Ascending cholangitis after successful surgical repair of biliary atresia

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Kobayashi, A., Utsunomiya, T., Ohbe, Y., and Shimizu, K. (1973). *Archives of Disease in Childhood*, **48**, 697. **Ascending cholangitis after successful surgical repair of biliary atresia.** Since the introduction of hepatic porto-enterostomy, encouraging results have been obtained in treating extrahepatic biliary atresia, particularly in the case of infants with atresia or agenesis of the extrahepatic ducts, who would not previously have been considered amenable to surgery.

Out of 17 successfully repaired cases who had shown good bile excretion after surgery and who had no jaundice, 8 (47%) developed ascending cholangitis $3\frac{1}{2}$ to $8\frac{1}{2}$ months after surgery.

Cholangitis of this type formed a recognizable picture, with repeated attacks of fever, reappearance of obstructive jaundice, raised erythrocyte sedimentation rate, leucocytosis with shift to the left, and anaemia. The condition was often resistant to antibiotic therapy, and was fatal in 3 cases.

Although some 4 to 18% of cases of congenital biliary atresia have been considered amenable to surgery (Holmes, 1916; Gerrish and Cole, 1951; Gross, 1953; Silverberg, Craig, and Gellis, 1960), the percentage of cases successfully repaired is much smaller (Gross, 1953; Moore, 1953). In the so-called surgically 'incorrectable' cases of biliary atresia, surgical intervention to establish bile drainage from liver to intestine has, until recently, been unsuccessful (Longmire and Sanford, 1948, 1949; Sterling, 1957; Sterling and Lowenburg, 1962). Recently more encouraging results have been reported by a few authors (Kasai *et al.*, 1963, 1968; Sawaguchi *et al.*, 1971, 1972), employing the operation of hepatic porto-enterostomy, first described by Longmire and Sanford (1948), and later by Redo (1954) and Kasai *et al.* (1963, 1968). Kasai *et al.* (1968) reported that 19 out of 53 cases showed good or fairly good excretion of bile after surgery, with complete cure in 6. Sawaguchi *et al.* (1971, 1972) reported similar results. However, about half of the cases who had shown initially good bile excretion developed ascending cholangitis several months after surgery. The condition was often resistant to antibiotic therapy, and was sometimes fatal. The purpose of this paper is to describe the clinical features of the condition in more detail.

Patients

From January 1967 to June 1972, 55 patients (35 females, 20 males) were admitted with the diagnosis of biliary atresia to the Department of Paediatrics, National Children's Hospital of Tokyo. The diagnosis was confirmed by laparotomy, when an operative cholangiogram was also carried out. Among these only 3 (6%) were of the so-called surgically 'correctable' type, the remaining 52 (95%) being of the surgically 'incorrectable' type. In the incorrectable cases the proximal hepatic ducts are absent or rudimentary, making it impossible to anastomose any portion of the extrahepatic ducts to the gastrointestinal tract.

Operation performed in all these incorrectable cases was hepatic portojejunostomy, as described by Kasai *et al.* (1968) and Sawaguchi *et al.* (1971, 1972). Two correctable cases were treated with hepaticojejunostomy and the other with choledochojejunostomy in Roux-en-Y fashion. Two methods were used to establish hepatic portojejunostomy: a one-stage and a two-stage method. The former, as described by Kasai *et al.* (1968), was performed by Roux-en-Y anastomosis and carried out in 12 cases in the present series; the two-stage method, devised by Sawaguchi *et al.* (1971) and shown schematically in the Fig., was performed in 40 cases.

In 13 patients out of 55 (24%) good bile excretion was observed after surgery and jaundice disappeared; 3 were the correctable type, and 10 were the incorrectable type (3, one-stage method; 7, two-stage method).

In addition, 4 cases that had been admitted with the diagnosis of biliary atresia to this hospital and had been

FIG.—Hepatic portojejunosomy, two-stage method. (a) First procedure, (b) second procedure.

successfully repaired by hepatic portojejunosomy for the inoperable type were referred for medical follow-up from the Department of Surgery. 3 of these 4 patients had had a two-stage procedure, and the other a one-stage procedure.

The age of the patients at operation ranged from 4 weeks to 3½ months with an average of 2·3 months in 17 successfully repaired cases, and from 6 weeks to 7½ months with an average of 3·5 months in 42 uncorrected cases.

