Hematologic Study of Three Generations of a White Family Showing Elliptical Erythrocytes

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Under normal circumstances the morphology of the red blood corpuscles is so uniform that any deviation is looked upon as evidence of a pathologic state. Everyone is familiar with the striking variations in the size and shape of the erythrocytes in pernicious and severe secondary anemias in which a wide variety of abnormal red cells may be seen but without the predominance of any one form. This is not true for all blood disturbances, however, for instances are recorded in the literature in which there have been observed quite characteristic variations in the shape of the erythrocytes with a preponderance of one type of abnormal cell. In this category belongs sickle cell anemia and the more rarely observed instances of elliptical erythrocytes in the blood of normal persons. In these blood disturbances heredity is apparently an important factor.

The condition now known as sickle cell anemia was first described by Herrick (1) in 1910. A year later Washburn (2) recorded the second instance, also in a negro.

Cook and Meyer (3) who reported the third case in 1915 were the first to point out its familial nature. Emmel (4) studied the blood from the father of Cook and Meyer's patient and noted latent sickling of his erythrocytes. Mason (5) reporting the next instance in 1922 was the first to call the disease "sickle cell anemia" and to suggest its racial selectivity. With the publication of the work of Sydenstricker, Mulherin and Houseal (6) and of Huck (7) in 1923 came the first real understanding of this unusual type of anemia. Their investigations showed that the anemic syndrome characterized by sickling of the erythrocytes is relatively common and not, as previously supposed, a medical curiosity. Both demonstrated its constant familial character and apparent limitation to the black race. Their studies further indicated that sickle cell anemia is a definite clinical entity characterized by a clear-cut symptom-complex and by specific blood findings and anatomic changes. Since the appearance of the work of Sydenstricker and Huck many investigators have become interested in the disease as evidenced by the increasing number of reports in the literature of each succeeding year.

In negroes the sickling tendency is not rare. Mulherin and Houseal (8) state that Sydenstricker in a study of 1000 negroes found sickle cells in 0.6 per cent, while in an equal number of whites the anomaly was never observed. More recent investigators report a much higher incidence. Cooley and Lee (9) observed sickling in 7.5 per cent of 400 negroes, Graham and McCarty (10) in 7.2 per cent of 608 colored persons and Miyamoto and Korb (11) in 19 of 300 negroes (6.3 per cent). The last named authors found no abnormal cells in 100 white controls.

Much rarer are reports of elliptical red blood cells in both white and colored people. The first recorded instance of this anomaly is that of Dresbach (12) in 1904. His subject was a healthy mulatto male 22 years of age in whom 90 per cent of the red blood cells were elliptical in outline. The corpuscles averaged 4.1 μ. in width, 10.3 μ. in length and 2 μ. in thickness, with a ratio of width to length of 1:2.5. No family history was obtainable. A brother of the patient had normal erythrocytes. Dresbach and others who examined the blood believed that the condition was probably congenital in nature. In 1914 Bishop (13) reported a similar case. His patient was a man (color not stated),

(1) Herrick, James B., Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia. Arch. Int. Med. 6:517, 1910.

(2) Washburn, R. E., Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia. Virginia M. (Semi-Month.) 15:490, 1911.

(3) Cook, Jerome E. and Meyer, Jerome, Severe Anemia with Remarkable Elongated and Sickle-Shaped Red Blood Cells and Chronic Leg Ulcer. Arch. Int. Med. 16:644, 1915.

(4) Emmel, Victor E., A Study of the Erythrocytes in a Case of Severe Anemia with Elongated and Sickle-Shaped Red Blood Corpuscles. Arch. Int. Med. 20: 586, 1917.

(5) Mason, V. R., Sickle Cell Anemia. J. A.M.A., 79:1318, (October 14) 1922.

(6) Sydenstricker, V. P., Mulherin, W. A., and Houseal, R. W., Sickle Cell Anemia, Report of Two Cases in Children with Necropsy in one Case. Am. J. Dis. Child. 26: 132, (Aug.) 1923.

(7) Huck, John G., Sickle Cell Anemia. Bull. Johns Hopkins Hosp. 34:335, (Oct.) 1923.

