Biliary Tract Disease in Sickle Cell Anemia:

Surgical Considerations

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SICKLE CELL anemia is a chronic hemolytic disease resulting from an abnormal hemoglobin. The autosomal recessive gene for sickle hemoglobin is carried by approximately 10% of the American Negro population,[10] but the disease is not expressed unless the patient is a homozygote. In sickle cell anemia, as in other chronic hemolytic states, the incidence of gallstones is increased. Confusion has existed, however, since this disease was first described in 1910[6] as to the significance of biliary tract disease in the clinical course of sickle cell anemia. Patients with sickle cell anemia are prone to frequent painful crises involving the bones, joints, chest, and abdomen. The abdominal crises are usually accompanied by an elevation of the serum bilirubin and often an elevation in serum alkaline phosphatase suggestive of biliary tract obstruction. These crises are usually attributed to the sludging of sickled erythrocytes in hepatic sinusoids with resultant ischemia and/or necrosis of hepatocytes. Such episodes, however, are often impossible to differentiate clinically from biliary tract disease. In the past, symptomatic biliary tract disease in sickle cell anemia has been considered unusual. It has been our impression, however, that symptomatic biliary tract disease in sickle cell anemia is not unusual, and that cholecystitis as well as common duct obstruction may occur with considerable frequency.

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Clinical Material

The records of patients with sickle cell anemia having one or more admissions to The Johns Hopkins Hospital during the years 1952 to 1970 were reviewed. The charts of 147 patients were available for study. Homozygous sickle cell hemoglobin disease had been confirmed in all by hemoglobin electrophoresis. Any one of the five following criteria was accepted as evidence of biliary tract disease being present: (1) opaque biliary tract stones visible on plain abdominal x-rays, (2) non-opaque stones visualized on oral or intravenous cholecystography, (3) non-visualization following oral cholecystography on 2 consecutive days when the total bilirubin was 5 mg. /100 ml. or less, (4) evidence at laparotomy of gallbladder inflammation or biliary tract stones, or (5) the finding at postmortem of gallbladder inflammation or biliary tract stones. All charts were examined for clinical symptoms or episodes that could be attributed to biliary tract disease. The tolerance of this group of patients to the stresses of general and spinal anesthesia,[4] and to pregnancy was also evaluated.

Findings

Incidence of Biliary Tract Disease. The age distribution of these 147 patients ranged from less than one year to 73 years of age. Approximately two thirds of the patients were 20 years of age or younger.

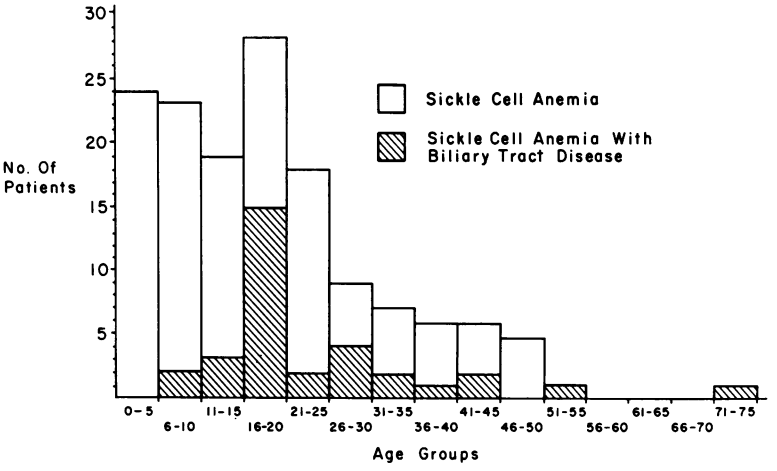

FIG. 1. Age distribution of all patients in series with sickle cell anemia, and patients with sickle cell anemia and proven biliary tract disease.

There were 73 males and 74 females in the series. Enough information was available to establish the presence or absence of biliary tract disease in 47 of the 147 patients. In this group of 47 patients, 14 were found to have no biliary tract disease. This left 33 patients, or 22% of the entire 147 patients, with proven biliary tract disease. When only those patients 15 years of age and over were considered, the incidence of proven biliary tract disease increased to 34% (Fig. 1).