At a time varying from 3½ to 8½ months after operation 8 of the 17 patients became ill with attacks of remittent fever, reappearance of obstructive jaundice, abdominal distension, raised erythrocyte sedimentation rate (ESR), leucocytosis with shift to the left, and anaemia. There was no evidence of respiratory infection, urinary tract infection, or septicaemia. Necropsy examination of 2 of the patients who had shown these signs and symptoms revealed bacterial cholangitis and multiple cholangitic abscesses. Organisms grown from the abscesses were intestinal flora. We concluded that ascending cholangitis was also responsible for the illness characterized by the above signs and symptoms in our

other patients. The 8 cases in whom this diagnosis was made are briefly described.

Case reports

Case 1. A male infant aged 3 months was admitted with the diagnosis of biliary atresia. Laparotomy at 3½ months revealed a small gallbladder and rudimentary hepatic and common duct. One-stage hepatic portojejunosomy was performed leaving a segment of the jejunum for bile drainage about 50 cm long. Bile excretion was good, resulting in disappearance of jaundice by the age of 6 months.

Six months after operation he developed high fever and obstructive jaundice, and was readmitted to the hospital. He showed pallor, marked abdominal distension, hepatosplenomegaly, and engorgement of the superficial veins of the abdominal wall. Laboratory findings at this stage are shown in Table I. A diagnosis of ascending cholangitis was made and antibiotic therapy was instituted using gentamicin, kanamycin, chloramphenicol, ampicillin, carbenicillin, lincomycin, and cephaloridine. The disease deteriorated progressively, jaundice deepened, and, in addition, ascites developed.

TABLE I
Laboratory data of 8 cases of cholangitis

Case no.	Hb (g/100 ml)	White blood cells			ESR (mm/hr)	CRP	CCF	TTT (unit)	ZnS (unit)	Bilirubin total/direct (mg/100 ml)
		Count (per mm ³)	Band forms (%)	Polymorphs (%)						
1	9·3	15,300	23	36	143	5+	2+	38·4	33·9	6·9/4·
2	10·9	15,800	26	26	59	2+	4+	7·0	8·4	8·4/5·
3	7·7	13,900	26	28	112	5+	2+	14·5	35·7	5·7/4·
4	9·9	14,000	15	21	122	3+	—	10·9	13·3	4·9/3·
5	9·0	12,100	12	12	151	1+	3+	17·4	27·0	2·5/1·
6	10·6	13,500			77			31·5	28·5	2·5/2·
7	8·9	13,000	30	19	38	4+	2+	12·5	8·6	9·9/7·
8	7·3	7,200			23	3+		8·0	4·7	4·9/4·

*K-K unit, Kind-King unit. CRP, C-reactive protein; CCF, cephalin-cholesterol flocculation; TTT, thymol turbidity test; ZnS, zinc sulphate test.

Laboratory studies at 14 months of age showed Hb 8.6 g/100 ml, ESR 149 mm/hr, total serum protein 8.0 g/100 ml with 1.8 g/100 ml albumin and 6.2 g/100 ml globulin, cephalin-cholesterol flocculation 3+, thymol turbidity 20.0 units, and zinc sulphate 42.8 units. Serum total cholesterol was 51 mg/100 ml, serum total bilirubin 15.0 mg/100 ml, SGOT 56 units, and SGPT 28 units.

Blood transfusion, intravenous plasma preparation, diuretics, and intramuscular vitamin K₁ were given, but despite the intensive therapy the patient died at the age of 15 months.

At necropsy the abdominal cavity contained about 500 ml ascitic fluid. Pus of pale greenish-yellow colour filled dilated intrahepatic bile ducts. The liver contained small multiple abscesses. Varices were present in the submucosa of the lower oesophagus. The heart was hypertrophied. Culture of hepatic abscesses revealed *Esch. coli* + + +, *klebsiella* + +, *Proteus mirabilis* +, and *Streptococcus mucosus* +.