(8) Mulherin, W. A., and Houseal, R. W., Sickle Cell Anemia from a Pediatric point of view. Tr. Sect. Dis. Child., A. M. A., p. 77, 1924.

(9) Cooley, Thomas B. and Lee, Pearl, The Sickle Cell Phenomenon. Am. J. Dis. Child. 32:334, (Sept.) 1926.

(10) Graham, George S. and McCarty, Sarah H., Notes on Sickle Cell Anemia, J. Lab. and Clin. Med. 12: 536, (March) 1927.

(11) Miyamoto, Kazuo, and Korb, J. H., Meniscocytosis (Latent Sickle Cell Anemia): Its Incidence in St. Louis. South, M. J. 20:912, (Dec.) 1927.

(12) Dresbach, Melvin, Science, 19:471, 1904.

*From the Department of Pathology, University of Oregon, Portland.

(13) Bishop, F. Warner, Elliptical Human Erythrocytes. Arch. Int. Med. 14: 388, 1914.

41 years of age, suffering from acute appendicitis. Routine examination of the blood revealed a polymorphonuclear leukocytosis, 5,400,000 red cells and 110 percent hemoglobin (Fleischl-Meischer). In stained smears there were many elliptical erythrocytes and repeated examinations over a period of several months showed that 75 to 80 percent were elliptical or distinctly elongated. Most of the elliptical cells measured about 13.0 by 5.0 microns. The possibility of mechanical distortion of the corpuscles was considered and eliminated. Suspecting that the abnormality might be hereditary, Bishop studied the blood of all available relatives of the patient consisting of the father, two sisters, and two nephews. Of these one sister, also in good health, exhibited the some blood picture. Bishop regarded this as strong evidence in favor of the condition being a congenital anatomical defect. More recently Huck and Bigalow (14) have described a poikilocy-

(14) Huck, John G. and Bigalow, Rena M., Poikilocytosis in Otherwise Normal Human Blood. (Elliptical Human Erythrocytes) Bull. Johns Hopkins Hosp. 34: 390, (Nov.) 1923.

tosis characterized by the presence of elliptical erythrocytes occurring in a healthy white woman 28 years of age. In the fresh preparations between 53 and 84 per cent of the corpuscles were elliptical or elongated, in hanging drop slides 59 to 70 per cent and in stained smears from 12 to 40 per cent. The average measurements of the cells varied from 12 x 5 μ. in the fresh preparations to 10 x 4 μ. in smears. The hemoglobin percentage, red and white cell counts and platelet counts were normal. A study of fourteen members of the subject's family distributed over four generations disclosed a similar condition in her mother. The authors feel that hereditary transmission, while not definitely established, is strongly suggestive. Huck and Bigalow were able to demonstrate that this was not an instance of sickle cell anemia since the abnormal corpuscles neither increased in number nor changed in form on standing as invariably occurs in sickle cell anemia. On the contrary the cells remained in the same state in which they were first observed until the preparations deteriorated. In Huck's experience with sickle cell anemia, in which more than 50 per cent of the corpuscles acquired bizarre forms on standing, there was an associated secondary anemia which was entirely lacking in this subject although 80 per cent of her cells were abnormal. Their observations show that such a poikilocytosis differs from sickle cell anemia in every respect save the hereditary factor apparently common to both.

Lawrence (15) has reported the

(15) Lawrence, John S., Elliptical and Sickle-Shaped Erythrocytes in the Circulating Blood of White Persons. J. Clin. Investigation, 5:31, (Dec.) 1927.

