S-C Hemoglobin: A Clinical Study

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MOST CLINICIANS are familiar with the chronically ill, eunuchoid appearance that typifies patients with sickle cell anemia. The subtleties in the clinical expression of hemoglobin S-C disease, however, offer a variety of pictures, sometimes even simulating life-threatening emergencies.

Confusion has arisen from the terminology pertaining to this hemoglobinopathy. We believe this state should be designated only by the terms “sickle cell-hemoglobin C disease” or “S-C hemoglobin disease.” The term “sickle cell disease” should be reserved for the homozygous sickle cell anemia.

Numerous investigators have helped in elucidating this hemoglobinopathy. It was as recent as 1950 that Itano and Neel, employing the method of paper electrophoresis, first identified the hemoglobin which was later designated hemoglobin C. Shortly before, Pauling, through the use of this method, had established the “molecular basis” of abnormal hemoglobins. In 1951, Kaplan and his co-workers described the clinical manifestations in three patients with hemoglobin S-C disease, establishing it as a syndrome with characteristic features. These were the first reports of electrophoretically proved cases of sickle cell-hemoglobin C disease, although certainly some of the reports of “sickle trait” and “atypical sickle cell anemia with splenomegaly” made prior to the availability of hemoglobin electrophoretic analysis were examples of this syndrome.

The inheritance of hemoglobins S, C, and A has been shown to be controlled by a pair of allelomorphic genes, so that patients with S-C hemoglobin must receive the gene for S hemoglobin from one parent and the gene for C hemoglobin from the other. This situation is designated as a doubly heterozygous state.

In the American Negro, the incidence of S hemoglobin has been estimated at from 8 to 11 per cent and that of C hemoglobin from 2 to 3 per cent. Although accurate statistics are not available, Chernoff has estimated the number of cases of S-C disease in the United States in excess of 10,000, a figure based on an incidence of 1:1500 in this population.
The most important recent development in the investigation of hemoglobins has been Ingram's\textsuperscript{a} work with proteolytic digestion, chromatography of the resultant peptide chains ("peptide finger printing"), and ultimate amino-acid analysis of the globin portion of the hemoglobin molecule. Thus, of the 300 amino acids constituting a half molecule of hemoglobin, hemoglobins S and C differ from hemoglobin A in the substitution of a single amino acid, lysine for glutamic acid in hemoglobin C, and valine for glutamic acid in the case of hemoglobin S.

**Clinical Features**

*Age, age at onset, sex, and race.* The age of our patients at the time of study ranged from 14 months to 66 years, with an average age of 26 years (fig. 1). The distribution of the age at onset of symptoms is given in figure 1 and contrasted with the age distribution at the time of study. Fourteen of the patients were over 40 years of age. The age data are in general agreement with the range cited by others. Conley and Smith's\textsuperscript{12} 75 year old patient remains an exception.

The average age at onset of symptoms was 11 years, with almost half of the patients having an onset by age 10. In all but two of our 60 symptomatic cases, disease complications developed by the age of 30. In one of our patients onset was at 40; one of Smith and Conley's\textsuperscript{79} patients did not become symptomatic until the age of 70. Fifteen of our patients never had any symptoms related to the hemoglobinopathy.

![Graph showing age of patients at time of study and onset of symptoms](image-url)
Many of the patients who reported “rheumatism” or “growing pains” as their initial manifestations of disease disclaimed any childhood symptoms unless the specific terms were used in the interrogation. When the pains were severe enough to warrant medical attention, “rheumatic fever” was the frequent diagnosis.

Females predominated 2.5:1.

All the patients were Negro, with the exception of one female (Case 50), in which case the father (of Sicilian descent) carried an A-C hemoglobin pattern; the mother (of Scotch, Irish, Holland-Dutch and “American Indian” descent) had an A-S hemoglobin pattern, suggesting Negro ancestry. This patient illustrated the problems of differential diagnosis, for although it is rare, a white patient may have S-C hemoglobin disease. Chernoff\textsuperscript{8} accepts two cases of S-C hemoglobin disease in white patients, one an Egyptian, and one originating from Greece.

**Longevity.** Since deaths have been reported from complications of S-C hemoglobin disease, the disease affects longevity, although obviously not so uniformly as does sickle cell anemia. Three deaths occurred in our series: one was a 63 year old woman with hypertensive cardiovascular disease who had a “saddle” embolus to the aortic bifurcation and died of surgical complications; one was a 37 year old man with recurrent pulmonary emboli of uncertain causation, and the third case was that of a 27 year old man who was a heroin addict with severe recurrent hepatitis. He died in crisis. The autopsy is described here in the section on pathology. Certainly death was related to the hemoglobinopathy and perhaps the second case was also so related, although in the absence of a postmortem examination, proof is wanting.

**Presenting symptoms.** Many patients had more than one presenting symptom. Pain, of moderate to severe intensity, characterized nearly half of the presenting symptoms whether in the abdomen, bones and joints, chest, flank, back, or head. In most cases the cause of pain was not demonstrable, although in some cases pneumonia, pyelitis, and rarely biliary colic were established diagnoses. Painless hematuria, vitreous hemorrhages, and priapism were additional complications of S-C disease, necessitating hospital admission. Table 1 shows that many patients presented with problems entirely unrelated to the abnormal hemoglobin; the diagnosis was established consequent to blood film abnormalities, investigation for anemia, or discovery of splenomegaly.

**Abdominal pain and gastrointestinal symptoms.** Bizarre abdominal pain, usually of obscure origin, was common. It is a striking complication, requiring careful collaboration between medical and surgical personnel in order to prevent unnecessary surgical procedures, but on the other hand, not to miss a condition requiring surgical intervention. Twenty-two patients (30 per cent) had had one episode or more. None of the ten patients having a prolonged episode of severe pain had more than one such attack. Pain was characteristically diffuse and sharp or lancinating, occasionally colicky in nature. Examinations of the abdomen revealed only moderate diffuse tenderness. Gallstones were demonstrated in one of these cases and a bleeding peptic ulcer is on record; surgical intervention was later required in both cases. Only two pa-
Table 1.—Presenting Complaints

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone and joint pain</td>
<td>16</td>
</tr>
<tr>
<td>Gonococcal arthritis</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14</td>
</tr>
<tr>
<td>Lead poisoning</td>
<td>1</td>
</tr>
<tr>
<td>Gonorrhea! salpingitis</td>
<td>2</td>
</tr>
<tr>
<td>Supra pubic pain</td>
<td>1</td>
</tr>
<tr>
<td>Chest pain</td>
<td>11</td>
</tr>
<tr>
<td>Flank pain</td>
<td>6</td>
</tr>
<tr>
<td>Hematuria</td>
<td>6</td>
</tr>
<tr>
<td>Jaundice</td>
<td>5</td>
</tr>
<tr>
<td>Back pain</td>
<td>4</td>
</tr>
<tr>
<td>Complications of pregnancy</td>
<td>4</td>
</tr>
<tr>
<td>Dysuria (Cysto-pyelitis)</td>
<td>3</td>
</tr>
<tr>
<td>Eye complaints</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting (ileus)</td>
<td>2</td>
</tr>
<tr>
<td>Epistaxis, severe</td>
<td>2</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2</td>
</tr>
<tr>
<td>Chills and fever (E. coli septicemia)</td>
<td>2</td>
</tr>
<tr>
<td>Stiff neck (meningismus)</td>
<td>1</td>
</tr>
<tr>
<td>Acute urinary retention</td>
<td>1</td>
</tr>
<tr>
<td>Nervousness (thyrotoxicosis)</td>
<td>1</td>
</tr>
<tr>
<td>Priapism</td>
<td>1</td>
</tr>
<tr>
<td>Skin disease (psoriasis)</td>
<td>1</td>
</tr>
<tr>
<td>Cyst of right knee (Baker's)</td>
<td>1</td>
</tr>
<tr>
<td>Head injury</td>
<td>1</td>
</tr>
<tr>
<td>Splenomegaly, accidently discovered</td>
<td>1</td>
</tr>
<tr>
<td>Melena</td>
<td>1</td>
</tr>
</tbody>
</table>

