A REMARKABLE DAILY VARIATION IN LEUCOCYTES IN SEVERAL DISEASES:

MALARIAL FEVER, HODGKIN'S DISEASE, CANCER.*

BY

DAVID THOMSON, M.B., CH.B. EDIN., D.P.H. CANTAB.,

CLINICAL PATHOLOGICAL RESEARCH ASSISTANT, SCHOOL OF
TROPICAL MEDICINE, LIVERPOOL.

Prefatory Note.

THESE observations were made by means of a new blood counting method devised by me to make exact enumerations of the number of parasites in malaria and sleeping sickness, as suggested by Sir Ronald Ross. Some of these enumerative researches have already been published: Ross and D. Thomson (1910), Fantham and J. G. Thomson (1911), Ross and D. Thomson (1911), Ross and J. G. Thomson (1911), D. Thomson (1911). Although it is recognized that the leucocytes in normal individuals do not vary beyond about 5,000 to 15,000 per c.mm., yet I have thought it advisable to make three controls to show that the method is accurate enough. The apparatus is at present in the hands of the instrument makers, and as soon as it is ready I shall publish a full description of the instrument, with the method of using it (1911).

MALARIAL FEVER.

In the *Annals of Tropical Medicine and Parasitology*, vol. v, No. 1, 1911, I published the results of a year's research on the behaviour of the leucocytes in malarial fever. In that article it was pointed out that isolated blood counts once daily were insufficient, and that it was necessary to examine the blood every four to eight hours before the true behaviour of the leucocytes could be ascertained.

The leucocyte charts obtained in this way were very remarkable, and justified the great amount of labour entailed.

It was noticed that the leucocytes changed very markedly in numbers and in variety according to the stage of development of the malarial parasites, and also according to the number of parasites present in the blood. During the sporulation of the parasites—that is, during the liberation of the malarial virus into the blood plasma, the percentage of mononucleated leucocytes falls markedly, and where many parasites are present the total leucocyte count is also low.

Simultaneously with the fall of temperature the leucocytes increase in number and also the percentage of mononucleated leucocytes rises. This leucocytic variation was found to be much more delicate than the temperature change. Long after the temperature remained normal and the disease was apparently cured by quinine the change in number and variety of leucocytes

continued in a very marked degree. Thus it was found that a very marked leucocytosis took place about the time of the day during which the sporulations of the parasites had formerly occurred. This marked increase in leucocytes continued only for a few hours, when they again fell to normal numbers. I attribute this phenomenon to the supposition that small numbers of parasites must still be alive and sporulate as before, in spite of continued quinine treatment, though they are, however, too few in number to cause a temperature reaction, or to be detected even by a prolonged microscopic search. The chart of Case T. H. (*P. falciparum*) shows this phenomenon very clearly. This case had quotidian fever, and later, when apparently cured, showed marked quotidian rises in the number of leucocytes occurring at the time of day when the fever was formerly due.

Strange to say, when the parasites are very numerous there tends to be a constant leucopenia; but as the numbers of parasites become reduced the leucocytes increase, and finally the marked periodic leucocytoses occur, when the parasites are too few to be detected.

In support of my belief that this latter phenomenon is due to the sporulation of small numbers of parasites, I found that a subcutaneous injection of five to ten million dead malarial germs, mixed with corpuscles, produced in one half-hour a marked and transient leucocytosis.

As these leucocytic variations might be of great value as a diagnostic sign of latent malaria, Sir R. Ross considered it advisable that I should examine the blood of various other diseases in a similar manner—namely, every four to eight hours over a period of several weeks. In septic diseases with suppuration it was found that the number of leucocytes remained more or less constantly high, with a tendency to be more numerous during the intervals between the swinging temperature. In other words, they swung at a high level inversely with the

temperature. This phenomenon has also been observed by Dr. Moore Alexander, Pathologist to the Royal Southern Hospital, Liverpool. In these septic cases also a high polymorphonuclear percentage is more or less constantly maintained.

HODGKIN'S DISEASE.

The next cases that I examined in this way were two of Hodgkin's disease and one of cancer of the stomach.

