

## **A case of severe haemocytolysis / by G.T. Wrench and J.H. Bryant.**

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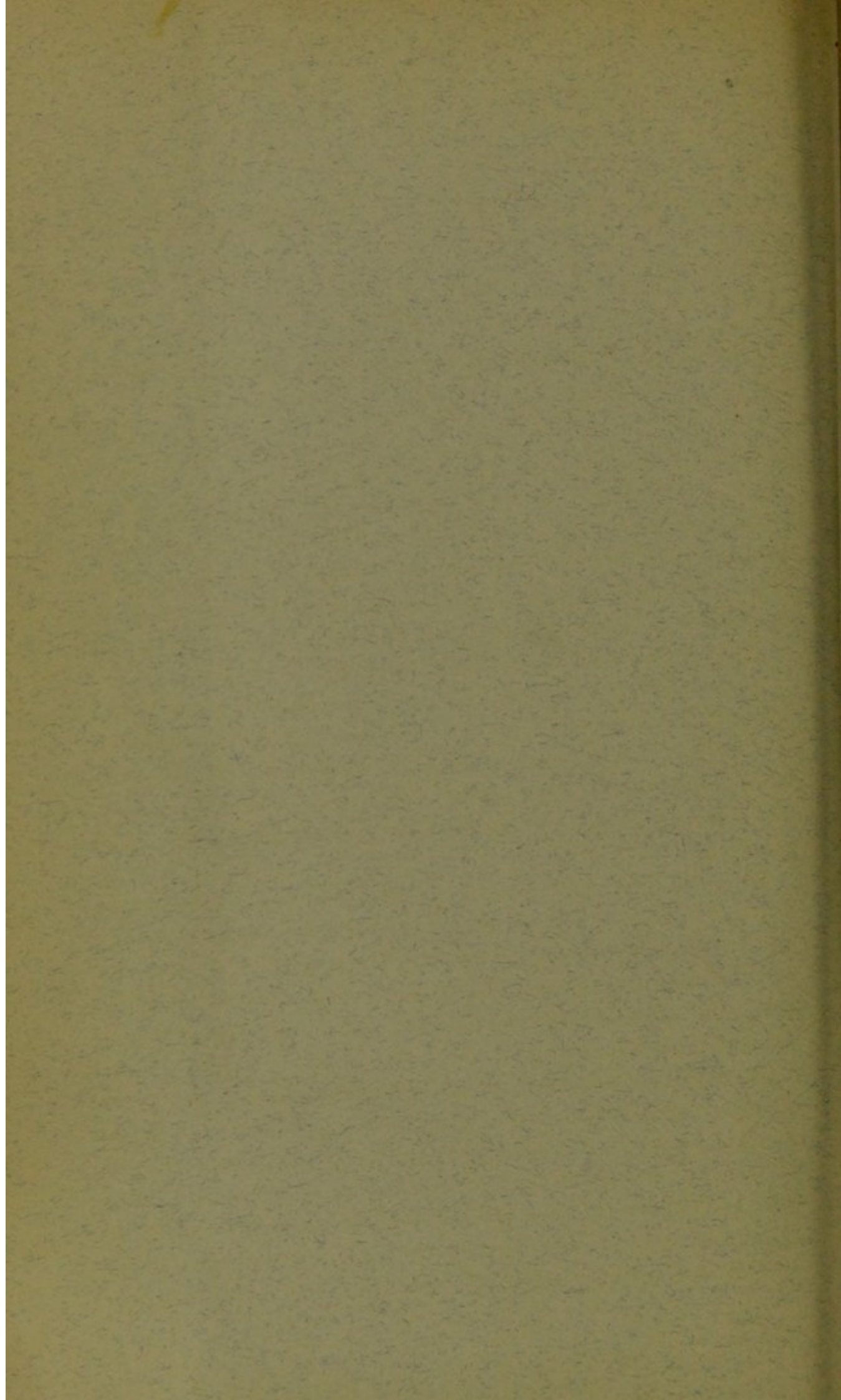
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## A CASE OF SEVERE HÆMOCYTOLYSIS.

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BY G. T. WRENCH, M.B., AND J. H. BRYANT, M.D.

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IN the following case of a girl, æt. 10, hæmocytolysis was present in such a marked degree, and the blood exhibited such extraordinary changes, that we have deemed it worthy of record. For a few days a fatal result appeared to be inevitable, but recovery took place eventually at the end of three weeks, with complete restoration of the blood to normal.

