in the peritoneal cavity. In such instances a sufficient portion of the bowel below the colostomy can be left, which when closed off can be brought out of the operative incision and anchored to the peritoneum. This area can be drained drawing the muscles and fascia over it. It is for the same reason in doing an anterior or abdominal resection where a stump of the rectum is left in a blind sacral cavity that we think it very important to put a perineal drain up to the stump to take care of possible infection. With the avoidance of direct suture of the colon and withdrawal of blind ends from the peritoneal cavity, peritonitis should be a rare complication.

SICKLE CELL ANEMIA*

A Report of Eight Cases, One With Necropsy

BY JOHN C. CORRIGAN, M.D.,† AND IRVING W. SCHILLER, M.D.†

SICKLE cell anemia, so far as we know, has not been the subject of a report from New England. In the past year, eight cases of this disease have been observed in the Boston City Hospital. This blood dyscrasia may present protean manifestations and has been known to masquerade under such diagnoses as rheumatic fever, tuberculosis, acute appendicitis, syphilis, and obscure anemias. Because these conditions are seen daily by clinicians, we feel that attention may properly be called to sickle cell anemia as worthy of consideration in the differential diagnosis of the more perplexing cases. In a few of these patients a simple blood examination may establish the diagnosis and save a large number of elaborate laboratory procedures. A drop of the patient's blood drawn on a cover slip and inverted on a glass slide and sealed with vaseline may demonstrate the alteration in the shape of the red cells known as "sickling".

In 1910 James B. Herrick[1] reported a case because of unusual blood findings in which "the shape of the reds was very irregular, but what attracted attention was the large number of elongated sickle-shape and crescent-shape forms." During the next thirteen years three similar cases with sickled erythrocytes were described in the literature by Washburn[2], Cook and Meyer[3], Emmel[19] and Mason[4], and to this last observer we owe the term "Sickle Cell Anemia." It was not until 1923 when two papers were published by Sydenstricker et al[5] and Huck[6] that attention was called to the importance of the condition, and established sickle cell anemia as a definite disease entity. Since this time an increasing number of noteworthy articles and case reports have appeared in the literature[7, 8, 9, 10, 30, 31, 32, 34].

The term "Sickle Cell Anemia" has been used in a very broad sense to include, not only those individuals who have evidence of the disease, but also a larger group of individuals apparently in good health who present no abnormality other than the phenomenon of sickling under certain conditions. About seven per cent of all Negroes fall into this group[11, 12, 13]. We prefer to designate this latter group as having the "Sickle Cell Trait" or "Sicklemia," and reserve "Sickle Cell Anemia" for those with definite evidence of the disease either in the latent or active form.

This report is concerned with eight cases of sickle cell anemia.* The clinical notes on these patients are given in the following case reports: the blood studies are summarized in chart I. On the basis of these and the other cases previously reported a discussion of the disease is given.

CASE REPORTS

CASE I. A 23-year-old colored female was admitted to a Surgical Service for excision and drainage of an abscess over the sternum of four months' duration. So far as she could recall, she had always been in poor health. She had been subject to frequent chest colds and had had numerous attacks of muscle and joint pains. She had had chronic leg ulcers over a period of four years. On admission to the hospital, the abscess was incised and creamy pus obtained. She was first seen by us because of anemia and "cardiac condition" and she was transferred to the Third Medical Service.

The patient had always been cared for by her aunt, and attempts at obtaining an accurate family history were always unsuccessful. Known contact with tuberculosis was denied. "All diseases which she suffered in childhood were very severe." She had no operations or injuries. Catamenia had always been irregular since onset at 19 years.

Examination disclosed poor general development and marked malnutrition. The breasts were underdeveloped, and pubic hair almost absent. She showed distinct pallor, most marked in conjunctivae and mucous membranes. Her sclerae were of greenish-yellow tinge. The tonsils were moderately enlarged. The chest was emphysematous and both lungs showed areas of consolidation scattered through the bases, with many fine moist râles throughout the patches. The apices were clear. The heart was enlarged to the left and right. A loud blowing systolic murmur was heard at the apex and the pulmonic second sound was abnormally accentuated. There were two large incisions over the sternal abscess, through which purulent material was draining. The liver extended three fingerbreadths below the margin of the ribs. The spleen could not be felt. External genitalia were infantile in character, and the uterus was very small. A large ulcer was present over the lower portion of the right leg, and there were two large ulcers over the malleoli of the left leg. There was lymphadenopathy in the cervical, epitrochlear, and inguinal regions.

