THE HAEMATOLOGY OF INFANTILE SEPSIS*

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This communication records the results of blood investigations in infantile sepsis. This condition includes numerous septic manifestations, such as skin lesions (abscesses; boils; pustules), otorrhoea, gastroenteritis, pyuria, etc., occurring soon after birth and up to end of first year. The work on this subject is comparatively new, as indeed, is infantile haematology in general, nor does literature provide any representative or systematic account of haematological investigation of mild sepsis in infancy. An attempt to elucidate this problem is made here and for this purpose the selected cases included every manifestation of sepsis in infants. The blood was obtained from the heel, provision being made to have the feet warm before commencing, and blood counts and smears were carried out at weekly intervals over a period of four to five months.

The haemoglobin level in the selected infants.

In order to make any deductions it is necessary to compare the haemoglobin level in disease with the findings in healthy infants. Average haemoglobin levels in healthy infants given in standard textbooks are numerous, and as different methods of estimation have been employed in each case, results have varied according to apparatus used, whether the prick was made at the heel or ear and on several other factors, e.g. birth weight. The higher the birth weight, the higher on an average is the haemoglobin level likely to be from one month old and during most of the first year of life.

Elvehjem, Paterson, and Mendenhall¹ in America employed the Newcomer method, which gives readings a little higher than those of Mackay, to which reference will be made later. Mackay's estimations were carried out by means of a Price-Jones-Haldane haemoglobinometer, which gives higher readings for the same absolute amount of haemoglobin in the blood than other methods used in this country. In spite of this, results by the Sahli method do not present gross differences from those of the Price-Jones-Haldane method. The method I have employed in every case has been the new Sahli method. The apparatus used was Sahli-Leitz with double comparator tubes, an accurately graduated pipette and a graduated diluting tube. The hydrochloric acid is placed in a graduated tube to mark 10. Next 20 c.mm. of blood are sucked up into the pipette and added to the

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acid in the graduated tube. The blood and acid are mixed by means of a stirring rod specially provided, and allowed to stand for one minute. Distilled water is then added and the colour matched with that in the graduated tubes, and reading recorded. The reading gives the per cent. of haemoglobin and the grammes of haemoglobin per 100 c.c. of blood.

Case records.

Case 1.—Artificially-fed infant, no iron treatment given. Birth weight unknown; weight at four weeks, 8 lb. 2 oz. Clinical findings:—skin sepsis, intermitten pyuria and occasional gastro-intestinal disturbance.

AGE IN WEEKS	HAEMOGLOBIN LEVEL (SAHLI METHOD)	AVERAGE HAEMOGLOBIN VALUES IN THE BOTTLE-FED (MACKAY'S FINDINGS) ²
	PER CENT.	PER CENT.
4	87	
5	80	
6	75	
6½	75	80
7	75	
8	73	
9	75	
10	80	69.4

The average haemoglobin from four to eight weeks was 77 per cent. as compared with 80 per cent. in the bottle-fed series, and in the second month 77.5 per cent. as compared with 69.4 per cent.

This conclusion associates itself with the remarks of Mackay³ when she says, 'Most slight infections, where the general health is not seriously impaired do not appear to influence the haemoglobin level. The next estimation taken after a cold in the head, an attack of bronchitis or a slight enteritis usually showed no drop which appeared attributable to the illness.'

Case 2.—Artificially-fed infant, weight at commencement of investigation, 5 lb. 8 oz., iron treatment given when ten weeks old. In this case the infant exhibited a generalized mild infection with dyspepsia, intermittent pyuria, skin sepsis, discharging ears. Despite these conditions of ill health, the haemoglobin level appeared to have been well maintained. (Detailed weekly haemoglobin levels are not quoted in each case.) The average haemoglobin level, between two and three months, was 73 per cent., as compared with corresponding 69.4 per cent. of the same age period given by Mackay, and 76 per cent. between three and four months as compared with 71 per cent.

Prematurity does not appear to have influenced the haemoglobin level as much as might be expected. According to Kunckel, Lichtenstein, Lande and others, there is a distinct and early impoverishment of the haemoglobin of the blood, which reaches its maximum about three to four months. According to Mackay the haemoglobin level in premature infants is high at birth, there is an early drop and minimum level is reached at three to four months of life. However, the above case appears to have a good haemoglobin level at three months.

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Case 3.—This child was a breast-fed infant until eight to nine months. Blood investigations were commenced at age of nearly eleven months and the weight then was 13 lb. 11 oz. Clinical manifestations:—discharging ears, interstitial pneumonia, abscesses of the skin.