Florence C., æt. 10, was admitted into Miriam ward on April 19th, 1902, under the care of Dr. Bryant, for profound anæmia. Three years ago she had an attack of measles, otherwise she had always been strong and healthy. Her parents considered her to be a strong child, and stated she rarely suffered from any ailments.

On April 11th, 1902, *i.e.*, eight days before admission, she was playing in the yard when she slipped and fell, striking her left side in the region of the spleen, against the shaft of a cart. She went indoors and complained to her mother of the injury, but soon went out again and resumed her game. She appeared to be quite well for the next two days.

On Sunday, April 14th, she complained of feeling ill; loss of appetite and headache. Her parents thought she had a bilious attack and took little notice until April 16th, when they observed that she had changed colour, her face being pale and of a somewhat yellowish tint. The pallor increased up to the time of her admission on April 19th. During this time she was able to take nothing but milk, or milk and egg. She was sick after food,

usually about three times a day, was very thirsty and complained of her tongue being rough and dry. There was no evidence of hæmorrhage and she had no rash. She was constipated for three days. She had neither headache nor mental symptoms.

Her parents are strong and healthy. She has six brothers and sisters, all of whom are living and well. On Friday, April 19th, she was admitted into Miriam ward.

*Condition on admission.*—Temperature 98°, pulse 96, respirations 24. She was a well-nourished child but markedly anæmic. The skin, however, had a curious yellowish-brown tint more like that of Addison's disease than of simple anæmia. She was very restless and was continually yawning. She had a wild look about the eyes although she was not delirious.

*Circulatory system.*—The impulse was seen and felt in the fifth left intercostal space, just beyond the nipple line. There was no thrill. The superficial cardiac dulness commenced above in the third left space and externally extended just beyond the nipple line. At the apex there was a systolic murmur which could be heard all over the front of the chest, but which was best marked in the pulmonary area. It was also traceable into the carotids and along the abdominal aorta and external iliac arteries. During a full inspiration the heart-beat was much slowed. There was a doubtful bruit de diable just above the clavicle but it was difficult to dissociate it from the systolic bruit.

*Abdomen.*—The abdomen was not distended. It was supple and there was no tenderness. The edge of the liver could be felt just below the costal margin in the right nipple line.

The spleen was enlarged. It could be felt half an inch anterior to the left nipple line, and below, it extended to within a finger's breadth of the level of the umbilicus. It was not tender. The edge was regular, sharp, and well defined.

*Skin.*—No rash present.

*Respiratory and nervous systems.*—There were no abnormal signs.

*The urine* was acid and contained neither blood, sugar, pus nor albumen.

*The vomit* contained no blood and no free hydrochloric acid.

The *faeces* were carefully examined for parasites and ova but none were detected.

*Blood*.—(In describing the different kinds of blood-cells, the nomenclature of Ehrlich, as given by Cabot (3rd edition) was used and all differential counts were made from specimens stained by Ehrlich's triacid stain. The blood-counts were made with the Thoma-Zeiss hæmocyto-meter and the hæmoglobin was estimated by Marie's hæmoglobinometer, and once by the specific gravity method).

April 19th.—

Red blood corpuscles	...	939·300	per cubic millimetre.
Hæmoglobin	... ..	27	per cent.
Nucleated red corpuscles	...	27·600	per cubic millimetre.
White	... ..	69·000	" "
Polymorphonuclear	...	66·4	per cent.
Small lymphocytes	...	22·2	"
Large lymphocytes	...	2·4	"
Myelocytes	... ..	1·8	"
Eosinophiles	... ..	2·0	"
Eosinophile myelocytes	...	0·2	"
Transitional	... ..	5·0	"

A microscopical examination of the films showed the majority of the red corpuscles to be undersized. A large number of red cells were nucleated. The nuclei were bipartite, tripartite or irregular. Some of the bipartite cells were dividing in equal proportion and with division of the protoplasm, suggested cell division. Some of the nuclei were deeply stained, probably old corpuscles, others, especially those of the large erythroblasts, were pale blue. Many of the red corpuscles showed well-marked polychromatophilia. There was no poikilocytosis, the corpuscles retaining their normal contour, nor were there fragments of broken corpuscles. The white corpuscles, although greatly increased in number, did not display any disproportion in their relative percentage, except for the presence of a few myelocytes.

