³⁴ See Loewy and Neuberg: Ueber Cystinurie. Zeitschrift f. physiologische Chemie, Band lxxiii, p. 338.

³⁵ Die Alkaptonurie. Biochemisches Centralblatt, Band iii, p. 173.

³⁶ See A. Oswald: Die Bedeutung der intracellulären Enzyme in der Pathologie. Biochemisches Centralblatt, Band iii, p. 365.

Original Articles.

A CASE OF LYMPHATIC LEUKEMIA IN A CHILD.*

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BESSIE C., a Jewess, was admitted to the Children's Hospital on the service of Dr. Morse Aug. 23, 1904, when three and one half years old.

Family History.—The family history was negative. Her father and mother and four other children were well. There had been no miscarriages. There was no history of tuberculosis in the family, or of exposure to tuberculosis.

Previous History.—She was normal at birth, weighed nine and one half pounds, and was nursed fifteen months. She had chicken pox at six months, anterior poliomyelitis involving the right arm and both legs at eighteen months, whooping cough at two years and measles at two and one half years. No sequelæ followed either the whooping cough or the measles. She had practically recovered from the infantile paralysis, except that she used the right arm less freely than the left.

Present Illness.—Loss of weight and strength, which began about the first of June, had progressed steadily but slowly. There had been an increasing pallor during the same time. Her only complaints had been of a tired feeling and of pain in the ears. Her appetite had been poor, and she had had occasional attacks of abdominal pain followed by nausea and vomiting. The vomitus contained mucus and food, with some bile. There had been a slight cough for some weeks. Puffiness of the face and swelling of the neck had not been noticed until two weeks before entrance. There had been no hemorrhages.

Physical Examination.—She was well developed and nourished and perfectly clear mentally. There was marked pallor of the skin, with a slight yellowish tint. The mucous membranes were pale. There was puffiness about the eyes. The ears and nose showed nothing abnormal. The tongue was moist and showed a thin white coat. The throat was normal. There was no tenderness or rigidity of the spine. There was slight lagging of the right chest. There was dullness on the right side below the second rib continuous with the liver and heart dullness and extending back to the anterior axillary line. There was hyper-resonance over the rest of the right side. The respiration was diminished in intensity in the dull area and bronchovesicular in character. The expiration was prolonged. Fluoroscopic examination showed a dark area corresponding to this area of dullness. The left lung was normal except for exaggerated respiration and an occasional sibilant râle. The cardiac impulse was visible and palpable in the fifth space in the nipple line. The upper border of the cardiac dullness was in the third space and the left in the nipple line; the right could not be determined. The action was regular, the sounds clear. The second pulmonic sound

was decidedly the louder. The abdomen was full and tympanitic. There were no evidences of fluid or of new growths. The lower border of the liver was palpable $4\frac{1}{2}$ cm. below the costal border in the nipple line. The spleen was just palpable. There was considerable atrophy of the muscles of the right forearm, with a weakened grasp on that side. Both legs were a little weak and the muscles on the right were flabby. The knee jerks were present, but diminished, on both sides. The plantar reflexes were normal. There was no edema of the dependent portions. There were firm swellings, not tender, in the region of the parotid and sub-maxillary glands. There were many large, firm, non-tender lymph nodes varying in size from that of a pea to that of a large cherry in the post-cervical, axillary and inguinal regions. The skin was not adherent over these enlarged nodes and showed no evidences of inflammation. The left epitrochlear gland was the size of a large pea; the right was not felt.

The urine was pale, acid, of a specific gravity of 1,020 and contained a trace of albumin, but no bile or sugar. The sediment showed a large amount of ammonium urate and a few crystals of cystin.

The blood at entrance contained 45% of hemoglobin, 2,080,000 red corpuscles and 16,200 white corpuscles. A differential count was not made.

Fowler's solution was begun at once, but had to be omitted on Aug. 30 because of vomiting.