hematologic findings in a white woman presenting what the author believes to be most of the blood changes generally associated with sickle cell anemia, but which appear to us to conform rather to the elliptical cell anomaly described by Dresbach, Bishop, Huck and Bigalow and ourselves. His patient was a woman 32 years of age who came to the hospital complaining of disability in walking. She gave a history of soreness of the mouth, bleeding about the teeth for several years, bleeding hemorrhoids for five years and profuse menses lasting from seven to nine days. She was the mother of three children, two of whom were living. Her present illness began ten months before admission to the hospital with a respiratory infection which she thought was influenza, following which she had been tired and weak. The patient appeared pale and undernourished with a slight pallor of the mucous membranes. The erythrocyte count was 3,850,000, hemoglobin 45 per cent (Sahli) and white cells 8,900. In stained smears there was a moderate achromia with rare polychromatophilic cells. Most striking was the decided tendency of the erythrocytes toward sausage forms. The platelets were apparently normal as was the differential white count. In a fresh sealed preparation examined one hour after it was taken most of the erythrocytes were observed to be fairly uniform in size with only a few small and no very large forms. From 5 to 10 per cent of the corpuscles were definitely sickle or sausage-shaped, some showing blunt or rounded ends while others were pointed. On many of the abnormal cells were slender processes from 1 to 10 micra in length which appeared to be attached to the membrane of the cells. In the crescent forms the processes were more marked and often free in the plasma. Rod-shaped bodies thought to be broken-off processes of the abnormal red cells were observed in many leukocytes. No nucleated red cells or myelocytes were found. A brother, one sister and a niece of the patient exhibited the same abnormality of the erythrocytes. Unfortunately ignorance and superstition on the part of the family made impossible any further study of either the patient or her relatives. In a control series of 102 normal white adults sickle-shaped, sausage and filamentous red cells were found three times. In addition evidence of sickling was noted in 6 adult whites and 4 colored adults suffering from various diseases. Definite evidence of latent sickling was lacking in the white subjects but was present in the negroes. Lawrence is uncertain as to the diagnosis of sickle cell anemia in the white woman because no proof of negro blood could be obtained.

Author's Observations

The family studied consists of Mr. and Mrs. A. Kl., their eight children and six grandchildren. (Chart 1) With the exception of one daughter (Adriana) living in Portland all reside near Missoula, Montana. The distance separating the two cities has made impossible a detailed study of any member except the above mentioned daughter, although one of us (W. C. H.) visited the remainder of the family and from the father, whose blood exhibited the presence of abnormal erythrocytes, obtained the following family history:

So far as known both parents are of pure Dutch stock. There has been no intermarriage with persons from

the Dutch colonies and prior to the emigration of Mr. and Mrs. Kl. to America none of the family had ever been outside the boundaries of Holland. For generations the men were farmers and lived in the village of Zevenhuizen, near Amsterdam. The father knew both his paternal and maternal grandparents and recalls nothing unusual in their color or facial characteristics. On his mother's side a number of aunts and uncles died from unknown causes before reaching middle age. His mother died at 40 from childbirth, his father at 75 from "old age." Two brothers and two sisters are alive and well.

Both Al. K. and his wife enjoy excellent health and neither has ever been seriously ill. In appearance the parents are decidedly Teutonic as are also most of their children and grandchildren. All are fair skinned and exhibit none of the facial characteristics of the black race.

The only member having outspoken symptoms of anemia is Adriana, whose residence in Portland has enabled us to make repeated blood examinations over a period of several months. She gives the following personal history:

Adriana N. Age 25. Married. Registered Nurse.

Past History

The patient was born in Holland and there spent the early years of her childhood. Her mother states that while she was still quite young an ulcer appeared on her right leg. The lesion was treated by a physician in Amsterdam and healed without difficulty. The cause of the ulcer was undetermined. In childhood she had measles, whooping cough, bronchopneumonia and an attack of arthritis involving the ankle joints. Following this she enjoyed good health but was never robust. In 1918 she had a severe attack of influenza and since then has always felt weak. Upon admittance to a nurses' training school in 1920 it was found that she was anemic, the hemoglobin at that time being only 60 per cent. She was allowed to enter training, however, and although anemic and always "tired out", finished in the usual three years. In 1923 while employed in the laboratory of a Portland hospital a blood examination revealed 3,000,000 red cells with 69 per cent hemoglobin (Dare). The technician who examined the blood noted the presence of abnormally shaped erythrocytes but no further investigation was made at that time.

Prior to tonsillectomy in 1923 the patient suffered from recurrent attacks of tonsillitis. For the past three years she had had bilateral maxillary sinusitis. Two years ago a pyelitis developed which did not clear up for nearly a year.