CASE I.—H. M., male, aged 14, under the care of Dr. Macalister at the Royal Southern Hospital, Liverpool, was diagnosed by him as a case of Hodgkin's disease.

History and Clinical Notes.—Two years previously two small masses were observed on the side of the patient's neck. The medical attendant operated and removed them, but the swelling again appeared, and grew slowly and painlessly on the left side of the neck between the ear and the shoulder. He came under the care of Dr. Macalister on February 28th, 1911. Since then the swelling has enlarged considerably, and is now as large as a goose's egg. Various other glands in the body are also enlarged

T. H. — (*P. falciparum*) Malaria.

— Asexual parasites per c.mm. - - - - - Total mononuclear percentage.
..... Leucocytes per c.mm. X = X rays ten minutes over spleen.

* This variation occurred in all of 40 cases of malaria examined; but with regard to the two latter diseases the author does not assert from his isolated cases that it is a constant occurrence.

but they are not so prominent as those on the left side of the neck. The liver extends 1½ in. below the costal margin, and the spleen is enlarged to 2 in. below the costal margin. The patient has bouts of daily pyrexia, alternating with periods of freedom from fever, as indicated on the chart. The patient is not, as a rule, confined to bed. The treatment has been chiefly the administration of arsenic preparations and the occasional application of x rays over the swelling in the neck.

I commenced to make observations on the blood of this patient every six to eight hours on April 6th, 1911, and continued these observations over a period of two months. From the accompanying chart it will be clearly observed that a very remarkable leucocytic phenomenon has been revealed in this case.

(a) There is a very marked daily variation in the number of leucocytes, showing occasionally a swing from 6,000 to 75,000 leucocytes per c.mm. of blood—a twelvefold increase.

(b) The percentage of total mononuclear leucocytes is abnormally high amounting to from 50 per cent. to 80 per cent. of the total leucocytes.

(c) The mononuclear percentage tends to rise with the rise in the number of leucocytes.

(d) The number of leucocytes rises with the fall of temperature and falls with the rise of temperature.

(e) This leucocytic variation takes place during the periods of freedom from fever, and tends to be even more marked during the apyrexial period than during the pyrexial period.

Here, then, we have a disease in which the leucocytic phenomena are very similar to those found in malarial fever. The chief point of difference is that in the latter the total mononuclear percentage does not remain so uniformly high as in the former. These leucocytic phenomena suggest to my mind the possibility that this obscure disease may be due to some protozoal parasite having a definite periodic development.

Leucocytes.

The blood in this interesting case is not typical of Hodgkin's disease, in which the leucocytes are said to be normal in number and quality, and any leucocytoses occurring are said to be due to an increase in the poly-

morphonuclear variety, whereas in this case they are due chiefly to an increase in the mononucleated variety. The mononuclear leucocytes in this disease were of the large type of lymphocytes. This case would seem therefore to lie midway between a Hodgkin's disease and an acute lymphatic leukaemia. Such cases are mentioned by Cabot (1904). He states that "transitions from Hodgkin's disease

leukaemia, it has been supposed, specially by French observers, that Hodgkin's disease is simply an early stage of true leukaemia, and that this would always become apparent were it not that the patients die of some intercurrent disease before the signs of leukaemia have time to show themselves in the blood."

I have no authority on these matters, and wish simply

to give an account of the leucocytic phenomena which have been revealed in this case. I would like also to lay stress on the importance of frequent daily blood examinations, as I now believe that no true estimate of the numbers of leucocytes can otherwise be obtained. In this case very occasional eosinophilic myelocytes were found. There were no mast cells, and there was no marked increase of eosinophiles.

The red cells showed very marked poikilocytosis, and in fresh blood films showed some amoeboid movement. Nucleated red cells were very scarce, but a considerable number showed basophilia. Microcytes were also occasionally seen. The number of red cells averaged about 4,200,000 per c.mm. of blood. The haemoglobin was on the average 75 per cent.

CASE II.—O. H., a boy aged 5. History.—Disease commenced about two years ago. Parents stated that the condition came on immediately after vaccination.