Patients were subjected to exploratory laparotomy, neither of whom had significant disease demonstrated at operation. Serum or urine amylase determinations, or both, when drawn during an attack were uniformly normal. The average age at the time of the attack was 15 years, with eight patients having an attack before the age of 10 and only two after the age of 26.

Gastrointestinal hemorrhage is a rare finding in these patients and when present is probably attributable to a second disease process. Although peptic ulcer seems rare in patients with S-C hemoglobin, the one patient in our series who presented with melena was shown roentgenographically to have a duodenal ulcer. We are aware of only one report of a case of gastrointestinal bleeding in a patient with S-C hemoglobin disease, a 12 year old Nego boy with rectal hemorrhage (Denny16).

Muscle, bone and joint pain. Of our 75 patients, 44 experienced pain in the extremities on at least one occasion. It is significant that 23 of the 34 patients questioned during re-study gave this history. They often failed to mention it on casual questioning, for they had learned to accommodate to its mildness. Sixteen of the 44 patients had only one episode. The age at the time of the initial attack ranged from 2 to 41 years, with an average age of 12.6 years. Twenty-three of these patients experienced this initial attack before their
10th year of life. Most patients with recurrent pain described a lessening in both frequency and intensity after the second decade. An occasional patient related a tendency to seasonal exacerbations, particularly in the spring and autumn. When the patient in Case 75 was seen at age 63, she had the typical deformities of rheumatoid arthritis, which made her history difficult to assess.

The frequency of pain in the extremity reported by others\textsuperscript{10,36,37,61,67,79} is approximately 70 per cent. Although the over-all incidence was slightly less than 60 per cent, it approached 70 per cent in the group re-studied. Thus, of the clinical manifestations of S-C hemoglobin disease, pain in the extremity surpasses all others in frequency. Neither sex nor the presence or absence of splenomegaly appeared to be correlated.

\textit{Epistaxis}. Five of our patients gave a history of significant epistaxis; two gave this as their principal historical symptom. Mild to moderate epistaxis was also commented on by Hook,\textsuperscript{36} occurring in one-third of his series of cases. Although the incidence in our series was low, its prominence in sickle cell anemia\textsuperscript{55} suggests that epistaxis is related to the underlying hemoglobinopathy.

\textit{Body habitus}. There was a wide range of variability in stature and body build. One patient (Case 1) was excessively tall and thin, but as a sibling with A-C pattern had an identical physique, this was probably a familial trait. None of the patients had the typical appearance of sickle cell anemia, a fact most probably related to the adequacy of their hemoglobin levels and therefore an absence of severe chronic hypoxia as is seen in some patients with sickle cell anemia or congenital heart disease. There was no evidence of arachnodactyly, "tower skull," or wide disparity between their stated and apparent ages.

\textit{Adenopathy}. In many of the patients, small shotty lymph nodes were palpable in the posterior cervical and inguinal regions, but only two had generalized adenopathy: one (Case 53) was a patient with sarcoidosis and the second (Case 62) had lymph node tuberculosis. Significant adenopathy in patients with S-C hemoglobin would indicate a second disease.

\textit{Eye manifestations}. Two general categories were formulated: those thought to be specifically related to S-C disease, and those due to other causes. We have included in the group of lesions related to S-C disease, tortuosity of the retinal vessels (so-called corkscrew appearance), vitreous hemorrhages (Eale's disease), retinal detachment in the absence of other causes,\textsuperscript{29,32,39,48} and aneurysmal dilatations of retinal vessels.\textsuperscript{78} A peculiar form of neovascularization seen as arborization of terminal arterioles, as well as of chorioretinal atrophy, has been well described by Hannon.\textsuperscript{32} The 33 patients studied at the time of this writing failed to show a high incidence of retinal disease. More abnormalities might have been found, had the examination been conducted by an ophthalmologist with the aid of retinal photography.\textsuperscript{56} Three patients had a documented history of vitreous hemorrhage; one patient had extreme tortuosity of the vessels. Four additional patients showed arborization, one slight, the others severe. Unrelated retinal disease consisted of one case of
sarcoid uveitis and four of varying degrees of hypertensive retinopathy. Three patients not available for re-study had had vitreous hemorrhages and two of these also had retinal detachments.

Cardiovascular System

Hypertension. Although 13 patients exhibited mild to moderate elevations in blood pressure, elevation was transient in five, occurring only on the day of admission. The eight patients manifesting persistent hypertension had an average age of 50 years (only two patients were below 40 years), an age when hypertension and hypertensive heart disease are endemic in our population. The four patients having roentgenologic evidence of cardiomegaly were in this group.

Cardiac auscultation. Except for soft systolic murmurs when anemia was present, cardiac murmurs were uncommon. This is in contrast to sickle cell anemia in which cardiac murmurs are characteristic. One patient was considered to have the typical murmur of mitral insufficiency and another that of combined mitral stenosis and insufficiency. Four other patients, two with persistent hypertension, had apical systolic murmurs.

Vascular disease. There was no evidence of association of S-C hemoglobin disease and peripheral vascular disease. That one patient had had an episode of thrombophlebitis, and another patient died of complications attending a “saddle” embolization of the aorta was considered a coincidence.

Electrocardiographic data. Electrocardiograms in the five cases of transient hypertension as well as for 16 normotensive persons were normal. As anticipated, six of the eight hypertensive patients had abnormalities of the electrocardiogram.

Pulmonary signs. An unexpectedly high incidence of pulmonary symptoms were exhibited in our case material. Chest pain, fever, and cough, together with leukocytosis and roentgenologic evidence of infiltration occurred repeatedly. None of the patients admitted to hemoptysis. Thirty patients gave a history of “pneumonitis” or presented with the condition, often repeated, for a total of 46 episodes. This striking frequency is in contrast to that in published reports in which the incidence is less than 5 per cent.