AGE IN MONTHS	HAEMOGLOBIN LEVEL (SAHLI METHOD)	NORMAL HAEMOGLOBIN LEVEL	AVERAGE HAEMOGLOBIN LEVEL
	PER CENT.	PER CENT.	PER CENT.
BREAST-FED (MACKAY'S FINDINGS)			
10 $\frac{3}{4}$	48	86	72.8
11 $\frac{1}{4}$	46		
11 $\frac{1}{2}$	46		
11 $\frac{3}{4}$	50	86	73.1
12	53		
12 $\frac{1}{2}$	55		
12 $\frac{3}{4}$	55	86	73.9
13	55		
13 $\frac{1}{4}$	60		
13 $\frac{1}{2}$	62		
13 $\frac{3}{4}$	68	86	76.4
14	68		
14 $\frac{1}{4}$	68		
14 $\frac{1}{2}$	69		
14 $\frac{3}{4}$	70		

By 'normal haemoglobin level' is meant the haemoglobin estimation in breast-fed babies weighing 6 lb. and upwards at birth, iron-treated from the third month onwards.

Here a profound degree of anaemia occurred at the outset; this will be referred to later. The haemoglobin level was correspondingly low and together with the septic process a change in the haematopoietic system was found. Whether sepsis produced this profound anaemia, or the anaemia was present first, and then septic infection followed, is a difficult issue, but I feel that sepsis was a causative factor in the production of the anaemia. Despite iron treatment, the haemoglobin level only gradually reached 70 per cent. The average haemoglobin levels were as follows:—

10-11 months.	48 per cent. as compared with 86 per cent. for breast-fed, iron-treated infants, and 72.8 per cent. untreated breast-fed infants.
11-12 months.	48 per cent. as compared with 86 per cent. for breast-fed, iron-treated infants, and 73.1 per cent. untreated breast-fed infants.
12-13 months.	55 per cent. as compared with 86 per cent. for breast-fed, iron-treated infants, and 73.9 per cent. untreated breast-fed infants.
13-14 months.	64 per cent. as compared with 86 per cent. for breast-fed, iron-treated infants, and 76.4 per cent. untreated breast-fed infants.

This case raises the question as to whether iron treatment has any effect in curing anaemia of septic infection. Mackay points out 'that in infants treated with iron, the haemoglobin level was raised from the third month onwards. It is possible with continuous iron to maintain a level of 77 per cent. in infancy and upwards from five to twelve months.' This refers to healthy infants. According to Parsons, in infections the beneficial effect of iron is greatly diminished or even absent. I am in agreement with the above view, for observations on septic infants, as compared with ordinary nutritional anaemias, show a poor response to iron therapy. That several factors are responsible for increase in haemoglobin level must be taken into account. When general health improves and resistance to infection is established, iron may be more efficacious in increasing the haemoglobin level.

Case 4.—Artificially-fed infant, weight at six weeks 7 lb. 12 oz. Iron treated since eleven weeks old. Presented numerous skin abscesses and respiratory complications. The average haemoglobin level between one and two months was 74.5 per cent. as compared with 80 per cent. of the bottle-fed series (Mackay). From two to three months this was 66 per cent. as compared with 69.4 per cent.; three to four months, 68.5 per cent. as compared with 70.1 per cent.

In this case, too, there appears only a small reduction from the standard given by Mackay. Indeed the haemoglobin level in this infection falls within limits of normal, bottle-fed infants. It is interesting to find that the mother's haemoglobin was 30 per cent. when the infant was seven weeks old, and that she was already receiving treatment for her profound degree of anaemia. According to the majority of authorities infants born of anaemic mothers derive from them their full complement of haemoglobin and Baar and Stransky state that anaemia of the mothers does not produce anaemia in the new-born child.

Case 5.—Artificially-fed infant, weight 5 lb. at 3 weeks. Clinical findings:—skin sepsis, discharging eyes and gastro-intestinal upset. The haemoglobin between one and two months was 70 per cent. as compared with 80 per cent. of bottle-fed series (Mackay); from two to three months 65.5 per cent. as compared with 69.4 per cent. In this case a dried milk containing extra iron was given for a period of a few weeks, and a small quantity of ferri et ammon. cit. given after this. Comparatively little difference exists between haemoglobin figures given by Mackay and those obtained in this case.

Case 6.—Artificially-fed infant, weight 6 lb. 12 oz. at five weeks. No iron treatment given. The infant failed to gain weight, showed a few skin lesions and had a mild gastro-intestinal upset. The average haemoglobin level for period one to two months was 74 per cent. as compared with 80 per cent. and two to three months 67 per cent. as compared with 69.4 per cent. (Mackay). Here, too, little divergence exists between the findings in septic infants and in normal infants.

