THE UNIVERSITY OF MINNESOTA

GRADUATE SCHOOL

Report

of

Committee on Examination

This is to certify that we the undersigned, as a committee of the Graduate School, have given Solomon Fineman final oral examination for the degree of Master of Arts . We recommend that the degree of Master of Arts be conferred upon the candidate.

Minneapolis, Minnesota

March 22 1921

J. Marx White
Chairman

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THE UNIVERSITY OF MINNESOTA

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Report

of

Committee on Thesis

The undersigned, acting as a Committee of the Graduate School, have read the accompanying thesis submitted by Solomon Fineman for the degree of Master of Arts. They approve it as a thesis meeting the requirements of the Graduate School of the University of Minnesota, and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Arts.

Hal Downey
Chairman

E. T. Bell.

1918

A Study of Microlymphoidocytic Leukemia with the Report of a Case.

A Thesis Submitted to the
Faculty of the Graduate School of the
University of Minnesota

by

Solomon Fineman

In partial fulfillment of the requirements
for the degree of
Master of Arts

STUDY OF MICROLYMPHOIDOCYTIC LEUKEMIA

WITH THE REPORT OF A CASE.

PREFACE.

In 1915 Citron reported a case of leukemia which, from the blood picture and clinical findings, was diagnosed as 'micromyeloblastic leukemia'.

The postmortem histological study carried out by Pappenheim and Citron showed that the bone marrow was entirely normal. However, the cells of the follicles as well as the cells of the interfollicular tissue of the lymph nodes and spleen contained a slightly enlarged, eccentrically placed, perfectly round nucleus, which resembled very closely the nucleus of a 'myeloblast'. The largest forms, however, were not as large as those found in 'myeloblastic leukemia'. (Citron)

While the blood showed a definite myelogenous picture, it was evident that the 'myeloblasts' and 'micromyeloblasts' of the blood were not coming to any extent from the bone marrow because the bone marrow was normal (Pappenheim and Citron).

On the other hand there was clear evidence that an actual proliferation in situ of the follicular as well as of the interfollicular tissue was taking place and furthermore that there was an actual metaplasia of lymphocytic cells into 'micromyeloblastic' cells.

Citron's conclusion, therefore, was that the 'micromyeloblastic' cells of the blood were being generated in the follicles and interfollicular tissue of the lymph nodes and spleen and that these 'micromyeloblastic' cells were passing from the follicles into the blood stream.

Citron concluded, therefore, that his case was of utmost significance in that it was the first case on record which would seem

to prove that the dualistic doctrine of the origin of white blood cells, namely the complete independence of the origin of myeloid and lymphoid blood cells did not always hold true.

Citron's case was one which anatomists and haematologists had long been looking for. It offered partial evidence in flat contradiction to the statements made by Naegeli, Meyer and Hynecke, Ziegler and other dualists that ' myeloid tissue' has never been observed in the germinal centers of spleen or lymph node follicles, that in all cases showing 'myeloid infiltration' of the spleen or lymph nodes the follicles are passive or atrophies.[c]

Our case shows not only a proliferation of the lymph node follicles but what is of utmost significance, a proliferation of 'micromyeloblasts' and 'myeloblasts' in the germinal centers of these proliferating germinal centers.

Altho an autopsy was not permitted, we were fortunate in obtaining a lymph node during the patient's life. This lymph node was fixed in Helly's fluid immediately after excision, so that the material studied was obtained under ideal conditions.

In brief, we had a case of leukemia in which the blood contained enormous numbers of cells, which ordinarily would be called " the rare micromyeloblasts". The blood picture would lead one to a diagnosis of a myelogenous leukemia. Clinically, however, we had evidence pointing to lymphopoietic activity, namely, a tremendously enlarged mediastinal tumor, as revealed by percussion and roentgen plates, a very marked enlargement of lymph nodes over the entire body, and a markedly enlarged spleen.

That the lymphopoietic organs were very active, was proven by the sections of our lymph node,which showed that the blood cells referred to above as 'micromyeloblasts' were in reality proliferating

right in the lymph follicles and germ centers of the node, and could be traced entering the circulation from the lymph node.

We believe, therefore, that our case offers strong evidence that the unitarian theory of the origin of white blood cells, which we will discuss further on in this paper, is the correct one.

HISTORY OF CASE.

Service E.T.F.Richards

Intern S. Fineman

Patient - girl - age 17 - single - American of Swedish descent.

Came to Univ. Hosp. Jan. 20 - 1919.

Present Complaint - Weakness and rapidly enlarging masses in the neck and axillae.

Fam. Hist. - neg.

Social and Occupational Hist. - neg.

Past History -

General Statement- Has been well up to 4 weeks ago (Dec.-1918)

Previous Diseases - Measles at the age 6 - 1908 - no sequellae.

Scarlet fever at the age 15 - 1917 - no sequellae.

Tonsillitis, acute, at the age 16 - Apr.1918 lasted 4 days could not swallow without pain. No enlarged glands at that time. Felt fine after attack subsided.

Head -

1. Eyes - Has had "eyestrain" last 4 mos. (Oct.1918 to Jan. 1919) - wore glasses with relief, vision good.

2. Ears - neg.

3. Nose - occasional 'cold' - otherwise neg.

4. Mouth and Throat -

Teeth filled summer 1918 -

Tonsillitis - Apr. 1918.

Cardiorespiratory - neg.

Gastrointestinal - neg.

Genitourinary - neg. except occasional nocturia $\frac{D-3-4}{n-o-1}$

Catamenia - began at the age 15 - neg.

Venereal - neg. direct and indirect questioning.

Neuromuscular - neg.

Skin - neg.

Habits - Good.

Weight - Best Summer 1918 - 135 lbs. Now apparently 120 lbs.

Present Illness.

Patient was well until Nov. 1918 - felt " fine and had red cheeks".

Beginning in Nov., and especially towards the last part of the month, she began to complain of being tired, especially so after coming home in the evening - neither patient nor her mother noticed any paleness at that time - no enlarged masses - Mother of patient did notice, however, that patient became very fretful and irritable.

On Dec. 23-1918 patient came home from work and complained of feeling very tired and of having a severe headache and pain in her knees - Mother thought that patient had 'influenza'.

Patient did not go back to work on account of weakness - she, also, at that time noticed a beginning pallor of face. Pain in

knees subsided in a few days, but weakness and pallor became progressive. Patient did not go to bed, however, for two weeks - At the end of that time, early part Jan., she noticed " lumps" in her neck esp. behind and below the ears. Her hearing became impaired, and once, when she blew her nose, she noticed blood on her handkerchief. A physician was called and diagnosed the case as 'mumps'.

Two days after appearance of masses behind and below the ears, patient noticed a "lump" under the Right jaw. These enlarged at first and then decreased, according to statement of patient.

Three weeks after onset, about January 14, patient noticed 'lumps' in both axillae, but none anywheres else.

From that time on the swellings gradually enlarged and mother began to notice a definite progressive paleness.

Patient denied fever, hemorrhages and sweats. She "caught cold" about 4 days before entering the hospital and developed a non-productive cough.

On entrance she had no headache, could read - nasal breathing was free. Had no pains, appetite was good - bowels regular, and she slept well.

PHYSICAL.

General - Temp. 100.6° Pulse 146

Patient lying in bed - has dry non-productive cough - voice hoarse - looks very anemic -

Development and nutrition good -

No edema, cyanosis, jaundice.

Neck and sides of face appear swollen with irregular shaped subcutaneous masses.

Head -

Sinuses and Mastoids.

Tenderness over frontal sinuses and mastoids and over Left Antrum.

Eyes -

Eye Grounds - show extensive fresh hemorrhages in both retinae and discs -

Disc margins indistinct but not chocked -

Sclerae- with slightly yellowish tinge.

Conjunctivae - very pale.

Visual fields - roughly O.K.

Ears -

Moderate deafness -

with watch - R. ear 3 1/2"

L. " 1/2"

Bone conduction greater than air conduction R.L.

Nose - neg.

Mouth -

Lips - extreme anemia and capillary pulse present.

Gums - " " - gingivitis present.

- gums tender and bleed on pressure.

Teeth - very crowded, especially in upper jaw where one protrudes in abnormal position - few are carious.

Mucosa - very pale.

Palate - very high and arched.

Tonsils - very large, glistening, pearly in appearance, so large that they almost occlude the entire pharynx.

Tongue - coated.

Glands -

Chains and matted masses of glands felt as follows :- ant. and post. auricular, submaxillary,- ant. and post. cervical, L.and R. subclavicular,- over both apices ant. and post, - over trapezii.- In axillae and in inguinal regions. These are all bilateral - vary ~~in size~~ from small pea to hen's egg size, - some round, some oval,and many are matted.

They are hard and not tender to pressure - are freely movable and not attached to skin.

For size of glands in detail and comparison of glands from day to day see special charts - Figures 1,2 & 9 Table 1.

Chest and Lungs -

Anteriorly

Inspection - neg. - except that chest comes down rather slowly with expiration.

Palpation - neg.

Percussion - Abnormally wide supracordial dullness. (See chart) Figure 3. 1-21-19

Auscultation - generalized 'cog-wheel' breathing - exaggerated, tubular over area of supracordial dullness. Vocal Fremitus and Whispered Voice increased over same area.

Posteriorly

Inspection - small masses over both trapezii.

Palpation - neg.

Percussion - diminished resonance for 5mc. to R.and L. of vertebrae - on levels I to VI D.

Auscultation - Cog-wheel breathing - generalized.

Tubular breathing from 1 - 6 D. for 5 cm. to R. and L.

Vocal Fremitus and Whispered Voice increased over spine 1 - 6 D. for distance of 5 cm. to R.

Breasts - neg.

Spine - Increased Whispered Voice and dullness to 6 Dorsal Vertebra

Costovertebral angles - neg.

Heart -

Insp. - neg.

Palp. - neg.

Perc. - see outline - Fig.3.

Cardiohepatic angle obtuse -

Absolute dullness increased.

Measurements

	R	L
2 Ics.	3cm.	4cm.
3 Ics.	2	6
4 Ics.	3	7
5 Ics.	4	8

Ausc.

Sounds - P2 - accentuated

1st sound at the apex accentuated

Murmurs -

Systolic murmur, short, transmitted but slightly into axilla - heard at apex, tricuspid & aortic areas, and clearest immediately to left of Sternum.

B.V. - O.K.

Pulse - rapid - sharp rise and fall -

B.P. - 130/40

Abdomen -

Insp. - neg.

Palp. - Spleen palpable 7 cm. below costal margin in midclavicular line. No notch felt - freely movable with respiration. No tenderness. - Liver not enlarged.

Perc. - Splenic dullness same as on palp.

Liver dullness 12 cm. in midclavicular line.

Extremities -

Upper - neg - except extreme anemia of nails.

Lower - old traumatic scar L. thigh - otherwise neg.

Sensation - normal.

Reflexes - O.K. with exception that R. knee jerk very sluggish and L. not obtainable.

No cloni, Babinsky, Gordon, Oppenheim.

Vibration Sense - present over all bony prominences.

Rectal - negative.

Laboratory data on Entrance.

Urine - trace albumen - S.G.1010 - acid - few leucocytes and few hyaline casts - Bence Jones body - neg. Guiac repeatedly neg.

Sputum - neg.

Stool - neg. for blood repeatedly with guiac.

Blood -

H B - 29% Dare

R B C - 1,900,000

W B C - 99,000

Differential - see charts. Table 4 & Figure 4.

P S P - 66% in 2 hours.

Bl. Wass. - neg.

Bl. Chem.- Sugar .105%, Creatinin 1.40 mg., Urea Nitrogen 10.50 mg.

Bl. Culture - neg.

Mosenthal test - neg.

Metabolic studies with excreta in urine and feces. See special chart. Tables 2 & 3.

Electrocardiograph tracing.

PROTOCOL.

All blood counting and staining was done by Dr. Swan Erickson and myself. We used the same set of pipettes throughout and on numerous occasions checked each other and followed as closely as possible the same technique throughout the entire stay of the case in the hospital.

In referring to spleen and liver measurements we mean measurement in midclavicular line below costal margin.

1-21-19 H B - 29% Dare R.B.C. 1,900,000 W.B.C. 99,000

1-22-19 W.B.C. before X-Ray treatment 44,000

X-Ray treatment over glands of chest and neck.

1-23-19 Glands diminished to from 1/4 to 1/6 of previous size -

Mediastinal width 8 cm.

Tonsils only half as large.

W.B.C. 9,600

1-24-19 W.B.C. 4,800

1-25-19 Transfusion 200 c.c. - no reaction - clinical improvement marked.

1-27-19 Glands, smaller than on 1-23.

Tonsils only about 1/6 of former size.

Spleen 3 cm.

Mediastinal dullness diminished.

1-30-19 R. and L. post. auric glands enlarging - hearing diminish-

ing - W.B.C. 33,000 - 11 a.m.

" " " 50,000 - 6 p.m.

1-31-19 Glands enlarging again.

Spleen 7 cm.

W.B.C. 50,000.

2-1-19 W.B.C. 8,000

Spleen 4 cm.

Mediastinal dullness 5 1/2 cm.

Transfusion - 300 c.c.

2-3-19 W.B.C. 9,000

2-4-19 Distinct swellings in front of R. and L. ears.

Tonsils enlarging - some of other glands enlarging.

W.B.C. 26,800 - 11 a.m.

49,000 - 6 p.m.

2-5-19 W.B.C. 70,300

Difficulty in breathing present - Restless - hearing poorer. Tonsils markedly enlarged - lacked 1 cm. of meeting in midline. Spleen 7 cm.

All glands definitely enlarged.

2-6-19 W.B.C. 90,000 - No reticulated cells - Platelets 90,000 per c.mm.

2-7-19 W.B.C. 72,000 - axillary lymph gland excised.

2-8-19 W.B.C. 42,000 at 10:30 a.m.

W.B.C. 68,000 at 7 p.m.

Patient's general condition in evening worse - dyspneic - nasal breathing impossible - Tonsils 1/2 cm. apart.

Facial and axillary glands enlarged. Spleen 7 1/2 cm.

Supracordial dullness 8 1/2 cm. in 2nd i.c.s.

2-10-19 W.B.C. 60,000 - general condition same.

2-11-19 W.B.C. 89,000

2-12 & 13. Practically no change in general condition.

W.B.C. 108,000

2-14-19 W.B.C. 108,000 at 9:30 a.m.

W.B.C. 68,000 at 2 p.m.

2:30 p.m. X-Ray treatment #3 over neck, tibiae and femurs.

Photograph taken this a.m. - Patient dyspneic - dilated veins over temples.

Mass of glands R. side of face - 8 cm. in diam. - Left 7cm. These masses palpable from back of ears to angle of eye - very prominent.

Tonsils and uvula practically obstruct nasopharynx.

Nasal breathing impossible. Spleen 9 1/2 cm.

2-15-19 Masses in front of both ears barely visible - patient breathing freely thru nose. W.B.C. 29,300 at 10:25 a.m.

Clotting and bleeding time 5 min. each.

1:30 p.m. transfusion #3 - 400 c.c. - Felt stronger immediately after transfusion. Facial glands still smaller not visible - just barely palpable as flat masses about 2 cm. in diam.

Tonsils about 1 1/2 cm. apart. Spleen 7 1/2 cm.

2-17-19 W.B.C. 10,000

Facial mass R. not palpable at all - on L. just barely palpable. Tonsils about 2 1/2 cm. apart - patient 'feels fine'.

H B. and R.B.C. approximately same as on entrance.

Onset of epistaxes and appearance of numerous petechiae on both legs - 2-3 mm. in diameter.

2-18-19 W.B.C. 20,000

2-19-19 Condition worse - H **B** - 26% V.F. R.B.C.1,860,000

W.B.C. - 140,000-3 p.m.

W.B.C. - 208,000 - 11:55 p.m.

Headache all day - constant dull abdominal pains.

Slow epistaxis all day - Complained of dimmed vision.

Numerous fresh petechial hemorrhages on legs with several large bluish areas 2-3 cm. in diameter.

Edema of feet.

Pressure over sternum, skull, humeri, ulnae, radii, femurs, tibiae elicited exquisite pain.

For first time numerous mitotic figures observed in blood in wet, and dry preparations.

2-20-19 Condition worse - H **B**. - 21% Dare R.B.C. 1,344,000

W.B.C. 242,000

Glands seemingly not enlarged - Transfusion #4 - 200 c.c,

Pulse weak irreg., thready - rate 160.

15 minims Benzol by mouth - Blood Chemistry - Sugar 0.117% - Creatinine 0.75 mg. Urea Nitrogen 9.188 mg.

2-21-19 8 minims Benzol by mouth in a.m.

W.B.C. at 9:30 a.m. 62,000

" " 1:00 p.m. 44,000

Blood culture - negative - 30 c.c. Blood of patient injected into rabbit's ear vein.

Nitrogen intake 9.6 G - Output 16.8 G in urine -

Blood Chem. - Blood sugar .099%, Creatinine 0.60 mg., Urea Nitrogen 9.96 mg.

2-22-19 Spinal puncture - 20 c.c. clear fluid under pressure - Nonné - neg. -cell count - 3 per c.mm.

Colloidal gold - neg. Wass. +

General condition good - W.B.C. 6,800

Lymph nodes in general smaller - Bone tenderness diminished. Several epistaxis during day.

2-23-19 Condition further improved - smiling, cheerful, laughed - insisted on being allowed to sit up in chair. Vision definitely impaired - could barely see large newspaper headlines, and small type not at all.

Glands and spleen somewhat smaller.

2-24-19 Condition worse - headache- anxious expression - lips seemed paler - spleen and some of glands (~~see chart~~) enlarged somewhat.

W.B.C. 10,000

2-25-19 Spleen still further enlarged - glands about the same.

W.B.C. 44,000 Platelet count 92,000

2-26-19 W.B.C. 82,000 - 23 minims Benzol by mouth.

2-27-19 W.B.C. 76,000 - 23 " " " "

2-28-19 W.B.C. H B. 13% D. R.B.C. 900,000 - felt fine - asked for second helpings of her meals - Benzol discontinued.

