Biliary Atresia Into the 21st Century: A Historical Perspective

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This commentary by the late Alex P. Mowat reflects his extensive knowledge and experience in pediatric liver disease; its genesis reflects his commitment to education as well as his personal qualities. Dr. Mowat had presented an overview of biliary atresia at the November 1995 meeting of the American Association for the Study of Liver Diseases. This included a very thoughtful historical perspective. Since we were preparing the manuscript on Biliary Atresia, found on page 1682 of this issue of HEPATOLOGY, we informally asked to review his lecture notes and slides regarding these "historical aspects." Dr. Mowat died three days later while attending a meeting in South America. Approximately one month after his death I was informed by his office that he had dictated these notes regarding biliary atresia; this draft was to be sent to me for commentary and possible inclusion with the manuscript. We are very pleased that HEPATOLOGY has agreed to publish this piece, which we have lightly edited. It is an appropriate posthumous recognition of Dr. Mowat's many contributions to this field and perhaps a glimpse of his personal side. While much could be said about the latter, I believe that the words of his fellow Scot Robert Burns are an appropriate tribute: "If there's another world, he lives in bliss; If there is none, he made the best of this."

—William F. Balistreri, M.D.

> Looking at the problem of biliary atresia from the vantage point of 30 years' experience with the lesion, we can say with certainty that the jaundiced baby who has had no extrahepatic bile duct has been the most disappointing patient for the surgeon in the whole realm of lesions theoretically correctable by a surgical procedure.
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> —C. Everett Koop, M.D., Sc.D. (1976)[1]

The last 20 years has seen a significant improvement in the prognosis for infants with biliary atresia because of the sequential employment of two major surgical techniques, portoenterostomy and liver transplantation.[2] There have also been significant advances in the management of complications of chronic cholestasis and in some complications of cirrhosis. We have reason to congratulate ourselves as a profession. However, important as these advances are, the diagnosis of biliary atresia and its consequences are devastating to a family who have, for the first few weeks of their infant's life, believed they had a normal child. They are angry, depressed, and frustrated when they find out that we have no idea what causes the condition and very little understanding of the pathogenesis and thus the prognosis. It is very timely, therefore, to examine the history of our current knowledge of biliary atresia and to consider possible strategies for the future.

HISTORICAL DESCRIPTIONS

The first clear reference in the English language to what seems to be a case of biliary atresia is to be found in the writing of Professor John Burns, of the Department of Surgery, University of Glasgow, who in his textbook the *Principals of Midwifery, Including the Diseases of Women and Children,* published in 1817, wrote as follows:

> The jaundice of infants is a disease attendant with great danger, especially if it appears very soon after birth, and the stools evince, a deficiency of bile; for we have then reason to apprehend some incurable state of the biliary apparatus.[3]

In 1769, Dr. John Cooke, in *A Plain Account of the Diseases Instant to Children; with an easy method of curing them; designed for the use of families,* had written about jaundice, ". . . many infants are affected by this disease, some are even born with it, but it is rarely mentioned, though a great many die of it." However, we are not clear whether he had in mind unconjugated hyperbilirubinaemia or bile duct obstruction.

We have a fine description of the clinical features of biliary atresia in the writing of Dr. Charles West (1816-1892), a physician pediatrician who founded the first children's hospital in England (Great Ormond Street) in 1852. In his hand-written notes, preserved from the hospital, he writes as follows:

> *Case 18*—fatal jaundice, absence of gall bladder, etc. On November 8, 1855, I saw a female child aged 13 weeks; the only child of healthy parents (Matthias and Jernby,

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> sent by Mr. E. M. Jones). It was born at full term, though small, apparently healthy. At 3 days however, it began to get yellow and at the end of 3 weeks was very yellow. Her motions at no time after the second day appeared natural on examination, but were white, like cream, and her urine was very high coloured.

The next important paper related to biliary atresia is the thesis of Dr. John Thomson, a physician pediatrician in Edinburgh who, in his thesis *On So-called Congenital Obliteration of the Bile Ducts (Clinical and Pathological),* in 1891, reviewed his own cases (n = 50) and those published at that time and came to conclusions about the pathology of extrahepatic bile ducts that have not been challenged in the next century.