Of the 47 patients in whom the status of the biliary tract was known, 26 underwent oral, and in some instances intravenous, cholecystography. In nine patients the gallbladder visualized normally and demonstrated no stones. In many of these patients total bilirubins of 3 or 4 mg./100 ml. were present, and in one patient normal visualization was obtained when the serum bilirubin was 10 mg./100 ml. In 13 patients, all with total bilirubins of 5 mg./100 ml. or less, there was no visualization on 2 consecutive days. Five of these 13 patients had radiopaque stones. In four patients normal visualization of the gallbladder occurred and showed stones. In three of these patients the stones were radiopaque. Seven of the 47 patients were examined at autopsy. Biliary tract stones were present in two, and the remaining five had normal biliary tracts at postmortem examination. In addition, one patient was found to have a normal gallbladder containing no stones at laparotomy for liver biopsy, and two patients were operated on at another hospital for gallbladder disease prior to being seen here. In one patient the gallbladder had ruptured.

Although the incidence of proven biliary tract disease in the entire series of 147 patients was only 22%, within that group of 47 in whom the presence or abence of biliary tract disease was definitely known, the incidence was 70%. Within that group of 33 patients in whom biliary tract disease was established, 61% (20 patients) had radiopaque tones. Of the 33 patients with proven biliary tract disease, 19 were females and 14 males. The youngest patient with proven biliary tract disease was 8 years, and the oldest 73 years.

Symptoms Suggestive of Biliary Tract Disease. Thirty-one of the 147 patients in this series had clinical symptoms or episodes that could be attributed to biliary tract disease. This included fatty food intolerance, episodes of upper abdominal pain compatible either with biliary colic or cholecystitis, and obstructive jaundice. Twenty-four patients with suggestive symptoms were found to have biliary tract disease. Three patients with clinically suspicious symptoms had no biliary tract disease. The remaining four patients with

TABLE 1. *Patients with Sickle Cell Anemia with Fatty Food Intolerance and/or Abdominal Pain Suggestive of Biliary Colic or Cholecystitis and/or Obstructive Jaundice*

Biliary Tract Symptoms		
31		
Biliary Tract Status Known		Biliary Tract Status Unknown
Disease Present	Disease Absent	
24	3	4

symptoms suggestive of biliary tract disease were found in that group of 100 patients in whom the presence or absence of biliary tract disease was unknown (Table 1).

Biliary Tract Surgery. Ten of the 33 patients with known biliary tract disease have undergone cholecystectomy (Table 2). This group ranged in age from 18 years to 47 years. Two patients were operated on at another hospital. One patient had a ruptured gallbladder. The remaining eight patients were operated on at The Johns Hopkins Hospital. Reasons for operation varied from fatty food intolerance to obstructive jaundice. Evidence of acute inflammation of the gallbladder was present in four of the eight patients operated on in this hospital. Gross evidence of chronic cholecystitis was present in an additional two patients at operation. Three patients underwent common duct exploration and in two patients common duct stones were found. The common duct was free of stones in the third patient. Microscopically, all gallbladders removed showed acute or chronic cholecystitis. There was no operative or hospital mortality in this group. There were no significant postoperative complications. One patient, however, clearly continued to have attacks of abdominal pain and jaundice similar to those for which she underwent cholecystectomy. At the time of operation her gallbladder was normal in appearance and there were no signs of acute inflammation, although stones were present.

Common Duct Stones. In the group of 33 patients with known biliary tract dis-

TABLE 2. *Biliary Tract Surgery in Patients with Sickle Cell Anemia*

Patient	Hospital	Age	Race	Sex	Surgical Indication	Operative Findings
M. S.	Outside	38	N	F	—	—
I. W.	Outside	28	N	F	Abdominal pain	Ruptured gallbladder
R. N.	JHH	45	N	M	Abdominal pain and jaundice	Inflamed gallbladder. Common duct stones
C. L.	JHH	31	N	F	Abdominal pain	Inflamed gallbladder. Common duct stones
K. B.	JHH	32	N	M	Fatty food intolerance	Thickened, scarred gallbladder
M. J.	JHH	47	N	F	Fatty food intolerance, abdominal pain	Inflamed gallbladder
J. N.	JHH	23	N	F	Biliary colic	Thickened, scarred gallbladder
A. J.	JHH	34	N	M	Abdominal pain, jaundice, common duct stone on x-ray	Inflamed gallbladder. Stone had passed
J. B.	JHH	18	N	F	Obstructive jaundice, common duct stones demonstrated on I. V. cholangiography	Grossly normal gallbladder with stones. Stones had passed
G. E.	JHH	30	N	F	Abdominal pain and jaundice	Grossly normal gallbladder with stones