Bacteriologic studies in our series have been unrewarding. The high incidence of pulmonary disease is thus probably due to factors favoring sickling in the pulmonary vasculature. Moser and Shea have written a comprehensive analysis of the pathogenesis of pulmonary disease in sickle cell states. They note that lowering of oxygen tension and blood pH, most marked in the pulmonary arteries, particularly under circumstances of increased metabolism, favors sickling. The areas of A-V shunt with narrowed arterioles known to exist in the lung promote additional anoxia and stasis as further inducement to sickling. These factors are offset by a concentration of hemoglobin S of less than 70 per cent, the minimal concentration necessary for sickling under “physiologic conditions” in vitro. It has been demonstrated that in contradistinction to fetal hemoglobin, hemoglobin C partakes in the formation of tactoids. Although hemoglobin A also partakes in tactoid formation with hemoglobin S, the potentiating is less. Thus we can envision a precarious equilibrium
readily driven by such factors potentiating sickling as temperature elevation, leukocytosis, and bacteremia. This concept might explain the intermittent nature and the frequency of pulmonary disturbances in patients with S-C hemoglobin disease. The mechanism of pulmonary disease is then postulated as a cycle involving anoxia, stasis, increased viscosity, sickling, tissue ischemia, thrombosis, and infarction. The term “ischemic necrosis” has been suggested by Kimmelstiel for these changes inasmuch as evidence of overt thrombosis is often lacking.

It has been suggested that marrow infarction with consequent pulmonary embolization by fat and marrow elements is a cause of sudden death in patients with S-C hemoglobin disease. At least three electrophoretically proved cases showed these conditions at autopsy. None of our patients had an episode suggestive of this mechanism. Rarely was severe bone or joint pain described in conjunction with “pneumonia”. The two patients reporting this association were critically ill with E. coli septicemia. One patient (Case 47) died at another hospital of what clinically appeared to be recurrent pulmonary emboli and cor pulmonale.

Chronic pulmonary disease was not evident in our cases. Two patients had been treated previously for pulmonary tuberculosis, and in a third, tuberculous adenitis was disclosed at autopsy. This incidence of acid-fast infection is not unexpected in our population.

Liver

Biochemical determinations. Determination of alkaline phosphatase, icteric index, cephalin flocculation, thymol turbidity, and gamma globulin turbidity was performed at least once in 49 cases. Seventeen patients demonstrated abnormality. These data are summarized in table 2. One patient was sarcoidosis, one, a case of chronic alcoholism, and a third with heroin addiction and recurrent hepatitis might reasonably be expected to have had pathologic values unrelated to hemoglobinopathy. Three additional patients with abnormalities gave a history of having received blood transfusions. Five patients had had jaundice, and one had had both transfusions and jaundice. The alkaline phosphatase was the most frequently elevated value, a finding that may be related to bone disease rather than liver dysfunction. Roentgenologic surveys were available for four of the patients with an elevated alkaline phosphatase. Three of these revealed bone changes.

Jaundice. Twenty-four patients had a determination of icteric index at a time when they were clinically well. The average was ten units, with a low of eight and a high of eighteen. This average is slightly but unquestionably elevated and correlates with the shortened cell survival observed in this disease.

Nineteen patients reported jaundice, 14 on only one occasion. The ages at the time of appearance of jaundice ranged from 5 to 40 years, with an average of 21. Two of the patients had gallstones, two others were alcoholics or “mainline” addicts or both, and two had had septicemia and toxic hepatitis when jaundiced.

Hepatomegaly. Hepatomegaly was defined as enlargement of the liver
Table 2.—Results of Liver Function Tests

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age/Sex</th>
<th>Splenomegaly</th>
<th>Hepatomegaly</th>
<th>History of jaundice</th>
<th>History of transfusions</th>
<th>Cephalin flocculation</th>
<th>Thymol turbidity</th>
<th>Globulin turbidity</th>
<th>Alkaline phosphatase</th>
<th>Icterus index</th>
<th>Diagnoses and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>58 F</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>N</td>
<td>7.0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Cholecystectomy for gallstones—5 years before.</td>
</tr>
<tr>
<td>12</td>
<td>29 F</td>
<td>+</td>
<td>800 Gm.</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>3+</td>
<td>N</td>
<td>N</td>
<td>14.2 N</td>
<td>Enlarged liver and large spleen. P.A. of pregnancy twice.</td>
</tr>
<tr>
<td>14</td>
<td>26 F</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>3+</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Chronic active osteomyelitis (E. coli).</td>
</tr>
<tr>
<td>43</td>
<td>27 F</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1+–4+</td>
<td>5.4</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Vitreous hemorrhage.</td>
</tr>
<tr>
<td>50</td>
<td>47 M</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>2.24 N</td>
<td>N</td>
<td>Hyperthyroidism and mitral stenosis. Liver biopsy: nonspecific.</td>
</tr>
<tr>
<td>52</td>
<td>47 M</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>6.0 N</td>
<td>N</td>
<td>Toxemia of pregnancy.</td>
</tr>
<tr>
<td>54</td>
<td>15 M</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>4.6–7.5 N</td>
<td>19–10 N</td>
<td>Abdominal pain (crises).</td>
</tr>
<tr>
<td>38</td>
<td>26 M</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>N</td>
<td>5.0</td>
<td>1.85</td>
<td>7.1 35</td>
<td>Chronic alcoholic with DTs. Alb. = 3.8, globulin = 3.8, hepatomegaly.</td>
</tr>
<tr>
<td>59</td>
<td>24 M</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>5.8 N</td>
<td>30</td>
<td>Abdominal pain (crises).</td>
</tr>
<tr>
<td>62</td>
<td>27 M</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>N</td>
<td>4+</td>
<td>16.3</td>
<td>3.68 N</td>
<td>4.6 39</td>
<td>Heroin addict with repeated episodes of abdominal pain and jaundice over 8 years. Death. (BSF = 28.4%, alb. = 4.9, glob. = 4.9).</td>
</tr>
<tr>
<td>66</td>
<td>27 F</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>5.6 N</td>
<td>N</td>
<td>Hematuria.</td>
</tr>
<tr>
<td>74</td>
<td>29 F</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>7.5 N</td>
<td>0</td>
<td>Gonorrheal arthritis and pelvic inflammatory disease.</td>
</tr>
<tr>
<td>69</td>
<td>44 F</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>3+</td>
<td>7.8</td>
<td>3.65</td>
<td>0</td>
<td>14</td>
<td>Cholecystectomy—3 years before. Hematuria.</td>
</tr>
<tr>
<td>26</td>
<td>66 M</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>7.1 N</td>
<td>N</td>
<td>Pneumonitis and arthritis.</td>
</tr>
<tr>
<td>47</td>
<td>37 M</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>21</td>
<td>Recurrent pulmonary emboli; death with cor pulmonale. BSF = 9%. E. coli septicemia.</td>
</tr>
<tr>
<td>22</td>
<td>23 F</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>N</td>
<td>4.7</td>
<td>N</td>
<td>9.8 N</td>
<td>42</td>
<td>Induced septic abortion.</td>
</tr>
</tbody>
</table>

0 = indicates not done, N = normal value.
greater than 2 cm. below the costal margin. This was observed in 14 cases; eight of those patients had biochemical abnormalities. Thus, almost half of the patients with chemical abnormalities demonstrated hepatomegaly as compared to 10 per cent in the remaining 58 cases. Hepatomegaly greater than 3 cm. was demonstrated in only seven patients, six of whom had chemical abnormalities.

**Histopathology.** Histologic examination of the liver was obtained in two instances: Case 50 in which there was a nonspecific reactive hepatitis and Case 62 in which severe congestion, fibrosis, and hemosiderosis were present.

We were able to discern little direct relationship between the presence of S-C hemoglobin and hepatic disease, although the occasional need for transfusion as well as the presence of cholelithiasis could result in injury to the hepatic parenchyma. Sickle cell anemia differs in that evidence of hepatocellular impairment is usual.