Clinical Signs and Symptoms.—These are unfortunately incomplete, as patient was only allowed to stay in hospital for three days. There is a very large swelling on the left side of the neck. The spleen is very much enlarged, extending beyond the umbilicus.

The Blood.—The leucocyte chart of this case also shows a daily swing. The fall of leucocytes took place at midday, thus differing from Case I, where the fall occurred at midnight. It also differed from the latter in that the percentage of total mononuclear leucocytes was not abnormally high.

Red Cells.—Basophilic cells were numerous. Nucleated red cells were scarce. There were a fair number of microcytes and megalocytes. Poikilocytosis was not quite so marked as in Case I. The leucocytes did not show much abnormality as regards variety. A very few mast cells were present. The haemoglobin averaged 50 per cent. The patient remained in bed during the period of examination.

CANCER.

CASE.—J. L., male, aged 53, under the care of Dr. Lloyd Roberts at the Royal Southern Hospital, Liverpool, and diagnosed by him to be a case of cancer of the stomach.

History.—Three years ago he had a sudden haematemesis while at work. He was quite well before that, except for pains in the back of about two years' duration. He had no previous sickness or vomiting. After the attack of haematemesis he remained fairly well, except for pain in the back, until a year ago, when a new pain developed in the region of the stomach below the left costal margin. He vomited very seldom. The pain became more severe and constant, and vomiting attacks came on more frequently, about twice a week. He has not vomited blood since the first occasion three years ago. He has no blood in his stools.

to leukaemia have taken place under the eyes of competent observers, but they are very rare. But few such cases are on record, so far as I know, that of Flescher and Penzolt,⁸ that of Mosler,⁹ and one reported by Senator,¹⁰ in which two sisters came under observation both suffering from Hodgkin's disease. One died of it. In the other the blood changed to that of leukaemia before death. Wende¹¹ reports a typical case of this transition. . . . From the existence of these very rare cases of a transition to

Clinical Signs and Symptoms.—He is much emaciated and very pale. The abdomen is slightly distended. At the inner half of the left costal margin a hard mass can be felt projecting downwards for a couple of inches. It is dull on light percussion. It is separated from the spleen, which is not enlarged, by a belt of resonance. It is continuous with the liver dullness. The liver does not extend below the costal margin.

The Blood.

The leucocyte chart of this case shows a very similar variation to that of the Hodgkin's disease. There is a marked daily rise and fall in the number of leucocytes. The variation on the average amounts to from 5,000 to 40,000 leucocytes per cubic millimetre of blood, an eight-fold increase. The leucocytes reach their height about midday, and are lowest about midnight.

The total mononuclear percentage, however, unlike that of Case 1 (Hodgkin), remains at about normal level, and there seems to be a tendency for the mononuclear percentage to fall with the leucocyte rise. The temperature of this case has so far remained normal, and during the period of observation the patient remained in bed.

Further Observations on the Blood.

Red Cells, 3,200,000 per cubic millimetre.—They showed some poikilocytosis and basophilia. Occasional nucleated red cells and occasional microcytes were found. Haemoglobin 30 per cent.

Leucocytes.—The eosinophiles were slightly increased, sometimes as many as 8 per cent. Occasional myelocytes were seen, and there was an occasional increase of large mononuclear leucocytes. This case, in my opinion, also suggests the possibility of the presence of a protozoal parasite having a definite period of development. Again referring to Cabot (1904), I find that the leucocyte counts in cancer of any part of the body are very variable, from 3,000 per c.mm. to considerably over 100,000 per c.mm. of blood. Isolated counts, however, seem only to have been made, usually not more than once daily, so that I am led to believe that the variations recorded depended chiefly upon the fact that the blood was taken at different periods of the leucocytic cycle, the cycle having been missed owing to the infrequency of the counts. It is stated also that a digestion leucocytosis is seldom found in cancer of the stomach, so that the daily variation revealed in this case can hardly be attributed to a digestion leucocytosis, in which the leucocytes seldom increase to even twofold their number. It appears also that considerable variations in the character of leucocytes are found in cancer cases. It is stated by Cabot that Taylor, Osler and McCrac have found an increase of the large mononuclear leucocytes in some cases amounting to 26 per cent.