3-1-19 W.B.C. 22,000

3-2-19 W.B.C. 61,000 - Condition worse - epistaxis in a.m. - glands and spleen about same.

3-3-19 W.B.C. 105,000 - 1:00 p.m. Condition worse - severe headache.

W.B.C. 176,000 - 7:00 p.m. profuse epistaxis in a.m. Lymph glands about same. Spleen 10 cm. and reached to umbilicus - not tender and no rub felt.

Liver 7cm. - Pulse 140-170 - gallop rhythm - Mitotic figures observed in both wet and dry preparations of blood - Transfusion #5 - 160 cc. followed by hypo. of morphine sulphate 1/6 of a grain and atropine sulphate 1/150 of a grain.

3-4-19 W.B.C. 95,000 - 2:00 p.m.
W.B.C. 106,000 - 7:00 p.m.

3-5-19 W.B.C. 75,200 - 10:30 a.m. Transfusion at 1:45 p.m. 150cc.

3-6-19 W.B.C. 26,300 - 1:30 p.m. X-Ray treatment #4 at 3:30 p.m. to spleen.

3-7-19 W.B.C. 4,000 at 9:30 a.m. - Transfusion #7 - at 10:25 a.m. 200 cc.

3-8-19 W.B.C. 2,300 Spleen by noon just barely palpable. ~~below cm.~~ General condition worse - sight poor Eye grounds - numerous fresh hemorrhages.

3-9 to 3-21 - The next 13 days, both as regards the white count and the patient's general condition, very well simulated a lull before an impending storm - The white count varied from 5,000 to 9,000 - patient felt fairly well and even insisted on getting out of bed.

We gave her her 8th and 9th transfusion 350 cc. in all

Epistaxis occured frequently.

Blood culture again negative.

The glands remained stationary - tonsils enlarged somewhat and the spleen measured 7 1/2 cm. on 3-13. From 3-13 to 3-21 spleen remained stationary.

3-11-19 W.B.C. 5,600 - Basal metabolism + 20%

3-14-19 W.B.C. 7,000 " " + 7%

3-22-19 W.B.C. 12,000 - general condition same.

3-23-19 W.B.C. 17,000 - complained of poor vision - facial glands enlarged slightly.
Spleen 8 1/2 cm. Basal Metabolism + 29% (restless)

3-24-19 W.B.C. 17,300 - felt fine - sat up in chair.
Spinal fluid - normal pressure - Nonné - neg. cell count - 1 per c.mm.
coll. gold - neg. Wass. - neg.

3-25-19 W.B.C. 25,000 - general condition good.

3-26-19 W.B.C. 34,000 - " " " , sat up in chair.
facial glands little more enlarged
Mediastinum 7 1/2 cm. on percussion.
Spleen 10 1/2 cm. on palpation

3-27-19 W.B.C. 80,000 - Condition worse - felt miserably - sat up very little - complained of dull abdominal pain - pulse very rapid and heart had gallop rhythm.

3-28-19 W.B.C. 115,000 - In bed all day - anxious expression - Ankle and feet edematous - suppuration set in under nail of L. big toe - hearing diminished- missed 3d menstrual period.

3-29-19 W.B.C. 247,000 - 10:00 a.m. - 10:38 a.m. transfusion #10- 300 cc.

W.B.C. 185,000 - 1:45 p.m. - Spleen 15 cm. and beyond umbilicus-xyphoid line.

W.B.C. 178,000 - 4:10 p.m. - Liver 6cm. Abd. pains severe. Ankles and feet more edem-

atous.

3-30-19 W.B.C. 260,000 - 11:00 a.m.

W.B.C. 295,000 - 5:00 p.m. - Spleen larger (see charts Fig. 5.)

3-31-19 W.B.C. 334,000 Severe abdominal pains - upper half. Pressure over spleen and sternum gave exquisite pain. Spleen still larger - Fluid + - in flanks. Edema lower extrem. increased - Dullness base l. lung post. probably due to enlarged spleen. Pneumonia not demonstrable.

4-1-19 W.B.C. 480,000 - 10:00 a.m. - Tonsils enlarged, 2cm. apart nasal breathing free - Transfusion #11 300 cc. X-Ray treatment #5 of spleen- 3 minutes only on account of poor condition of patient. Edema R.hand - wrist and sacrum - Patient very stuporous and complained of severe pain over the spleen.

4-2-19 W.B.C. 500,000 - Condition slightly improved -

4-3-19 W.B.C. 485,000 - Condition still better - talkative and bright.

4-4-19 W.B.C. 578,000 at 2:30 p.m. - X-Ray treatment #6 at 1:30p.m. over spleen. Liver 10cm. - tender Basal metabolism + 29%

4-5-19 W.B.C. 545,000 at 4:00 p.m. - Transfusion #12 - 200 cc. at 11:00 a.m. - Patient felt better - sat up one hour in bed.

4-6-19 W.B.C. 541,000 - Condition worse.

4-7-19 W.B.C. 646,000 - 2:00 p.m. - X-Ray treatment #7 at 1:30p.m. 9 min. to spleen. Frequent severe epistaxis during day with several emeses of clotted blood - At night breathing became stertorous and at midnight patient could be awakened only with great difficulty - when awake was rational -

4-8-19 At 12:15 a.m. cried out several times with inspiratory gasps - pulse at that time was very rapid but of good quality - Death occured a few seconds later of Respiratory failure.

DISCUSSION.

Blood.

All the blood work was done by Dr. Swan Erickson and myself. We employed a similar technique and used the same set of pipettes throughout.

1. Hemoglobin and Red Blood Cells.

The hemoglobin and red blood cell count remained low throughout and both progressively diminished, in spite of twelve transfusions, a total of 2760 cc. of blood.

2. White Cell Count.

The white count showed some extraordinarily sudden unaccountable fluctuations. The rise or fall of the white count during twenty four hour periods would sometimes be so great that we were obliged to make three or four counts in twenty-four hours to check our findings.

On entrance to the hospital the patient's white count was 99,000. In twenty-four hours, before any treatment was instituted, the count fell to 44,000, followed by a further fall after roentgen ray exposure of the lymph nodes of the neck and mediastinum.

From then on the white count kept oscillating between counts as low as 2,300 and as high as 646,000 on the day of death. By making blood counts several hours apart on the same day we were able to demonstrate the following:-

On Jan. 30 , a rise of 17,000 white cells in 7 hours.
" Feb. 8 " rise " 28,000 " " " 8 1/2 hours.
" " 14 " fall " 44,000 " " " 4 1/2 "
" " 19 " rise " 68,000 " " " 9 hours.
" Mar. 3 " rise " 71,000 " " " 6 "
" " 29 " fall " 62,000 " " " 3 "

The rapidity with which a rise or a fall of the white cell count would occur in this case was astounding. Thus we see a rise from 10,500 cells on February 17th, to 242,000 cells on February 20th, and just as rapid a fall to 6,800 cells by February 22nd. We see another sudden rise from 22,000 cells on March 1st, to 176,000 cells on March 3rd, and just as sudden a fall to 2,300 cells by March 8th. Up to March 8th, some of the white count fluctuations seem to occur entirely spontaneously. At times, however, it seemed to us as if the transfusions and roentgen ray exposures had an immediate effect in causing a drop in the white count. Fig. 6 , showing the daily blood counts and therapy, would seem to indicate that such was the case.

On March 22, the white count began to rise with lightning like rapidity and rose from 6,000 to 646,000 cells in the next seventeen days. From the beginning of this last rise the white count, transfusions, and roentgen ray exposures had practically no effect on the white count and the patient died with the highest white count demonstrable during her stay at the hospital.

On looking over the blood chart (Fig. 6) one is struck by the seemingly periodic exacerbation of the white count rise, each period lasting from five to six days. It is of interest to note here that with each rise in white count the patient's general condition became definitely worse. As a matter of fact, we could usually note a beginning rise in the white count by the change in the patient's general condition. During the periods of low count she would be happy and feel so well that she would insist on being permitted to sit up in a chair. As soon as the white count would begin to rise, the patient would stay in bed and complain usually

of headache, abdominal distress and would have an anxious expression.

It is of interest to note here that Krjukow describes a case of 'micromyeloblastic' leukemia in which there were sudden fluctuations in the white count, associated with rapid fluctuations in the size of the spleen.

3. Mitotic Figures.

A very interesting finding, with counts over 50,000, was the presence of numerous mitotic figures in the blood. These cells in all stages of mitosis were easily demonstrable in both the 1% acetic solution, and in the dry stained blood preparations. The higher the count the greater would be the number of mitotic figures. At one time we demonstrated as high as fifteen cells in mitosis in a single field under the low power lens of the microscope and a #10 eyepiece.

Gordon Ward describes a "peculiar case of acute leukemia", which from his description might very well have been a case of microlymphoidocytic leukemia, in which he observed as many as thirty-seven mitotic figures per cubic millimeter of blood. Krjukow, noted in his case, numerous mitotic figures in the blood during the periods of splenic enlargement.

In an attempt to determine whether these mitotic cells, which in al probability were being forced out from the rapidly proliferating lymphatic tissue into the blood stream, would continue the process to completion in vitro, Dr. Swan E. Erickson and I made a study of these cells in 1% acetic, normal saline, 1 1/2 % sodium citrate in saline, 1 1/2% sodium citrate in water, stock blood serum of groups 2 and 3, and also in patient's own serum, which was of group 4. We used a warm stage and kept the cells under observation in the above mentioned solutions at body temperature for as long as

36 hours. We did not observe a single instance of continuation of the process of mitosis in vitro.

4. Differential Counts.

The differential counts gave interesting findings (Table 4). The percentage of the various cells was calculated on a basis of from 300 to 700 cells. The percentage of polymorphonuclear neutrophiles varied from as low as .4% to 33.66±%. The total number of polymorphonuclear neutrophiles did not at all follow the relative percentage. For example, with the lowest count of 2,300, the percentage of polumorphonuclear neutrophiles was 19.33±%, and the total number of polymorphonuclear neutrophiles per cu. mm. was 445. With the highest count of 646,000 the percentage of polymorphonuclear neutrophiles was only 1.4% with an absolute number of 9044 polymorphonuclear neutrophiles per cu. mm. The highest percentage of polymorphonuclear neutrophiles, namely 33.66±% was present with a total of 6,000 white cells per cu. mm. The number of polymorphonuclear neutrophiles per cu. mm. in the normal blood is about 6,000. In this case even with counts as high as 242,000, the total number of polymorphonuclear neutrophiles per cu. mm. was only 3388. Only shortly before death did the absolute number of polymorphonuclear neutrophiles go up above the normal, as follows:-

March 29	Total white cells,	247,000-------	Total pmns.	14,820
April 2	"	"	"	500,000-------	"	"	9,150
" 7	"	"	"	646,000-------	"	"	9,044

5. Nucleated Red Blood Cells and Myelocytes.

Nucleated red blood cells and myelocytes were present in small numbers. These probably were an irritation phenomenon due to the extreme anemia, which at its lowest point gave a hemoglobin of 13% on the Von Fleischl-Miescher instrument, and a red count of only

900,000.

6. The 'Micromyeloblast'.

The most interesting cell was the so called 'micromyeloblast' of Naegeli and Schridde, or the 'microlymphoidocyte' or 'stem cell' of Pappenheim. The total number and relative percent of this cell was practically directly proportional to the total count (Fig. 4) With the rise in total white count our patient was always clinically worse and the disease could be said to have assumed a more severe aspect. Coincidentally with the increase in the severity of the disease the 'micromyeloblast' would increase in number and percentage a finding which is similar to the findings of Panton and Tidy in a series of three cases.

With a white count of 2,300, the total 'micromyeloblast' count was 153. With a white blood cell count of 500,000, the 'micromyeloblast' count rose to 75,800. On the last day before death the total white count was 646,000, but the 'micromyeloblast' count was only 2,548, probably an exhaustion phenomenon.

7. Therapy.

Our therapy consisted of a high carbohydrate diet, roentgen ray exposure and transfusions. Benzol was tried on two occasions, but in amounts so small and for so short a period of time that it's effect can safely be discounted.

We have already mentioned the peculiar sudden fluctuations in the white count, associated with an improvement in the patient's general condition during the periods of low count.

In view of such findings we must accept with considerable caution such reports as those of Haughwont and Azuzano, in which they claim improvement in forty-eight hours following the administration of benzyl benzoate.

The roentgen ray treatment varied a great deal in its effect on the enlarged spleen and lymph nodes, and on the white count. Seven treatments were given by Dr. Frank S. Bissell. The white count diminished after each treatment, with the exception of the treatments given a few days before the patient's death, at which time the white count rose from 6,000 to 646,000. It must not be forgotten, however, that on six occasions there occured diminutions in the white count, varying from 44,000 to 236,000 cells, without roentgen ray treatment.

The transfusions also had a varied effect on the patient. They were twelve in number and we gave a total of 2,760 cc. The hemoglobin and red cell count gradually diminished. In the beginning it seemed as if the transfusions might be a factor in lowering the white count and improving the patient's general condition. The last few transfusions seemed to have had no effect, whatever, on the patient.

With the first few transfusions we had very severe reactions. We were able to eliminate these reactions, practically entirely, by the use of small doses of morphine and atropine, given immediately after the transfusions.

An interesting finding during the last few days of the patient's life was the peculiar changed morphology of the red blood cells. Whereas at the beginning the great majority of cells were very pale, irregular in size and shape, the majority of cells towards the end of the patient's life appeared like perfectly normal red blood cells. Our impression was that these were functionating transfused cells and that the patient was practically living on the transfused blood. Ashby has shown that transfused red blood cells may functionate in the recipient for thirty days.

8. Temperature Curve.

The temperature varied between 96.6° and 104°. A rise in the temperature was usually associated with a rise in the white count, enlargement of spleen, and lymph nodes and tonsils, and a marked increase in general malaise. The whole picture would suggest as exacerbation of an infective process.

9. Blood Culture Studies.

Blood culture studies on media and by injection into rabbits were negative. Baar and Kornitzer and several other authors report positive cultures in the blood of leukemic patients. These, however, were usually found just antemortem and were probably due to secondary infections. To date no one has succeeded in transfering human leukemia to laboratory animals. Ellerman and Bang could produce anatomical and haematological leukemic lesions in healthy hens by injections of cell free Berkefeld filtered organ emulsions of a leukemic hen. Hirshfeld and Jacoby observed spontaneous leukemia in hens and were successful in transmitting the disease thru five generations. Schmeisser also observed spontaneous leukemia in fowls and was successful in transmitting it into other fowls. Ellerman claims that a myeloid type of leukemia may occur in one generation and a lymphatic in the next and that this is highly suggestive that both forms are due to the same infective agent.

10. Metabolic Studies.

A. The urine and stool chemistry were studied by Drs. Egerer-Seham and F.Ford. We could not demonstrate any definite relation between our blood and clinical findings, and the chemical findings. Tables 2 & 3 gives the findings of only a few days on which high fluctuations in white count and splenic dimensions occured.

In Krjukow's case the diminution of splenic enlargement was assoc-

iated with an increased excretion of ureates.

Ordway reports that radium over the spleen in leukemia increases the protein and phosphate constituents of the urine.

Table 2.

Chemistry of the Urine.

Date	White ct.	Gms. NaCl	Gms. H.	Gms. Urea N.	Gms. NH_3	Gms. Inorg. Total Phos.	Gms. Creat-inine.	Gms. Uric acid.
1-20-19	99,000	4.69	4.89					
1-24-19	4,800	5.73	5.93					
2-19-19	208,800	0.70	1.86	1.09	0.25		0.17	0.10
2-22-19	6,800	4.84	7.21	3.82	0.32		1.81	1.93
3-2- 19	61,000	2.66	5.87	2.49	0.74	0.07	1.90	1.02
3-3- 19	176,000	2.31	6.24	2.97	1.04	0.53	1.12	0.88
3-4- 19	106,000	3.78	6.09	3.11	0.85	1.78	1.84	0.99
3-7- 19	4,000	3.22	9.82	4.77	0.88	2.59	2.21	2.87
3-8- 19	2,300	2.39	6.33	3.62	1.00	2.20	1.76	3.66
3-9- 19	5,600	2.41	7.14	3.98	0.87	0.81	1.34	1.88
3-24-19	17,000	1.43	2.01	1.00	0.37	0.05	0.50	0.16
4-1- 19	480,000	4.08	4.66	3.68	0.48	0.08	0.46	0.25
4-2- 19	500,000	1.06	3.70	1.62	0.56		0.52	0.42

Table 3.

Chemistry of the Feces.

Date	White count	Inorganic phosphates Gms.	Total phosphates Gms.
2-27-19	76,400	0.53	2.10
2-28-19	34,200	0.75	1.11
3-1-19	22,000	0.66	1.14
3-3-19	176,000	0.53	1.58
3-4-19	106,000	1.78	2.58
3-16-19	9,600	0.53	0.76
3-24-19	17,300	0.05	0.16

B. Blood chemistry studies did not yield data that could be correlated in any way with our white count variations.

C. Basal metabolism studies were as follows:

3-11-19 . . . . . +20 per cent . . . . . W. B. C. 5,600

3-14-19 . . . . . + 8 per cent . . . . . W. B. C. 7,000

3-23-19 . . . . . +29 per cent . . . . . W. B. C. 17,000

4- 3-19 . . . . . +41 per cent . . . . . W. B. C. 485,000

11. Blood in Feces and Urine.

Feces and urine showed no chemical or microscopical blood at any time.

12. Spinal Fluid.

The first specimen had a positive Wassermann, but was otherwise normal. Fluid obtained at a subsequent puncture was completely normal.

13. Kidney Function.

The phenolsuphonphthalein excretion, Mosenthal test and blood chemistry gave normal values.

14. Spleen.

At first the spleen did not seem to play much of a role in the leukemic process. On 1-21-19, it was palpable about 3 cm. below the costal margin in the midclavicular line. From 1-21 to 3-3 marked fluctuations in the size of the spleen occured. It was rather a peculiar effect or coincidence that roentgen ray exposure of the mediastinal, and facial and neck lymph nodes was followed by marked diminution in the size of the spleen, followed, however, each time by an enlargement of the spleen greater than on each previous occasion. (Fig. 3, 7 and 8).