Laboratory: Blood smear (Wright's stain) showed

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*The patients in our series who showed only the sickle cell trait will be included in a subsequent communication.

BLOOD CHART I—CASES I TO VIII

Case No.	Type of Case	R. B. C.* millions per cu. mm.	Hemoglobin (Sahli)† per cent	Color Index	Nucleated R. B. C.‡	Reticulocytes per cent	W. B. C. thousands per cu. mm.	Differential White Cell Count						Sickling in Wet Preparations					
								P. M. N.	P. M. E.	P. M. B.	Lymphocytes	Monocytes	Myelocytes	Sickling on stained preparation per cent	At once per cent	4 hrs. per cent	12 hrs. per cent	24 hrs. per cent	Reversal of Sickle Cells to normal
		1.6	30	.9	6	15	13.4	49	1	0	37	11	3	2	20	20	30	30	7 days
		1.3	30	1+	4	33	25.5	47	0	1	40	2	10	8.4	20	60	60	80	6 days
		1.4	24	.9	3	34	23.6	57	3	1	23	2	14	8.2	80	100	100	100	7 days
		1.1	23	1+	4	21	30.0	67	0	1	20	6	6	6	40	75	100	100	5 days
		.87	20	1+	4	15	21.0	58	6	0	35	0	1	2.1	100	100	100	100	4 days
I	Active	.73	18	1+	12	40	32.0	46	4	2	42	6	0	8	75	100	100	100	21 days
		1.1	22	1	8	46	18.0	65	0	1	22	6	6	5	40	50	75	100	3 days
		.93	20	1+	8	12	19.5	71	8	0	20	0	1	5	100	100	100	100	3 days
		.74	19	1+	8	26	20.0	68	2	0	28	2	0	8.3	50	75	90	90	21 days
		1.1	27	1+	8	39	22.0	72	5	0	20	3	0	6.2	100	100	100	100	6 days
		1.6	35	1+	5		36.0	18	0	0	80	0	0	4.0	8	25	80	100	15 days
II	Active	2.2	44	1.0	6	8	42.0	57	1	2	33	7	0	5.5	18	40	60	90	5 days
		2.9	55	0.9	12	11.2	11.4	36	1	1	55	3	4	5.8	12	20	60	75	3 days
		3.0	45	0.7	15	15.0	19.0	31	1	0	61	5	2	0.6	25	40	80	100	6 days
		2.4	50	1+	35		60.0												
III	Active	3.2	55	0.8			22.3												
		3.8	59	0.7	5	6.0	18.3	43	4	0	43	10	0	0.1	2.0			100	14 days
IV	Latent	4.6	68	0.7	0	2.0	5.3	48	3	1	44	3	1	0	0			75	5 days
V	Latent	4.4	65	0.7	0	3.0	8.9	63	1	0	30	4	2	0.1	0			75	4 days
VI	Latent	4.8	75	0.7	1	2.0	11.2	40	0	0	54	5	1	0.2	0.2			100	6 days
		2.9	60	1+	8	12.0	14.3	44	5	0	39	12	0	0.6	0.4			100	12 days
VII	Active	3.9	45	0.6	3	10.0	12.0	40	9	1	38	12	0	0.5	2.0			100	6 days
VIII	Latent	4.6	80	0.8	0	0	6.9	33	4	1	48	14	0	0	0			75	8 days

*The erythrocytes on stained preparations in cases I, II, and III showed moderate to marked anisocytosis and poikilocytosis and slight punctate basophilia; in case VII slight anisocytosis and poikilocytosis.

†100 per cent is equivalent to 15.6 Gm. of hemoglobin.

‡The figures given in this column represent the number of nucleated red blood cells seen in doing a differential count of two hundred white blood cells.

sickle-shaped erythrocytes. The other blood findings are given in abstract in chart I. Additional laboratory data are as follows: icteric index 35 to 38; van den Bergh positive in the indirect phase; bilirubin 1.8 mgm. per 100 cc.; blood non-protein nitrogen 33 to 38 mgm. per 100 cc.; total plasma protein 6.8 Gm. per 100 cc.; blood calcium 7.8 mgm. per 100 cc.; blood phosphorus 4.5 mgm. per 100 cc. Bleeding and clotting time were normal. Fragility test of erythrocytes was normal on one occasion and later