The blood was examined again on Aug. 31, with the following result:

Hemoglobin,	40%
Red corpuscles,	1,765,000
White corpuscles,	19,000
Small mononuclear,	58%
Large mononuclear,	9%
Polynuclear neutrophils,	32.8%
Eosinophiles,	.2%

The red corpuscles showed considerable variation in size and moderate variation in shape. There was no polychromatophilia, but a little stippling. Two microblasts, 13 normoblasts and 22 megaloblasts were seen in counting 400 white cells.

Although the percentage of the mononuclear cells, and especially of the small mononuclear cells, was large, it was felt that when the age of the child and the total number of white corpuscles were taken into consideration that the diagnosis of lymphatic leukemia was not justified and that search must be carried further. It seemed possible to exclude syphilis on the family history and the absence of past or present signs of the disease. Tuberculosis was excluded because 3 mgms. of tuberculin caused no reaction. No parasites or eggs of parasites could be found in the dejections.

Several small lymph nodes were removed from the left groin under ether for pathological examination on Sept. 1. These nodes had the general outlines and under low power the appearance of lymph nodes. There was some general increase of the connective tissue stroma. In many places the follicles were well distinguished; some of the lymph sinuses were filled with small lymphoid cells.

Studied under the high power (magnification 900 diameters), the cells were seen to be mostly

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SPEC. 1. The small, round cells are separated by a fair amount of stroma. Occasional large irregular cells and many eosinophiles, six of which are present in this field.

SPEC. 2. Practically all small lymphoid cells, showing a very great number of mitotic figures.

FIG. 1. Photograph at entrance.

FIG. 2. Photograph Sept. 30.

small lymphoid cells with the stroma pretty nearly uniformly distributed between them. Their nuclei were comparatively large and rather lightly stained except for the numerous dark blue chromatin granules. In many places they showed rather numerous mitotic figures. There were also great numbers of the larger type of lymphoid cells.

There were a number of large endothelial cells with large, irregular vesicular nuclei and considerable cytoplasm. These seemed to be associated with the reticulum. There were a few polymorphonuclear neutrophils. In places there was much blood in the lymph spaces, but no abnormal forms of red cells were seen.

Especially noticeable was the large number of eosinophiles that were present. There were occasional large cells, with one or more irregular vesicular nuclei. None of these were phagocytic, and although not giant cells, they were similar to some of the large cells in sarcoma.

From this tissue a microscopical diagnosis of malignant lymphoma or lymphosarcoma was made, and (considering the slightly altered condition of the blood at that time) the possibility of its being a case of beginning Hodgkin's disease was considered.

Three-quarters of a grain of citrate of iron was given subcutaneously every other day throughout September. The general condition improved decidedly during the first three weeks of the month. The appetite and digestion were much better. The color of the skin and mucous membranes improved quite markedly and the puffiness of the face diminished. The masses in the neck, the general enlargement of the lymph nodes and the dull area in the right chest remained unchanged. The liver was palpable 5 cm. and the spleen 2 cm. below the costal border. The blood condition improved at the same time.

Examination of the blood on Sept. 16 showed

Hemoglobin,	70%
Red corpuscles,	4,800,000
White corpuscles,	29,000
Small mononuclear,	56%
Large mononuclear,	16%
Polynuclear neutrophils,	24.8%
Eosinophiles,	.2%
Myelocytes,	2%
Mast cells,	1%

There was considerable variation in the size and shape of the red corpuscles, moderate polychromatophilia and slight stippling. Twenty-six normoblasts and 12 megaloblasts were seen while counting 400 white cells.

About this time interference with respiration during sleep developed. The breathing was noisy, although the mouth was kept closed. There was no enlargement of the tonsils and no increase of adenoid tissue in the throat. The obstruction appeared to be below the pharynx. Dr. Langmaid found no cause for the obstruction on examination and thought that the trouble with the respiration was due to pressure of the growth in the chest on the nerve trunks. A

nasal discharge with a markedly septic odor soon developed. Cultures from both nose and throat showed no Klebs-Loeffler bacilli. A firm new growth then appeared in the posterior pharynx and increased somewhat in size. The obstruction to respiration and the nasal discharge with the resulting septic absorption caused a great deal of difficulty for several weeks; later they were much less troublesome.