On March 6th, the spleen was palpable in the midline of the abdomen and 10 cm. below the costal margin in the midclavicular line. It was again exposed to the roentgen rays and again either as a result of the roentgen ray exposure or simply as a pure unexplainable coincidence it had reduced in size in forty-eight hours to such an extent that it was just barely palpable. (Fig. 33). In this connection it is of interest to note that the white count fell coincidently to 2300 per. c. mm.

On March 8th, the spleen began to enlarge again very rapidly (Fig. 5) and by March 31st it was 5 cm. beyond the midline and 16 cm. below the costal margin in the midclavicular line. This rapid enlargement took place in spite of three exposures to the roentgen ray. The white count also did not seem to be influenced by the roentgen ray exposures and rose from 2,300 to 646,000 on the day of death.

15. Lymph Nodes.

On entrance to the hospital the lymph nodes of the face, neck, axillae, groin and mediastinum were markedly enlarged. Photographs (Figs. 1 and 9) taken before and after roentgen ray exposure show a remarkable difference in the size of facial lymph nodes. Here again, it is an open question as to whether these changes were caused by the roentgen ray therapy or whether they were simply a part of the peculiar unexplainable fluctuations of the lympho-poietic system. Fig. 2 shows the relative fluctuations in the size of the facial lymph nodes.

A comparison of Fig. 7 and Fig. 12 shows a definite diminution in the size of the mediastinal shadow. This diminution occured within forty-eight hours after roentgen ray exposure of the chest. Plates showed the same thing. (Figs. 10 and 11).

16. Tonsils.

These also seemed to take a very active part in the leukemic process. With rises in the white count and enlargement of the lymph nodes or spleen, they too would enlarge, so much so, that not only would nasal breathing become impossible but even mouth breathing would be very difficult. Roentgen ray exposure over the face and neck seemed to produce a definite diminution in the size of the tonsils so that the patient could breathe with ease through the nose and mouth. See table No. 1 showing the fluctuations in the size of the tonsils.

17. Liver.

At first it was not palpable. Towards the end, it also enlarged and could be palpated 10 cm. below the costal margin in the midclavicular line.

Clinical Summary.

1. In spite of the twelve transfusions, of a total of 2,760 c.c. of blood, the patient's hemoglobin and red blood cell count steadily diminished. With a hemoglobin of 15 per cent, on the Von Fleischel Miescher instrument, and a red count of 900,000, the majority of red blood cells were full sized, round, stained well and had every appearance of normal cells. It seems probable, therefore, that the functionating transfused red blood cells prolonged an illness, usually acute and of very short duration.

2. The white count showed extraordinary sudden fluctuations. A fluctuation of 70,000 cells in six hours occured on March 29, 1919. The blood chart (Fig. 6) shows fourteen more of such sudden fluctuations.

3. A study of the blood chart (Fig. 6) shows an apparent rhythmical occurence of these fluctuations, a seemingly definite cyclic change of five to seven days duration.

4. Numerous beautiful cells in all stages of mitosis were demonstrable in the blood, both in the 1 per cent acetic solution and in the dry stained smears.

5. Injection of the patient's blood into a rabbit was negative.

6. Morphine and atropine administered after transfusions eliminated practically all reaction.

7. We could not demonstrate a definitely beneficial effect from roentgen ray therapy over lymph nodes and spleen and long bones. At first the spleen diminished in size when roentgen ray therapy was applied to the chest and lymph nodes or long bones. Whether this was purely coincidental or whether it had any relation to the roentgen ray therapy, we do not know. One exposure over the spleen was associated with a very pronounced diminution in the size of the spleen. Subsequent roentgen ray exposures had no effect whatever.

Exposure of the facial, cervical, axillary and mediastinal lymph nodes to the roentgen ray was followed by marked diminution in their size. Whether this was a direct result of the therapy, or simply coincident with it, is an open question. It is of interest to note that cervical and facial roentgen ray exposure was followed by a marked diminution in the size of the tonsils.

8. Enormous rapid fluctuations in the white count occured, which could not be accounted for by therapy.

9. A marked rise in the white count was usually preceded and accompanied by a rapid enlargement of the spleen or of some group of lymph nodes.

10. The clinical picture of more or less rhythmically varying white blood counts; clinical improvement during the periods of low white count, and diminution in size of lymph nodes or spleen, suggest the possibility of an infectious etiology of the disease.

11. The biopsy of a lymph node showed that at least a great number of our 'micromyeloblasts', a cell definitely myeloid according to the dualist view, were being generated in the very germ center of the lymph node follicles and

and were passing out from the lymph node into the blood stream. Such a possibility has always been denied by the dualists.

12. Clinically our case had all the ear marks of a lymphatic leukemia. The blood, however, showed in great numbers a cell, the so called 'micromyeloblast', which is believed by the dualists to originate in the myeloid tissue. To date, the dualists deny the possibility of such a cell originating in the germ center of a lymph node follicle.

A lymph node obtained under the very best possible conditions offers very good evidence in flat contradiction to the dualistic view.

We report our case, because we believe that it offers strong evidence in favor of the unitarian theory of the origin of blood cells.

Part II.

MORPHOLOGICAL STUDY.

Modern haematologists are divided into two strong groups, the so-called unitarians or monophyletists on the one hand; and the dualists and polyphyletists on the other hand. The bone of contention between these groups is the so-called 'stem cell'.

The dualists and polyphyletists consider the lymphopoietic and myelopoietic tissues as two separate tissues, entirely distinct from each other and never interchangeable. They contend that all the cells produced in lymphopoietic tissues come from their own specific stem cells, the "lymphoblasts" and in the same manner all cells produced in myelopoietic tissues come from their own specific stem cells, the "myeloblasts". They claim to be able to demonstrate a difference between "lymphoblasts" and "myeloblasts".

The unitarians or monophyletists deny the specificity of 'lymphopoietic' and 'myelopoietic' tissues. They claim and bring forth admirable evidence that under certain conditions myeloid cells may be produced by 'lymphopoietic' tissue and, vise versa, lymphoid cells may be produced in 'myelopoietic' tissues. Pappenheim and his followers derive all blood cells from a single stem cell which they call "lymphoidocyte". While some unitarians do not, others do admit morphological differences between the 'myeloblasts' and 'lymphoblasts' but deny the specificity of the mother tissues from which these cells come.

Among the chief exponents of the unitarian theory are Pappenheim, Grawitz, Weidenreich, Maximow, Downey, Ferrata, Du Toit, Arnold, Neuman, May, Uskow, Benda and Danchakoff.

Among the chief exponents of the dualistic and polyphetic theories are Naegeli, Ehrlich, Stockard, Ziegler, Turk, Schridde,

Fisher, Butterfield, Stillman, Meyer and Heinecke, Helly, Pinkus, Wolf, Sternberg, Banti, Mosse and Michaelis.

Ehrlich (1880) divided all white blood cells into granulated and non-granulated forms. It is this division which forms the basis of the modern dualistic teaching.

He placed the lymphocytes, large mononuclears, and transitionals amongst the non-granulated cells. The eosinophilic, basophilic and neutrophilic polymorphonuclears were the granulated cells. He believed the transitionals to be an intermediate form between the mononuclear and the neutrophile. Ehrlich believed that the lymphocytes came from lymphoid tissue; that is lymph node and spleen follicles and that the granulocytes came from myeloid tissue, that is principally bone marrow. Today this teaching, practically unchanged is accepted by the dualists and the great majority of clinicians.

According to Naegeli's scheme the mesenchyme cell gives rise to the normoblast and this in turn to the normocyte. The mesenchyme also gives rise to the lymphocyte of the "quiet zone" of the follicle, this in turn to the 'lymphoblast' of the germ center and the 'lymphoblast' to the small lymphocyte of the blood. The 'myeloblast', the 'stem cell' of the monocytes, megakaryocytes, and polymorphonuclears, also comes originally from the mesenchyme cell. In ~~the~~ post-foetal life, therefore, all the blood cells come from their own specific 'stem cells'. He denies all transitions between the myeloid and lymphatic systems. He and other dualists meet the argument that myeloid metaplasia may occur in the spleen and lymph nodes, in the absence of myeloid elements in the blood by declaring that lymph nodes and spleen are composed of two types of tissue, myeloid and lymphoid. The lymph node and spleen follicles are supposed to be lymphoid, while the interfollicular tissue of the nodes and splenic

pulp are myeloid. They further claim that these two types of tissue are sharpely contrasted and are distinct from each other. The myeloid function, however, does not manifest itself normally, but comes into play in anemias, infections, and myelogenous leukemias.

Schridde derives his lymphocytes from the endothelial lining of lymph vessels, and his myeloid tissue from the endothelial lining of blood vessels.

This view, however, is untenable, because Downey and others have shown that in the spleen, where a large production of lymphocytes takes place, there are no lymph vessels.

Fisher, a strong supporter of Naegeli's views, admits that myeloid cells may develop from endothelium of blood vessels and from connective tissue cells.

Hirschfeld admits that the spleen and lymph nodes can produce granulocytes. They come,however, not from the specific follicular tissue but from the pulp and interfollicular tissue, probably from the perivascular tissue (Hirschfeld).

Stockard adopts the extreme polyphyletic view. The fixed mesenchymal cells of the embryonic body, even before they begin their migration are already specialized to such an extent that differentiation can take place in one direction only.

Pappenheim and his pupils hold a moderated monophyletic view. The 'histioidocyte' a tissue cell gives rise to the 'lymphoidocyte'. The lymphoidocyte is the only stem cell and gives rise to megakaryocytes, monocytes, polymorphonuclears, lymphocytes, and red cells. The lymphocytes are fully differentiated cells and can not change into granulocytes.

Ferrata and his pupil Neigreiros - Rinaldi, accept a modified monophyletic view, similar to the one proposed by Pappenheim. They

believe that all the blood cells come from a single stem cell, which they call the "haemocytoblast", but they do not believe that fully differentiated lymphocytes are capable of differentiating into granulocytes or red blood cells.

Ferrata considers the connective tissue as a diffuse haemopoietic organ. This tissue gives rise to the 'haemohistoblast' (Resting-wandering cells of Maximow, - clasmatocyte of Ranvier). In the early embryo this cell differentiates into the primitive transitory haemocytoblast and this in turn to the primitive red cell of the embryo (megalocytes), while in the adult, lymphoid and myeloid haemocytoblasts (functional differences only) and monocytes are the products of its differentiation. ~~The lymphoid and myeloid haemocytoblasts.~~

Grawitz, Weidenreich, Danchakoff, and Maximow, hold the extreme monophyletic view. They believe that all blood cells may come from fixed tissue cells, such as reticular cells, fixed cells of omentum and messentery, as well as from the widely distributed clasmatocytes. These may give rise to free lymphoid cells, and these lymphoid cells may occur anywheres in the body of the adult.

Fully differentiated lymphocytes, derived from these lymphoid cells, may according to some authors dedifferentiate into the more primitive type of lymphoid cell, which in turn might differentiate into other forms of white cells, or these fully differentiated lymphocytes might metamorphose into other forms of leucocytes without dedifferentiation. Grawitz believes that lymphocytes can change into granulocytes in the circulating blood.

Weidenreich and Downey do not recognize the term 'lymphoblast'. They have shown that all the types of lymphocytes are concerned in regeneration and differentiation from one type to another. The

reticulum of lymphoid tissue, wherever found, serves as a mother tissue. All types of lymphocytes may be derived from it and these in turn may become transformed into other types of lymphocytes. Therefore no one type of lymphocyte can be recognized as being more highly differentiated than any other type. They claim, therefore, that one can not speak of a 'stem cell' of the lymphocyte in the same sense that one can speak of the 'stem cell' of the myeloid cells.

Lymphocytes are not in any sense of the word a final product. Downey, Weil, Weidenreich, and other observers have shown that all forms of lymphocytes can differentiate specific leucocyte granules, thereby becoming granular leucocytes.

Such widely differing opinions indicate the unsettled state of many hematological questions. These questions regarding the relationships of the blood cells depend primarily on the various theories of post-fetal regeneration. Is Naegeli correct, for instance, in assuming that the 'myeloblast' is a specific myeloid cell which is in no way related to the lymphatic tissues? He claims that he can differentiate morphologically between the myeloblast and large lymphocyte (lymphoblast). Pappenheim claims that Naegeli's myeloblast is not a stem cell but is the cell which he calls the leucoblast, a cell already partly differentiated along myeloid lines.

The following points are usually considered by the dualists as differentiating between 'myeloblasts' and 'lymphoblasts'.

1. Character of chromatin arrangement.

Naegeli (1907) describes very poor chromatin content as characteristic for lymphoblasts.

Klein (1910) finds that the chromatin content is not characteristic of the cell. He shows lymphoblasts (Folia

Haem. 1910 - Tafel XI - Figures 1,2 & 6) which are identical with Du Toit's and Pappenheim's lymphoidocytes and with Naegeli's myeloblasts.

2. Number of nucleoli.

Naegeli (1907) claimed that nucleoli of the "lymphoblasts" are 1-2 in number, and of myeloblasts. 2-4 in number.

Pappenheim, Klein, Butterfield and others have shown that this is not true. Naegeli himself admitted later (1912) that this does not hold true in pathologic blood.

3. Altmann - Schridde granules.

The dualists claim that they occur in lymphoid cells and are absent in myeloid cells.

Türk (1912) has shown that these granules are not specific for lymphoid cells.

4. Oxidase Reaction.

The dualists claim that the oxidase reaction, the staining of the oxidase granules with the indophenol blue dye, is positive in myeloblasts and negative in lymphoblasts.

Hyneck, Decastello, Blühdorn , Jochman, Glaus, Dunn report cases in which the so-called "myeloblasts" did not give the oxidase reaction. Klein showed that ordinary lymphocytes may give a positive reaction.

Schulze found that the myeloblasts of the normal marrow usually do not give the reaction while the pathological myeloblasts in the blood and in the organs usually do give the reaction.

According to Menten the reaction is not specific for myeloid cells. She found that lymphocytes may give a well marked reaction

She also found that many tissues give this reaction, so that it is by no means specific for blood cells.

Forman and Hugger found 'large mononuclears' both with and without the indophenol oxydase granules.

Baéchat and Belz, Steffan and Krjukow , claim that the reaction is not specific for myeloblasts.

Naegeli himself wavers on the question of specificity of the oxydase reaction. In his book " Blutkrankheiten und Blutdiagnostic" 1912 S.222, he makes the statement that, " The oxydase reaction is present in normal myeloblasts and for the most part in pathological myeloblasts, but in some of these the reaction may be not so strong and less diffuse".

Pappenheim and Dohrer's conclusion regarding the oxydase reaction is, that it does not indicate an absolute unfailing histogenetic difference between two heterogenous cell races. It is clear, therefore, that the opinion of the majority of observers is against the specificity of the oxydase reaction and against any of the other differential points usually picked on by the dualists for the differentiation of lymphoblasts and myeloblasts.

Du Toit says that morphologically we can not differentiate between 'lymphoblasts' and 'myeloblasts'.

Krjukow referring to his case of microlymphoidocytic leukemia says, " It seems to me that the most skillful dualists could not possibly differentiate our microlymphoidocytes from true micromyeloblasts, except perhaps by the use of the various methods that the dualists are wont to use".

Hirschfeld could not see any morphological difference between myeloblasts and germ center cells.

Damarus, Wolf and Türk can see no morphological difference be-

tween the stem cells of lymphocytes and granulocytes.

Parkes Weber describes a case of leukemia in which "The conclusion was unavoidable that the lymphoid cells which permeated the various tissues of the body were of the same kind as the lymphoid cells which during the patient's life constituted by far the greatest portion of the white cells of his circulating blood. I thought at the time that the cells in question were probably to be regarded as lymphoblasts but from the fact that a few of the cells gave a positive oxydase reaction and from a comparison with case IV, I now think that they were probably myeloblasts".

Similarly Chosrojeff reports a case of 'micromyeloblastic leukemia' in which he found in the blood all transition forms from myeloblasts to small lymphocytes and " were it not for the oxydase reaction one could not tell what type of leukemia he was dealing with".

We have shown so far that 'lymphoblasts' can not be differentiated from ' myeloblasts' neither by morphology, that is cytoplasm, nuclear chromatin arrangement, nucleolar content, Altmann-Schridde granules, nor by the oxidase reaction. The dualists trace all the white blood cells from these two stem cells and claim that the lymphopoietic tissues derived from these two mother cells are entirely distinct, and that lymphoid tissue can not produce myeloid cells and, vice versa, that myeloid tissue can not produce lymphoid cells. In the presence of a vast amount of recently accumulated evidence to the contrary, both experimental and clinical, it becomes doubtful whether there exists such a cell as is usually described by the dualists as a 'lymphoblast'.

The following points are evidence against the dualistic and polyphetic theories.

1. Downey and Weidenreich have demonstrated that cells such as are described for the germ centers may be found in the interfollicular tissue, in the spleen pulp, and in the lymph vessels. They have also shown that morphologically and genetically the lymphocytes of the cortex and medulla of lymph nodes are identical, and that follicles with germ centers may arise anywhere in the node.
2. Weidenreich describes these same cells in the chyle of the thoracic duct.
3. Dominici has shown that in certain infections, in man and in the laboratory animals, neutrophilic and eosinophilic myelocytes and normoblasts may develop in the spleen and lymph nodes, from lymphocytes.
4. Sacerdotti and Frattin, by tying off the blood vessels of one kidney in dogs have produced true bone marrow in the pelvis of the kidney.
5. Maximow reproduced these same results and found that these granulated and red blood cells of the bone marrow came from typical lymphocytes of the blood.
6. Downey and Weidenreich have shown that the lymphocytes of the germ center are extremely irregular in size and form and that only a very few of them conform to the descriptions given by Naegeli, Türk, Pappenheim and others.
7. Naegeli himself at one time describes the lymphoblasts as being very rich in chromatin and at another time as being very poor in chromatin.
8. Weidenreihh, Lewis and Schott have shown that lymphocytes may be transformed into polymorphonuclear eosinophiles, and Weidenreich and Weil claim that lymphocytes may

differentiate into neutrophile leucocytes.