**Cholelithiasis.** The occurrence of gallstones in patients with sickle cell anemia is well reorganized as is the decreased incidence in Negroes, particularly in the younger age group. Six of our patients with S-C hemoglobin disease were known to have had gallstones (fig. 2), three of whom had had cholecystectomy. The average age at time of discovery of the stones was 43 years; only one patient was under 35 years of age.

There were 14 patients over the age of 40 at the time of study. Five of the six patients with gallstones were in this age group. Among our older patients 35 per cent (five of 14) had cholelithiasis, an incidence distinctly greater than expected in our hospital population.

**Spleen**

Although demonstrable splenomegaly is a definitive aid in the diagnosis of S-C hemoglobin disease, a third of our cases (25 of 75) lacked this finding. In 160 cases in which the degree of splenomegaly was reported, absence of splenomegaly was noted in 40 per cent of the patients (14 of 64).

The degree of splenomegaly varied from just palpability to 15 cm. below the costal margin. Surgical and postmortem specimens have also varied considerably. Six instances of atrophied spleens have been reported: one by Ober, weighing 70 Gm., two by Conley, weighing less than 40 Gm., one by Huestis, weighing 23 Gm., one by Lau, weighing 10 Gm., and one by Smith, in which the weight was not designated.

Regarding splenic enlargement, Edington, in a review of five cases of S-C hemoglobin disease, reported the spleen weight to range from 315 to 850 Gm. Curtis reported a spleen of 1400 Gm. Our patient (Case 12) who was splenectomized because of possible recurrent infarction in a progressively enlarging organ, had a spleen of 1,800 Gm. This is the largest spleen thus far reported in a patient with S-C hemoglobin disease. Other observers have reported a higher incidence of splenomegaly in the older age group. They also noted progressive enlargement in some patients whose disease state varied from milder to entirely asymptomatic. Splenomegaly could not be correlated in our patients with age or symptomatology, although an increased incidence
Fig. 2.—Case 69. A 44 year old Negress, gravida VI, para V, with S-C hemoglobin disease: history of several episodes of hematuria requiring transfusion. Multiple radiolucent stones were demonstrated on Graham-Cole examination. Cholecystectomy was performed.

of splenomegaly was present in women who had been pregnant. The spleen has been reported to show remarkable changes in size, frequently associated with increased severity of anemia. Chernoff reported subcostal spleen at the onset of crises, enlarging to 10 cm., then reverting to previous size within five or six days.

One of our patients (Case 12) probably demonstrated the phenomenon of transient hypersequestration. Pain in the left upper quadrant was associated with splenic enlargement of 15 cm. and a red blood cell count of 2.28 M. During the following two weeks the red blood cell count reverted to the patient's usual level of 4.05 M. although frequent reticulocyte determinations
during this period were consistently 1 per cent. Although marrow aspiration was refused by the patient, the rapid return of her circulating red cells in the absence of reticulocytosis might indicate transient trapping of these cells in the massively enlarged spleen. With rapid return of red cell mass from increased hemolysis, red cell aplasia or folic acid deficiency, significant reticulocytosis would have been found.

At least seven cases of splenic infarction during exposure to high altitudes are known to have occurred in this syndrome.11,13,19,26,69,80,119.5

A decrease in oxygen tension sufficient to cause sickling in patients with this hemoglobinopathy occurs at altitudes above 5,000 feet, an altitude attained by commercial and military flights. Although the same phenomenon occurs in patients with sickle cell trait, an altitude above 10,000 feet seems prerequisite to splenic infarction. Our patient (Case 12) had a splenic infarction without exposure to high altitude. Other such cases have been reported. Although the exact mechanism of splenic infarction in these cases is unknown, S hemoglobin is obviously at least in part causative.

When splenectomy was performed following infarction, the spleen was congested and hemorrhagic. We believe that splenectomy should be limited to those patients manifesting rapid or massive enlargement or rupture following infarction. Hypersplenism has not been reported in this syndrome, although if established would also indicate a need for splenectomy.

As in sickle cell anemia, in some patients with S-C hemoglobin siderofibrotic nodules develop in the spleen.23,51,64 Jacobson,41 investigating whether these nodules were roentgenographically demonstrable, found one report to which he added four others. Although hemoglobin electrophoresis was not done in these cases, one patient was a 37 year old Negress with splenomegaly, aseptic necrosis of the femoral heads, but without anemia.

In two of 24 patients, a diffuse mottled appearance of the spleen was noted on scout films. The softness of these splenic deposits in our cases differs from the hard calcifications associated with the granulomas. In patients with S-C hemoglobin the fine quality of these deposits imparts a stippled appearance (fig. 3). We have observed this phenomenon of splenic "stippling" in five cases of sickle cell anemia in addition to our two cases of S-C hemoglobin disease. This roentgenographic finding has been observed only in patients with the sickling phenomenon, although it might conceivably result in the same abnormality in any disease leading to perifollicular hemorrhage and siderofibrotic nodules.

Genitourinary Data

Urinalysis. Random specific gravities in 52 cases ranged from 1.003 to 1.024 with an average of 1.011; 85 per cent of patients had an acid urine.

A defect in maximal concentrating ability has been demonstrated in this disease.29,47 The reduction is comparable to that seen in sickle cell trait but is less severe than that seen in sickle cell anemia. Transfusion with normal blood has corrected this defect in some children with sickle cell anemia.47 Because the correction appeared to be due to suppression of S hemoglobin...
Fig. 3.—Case 63. A 21 year old Negro with sickle cell anemia: admitted because of persistent pain in the left shoulder and fever secondary to Salmonella typhimurium osteomyelitis. Febrile agglutinins for paratyphoid A was 1:640, paratyphoid B was 1:5120, and typhoid was 1:160. The alkaline phosphatase was 12.1 Bodansky units. This roentgenogram demonstrated the characteristic stippled appearance of hemosiderosis of the spleen occasionally seen in SS and SC hemoglobin disease.

and not to overcoming anoxia, it would seem reasonable to expect a similar correction in patients with S-C hemoglobin.

_Hematuria._ Fourteen patients experienced a total of 20 episodes of hematuria, all of which subsided without surgical intervention. Later, in Case 52, a right heminephrectomy was performed for a cyst demonstrated roentgenologically and confirmed at operation. In the nine instances in which the site of the bleeding was determined by cystoscopy, six were on the right and three on the left. This is not in agreement with most of the published series, which reported predominant bleeding from the left kidney. The explanation offered for this predominance was that the venous drainage of the left kidney encourages stasis.

Two of our cases were shown to bleed from the right kidney at one time and the left at another, which emphasizes the futility of nephrectomy as the
treatment of this complication. That the hematuria may be exsanguinating is illustrated by Case 69 in which a hemoglobin of 3.7 Gm. per cent was recorded.

The average age at the time of the episode of hematuria was 30 years; none occurred under the age of 20. Although several cases of hematuria during childhood and adolescence have been reported, this remains on the whole a complication of adult life.

At least 24 patients with S-C hemoglobin disease and hematuria have been reported. Although there can be no doubt of the causal relationship between the hemoglobinopathy and hematuria, appropriate investigations must be performed in each case to exclude other possibilities.

Intravenous pyelography was done in a number of cases of hematuria and the result was usually normal. An unequivocal case of chronic pyelonephritis and two others of suggestive changes of mild clubbing of the calices were encountered. In one case a filling defect was present in the right kidney; at operation, a hemorrhagic cyst was removed.