For a long time she has experienced intermittent attacks of severe pain in the left hypochondrium and gastric distress described as "bilious attacks". At times she feels very well the first part of the day but is tired out by night especially when working. In spite of this she has continued to do her housework and part-time nursing. Numbness and tingling of the extremities has been noted for several years. The patient never sought treatment for the anemia.

Menstruation began at 20 and was irregular until after marriage two years ago. The periods now occur every 28 days, usually lasting 4 days. As a rule the flow is not excessive. There have been no pregnancies.

Present History

Our attention was first drawn to the case in October, 1927, when one of us (W. C. H.) was asked to examine the differential smear of the patient's blood. At this time (Oct. 3) Mrs. N. was able to work although she felt tired and weak and appeared distinctly anemic.

Physical Examination.

(Dr. Karl P. Moran)

October 21, 1927.

The patient is well developed and well nourished. There is a distinct cutaneous pallor.

Eyes: sclerae clear; conjunctivae pale; pupils react to light and accommodation.

Ears and nose: negative.

Mouth: mucous membrane pale; several devitalized teeth; tonsils absent; pharynx negative.

Neck: anterior cervical lymph nodes slightly enlarged; thyroid palpable but is soft and not nodular.

Thorax: heart and lungs normal.

Abdomen: area of liver dullness is within normal limits; slight tenderness over gall bladder region; outlines of spleen cannot be percussed or palpated.

Extremities: old scar 1.5 by 2.5 cms. on medial surface of right calf; no palpable enlargement of axillary or epitrochlear lymph nodes.

Pelvic: complete retroversion of uterus; adnexa negative.

Reflexes: all are present but are quite sluggish.

Blood pressure: 118 systolic, 70 diastolic.

Temperature: 98.6° F.

Hematologic Findings

Examination of stained smears of Mrs. N.'s blood revealed a striking abnormality in the shape of the corpuscles with distinctly elliptical or oval forms predominating. Less numerous were much elongated rod-like or curved sausage-like forms and pear-shaped, sickle-like and other irregularly shaped poikilocytes, often having one or more thin filamentous processes with knob-like ends. Only a small percentage were round. Repeated counts of one thousand cells gave the following average percentage of the different varieties: oval 84.0%, round 6.7%, elongated 5.8%, irregular processed forms 4.5% (See Chart II). Achromia was lacking but some cells exhibited polychromatophilia.

Sealed fresh preparations of the whole blood under number O cover glasses were set up, left at room temperature and examined immediately and at frequent intervals until the erythrocytes disappeared, usually within four to seven days. In these preparations the oval form was approximately 10 per cent less than in stained smears while the elongated cells were proportionately increased. Other varieties showed less variation. (See Chart II) The figures are based on daily counts of one thousand cells made over a period of a week, using the same prep-