9. Downey has shown that lymphocytes may differentiate into histogenous mast cells.

10. Dominici has observed myelocytes in lymph follicles.

11. In a case of eosinophilic polymorphonuclear leukemia recently reported by Giffin, Downey has found eosinophilic myelocytes in the germ centers of the follicles of the lymph nodes and spleen. (unpublished observations).

12. Hertz, using pyrogallol, has produced myeloid metaplasia of the spleen pulp with hyperplasia of the splenic follicles. This is contrary to the usual statement that myeloid metaplasia is accompanied by reduction in the size of the follicles, which is used as an argument in favor of the supposed antagonism between pulp and follicles.

13. Downey has demonstrated eosinophilic myelocytes in the germinal centers of lymph nodes of experimentally hemorrhaged rabbits in which there were no myelocytes in the blood so that the development of these myelocytes must have taken place in loco.

14. Roman has observed germ centers containing myelocytes. (cited by Citron).

To briefly summarize we have attemped to bring out the following points.

1. Haematologists are divided into two main camps, the dualists or polyphyletists, and the unitarians.

2. The dualists and polyphyletists believe that the blood cells and blood forming organs are divided into two main distinct divisions, the myeloid and lymphoid. These two never change

from one into the other either in the tissues or in the blood.

3. The Unitarians believe that all blood cells come from the 'lymphocyte' found in the bone marrow, spleen, lymph nodes, and other tissues of the body, or, according to Pappenheim and his followers, from the 'lymphoidocyte', which, in the adult, is confined to the marrow.

4. The dualists claim that they can differentiate between the 'lymphoblast' and 'myeloblast '. They regard the oxidase reaction as being of prime importance for such differentiation.

5. The unitarians claim that such a differentiation is impossible; that the 'lymphoblast' as a cell per sē does not exist; that the 'lymphoblast' is given various descriptions by various authors; that Naegeli himself makes contradictory statements regarding this cell; that the 'lymphoblast' may be found anywhere in lymphoid tissue and not only in the germinal centers as claimed by the dualists; and that the oxidase reaction, the main-stay of the dualists is not a specific test for the myeloblast.

6. A vast amount of experimental evidence is accumulating, which is in favor of the unitarian theory.

We now wish to call attention to histological and haematological evidence in favor of the unitarian theory, reported to date in the literature on leukemia.

Professor Downey has been kind enough to permit me to study the blood from a recent case of leukemia in which all the transitions stages between the lymphoidocyte (myeloblast of Naegeli) and lymphocyte were present. (Note - This case not yet reported in the liter-

ature).

Fleishmann reports a case of monocyte leukemia (second case on record) in which he found on June 1913, 65% mononuclear leucocytes and 19% small and large lymphocytes. On November 1913, a bone marrow puncture gave polymorphonuclears, small lymphocytes and 'mononuclears' identical in morphology with those found in the blood. Shortly before death, the 'mononuclears' dropped to 25% and there appeared, in the blood, myelocytes 12 1/2%, promyelocytes and 'myeloblasts'. At the autopsy there was found myeloid change everywhere. Amongst the myeloid cells were cells which corresponded to the blood monocytes. The follicles were shrunken in the spleen and the lymph nodes.

Fleischmann concludes the report by suggesting the possibility that the monocytes changed into myeloid elements under the influence of some pathologic stimulus.

Pappenheim, Walz, Körmoczy and Dennig have reported cases which hematologically were cases of lymphatic leukemia. Yet, in these cases the spleen and lymph nodes were not involved, but the bone marrow had become lymphoid.

Krjukow (1913) reports a case of microlymphoidocytic leukemia in which the blood showed all transition forms from the stem cell to the mature granulocyte, yet the pathological histological changes were those of a lymphatic leukemia. The bone marrow showed only slight activity. The pulp of the spleen and some lymph nodes showed slight myeloid metaplasia. The thymus was hyperplastic and spleen and lymph nodes showed typical lymphatic leukemia changes. He concludes that the myeloid elements of the blood were coming from the lymph nodes and spleen. He also states that the most skillful dualist could not differentiate morphologically between micromyeloblasts

and his microlymphoidocytes. He is loath, tho , to conclude from this that the myeloid cells of the blood were coming from lymphoid cells and so decides that he has here a case of 'mixed leukemia', with a prevailing lymphatic component. He also concludes that in acute leukemias even the presence in the blood of myelocytes and promyelocytes and stem cells does not necessarily diagnosticate a myelogenous leukemia.

Klein (1910) reports a case in which the blood showed all the transition stages between the lymphoidocyte (myeloblast) and the ordinary lymphocyte. The histological studies showed a lympho-leukemic involvement of all the lymphoid tissues.

Türk (1910) reports a case of mixed cell leukemia which changed into a lymphatic leukemia.

Hirschfled has found, in cases of mixed cell leukemia, hyperplasia of the lymph follicles and a myeloid metaplasia in the rest of the lymph nodes. He has also found in a true case of lymphatic leukemia clumps of myelocytes in the spleen and lymph nodes.

Vespremy, Glinski, Walter Schutze, Pappenheim - Hirschfeld and Wechselm - Hirschfeld describe cases of acute lymphatic leukemia in which there was atrophy of the follicles of the spleen and lymph nodes with marked proliferation of the splenic pulp and interfollicular tissue. Hematologically these cases were the same as any ordinary acute lymphatic leukemia, yet histologically we find the proliferation where it should occur in myeloid cases (Hirschfeld).

Herz (1915) reports a case of lymphatic leukemia in which 15.0% of myelocytes appeared before death. Sections of lymph nodes showed lymphatic proliferation. In the bone marrow, follicle like aggregations of lymphocytes were present, besides the myelocytes and myeloblasts. The spleen pulp was myeloid, while the follicles were

atrophied. Herz has also reported a case practically similar to the above in 1909.

Chosrojeff (1915) reports a case of 'micromyeloblastic' leukemia in which the blood showed all transition forms between the 'myeloblast' to the small lymphocyte. He bases his diagnosis on a positive oxydase reaction and says, " Were it not for this reaction one could not tell what type of leukemia he was dealing with".

Herxheimer(1915) reports a case of mixed leukemia. The blood contained 69.8%, small lymphocytes and 25.4% 'myeloblasts'. The bone marrow showed mostly lymphocytes with a few islands of 'myeloblasts'. The spleen showed a hyperplasia of follicles, which consisted of large and small lymphocytes. The pulp showed a hyperplasia of its lymphoid constituents and a profuse scattering of 'myeloblasts'. The lymph nodes showed a hyperplasia of follicles, and occasional 'myeloblasts'. In the bronchial nodes the'myeloblasts' predominated. The mediastinum showed compact parts consisting largely of lymphocytes and loose areas containing many 'myeloblasts'. The 'Myeloblasts' were diagnosed by means of the oxidase reaction.

From these cases the following is evident:-

1. (Downey) The blood may show all transition forms from the 'myeloblast' (lymphoidocyte) to the ordinary lymphocyte.
2. (Fleishmann) A monocytic leukemia blood and bone marrow picture changed to a myeloid picture. The autopsy showed myeloid proliferation everywhere. Amongst the myeloid cells some monocytes were present.
3. (Pappenheim and others) The blood picture was one of lymphatic leukemia. The bone marrow had undergone a lymphoid change and nodes and spleen were normal.

4.(Krjukow) The blood showed all transition forms from the 'micromyeloblast' to the granulocyte. These 'micromyeloblasts' were coming from lymphoid tissue, - "from the myeloid parts of these organs", according to the writer.

5.(Klein) The blood showed all transition stages between the 'myeloblast' and the ordinary lymphocyte. The tissues showed only lymphoid proliferation.

6.(Türk) A mixed cell leukemia changed into a lymphatic leukemia.

7.(Hirschfeld) Clumps of myelocytes were present in the spleen and lymph nodes in a case of lymphatic leukemia. In a case of mixed cell leukemia, both myeloid and lymphoid proliferation were present in the lymph nodes.

8.(Vespremy and others) Cases of acute lymphatic leukemia showed atrophy of the follicles of the spleen and lymph nodes and a proliferation of the interfollicular tissue and spleen pulp, tissue which according to the dualists is myeloid in nature.

9.(Herz) Two cases of lymphatic leukemia in which numerous myelocytes appeared before death. The bone marrow showed lymphocytes in follicle arrangement and the spleen pulp showed myeloid proliferation.

10.(Chosrojeff) In the blood all transition forms from the 'myeloblast' to the lymphocyte were present. The diagnosis of 'myeloblast' is made on the strength of the oxidase reaction.

11.(Herxheimer) A case of mixed leukemia. The bone marrow showed mostly lymphocytes with a small number of 'myeloblasts'. The spleen, lymph nodes and mediastinal tumor

showed hyperplasia of lymphoid and myeloid cells. Here too the diagnosis of 'myeloblast' was based on the oxidase reaction.

All of the above evidence is more or less of an indirect nature.

Meyer, Heinecke, Ziegler, Naegeli and other dualists claim a biological antagonism between the follicles and interfollicular tissues. They claim that no one has ever observed myeloid tissue in the germinal centers of the spleen or lymph nodes.

In 1912 Pappenheim made the statement that the dualistic theory will receive a serious blow at the moment that a case would be found in which the so called 'myeloblasts' could be shown to originate from lymphatic tissue, that is from the follicles and follicular cords. In other words, when in the blood the cell morphology will be that of a 'myeloblastic' leukemia, while the tissues will show lympho-leukemic changes, i.e., follicular hypertrophy and presence of myeloblasts within the lymph follicles.

Hirschfeld (1908) says that so far researches have shown that altho the spleen and lymph nodes can produce granulocytes yet they come not from the specific follicular tissue but from the pulp and interfollicular tissue.

Naegeli (1910) makes the statement that under no circumstances has it ever been proven that the germinal center of the lymph nodes can act as the site of origin of myeloid cells.

In 1915 Citron published his case of which he says,"It is the only one to date which shows in a seemingly certain and irreproachable manner, that the dualistic division does not always hold true; that not in all cases in which a myeloid metaplasia takes place is it necessary to conclude that a substitution of the lymphatic tissue has taken place by extra parenchymatous myeloid tissue; that in some cases a direct autocellular change of lymphatic follicular

lymphocytes into myeloid cells may take place. Citron bases this statement on the following findings.

1. The blood showed a monotonously uniform picture of the so called 'myeloblasts' of Naegeli or 'lymphoidocytes' of Pappeneheim.
2. The bone marrow was normal.
3. In the lumina of the blood vessels of the spleen and lymph nodes the cells were exactly the same as those which permeated these organs.
4. The splenic pulp and interfollicular tissue of the lymph nodes consisted of cells similar in all respects to the cells of which the follicles were composed.
5. No signs of follicular atrophy were present.
6. No evidence of myeloid metaplasia of the interfollicular tissue was present.
7. The nuclei of the cells of the follicles and of the interfollicular tissue were not those of lymphocytes but of 'myeloblasts'.
8. These 'myeloblasts' could be seen entering the circulation from the hyperplastic lymph follicles.

HEMATOLOGICAL AND HISTOLOGICAL FINDINGS.

A. Blood.

The differential counts are shown in Table 4 . The various interesting findings of the blood have already been referred to in our clinical discussion of the case. We wish again, however, to call attention to the presence of numerous "stem cells", (lymphoidocyte of Pappenheim),(myeloblast of Naegeli). These cells were present in the blood during the entire stay of the patient in the hospital. They were very variable in size. Some were as large as

a large lymphocyte, others smaller than a red cell. In the differential counts we included all sizes under the heading 'lymphoidocytes' 'myeloblasts', 'micromyeloblasts' or 'stem cells'. As seen in smears stained in Wright's stain our cells (figs. 14, 15 & 16) are morphologically identical with those described by Pappenheim. Their cytoplasm is basophilic, and scant in amount. The majority of cells did not contain azure granules. The structure of the nuclei froms the diagnostic feature of these cells. The chromatin forms a very fine, evenly distributed sieve like meshwork, in contrast to the large clumped chromatin blocks which characterize the nucleus of the lymphocyte. Nucleoli very variable in number are usually present. The staining of the chromatin, sieve like, network of the stem cell is much lighter than that of a lymphocyte. With the slightest overstaining the typical appearance of the stem cell becomes altered and differentiation from the lymphocyte is difficult.

The oxidase reaction was positive in the polymorphonuclear leucocytes but negative in all other cells. As we have already pointed out before, the failure of our stem cells to show the oxidase granules is to our mind of no significance one way or another. Citron and others refer to cases of unquestionably myeloid character in which this reaction was negative.

Naegeli himself (1912) wavers on the specificity of the oxidase reaction. He says that the oxidase reaction is positive in normal myeloblasts and for the most part in pathological myeloblasts.

Pappenheim, Dohrer, Dunn, Jockmann and Blühdorn declare that the oxydase reaction need not be positive in unripe myeloid cells.

Baechat and Belz claim that the reaction is not specific.

Klein has shown the even lymphocytes may give a positive oxidase reaction.

Menten has shown that lymphocytes and many tissues give a positive reaction, so that the reaction is not only not specific for myeloid cells, but is not even specific for blood cells.

Morphologically our cells were identical with those the dualists call 'myeloblasts' and 'micromyeloblasts'. If the blood alone were examined the diagnosis from the dualists point of view would be acute micromyeloblastic leukemia. We will endeavor to show that these 'micromyeloblasts' were coming, probably the majority of them, but certainly a great many of them, from the follicles and germinal centers of the lymph nodes.

We had in the blood numerous transition forms between these 'micromyeloblasts' and lymphocytes. We have already pointed out that the slightest overstaining alters the appearance of these cells. Our transition forms, however, are to be found in well stained smears side by side with the typical 'micromyeloblasts'. We believe these transition forms to be another bit of evidence showing the relation of our 'micromyeloblasts' to lymphopoietic tissues.

The number of the 'micromyeloblasts' varied roughly with the total white count. Table # 4 shows these variations. Fig.# 4 shows three curves expressing the relation between the total white count, the total 'micromyeloblast count' and the relative percentage of these cells. The rise in total number of these 'micromyeloblasts' was invariably associated with an exaggeration of all clinical symptoms, and an enlargement of either the spleen, lymph nodes, or tonsils. It would appear, therefore, that the increase of these cells in the circulation was closely associated with the increased activity of the lymphopoietic tissues.

Our numerous mitotic figures in the circulating blood led us to suspect the possibility of multiplication of these cells in the

blood. Our experimental work, while not conclusive, leads us to believe, however, that such probably was not the case.

It is not our intention in this paper to prove or disprove that 'myeloblasts' and 'lymphoblasts' are identical cells. We do wish to show, however, that in our particular case, great numbers of cells were circulating in the blood, which were morphologically identical with 'micromyeloblasts', cells which ordinarily are known to be derived from the bone marrow. We have good evidence that a great many of our 'micromyeloblasts' were being generated into the lymphopoietic tissues and were passing out from these tissues into the blood circulation.

Myelocytes were not found on some days, but there were as many as 3% on other days. No promyelocytes were seen. Nucleated red cells were present in small numbers. We consider the appearance of the myelocytes and nucleated red cells as the result of the irritation of the bone marrow due to the severe anemia.

B. Lymph Node .

The lymph node was obtained during life and was immediately fixed in Helly's fluid. The Dominici and Methyl Green Pryonin stains were used. The appearance of the node with a magnification of eight times is represented in figure #19. With low power the usual markings of a lymph node are pretty much obliterated. The structure of the medulla is not as dense as that of the cortex. The follicles of the cortex are not clearly discernable, with the exception of an occasional one. In examining a hundred sections only six slides were found, showing a single clear follicle containing a germinal center. The remainder of the cortex shows a merging of the follicles with the interfollicular tissue.

The peripheral sinus is filled with cells. The lymph sinuses

surrounding the trabeculae are practically all filled with dark staining cells, and the same holds true for the plexus of sinuses throughout the entire node. The medullary cords do not stand out prominently but fuse more or less with the rest of the tissue. The blood vessels contain red cells, which are rather indistinct with this low power lens, and white cells which show up very distinctly. The capsule is very much thickened and infiltrated. In places it appears to be necrotic. The fatty tissue outside of the capsule is also infiltrated with many dark staining cells. With this low power the Dominici and Methyl Green Pyronin sections show a great many cells which stain paler than the rest.

With the Zeiss apochromatic 1.5mm oil immersion lens and the #8 Zeiss compensating ocular, the following can be made out.

Besides the usual normal cellular constituents, the entire lymph node is permeated by atypical cells. In size they are quite variable. Some are larger than the largest lymphocytes to be seen in the node. Others are very small and are about the size of a small lymphocyte. The cytoplasm of most of the cells forms but a thin ring around the nucleus. (See Fig.# 20) In a few cells, especially those of the germ center it projects out in the form of pseudopodia (see cells 1,2,3 - figure # 21). These cells are free and in all probability migratory in nature. The cytoplasm stains basic and is darker than the cytoplasm of the lymphocytes and has a homogeneous appearance. (See figs. 20-22) In some cells the area immediately around the nucleus stains considerably lighter than the peripheral portion. No granules are demonstrable in the cytoplasm of the cells in the sections.

The nuclei here as well as in the blood form the diagnostic feature of the cell. They are usually eccentrically placed. Some

are round, the majority are ovoid, but many very irregular in shape, especially in the cortical regions, where proliferation seems to be very profuse and the cells are crowded. The nuclear membrane is very thin and hardly to be made out in some cells. The nucleus as a whole stains much lighter than the cytoplasm and can very readily be differentiated from the majority of the nuclei of the lymphocytes which stain considerably darker. Practically all of these atypical cells contain one or more nucleoli. The chromatin arrangement is entirely different from that of the lymphocytes. Whereas the chromatin of the lymphocytes, large and small is arranged in blocks, taking a dark stain and usually arranged at the periphery of the nucleus, the chromatin of these atypical cells forms a fine network of tiny particles, which stain very lightly and seem to be linked by fine threads running in every direction thru the nucleus. In some nuclei one may observe from one to four very small blocks of chromatin, which stain very lightly and are irregularly placed.