Case 2. A female infant was admitted with jaundice and clay-coloured stools at the age of 1½ months. Laparotomy at 2 months of age revealed that the hepatic ducts were rudimentary and the gallbladder small. The proximal choledochus was cystic. One-stage operation of hepatic portojejunostomy was performed in a Roux-en-Y fashion, leaving a segment of the jejunum for bile excretion about 50 cm long. Bile excretion was good, and serum total bilirubin was abruptly reduced from the pre-operative level of 8.2 to 1.45 mg/100 ml 4 days after operation. Thereafter, her clinical course was uneventful and she was discharged. 8½ months after operation she developed high fever and obstructive jaundice of moderate degree. The abdomen was prominent with distended superficial veins but no detectable ascites. Laboratory studies at this stage are shown in Table I. Ascending cholangitis was diagnosed and intramuscular and, later, oral chloramphenicol was given. This had an impressive effect; symptoms disappeared, the ESR returned to normal, and CRP became negative. 3 weeks later fever, jaundice, and abdominal distension recurred. Antibiotic therapy was

reinstated, chloramphenicol, gentamicin, carbenicillin, kanamycin, cephaloridine, and ampicillin now had little effect on the disease. She deteriorated progressively, jaundice increased, ascites developed, and she died aged 1 year 11 months.

Necropsy showed multiple small cholangitic abscesses, culture of which gave *klebsiella* sensitive to chloramphenicol, kanamycin, cephaloridine, and gentamicin.

Case 3. A female infant was admitted at 2½ months with the diagnosis of biliary atresia. Laparotomy at 3½ months showed obstruction of the distal choledochus. The hepatic ducts were moderately dilated. A blind common duct was anastomosed to the jejunum in Roux-en-Y fashion. Postoperative course was without incident, bile excretion was fair, and jaundice disappeared completely by 8 months of age.

Seven months after operation fever, abdominal distension, and obstructive jaundice developed. Laboratory findings at this stage are shown in Table I. A diagnosis of ascending cholangitis was made. Antibiotic therapy included gentamicin, chloramphenicol, cephaloridine, and kanamycin. Her condition deteriorated progressively and laboratory studies at 15 months showed serum total bilirubin 17.2 mg/100 ml (direct bilirubin 12.6 mg/100 ml), SGOT 57 units, SGPT 18 units, serum albumin 1.72 g/100 ml, and serum globulin 6.22 g/100 ml. She died at 18 months. Necropsy examination was not made.

Case 4. A male infant was admitted at 8 weeks with the diagnosis of biliary atresia. Laparotomy at age 2 months revealed absence of the hepatic ducts; the gallbladder was small and contained only colourless fluid. A small but patent proximal and distal choledochus was found by operative cholangiogram. The two-stage operation of hepatic portojejunostomy was performed. A segment of the jejunum used for bile drainage was about 50 cm long.

Bile excretion was good after operation. Total serum bilirubin of 13.9 mg/100 ml before operation fell to 1.27 mg/100 ml 3 months after operation. Other blood chemical findings at this stage were as follows: thymol

I after hepatic portojejunostomy

Alkaline phosphatase (K-K unit)*	Cholesterol (mg/100 ml)	SGOT (unit)	SGPT (unit)	SLDH (unit)	Serum protein (g/100 ml)	Serum albumin (g/100 ml)	Serum γ-globulin (g/100 ml)	Serum IgG (mg/100 ml)	Serum IgA (mg/100 ml)	Serum IgM (mg/100 ml)
36.8	108	32	2	388	7.6	2.1	3.5	2800	250	240
45.8	119	41	36	302	5.9	2.3	1.5	1700	170	28
83.4	136	92	46	254	8.0	1.6	4.3			
54.7	129	42	22	491	6.9	2.7	1.6	1700	190	180
65.0	148	18	7	372	9.5	2.4	4.6	2900	350	90
61.0	144	47	16	400	7.7	3.1	2.4	1200	160	210
68.0	1050	122	96	578	9.4	3.7	2.4	2000	250	160
69.5	230	62	25		6.5	3.8	1.1			

SLDH, serum lactic dehydrogenase.

turbidity 0.7 units, zinc sulphate 0.4 units, alkaline phosphatase 22.6 Kind-King units, SGOT 46 units, SGPT 40 units, total cholesterol 100 mg/100 ml, and total protein 7.3 g/100 ml.

Four months after the first-stage operation the second operation was performed. Postoperative course was without incident for the next 1½ months, but fever then appeared with mild jaundice and abdominal distension. Laboratory data at this stage are shown in Table I. Ascending cholangitis was diagnosed and antibiotic therapy begun. Chloramphenicol had a clear effect, while gentamicin, kanamycin, cephaloridine, carbenicillin, nalidixic acid, lincomycin, and ampicillin seemed to have none. After several courses of chloramphenicol he is now asymptomatic, with normal serum bilirubin, serum protein, and γ -globulin levels.

Case 5. A male infant was admitted at 2 months with the diagnosis of biliary atresia. Laparotomy at 2½ months revealed absence of the hepatic ducts and distal choledochus. The proximal choledochus was cystic. The gallbladder was small. The liver was dark brown in colour.