She was given an ounce of peptonized milk every hour and large nutrient enemata every six hours.\* 0·6 c.c. of cacodylate of soda solution was injected into the axilla at 10 p.m.

\* A sterile solution was used which contained 0·05 gm. *i.e.*  $\frac{3}{4}$  grain of Cacodylic Acid in 1 c.c. (17 minims).

She was very restless during the night and made several attempts to get out of bed, and was once found sitting on a chair by her bed.

April 20th. She was in much the same condition as on admission. She was rational with her own relations, but with nobody else. The bowels were opened, but both urine and fæces were passed unconsciously. The motion was very dark, but contained no blood. There was no epistaxis, hæmatemesis, melæna, hæmaturia nor purpura. She did not complain of pain. The spleen was the same size as on the 19th. Her grandmother, who had watched her from the beginning of her illness, considered her colour better to-day. The highest recorded temperature was 99·8° at 10 a.m. At 6 p.m. the pulse was 160, and the lowest rate was 136 at 10 a.m. Urine: 1022, pinkish deposit of urates, urea 2·05 per cent., no albumen, sugar, bile, pigment or indican; a little urobilin was detected. At 9 p.m., 0·9 c.c. of cacodylate of soda solution was injected into the axilla.

The eyes were examined and a few retinal hæmorrhages were seen.

The blood-count showed the following:—

Red blood corpuscles	...	...	...	1,164,500
White blood corpuscles	...	...	...	105,500

The differential count was not markedly different to that made on the 19th, except for the smaller percentage of polymorphonuclear cells (53·8 per cent.), the larger percentage of small lymphocytes (28·8 per cent.), and the appearance of new cell-like bodies which were not present in the films made and examined on the 19th.

They did not conform to any type of leucocyte described by Cabot, Ewing, or Von Limbeck. They have been placed in the list of the differential counts amongst the leucocytes and named "vacuolated bodies." In appearance these "vacuolated bodies" presented fairly definite masses of protoplasm which took on basic stains either lightly or darkly, but as a rule to a tint that was less deep than the nuclei of the concomitant leucocytes. This stained protoplasm was much vacuolated, and was bound

together by a kind of fibrillar network. The margins of the vacuoles were either closely defined or merged into the blue-stained protoplasm. These bodies varied greatly in size but the average was considerably above the measurement of the leucocytes. Some only measured  $9\mu$  by  $10\mu$ , but many as much as  $16\mu$  by  $14\mu$  or even  $12\mu$  by  $28\mu$ .

At first it was thought they might be basophiles, but their staining reactions with Jenner's stain and methylene blue did not correspond with this kind of cell. True basophiles were seen only on one day (April 24th). The shape of the vacuolated bodies was often irregular with protrusions comparable to the pseudopodia of amœba. A few specimens of fresh blood were examined, but nothing of a parasitic nature was noticed. No special search with a warm stage was made for parasites, as this interpretation of the bodies was not thought of at the time. They had no definite nucleus, and no granules.

With Jenner's stain they presented a similar uniformly stained vacuolated mass. With eosin and methylene blue they presented the same appearance as with Ehrlich's triacid or Jenner's stain. Sometimes similarly stained uniform, but unvacuolated, protoplasm was seen with fine oxyphile granules near them and occasionally these fine granules were observed apart from any protoplasm, as if lying loose in the blood-stream or separated from their cell in the process of making the film.

April 21st. She was in much the same condition, but the spleen was a little smaller. The tendency to delirium was still present. The eyes were examined and hæmorrhages into both retinae were found. She appeared to have a slightly better colour. She was still troubled with vomiting. The highest recorded temperature was  $99.4^{\circ}$  at 2 p.m., and the lowest  $97.8^{\circ}$  at 6 p.m. A few uric acid crystals were found in the urine.

She was given some bread and milk, but vomited it soon afterwards. Plasmon  $\zeta$ j. and Extract of Malt  $\zeta$ ii. was ordered for her, to be taken three times a day.

22nd. She was improving in every respect, being more sensible and of a better colour, and the spleen was appreciably



smaller; 13 minims of cacodylate of soda solution were injected into the axilla.

23rd. She was less anæmic in appearance and much more sensible. The spleen was smaller. The temperature was 99°; 20 minims of cacodylate of soda solution ( $\frac{1}{7}$  grs.) were injected subcutaneously at 11.45 a.m.