The morphology of these cells, therefore, corresponds exactly with the morphology of myeloblasts and micromyeloblasts as described by Naegeli, or to the lymphoidocytes of Pappenheim. (1912).

Throughout the entire lymph node numerous cells in all stages of mitosis are seen. (Fig.# 21 cells /). The blood vessels show these 'micromyeloblasts' in large numbers. They are easily distinguishable from the ordinary lymphocytes. Fig.# 23 shows a small blood vessel containing a lymphocyte, a 'micromyeloblast', and red cells. Occasional mitotic figures can be seen in the lumina of the blood vessels. Fig. #24 shows such a figure in a blood vessel.

The lymph sinuses likewise are filled with enormous numbers of these 'micromyeloblasts'. Fig.#25 shows several such cells in

a lymph sinus in the cortex of the node. They are here, also, readily distinguishable from the large and small lymphocytes. In this figure cells 1,2,3 and 4 are 'micromyeloblasts' in the reticulum. They are identical with those in the lymph sinus, but are somewhat angulated, due probably to pressure. The cells of the reticulum proper can easily be differentiated from the lymphocytes and the 'micromyeloblasts'. The cytoplasm of the reticulum cells is large in amount and stains very lightly. Cytoplasmic processes extend in all directions so that the cell assumes a stellate appearance. The cell membrane is exceedingly fine. In the majority of reticulum cells only part of the cytoplasm is visible, the remainder fading out into the adjacent tissue or being concealed by overlying cells. The nucleus is surrounded by a sharply defined membrane, which in many cells is invaginated and may form long grooves over the surface of the nucleus. (Cells 31, 33 and 34 in Fig.# 21). The nucleus is exceedingly poor in chromatin and appears to be very vesicular. A nucleolus may or may not be present. Occasional small blocks of chromatin may be present. In some cells the chromatin surrounds the nucleolus, in others it is scattered about.

The capsule is thickened and is infiltrated with lymphocytes 'myeloblasts' and 'micromyeloblasts'. Fig.#24 shows a small blood vessel of the capsule containing a cell in mitosis. In this figure cell 1 is an endothelial cell, cell 2, a connective tissue cell, and the remaining cells all 'myeloblasts'. A study of the various cells in the capsule shows transition forms between our 'myeloblastic' cells and lymphocytes as well as connective tissue cells. These transition forms are of both large and small cells.

In some places all the cells are flattened and elongated, while in other places actual necrosis is present.

Mitotic figures are also present in the capsule. The 'myeloblasts' and 'micromyeloblasts' are present in far greater numbers than the lymphocytes. There were also many transition forms between our atypical cells and the lymphocytes, which are recognizable by the fact that in these cells, having all the cytoplasmic characteristics of an atypical cell, we find the chromatin arranged in the form of dark staining blocks which vary in number in the different cells. The majority of these chromatin blocks are usually to be found at the periphery of the nucleus or abutting the nuclear membrane. Similar transition forms were found in the germ centers of the follicles and will be described in detail under that heading. In the capsule a whole series of cells can be found between our atypical cells and lymphocytes.

We also have evidence indicating relationship between the connective tissue cells of the capsule and our atypical cells. We find typical elongated connective tissue cells, with the clear, pale, almost homogeneous cytoplasmic processes, and vesicular, pale nuclei. The next cell in the series shows a shortening of these processes. Then we may find one that is completely rounded out or oval in shape. These take on a more basic stain, which is usually a sign of cell activity, and the nucleus shows more and more the characteristics of our atypical cells.

In the medulla an occasional cord can clearly be made out. The majority of cells in these cords are lymphocytes. However, scattered everywhere among them we find our atypical cells. Here too mitotic figures are numerous. The rest of the medulla contains a majority of our atypical cells. These are also present in large numbers in the blood vessels and sinuses.

The cortex shows but a very few follicles with germinal centers. In a hundred sections only six were found. Follicles without germ-

inal centers are more numerous. No signs of follicular atrophy are present. All evidence points towards increased activity. Mitotic figures are numerous. Our atypical cells are present everywhere. Between the follicles they constitute the majority of cells, but they are very numerous all thru the follicle, and are present in large numbers in the very centers of those follicles which do not show germ centers and in the germ centers of the six follicles studied.

Transition forms between our atypical cells and lymphocytes, as well as between lymphocytes and cells of the reticulum are present all thru the parenchyma of the node.

The germ center of a follicle, as represented in Fig. 21 is typical of all other germ centers found.

The 'micromyeloblasts' are of about the same size as a small or medium sized lymphocyte (cell 4). All gradations in size up to the size of a very large lymphocyte are present. (Cells 5,6,7,8,9 and 10). This variation in size is evident all thru the node. With Methyl Green Pyronin the cytoplasm stains an intense red. The red color is more pronounced in these cells than in the cytoplasm of the lymphocytes. In these India ink drawings the red staining cytoplasm is represented by various shades of gray, arranged proportionately to the intensity of the staining reaction. Compare cytoplasm of cell 11, a lymphocyte, with that of cell 7, a medium sized 'myeloblast'. Light staining areas in the cytoplasm, (cell 12), or around the nuclear membrane (cells 9 and 5) are present. The shape of the cell varies considerably. It may be round (cell 4) or oval (cells 2,7) or considerably elongated (cells 13 and 8). Some of the cells are more or less angular, like 9 and 14. Pseudopodia-like cytoplasmic processes are to be seen on some cells, probably indic-

ating their migratory nature (cells 3,8,12,15). The cytoplasm looks homogeneous and no granules are distinguishable with either the Methyl Green Pyronin or Dominici stains. The cytoplasmic rim varies in size. In the majority of cells it is rather narrow but well defined (cells 7,6,3). In some cells it is considerably larger (cells 10,12,8,9).

The nucleus may be eccentrically or centrally placed, in the majority of cells it is eccentric. The nucleus is large and occupies the greater portion of the cell. It varies greatly in shape. It may be round, oval, or angular (cells 6,7 and 9). Bottle neck like constrictions may occur (cell 16).

The nuclear membrane is well defined but thin. It may invaginate the nucleus and form folds which may be mistaken in cross section for nucleoli, cell 10 shows three such invaginstions, which could easily be mistaken for nucleoli, since the nucleoli and the cytoplasm both stain red. Careful focussing, however, shows these to be continuous with the cytoplasm.

One or more nucleoli are usually present. These take the Pyronin dye and stain red. They may be located anywhere in the nucleus and vary considerably in size. Compare nucleoli in cells 9 and 2. Small masses of chromatin may surround the nucleoli (cell 12).

The arrangement and quantity of the chromatin is the chief diagnostic characteristic of the cell. The chromatin and parachromatin are approximately equal in amount. The chromatin, taking a dark greenish violet stain with Methyl Green Pyronin, is in the form of extremely fine dust like particles, scattered rather uniformly thru the entire nucleus (cells 2,9,6,12). In some cells coarse chromatin masses are entirely absent (cell 6), while in others, one or more

may be present (cells 10,7,13).

The ordinary lymphocytes are easily distinguishable from our atypical cells. They vary greatly in size (cells 17 and 18). Their cytoplasm also takes the red stain, but not so intense a red as the cytoplasm of the atypical cells. In the majority of lymphocytes, the cytoplasm forms but a very narrow rim about the nucleus, visible only where the nuclear membrane is invaginated (cell 19), or only on one side of the cell (cell 11), or not at all (cell 18).

The nuclei of these lymphocytes are also characteristic. They stain considerably darker than the nuclei of the atypical cells, (cell 18). Numerous coarse chromatin strands run in all directions. Chromatin blocks, triangular, square, oblong and irregular in shape are present. These, in many cells, have a tendency to arrange themselves around the nuclear membrane (cell 20). Nucleoli may be, but usually are not present.

In this germ center (Fig. 21) as well as thru the parenchyma many transition forms between lymphocytes and our atypical cells may be seen. Beginning with a cell like 6, which represents a fairly small 'myeloblast' we may find a cell like 22. In this cell the nucleolus is surrounded by chromatin, and small masses of chromatin line the nuclear membrane. Two other chromatin blocks are to be seen below the nucleolus. The cytoplasm does not show any changes.

The next in the series would be one like cell 5. In this cell the chromatin blocks are more numerous and larger. A nucleolus is present. The nucleus is indented in several places. The cytoplasm stains a slightly lighter red.

The next stage is represented by cell 23. The cytoplasm is definitely less red than in cell 5. The nucleus still retains the

basic character of a 'myeloblast'. It is lightly stained and fine dust-like particles of chromatin are in evidence everywhere. Here, however, we have eight triangular shaped, dark staining, large chromatin blocks arranged in 'radkern' fashion about the nuclear membrane. In addition four more or less large irregular chromatin blocks, and several smaller blocks occupy the central portion of the nucleus. At first sight such a cell has all the ear marks of a lymphocyte. A detailed and careful study and a comparison with typical lymphocytes and 'myeloblasts' shows that it is neither one nor the other but a cell which must be placed halfway between the two.

The next cell in the series is cell 24. In this cell the cytoplasmic rim is considerably narrowed, and is practically invisible in part. The nuclear membrane is thick and is lined all the way around with chromatin strands and blocks. Numerous coarse chromatin blocks and strands are to be seen amidst the finer chromatin groundwork which we have described for the 'myeloblast'. This cell is past the half way mark in the transition series.

Cell 25, is practically a normal lymphocyte. In comparing it with cell 18,which we consider to be a typical lymphocyte, the only diagnostic differential point is the character of the nucleus.The nucleus of cell 25, is practically a lymphocyte nucleus. However, it lacks the coarse irregular chromatin strands, so frequently found in lymphocytes, and it still shows a rather fine distribution of small chromatin particles all thru the nucleus.

Other cells which we consider as transition forms are 26,27,28. And so all thru the parenchyma of the lymph node we find complete series of transition forms. Whether the lymphocyte is the mother cell of our atypical cell or vice versa, we do not know. Our evi-

dence is such as to show a relation between the two types of cells.

Another type of cell present, as shown in Fig. 21 by cells 31, 32,33 and 34, is the reticulum cell. This cell varies considerably in size and can very easily be differentiated from the various types of lymphocytes, atypical cells, and transition forms. The cytoplasm of this cell takes an extremely light pinkish stain. In most of the cells as in 31 and 32 no definite cytoplasmic rim can be made out. Cell 34 shows the cytoplasm and the cytoplasmic processes very well. The nuclei of these reticular cells are very vesicular. The nuclear membrane is sharply outlined. The nucleus may be almost triangular as in cell 31, or oval as in cell 32 or elongated as in cell 33. The chromatin content is extremely meager as cells 31, 32 and 33 show. It usually consists of a few small blocks and a few strands. A rather large nucleolus, staining red, and usually surrounded by some chromatin may be present (cells 31 and 32). Here too, we have evidence showing a relationship between our atypical cells and the reticulum cells, as well as a relation between the reticulum cells and the lymphocytes.

A rather incomplete series may be represented by cells 35,36, 28,23 respectively. The nucleus of a small reticulum cell is shown at 35; 36, shows a beginning formation of chromatin blocks and a darkening of the karyoplasm. Cell 28 shows a small amount of well defined cytoplasm, the nucleolus is prominent, and chromatin arrangement and karyoplasm staining are suggestive of a cell between a 'myeloblast' and lymphocyte, as well as between a lymphocyte and a reticulum cell. Cell 23 might very well fit in as the next in the series. It has already been described as a transition cell between a lymphocyte and a myeloblast, so that by including it also in our reticulum lymphocyte series we believe to have demonstrated a

relation between the reticulum cells, lymphocytes, and atypical cells. In our own mind this relation of reticulum cells to the other two is not as definite as the relation between lymphocytes and our atypical cells. Not enough transition stages are shown in this one germ center. A study of other parts of the parenchyma would reveal much more conclusive evidence.

In comparing our atypical cells with the various cells found in supposedly normal lymph nodes, human and animal we did not find any cells at all comparable to our 'myeloblasts' and 'micromyeloblasts'. Even germ centers cells, the so called ' lymphoblasts' were not comparable to our atypical cells. In these 'lymphoblasts' the cytoplasm takes on a lighter stain, and the chromatin occurs as fairly coarse dark staining blocks. The fine dust like particles of chromatin scattered fairly uniformly thru the entire nucleus are lacking.

DISCUSSION.

It should be pointed out, that in comparing cells in blood smears with cells in sections we must keep in mind certain morphological differences which are always present due to the difference in technique. In making a blood smear the drop of blood is quickly spread out over the slide and dried. The capillary traction flattens out the cells so that they appear much larger than they actually are. In sections, however, the various cells are exposed to the action of fixing fluids and consequently undergo a certain amount of shrinkage, even with the best of fixing fluids such as Helly's solution. Furthermore, an identical Wright's stain technique can not be used satisfactorily in sections and blood, so that in comparing blood and tissue cells we must bear this also in mind.

In comparing a normal lymphocyte in the blood with a normal lymphocyte in sections we notice a definite morphological difference. The chromatin of the blood lymphocyte is arranged in a more or less definite network, while in the lymphocytes of sections the chromatin is arranged in coarse blocks and irregular strands. The lymphocytes in the blood vessels of sections also show these coarse blocks and irregular strands. The same holds true for myeloblasts in the blood and in sections. Whereas, myeloblasts in the blood show a beautiful sieve like nuclear chromatin network, in the tissues there is more of a tendency to formation of fine particles with occasional chromatin block formation. This same change is also evident in the myeloblasts in section blood vessels.

The 'micromyeloblasts' and 'myeloblast' are very frequently mistaken for lymphocytes, because they overstain very easily, thus loosing their typical appearance.

The presence of the stem cell (microlymphoidocytes and lymph-

oidocytes' of Pappenheim or 'micromyeloblasts' and 'myeloblasts' of Naegeli) in large numbers in the blood is usually associated with an acute and rapidly fatal course of the disease.

A blood picture alone will often lead us to a wrong diagnosis. In some cases, for a correct diagnosis, histological studies must supplement the blood studies. Krjukoff diagnosed myeloid leukemia from the blood, yet the bone marrow showed only slight activity and he was forced to conclude that his myeloid cells were coming from the 'myeloid parts' of lymph nodes and spleen.

Similarly Citron diagnosed 'micromyeloblastic' leukemia, yet he found the bone marrow normal and lymph follicles hyperplastic and proliferating these 'myeloid' cells.

The dualists, however, deny the possibility of 'myeloid'cells originating from lymphatic tissue. They argue that in lymphatic leukemia the follicles of the lymph nodes atrophy or are at least quiescent. They deny absolutely the possibility of 'myeloid' cells ever occuring in <u>follicles</u> and especially in the <u>germ centers</u> of follicles.

Citron's case, however, showed the 'myeloblasts' of the dualists in the <u>follicles</u> of the lymph nodes and spleen.

Naegeli, referring to Citron's case, belittles the findings because ' the patient died as a result of overdosage of benzol'. We find that only one dose of six grams was given by rectum. Boni gave 5 grams daily for three weeks. Josephson gave 96 grams in 6 weeks. Krokiewiez gave one case, a total of 206 grams. Weber gave 3 grams daily. No ill results were observed in these cases.

Naegeli also belittles the findings in cases which had excessive roentgen ray therapy.

Our case at the time the axillary lymph node, upon which we

base our study, was removed had not had any benzol, nor had there been any direct roentgen ray exposure of the axillary lymph nodes.

We believe our case to be even more convincing than Citron's for two reasons: The lymph node was obtained in vivo, so that post-mortem changes can be ruled out. Whereas, Citron speaks of 'myeloblasts' and 'micromyeloblasts' in the follicles he does not say that he found them in the germ centers. The germ centers in our cases contained many of these cells.

We present our case in the belief that it offers evidence in favor of the unitarian theory of Pappenheim and Ferrata. The cell which has been described as a 'myeloblast' and which the dualists have assumed to be a specific myeloid cell was found to originate in the germ centers and follicles, as well as in the medullary portion of the node. This case and the case reported by Citron prove, therefore, that the cell in question may be related to lymphocytes as well as to cells of the myeloid series.

SUMMARY.

Morphological Part.

1. The blood, at all times, showed numerous stem cells, (lymphoidocyted of Pappenheim), (myeloblasts' of Naegeli) of all sizes. Our cells, which we shall refer to as atypical cells, had a basophilic cytoplasm and a nucleus in which the chromatin formed a very fine evenly distributed sieve like network. Morphologically our atypical cells were indistinguishable from typical myeloblasts.
2. Very careful staining was essential in bringing out the finer details of these atypical cells.
3. The oxidase reaction was negative in these cells in the blood smears.
4. The diagnosis from the blood alone would be 'micromyeloblastic' leukemia.
5. The presence of numerous mitotic figures in the blood stream suggested the possibility of cell proliferation in the blood stream. We could not demonstrate such to be the case.
6. Lymphocytes, normal in appearance were always present in the blood. The contrast between the lymphocytes and the atypical cells was very marked. Numerous transition forms between the lymphocytes and the atypical cells were present in the blood.
7. Some myelocytes and nucleated reds were present. The severe anemia might easily account for these.
8. The biopsy of a lymph node showed these atypical cells proliferating in great numbers in the capsule, interfollicular tissue, lymph cords, lymph follicles and in the germ centers of the lymph follicles.

9. Transition forms between the connective tissue cells of the capsule and these atypical cells as well as between lymphocytes and these atypical cells were present in the capsule.
10. In the interfollicular tissue as well as in the follicles and even in the germinal centers transition forms between these atypical cells and reticulum and lymphocytes were also present.
11. The lymph follicles and lymph cords showed no signs of atrophy, but had all the ear marks of marked activity. Mitotic figures were numerous. The only signs of atrophy or necrosis were found in the capsule.
12. These atypical cells formed the majority of the cells of the parenchyma.
13. These atypical cells constituted by far the majority of the cells in the lymph sinuses and were very numerous in the blood vessels of the node.
14. We are justified in concluding from the evidence at hand that in all probability the majority of the 'myeloblasts' and 'micro-myeloblasts' of the blood were coming from the lymphoid organs, not only from the portions which, according to the dualists, may give rise to myeloid cells, but from the sanctum sanctorum of the lymphoid tissues, namely the follicles and germ centers.