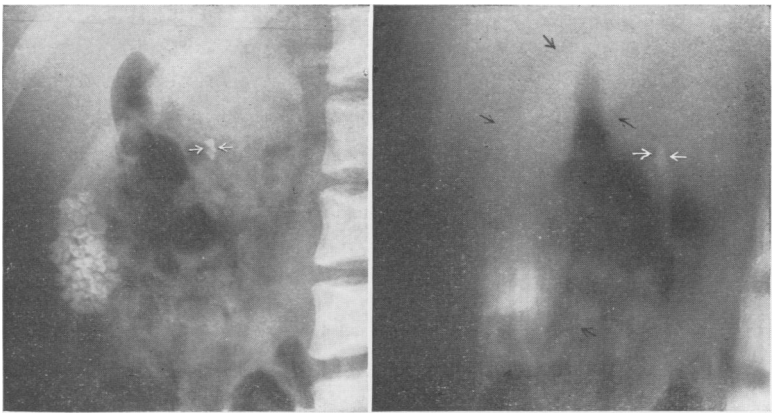

FIG. 2. a. Plain abdominal x-ray of patient 4 showing multiple opaque stones in the region of the gallbladder, and two stones in the area of the porta. b. Intravenous cholangiogram demonstrating that the stones are in the common duct.

ease, six were proven to have common duct stones. Two were demonstrated at operation, one was discovered at autopsy, two were proven by intravenous cholangiography, and one was demonstrated by a series of plain abdominal x-rays. Short summaries of these six cases are reported.

Case Reports

Case 1. C. L. A 31-year-old negro woman with radiopaque gallstones was operated on in February, 1957 after years of symptoms compatible with biliary colic and cholecystitis. Just prior to operation she had an attack of upper abdominal pain. At operation her gallbladder was thick-walled and edematous. An operative cholangiogram showed multiple common duct stones with some duct dilatation. Her common duct was opened and multiple stones were extracted. Postoperative course was uneventful and she has had no subsequent symptoms of biliary tract disease over a 10-year follow-up.

Case 2. R. N. A 45-year-old negro man was explored in November, 1970 for jaundice and abdominal pain. Six weeks earlier he had been admitted for right upper quadrant pain and jaundice. Oral cholecystography failed to visualize the gallbladder. At operation his gallbladder was acutely inflamed and the common duct was dilated. Many small stones were removed from the common duct. Postoperative course was benign and he has continued to do well.

Case 3. M. P. A 20-year-old negro woman died in hepatic coma in 1958. Over the prior 5 years she had been admitted on at least two occasions with symptoms suggestive of biliary tract disease. On last admission the total bilirubin rose to 55 mg./100 ml. and direct bilirubin to 36 mg. /100 ml. At post-mortem examination the liver was large and cirrhotic. Her gallbladder was markedly enlarged and, along with the common duct, filled with "white bile." There were multiple calculi completely obstructing the main hepatic duct at its bifurcation. The intrahepatic biliary system was dilated.

Case 4. J. B. An 18-year-old negro woman was admitted in August, 1969. She had right upper guadrant pain and jaundice. An intravenous cholangiogram demonstrated radiopaque stones in the gallbladder, and two stones in the common duct (Fig. 2). At operation 2 weeks later common duct exploration revealed that the stones had passed.

Case 5. R. W. A 21-year-old negro man was admitted in March, 1970 with fever, right upper quadrant pain, and an elevated alkaline phosphatase and bilirubin. Oral cholecystography failed to visualize. An intravenous cholangiogram demonstrated a common duct stone (Fig. 3). Surgical treatment was refused and the patient was discharged. He missed his initial follow-up visits but was seen 12 months later and was asymptomatic.

Case 6. A. J. A 35-year-old negro man with radiopaque stones was admitted with abdominal pain and jaundice in April, 1960. Bilirubin fell after admission and concurrently a series of plain abdominal x-rays demonstrated the passage of the gallbladder was inflamed, and a liver biopsy showed bile stasis.