After resection of the gallbladder and choledochus cyst the first-stage operation of hepatic portojejunosomy was performed leaving a segment of the jejunum for bile drainage 60 cm long. Bile excretion was excellent and jaundice subsided. The pre-operative serum bilirubin of 14.7 mg/100 ml was reduced to 1.3 mg/100 ml 2 months after operation, when the second-stage operation was carried out.

Blood chemistry at 5 months of age (2½ months after operation) was cephalin-cholesterol flocculation negative, thymol turbidity 4.6 units, zinc sulphate 5.3 units; total bilirubin <1.0 mg/100 ml, alkaline phosphatase 74.0 Kind-King units, SGOT 48 units, SGPT 28 units, SLDH 364 units, total cholesterol 191 mg/100 ml, and total protein 6.9 g/100 ml.

Postoperative course was without incident. 2 months after the second-stage operation, however, fever suddenly developed, with slight jaundice (Table I). A diagnosis of ascending cholangitis was made and antibiotic therapy was instituted. Gentamicin had a clear effect and two courses were given during 5 weeks. Since then he has been asymptomatic. At 19 months abdominal examination showed no ascites, and the liver was 3 cm below costal margin. Investigations: cephalin-cholesterol flocculation negative, thymol turbidity 2.2 units, zinc sulphate 4.5 units, alkaline phosphatase 27.3 Kind-King units, SGOT 26 units, SGPT 22 units, total cholesterol 139 mg/100 ml, and total protein 7.1 g/100 ml with 3.8 g/100 ml albumin and 3.3 g/100 ml globulin.

Case 6. A female infant of 1½ months was referred to this hospital with the diagnosis of biliary atresia. Laparotomy at 2 months revealed a greenish firm liver, a choledochus cyst, and a small gallbladder. The hepatic ducts were patent. The distal choledochus was rudimentary. The gallbladder and choledochus cyst

contained colourless fluid. Hepaticojejunosomy with Roux-en-Y anastomosis was performed leaving a segment of the jejunum for bile drainage 45 cm long.

Her postoperative course was uneventful. Bile excretion was good and jaundice disappeared 6 weeks after operation. Blood chemical studies at this stage showed the following: thymol turbidity 2.0 units, zinc sulphate 1.3 units, alkaline phosphatase 40.0 Kind-King units, SGOT 69 units, SGPT 41 units, total cholesterol 144 mg/100 ml, and total protein 6.0 g/100 ml with 3.6 g/100 ml albumin and 2.4 g/100 ml globulin.

Fever and slight jaundice developed 3½ months after operation. The abdomen was distended but with no detectable ascites. The liver was palpable 8.5 cm, and the spleen 3.5 cm. Laboratory findings at this stage are shown in Table I. A combination of intermittent oral cephalixin and kanamycin led to improvement of her condition.

Case 7. A female infant of 3 weeks of age was referred with the diagnosis of biliary atresia. Laparotomy at 1 month revealed a rudimentary hepatic and common duct. The gallbladder was small but patent. The first-stage operation of hepatic portojejunosomy was performed, leaving a segment of the jejunum for bile drainage about 40 cm long. Bile excretion was good and jaundice was negligible at 2 months of age, when the second-stage operation was carried out. Blood chemistry at this stage showed cephalin-cholesterol flocculation 2+, thymol turbidity 1.1 units, zinc sulphate 0.8 units, total bilirubin 1.19 mg/100 ml, alkaline phosphatase 51.0 Kind-King units, SGOT 75 units, SGPT 58 units, total cholesterol 200 mg/100 ml, and total protein 6.2 g/100 ml.

Three months after the second-stage operation she developed attacks of fever with abdominal distension; intramuscular cephaloridine was given. The stools became acholic and obstructive jaundice of moderate degree reappeared, which deepened during the febrile periods (Table I).

Attacks of fever continued over a period of 8 months, but then disappeared; since then she has complained of severe pruritus and has developed generalized xanthomata. Blood chemistry at this stage was zinc sulphate 15.6 units, total bilirubin 9.9 mg/100 ml, alkaline phosphatase 91.5 Kind-King units, SGOT 181 units, SGPT 124 units, and total cholesterol 1290 mg/100 ml.