Renal failure was not observed in our patients. Blood urea nitrogen values were well within normal limits in all patients except two who had E. coli septicemia; return to normal was rapid.

Priapism. Priapism is an uncommon ailment which is known to take place in the presence of sickle cell anemia. After a review of reports of S-C hemoglobin disease, it appears to be rare in this syndrome; Denny16 reports one case. One of our patients (Case 4) presented with this problem which failed to respond to all conservative measures. Irrigation with a large bore needle was finally resorted to, and, although effective, resulted in impotence.

Pregnancy

Deleterious and occasionally fatal effects of the gravid state on patients with S-C hemoglobin disease have been noted. Some observers have gone so far as to advocate sterilization under certain circumstances.4 Several deaths during pregnancy have been attributed to this hemoglobinopathy.2,15,21,23,27,54,74,79 On careful analysis, however, only six cases were proved by electrophoresis of the patients’ hemoglobin. The others were included because of family studies or clinicopathologic similarities or both.

We observed a 27 year old Negress in her thirty-second week of gestation, in whom a severe hemolytic crisis necessitated massive transfusion. She had never been ill before and a previous pregnancy was uneventful except for mild anemia. Her spleen was massively enlarged and target cells were common on the blood film. Nevertheless, by all the usual laboratory criteria, the patient had sickle cell anemia.

In many of the cases of death in pregnant “sicklers” reported prior to the advent of hemoglobin electrophoresis, the patient had extreme splenomegaly.27 Although many observers have assumed that these cases were examples of S-C hemoglobin disease, the cases may well have been atypical cases of sickle cell anemia, such as the one cited27 and those reported by Watson.84 They also may have been cases of sickle-thalassemia.

There can be no doubt of the fertility and fecundity of our patients, as all
women over the age of 21 have been pregnant. The 25 gravid patients averaged 3.5 pregnancies and 2.8 live births. Our obstetrical data obtained from 29 women over the age of 12 is detailed in table 3.

An unexpectedly high percentage of splenomegaly (80 per cent) was observed in the 25 patients who had been pregnant, irrespective of whether complications had been experienced. This frequency far exceeded the 50 per cent incidence in the remaining 50 patients.

Approximately 19,000 Negro deliveries take place annually at Cook County Hospital, 3,000 of which are abortions. On the basis of an expected 1:1500 incidence, approximately 125 pregnancies have occurred in patients with S-C hemoglobin during the last ten years, yet during this ten-year period there have not been any known maternal deaths in “sicklers” in this institution. The complications listed in table 4 suggest the conclusion that some were unrelated to the presence of S-C hemoglobin and many were not serious.

The literature shows reports of 28 patients who had at least 80 pregnancies, of which 32 were complicated. Among these, were six maternal deaths. The data include only those patients having complications of pregnancy and, therefore, are not applicable to the general group of women with S-C hemoglobin. The stress of pregnancy in this hemoglobinopathy is real and under certain circumstances may cause the death of the patient. We do not believe, however, that sterilization is warranted unless performed at menarche, for

Table 3.—Obstetrical Data (25 Patients)

<table>
<thead>
<tr>
<th>Number of pregnancies</th>
<th>87</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of abortions</td>
<td>17</td>
</tr>
<tr>
<td>Number of stillbirths</td>
<td>9</td>
</tr>
<tr>
<td>Number of live births</td>
<td>69*</td>
</tr>
<tr>
<td>Number of patients with complications of pregnancy</td>
<td>9</td>
</tr>
<tr>
<td>Number of complicated pregnancies</td>
<td>14</td>
</tr>
</tbody>
</table>

*One patient had two sets of twins.

Table 4.—Complications of Pregnancy

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age when studied</th>
<th>Gravida</th>
<th>Para</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>21</td>
<td>III</td>
<td>II</td>
<td>“Pneumonia” and anemia; 2 units of blood given.</td>
</tr>
<tr>
<td>12</td>
<td>29</td>
<td>VII</td>
<td>VI</td>
<td>P.A. of pregnancy, twice.</td>
</tr>
<tr>
<td>51</td>
<td>29</td>
<td>VI</td>
<td>V</td>
<td>Anemia once; no treatment.</td>
</tr>
<tr>
<td>24</td>
<td>26</td>
<td>III</td>
<td>III</td>
<td>Pain “crisis” and toxemia at 36 weeks.</td>
</tr>
<tr>
<td>39</td>
<td>24</td>
<td>III</td>
<td>III</td>
<td>Painless bleeding in 3rd trimester of each pregnancy. Five units of blood 2nd time, 3 units 3rd time.</td>
</tr>
<tr>
<td>61</td>
<td>27</td>
<td>II</td>
<td>I</td>
<td>Caesarean section for toxemia.</td>
</tr>
<tr>
<td>75</td>
<td>63</td>
<td>III</td>
<td>III</td>
<td>Episode of jaundice with 1 pregnancy.</td>
</tr>
<tr>
<td>68</td>
<td>21</td>
<td>I</td>
<td>I</td>
<td>Severe anemia 3rd trimester. No treatment.</td>
</tr>
<tr>
<td>69</td>
<td>44</td>
<td>VI</td>
<td>V</td>
<td>Severe hematuria with 3 pregnancies, requiring transfusion.</td>
</tr>
</tbody>
</table>
many of the serious complications and most of the deaths occurred in the primigravida or patients with previously uncomplicated pregnancies. A more optimistic outlook than voiced previously is justified during pregnancy in patients with S-C hemoglobin disease.

Miscellaneous Observations

Transfusions and surgical procedures. Surprisingly few of the patients gave a history of having received blood transfusions, although many of them knew that at one time they had been anemic. Only 15 had been transfused and most of these had received blood on only one occasion.

A total of 21 surgical procedures, performed on 16 patients, are listed in table 5. The infrequent surgical procedure is remarkable considering their age distribution and the frequency of abdominal pain in this group of patients.

Neuropsychiatric disease. A list of patients with severe neuropsychiatric disorders is given in table 6. Perhaps the bizarre neurologic disorders noted in Cases 11 and 13, and perhaps also the cases of meningismus, were obscurely related to the hemoglobinopathy. Certainly the psychiatric disorders were related more closely to the uncertainties and stresses of the patient’s environment. None of our patients had anything suggestive of bleeding into the central nervous system and none reported convulsive seizures. Although in specific cases neurologic diseases may be related to the presence of S-C hemoglobin and coma is common as an agonal event, it is our impression that such an association is infrequent and perhaps coincidental.

Dermatologic problems. Leg ulcers are common in all cases of severe chronic hemolytic anemias and occur in 50 per cent of the patients over the age of 14 with sickle cell anemia. Four of our patients had had leg ulcers, usually following trauma; all healed without recurrence and without specific therapy. It is possible that they were unrelated to the presence of abnormal hemoglobin.

Endocrine problems. Only one diagnosed endocrine problem was encountered. The patient in Case 40 had classical hyperthyroidism with an 131 uptake of over 50 per cent. It would seem that this problem was entirely unrelated.