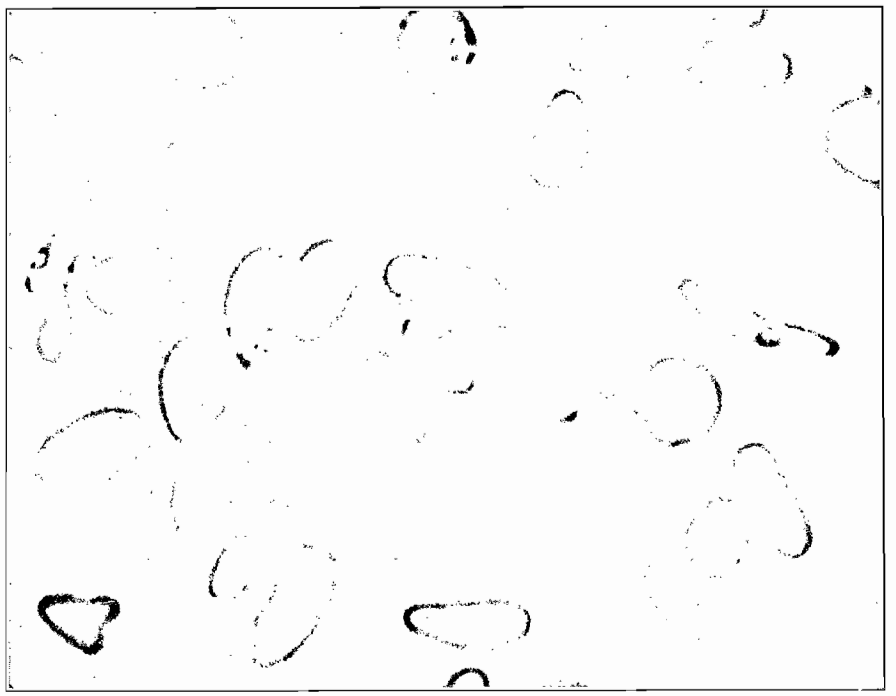

FIG. 1. High power microphotograph from sealed fresh preparation of blood of Adriana N. In this field elliptical shaped erythrocytes predominate.

aration and as nearly as possible the same portions of the slide. The lack of any appreciable morphological change definitely ruled out the possibility of sickle cell anemia. At times the long filamentous processes were seen to break off and move about freely in the serum. The abnormality of the corpuscles persisted in specimens washed in physiological salt solution and replaced in the patient's serum or that from normal individuals. It also persisted in cells in physiological saline. Her serum produced no deformity in the erythrocytes of normal persons. Phagocytosis of red blood cells was not observed in fresh specimens and was seen only twice in stained smears. At an incubator temperature of 54° C. all erythrocytes in fresh preparations assumed the discoid form within thirty minutes.

On two occasions the fragility test showed hemolysis beginning at 0.45 and complete at 0.36. Both the qualitative and quantitative van den Bergh tests have been repeatedly negative. Blood cultures have failed to show a growth of bacteria. Further details of the blood findings will be found in Chart III.

TREATMENT

When first seen by us on October 3, 1927, the patient was weak and definitely anemic. Treatment was begun on October 10th. The good results obtained by Larsell and others (16) in

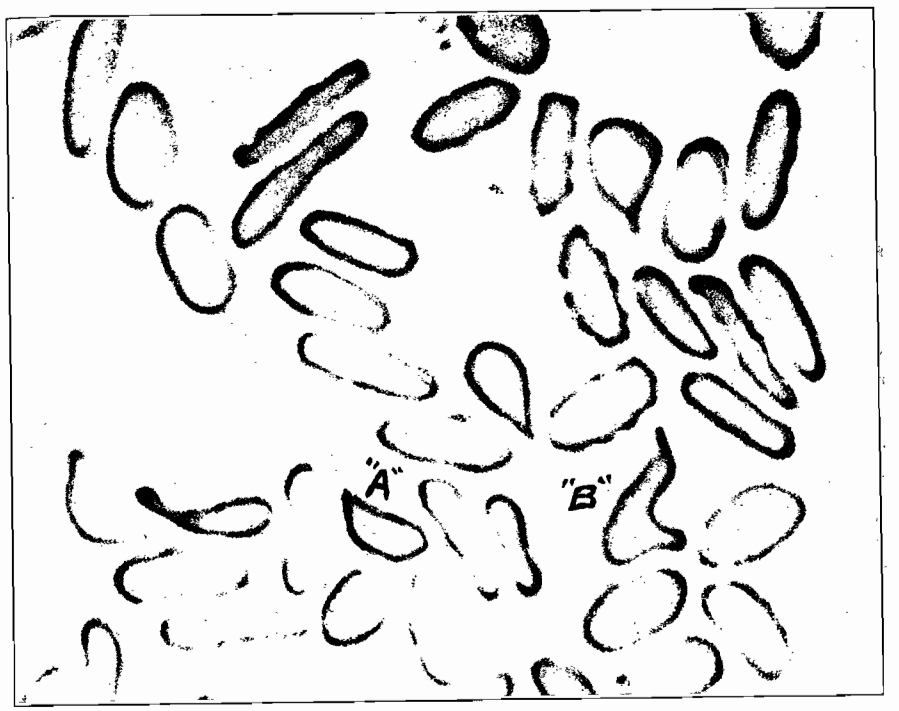

FIG. 2. Another field from the same slide as Figure 1. In this area elongated erythrocytes are particularly numerous At "A" is a corpuscle showing a long filamentous process. "B" is an unsually irregular poikilocyte.