In this century, we have seen the description of the inspissated bile syndrome in 1927, spontaneous perforation of the bile ducts in 1932, inspissated bile plugs in 1935, the same year as it was appreciated that vitamin K was an important coagulant component.[4,5] In 1952, "giant cell hepatitis" was described by Craig and Landing[6]; in the intervening years, we have come to appreciate that this should be regarded as a syndrome of many causes, which may be grouped as follows: infectious, inborn errors of metabolism, genetic, endocrine, hematologic, vascular, chromosomal, toxic, related to complications of prematurity, and parenteral nutrition, but still leaving a large residual group of disorders, termed idiopathic neonatal hepatitis. For an increasing number of the intrahepatic disorders, specific therapy has become available.[5] There is no specific therapy for biliary atresia.

SURGICAL APPROACH

The results of surgery for 11 infants explored for "obstructive jaundice" were reported in 1928, by Ladd from Boston; 8 were found to have surgically remedial lesions.[7] This experience led Ladd to recommend that surgery be carried out before 4 months of age.[8] The preferred approach to establishment of bilioenteric continuity was further described in 1940.[9] Gross reviewed the Children's Hospital of Boston experience in his 1953 text; of 146 infants with biliary atresia, 27 infants (18%) were found at the time of surgical exploration to have a biliary structure suitable for anastomosis to the duodenum.[10] Only 12 of these patients became jaundice-free; 15 of the infants with "correctable" pathology died. None of the 119 infants who were thought to have an "uncorrectable" lesion at exploration survived. Gross summarizes, "In most instances death followed a downhill course, characterized by progressive jaundice and inanition, sometimes with marked ascites, occasionally with rickets and fractures, usually terminated by superimposed infection and in few cases by hemorrhage."[10]

This general frustration led to multiple surgical maneuvers in efforts to establish bile flow[11-13]; these were unsuccessful. In the words of Willis J. Potts in 1959, "Congenial atresia of the bile ducts is the darkest chapter in pediatric surgery."[14]

In the 1950s Professor Kasai of Sendai, Japan, starting in Los Angeles and continuing the work in Japan, investigated the pathology of the intrahepatic and extrahepatic bile ducts in patients with biliary atresia.[15,16] He showed that there was progressive destruction of the intralobular bile ducts with a gradual diminution of the degree of pseudoductular proliferation of the portal tracts between 2 and 12 months of age.[15] He described microscopic bile ducts within the fibrous remnant of the atretic biliary tree at the porta hepatis. He made the critical observation that if the extrahepatic bile ducts were removed at a time when there was some continuity between the ductal plate of the porta hepatis and the intrahepatic biliary system, the progression of biliary atresia could be arrested.[17,18] This operation, the so-called Kasai hepatoportoenterostomy (or modified forms), has become the current standard approach.[2,5]

The key to success of the Kasai procedure is early diagnosis. The early clinical features of biliary atresia are mild jaundice (which is continuous with physiological jaundice), urine that is persistently yellow from birth, and acholic, pale stools. Please note that in the first weeks of life stools may contain bile pigment in ~30% of patients, proving that in some infants the process of bile duct obliteration is not complete at that stage. Systematic investigation includes an ultrasound examination to exclude choledochal cyst and a percutaneous liver biopsy looking for features of bile duct obstruction in every portal tract. If these are present, and genetic disorders such as α_1-antitrypsin deficiency and cystic fibrosis have been excluded, laparotomy is required to exclude biliary atresia. In ~10% of infants, the percutaneous liver biopsy may be equivocal and need to be repeated within a week. It is useful if one can confirm bile duct patency using hepatobiliary scintigraphy and, in a small percentage of infants, by cholangiography.

Because the Kasai procedure is not uniformly successful, some have looked on transplantation as the initial operation of choice for biliary atresia. The rates of morbidity and mortality associated with liver transplantation are much greater than that with the successful Kasai procedure. Thus, even if enough donor livers were available to allow transplantation to be the initial procedure, we believe that this would not be the best option.

SCREENING FOR HEPATOBILIARY DISEASE IN INFANCY: THE "YELLOW ALERT"

Because so many infants in the United Kingdom still come to surgery too late for optimum results from portoenterostomy, the Children's Liver Disease Foundation, with the assistance of the Department of Health, decided in 1993 to extend teaching on biliary atresia from the medical profession to health visitors, midwives, and parents.[19-21] The message was that any infant who was jaundiced after 14 days of age should be carefully assessed for conjugated hyperbilirubinemia.