About the same time that the difficulty with respiration appeared, the signs of a new growth in the chest began to increase. Dullness developed under the sternum and to the left of the heart. The respiration on the right side was as before. The left chest moved less than the right and the respiration was decidedly diminished although not changed in character. The masses at the sides of the face also began to increase in size, the lymph nodes throughout the body became larger and new ones appeared. The enlargement of the masses and lymph nodes increased progressively, and during the latter part of September the general condition fell off decidedly.

The examination of the blood Sept. 30 resulted as follows:

Hemoglobin,	70%
Red corpuscles,	4,200,000
White corpuscles,	34,000
Small mononuclear,	50%
Large mononuclear,	12%
Polynuclear neutrophils,	34%
Eosinophiles,	1%
Myelocytes,	2.5%
Mast cells,	.5%

There was moderate variation in the size and shape of the red corpuscles with considerable polychromatophilia and slight stippling. Twenty-one normoblasts and 5 megaloblasts were seen while counting 400 white cells. Even at this time the diagnosis of lymphatic leukemia seemed hardly justified, that of Hodgkin's disease or lymphosarcoma seeming far more probable. The patient then came into the charge of Dr. T. M. Rotch, owing to a change in service.

Lugol's solution, in doses of from 1 to 5 minims three times daily, was begun about the first of October and continued until death.

Early in October the gums became spongy and bleeding and fine petechial spots appeared all over the body. A few large ecchymoses also appeared on the sacrum and thighs. About the middle of October there was a perforation of the hard palate on each side of the median line by a dark, soft, irregular substance resembling a new growth about to break down. The blood picture changed materially as regards the differential count at this time. An examination of the blood Oct. 10 by Dr. Richard C. Cabot resulted as follows:

Hemoglobin,	55%
Red corpuscles,	3,216,000
White corpuscles,	30,600
Lymphocytes,	91.4%
Polynuclear neutrophils,	8%
Eosinophiles,	.4%
Mast cells,	.2%

The blood showed the usual changes of severe secondary anemia. Forty-seven normoblasts and 24 megaloblasts were seen while counting 400 white cells.

The diagnosis of lymphatic leukemia was then made on account of the high percentage of lymphocytes in spite of the comparatively low white count.

A gland was removed from the left side of the neck by Dr. H. L. Burrell on Oct. 17. The examination of this tissue showed little resemblance to a normal gland; no follicles could be distinguished, and the tissue was nearly uniform throughout the section. With the high power

and mucous membranes. The signs of new growth in the chest did not increase a great deal, but respiration continued difficult. There were no further hemorrhages. The nasal discharge diminished during the last two weeks. The urine was always normal. The hemoglobin and the number of red corpuscles diminished steadily, while the number of white corpuscles increased, reaching 174,600 the day before death, which occurred on Nov. 4, five months after the onset. The percentage of mononuclear cells remained high, varying, however, at different examinations. The results of the later examinations are shown in the table. An autopsy was refused.