General Anesthesia and Pregnancy. Fifty-six out of the total series of 147 patients underwent one or more general anesthetics for a variety of surgical procedures. A total of 91 general anesthetics were administered. In addition, two patients underwent a total of three spinal anesthetics. The operative procedures varied from simple skin grafting to major intraabdominal operations (Table 3). There was no operative mortality. The incidence of postopera-

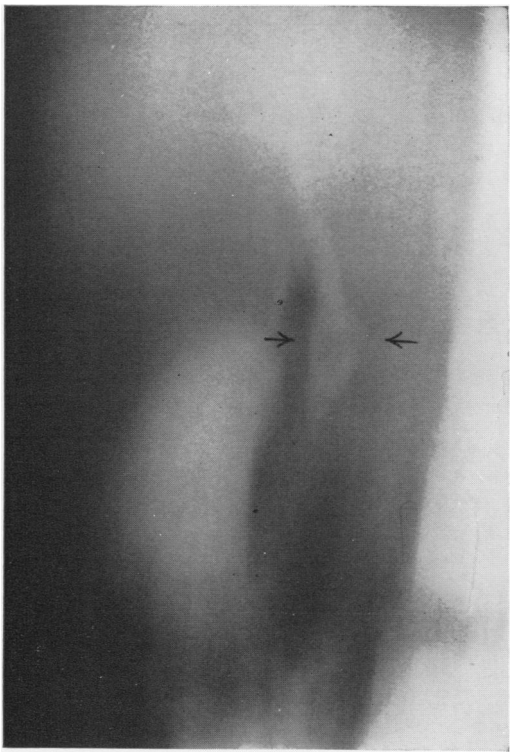

FIG. 3. Intravenous cholangiogram of patient 5 demonstrating one large common duct stone.

tive morbidity is difficult to establish because approximately one third of these procedures were performed in other hospitals, or performed so far in the past that records were lost or incomplete. However, there were no major postoperative complications over and above atelectasis and/or pneumonia. There did not appear to be any wound healing problems and there were only two documented wound infections.

Twenty-three of the 73 females in this series underwent a combined total of 50 pregnancies. Twenty-eight of the 50 pregnancies went to term and delivered spontaneously. Two of the births were stillborn. One pregnancy was ectopic and was terminated early. Nineteen spontaneous abortions occurred. Two patients underwent caesarian sections. There were no maternal deaths. There was considerable maternal morbidity, however, and crises during and immediately after pregnancy were frequent. Transfusions during the pregnancies were common. Three of the 28 patients developed endometritis after delivery and two had significant postpartum bleeds. Many of the pregnancies were followed at other hospitals, so a true incidence of maternal morbidity was impossible to obtain.

Discussion

The reported incidence of biliary tract disease in sickle cell anemia has varied from 6% to 37%.[2, 5, 7, 9, 14, 15] This great variability is secondary to the age groups studied, and the means used to detect biliary tract disease. The present group of 147 patients represents the largest series to date in which this problem has been examined. The incidence of biliary tract disease in 22% of the entire series, and in 34% of those over 15 years of age is only an indication of the frequency of this association. In most patients in this series the status of the biliary system had not been investigated. When only those 47 patients are considered about whom there is adequate information to determine whether biliary tract disease was present or absent, the incidence increases to 70%. In addition, the incidence of 61% radiopaque stones among the 33 patients with known biliary tract disease is very high. This suggests either that radiopaque stones are much more common in sickle cell anemia, or more likely that those sicklers with radiopaque stones are much more likely to be diagnosed as having biliary tract disease, and that many sicklers with non-opaque stones have remained undiagnosed. Further data suggesting that our overall incidence of 22% is a minimum figure is suggested by the fact that six out of our 33 patients with biliary tract disease were proven to have common duct stones. This is roughly twice the expected incidence.[1] It is possible that as patients with sickle cell anemia are examined more closely for biliary tract disease, and as they live longer periods with improved management, the incidence will approach 100% in the older age groups. The magni-

tude of this problem can be appreciated when it is realized that about 10% of the American Negro population carry the gene for sickle cell anemia,[10] and that it is estimated that one in every 500 negro births is an infant with homozygous sickle cell anemia. The disease is not manifest in the great majority of negroes heterozygous for sickle hemoglobin (sickle cell trait).

