SICKLE-CELL DISEASE: AN ANESTHESIOLOGICAL PROBLEM • †

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Sickle-cell anemia is a chronic, familial, hemolytic anemia of unknown etiology which usually is found in the Negro race. It was known originally as Herrick’s anemia after the man who first (1) reported a case of the syndrome, but, in 1922, Mason (2) described the fourth case to be reported and coined the name “sickle-cell anemia” in token of the appearance of the cells. In 1926, Cooley and Lee (3) gave us the term “sicklemia” in reference to the milder forms of the disease, and reserved the term “sickle-cell anemia” for the most severe forms with systemic manifestations. Since that time, the latter terms have become widely accepted as descriptive.

The first report of abnormal cells of this type in man was published in 1904 by Dresbach (4), of The Ohio State University. It was noted that a mulatto medical student, in examining his own blood, found elliptically shaped cells. This student died a few months thereafter, in spite of apparent good health at the time of the blood discovery, and further tests on him could not be obtained. Prior to this, in 1840 Gulliver (5) had described sickle cells in a deer in a London zoo, and further animal investigation revealed that the deer is the only animal species showing this phenomenon. Singer (6) described the death of deer in the Michigan forests from sickle-cell anemia.

In 1910, Herrick (1) reported the first case of sickle-cell anemia, describing a 20 year old professional student with shortness of breath, palpitation, jaundice, leg ulcers, generalized lymphadenopathy, dark urine, epigastric pain, anemia, and sickling of the erythrocytes. Sydenstricker (7) called the attention of the medical profession to the frequency of incidence of this disease, and since this time innumerable investigations have added bits to our knowledge of it. Speculation about the etiology of the disease has passed through many phases, implicating chronic anoxemia, malarial parasites, agglutinogen reactions, and blood types, finally reaching the concept that the disease is a genetically inherited entity with the genes causing the disease being

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Mendelian dominants. This last has been modified by Neel (8), who postulates that a person with sicklemia has inherited a gene from one of his parents, while a person with the anemia has inherited the gene from both parents. Finally, Pauling (9) has shown by electrophoretic studies that the erythrocytes of sicklemia and sickle-cell anemia patients contain an abnormal hemoglobin, present in approximately equal amounts with normal hemoglobin in persons with sicklemia and forming 100 per cent of the hemoglobin of persons with sickle-cell anemia. These findings of Pauling's appear to support the concept advanced by Neel.