(16) Larsell, Olof., Jones, N. W., Phillips, B. I., and Nokes, H. T., The Hematopoietic Effect of Nuclear Extractives in Anemia. J. A. M. A. 90: 75, (Jan. 14) 1928.

the treatment of anemias with the nuclear extractives of liver made us anxious to try this form of therapy, especially when we found that liver had not been used in the treatment of any of the reported cases of such blood disturbances. The nuclear extractives prepared in Dr. Larsell's laboratory are put up in 0.5 gm. capsules, six of which represent the nuclear material from one-half pound of liver. From the beginning the patient has taken, except for rest periods of a week or two, two capsules t.i.d. The results, while not as striking as in secondary anemias, have been encouraging. The hemoglobin has increased from 62 to 80 per cent and the erythrocyte count from 3,750,000 to 4,560,000. Subjective improvement has been out of all proportion to that in the blood picture. While under treatment the patient has carried on her household and nursing duties, gained 12 pounds in weight, and at present (April, 1928) feels stronger than she has for years. As the anemia decreased the gastrointestinal symptoms entirely disappeared and have not recurred. The pallor of the skin and mucous membranes is much less marked than formerly.

Only brief mention need be made of the blood and physical examinations of the remaining members of the patient's family.

Chart I shows the incidence of the abnormality in the entire family group. It is rather remarkable that all members of the second generation exhibit varying degrees of the anomaly. The diagnosis was made by setting up sealed fresh preparations of the blood from each individual and examining the slides at intervals over a period of 4 days. The erythrocyte count and hemoglobin are lower (Chart IV) than might be expected at the altitude of Missoula (3223 feet). However, with the exception of Johanna S. and William Kl., none of the family have symptoms of anemia. All others appear strong and healthy. Because of the limited time at our disposal physical examination was not done. Discoloration of the sclerae was carefully looked for but was not observed. None of the family give a history of leg ulcer.

Discussion

The abnormality of the erythrocytes in this family is obviously hereditary since it occurs in one parent, all of his children and three of his six grandchildren. The incidence is greater than in Huck and Bigalow's group in which only two out of fourteen persons distributed over four generations had abnormal erythrocytes. The present study confirms Huck's suspicion of hereditary transmission of this condition. In our family, however, both sexes transmitted the anomaly, whereas in Huck's group only females gave evidence of its presence. Bishop's and Huck's subjects enjoyed good health and their blood was normal in every respect except for the abnormality of the erythrocytes. In our family the red cell counts and hemoglobin figures are generally low in spite of the apparent good health of the subjects. The one member whom we had the opportunity of studying carefully had a distinct anemia without a demonstrable cause. The role of the erythrocytic anomaly as a cause of the anemia is problematical, but the low red cell count and hemoglobin shown by so many of the group who were in apparent good health suggests the possibility of some hematopoietic disturbance.

A striking similarity exists between case L. B. S., described by Lawrence, and our patient, Mrs. A. N. His description and microphotographs of the blood are almost identical with the findings in our patient. His patient also had a secondary anemia but with more obvious causes than ours.

During the course of the study we were fortunate enough to observe an instance of the sickling tendency in a negro who was also suffering from multiple myeloma. A comparative study of the blood of the white and colored patients leaves no doubt that a difference exists between them. The erythrocytes of the negro sickled in the manner described and illustrated by everyone who has written on the subject of sickle cell anemia, while in the white patient the long spine-like processes at the ends of the cells were either lacking, or when present were blunted or rounded. In the gas chamber of Hahn and Gillespie (17) the