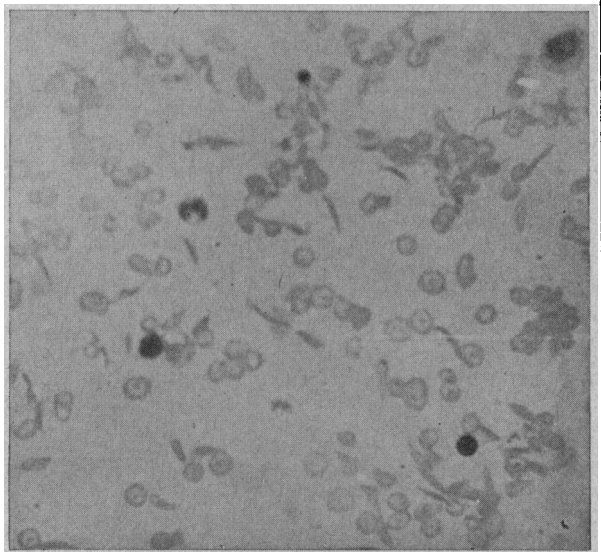

FIGURE 1.* (Case I.) Stained blood preparation (Wright's stain).

increased. Eight blood cultures were negative. Urinalyses always showed heavy trace of albumin, few white cells, and an occasional red cell and granular cast. Urobilin test on urine was strongly

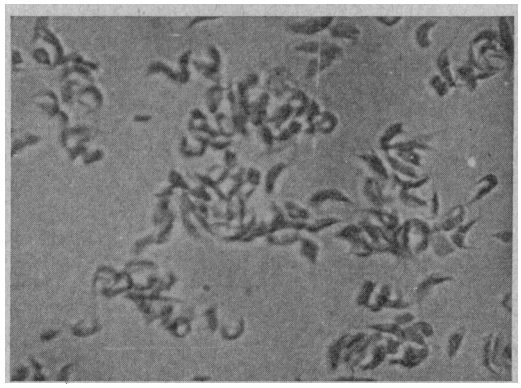

FIGURE 2. (Case 1.) Moist blood preparation, photomicrograph taken after standing twenty-four hours at room temperature, showing 100 per cent sickling.

positive. Gastric analysis showed no free hydrochloric acid one hour after histamine stimulation. Serological tests: (patient febrile) Kahn, positive three times, Hinton doubtful once, positive twice, Wassermann negative. X-rays of chest showed consolidation in lungs, cardiac enlargement, periostitis of bone beneath leg ulcer, general bone atrophy and trabeculation characteristic of sickle cell anemia. Dark field examination of ulcers negative; biopsy by Dr. Harold E. MacMahon showed non-specific chronic inflammatory tissue. Electrocardiogram was within normal limits.

*We are indebted to Raymond Yeaton, M.S., Tufts College, for the photomicrography.

Progress: Her course on the ward was characterized by marked diurnal swings in temperature and progressive emaciation until death during the eighteenth week. At times there was oozing from the gums and epistaxis. She complained of pains in her knees and ankles. On three occasions there were severe abdominal crises in which vomiting was the most striking feature. Examination of the abdomen at these times showed slight generalized tenderness but no spasm. The liver remained palpable throughout, but the spleen was never felt. The ulcer over the sternum became chronic, but x-rays of the sternum and probing failed to give any evidence of osteomyelitis. Her lungs became generally involved with patches of consolidation and coalescence at the bases. A non-productive cough was frequently troublesome. Two weeks before death she had a generalized convulsion, but there were no subsequent neurological signs.

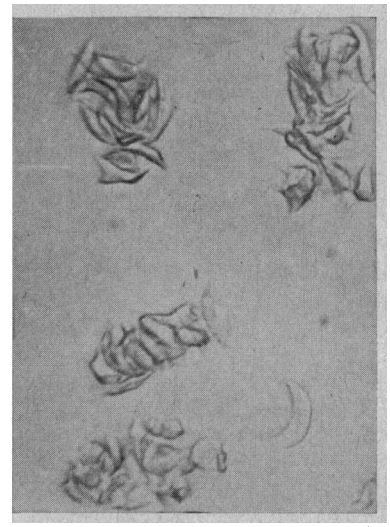

FIGURE 3. (Case 1.) Moist blood preparations showing clumping of sickled cells, a phenomenon frequently observed.

Therapy: Patient received four blood transfusions. Twenty-one consecutive daily injections of liver extract 343 (N.N.R.) intramuscularly showed no alteration in her blood picture. She was given iron and ammonium citrate 8-12 Gm. daily for a long period. Spleen extract (Armour)* and bone medullary extract (Armour)* were apparently ineffective. High-vitamin and high-mineral diet with profuse quantities of accessory vitamins A, B, C, D, and E were given in the form of Haliver oil, Vegex, fruit juice, etc. She also received ultraviolet radiation, but none of these procedures produced any change in the x-rays or alterations in her blood calcium studies.