Throughout the years since 1923, extensive investigations have been made in attempting to determine the incidence of erythrocyte sickling. It generally is assumed that the sickling phenomenon does not occur in people of white ancestry. Various investigators, testing a total of 5,464 white cases, found only 11 cases of erythrocyte sickling, all of whom were from Brazil or Mexico, in which countries racial intermixing is not rare. While it is possible that the gene may be present in a white person, having passed down from an unknown ancestor of Negroid blood, it may safely be said that the disease for practical purposes is confined to the Negro race. Negroes in Africa appear to have a higher incidence (14.32 per cent) than those in North America (9.0 per cent). However, those Negro tribes which live farther away from the tribes of Semitic origin have incidences as high as 26 per cent and 30 per cent, while a single tribe located in an extremely remote mountain area has an incidence of 45 per cent. Those tribes which live near the Caucasian conquering tribes, and those which have been slaves to these tribes of Caucasian origin for centuries, have the lowest incidence (2 per cent). Many other studies show that the yellow races and the various tribes of Amerinds in both the Americas are negative for the sickling phenomenon (10, 11, 12, 13). There is no apparent difference in sex incidence (14, 15). Figures for the American Negro generally approach 11 per cent incidence (14). Many figures have been quoted as to the incidence of sickle-cell anemia among those having the erythrocyte sickling phenomenon, but generally hematologists are in agreement with the figure first quoted by Diggs et al. (16) of 1 to 40. Lest one be lulled into false security by the apparent smallness of the percentage, it should be emphasized that one would expect, at any one time, 1,600,000 American Negroes to be affected by sicklemia, and 40,000 to have the severe manifestations of sickle-cell anemia. Raper (17) estimates that there are 200,000,000 Negroes living between the Sahara Desert and Capetown, with an incidence rate approximating 20 per cent. This high incidence of the ailment makes mandatory an understanding of this disease, and continuing suspicion a necessity for those anesthesiologists who practice in areas where large numbers of patients of Negro extraction are presented for treatment.
Several features have been discovered which shed light on the pathological processes whereby the gross pathology of sickle-cell anemia affects the patient. Diggs and Bibb (18) found that the sickle cell is more susceptible to mechanical trauma than the ordinary erythrocyte, while Murphy and Shapiro (20) noted that the sickle cell is brittle and rigid in appearance when compared with the flexible and sponge-like normal red cell. Callender and Nickel (21) found that the normal red cell lives approximately one hundred and twenty days in the blood stream, while the same authors (21) and Singer (22) found that the abnormal erythrocyte lives only thirty days. In 1927, Hahn and Gillespie (23) showed that the shape of the erythrocyte in patients with sickle-cell anemia could not be altered by pH changes or osmotic-pressure variations provided the oxygen tension was maintained at an adequate level. In the presence of low oxygen tensions, sickling occurred and the cells could not be returned to their normal shapes until the oxygen tension was returned to normal. Numerous other authors (24, 25) have investigated the behavior of the sickle cell and confirm the fact that normally tissue oxygen tension is low enough to permit the sickling of the sickle cells, but not low enough to cause the sickling of the cells in a patient who has sickleemia without the anemia. Reinhard (26), who administered 80 to 100 per cent oxygen to patients over periods ranging from eight to twenty days, found that while the intravascular sickling was reduced, the degree of hemolysis and muscular pain was not diminished, and in addition the reticulocyte response to hemolysis was reduced with an attendant decrease in the total red cell count. This would appear to preclude the use of 100 per cent oxygen in the therapy of sickle-cell anemia.

The proximate pathology of sickleemia and sickle-cell anemia is due to several factors. First, the generalized anemia causes manifestations of weakness, lassitude, respiratory difficulty, inability to resist infection, and interference with proper tissue oxygenation. Second, the assumption of bizarre shapes by the erythrocytes increases blood viscosity and markedly changes the body hemodynamics. Third, the cells produce a sludging effect in the circulating blood, with the resultant formation of emboli which plug capillaries and serve as nidi for the propagation of thrombi. These factors give rise to symptoms and syndromes which may be referable to almost any organ or system of the body. These have been described frequently and the general patterns are comparatively well known.

Changes in the general body habitus have been recorded by various authors (15, 27, 28, 29). Children fail to gain weight, and a spider-like appearance of the hands is common. Signs of hypogonadism are apparent in males. The legs are spindly, with a similar decrease in head circumference, weight and height are usually subnormal, and the abdomen is often protuberant. Jaundice is common (30). Chronic leg ulcers, or the scars of chronic leg ulcers, are a common finding in cases
of the disease, and are considered to be due to a combination of chronic hypoxemia and recurrent thromboses of the vessels (1, 30, 31), but, according to Diggs and Ching (32), the ulcers are infrequent in children but are present in 75 per cent of adults affected with the disease. They usually develop on the inner medial aspect of the leg, just above the ankle (30), but no part of the skin is really exempt.

Cardiac enlargement may occur, primarily on the basis of the anemia itself and Anderson and Ware (31) and Wintrobe (19) found cardiac enlargement in 76 per cent of the cases with anemia. Klinefelter (24) reported cardiac enlargement in all of his 12 cases. Yater and Hansmann (33) believe that the cause of the enlargement is multiple thrombi in the vessels of the pulmonary circulation, with a resulting cor pulmonale progressing to failure. Coronary insufficiency due to thromboses of the myocardial vessels is a possibility.