<table>
<thead>
<tr>
<th>Table 5.—Surgical Procedures (Sixteen Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholecystectomy ........................................ 3</td>
</tr>
<tr>
<td>Exploratory laparotomy for abdominal pain ............ 2</td>
</tr>
<tr>
<td>Sequestrectomies for chronic osteomyelitis ............ 2</td>
</tr>
<tr>
<td>Splenectomy ............................................. 2</td>
</tr>
<tr>
<td>Cholecystotomy .......................................... 1</td>
</tr>
<tr>
<td>Repair of a perforated peptic ulcer .................... 1</td>
</tr>
<tr>
<td>Hemorrhoidectomy ....................................... 1</td>
</tr>
<tr>
<td>Resection of a hemorrhagic renal cyst ................. 1</td>
</tr>
<tr>
<td>Removal of a benign tumor of the arm .................. 1</td>
</tr>
<tr>
<td>Hysterectomy ............................................ 1</td>
</tr>
<tr>
<td>Ovarian cystectomy ...................................... 1</td>
</tr>
<tr>
<td>Caesarian section ........................................ 1</td>
</tr>
<tr>
<td>Tibial osteotomies (post poliomyelitis) ................ 1</td>
</tr>
<tr>
<td>Bone biopsy .............................................. 1</td>
</tr>
<tr>
<td>Amputation right arm (trauma) .......................... 1</td>
</tr>
</tbody>
</table>

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Osteomyelitis

S-C hemoglobin does not appear to predispose to the usual infections due to gram-positive organisms. Blood cultures performed in two cases of presenting pneumonia and septicemia yielded E. coli. Pathogens were isolated from the urine specimens of four patients with acute pyelonephritis and in each instance E. coli was the offending organism.

Salmonella typhimurium (fig. 4) and E. coli (fig. 5) were isolated respectively in our two cases of osteomyelitis. To the best of our knowledge, this is the first report of an E. coli osteomyelitis in a patient with S-C hemoglobin disease. Lohmuller's case was due to a paracolon organism; the organism isolated in Silver's case was Salmonella typhimurium.

Hook in 1965 was able to find 27 cases of Salmonella osteomyelitis in sickle cell anemia, to which he added three of his own. He also reported on three other cases of Salmonella infection.

The entrance of coliform organisms into the blood stream and their establishment in osseous tissue has been explained by micro-infarction of the small bowel in conjunction with bone infarction. Comparable abnormalities of cell metabolism and oxygen content in carcinomatous tissue and hematomata predispose to Salmonella infections.

Roentgenologic Observations

Roentgenograms of the skull made of 33 patients failed to show the massive diploic widening, tower skull, or "hair on end" effect so frequently seen in se-

<table>
<thead>
<tr>
<th>Case no.</th>
<th>S-C Hb. complaints</th>
<th>N-P disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>Abdominal pain and ileus</td>
<td>Meningismus.</td>
</tr>
<tr>
<td>71</td>
<td>Pain in legs, often hip pain, jaundice</td>
<td>Meningismus.</td>
</tr>
<tr>
<td>47</td>
<td>Bone and abdominal crises</td>
<td>Severe depressive reaction.</td>
</tr>
<tr>
<td>56</td>
<td>Cholelithiasis</td>
<td>&quot;Nervous breakdown.&quot;</td>
</tr>
<tr>
<td>52</td>
<td>Cholelithiasis</td>
<td>Chronic paranoid schizophrenia.</td>
</tr>
<tr>
<td>62</td>
<td>&quot;Rheumatic Fever&quot;</td>
<td>Episode of &quot;blindness&quot; in past.</td>
</tr>
<tr>
<td>13</td>
<td>&quot;Rheumatic Fever,&quot; hip pain</td>
<td>Heroin addiction.</td>
</tr>
<tr>
<td>38</td>
<td>None</td>
<td>Alcoholism and heroin addiction.</td>
</tr>
<tr>
<td>11</td>
<td>One pain crisis</td>
<td>Alcoholism and heroin addiction.</td>
</tr>
</tbody>
</table>

From www.bloodjournal.org by guest on April 19, 2017. For personal use only.
Fig. 4.—Case 16. A 17 year old Negress with S-C hemoglobin disease: history of hematuria, generalized arthralgia and painful bones since infancy which had become worse in the last six months, especially over the right upper arm and left femur. Culture from draining sinuses revealed *Salmonella typhimurium*. Roentgenograms of the right humerus and left femur revealed multiple areas of osteoblastic and osteolytic activity, dense cortical thickening, and the longitudinal intracortical fissuring characteristic of osteomyelitis complicating sickle cell anemia and its variants.
Fig. 5.—Case 14. A 26 year old Negress, gravida V, para IV, with S-C hemoglobin disease: history of pain in right arm and left leg for three months. Previous hospitalization for *E. coli* septicemia, pyelonephritis, and toxic hepatitis. Roentgenograms of the right humerus, right radius, and left femur revealed extensive destructive changes of the shafts, and periosteal reaction of the type seen in osteomyelitis. Cultures were positive for *E. coli*.

vere hemolytic anemias, such as sickle cell or Cooley's anemia. Changes were confined to slight thickening of the calvarium and slight stippled osteoporosis, of which one or both were seen in eight cases.

Long bone roentgenograms revealed changes of cortical sclerosis, coarsened trabeculation, periosteal reactions, and evidence of bone infarctions in a surprising number of cases. These conditions were often of the same severity as
in sickle cell anemia. Widening of the medullary canal, usually attributed to pressure atrophy from hyperplastic marrow, was conspicuously absent. This is in keeping with the mildness of the hemolytic process. The most striking finding was bone infarction, which in our patients was apparently more frequent than in patients with sickle cell anemia53 (figs. 6, 7 and 8).

Cockshott19 reported slight changes in the long bones of his patients, but this has not been our experience. Eighteen of our 33 cases showed evidence of long bone changes, 11 of them advanced. The single abnormality was bone infarction, although all the other changes listed were observed alone or in combination.

Two patients had chronic active osteomyelitis in multiple long bones and both had so-called cortical fissuring.35 Three patients not available for review were known to have had coarse trabeculations and bone infaracts, one of them (Case 58) severe. Thirteen of the 33 patients had pathologic changes in their femoral heads, four with aseptic necrosis. Two patients not available for re-study (Cases 48 and 58) had had roentgenologic diagnoses of aseptic necrosis of the femoral heads.

Similar lesions of the humerus were seen in several cases when roentgenograms were obtained because of symptoms referable to this area. The lesions were usually minimal. A summary of the roentgenologic changes is given in table 7.

The roentgenologic observations which were considered to be unrelated to the abnormal hemoglobin included hilar adenopathy in a case of sarcoidosis, scoliosis, osteoarthritis, hyperostosis frontalis, and osteitis condensans illi.

Red Blood Cells

The presence or absence of anemia was ascertained by the level of the red blood cell count (RBC) in all but seven patients for whom only hemoglobin determinations were available. The hemoglobin level in six of these cases was above 12 Gm. and it was inferred that a simultaneous RBC would have been above four million in each instance. One patient whose hemoglobin was 10.5 Gm., and for whom RBC count was not available, has not been included in our analysis.

Sixty-two of 74 cases (84 per cent) had RBC levels of four million or above. In 12 cases the highest count recorded was less than four million: ten in the range of three to four million and two in the range of two to three million.

In all instances in which the highest count recorded was below four million, a reasonable explanation for the anemia could be had in the presence of infection, bleeding from the nose or genitourinary tract, recent pregnancy or recent surgical procedure. Some of these were single determinations in patients unavailable for re-evaluation.