During the last week she was profoundly weak, and slowly drifted off to death.

Postmortem Examination†

By William H. Holtham, M.D.,
Department of Pathology, Boston City Hospital

The autopsy was performed 15 hours after death. The body was poorly developed and extremely emaciated. A small sinus, situated over the third interspace, just to the right of the sternum, was draining thick, purulent material. Large superficial ulcers of the skin were present over the ankles.

The heart weighed 360 grams and showed mod-

*We wish to thank Armour and Co. for supplying this material.

†Abstract of necropsy findings; further studies with photomicrographs to be reported in detail in subsequent communication.

erate hypertrophy of both ventricles. Extensive caseous tuberculosis involved the mediastinal, hilus, aortic, mesenteric, and pelvic lymph nodes. Numerous caseous nodules were scattered throughout the lungs. A few were found in the kidney. A large retroperitoneal tuberculous abscess was located anterior to the sacrum with involvement of the fifth lumbar and first sacral vertebra and the intervening disc. Tuberculous ulcers were found in the ileum with small tubercles scattered over their serosal surfaces.

The spleen, greatly reduced in size, weighed only 0.87 grams, and had a pale, wrinkled, greyish-white surface. The splenic artery diminished progressively in size, with thickening of the wall and narrowing of the lumen, as it approached the hilus of the spleen. On sectioning the spleen, many small foci of calcification were encountered. The surface had a pale, brownish-grey, fibrous appearance and normal markings were absent.

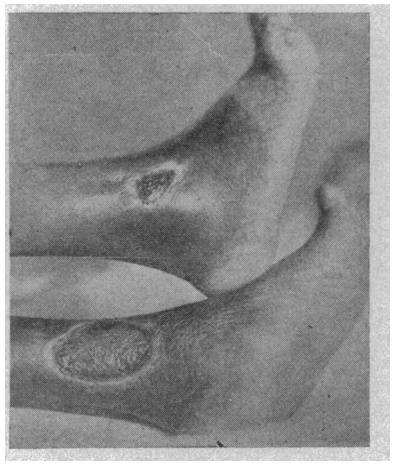

FIGURE 4. (Case 1.) Leg ulcers.

The kidneys were congested.

The vertebrae, sternum, ribs and femur showed thinning of the cortex and trabeculae. The marrow of all these bones was dark red.

The other organs and tissues were negative.

The positive microscopic findings were as follows:

Tuberculosis was found in the liver, bone marrow and sinus tract in the chest wall, in addition to the areas described grossly. The skin ulcers showed a non-specific inflammatory process.

The capsule of the spleen was wrinkled. The parenchyma was composed of many trabeculae crowded together with a small amount of connective tissue between them. There were scattered areas of calcification in the capsule and trabeculae. The intima of the small arteries was thickened with narrowing of their lumina. No splenic pulp or Malpighian corpuscles were present.

The liver showed extensive sclerosis of the central areas. The sinusoids were distended by sickled red cells.

In the kidney, the glomerular capillaries were distended by red cells.

There was marked intimal thickening and extensive sclerosis of the media of the aorta, suggesting syphilis.

The bone marrow was very hyperplastic. There were numerous islands of stem cells. Erythropoiesis was marked. Many erythroblasts, normoblasts, a great many nucleated red cells and sickled cells were present. Frequent mitotic figures were found. A number of nucleated red cells appeared sickled. Scattered islands of active white cell formation occurred.

The liver cells and macrophages in the liver, lymph nodes and bone marrow contained hemosiderin. Large amounts of hemosiderin were present in the epithelial tubule cells of the kidney. A very pale, yellowish-green to pinkish-brown, highly refractile, granular material was found in many liver cells and in numerous macrophages in the liver, lymph nodes and bone marrow.

Large macrophages filled with sickled red cells were found in the sinusoids of the liver and in the sinuses of several lymph nodes. They were also found in the bone marrow.

CASE II. A two-year-old colored female was admitted to the Pediatric Service because of failure to gain weight for four months, and diarrhea of one week's duration.

Mother and father were living and well; two brothers living and well; one sister, age six months, had been "sickly" almost since birth.