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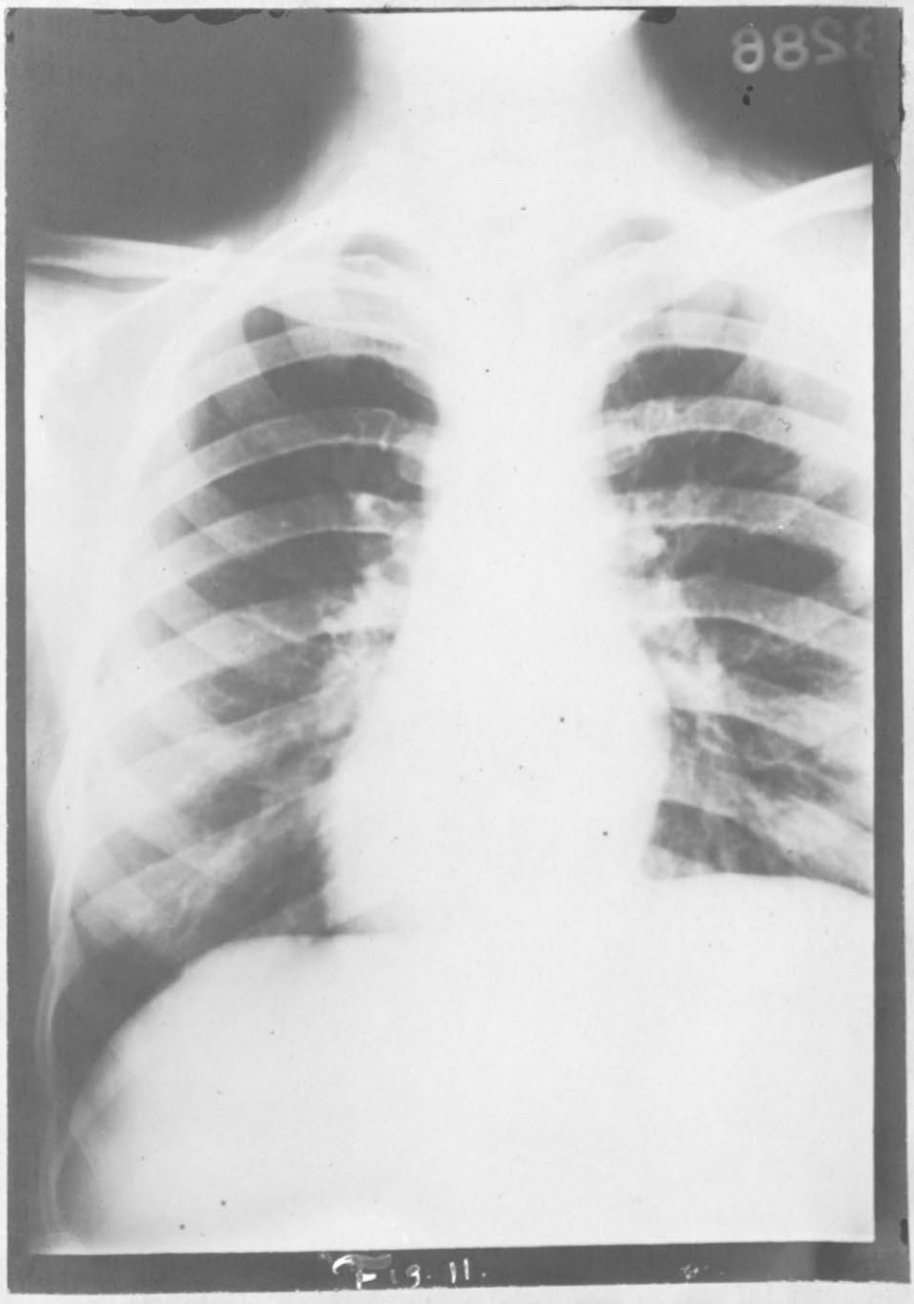


Fig. 11.

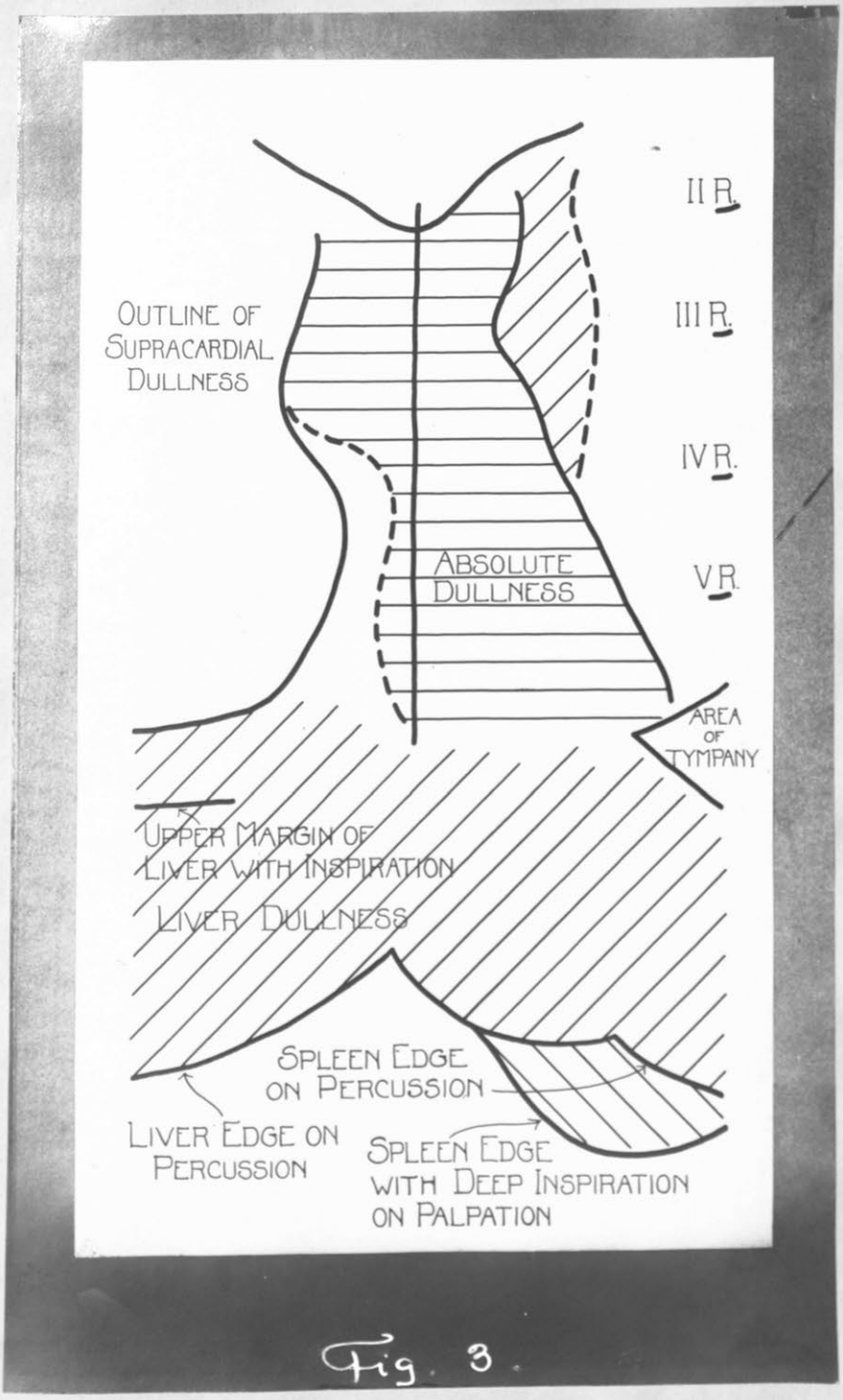

II R.
III R.
IV R.
V R.
OUTLINE OF SUPRACARDIAL DULLNESS
ABSOLUTE DULLNESS
AREA OF TYMPANY
UPPER MARGIN OF LIVER WITH INSPIRATION
LIVER DULLNESS
SPLEEN EDGE ON PERCUSSION
LIVER EDGE ON PERCUSSION
SPLEEN EDGE WITH DEEP INSPIRATION ON PALPATION

Fig. 3

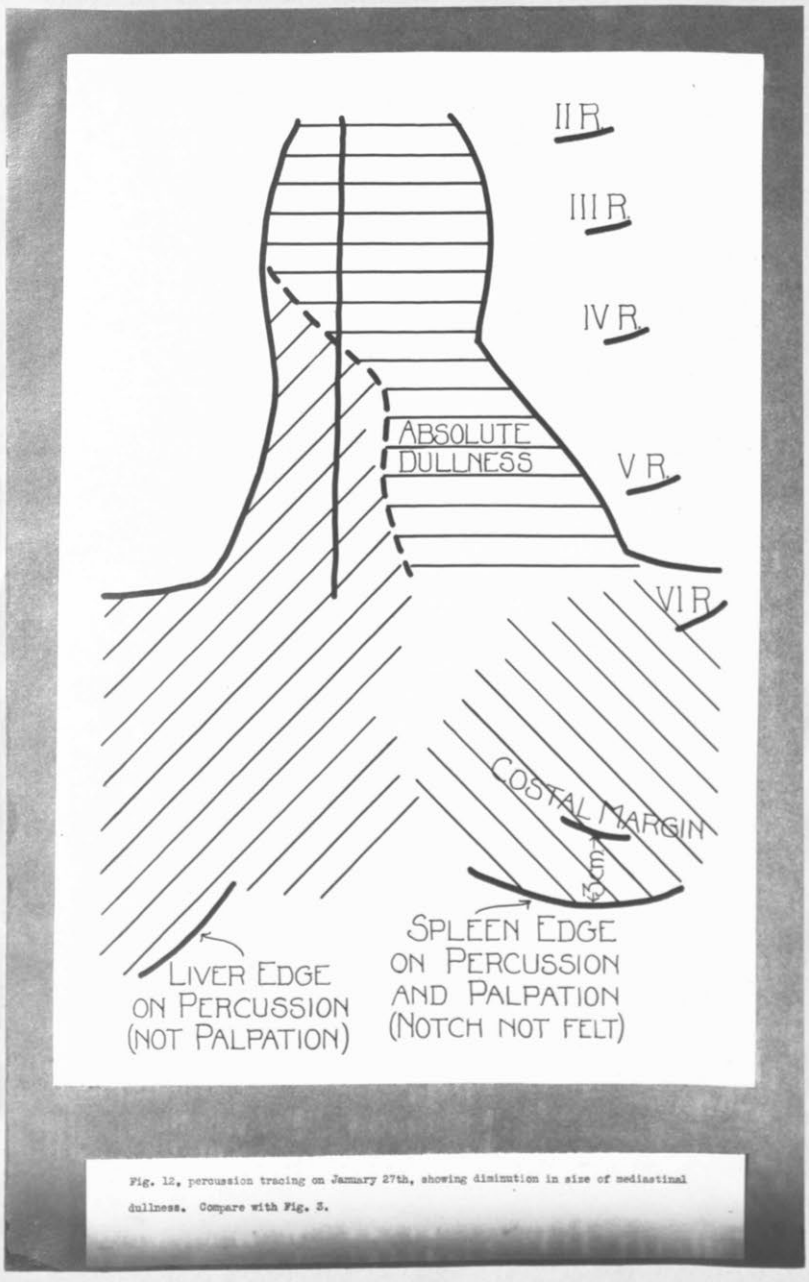


Fig. 12, percussion tracing on January 27th, showing diminution in size of mediastinal dullness. Compare with Fig. 3.

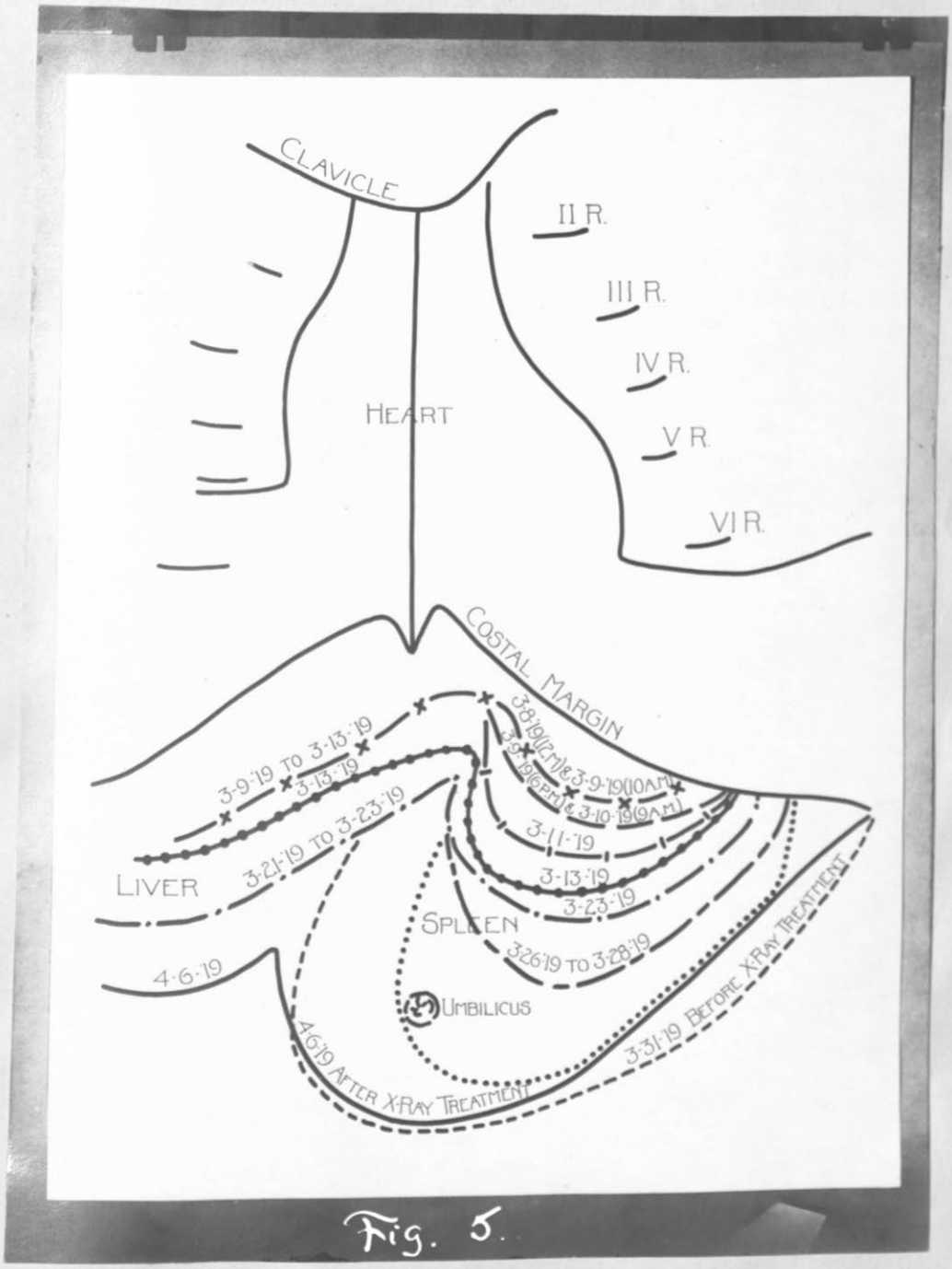
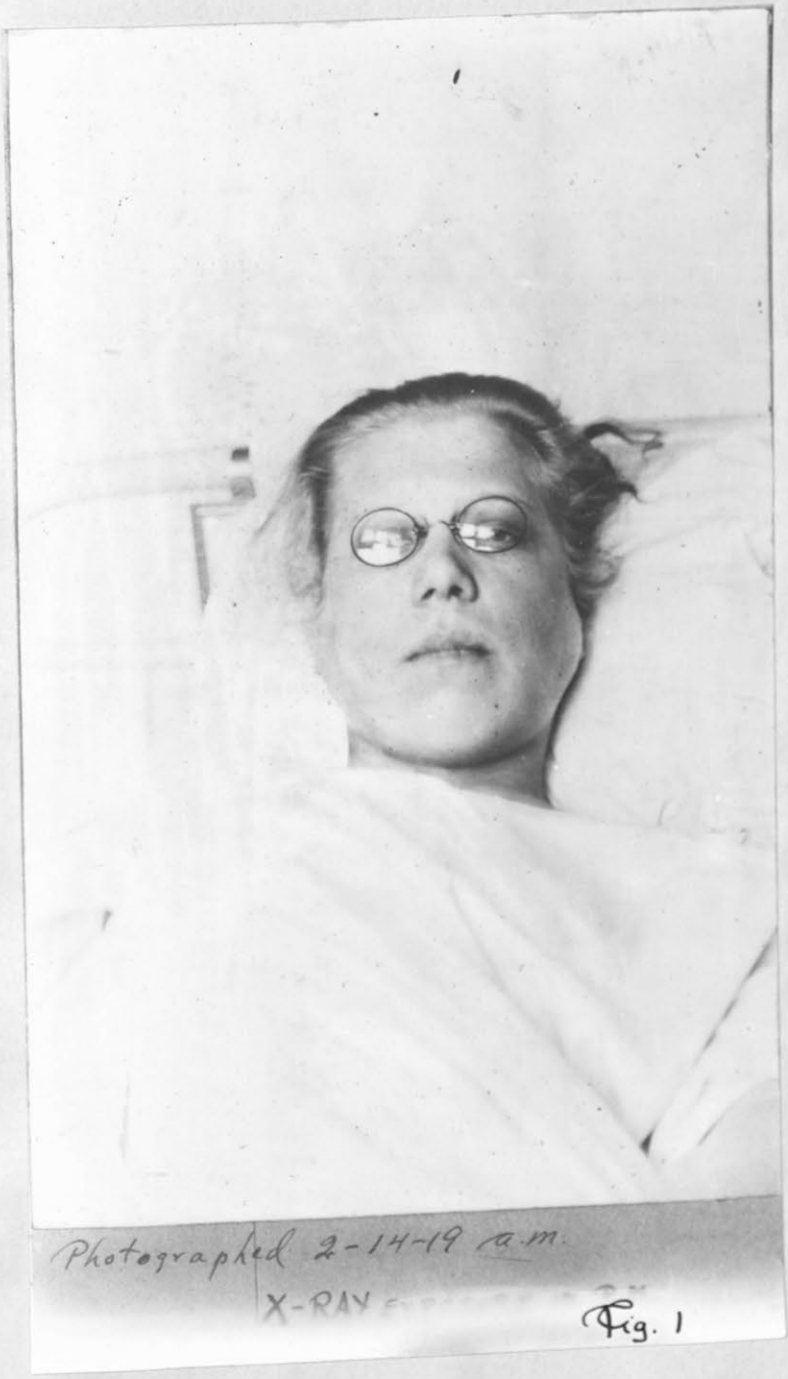

CLAVICLE
II R.
III R.
IV R.
V R.
VI R.
HEART
COSTAL MARGIN
3-8-19(12 PM) & 3-9-19(10 AM)
3-9-19(6 PM) & 3-10-19(9 AM)
3-9-19 TO 3-13-19
3-13-19
3-21-19 TO 3-23-19
3-11-19
3-13-19
3-23-19
LIVER
SPLEEN
3-26-19 TO 3-28-19
4-6-19
UMBILICUS
4-6-19 AFTER X-RAY TREATMENT
3-31-19 BEFORE X-RAY TREATMENT

Fig. 5.