Pulmonary manifestations, so important to the anesthesiologist, are not infrequent. Yater and Hansmann (33) contend that multiple pulmonary infarctions occur, many of these so minor that diagnoses of pneumonia are made originally. Steinberg (34) reported a case which showed fresh and old infarctions at autopsy.

The central nervous system and the bones are not spared by the disease. Neurologic manifestations are certainly not unusual. In 1940, Hughes, Diggs and Gillespie (35) evaluated 31 cases from the literature and from their own files, and recorded 28 separate neurologic findings, many of which were present in more than 1 case. Drowsiness or coma was the most common finding, with hemiplegia, aspasia, headache, concussions, and stiff neck following in that order. Patterson et al. (36) reviewed 143 cases and found 57 with neurologic disturbances which more or less paralleled the findings of Hughes, Diggs and Gillespie (35). Other reports of neurological involvement are myriad. These findings probably are dependent on the extent of hypoxemia and on the site and the size of vascular thromboses.

Bone and joint pain is a common finding, and this, in combination with the presence of cardiac findings, frequently results in confusion of the diagnosis with rheumatic fever. Joint pain was reported in 186 of 214 cases by McGavack and Nussbaum (30). There are changes in the actual structure of the bone, with the skull being involved most frequently. Danford, Marr and Elsey (37) have described the characteristic radiographical finding as cortical thickening with spicules of bone radiating from the flat bone plates to give the appearance of "hair standing on end." It is interesting to note that this same appearance has been reported in x-ray pictures of ancient Mayan skulls from Mexico (38), and in an Indian whose skull is on display in the Peabody Museum in Cambridge, Massachusetts (39). The changes in the long bones simulate osteomyelitis, and many (30) have undergone surgery in an attempt to correct what was thought to be only a localized lesion.
A situation occurring with some frequency is priapism. This was first described in 1934 by Diggs and Ching (32), and since then numerous authors (36, 40, 41, 42, and others) have recorded the occurrence of this feature. The condition may or may not be accompanied by sexual desire, and is usually extremely painful. It begins with venous congestion, and then lowered oxygen tension occurs, which causes increased sickling, and this produces further stasis, etc. Thus a vicious cycle is instituted. The condition is often treated surgically by incision and drainage, but this treatment has not been too successful because of the possibility of tissue necrosis, sloughing, and the formation of chronic ulcers. The anesthesiologist is sometimes called upon for treatment of the condition through the administration of caudal, low spinal, block, or even general anesthesia to remove the pain element and to reduce the vascular spasm which accompanies the engorgement. In one case observed by one of us (N. D. S.), none of these measures was of avail. The condition may occur at any age, with the reported cases varying between eight and twenty nine years, and it may accompany other manifestations of the disease. Two of the 6 cases with abdominal crisis reported by Campbell (40) also had priapism.

Abdominal findings are so common and so widely varied as to preclude any but the most exhaustive discussion. The kidneys are susceptible to the formation of thrombi, and frank infarcts have been located in many cases. In cases of long-standing sickle-cell anemia, degenerative and proliferative changes are frequent (32). Albuminuria is common, as is microscopic hematuria. However, gross hematuria is unusual, with several of the cases of gross hematuria being questionable as far as the actual diagnosis of sickle-cell anemia is concerned. The liver is large in acute cases, with McGavack and Nussbaum (30) reporting definite liver enlargement in 100 of 214 cases from the literature. Other reports (25, 43, 44) substantiate this finding. Grover (43) writes of sudden increase in the size of the liver and the spleen during crisis, with correspondingly rapid reduction in the size of the organs after crisis has passed. Lowe and Adams (45) reported 4 cases of hepatomegaly during crisis. Various laboratory findings are changed during crisis, indicating interference with physiological function. Splenomegaly is common among children, but, with the passage of time and with repeated infarction, the organ tends to become shrunken and atrophic. Spleen size has been recorded by many authors, with the weight being as great as 621 Gm. (46) and as small as 1 Gm. (47). Bridgers (48) followed a case in which splenomegaly originally existed, fibrosis occurred, and spleen weight at autopsy was recorded at 1.5 Gm. Gallstones are common and present a diagnostic problem for the surgeon in cases with right upper quadrant pain and concomitant sickle-cell anemia. They occur in approximately one third
of cases, according to Mayo (49). Others (50) confirm this finding. Peptic ulcer, for some unknown reason, is rare.