24th. A further improvement in her colour and also in her manner was noticeable. The spleen was a little smaller. Urine acid, no albumen, urea 2.4 per cent.; no uric acid crystals; Indigo red present but no indican blue: no urobilin. 14 minims of cacodylate of soda solution ( $\frac{2}{3}$  gr.), were injected into the axilla at 11.45 a.m.

25th. She appeared to be steadily improving in every respect; 10 minims of cacodylate of soda solution were injected.

26th. The spleen was smaller. Urine: 1025; acid, urobilin present. 15 minims of cacodylate of soda injected.

27th. She felt and looked comparatively well. She was now able to take (minced) fish for dinner and bread and milk for breakfast; 15 minims of cacodylate of soda solution injected. Urine 1025; a good deal of urobilin was present.

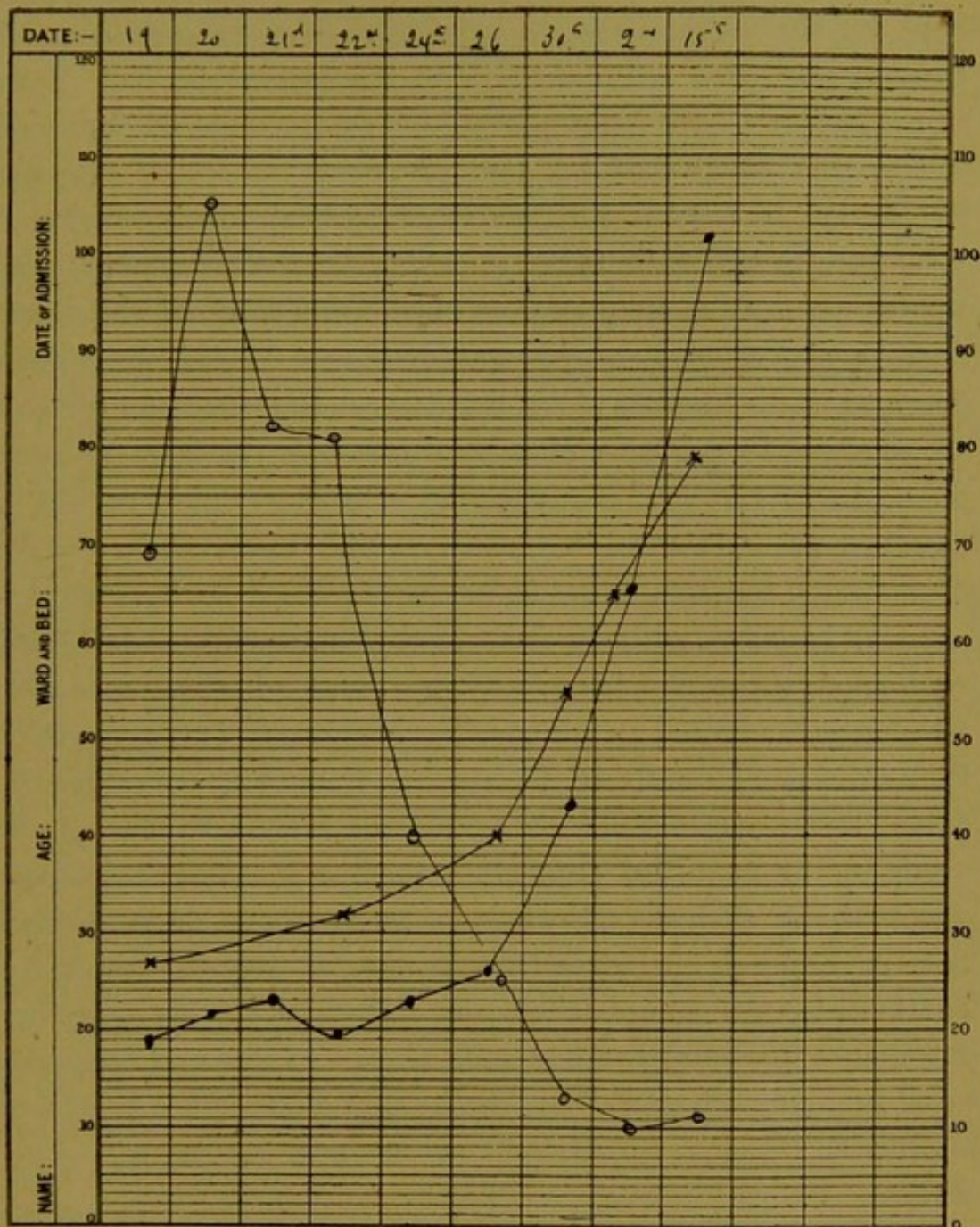
28th. The administration of one-fifth grain of cacodylate of soda in the form of a pill three times a day was now commenced.