Photographed 2-14-19 a.m.

X-RAY

Fig. 1

Photographed 2-17-19 a.m.

Fig. 9

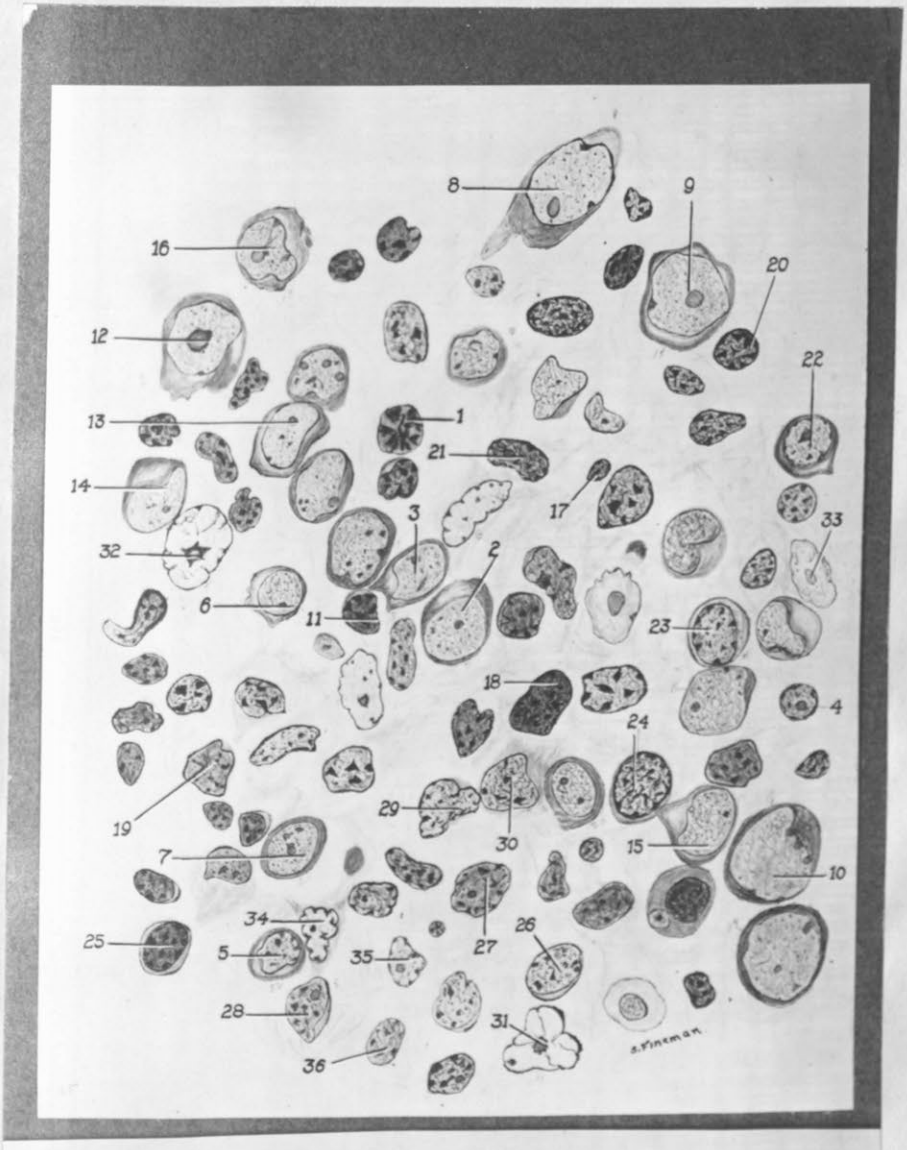

8
9
16
20
12
22
13
1
21
14
17
3
33
32
2
6
11
23
18
4
24
19
29
30
15
10
7
34
25
5
35
27
26
28
31
36
S. Fineman

Fig. 21.

Fig. 24.

Fig. 25

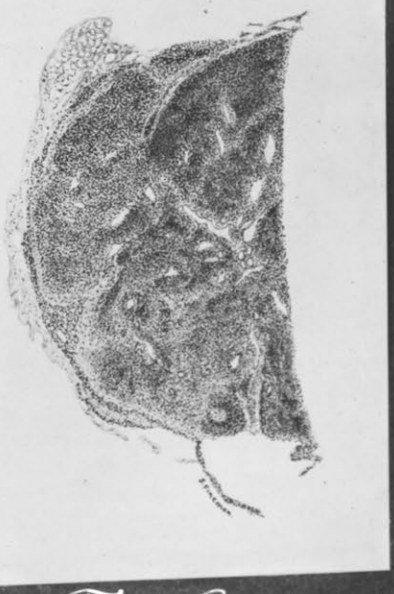


Fig. 19

Fig. 23.

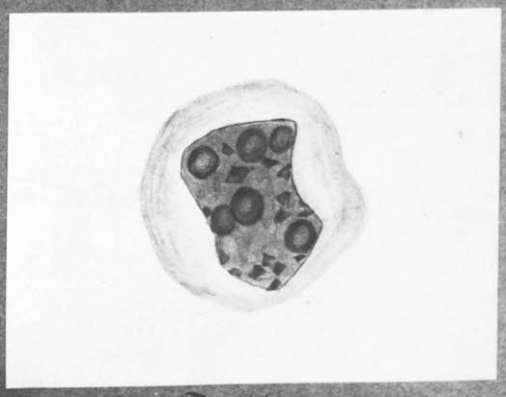


Fig. 26

Fig. 27

Fig. 28

Fig. 20

Fig. 29

Fig. 22

Fig. 30

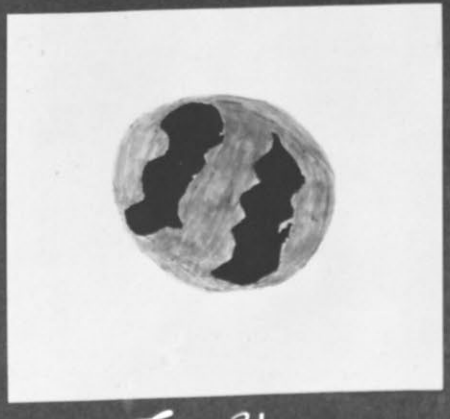


Fig. 31

Fig. 32

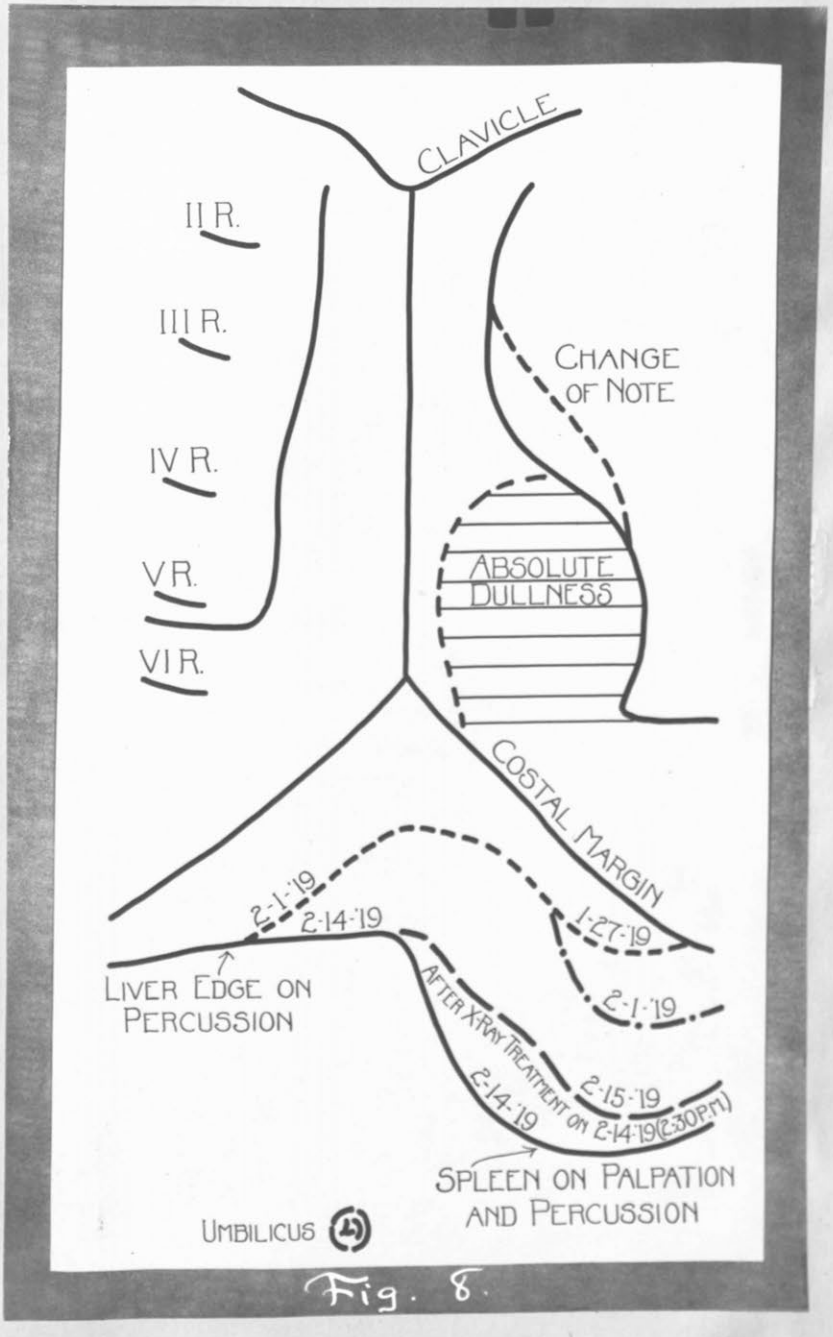

CLAVICLE
II R.
III R.
IV R.
V R.
VI R.
CHANGE OF NOTE
ABSOLUTE DULLNESS
COSTAL MARGIN
2-1-19
2-14-19
1-27-19
2-1-19
LIVER EDGE ON PERCUSSION
AFTER X-RAY TREATMENT ON 2-14-19 (2.30 P.M.)
2-15-19
2-14-19
SPLEEN ON PALPATION AND PERCUSSION
UMBILICUS

Fig. 8.

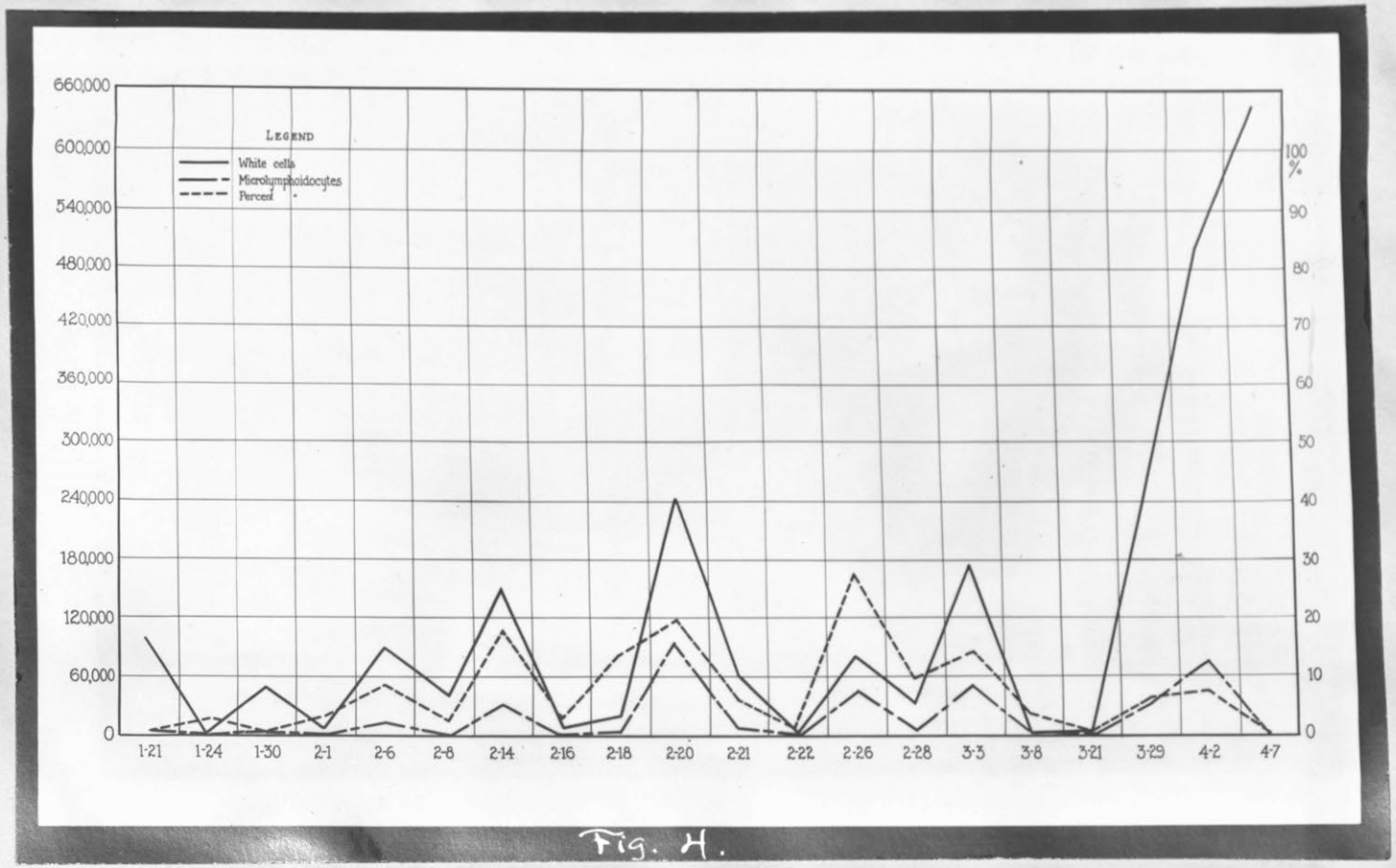

LEGEND
White cells
Microlymphoidocytes
Percent
660,000
600,000
540,000
480,000
420,000
360,000
300,000
240,000
180,000
120,000
60,000
0
100 %
90
80
70
60
50
40
30
20
10
0
1-21
1-24
1-30
2-1
2-6
2-8
2-14
2-16
2-18
2-20
2-21
2-22
2-26
2-28
3-3
3-8
3-21
3-29
4-2
4-7

Fig. H.

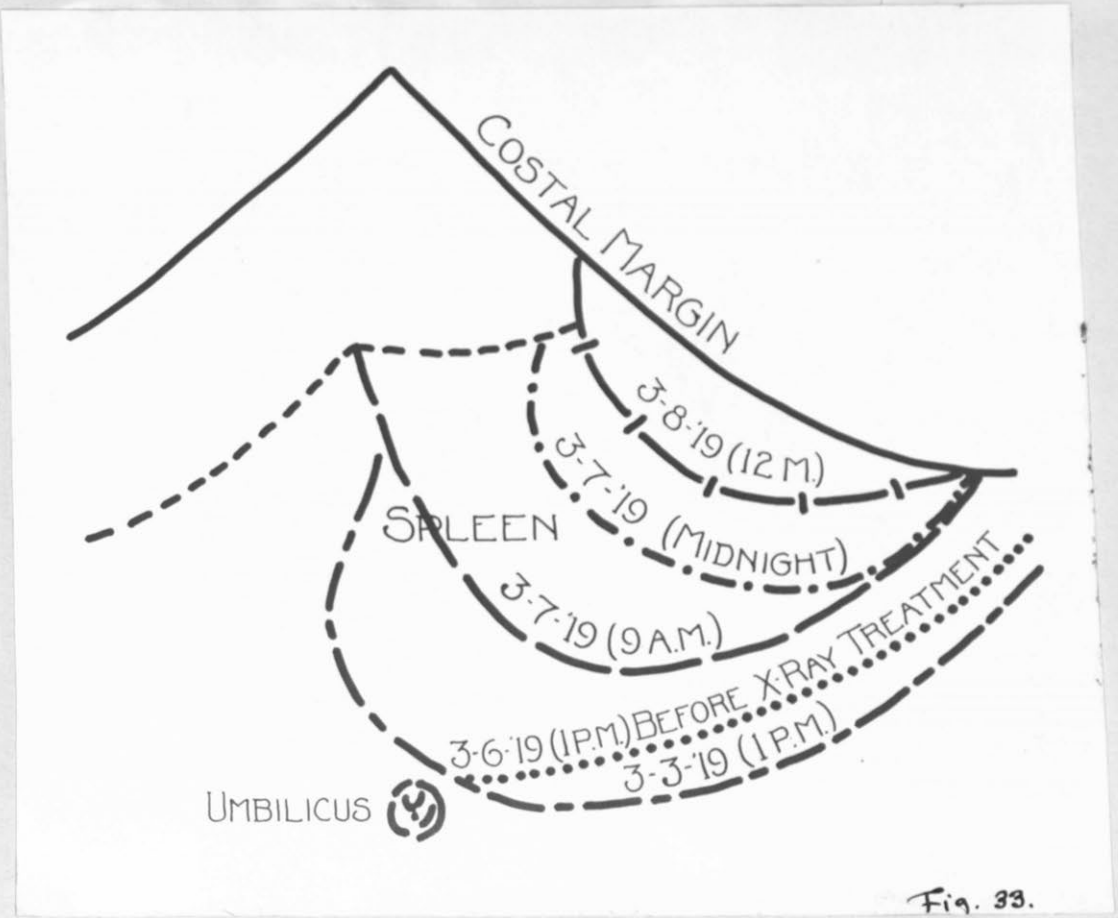

COSTAL MARGIN
3-8-19 (12 M.)
3-7-19 (MIDNIGHT)
SPLEEN
3-7-19 (9 A.M.)
3-6-19 (1 P.M.) BEFORE X-RAY TREATMENT
3-3-19 (1 P.M.)
UMBILICUS

Fig. 33.