A further group of haemoglobin estimations were taken from patients reported to have had sepsis in infancy, who had reached the age of one, two, three years.

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IN GROUP 1-2 YEARS.

AGE (YEARS).

HAEMOGLOBIN.
PER CENT.

1	65
$1\frac{1}{2}$	57
1	58
$1\frac{1}{2}$	48
2	55

IN GROUP 2-3 YEARS.

$2\frac{1}{2}$	60
$2\frac{1}{2}$	60
3	65

IN GROUP 3-4 YEARS.

Nearly 4	67
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In group one to two years, the haemoglobin is rather lower than the given standard, and if 65 per cent. be included in the normal ratio, the other cases are much reduced. In most of these cases rickets has complicated the picture, and the resultant reduction of haemoglobin may be attributable to the anaemia of rickets. Then, too, malnutrition in these cases is an important factor, since many of these children are the victims of poor circumstances and improper nutrition.

In age group two to three years, the haemoglobin level lies in the neighbourhood of 60 to 65 per cent. In second year the haemoglobin rises and should be in the neighbourhood of 70 per cent., so that here, too, there is only a slight disparity in the findings. Similarly, in group three to four years, the patient showed a level of 67 per cent., which does not really fall far short of the findings in town children living under poor conditions.

Conclusions.—The haemoglobin in mild sepsis in infancy shows little appreciable reduction from the standard laid down by Mackay for normal infants of that period. In the older group of children, the haemoglobin seems variable, being much reduced in age group one to two years, other factors such as rickets and malnutrition complicating the picture. It seems quite definite that this lowering of the haemoglobin level has no connection with the previous history of sepsis. In the group two to three years, the haemoglobin more nearly approaches the normal standard. In the group three to four years, almost normal standards have been approached.

Number of red blood corpuscles.

As a result of repeated blood counts, it is concluded that the red cells do not appear to fall below normal limits, and there is little to be learnt from this investigation alone. Its use lies in the estimation of the colour index.

The colour index.

It has been said that in infections in infancy, the colour index becomes low. Kugelmass⁷ states that sepsis shows a rapidly developing anaemia with

a low colour index. In infants this fact has not come to light, the colour index being either $\cdot 8$ or $\cdot 9$ and in a few instances $\cdot 7$. In the older infant (case 3) the colour index was low and remained at $\cdot 6$ for a long period, finally reaching $\cdot 7$.

Reticulocytes.

This estimation proves very variable. In some instances out of 600 cells counted, only 2 showed reticulation. In one instance only did they number between 6 and 8 per cent.

The white blood corpuscles.

There are no absolute and uniform standards for the behaviour of the white blood corpuscles in infants. It is regrettable that the whole blood picture in infancy is not of greater value than it is. So little has been known of the normal physiological reactions of the infantile blood system, and even though the behaviour of the red cells, haemoglobin and colour index are now fairly elucidated, there still remains considerable ignorance of the white cell response. The number of white blood corpuscles varies according to the time of day, from person to person, and different estimations for the normal standard have been presented for nurslings as follows (all quoted from Schilling⁴): Gundobin 9,000 to 15,000, Benjamin 8,000 to 12,000, Rominger 9,200 to 23,700, Hofmann and Welker 6,200 to 21,600, all of which constitute an extreme range of figures. All cell counts were done at corresponding times on different days and ranged between 7,000 and 12,000.

The differential count.—The most valuable information is to be obtained from the differential count with its distribution of the neutrophil series in relation to other components of the blood film. I have consistently used Leishman's stain and counted 200 cells by the Schilling method. The Schilling haemogram and clinical picture were then correlated. In the Schilling count, the polymorph neutrophils are divided into groups according to their degree of maturity:—

1. myelocytes, 2. metamyelocytes, 3. band forms, and 4. segmental forms.

This enables one to estimate the shift to the left (Arneth) which represents an increase in metamyelocytes and band forms indicating an irritation of the bone marrow to increased activity from infection. Schilling⁴, Feldman⁵ Piney⁶, Kugelmass and Lampe⁷, Rogatz⁸, Weiss⁹, Schmal, Schmidt and Serebrijski¹⁰, and others state that in infective processes the differential count shows a shift to the left, and during the phase of recovery this shift is decreased, lymphocytes are increased as well as the eosinophiles. Normal haemogram variations are wide.