This involves asking whether the urine has ever been colorless as it is in unconjugated hyperbilirubinemia. If the urine is persistently yellow, the infant has hepatobiliary disease, which requires confirmation by measuring total and direct serum bilirubin concentrations, the latter being the specific indicator of cholestasis. If the stools contain no yellow or green pigment, early referral to a center with the skills to exclude other causes of biliary atresia and to perform this difficult operation must be a priority. We have estimated that if this program were to be instituted in the United Kingdom, it would be cost-effective in reducing the costs of liver transplantation, even if only 10% of affected infants were found to be jaundiced in the third week of life.[19-21]

We have known about biliary atresia for well over a century. However, we still have a rudimentary understanding of many aspects of this disease. Our current goals when evaluating an infant with cholestasis are to exclude all other causes of hepatobiliary disease by 4 weeks of age to allow portoenterostomy to be performed by an expert surgeon when the infant is 5 to 6 weeks old. We must provide the optimum postportoenterostomy care, particularly in the prevention of sepsis and cholangitis, and work hard to optimize the outcome of liver transplantation for those infants in whom portoenterostomy is ineffective. In the meantime, we must double our efforts to identify the etiology of this rare and unique but deadly disorder.

REFERENCES

1. Koop CE. Biliary obstruction in the newborn. Surg Clin North Am 1976;56:373-377.
2. Otte JB, de Ville de Goyet J, Reding R, Hausleithner V, Sokal E, Chardot C, Debande B. Sequential treatment of biliary atresia with Kasai portoenterostomy and liver transplantation: a review. Hepatology 1994;20(Suppl):41S-48S.
3. Burns, J. Principals of midwifery, including the diseases of women and children. London: Longman, 1817:601.
4. Colon AR. Pediatric hepatology—a historic overview. In: Colon AR, ed. Textbook of pediatric hepatology. Chicago: Year Book Medical, 1990:1-5.
5. Mowat AP. Liver disorders in childhood. 3rd ed. Oxford, England: Butterworth-Heinemann, 1994.
6. Craig CM, Landing BH. Form of hepatitis in neonatal period stimulating biliary atresia. Arch Pathol 1952;54:321-333.
7. Ladd WE. Congenital atresia and stenosis of the bile ducts. JAMA 1928;91:1082-1085.
8. Ladd WE. Congenital obstruction of the bile ducts. Ann Surg 1935;102:742-751.
9. Ladd WE, Gross RE. Surgical anastomoses between the biliary and intestinal tracts of children. Ann Surg 1940;112:51-63.
10. Gross RE. The surgery of infancy and childhood, Philadelphia: Saunders, 1953.
11. Fonkalsrud WE, Kitagawa S, Longmire WP. Hepatic lymphatic drainage to the jejunum for congenital lymphatic drainage to the jejunum for congenital biliary atresia. Am J Surg 1966;112:188-194.
12. Longmire WP, Sanford MC. Intrahepatic cholangiojejunostomy with partial hepatectomy for biliary obstruction. Surgery 1948;24:264-276.
13. Sterling JA. Artificial bile ducts in the management of congenital biliary atresia: a clinical report. J Int Coll Surg 1961;36:293-296.
14. Potts WJ. The surgeon and the child. Philadelphia: Saunders, 1959.
15. Kasai M, Yakovac WC, Koop CE. Liver in congenital biliary atresia and neonatal hepatitis: a histopathologic study. Arch Pathol 1962;74:152-162.
16. Hays DM, Kimura K. Biliary atresia: the Japanese experience. London: Harvard University, 1980.
17. Kasai M. Treatment of biliary atresia with special reference to hepatic portoenterostomy and its modifications. Progr Pediatr Surg 1974;6:5-52.
18. Kasai M, Kimura S, Asakura Y. Surgical treatment of biliary atresia. J Pediatr Surg 1968;3:665-675.
19. Mieli-Vergani G, Howard ER, Portman B, Mowat AP. Late referral for biliary atresia—missed opportunities for effective surgery. Lancet 1989;1:421-423.
20. Hussein M, Howard ER, Mieli-Vergani G, Mowat AP. Jaundice at 14 days of age: exclude biliary atresia. Arch Dis Child 1991;66:1177-1179.
21. Mowat AP, Davidson LL, Dick MC. Earlier identification of biliary atresia and hepatobiliary disease: selective screening in the third week of life. Arch Dis Child 1995;72:90-92.