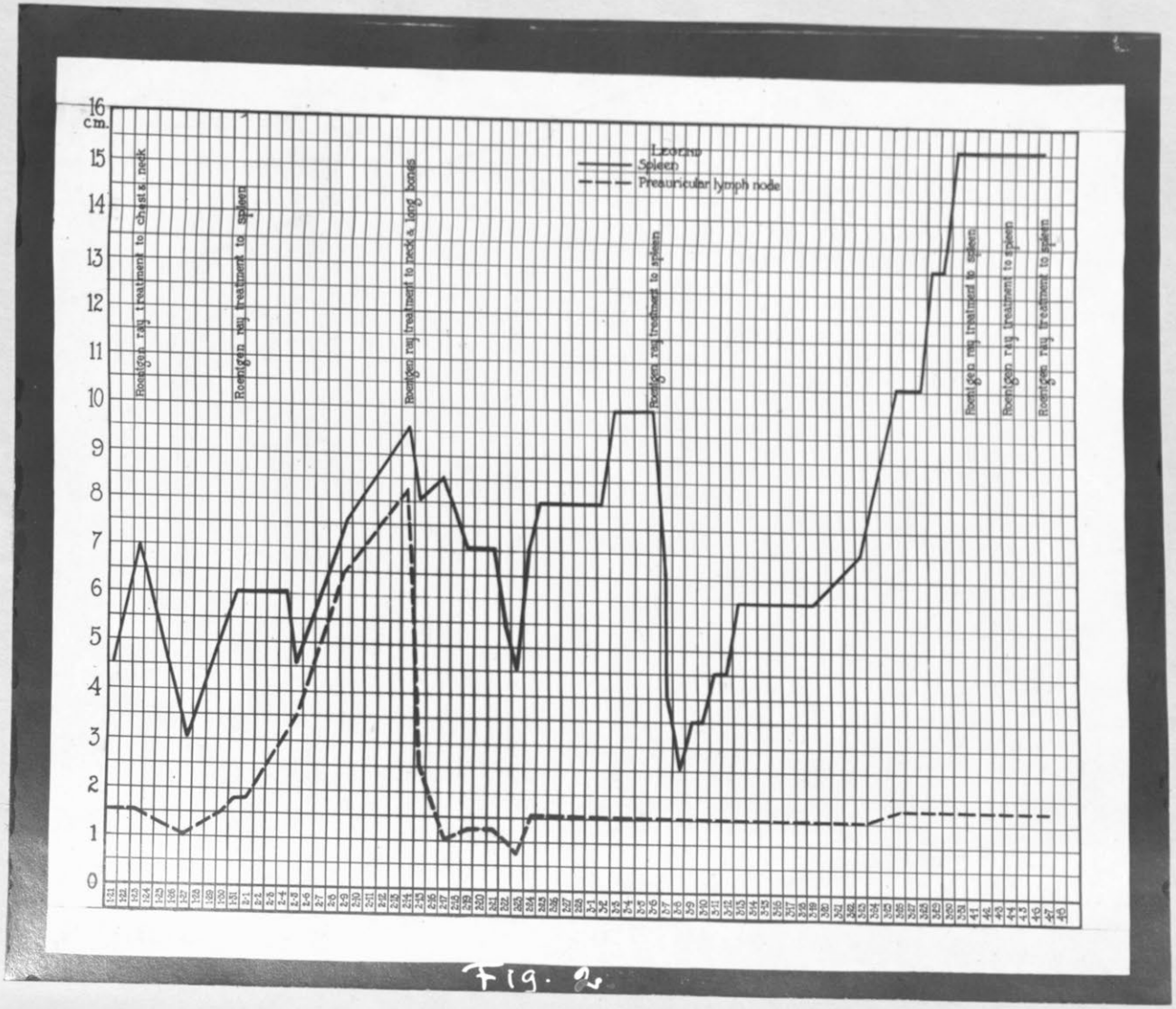

16
cm.
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Liver
Spleen
Preauricular lymph node
Roentgen ray treatment to chest & neck
Roentgen ray treatment to spleen
Roentgen ray treatment to neck & long bones
Roentgen ray treatment to spleen
Roentgen ray treatment to spleen
Roentgen ray treatment to spleen
Roentgen ray treatment to spleen

Fig. 2

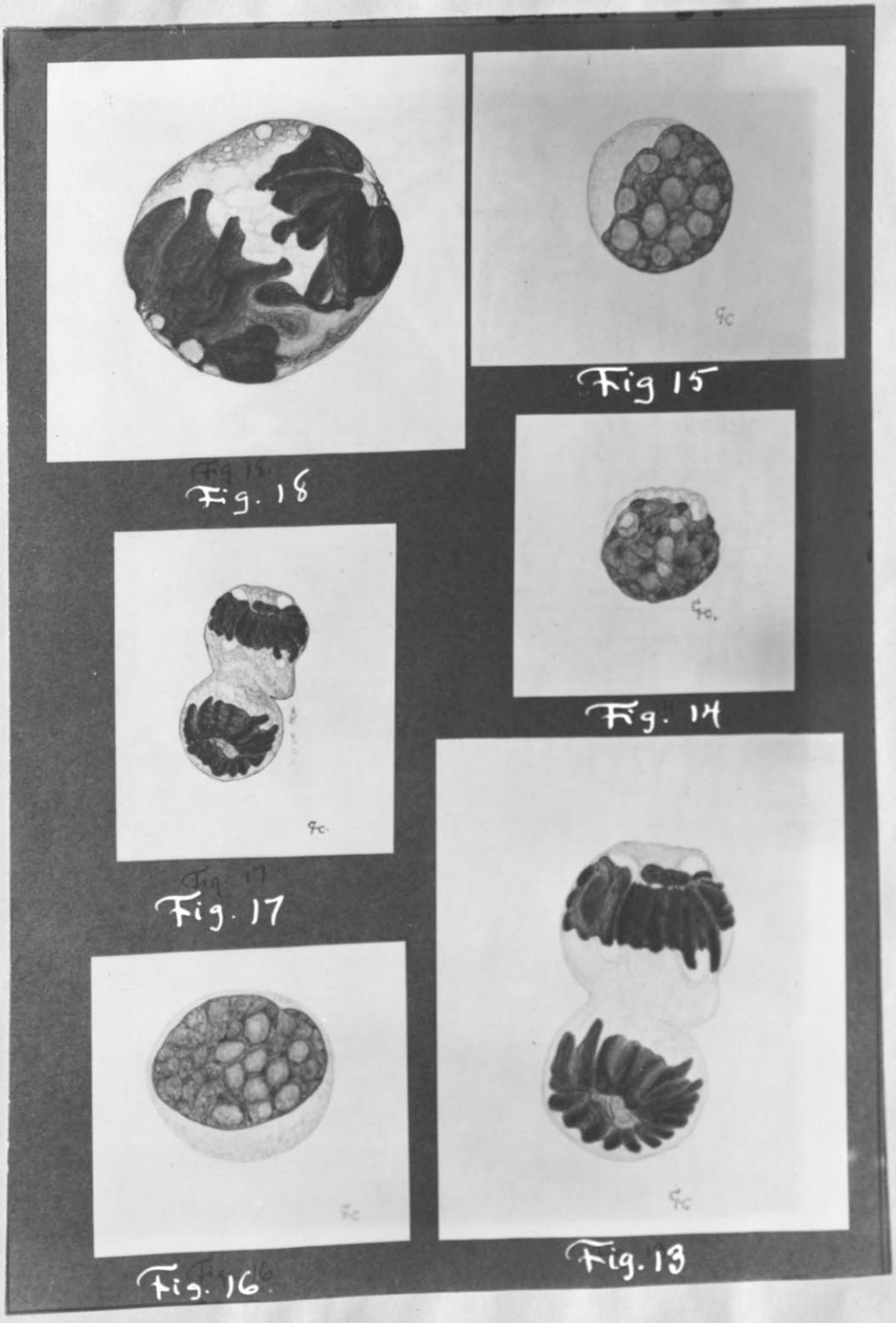


Fig. 18

Fig 15

Fig. 14

Fig. 17

Fig. 16

Fig. 13

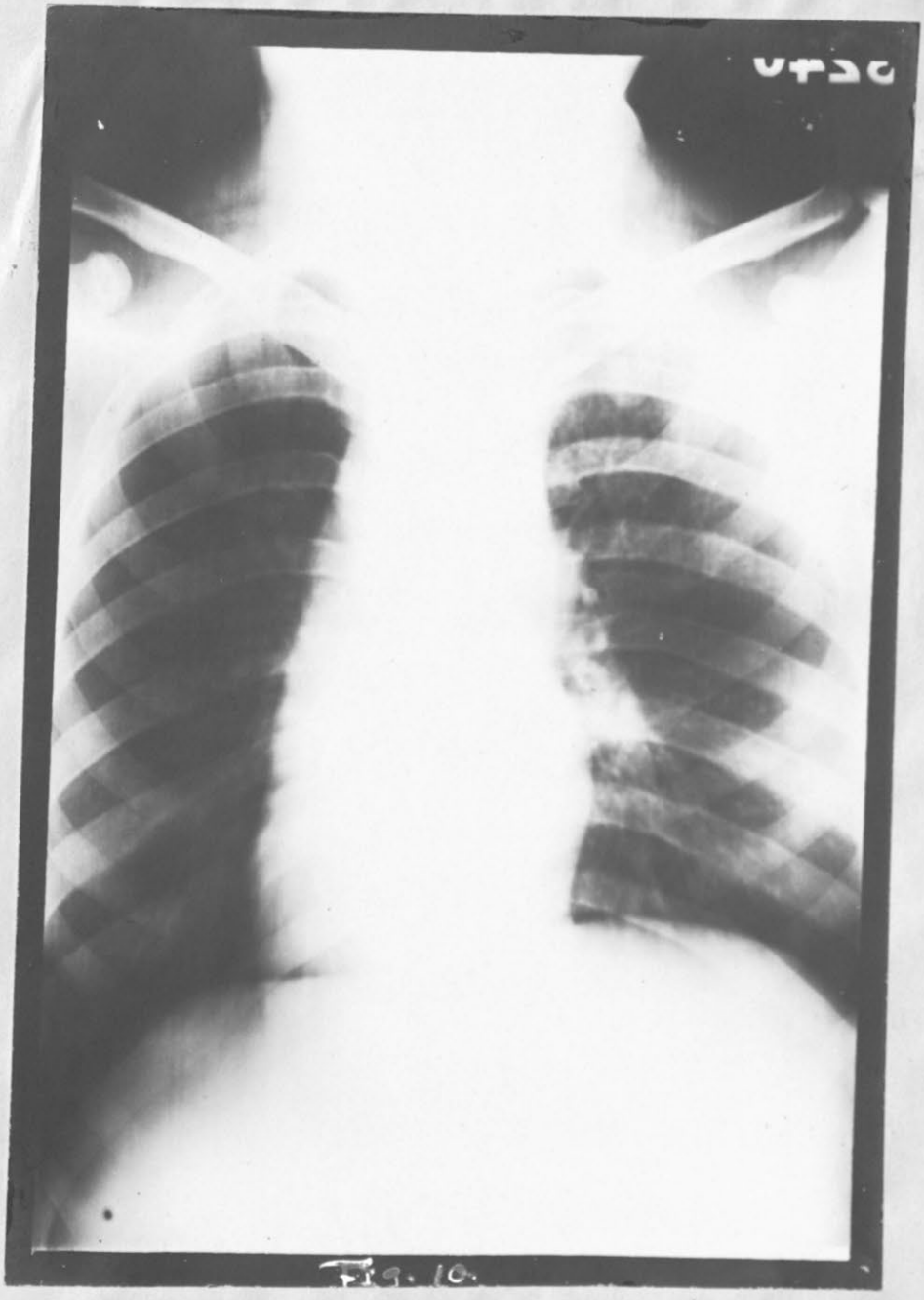


Fig. 10.

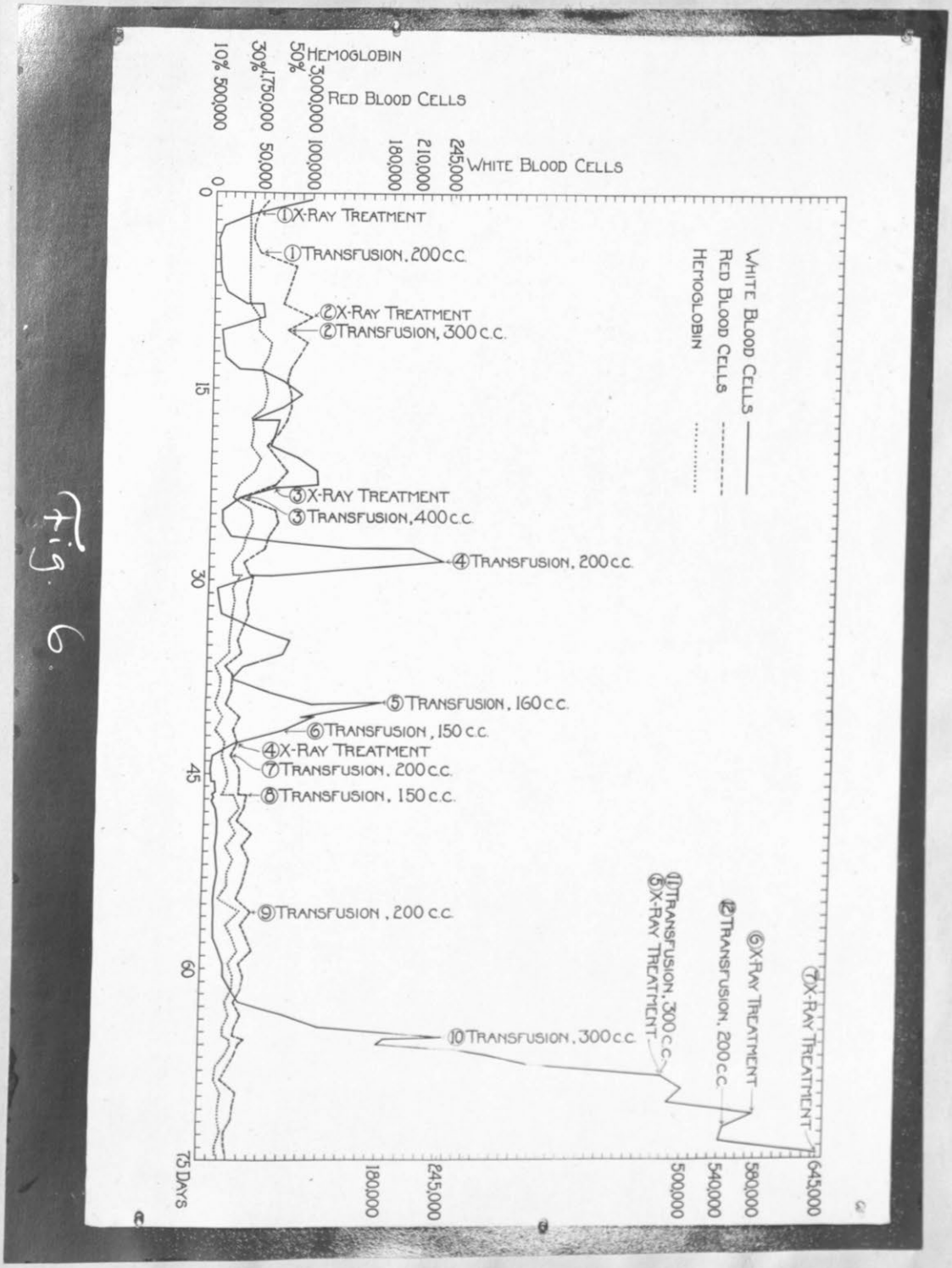

HEMOGLOBIN
RED BLOOD CELLS
WHITE BLOOD CELLS
10% 500,000
30% 1,750,000
50% 3,000,000
50,000
100,000
180,000
210,000
245,000
0
15
30
45
60
75 DAYS
①X-RAY TREATMENT
①TRANSFUSION, 200 C.C.
②X-RAY TREATMENT
②TRANSFUSION, 300 C.C.
③X-RAY TREATMENT
③TRANSFUSION, 400 C.C.
④TRANSFUSION, 200 C.C.
⑤TRANSFUSION, 160 C.C.
⑥TRANSFUSION, 150 C.C.
④X-RAY TREATMENT
⑦TRANSFUSION, 200 C.C.
⑧TRANSFUSION, 150 C.C.
⑨TRANSFUSION, 200 C.C.
⑩TRANSFUSION, 300 C.C.
⑪TRANSFUSION, 300 C.C.
⑤X-RAY TREATMENT
⑥X-RAY TREATMENT
⑫TRANSFUSION, 200 C.C.
⑦X-RAY TREATMENT
WHITE BLOOD CELLS ——
RED BLOOD CELLS - - - -
HEMOGLOBIN .....
180,000
245,000
500,000
540,000
580,000
645,000

Fig. 6.