Extreme variation of the red cell level occurred in 14 persons, 12 of whom were patients whose highest count was four million or greater. A transient anemia of moderate intensity occurred in four cases, and of severe intensity in eight. In these eight cases the RBC fell below three million. Only two patients (Cases 69 and 12) had an RBC count below two million, both during pregnancy. Hematuria and megaloblastic anemia of pregnancy were evident.
Figs. 6–7.—See legend, facing page.
The patient with "pernicious anemia of pregnancy" manifested the lowest count recorded in our series, an RBC count of 0.78 million per cu. mm. The next lowest was an RBC count of 1.57 million per cu. mm. (Case 69). A five year old, Negro boy (Case 45) had an RBC count of 1.64 million during severe crisis.

It is important to realize that when RBC determinations were repeated during follow-up evaluation, all patients with severe anemia were subsequently in the range above three million. When patients were entirely well, the counts were usually four million or above.

As anticipated, the 15 patients considered to be asymptomatic (having never experienced symptoms secondary to S-C hemoglobin) were not anemic. In the presence of pneumonia, however, in two of these patients (Cases 35 and 27) a moderately severe anemia developed (2.02 million and 3.50 million per cu. mm.) respectively. In a third patient (Case 39) an anemia developed secondary to vaginal bleeding in the last trimester of each of three pregnancies.

It may be said, then, that in the absence of a second disease process, asymptomatic patients with S-C hemoglobin disease are not anemic. This is so regardless of the absence of a history of symptoms referable to S-C hemoglobin disease. It is important to stress, however, that during periods of illness, anemia may become significant.

**Morphology of Red Cells**

Anisocytosis was characteristic of all blood films, although never severe. As might be expected, there was some tendency for the degree of anisocytosis to parallel the degree of symptoms. Poikilocytosis was uncommon. Its presence in the blood film of a patient with S-C hemoglobin disease should stimulate further investigation. Macrocytosis is common in hemolytic syndromes and our group was no exception. A megaloblastic marrow was present in the one patient whose blood film revealed a high degree of poikilocytosis and anisocytosis in addition to macrocytosis. Polychromatophilia appeared in many of the blood films regardless of the patient's clinical status. Its presence reflected the accelerated erythropoiesis.

Many of our patients, as well as those whose cases have been previously reported, had occasional typical sickled cells (fig. 10). This finding in the blood films was not related to degree of illness, although the quantity of deformed...
cells was greater during crises or in the presence of severe anemia. The morphologic changes of the red cells in the sealed wet preparation were intermediate between that seen in sickle trait and sickle cell anemia, being filamentous and "holly wreath" in varying proportions (fig. 9).

All but five patients manifested sickling of the red blood cells. Unfortunately, these patients were not restudied during their hospital stay and subsequently were not available for re-evaluation. Because these five cases (Cases 70, 71, 72, 74, 75) did not differ in any regard from the others, we have included them. This was done with the knowledge that a remote possibility exists that these may have had C-D hemoglobin.

Target cells are characteristically thin; on that basis one-third of the blood films were considered hypochromic, although proved instances of iron deficiency were infrequent. Severe iron deficiency was present in two cases in which anemia was moderate. In Case 6 the patient had a serum iron of 48 gamma (98 gamma control); Case 68 had a diminution of stainable marrow iron.

Targeting was observed in all cases and is probably a sine qua non of this syndrome (fig. 10). Not infrequently the number of target cells was less than 1 per cent, and occasionally over 80 per cent, with an average between 5 and 15 per cent; 50 per cent of the patients had a normal reticulocyte count when well. In no instance did it exceed 8.6 per cent. In contrast, a pronounced reticulocytosis, often greater than 10 per cent, was characteristically present.
Table 7.—Roentgenologic Changes

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age &amp; sex</th>
<th>History of extremity pain</th>
<th>X-ray changes in</th>
<th>Skull</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hip†</td>
<td>Long bones†</td>
</tr>
<tr>
<td>3</td>
<td>40/F</td>
<td>+</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>27</td>
<td>20/F</td>
<td>0</td>
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<td>+</td>
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<td>25</td>
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<td>4</td>
<td>31/M</td>
<td>0</td>
<td>+</td>
<td>+</td>
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<td>28</td>
<td>57/M</td>
<td>0</td>
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<td>+</td>
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<td>31/M</td>
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<td>59/M</td>
<td>once</td>
<td>+</td>
<td>++</td>
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<td>+</td>
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<td>+</td>
<td>++</td>
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<tr>
<td>58</td>
<td>49/M</td>
<td>++++</td>
<td>AN</td>
<td>++++</td>
</tr>
</tbody>
</table>

*Chronic active osteomyelitis.
†Aseptic necrosis of femoral head indicated by AN.
‡Severity indicated 0 to ++++.

during periods of illness. The only exceptions were in patients with severe bacterial infection in whom depression of reticulocytosis is not unexpected.

**Red Cell Survival**

Information regarding red cell survival in S-C hemoglobin disease is meager. Kaplan⁴⁵,⁴⁶ reported a greatly shortened survival in three patients. Wein-stein,⁸⁵ using cells tagged with radioactive sodium chromate, obtained a half-life of 20 days. This result, when converted to mean cell survival, indicates a red cell life span of 50 days with a daily destruction rate of 2.4 per cent. Further studies are obviously indicated.

**Leukocytes**

The white blood count, in general, was below 10,000 during asymptomatic periods and often above 18,000 when illness was present. The white blood cell differential was unremarkable except for the occasional presence of immature granulocytes when patients were symptomatic. Toxicity of the granulocytes, when present, was usually a reflection of concomitant infection.

**Marrow Observations**

Marrow aspirations were performed in eight patients. In each the cellularity
was moderately to greatly increased. The megakaryocytes were adequate, except in Case 12 at the time of megaloblastic anemia. The nucleated RBC: WBC ratio varied from 1:1 to 3:2 in patients whose disease status was uncomplicated. Erythropoiesis was normoblastic. The marrow finding of accelerated erythropoiesis, similar to that previously reported, was a reflection of the underlying hemolytic state. In one instance complicated by septicemia, granulocytic hyperplasia so altered the ratio that accelerated erythropoiesis
was obscured. The patient with "pernicious anemia of pregnancy" had the
typical marrow of a nuclear maturation arrest in erythropoiesis and giant gran-
ulopoiesis. Jonsson\(^4^3\) has also reported the occurrence of megaloblastic erythro-
poiesis in a pregnant Negress with S-C hemoglobin disease. Addisonian per-
nicious anemia was ruled out in his case as well as ours by the presence of
free hydrochloric acid on gastric analysis.

Although determinations of serum folic acid and vitamin B\(_{12}\) levels were not
obtained in these cases, a state of depletion may be presumed. It is a generally
accepted clinical concept that these substances are utilized at a rate greater
than normal when red cell production is accelerated. If the supply of these
substances is not proportionately increased, a state of deficiency results. This
deficiency worsens when poor nutrition, intensified by the anorexia and nausea
of pregnancy, is superimposed. When further aggravated by fetal parasitism,
this deficiency becomes sufficiently severe to cause megaloblastic erythropoiesis.
We believe that the mechanism operative in our patient as well as in many
others with pernicious anemia of pregnancy is one of supply and demand in
which supply is inadequate and demand is overwhelming.