CHART I

OCCURRENCE OF ELLIPTICAL CELLS IN THREE GENERATIONS OF A WHITE FAMILY

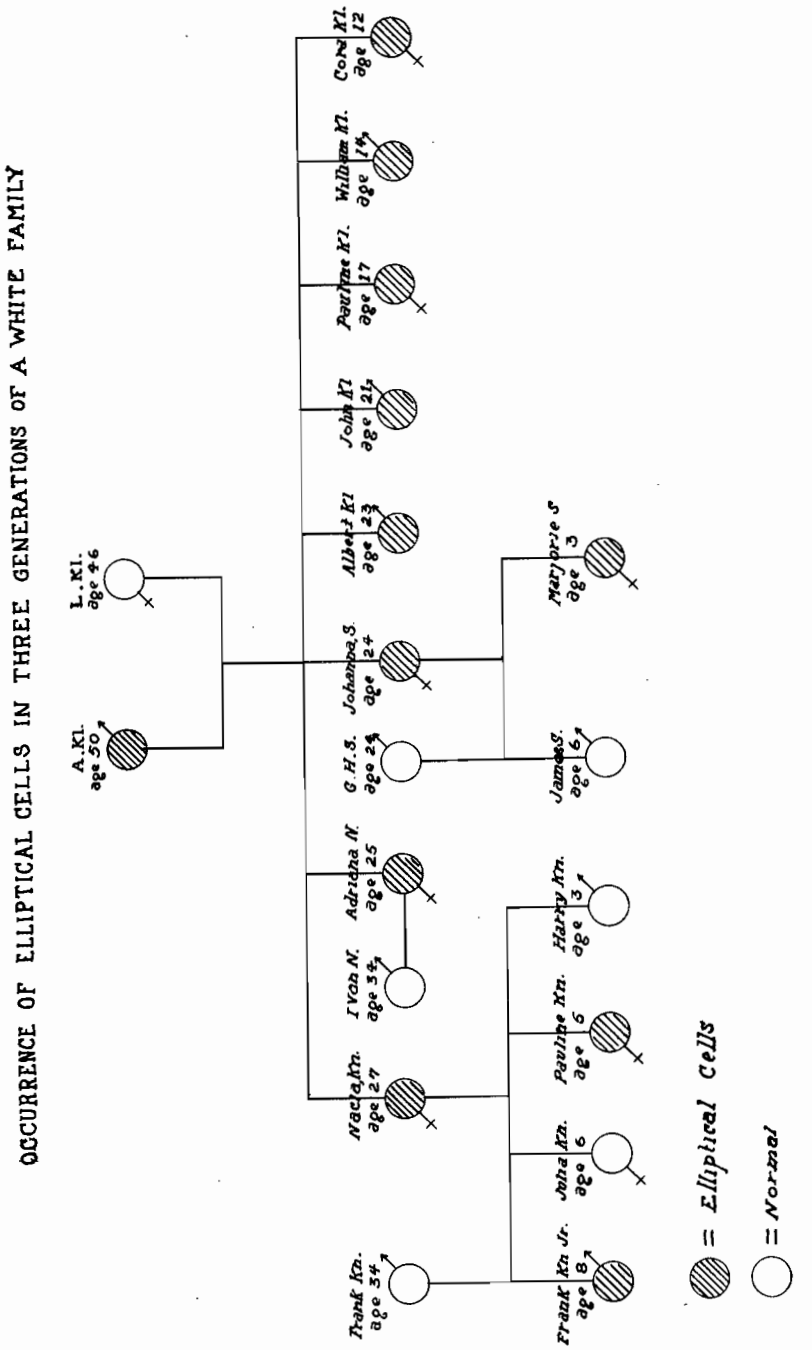

CHART II

Shape of corpuscles	Stained smears	Fresh Preparations	Average dimensions of cells
Round	6.7%	2.4—11%	9 μ.
Oval	84.0%	72.1—76.8%	7 x 11 μ.
Elongated	5.8%	10.0—21.2%	4.8 x 13.4 μ.
Processed (irregular)	4.5%	4.9— 7.3%	Variability too great to give average figures

Types of erythrocytes occurring in the blood of Adriana N.

(17) Hahn, E. Vernon, and Gillespie, Elizabeth B., Sickle Cell Anemia. Report of a Case Greatly Improved by Splenectomy. Experimental Study of Sickle Cell Formation. Arch. Int. Med. 39: 233, (Feb.) 1927.

negro's erythrocytes sickled rapidly under the influence of carbon dioxide gas and reassumed the discoid form when oxygen was passed into the chamber. Such a change was lacking in the blood of the white patient. On passing carbon dioxide into the chamber a few cells became bilobed but nothing further developed.