Physical examination revealed an extremely dehydrated and listless colored female child, unusually small for her age. The head was normal in size and shape. The fontanelles were closed, and there was no craniotabes. There was no evidence of scleral jaundice. There was a slight mucopurulent discharge from the nose, and both ears were discharging thick yellow pus. The lips were dry. The teeth were normal. The tongue was coated, and the throat was moderately injected. The tonsils were hypertrophied and injected. The lungs were clear, and the heart was negative. The spleen and liver were not palpable. There were no scars or ulcerations of the extremities. The reflexes reacted sluggishly.

On admission she was found to have bilateral bronchopneumonia which subsided after several weeks. Following this she continued to run a low-grade temperature for five weeks, which was attributed to the bilateral otitis media.

The blood smear (Wright's Stain) showed sickle-shaped erythrocytes. Other blood studies are shown on chart I. The urines showed strong test for urobilin, but were otherwise negative. Van den Bergh was positive in the indirect phase. Kahn was negative. The Mantoux test was negative. The red blood corpuscles showed slightly increased fragility to varying strengths of saline solutions.

While in the hospital the patient received orange juice, cod liver oil, and iron and ammonium citrate 3 grams daily. While under this treatment she picked up considerably and was discharged after three months to the Out-Patient Department.

CASE III. A seven-year-old colored male was referred to the South Department for Contagious Diseases, Service of Dr. Edwin H. Place, with a diagnosis of pertussis. He had been staying at the time of admission at a convalescent home following discharge from a local hospital where a diagnosis of sickle cell anemia was made. Family history was not significant. Parents stated that he had always been in poor health. At the age of three years he was operated on because of abdominal pain simulating appendicitis and a normal appendix was removed. At that time he also had joint pains. During the next three years he was readmitted on two occasions with the diagnosis of rheumatic heart disease and adenotonsillectomy performed at the second admission.

Several months before his present entry he was brought back to the hospital because of loss of weight, fever, convulsions, irritability and pains in knees and elbows. Examination at that time disclosed a well-developed, poorly nourished Negro boy, appearing acutely ill. Respirations were rapid and

slightly labored. Mucous membranes were very pale; the neck was found to be slightly resistant on anterior-posterior flexion. His heart percussed 1.5 cm. outside the nipple line, and a loud blowing systolic murmur was present, heard best at the apex. The lungs showed questionable diminished breath sounds over the entire upper chest. The abdomen was very tense, with moderate tenderness in the right upper quadrant. The liver was not felt; the spleen was hard and extended one fingerbreadth below the costal margin. There was generalized shotty lymphadenopathy.

Blood studies showed sickle-shaped erythrocytes. The other blood findings are shown on chart I. (The first two readings have been taken from his previous hospital entry.) Urine showed slightest possible trace of albumin. Tuberculin test 1:1000 was negative. Blood Wassermann was positive on two occasions (fever); doubtful on another; Hinton negative on two occasions. X-ray films of the heart showed shadow larger than normal.

The patient showed gradual improvement and at the time of discharge it was felt that sickle cell anemia accounted for his symptomatology.

On admission to this hospital his condition was fairly good and there was no essential change in his blood picture. The spleen reached 3 cm. below the costal margin. There was no cardiac enlargement but because of pathological accentuation of the pulmonic second sound and a moderately loud blowing systolic murmur, the question was again raised as to whether a diagnosis of rheumatic heart disease should be made in addition to sickle cell anemia.

CASE IV. A twenty-seven-year-old married colored female, mother of cases II, V, VI, and VII. She was one of fourteen children who are living and well. Father has had "asthma" for many years. Her husband's father died of "unknown disease" which she thinks was "anemia". She complained of weakness, occasional attacks of abdominal pain, generalized joint pains without local signs and paresthesias of the legs. Fresh blood preparations showed 75 per cent sickling after twenty-four hours.

CASE V. A seven-year-old colored male, who was admitted to the South Department, Service of Dr. Edwin H. Place, with varicella. Diet included adequate vitamin intake. First dentition appeared at fifteen months. He was always underweight, apathetic, and "never cared to play". Adenotonsillectomy was done in the past because of frequent head colds. Has been subject to violent attacks of vomiting followed by abdominal pains; has had indolent ulcers, which left scars about both elbows; and periods of yellow discoloration of the sclerae. Fresh blood preparations showed 75 per cent sickling after twenty-four hours.

CASE VI. A four-year-old colored male, who was admitted to the South Department, Service of Dr. Edwin H. Place, with varicella. Adenotonsillectomy was done because of frequent colds. He has had periods of yellow discoloration of the sclerae, indolent ulcers with residual scars about the elbows, and at times he has cried for several days, although the mother could not elicit any definite complaints. He has also had numerous attacks of abdominal pain and vomiting of two to three days' duration. Fresh blood preparations showed .2 per cent sickling at once and a progression to 100 per cent after twenty-four hours.