Although it is now well established that biliary tract disease is a frequent accompaniment of sickle cell anemia, its contribution to the symptoms of sickle cell anemia remains controversial. In the first description of sickle cell anemia by Herrick in 1910,[6] this problem was evident. The patient he described had "bilious attacks" accompanied on at least one occasion by severe epigastric pain, vomiting, dark urine, and yellow sclerae. In 1911 a second case of sickle cell anemia was reported by Washburn.[12] The patient underwent a cholecystectomy for symptoms suggestive of biliary tract disease, with no symptomatic improvement. In 1935 Campbell[4] reported six patients from The Johns Hopkins Hospital, all with sickle cell anemia and acute abdominal pain. Four patients underwent laparotomy. Findings were negative in three, and the fourth had cholecystitis. One of the remaining two patients who were not explored was suspected of having acute cholecystitis. In 1942 Schaefer[12] reported a patient with sickle cell anemia with common duct obstruction proven at operation. Since then only two subsequent patients with common duct stones and sickle cell anemia have been reported.[2] Likewise, documented cases in the literature of cholecystitis have been few in number and many have felt that despite the increased incidence of gallstones in sickle cell anemia, symptomatic biliary tract disease was rare.

Episodes of abdominal pain, usually with bilirubin elevations, are frequent in sickle cell anemia. These are often attributed to *hepatic crises* and are said to occur in 10% of all patients with sickle cell anemia.[2] The etiology of these crises is not entirely clear. Green *et al.*[5] in 1953 first described sickled erythrocytes engorging hepatic sinusoids and Kupffer cells distended with phagocytized red cells and felt that these changes could lead to impaired hepatic blood flow with liver ischemia and/or necrosis. These findings were confirmed by Bogoch *et al.*[3] and by Song.[14] More recently evidence has been presented to suggest that such changes occur in the liver during sickle crises not only in patients presenting with hepatic crises, but even in patients presenting with primarily bone and joint pain.[11] That such sludging of hepatic blood flow can produce symptoms of upper abdominal pain, and lead to cholestasis, is well established. The patient in our series who continued to have recurrent episodes of upper abdominal pain with bilirubin and alkaline phosphatase elevations following cholecystectomy is a good example. Perhaps because this entity is well accepted, however, other causes of abdominal pain and jaundice are not considered as thoroughly as should be when a patient with sickle cell anemia has a crisis. Hepatitis, or a congested liver, can at times present with similar symptoms. These entities can often be differentiated after study. Biliary tract disease, however, often cannot. The clinical presentation and biochemical picture in a patient with sickle cell "hepatic crisis" is frequently indistinguishable from an episode of biliary

TABLE 3. *Operative Procedures Performed under General Anesthesia on Patients with Sickle Cell Anemia*

Operations	
Procedure	No.
Appendectomy	13
Tonsillectomy and adenoidectomy	12
Tubal ligation	11
Cholecystectomy	10
Dilatation and curettage	6
Skin grafts	6
Curettement of osteomyelitis	4
Nephrectomy	1
Caesarian section	2
Laparotomy	13
Miscellaneous	13
Total	91

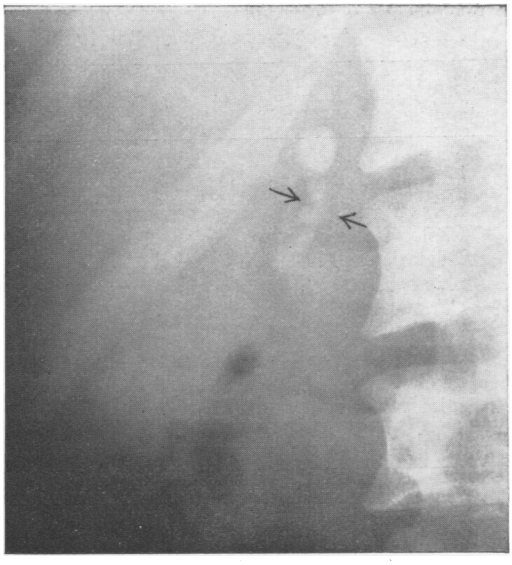

FIG. 4. a. A plain abdominal x-ray of patient 6 one year prior to admission demonstrating one large and four small radiopaque gallstones.

tract disease, as well documented by Barrett-Connor.[2]