29th. She looked quite well. She had no pain and was able to take full diet without any discomfort.

May 1st. The mucous membranes were still a little pale. Systolic murmurs were audible in the pulmonary and mitral areas. The cardiac impulse was in the fifth left space about three-quarters of an inch outside the nipple line. The spleen was just palpable below the left costal margin.

3rd. The spleen was not palpable.

9th. She was discharged, having been up and about the ward for several days. Her colour had greatly improved. She had a distinct red tint about the cheeks, but elsewhere the skin was sallow. She was no longer sick and the bowels acted regularly every morning. No hæmic murmurs could be detected. Neither the spleen nor the liver could be felt beneath the costal margin. The retina presented a normal appearance.



Percentage of Red Corpuscles										
MP of Red Corpuscles per Cubic mm.	479,733	1,064,477	1,299,417	913,750	1,299,896	1,615,000	2,364,317	3,576,000	5,230,000	x x x x x
Percentage of Haemoglobin	27%	-	-	32%	-	40%	55%	65%	75-80%	● ● ● ● ●
MP of White Corpuscles per Cubic mm.	69,000	115,833	82,455	84,250	46,104	25,000	13,183	10,000	11,200	○ ○ ○ ○ ○

One of the most interesting points to be determined in this case was the cause of the remarkable changes in the blood. The parents attributed her condition to the injury she had received in the region of the spleen and the enlargement of that organ, which was discovered on her admission with its subsequent diminution in size as she recovered, seemed to corroborate this view and to point to some injury or to some derangement in the function of the spleen as the most likely cause of the anæmia.

What pathological changes would account for such an enormous decrease in the number of red blood corpuscles (939,333 per c.mm. *i.e.* to about 18 per cent. of normal) the relative large amount of hæmoglobin (27 per cent.) giving a colour index of 1.5, the leucocytosis (69,000 per c.mm.) and the extraordinary number of nucleated red corpuscles (27,600 per c.mm.)?

In all respects, with the exception of leucocytosis, the changes resembled those which are usually found in advanced cases of pernicious anæmia. In all marked examples of this disease the leucocytes are diminished in number, frequently below 4,000 per c.mm. and even to 2,000 or 1,500. Leucocytosis, when it does occur in the course of pernicious anæmia in adults is invariably due to some such complication as hæmorrhage or suppuration, but in children it takes much less to induce leucocytosis. In this case no complication was discovered to account for it. Pernicious anæmia is rare at such an age as ten, and further, the onset is much less acute and recovery is much more protracted; additional reasons which help to exclude a diagnosis of this disease.

The extreme pallor, the restlessness, and the constant yawning suggested the possibility of a severe hæmorrhage. There was no history of epistaxis, hæmatemesis, hæmoptysis, nor of any other form of hæmorrhage, nor did a careful physical examination of the chest and abdomen yield any signs of an internal hæmorrhage.

The injury to the left side and the enlargement of the spleen made us consider whether that organ had been ruptured and bleeding had occurred into the peritoneal cavity.

A simple hæmorrhage, however, would hardly account for such marked changes in the blood. As a result of the loss of a

considerable quantity of blood there is a diminution in the number of red blood corpuscles, and the hæmoglobin is much reduced, so that the colour index is usually below one. The presence of such a large number of nucleated red corpuscles was compatible with a severe hæmorrhage, for after the loss of a considerable quantity of blood it is usual to find a large number of normoblasts and microblasts in the blood. Ewing writes, "Small and repeated hæmorrhages, on the other hand, have led to some of the most severe forms of anæmia ever recorded in which the morphological changes of pernicious anæmia are pronounced, but the prevailing feature of the blood is the loss of hæmoglobin." It is usual to get a leucocytosis after hæmorrhage, but the number of leucocytes per cubic millimetre do not as a rule exceed 40,000. A differential count shows a relative lymphocytosis. There are no grounds for supposing that in this case there had been repeated small hæmorrhages. If the anæmia was due to hæmorrhage it must have been connected with the injury to the side and to bleeding into or from the spleen.