I think that these facts are also significant, as in malarial fever, in which there is a marked leucocytic cycle, marked variations also take place in the relative variety of leucocytes, and there is a marked increase in the number of large mononuclears.

Controls A, B, and C.—The leucocytes in these controls showed no abnormality in variety or numbers. Control A was a healthy female, aged 26; controls B and C were healthy males, both 27 years of age. From this paper it will appear that repeated daily counting of leucocytes is likely to give a valuable method of diagnosis in various diseases.

N.B.—None of the above cases, nor the controls, had any history of malarial fever, neither had they any septic complications.

Before concluding I would beg to thank Dr. Macalister and Dr. Lloyd Roberts for their kindness in giving me full scope in the examination of the blood of their patients.

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⁸ *Deut. Arch. f. klin. Med.*, vol. xvii.

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¹¹ *Amer. Journ. Med. Sciences*, December, 1901.

¹² D. Thomson (1911): A New Blood-Counting Pipette for Estimating the Numbers of Leucocytes and Blood Parasites per Cubic Millimetre. *Annals of Trop. Med. and Parasit.*, vol. v, No. 3.

THE DANGERS OF SALINE INJECTIONS.

BY

EDWARD C. HORT, F.R.C.P. EDIN.,

AND

W. J. PENFOLD, M.B., C.M.

(From the Lister Institute.)

In recent years the practice of injecting hot solutions of saline into a vein, or under the skin, has greatly increased. The use of these injections in the prevention or treatment of operative shock, in the treatment of cholera or severe haemorrhage, or as a vehicle for salvarsan or anaesthetics has fully proved their value. It appears, however, to be widely believed that the intravenous or subcutaneous injection of large quantities of saline is an entirely innocent procedure. On looking for trustworthy evidence in support of this belief, one is met with two striking facts: (1) The great variation in the quantities of liquid injected, together with absence of any serious attempt to graduate the volume of injection according to the body weight; (2) the wide variation in the absolute quantities of salt injected.

For some considerable time we have been studying the effects on animals of injection of saline solutions of various strengths, of distilled water, and of other liquids. Though our experiments were undertaken for a very different purpose, the results may have some value in helping us to determine how far the administration to man of saline injections can be safely carried. We have, therefore, briefly summarized those points that bear on this question. We find that the injection of large quantities of normal or slightly hypertonic saline solutions into a vein or under the skin is not nearly so innocuous a proceeding as is often supposed. The quantities injected were usually far smaller than the quantities, relatively to body weight, that are frequently given in man. The undesirable effects that we encountered include fever, rigors, subnormal temperatures, diarrhoea, intestinal haemorrhage, Cheyne Stokes breathing, convulsions, and sudden death. The last two we have only met with after injection of strongly hypertonic solutions, and, except in the case of young animals, only when the injection has been given rapidly. For all practical purposes of injection in man these accidents may probably be neglected, though their occurrence in animals accentuates the need for caution in human injections. The other accidents mentioned occur very frequently after injection into a vein or under the skin of normal or slightly hypertonic solutions. The grave sequel to large saline injections (in man) of pulmonary oedema has recently been noted in this JOURNAL.¹ To this list of clinical drawbacks to saline injections in animals may be added the onset of glycosuria recorded by Martin Fischer and quoted by Bingel.² We must also note the histological changes observed by other workers on this subject. Raum,³ for example, showed that intravenous injection of the dog with normal saline was followed by vacuolation of the liver cells. Allbrecht⁴ found that the red cells of animals were damaged by large injections of normal saline; Rössle⁵ observed degenerative changes in the heart muscle and capillary walls of animals similarly injected, and Hössli⁶ found that saline injections caused in animals fatty changes in the heart muscle and kidneys. We cannot here discuss in detail all of these effects of saline injections, but one result—namely, fever—we may refer to, because it illustrates the points on which we wish to lay stress. It has long been known that injections of saline into a vein or under the skin in man or animals may set up fever. In the last two years several papers have appeared on this subject in Germany, and in them it is often assumed that the fever which follows injection of saline is solely due to the salt injected and not to the water in which the salt is dissolved. In consequence, therefore, of the absence of proper controls, no constant