Oral cholestyramine (a bile-acid-sequestering resin) 4 to 6 g daily, was instituted at the age of 18 months; the xanthomata gradually decreased and the pruritus was much improved. Serum total cholesterol and bilirubin was reduced to 272 mg/100 ml and 4.5 mg/100 ml, respectively, at 3½ years.

Case 8. A female infant of 2 months was admitted with the diagnosis of biliary atresia. Laparotomy at 3½ months revealed absence of the hepatic ducts, a small gallbladder, and rudimentary common duct. The first-stage hepatic portojejunosomy was carried out, leaving a segment of the jejunum for bile drainage 40 cm long.

Bile excretion was good and serum total bilirubin level fell from the pre-operative level of 12.8 mg/100 ml to 2.5 mg/100 ml 8 weeks after operation. The second operation was performed at 5 months of age, and she was discharged home at 6 months. Laboratory findings at this stage showed Hb 13.2 g/100 ml, white blood cell count 8800/mm³, thymol turbidity 1.6 units, zinc sulphate 1.3 units, serum total bilirubin 2.4 mg/100 ml, serum alkaline phosphatase 47.1 Kind-King units, SGOT 56 units, SGPT 54 units, and serum total cholesterol 191 mg/100 ml.

She appeared quite well, except for some prominence of the abdomen, for the next 5 months. Fever then developed, with slight jaundice and pruritus. Chloramphenicol proved effective and several courses were given orally. Attacks of fever, however, still continued during the following 3 years. Xanthomata developed at 1½ years. Cholestyramine, 2 g daily, has been given for pruritus and xanthomatosis from 1 year. Jaundice has occurred only when fever has been present. Laboratory findings during the febrile period are given in Table I.

Results

Incidence of ascending cholangitis after surgery. Out of 17 successfully repaired cases who had shown satisfactory bile excretion after surgery and who had no jaundice, 8 (47%) developed the syndrome of ascending cholangitis.

4 of these 8 cases received a two-stage procedure of hepatic portojejunostomy, 2 received a one-stage operation, 1 had a choledochojejunostomy, and 1 a hepaticojejunostomy. Incidence of ascending cholangitis among successfully repaired cases in each operative group was as follows: one-stage operation 2/4 (50%), two-stage operation 4/10

(40%), and choledocho- or hepaticojejunostomy 2/3 (67%).

Three of 8 cases died from the disease. Necropsy was carried out in 2 and revealed multiple cholangitic abscesses.

By contrast, none developed cholangitis in the surgically uncorrected group, suggesting that patency of the intra- and extrahepatic biliary passages was essential for the development of the disease.

Clinical features of ascending cholangitis (Table II). Acute ascending cholangitis after hepatic portoenterostomy was characterized by repeated attacks of high remittent fever, abdominal distension, hepatosplenomegaly, and reappearance of obstructive jaundice of slight to severe degree. The onset of the symptoms was 3½ to 8½ months after operation, with an average of 5.6 months. In fulminating cases there was no response to any antibiotic, with formation of multiple cholangitic abscesses of the liver (Cases 1 and 2). In the prolonged type of case, severe pruritus and xanthomata developed. Relapse was common (Cases 7 and 8).

Laboratory findings in ascending cholangitis (Table I). Laboratory studies showed anaemia, leucocytosis with shift to left, marked rise of ESR, and positive CRP. Blood chemistry showed mild to moderate jaundice of obstructive type. Serum transaminases were normal to slightly raised. Serum alkaline phosphatase levels were moderately raised. Serum total cholesterol levels were normal

TABLE II
Clinical findings of 8 cases of cholangitis after hepatic portojejunostomy

Case no.	Age (yr) (mth)		Sex	Age at operation (dy)	Corrective surgical procedure	Onset of cholangitis (mth after surgery)	Fever	Icterus	Pruritus	Clubbing	Xanthomata
1	1	3*	M	101	Hepatic portojejunostomy	6	Yes	Severe	No	Yes	No
2		11*	F	64	Hepatic portojejunostomy	8.5	Yes	Severe	No	No	No
3	1	3*	F	102	Choledocho-jejunostomy	7	Yes	Severe	No	No	No
4	2	3	M	65	Hepatic portojejunostomy	5.5	Yes	Mild	No	No	No
5	2	10	M	76	Hepatic portojejunostomy	4	Yes	Minimal	No	No	No
6	1	7	F	63	Hepatico-jejunostomy	3.5	Yes	Minimal	No	No	No
7	3	11	F	29	Hepatic portojejunostomy	4	Yes	Severe	Yes	Yes	Yes
8	2	2	F	101	Hepatic portojejunostomy	6.5	Yes	Mild	Yes	No	Yes

*Age at death.

in the acute form, but raised in the prolonged cases. These findings were in agreement with the laboratory features of cholangitis reported by Wissmer (1965) and Matzander (1972). Serum albumin was reduced in the acute type, but normal in the prolonged cases. γ -Globulin was increased. Blood cultures carried out in 5 cases were negative. Echography of the abdomen showed no cystic pattern suggestive of a hepatic abscess.