During my work on the blood films I have been interested in the great number of immature forms of cells, that is, metamyelocytes and band forms, which determine the degree of shift. In a count of 200 cells it has been by no means unusual to find the existence of as many as 47 'bands' and in quite

a number of cases these vary between 20 and 40, these figures being very much higher than the normal standard given by other observers. Even in the blood of normal healthy infants up to the age of two years, I have been struck by the greater number of band forms as compared with the mature segmental forms. Indeed, very few polymorphs show the true segmentation, that is to say, cells showing only a mere thread of chromatin uniting the nucleoli. Consequently one is inclined to feel that the standards set by Ockel, Hofmann and Welker (quoted by Schilling⁴) are low as far as band forms are concerned. If five 'stabs' (band forms—Schuessler and Schilling) are considered pathological this would bring every nursling into the field of ill health. The blood picture of the adult reacts entirely differently and can in no way be compared with that of the child. Wide variations may occur from time to time. Schilling states that the erythrocytic and leucocytic blood picture of a child is highly labile, often responding to irritation in a disproportionate manner. It must be remembered that in artificially-nourished infants a rapid activity of the lymphocytic apparatus is developed. In most cases the reaction has been of the lymphocytic type, which is in accordance with the findings of most observers. It is often claimed that monocytes are high. One case showed 19 per cent. Piney does definitely state that a high monocyte count occurs in infancy and quite readily disappears as the blood assumes a more mature picture. The following observations were made in the course of the present investigation:—

1. On one occasion a hyperleucocytosis with the presence of 6 per cent. eosinophils occurred and this proved a rather favourable situation.
2. On quite a few occasions an increase in lymphocytes occurred during the phase of gastro-intestinal upset; this lymphocytosis was probably a defensive mechanism during the period of bowel infection.
3. A moderate or high white blood count occurred quite frequently with a marked shift, a slight decline in lymphocytes and few eosinophils, even in a phase of recovery, so that this finding cannot be regarded in an unfavourable light. However, this interpretation is not adequate unless correlated with the clinical picture.
4. At no time was there complete absence of eosinophils.
5. In some instances I have found a decreased shift and a corresponding increase in lymphocytes and eosinophils with recovery from the clinical standpoint.
6. The eosinophils appeared to be increased when the patient was putting up a resistance to infection, and would appear to be a favourable phenomenon.

Case records.

The cases are not given in detail, but sufficient notes to draw deductions are given. In each case the first and last week's blood counts are referred to. (These cases are the same series as those used for haemoglobin estimations.)

Case 1.—Age four weeks. Skin sepsis, pyuria, gastro-intestinal upset.

- 25.5.33. White blood cells 11,800. Marked shift to the left, 44.5 per cent. immature forms of polymorphs (metamyelocytes and band forms). Lymphocytes 40 per cent., eosinophils 2 per cent., monocytes 6 per cent.
- 3.7.33. In the phase of improvement the lymphocytes numbered 67.5 per cent., eosinophils 4.5 per cent., monocytes 3.5 per cent., and shift decreased showing 21 per cent. of immature forms of polymorphs. W.B.C. 10,000.

Case 2.—Premature infant. Blood investigations commenced at eight weeks old and in a phase of recovery. Skin sepsis, pyuria, gastro-intestinal disturbance and discharging ears.

- 19.5.33. W.B.C. 9,300. Immature forms of polymorphs 17 per cent., lymphocytes 70 per cent., eosinophils 3 per cent., monocytes 9 per cent.
- 17.7.33. W.B.C. 8,000. Infant on road to complete recovery. Immature forms 36 per cent., lymphocytes 58 per cent., eosinophils 1 per cent., monocytes 1 per cent. This case definitely deviates from rules laid down for the response of blood in infection; for the lymphocytes are decreased as well as eosinophils and the shift to the left is great during recovery. Premature children are supposed to have a high lymphocyte count with neutrophilia at first, this then recedes with marked nuclear shift. Several observers have declared that in the fourth week the lymphocytes range between 75 and 82 per cent. in premature infants but they do not state the behaviour of the lymphocytes at the age of two months. At no time has there been a lymphocytosis of over 70 per cent. in this case.

Case 3.—An older infant, age nearly eleven months, with septic manifestations following one another at frequent intervals. Discharging ears, abscesses of the skin, interstitial pneumonia.

- 23.4.33. W.B.C. 8,740. Immature forms 19.5 per cent., lymphocytes 54 per cent., eosinophils 2 per cent., monocytes 14.5 per cent. Clinically in the stage of improvement. Weekly blood count till 31.7.33 Immature forms 21 per cent. (that is a greater degree of shift to the left), lymphocytes 75 per cent., monocytes 1.5 per cent., eosinophils 1 per cent., W.B.C. 7,800.