**Abnormal Hemoglobins**

Hemoglobin electrophoresis was carried out on paper\(^2^0\) and agar,\(^6^8\) as well
as starch block\(^5^0\) in selected cases. Elution and quantitation of the amounts of
hemoglobin S and C were performed routinely on all paper graphs.\(^4^4\) Fetal
hemoglobin determinations were made by the Singer method,\(^7^5\) although in
two cases (31 and 32), the Chernoff capillary tube technic\(^9\) was employed.
Apparently a relationship does not exist between the amount of F hemoglobin and any facet of the clinical condition. The values were normal in 39 patients and only slightly elevated in 19 (2.1 to 3 per cent). We were unable to discern any distinguishing features in the 17 cases of elevated values. The two highest F hemoglobin determinations of 6.4 and 11.1 per cent were in asymptomatic patients who were siblings of a patient who also had a slightly elevated level of 2.5 per cent. These three cases in one family suggested that genes other than those controlling S and C hemoglobin were operative.

Quantitation of hemoglobins S and C was also performed in 35 instances. The percentages of these hemoglobins were nearly equal in most cases. Differences greater than 5 per cent were considered significant. This occurred in 11 cases. In each instance hemoglobin C predominated. In these 11 cases the average amount of C hemoglobin was 53.4 per cent with a high of 58.8 per cent. As in the case of F hemoglobins, we could not segregate any clinical data on the basis of the percentage of abnormal hemoglobins present.

Platelet and coagulation tests. Thrombocytopenia was neither suggested nor demonstrated in our patients. At least three cases of thrombocytopenia have been reported, but we do not believe that there was a direct association with the presence of S-C hemoglobin.

Many of the patients with hematuria had had routine coagulation tests performed. Neither our patients nor those whose cases were reported were abnormal.

Uric acid. Uric acid determinations were performed for 31 patients at a time when most were well. Twelve patients had abnormal levels, ranging from 6.8 mg. per cent to 9.4 mg. per cent. Most cases with reticulocytosis greater than 5 per cent had an elevated blood uric acid. This finding was anticipated in view of the known association of increased red cell formation and increased uric acid production.

Gouty arthritis has been reported in patients with sickle cell anemia as well as other chronic hemolytic states; however, we are unaware of any case of gout in a person with S-C hemoglobin disease.

Pathology

Autopsy data have been described in at least ten proved cases of S-C hemoglobin disease. In addition, surgically removed specimens of spleen and kidney have been described in detail. Intense congestion and widespread intravascular sickling have predominated pathologically. These changes were striking in the spleen removed in Case 12. The spleen weighed 1800 Gm. and showed hemorrhages and necrosis with occasional siderotic nodules in addition to congestion and sickling. Reported weights of spleens have ranged from 10 Gm. to 1400 Gm., the smaller ones being similar to the atrophic organ seen in sickle cell anemia.

In Case 62, the patient, a heroin addict with recurrent bouts of hepatitis, died in crisis. Postmortem examination revealed the usual engorgement and sickling. Mild hemosiderosis was present in all organs. The lungs did not show any evidence of thrombosis, embolization, or infarction. Connective tissue
stroma increased in the liver and cellular infiltration, chiefly by lymphocytes, was present. The spleen weighed 400 Gm. and had a thickened capsule which was irregularly scarred. A severe tracheobronchitis was considered to have triggered the crisis. Evidence was lacking of marrow infarction or embolization of the lungs by marrow elements, as has been reported by others. Caseation necrosis, compatible with tuberculosis, was present in the lymph nodes. The kidneys showed the characteristic changes of congestion and sickling; there was no extravasation of blood cells or papillary necrosis, such as seen by Mostofi in kidneys removed because of hematuria.

In summary, the primary pathologic changes in our case as well as those reported by others are referable to the presence of S hemoglobin. Regardless of the specific electrophoretic pattern, the characteristic changes are congestion and intravascular sickling. All other autopsy data are either a result of these changes or are related to a second disease.

**COMMENTS**

It has become clear that a basic difference does not exist between patients with S-C hemoglobin and those with sickle cell anemia. The course of both is episodic and in both the complications are intimately related to intravascular sickling. The difference is only one of degree.

Certain complications are surprisingly frequent in patients with S-C hemoglobin disease, such as joint and abdominal pains, hematuria, epistaxes, and concomitant infections. It seems paradoxical that these complications occur less frequently in the severer syndrome of sickle cell anemia. The paradox is partly resolved once it is realized that the greatest frequency of these complications in S-C hemoglobinopathy occurs at an age not attained by most patients with sickle cell anemia. Hematuria and vitreous hemorrhages are typically complications of adult life. The fertility and fecundity of patients with S-C hemoglobin as well as the duration of their reproductive period make their exposure to the stress of pregnancy far greater than that of sickle cell anemia.

The pathogenesis of these complications can be understood in terms of the delicate balance of factors discussed in the section on pulmonary disease, for this mechanism pertains to the venous drainage of all organs, particularly those with poor collateral circulation.

The complications of pregnancy can be understood in relation to the changes attending the gravid state. These changes of increased metabolism, temperature elevation, leukocytosis, and venous stasis are all known to potentiate sickling.

The frequency of extremity pain in youth and its tendency to decrease with age are probably related to the increased metabolism and relatively inadequate blood supply of rapidly growing tissue.

Persistence of splenomegaly in adult life depends on the absence of repeated infarctions with consequent fibrosis. The occasional occurrence of atrophic spleens in patients with S-C hemoglobin is evidence that the sickling can result in infarction with consequent fibrosis.

Thus, these syndromes are essentially varying expressions of the same process. The molecular basis of this variation allows complete in vitro separation
of the two syndromes on the basis of physical characteristics under known conditions. This physiochemical separation can be correlated with the respective clinical syndromes. It is reasonable, however, that in the presence of modifying forces in vivo, this sharp distinction fades and under certain circumstances, the two syndromes merge.

Summary

1. Seventy-five cases of S-C hemoglobin disease were studied, ranging in age from 14 months to 66 years.
2. Pain in the splenic area was the most common presenting complaint, splenomegaly being readily demonstrable in about two-thirds of the cases.
3. Hematuria, epistaxes and concomitant infections occurred with sufficient frequency to suggest a relationship to the underlying S-C disease.
4. Pregnancy was tolerated fairly well.
5. Although a number of clinical and hematologic features are suggestive of S-C disease, the diagnosis must still be based on electrophoretic studies of the hemoglobin.

Summary in Interlingua

1. Esseva studiate 75 casos de morbo de hemoglobina S-C. Le etates del patientes variava ab 14 menses ad 66 annos.
2. Dolores in le area splenic esseva le plus communmente le gravamine de presentation, e splenomegalia esseva prestemente demonstrabile in circa duo tertios del casos.
3. Hematuria, epistaxis, e infectiones concomitante occurreva con un frequentia sufficiente a suggerer un relation con le subjacente morbo de hemoglobina S-C.
4. Pregnantia esseva tolerate satis ben.
5. Ben que il existe un numero de phenomenos clinic e hematologic que pote sugerir le presentia de morbo de hemoglobina S-C, le establimento del diagnose continua depender de studios electrophoretic del hemoglobina.

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S-C Hemoglobin: A Clinical Study

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