Discussion

In the present series, after operation, excellent bile flow was observed in 13 cases out of 55 (24%). These figures are obviously superior to those of Thaler and Gellis (1968) who reported that only 3 of 135 cases (2%) of biliary atresia were successfully repaired during a 10-year period. Patients with atresia or agenesis of the hepatic ducts, not previously thought to be amenable to operation, may benefit from hepatic portojejunostomy if there is a true continuity of the intrahepatic biliary system.

It appeared obvious from the present series that the earlier the operation the better the results, so that operation should not be delayed, despite the difficulty of differentiating this condition from neonatal hepatitis (Redo, 1954; Schnug, 1958; Rickham and Lee, 1964).

The successful repair of biliary atresia, however, has given rise to a serious complication, ascending cholangitis. The complication was critical to determine the prognosis of the patients because some of the patients, who had shown excellent bile excretion after operation and had been symptom free, died of the disease.

Ascending cholangitis usually results from biliary stasis, as urinary tract infections result from urinary stasis. Necropsy examinations of Cases 1 and 2 in the present series, however, showed that the anastomosis between jejunum and porta hepatis was wide open. Ascending cholangitis reported here affected the patients in whom the biliary passages had been surgically repaired, and 'excellent' bile excretion had led to decrease in jaundice. It never occurred in the surgically uncorrected patients. However, 'excellent' bile excretion after hepatic portojejunostomy for biliary atresia was never as good as in adults after similar drainage of bile ducts into Roux-en-Y loops of the jejunum. The intrahepatic bile ducts were usually very narrow, even in the cases of extrahepatic biliary atresia. Furthermore, cirrhosis of the liver developing in this condition might contribute to narrowing the intrahepatic bile ducts. When the hepatic duct or the mass of the prevascular connective tissue of the hepatoduodenal ligament was cut as close as possible

to the liver at operation, there were usually no wide openings of the intrahepatic bile ducts, but tiny greenish spots of less than 1.0 mm diameter were seen in some cases. Bile excretion was much decreased after hepatic portojejunostomy for biliary atresia compared with that seen in adults with a similar operation, and bile flow was very slow, though the anastomosis between jejunum and porta hepatis was wide open. On the other hand, in the surgically uncorrected patients bile excretion was absent and no anatomical connexions were found between the jejunum and the intrahepatic bile ducts at necropsy. On the basis of these findings cholangitis of this type occurred only in the patients with 'excellent' bile oozing, and never in the surgically uncorrected cases.

In the acute fulminating cases, who showed no response to any antibiotic agent, multiple abscesses of the liver were formed and the patients died from the lesions. The prolonged cases developed pruritus and xanthomata.

Causative organisms grown from the abscesses of the liver were intestinal flora: *Esch. coli*, klebsiella, *Pr. mirabilis*, *Strep. mucosus*, etc. It is reasonable to conclude that this cholangitis was of the ascending type.

In the present series chloramphenicol was effective in 2 cases, gentamicin in 1, cephaloridine in 1, and oral cephalixin plus kanamycin in 1. 3 patients did not respond to any agent and died. Effectiveness of the antibiotic drugs seemed to be dependent on the extent of the disease, because the causative organisms in Cases 1 and 2 were shown to be sensitive *in vitro* to some of the drugs used.

The disease developed 3½ to 8½ months after operation and was never observed after the age of 12 months in the present series. It is therefore necessary to treat patients with antibiotics for at least 10 postoperative months to prevent ascending infection. Because long-term antibiotic therapy may be harmful, it is advisable to administer antibiotics intermittently. For example, patients should be treated for 4 days of each week and receive no antibiotics on the subsequent 3 days. We are now studying the efficacy of long-term prophylactic intermittent antibiotic therapy.

We thank Drs. Shigenori Sawaguchi, Hiroshi Akiyama, Takashi Hori, and Takatoshi Kitamura, Department of Surgery, National Children's Hospital of Tokyo, for their helpful advice and guidance.

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