹ *Journ. Path. and Bacteriol.*, Edin. and London, vol. ii. p. 354.

nicious anæmia. This change is doubtless a conservative one, to allow of new red corpuscles being turned out in large numbers to replace those so rapidly being destroyed by the fever. Moreover, there is already plenty of iron in an organic combination stored up in the liver and spleen, from which hæmoglobin can be formed wherewith to restock the red corpuscles as they are formed by the bone marrow, and consequently the hæmoglobin value is maintained, and the anæmia resulting is of the true pernicious type.

On the other hand, in the case of the anæmia of anchylostomiasis, both the hæmoglobin and the red corpuscles are equally lost to the economy, through the constant slow drain of blood from the intestine by these blood-sucking worms. In this instance, as soon as the reserve iron stored up in the liver becomes exhausted, as has been proved to take place by the analyses of Bevan Rake,¹ the hæmoglobin can only be formed with great difficulty, and the red corpuscles, being more easily replaced than the hæmoglobin, the hæmoglobin value of each falls, just as Ralph Stockman² has shown to occur after bleeding dogs. It may be mentioned that I have found the bone marrow of the shafts of the long bones in anchylostomiasis of a pale strawberry-red colour, but never of so dark a hue as it often is in malarial cachexia, doubtless owing to the absence of the pigment which is found in the bone marrow as well as in the liver in the latter disease.

The great decrease in the number of the white corpuscles, both absolutely and relatively to the red, in malaria, is probably due to the losses sustained by them in their constant fight with the malarial organisms, as is indicated by the leucocytosis, which is so marked a feature of the malarial paroxysms in recent cases, but which becomes less marked as their number becomes reduced. The great reduction in the proportion of the multinuclear corpuscles, and the increase in small and immature lymphocytes, points in the same direction. In anchylostomiasis, on the other hand, there is no special destruction of the white corpuscles, while they are more easily replaced than are the red ones, and consequently, although they are absolutely reduced in numbers, yet relatively to the red ones they become increased.

The greater reduction in the specific gravity of the blood in anchylostomiasis than in malarial anæmia, in cases presenting equal degrees of anæmia, must be due to the constant loss of plasma in the former disease being inadequately compensated for in the patients who have lost much of their digestive power, and moreover cannot afford a very nutritious diet. The differences met with in the anæmia in these two diseases are, then, in accordance with the manner in which the blood changes are brought about in the two cases, and their importance, from the diagnostic and therapeutic standpoints, will be evident.

¹ *Journ. Path. and Bacteriol.*, Edin. and London, vol. iii. p. 107.

² *Ibid.*, vol. iii. p. 385.

various anemias. This change is due to the fact that a considerable number of new red corpuscles being turned out in large numbers to replace those so rapidly being destroyed by the fever. Moreover, there is already plenty of iron in an organic combination stored up in the liver and spleen from which ferruginous may be formed wherever it is needed, the red corpuscles as they are formed by the bone marrow, and consequently the ferruginous value is maintained, and the anemia resulting is of the hypochromic type.

On the other hand, in the case of the anemia of anachylostomiasis both the hemoglobin and the red corpuscles are equally lost to the economy, through the constant absorption of blood from the intestine by these blood-sucking worms. In this instance, as soon as the worms are stored up in the liver become exhausted, as has been proved to take place by the analysis of Beaver Lake, the hemoglobin can only be formed with great difficulty, and the red corpuscles being more easily replaced than the hemoglobin, the hemoglobin value of each falls just as Ralph Stearns has shown to occur after bleeding dogs. It may be mentioned that I have found the same manner of the death of the body bones in anachylostomiasis of a pale starved red color, but never of so dark a hue as it often is in material cachexia, doubtless owing to the absence of the pigment which is found in the bone marrow as well as in the liver in the latter disease.

The great defect in the number of the white corpuscles, both absolutely and relatively to the red, in malaria is probably due to the loss sustained by them in their constant fight with the malarial organisms, as is indicated by the leucopenia which is so marked a feature of the malarial parasites in recent cases, but which becomes less marked as their number becomes reduced. The great reduction in the proportion of the malarial corpuscles and the increase in small and immature lymphocytes points in the same direction. In anachylostomiasis, on the other hand, there is no special destruction of the white corpuscles, while they are more easily replaced than are the red ones, and consequently, although they are absolutely reduced in number, yet relatively to the red ones they become increased.

The greater reduction in the specific gravity of the blood in anachylostomiasis than in malarial anemia, in cases presenting equal degrees of anemia, must be due to the constant loss of plasma in the former disease being inadequately compensated for in the patients who have lost much of their digestive power, and moreover cannot afford a very nutritious diet. The difference met with in the anemia in these two diseases are then in accordance with the manner in which the blood changes are brought about in the two cases and their importance from the diagnostic and therapeutic standpoint, will be obvious.