The enlargement of the spleen suggests the possibility of some disorder or derangement of the function of that organ as a result of the injury.

In two cases of splenectomy (of the healthy spleen) mentioned by Dr. Rolleston (Clifford Allbutt's System of Medicine, vol. lv.), the following group of symptoms occurred:—

1. Progressive loss of strength and weight and of emaciation.
2. Extreme anæmia.
3. A daily rise of temperature 1° to 3° Fahrenheit.
4. Increased frequency of the pulse.
5. Fainting attacks, with increased pallor of the surface.
6. Headache, drowsiness and great thirst.
7. Severe griping pains in the abdomen and pain in the legs and arms. In one case tenderness along the tibia, which was thought to indicate compensatory changes in the red marrow of the bones.
8. Enlargement of the external lymphatic glands, which remained permanently increased in size.

9. Blood changes, which consisted of a diminution in the number of the red blood corpuscles and an increase in the number of leucocytes.

In this case, with the exception of 7 and 8, all these symptoms were prominent and striking, especially the diminution in the number of red blood corpuscles and the increase in the number of leucocytes.

Could the injury, which she had received in the region of the spleen, in some obscure manner, have put that organ temporarily out of action, as when splenectomy removes the splenic function from the living subjects?

This explanation, however, was by no means satisfactory. In the first place, we were not able to find any previous record of such severe hæmocytolysis and illness following an injury in the splenic area, and in the second place, the injury was slight, for there was no external evidence of it in the form of bruising, and the child, as has already been stated, was quickly enabled to return to her play.

Casting around for some other cause we naturally thought, in the absence of any evidence of hæmorrhage, of the possibility of her condition being due to the influence of some poison. Cabot (*Clinical Examination of the Blood*, 3rd edition) quotes a case reported by Brandenburg of acute anæmia with marked leucocytosis as the result of poisoning by chlorate of potash and another case, reported by Ehrlich and Lindenthal of a similar condition due to poisoning by nitrobenzol.

This last mentioned case is also quoted by Ewing (*Clinical Pathology of the Blood*, 1st edition, 315). The blood became chocolate-coloured ten hours after the initial symptoms and methæmoglobin was visible by spectral analysis until the eighth day. On the fifth day the red cells were reduced to 2,275,000 and before death fell to 300,000 per cubic millimetre. Poikilocytosis was noted on the third day. Nucleated red corpuscles were first seen on the third day, and on the ninth day 24,700 to the cubic millimetre were counted. On the ninth day the leucocytes rose to 61,000. The hæmoglobin fell to 40 per cent., so that with 900,000 red blood corpuscles to the cubic millimetre

and this percentage of hæmoglobin the colour index was remarkably high. "The morphological characters of the blood described by Ehrlich and Lindenthal probably represent an extreme degree of the effects upon the blood of the entire group of anilin poisons."

Some such poison, we thought, might have been the cause of the hæmocytolysis in our case but all enquiries and efforts at discovering such a cause proved to be unavailing until six weeks after the patient's discharge, when our suspicions received confirmation in an unexpected manner. The quarterly gas bill was sent to the father of our patient and found to be considerably more than usual, in fact was nearly double the amount of the corresponding quarter for the previous year. Recalling our persistent questioning as to the possibility of his daughter having taken some poisonous substance, he looked for a leak in the gas-pipe of her bedroom and discovered an escape of gas which was situated under the floor immediately over which her bed was placed. We feel justified therefore in attributing the illness of our patient to the subacute toxic effects of coal gas.

We did not notice any marked difference in the general naked-eye appearance of the blood; it certainly was not a bright cherry red nor was it chocolate coloured. We did not obtain a history suggesting hæmoglobinuria, nor after admission did we find any evidence of such a condition. Although we have not been able to find a similar case of anæmia which has been attributed to chronic coal gas poisoning, we are of opinion that this form of toxæmia is the most satisfactory explanation of this interesting and remarkable case.

The rapid recovery was also of very great interest, but whether it was due to the treatment with cacodylate of sodium or to the change of environment, and so the removal of the apparent cause, we prefer to leave an open question.

She was examined two months after discharge. She was quite healthy and the blood-count was normal.