Date.	Hemoglobin.	Red Corpuscles.	White Corpuscles.	Small Mononuclear.	Large Mononuclear.	Polynuclear Neutrophiles.	Eosinophiles.	Myelocytes.	Mast Cells.	To 400 Whites.			Polychromatophylla.	Variation in size.	Polkilocytosis.	Stippling.
										Microblasts.	Normoblasts.	Megaloblasts.				
Aug. 23	45%	2,080,000	16,200													
Aug. 31	40%	1,765,000	19,000	58.0%	9.0%	32.8%	0.2%			2	13	22	None	Consid.	Mod.	?
Sept. 16	70%	4,800,000	29,200	56.0%	16.0%	24.8%	0.2%	2.0%	1.0%	26	12		Mod.	Consid.	Consid.	Slight
Sept. 30	70%	4,200,000	34,000	50.0%	12.0%	34.0%	1.0%	2.5%	0.5%	21	5		Consid.	Mod.	Mod.	Slight
Oct. 10	55%	3,216,000	30,600		91.4%	8.0%	0.4%		0.2%	47	24		Usual changes of severe secondary anemia.			
Oct. 20				58.6%	27.7%	11.7%	1.0%	1.0%								
Oct. 25	25%	2,960,000	49,000	48.0%	28.0%	20.0%		2.0%	2.0%	4	12		Mod.	Mod.		
Nov. 3	20%		174,600	72.5%	17.5%	6.0%		4.0%				6	18			

(magnification 900 diameters) there was seen to be a very great proliferation of lymphoid cells. These cells were not of the type of the usual small lymphocytes, but had the characteristics of the cells in the germ centers of the follicles and other places where there is active proliferation of lymphoid tissue. These cells had fairly large vesicular nuclei and showed enormous numbers of mitotic figures. In the greater part of the tissue there were no other cells. There was very little stroma and in large areas there was none at all to be seen.

The larger cells similar to those seen in lymphosarcoma were absent. There were only occasional eosinophiles. There were numbers of nucleated red blood corpuscles in the sinuses.

A diagnosis of anemia associated with lymphatic hyperplasia or acute lymphatic leukemia was made from this examination.

All the sections in this case were studied with eosine and Unna's polychrome methylene blue stain. Several sections from each specimen were also stained and examined for tubercle bacilli, but none were found.

Failure was progressive from this time on. There was a steady increase in the size of the lymph nodes with progressive failure in the general condition and in the color of the skin

This case is of interest in that it afforded an opportunity to study the development of the changes in the blood and lymph nodes during a considerable period, and that although it was most carefully studied, the correct diagnosis could not be made until a comparatively short time before death. It is unfortunate that the picture could not have been completed and the diagnosis still further verified by autopsy. It shows, however, that the character of the changes in the blood may not develop to a degree sufficient to justify a positive diagnosis for many months. It also shows that the changes in the lymph nodes may be, not only at first but even for a considerable time, materially different from those which are usually considered to be typical of this disease. It is noteworthy that the characteristic changes in the blood and lymph nodes appeared at essentially the same time.

The only inference that can be made from the histological study of these tissues at different stages of the disease is that lymphatic leukemia may have its origin in a malignant growth affecting the lymphoid tissues more or less generally, and that not until there is a secondary proliferation of the lymphoid cells do we get the typical tissue picture and blood condition which is char-

acteristic of lymphatic leukemia. It suggests that leukemia, pseudo-leukemia and malignant lymphoma cannot be separated as three distinct entities, and that they do not always differ characteristically in the histological structure of their lymphoid tissues; and that the microscopical sections in these cases will be often wrongly judged in the absence of complete clinical data as regards the distribution of the process and the examination of the blood.

In short, this case emphasizes again our ignorance as to the development of the pathological changes in the diseases of the blood and lymph nodes. It does not warrant any definite conclusions, either specific or general, but is reported simply as a contribution to the literature of these subjects with the hope that it may be of some assistance in the solution of the problems connected with them.

A FURTHER CONTRIBUTION TO THE STUDY OF BACILLURIA IN TYPHOID FEVER AND ITS TREATMENT WITH UROTROPIN.*

BY CHAS. D. EASTON, M.D., BOSTON.

THE literature on the subject of bacilluria in typhoid fever and the use of urotropin in its treatment, up to the year 1899, may be found in Dr. Mark W. Richardson's paper in the *Journal of Experimental Medicine*, vol. iv, No. 1, 1899. I have tried to bring the subject up to date.