Child considerably improved. Gained weight. Haemoglobin increased to 70 per cent. Increase in number of immature forms. Increase in lymphocytes. Eosinophils decreased to 1 per cent. The monocytes have decreased considerably from 14.5 per cent. to 1.5 per cent.

Case 4.—Infant six weeks old. Numerous skin abscesses. Respiratory involvement and occasional pyuria. W.B.C. 10,900.

- 2.7.33. Immature forms 33 per cent., lymphocytes 65 per cent., eosinophils 1.5 per cent., monocytes 2 per cent. Infant was in a highly infective state, losing weight, marked gastro-intestinal disturbance and skin sepsis. Weekly blood counts till 21.8.33. W.B.C. 9,300, immature forms 22 per cent., lymphocytes 68 per cent., eosinophils 7 per cent., monocytes 3 per cent. Immature forms had decreased in number, lymphocytes and eosinophils had increased and the monocytes showed no change, being in the neighbourhood of 2 per cent.

The general condition was good, and this case does apparently adhere to the rules laid down by haematologists in septic infections.

Case 5.—Aged three weeks. Unable to suck. Mild skin lesions. Discharging eyes and ears.

- 11.7.33. W.B.C. 40,000. Immature forms 30 per cent., lymphocytes 62 per cent., eosinophils 6 per cent., monocytes 2 per cent. Clinical condition poor.

Weekly blood count till 28.8.33. W.B.C. 17,100, immature forms 34 per cent. (shift to the left is large), lymphocytes 58 per cent., eosinophils 1 per cent., monocytes 2 per cent. Clinical condition good. Throughout the haemogram, the eosinophils were evident. This constant presence of eosinophils and the hyperleucocytosis of the first examination proved a favourable situation. In the final phase there was a good gain in weight, clear urine, the blood picture showed increased shift to the left. Lymphocytes and eosinophils were decreased.

Case 6.—Aged six weeks at commencement of blood investigations, presenting gastro-intestinal upset, peeling of skin and failure to gain weight.

22.7.33. W.B.C. 8,000, immature forms 23 per cent., lymphocytes 66 per cent., eosinophils 2 per cent., monocytes 5 per cent. Clinical picture showed a distinct improvement since admission to the hospital. Weekly blood counts till 30.8.33. W.B.C. 9,500, immature forms 15.5 per cent., (there is a much lesser degree of shift to the left), lymphocytes 74 per cent., eosinophils 3 per cent., monocytes 3.5 per cent. Infant made good progress. Weight increased from 7 lb. 3 oz. to 9 lb. Here the shift has decreased; lymphocytes and eosinophils increased, so that the response in this blood picture has been similar to that of acute infections in adults.

These six cases fall into two groups. Three have shown a typical response to sepsis as referred to in text books, and three showed atypical results. There are little in the way of normal standards for comparison, and results which may be classed as normal for adults with infection do not appear to be consistent in infants.

In examining the blood film, the reds in a great number of cases have been poorly filled, i.e., they have shown hypochromia. Some of the blood corpuscles were irregularly shaped and sized, and only in a few instances were nucleated reds and megaloblasts seen. The resultant microcytic hypochromic anaemia has been evident to a mild degree with the exception of case 3. As all these cases of sepsis were sub-acute or chronic, it seems feasible that the haemopoietic system like other tissues is likely to suffer as well from the infective process.

How do these infections produce anaemia? In mild sepsis the infection probably acts by suppressing the myeloid function, and this may be so small as to produce no apparent results in the blood. In the sub-acute and chronic infections, the rate of regeneration of haemoglobin and red blood cells may be depressed to a slight extent. Hypochromia may be regarded as due to the fact that haemoglobin saturation of the young cells is the last stage of erythropoiesis. Improvement in the general condition of the infant and of the blood picture occurred together.

Summary.

1. In infantile sepsis the haemoglobin is not reduced to any appreciable degree except in the small group of out-patients in whom rickets and malnutrition complicated the picture.

2. The colour index was between 0.8–0.9, red cells $3\frac{1}{2}$ to $4\frac{1}{2}$ millions per c.mm.; reticulocytes between 1 and 2 per cent. The white cells varied from

8,000 to 15,000 or 16,000 per c.mm., and the differential count in all cases showed a preponderance of immature forms with very few segmental or mature polymorphs in the neutrophil series.

3. In three out of six cases fully investigated there was a decrease in the shift to the left, and an increase in lymphocytes and eosinophils during the final phase of recovery. In others, the findings varied.

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