In our series of 33 patients with proven biliary tract disease, six had common duct stones demonstrated and thus clearly had their symptoms on the basis of biliary tract disease. Six of the eight patients operated upon in this hospital had gallbladders that were thickened and scarred, or showed evidence of acute inflammation. Microscopically, all eight showed evidence of cholecystitis. In addition, one of the two patients operated upon at another hospital had a ruptured gallbladder. Thus there is ample direct evidence from our series to correlate symptoms of abdominal pain and jaundice with biliary tract disease in patients with sickle cell anemia. How many other patients in our series with symptoms suggestive of biliary tract disease have their symptoms on that basis, and not secondary to hepatic sludging, is a matter of conjecture. The direct evidence presented above, however, suggests that symptomatic biliary tract disease in sickle cell anemia certainly is not rare, and may occur with considerable frequency. Perhaps all patients with sickle cell anemia should have the status of their biliary tract evaluated periodically by oral and/or intravenous cholecystography so that when they present with abdominal pain and jaundice some information of value is available as an aid in differential diagnosis. Recently evidence has been presented suggesting that gallstones may result from abnormal bile secreted by the liver, rather than from normal bile modified by a diseased gallbladder.[13] The corollary follows that gallbladder inflammation is secondary to the presence of gallstones, and not the cause of them. Thus the complications of gallstones should be as frequent in patients with sickle cell anemia, as in a normal population of patients with gallstones. As sicklers survive for longer periods, this may become more evident.

Many of the patients with sickle cell anemia in our series without suggestive symptoms, if investigated, might well prove

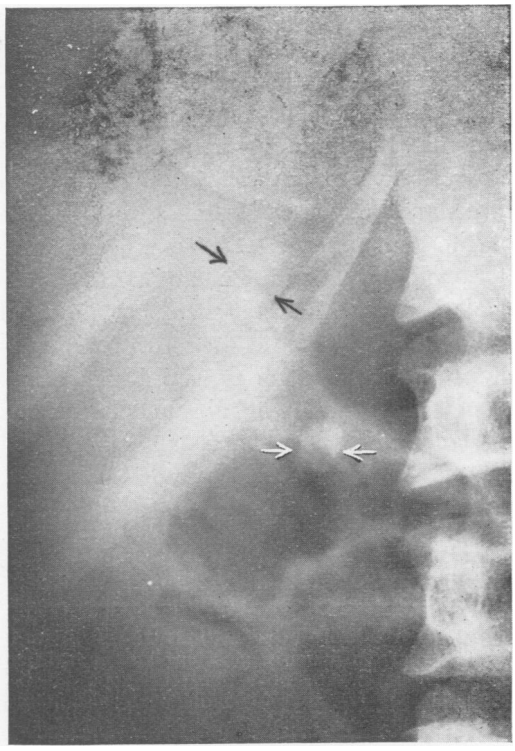

FIG. 4. b. At time of admission a flat plate demonstrated that the large stone had passed into the distal common duct. Note the duodenal air overlying the large stone.

to have biliary tract disease. The question of whether or not these patients with sickle cell anemia and demonstrated asymptomatic biliary tract disease should undergo elective cholecystectomy has recently been raised by Barrett-Connor.[2] In normal populations if patients with asymptomatic biliary tract disease are followed for long periods, it has been shown that 50% will develop severe symptoms or complications of the biliary tract disease.[8, 16] Since in this group of patients elective cholecystectomy carries a mortality of less than 1%, routine cholecystectomy is advised. Patients with sickle cell anemia, however, represent a high risk group and still have a markedly decreased life expectancy, although it is being lengthened yearly. Multisystem disease is frequently present, crises can be precipitated during periods of stress, and sicklers are particularly vulnerable to periods of anoxia. Surprisingly, however, if handled with care, these patients will tolerate general anesthesia well. In the past preoperative transfusions, and more recently exchange transfusions lowering the percentage of sickle hemoglobin to the range of 50%, have been considered helpful. Careful handling by the anesthesiologist with strict avoidance of anoxia is essential. With this type of care there has been no mortality in 91 general anesthetics in our series, and operative morbidity has not appeared increased. Infectious complications have not been increased as suggested in another series.[2] From our data, pregnancy represents a greater stress than general anesthesia, and carries considerable risk of fetal mortality and maternal morbidity.

However, even assuming their anesthetic risk is not great, and considering the increasing length of survival of patients with sickle cell anemia, elective cholecystectomy for asymptomatic biliary tract disease at this point seems unwise. In those patients with biliary tract disease, however, with symptoms that are compatible with biliary tract disease, elective cholecystectomy is strongly recommended. In the future needle biopsy of the liver or perhaps transhepatic cholangiography might provide a more selective basis for cholecystectomy in those patients with marked jaundice. Such studies are now in progress. Until then, however, our data suggest that the potential risks of elective cholecystectomy are outweighed by the real danger of morbidity and mortality from biliary tract disease in symptomatic patients.