The condition is apparently identical with the elliptical cell anomaly in negroes and whites described by Dresbach, Bishop and Huck and Bigalow. We are in full agreement with Huck and Bigalow that this condition may be differentiated from sickle cell anemia by the fact that the corpuscles are abnormal in outline on immediate examination and do not require a time interval for development as in sickle cell anemia. Careful counts over a period of several days have failed to disclose any appreciable change in the form or number of abnormal erythrocytes.

SUMMARY

1. A rare familial and hereditary abnormality of the red blood cells occurring in members of three generations of a white family is described.
2. The abnormality is characterized by the presence of elliptical, elongated and irregular shaped erythrocytes present in the circulating blood of the affected individuals. In sealed fresh preparations of the blood no time interval is required for the development of the abnormal forms nor do these increase in number or show alteration in shape on standing as occurs in sickle cell anemia.
3. In contrast with two previously reported studies of this kind several of our subjects were more or less anemic.
4. One member of the family having well marked anemia and treated exclusively with the nuclear extractives of liver has shown an appreciable improvement in the hematological and clinical picture.

CHART III
(Adriana N.)

Date	10/6/27	10/10/27	10/23/27	11/12/27	12/12/27	1/6/28	2/22/28	3/22/28
Hb (Sahli)	62%	63%	65%	71%	76%	79%	68%	80%
R.B.C.	3,750,000	3,850,000	3,936,000	4,016,000	4,350,000	4,480,000	3,500,000	4,560,000
C. I.	0.8	0.79	0.76	0.85	0.83	0.86	0.94	0.86
Anisocytosis	Moderate	Moderate	Moderate	Moderate	Slight	Slight	Moderate	Slight
Poikilocytosis	Marked	Marked	Marked	Marked	Marked	Marked	Marked	Marked
Nuc. R.B.C.	1 Normoblast	1 Normoblast	1 Normoblast	none	none	none	none	none
W.B.C.	....	9,400	5,600	8,400	14,400	11,400	5,100	8,400
P.MN.	78%	62%	69%	66%	76%	....	67%	72%
P.M.E.	1%	1%	0%	0%	2%	....	0%	1%
PM.B.	0%	0%	0%	0%	0%	....	0%	0%
L. Lymphs	2%	1%	2%	3%	2%	....	2%	1%
S. Lymphs	16%	%1٤	29%	30%	20%	....	26%	24%
Other W.B.C.	none	none	none	none	none	....	none	none
Trans.	3%	5%	0%	1%	0%	....	5%	2%
Remarks	Before treatment	Treatment started	Under treatment	Under treatment	Under treatment	Under treatment	Menorrhagia	Under treatment

CHART IV

Name	Sex	Age	Date	R.B.C.	Hb. Sahli	Abnormal R.B.C.	Leuko-cytes
A. Kl.	M	50	10/30/27	4,118,000	96%	Many rod, oat and sickle-like forms	6,840
Mrs. L. Kl.	F	46	10/30/27	5,544,000	108%	none	9,200
Nacia Kn.	F	27	10/30/27	3,760,000	84%	Few rod and sickle-like cells	8,860
Johanna S.	F	24	10/30/27	3,304,000	85%	" "	7,700
Albert Kl.	M	23	10/30/27	4,280,000	94%	" "	6,620
John Kl.	M	21	10/30/27	4,224,000	84%	" "	10,400
Pauline Kl.	F	17	10/30/27	2,936,000	79%	Many elongated, pear-shaped and sickle cells	8,800
William Kl.	M	14	10/30/27	3,056,000	74%	" "	7,900
Cora Kl.	F	2	10/30/27	3,320,000	83%	" "	11,600
Frank Kn. Jr.	M	8	10/31/27	3,900,000	85%	Few elliptical and rod forms	9,700
Julia Kn.	F	6	10/31/27	.....	....	none	....
Pauline Kn.	F	5	10/31/27	4,600,000	86%	Very few oval and rod-like cells	....
Harry Kn.	M	3	10/31/27	.....	....	none	....
James S.	M	6	10/31/27	.....	....	none	....
Marjorie S.	F	3	10/31/27	4,640,000	96%	Few oval cells	15,200