CASE VII. A six-months-old colored female. She was delivered normally at full term; was breast-fed one month and then formula-fed with adequate amounts of cod liver oil and orange juice. She has been treated for "bronchitis" since three weeks of age. Her mother stated that the child did not appear to develop normally since the third month. When seen by us she had bilateral otitis media, rhinitis, and acute bronchitis. Fresh blood preparations showed .4 per cent to .2 per cent sickling at once and 100 per cent after twenty-four hours.

CASE VIII. A thirteen-year-old colored male, complaining of joint pains of four months' duration. He had appendectomy two years ago and a normal appendix was removed. Has had similar attacks of joint pains in the past; periods of chronic productive cough. Fresh blood preparations showed 75 per cent sickling in twenty-four hours.

INCIDENCE

The hereditary characteristic of the disease was established by Huck[6]. It is a disease which occurs in young people. The average age in our series is ten years, the youngest six months, and the oldest twenty-seven years. Although our cases show an even sex distribution, in the reported cases males are affected more than females in the ratio of two to one. The cases we are reporting occurred in Negroes, a finding which agrees with the usual race incidence. It must be indicated, however, that the existence of this condition outside the Negro race has definitely been established[9, 14, 15, 16, 17, 18].

THEORIES OF FORMATION OF SICKLE CELLS

Investigators of this subject have offered many theories as to the causation of the sickling phenomenon but at this time none of the explanations has met with universal acceptance. The presence of nucleated sickle cells, both in the bone marrow and circulating blood, has been established[5, 20] (Cf. Case I), which suggests that the operative forces that influence the change in the shape of the red cell are equally active in both locations.

Hahn and Gillespie[21] in a series of experiments in which they introduced various gases (carbon dioxide, nitrous oxide, and hydrogen) into fresh blood preparations of persons with the sickle cell trait, found that they were able, in this manner, to transform the cells in these preparations into sickle-shaped erythrocytes. The sickle distortion they found to be a reversible phenomenon; oxygen or carbon monoxide could induce restoration to the discoid form. They offer the hypothesis that sickle cell formation in vivo is probably induced also by anoxemia and they believe that disease of the heart and lungs, which is commonly present in this condition, plays an important rôle. Sydenstricker[22] states that he found that the true sickle cells in the blood of an active case are absolutely unaffected by oxygen.

Scriver and Waugh[23] demonstrated in vivo a direct proportion between decreased oxygen tension and the degree of sickling: they produced circulatory changes in the arm by alternating the application of an Esmarch bandage with stimulation by heat and massage. In our at-

tempts at confirming these observations the results have been inconstant. A factor to be considered in the interpretation of these results is the variation that occurs in the percentage of sickling in immediate moist preparations made under similar conditions. Graham and McCarty[11] failed to find an increase in the percentage of sickle cells twenty-seven hours after death in their heart's blood specimen, taken under anerobic conditions. It appears that further study of the influence of oxygen tension in vivo should be pursued[33, 24].

SYMPTOMATOLOGY

Sickle cell anemia may exist in either of two phases, the latent and the active phase according to the clinical manifestations and the blood changes. The patient with the latent phase may give a history of many or all the manifestations of the active phase some time during the past (Cf. Cases IV, V, and VIII). When they are seen by the physician, their complaints may be vague, their physical findings few in number and their blood picture essentially normal except for the sickling phenomenon. These vague complaints are weakness, shortness of breath, joint pains and easy fatigability, and are often associated with a history of chronic ill-health since early childhood. During the period of relapse, the syndrome of painful joints, fever, and leucocytosis suggesting rheumatic fever, may appear. The surgeon may be called because of the patient's acute abdominal pain with scleral jaundice resembling gallbladder disease. Some of these patients have had appendectomy because of vomiting, fever, and right lower quadrant pain with spasm and tenderness (Cf. Cases III and VIII). Others come to the clinic for treatment of a chronic leg ulcer. The association of the anemia with respiratory infection is striking. Frequent attacks of sore throat, head colds, and pneumonia, are common. Tuberculosis is often seen with this condition.