Gwynn¹ treated successfully 5 cases of cystitis by irrigations with corrosive sublimate 1-50000. Two cases were given urotropin. In one the number of bacilli was much diminished but they were still present at the last report. In the second case they finally disappeared after seventeen days. In a later paper² he had 10 cases, in 3 of which the bacilli appeared in the urine before the Widal reaction. He thinks this may be of value in diagnosis. Stress is laid on the importance of urinary disinfection. Urotropin was tried in two of three cases without effect. He prefers mercuric chloride irrigations 1-50000. Further work on the subject³ seems to strengthen his former views. He says milk of lime and chlorinated lime are of some value. He also tried formaline, but thinks it is too expensive to come into general use.

Schichold⁴ out of 17 cases found bacilli present in 5, but thinks that the bacilli are excreted only when the kidney is diseased, beginning immediately as soon as the kidney is affected.

The observations of Walker⁵ and Neufeld⁶ agree with others and both advise the use of urotropin. Walker cites an instance of a well which was infected by the urine of a trooper returning from the army. Twelve persons took the disease.

Horton-Smith⁷ found bacilli in the urine as early as the thirteenth day of the disease, and as late as the fourteenth day of convalescence, and says that they may persist for years.

*Read at the semi-annual meeting of Suffolk District Medical Society, April 29, 1905.

He reports in all 45 cases with 11 of bacilluria. Urotropin was tried in 10 of these and all were cured, but in some cases the bacilli returned and urotropin had to be given again. His idea is that in cystitis the organisms work down into the wall of the bladder.

Lewis⁸ examined 45 cases, but only found bacilli in the urine of 1 case. He speaks well of urotropin and advises its use.

Loida⁹, Schuder¹⁰, Gehrmann¹¹, Klemenko¹², Vincent¹³ and Jacobi¹⁴ agree with other investigators as to the occurrence of bacilli in the urine of their cases. Jacobi reports 643 cases, 27.8% of which had bacilluria. He did not use urotropin, and considers it of little value because relapses occur and the bacilli return in the urine. Vincent in cystitis uses potassium permanganate irrigations. No other treatment is mentioned in his paper. Neither Klemenko or Schuder used urotropin.

Richardson¹⁵ reports the finding of the bacilli in the urine as early as the eighth day, while in other cases they were not present until the forty-second day of the disease.

Drake-Brockman¹⁶ writing on the practical application of urotropin as a urinary antiseptic has seen no untoward results from its administration and thinks it has not received sufficient notice in England.

Ehrmann¹⁷ used urotropin in a number of affections with success. One case of cystitis was irrigated with silver nitrate and severe hemorrhage followed. Even after bladder irrigations with boracic acid and silver nitrate a cure cannot be expected until urotropin is used in addition. Gordon¹⁸ reports a case of cerebral syphilis in which urotropin was used and supposed to have caused hematuria. Cammidge¹⁹ concludes that by the systematic use of urotropin in all cases the very real danger from the urine which is so frequently overlooked may be avoided.

Brown²⁰ reports 2 cases of typhoid which he treated with urotropin. One after taking 10 gr., *t. i. d.*, for two days had painful micturition, and after five days had blood in the urine. The other after 10 gr. for seven days had hematuria. Urotropin was omitted and recovery took place in forty-eight hours. Urotropin was given in 13 out of 82 other cases and there was no trouble except in one which was also having turpentine. He believes that the urinary discomfort which precedes hematuria should be considered a danger signal. Millijan²¹ gave 5 gr., *t. i. d.*, and in seven days produced pain in the bladder followed by hematuria. Urotropin was stopped and ill effects ceased in two days.

Griffith²² gave 10 gr., *t. i. d.*, and next day there was urinary pain, after ten days backache and swollen eyelids. There was evidently no hematuria in this case. Urotropin was omitted and untoward symptoms ceased after three days. Forbes²³ also reports a case of pain in bladder and hematuria after 10 gr., *t. i. d.*

Schumberg²⁴ tries to prove that because solutions of urotropin outside the body do not always kill typhoid bacilli that it is of no value