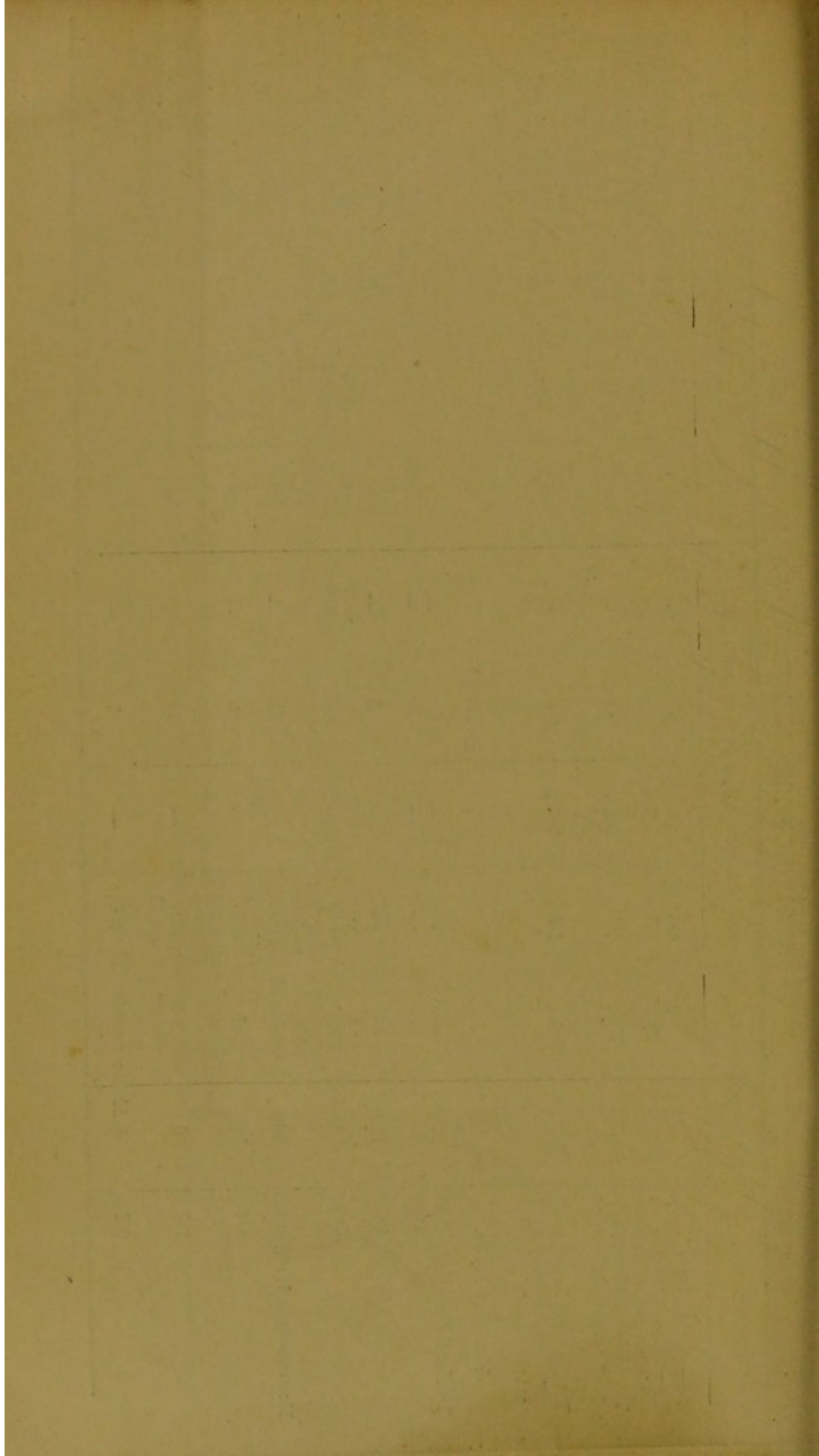
A CASE OF SEVERE HÆMOCYTOLYSIS.