Careful examination of the patient discloses the stigmata of ill health and, frequently, defective general and genital development. Pallor is present in proportion to the degree of anemia. The eyes may show a peculiar greenish-yellow type of scleral discoloration described by some observers as typical of the disease. General lymphadenopathy is common. The lungs usually show congestive changes at the bases. Anderson and Ware[34] report that cardiac enlargement may be present in about half of the cases and the problem of ruling out rheumatic heart disease may be difficult (e.g., Cases I and III). The anemia alone may account for the systolic murmur commonly present in the cases studied. Abdominal examination is usually not helpful. In about one-half of the cases the liver has been felt below the costal margin. The spleen is usually found to be markedly enlarged in young children, but seldom can be felt in the older age group. Finding of punched-out leg ulcers (cf. figure 4) suggesting syphilis is more likely in patients over fifteen years of age, but cases IV, V, and VIII of our series had healed scars consistent with this lesion.

Dresbach[25] and others[26, 27] have described the occurrence of elliptical erythrocytes not associated with anemia or other abnormality. This condition is seen in both the white and colored races, and the number of elliptical cells does not increase in sealed preparations.

PATHOLOGY

The spleen, and to a lesser degree, the liver and bone marrow present the most interesting pathological findings. Enlargement of the spleen, frequently very marked, occurs in infants, but atrophy sets in about the age of five or six years and may progress to almost complete disappearance of this organ. The weight of the spleen in our autopsied case was 0.870 grams.

Grossly the spleen shows increased consistency and thickening and wrinkling of the capsule. On cross section areas of infarction may be present. Microscopic examination presents a characteristic picture which Rich[29] has described as the specific pathology of this disease. The splenic nodules (Malpighian corpuscles) are greatly diminished in size and show fibrosis and disappearance of the germinal centers. (In the spleen of case I these changes had progressed to total disappearance of the nodules and pulp.) The sinuses about the corpuscles are markedly distended with red cells, giving the appearance of islands of tissue floating in pools of blood. The splenic pulp is present in proportion to the size of the spleen and is either swollen and interspersed with numerous imbedded red cells or fibrotic and contracted.

The liver, as a rule, shows enlargement. There is congestion and dilation of the sinusoids and degenerative changes in the liver cells. Sickle cells may be seen in the large macrophages. The bone marrow shows striking hyperplasia with numerous islands of stem cells, many nucleated red blood cells, a number of which are sickle-shaped. The inner cortex shows trabeculations which may be recognized in the roentgenograms taken before death. Hemosiderin is found generally deposited in the cells of the liver, kidneys, lymph nodes, and bone marrow.

The leg ulcers show non-specific inflammatory changes.

LABORATORY FINDINGS

Individuals with the sickle cell trait or latent sickle cell anemia may show no abnormal blood findings other than the presence of sickled erythrocytes. The sickle cells may be recognized accidentally in a counting chamber preparation during a routine erythrocyte count.

The active cases usually show hemoglobin values varying from 30 to 60 per cent (Sahli)

and a red cell count of 1.5 to 3.5 million per cu. mm. with a normal or elevated color index. In the very severe cases, the red blood count may drop to one million or less, and the hemoglobin to about 10 per cent. The white cell count ranges from 10,000 to 20,000 per cu. mm. and those with intercurrent infections may show from 30,000 to 50,000 per cu. mm. The differential leucocyte count is not distinctive. At times an increase in the eosinophiles may occur, and myelocytes form the larger percentage of abnormal white cells present. Anisocytosis and poikilocytosis are usually moderate in degree; there is moderate polychromatophilia; punctate basophilia is the rule. Nucleated red cells are found, and in one of our cases (case II) .01 per cent of total red blood cells was seen to be nucleated that is, the number of nucleated red blood cells was approximately equal to the number of leucocytes on stained smear. The percentage of sickle cells in the stained preparation varies from 0.5 to 5 per cent or more, depending on the severity of the anemia. Phagocytosis of the red cells by large mononuclear leucocytes is seen in both stained and fresh blood preparations. This phenomenon is stressed by many writers, but we were impressed by the infrequency with which we observed it in the blood of our cases. Reticulocytes are found to be increased: Case II showed on one occasion as high as 56 per cent. Case I showed constantly 30 to 40 per cent with higher percentages on many occasions. The platelets are normal or slightly increased. The fragility of the red blood cells in the active cases is normal or slightly increased to varying strengths of saline solutions. The coagulation and bleeding times are normal. The van den Bergh test is almost always positive in the indirect phase. Blood cultures are negative. Gastric achlorhydria is usually present. The urine shows low fixed specific gravity, large twenty-four hour amount, reduced excretion of phenolsulphonphthalein and generally the presence of albumin in small amounts. Urobilin is constantly present in active cases.