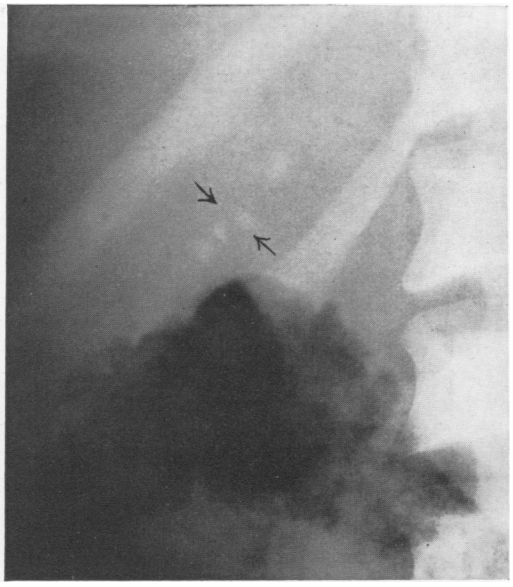

FIG. 4. c. Four days later the jaundice had cleared, and a plain abdominal x-ray demonstrated that the large stone had passed.

Summary

The charts of 147 patients with sickle cell anemia were examined for evidence of biliary tract disease. Twenty-two per cent of the entire series, and 34% of those over age 15 years had biliary tract disease. This is considered a minimum figure since most patients did not have the status of their biliary tract investigated. Many of these patients had symptoms compatible with biliary tract disease, and six patients were proven to have common duct stones. Ten patients underwent biliary tract surgery with no mortality or morbidity. The difficulty in differentiating sickle cell "hepatic crises" from tract disease is discussed. Elective cholecystectomy is recommended for

any patient with sickle cell anemia and proven biliary tract disease who is having clinical symptoms or episodes that are compatible with biliary tract disease. In those patients with sickle cell anemia with asymptomatic biliary tract disease, elective cholecystectomy at this time does not appear warranted.

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Discussion

Dr. George L. Jordan, Jr. (Houston): We too have been interested in this problem, and particularly the problem of gallstones in children. Although the hemolytic jaundice patient is felt by many to be the one most commonly having gallbladder problems in childhood, gallbladder disease actually occurs more frequently in patients without hemolytic abnormalities. Of those hemolytic diseases which cause gallstones, however, this disease appears to be second only to congenital hemolytic jaundice in frequency of gallstone formation.

In a review of patients in our institution, we found that 10% of the patients under 20 years of age with sickle cell anemia have gallstones, and this year we have operated upon two patients. One had common duct stones at age 6-½ years, and underwent successful cholecystectomy and common duct exploration. The other was 8 years of age.

We agree completely with the indications for surgery as mentioned here, and would like to ask the opinion of the essayists concerning the asymptomatic patient with proven gallstones at age, say, 10. Should this patient be operated upon because of the chance of later difficulty, or should this patient be observed? There are many who believe that patients, once they develop sickle cell crisis, have a limited life expectancy, and thus they will not have as high a likelihood of developing problems due to their gallstones as the patient in the normal population with a normal life expectancy.

The incidence of calcification reported here parallels that in the literature for gallstones in children from other causes as well as sickle cell anemia, and I wonder if the authors have conducted any studies of the composition of these gall stones, since presumably they are initiated by the breakdown products of hemoglobin.

Lastly, I would like to ask what their sex ratio has been in their younger patients. The literature would lead one to believe that in children there is a predominance of the male sex in patients with gallbladder disease, in contradistinction to gallbladder disease in the older age groups, but I do not think these data are conclusive at the moment, and I wonder if the authors would support this observation.

Dr. John L. Cameron (Closing): We have a large population of patients with sickle cell anemia in Baltimore, and we have just instituted recently a prospective randomized study including patients with asymptomatic biliary tract disease with sickle cell anemia. Currently it is the opinion of most that asymptomatic patients with sickle cell anemia and biliary tract disease should not be operated on, but we are convinced that a lot of hepatic crises could not be averted in patients if they had their gallbladder and stones removed.

The composition of these stones has been studied by others—not by us—and the great majority of them are calcium bilirubinate stones.

The sex ratio in our series is nearly equal at all ages of patints with sickle cell anemia, both with and without stones.