Day of Disease.	Mar. 19, 1902	April 20, 1902	April 21, 1902	April 22, 1902	April 24, 1902	April 26, 1902	April 30, 1902	April 2, 1902	May 5, 1902	Remarks.
Total number of reds per c. mm.	939,333	1,164,477	1,299,417	993,750	1,299,896	1,625,000	2,364,327	3,575,000	5,280,000	
Total number of whites .	69,000	105,833	82,458	81,250	40,105	25,000	13,183	10,000	11,200	
Hæmoglobin ...	27%	—	—	32%	—	40%*	55%	65% †	75% †	*Taken actually on the 25th by the spec. grav. method (1041).
Colour index ...	1.5	—	—	1.6	—	1.3*	1.3	0.93†	0.8	†This was taken on April 5th. It is inserted here for the sake of comparison.
Proportion of white to red	1:17	1:11	1:16	1:13	1:305	1:65	1:172	1:350	—	
Proportion of nucleated red to white	1:2	1:4	1:2	1:12	1:106	1:285	—	—	—	
Proportion of nucleated red to red	1:34	1:44	1:33	1:15	1:31	1:3000	—	—	—	
<i>Reds not showing mitosis—Differential count.</i>	500 counted	500 counted	500	500	500	200 a bad slide	300	300	300	
Polymorpho-nuclear neutrophils	66.4%	53.8%	77.0%	56%	57.8%	61%	62%	63%	57% †	†These include loose and torn cells with fine oxyphile granules and pale blue nuclei.
Small lymphocytes ...	22.2 "	28.8 "	20.8 "	29.4 "	27.1 "	30 "	30.3 "	29.3 "	36 "	Transitional between polymorph. and lymphocytes were small mononuclear (nomad) neutrophiles.
Large lymphocytes ...	2.4 "	3.2 "	1.8 "	3.2 "	4.6 "	5 "	6 "	6 "	3.8 "	
Eosinophiles ...	2 "	6.6 "	0.6 "	0.2 "	1.9 "	1.0 "	0.6 "	1.7 "	1.1 "	
Myelocytes ...	1.8 "	2.6 "	1.8 "	1.8 "	1.8 "	1.2 "	—	—	—	
Eosinophiles myelocytes ...	0.2 "	—	—	—	—	—	—	—	—	
Basophiles ...	—	—	—	—	0.1 "	—	—	—	—	

A CASE OF SEVERE HÆMOCYTOLYSIS—continued.

Day of Disease.	Mar. 19, 1902	April 20, 1902	April 21, 1902	April 22, 1902	April 24, 1902	April 26, 1902	April 30, 1902	April 2, 1902	May 15, 1902	Remarks.
Vacuolated bodies	— %	5 %	1.4 %	4.6 %	3.4 %	0.6 %	0.6 %	—	1.1 %	¶ These were definite masses of protoplasm, much vacuolated, bound together by a sort of fibrillar network. They varied greatly in size, measuring from 12 μ up to 30 μ across.
Transitional between polymorph. & myelocyte	1.4 "	1.4 "	2 "	1.6 "	—	0.6 "	0.3 "	—	—	
Transitional between polymorph. & lymphocyte	1.6 "	0.8 "	0.4 "	0.6 "	0.5 "	—	—	—	—	
Transitional between small and large lymphocytes	2.0 "	3.8 "	1.2 "	2.6 "	2.8 "	0.6 "	—	—	1 "	
Sizes of red cells.	Of each measured				50 measured					
Nucleated red	100	—	—	—	24	—	—	—	—	Taking 5-9 as the normal limit of a red blood cell, there was at first a general undersize, no megalocytes, and but few megaloblasts. Many nucleated red had light blue nuclei young corpuscles.
	22	—	—	—	23	—	—	—	no nucleated reds	
	46	—	—	—	3	—	—	—	100 measured	
	27	—	—	—	100 measured	none measured	—	—	measured	
	4	while counting whites	while counting whites	none measured	—	—	—	—	—	Polychromatophilia present at first and slightly on 30th. No poikilocytosis.
	1 100	1 nucleated	3 largest nucleated	measured	19	—	—	—	—	
Non-nucleated red	29	red measured	red measured	—	32	—	—	—	—	
	59	12.5 μ × 11 μ otherwise wise	14.5 μ × 14.5 μ × 11 μ × 11 μ	—	42	—	—	—	—	
	9	no megaloblasts	11 μ × 9 μ	—	7	—	—	—	—	
	3 100			—		—	23	—	—	
				—		—	56	—	—	
				—		—	21	—	—	





No available reprint of Dr. Byrd's  
paper on, A case of Typhoid fever  
without any lesion of the intestine

Vide-

British Medical  
Journal

April 16<sup>th</sup> 1899