By far the most severe manifestation of the clinical course of sickle-cell anemia is the abdominal crisis. This attack consists of severe pain, usually sudden in onset, and frequently recurrent. Because any abdominal organ may be affected, the symptoms are those of that particular organ. Appendicitis, cholecystitis, salpingitis, ruptured viscus, and mechanical ileus may be simulated. In its mimicking of the pain of other diseases, sickle-cell anemia approaches syphilis as an imitator. The attacks frequently are accompanied by leukocytosis jaundice, fever, vomiting, and muscle spasm. The actual cause of the pain of the crisis has been variously attributed to stretch of the liver capsule, thrombosis, hypoxemia, mesenteric adenitis, nerve-root anoxemia, etc. It frequently happened, particularly in the early days of knowledge of the disease, that laparotomies were performed on these patients, with treatment being then complicated by the iatrogenic factor of a surgical incision and postoperative metabolic disturbances. From McGavack and Nussbaum's (30) study, incorrect diagnoses of abdominal conditions were made in 39 of 214 cases. Six of 14 with a diagnosis of appendicitis were subjected to surgery. Seven of 14 cases diagnosed as cholecystitis were operated on. In none of these was a surgical pathological condition found. Campbell (40) reported 3 cases which were operated on, the third of which underwent abdominal exploration on 3 separate occasions. Other reports, too numerous to mention in a short article, stud the literature with descriptions of operation for incorrectly diagnosed surgical conditions. Happily, with the increasing amount of information available concerning the disease, and with the greater awareness by physicians of the disease and its incidence, surgical intervention through diagnostic error is approaching a minimum.

The hazards of surgery in these patients are not always those which are attendant upon conditions suggesting emergency surgery. Many of the chronic conditions which are present in sickle-cell anemia patients often are regarded as surgically correctable lesions. However, the presence of the basic disease increases the hazard of surgery, and, of course, of anesthesia. For example, Bauer (51) reports the case of a 10 year old girl from whom a thyroglossal duct cyst was removed. Postoperatively, she developed what appeared to be an acute nephritis, and she died in uremia. Autopsy revealed a massive necrosis of the renal cortex with the vessels completely plugged with sickled erythrocytes. The diagnosis of sickle-cell anemia had not been made prior to surgery. Another example is the case of a young Negro male, reported by Abel and Brown (52), who underwent a left nephrectomy for neoplasm because of a filling defect in the left renal calyces. The surgical specimen showed only sickled cells filling the arterioles. Many
other situations are described in the literature, pointing that diagnosis may be in error even when the condition has permitted delay for evaluation of the patient and for planning of elective surgery.

Unfortunately, the preoperative diagnosis of sickle-cell anemia or sickleemia is not always accomplished. Many patients who are brought to the operating suite have been admitted to the hospital the previous evening, and only routine laboratory investigation has been accomplished. Cell counting according to the common techniques will not disclose the presence of the abnormal erythrocytes, and the growing tendency to utilize photoelectric methods of hemoglobin determination further precludes the discovery of the existence of the disease. There are several methods of determining the presence of the sickle cell, with the simplest ones probably being that of Scrivener and Waugh (53), in which sickling is induced by the placing of a rubber band around a finger, and that of Daland and Castle (54) in which a reducing agent, sodium bisulfite, is added to the cells after a drop of blood has been removed from the patient. These tests are simple enough for the ordinary technician to accomplish.