CHARACTERISTICS AND BEHAVIOR OF THE ERYTHROCYTES IN FRESH PREPARATIONS

Fresh preparations of the blood, from patients with the latent or inactive phase of the disease, when made by bringing a clean cover slip in contact with a drop of blood and mounted immediately on a glass slide and rimmed with vaseline or paraffin show very little change in the red blood cells on immediate microscopic examination. Rarely an occasional sickle-shaped cell may be seen. After standing, however, from one to six hours at room temperature, the preparations may show as many as 25 per cent distorted red cells, most of which have changed into bizarre elongated crescent-shaped forms with long, threadlike processes. At the end of twenty-four hours as many as 90 or 100 per cent of these unusual or bizarre-shaped red cells may be seen.

In the active phase of the disease, when sickle cells may be found in the circulating blood, we have frequently observed 100 per cent crescent forms on immediate examination of moist preparations. Usually, however, one finds five to ten per cent on immediate examination of the fresh blood and a conversion to the maximum after standing at room temperature from twenty-four to forty-eight hours. If the fresh preparations from either the latent or active cases are preserved at room temperature from three days to six weeks, many of the preparations will be found to have reverted to the normal discoid form.

PROGNOSIS AND TREATMENT

Active sickle cell anemia is characterized by relapses and remission and the ultimate prognosis is uncertain. Sydenstricker believes that the prognosis for adults is good, but for children is guarded. He found a high rate of mortality in sickle cell anemia families, and all of his cases died of intercurrent disease. Wollstein and Kreidel report two patients in whom the disease appeared to be the sole cause of death. Tuberculosis is prominently recorded as a cause of death in this disease[24, 28].

While the mechanism of sickling in this disease remains unknown, it is likely that no satisfactory method of treatment will be found. Blood transfusions may tide the patient over a critical period, but probably have no lasting effect. Full doses of iron, arsenic, and a high intake of vitamins apparently have no specific effect. We feel that liver is of no value in the treatment of this disease. Case I was given twenty-one consecutive daily injections of 5 cc. liver extract 343 N.N.R. without any appreciable effect on the reticulocyte count or general blood picture. (The patient was constantly showing 30 per cent reticulocytes before liver was exhibited.)

Splenectomy is reported to be beneficial in the patients who present splenic enlargement[15, 16, 21, 31, 33, 35, 36]. In the reported cases, more than half showed freedom from symptoms and some improvement in the general blood picture, but the sickle cell trait remained unchanged.

SUMMARY AND CONCLUSIONS

1. Sickle cell anemia is a definite clinical entity of familial nature, the distinctive feature of which is the finding of sickle-shaped erythrocytes in the patient's blood.
2. The literature on sickle cell anemia has been reviewed; the appearance of the disease in New England is noted for the first time.
3. Three cases of sickle cell anemia are reported in detail, one with necropsy, and notes on five cases are recorded.
4. The recognition of the sickle cells in fresh

blood preparations is a simple laboratory procedure.

5. Sickle cell anemia may masquerade under such diagnoses as rheumatic fever, tuberculosis, acute abdominal conditions, syphilis, and obscure anemias. The high percentage of Negroes among those with this disease warrants the study of fresh blood preparations when such diagnoses are considered in patients of this race.

6. The existence of sickle cell anemia has been established outside the Negro race, and should be considered in all perplexing blood problems.

7. The histological findings in the spleen, liver, and the marked bone marrow hyperplasia are the prominent pathological findings; the 0.870 gram spleen found in case I appears to be the smallest on record.

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INCIDENCE OF SYPHILIS IN THE GENERAL POPULATION AND A COMPARISON OF THE KAHN AND WASSERMANN TESTS*

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THE incidence of syphilis in the general population is a much discussed and mooted question. Many estimates have been made in former years based often on small and inadequate statistics. In recent years a number of attempts have been made by health departments and by individual physicians to broaden the scope of the inquiry and obtain more adequate and accurate data. Kiser and Bohner in a recent article[1] summarized much of the current literature on the subject and gave their own findings on the incidence of syphilis in private practice in 2,872 consecutive examinations made from September 1, 1925 to January 1, 1932. Table 1 contains a re-statement of their summary together with their own observations.

A study of the figures shows that the incidence of syphilis varies with the age and type of group studied. A group of young adult college students, presumably above the average in intellect and social position, shows an incidence of only 0.2 per cent while a group of military recruits probably only a few years older on the average but drawn from the general white population shows an incidence of 10.5 per cent. It is generally conceded that syphilis is consider-

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