The anesthesiologist continually faces the possibility of a Negro patient's undergoing a sickle-cell crisis or other manifestation during an anesthetic procedure. The cells are extremely susceptible to hypoxia, and hypoxia is a condition which must be combatted in every anesthetic administration. Any cause of anoxic, anemic, stagnant, or histotoxic hypoxia is dangerous, yet anesthesiologists commonly are using drugs and techniques which themselves tend to produce one or more of these causes of hypoxia and which require intimate attention to the condition of the patient lest an anoxic situation ensue. This article is not intended to be a discussion of the causes or the characteristics of hypoxia, but it may not be amiss to mention the possibilities of overheavy premedication, hypotension, pre-existing anemia in these patients, visceral vessel dilatation with blood stagnation in high spinal analgesia, localized stasis from positioning of the patient, respiratory depression inherent in the nature of certain anesthetic agents, generalized tissue depression in hypothermic anesthesia, and so forth. Strict attention to the maintenance of high oxygen saturation throughout the course of anesthetic administration is essential in dealing with patients in whom sickle-cell anemia is even a remote possibility.

An investigation was made of the cases of sickle-cell anemia which came to surgery at the John Gaston Hospital, Memphis, Tennessee, during the period January, 1945 to December, 1952. This represented only those cases which actually had been diagnosed as active cases of the disease. All of these were operated on for a definite surgical entity. No cases were subjected to surgery who were apparently in some form of sickle-cell crisis, and who did not have a concomitant indication for surgery. No attempt was made to estimate the number
of patients admitted to this hospital who were treated medically for nonsurgical manifestations of the disease, nor was an attempt made to mass-test the total admissions to the hospital for the incidence of sickle-cell trait. Hence the cases presented are not of statistical significance, except to point out that in the previous period of years several patients were brought to surgery through inability of the attending surgeons to rule out the presence of a surgical entity. As mentioned before, during the previous period information as to the manifestations of this disease was not so widespread as it is today.

A total of 15 patients underwent some form of surgical procedure during the period considered. Of these, 1 patient had 9 operations, 2 patients had 4 each, and 2 patients had 3 each. These operations were grouped as follows:

<table>
<thead>
<tr>
<th>Site</th>
<th>Number</th>
<th>Complications</th>
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</thead>
<tbody>
<tr>
<td>Skin</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Abdomen</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Chest</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Extremities</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Obstetrical</td>
<td>18</td>
<td>4</td>
</tr>
</tbody>
</table>

Anesthesia was administered as follows:

<table>
<thead>
<tr>
<th>Type</th>
<th>Number</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Spinal</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Local or block</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>None</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Three of the obstetrical complications were premature stillbirths, and in one of these the mother died after massive transfusions, oxygenation, and so forth. This patient had no anesthesia, but arrived at the hospital with a hemoglobin too low to be recorded by the devices available—less than 3 Gm. per 100 cc. of blood. The other obstetrical complication was an infected episiotomy requiring a secondary closure. The skin complications included failure of 1 graft to take, and 2 cases of wound slough. The chest complication was a postoperative atelectasis with a prolonged morbidity period.

With such a small number of cases, a correlation of anesthetic and surgical techniques with complications is difficult to make, but the existence of 8 definite complications in 37 operative procedures is certainly a very high percentage, and is indicative of the problems facing anesthesiologists and surgeons alike in the management of cases with this disease.

In summary, a brief evaluation of sickle-cell disease has been presented, with a report of 37 cases operated at the John Gaston Hospital during the period January, 1945 to December, 1952. The importance of the anesthesiologist in the management of the sickle-cell patient during surgery has been brought to attention.
SICKLE-CELL DISEASE

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34. Steinberg, B.: Sickle Cell Anemia, Arch. Path. 9: 876 (April) 1930.