more importance to success in infant cardiac surgery than is the method of cardiopulmonary bypass employed. In this regard, it should be added that there is far less room for error in the infant than there is in the child or adult, and that miniature equipment and instruments can be very helpful.

Finally, two things in particular have proved very useful in dealing with these infants. Firstly, artificial ventilation with warmed and humidified oxygen - air mixtures not only prevents chest complications and helps to deal with pneumonia, but has enabled us to maintain normal body temperatures postoperatively almost without exception. Secondly, intravenous isoprenaline is invaluable postoperatively as it prevents metabolic acidosis, by increasing cardiac output and by causing peripheral vasodilatation.

CONCLUSION

We have been gratified by our measure of success in primary surgical closure of ventricular septal defect in infants, and provided that correction is carefully performed and complete, we consider this to be the procedure of choice in dealing with infants who fail to respond to medical management.

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Liver Transplantation in Biliary Atresia with Concomitant Hepatoma*

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SUMMARY

Two cases are reported in which the very infrequently reported association was found of liver cell carcinoma and biliary cirrhosis secondary to congenital biliary atresia. A search of the literature revealed 4 previous reports of cases with similar pathology. Our 2 patients were both operated upon within the first few months of life, at which time congenital biliary atresia was documented, and in 1 instance temporarily corrected. They ran a progressive downhill course until they both received replacement livers, one at 4 years of age and the other at 12, at which times hepatoma was found in the excised cirrhotic livers. One patient is in good health 18 months post-transplantation. The other developed metastases but died of gastro-intestinal bleeding and pneumonia 76 days post-transplantation.

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Congenital biliary atresia ranks high in the candidacy list for hepatic transplantation, and constitutes the single most frequent indication for liver replacement in a series reported from our institution.[5] In 2 patients treated in this manner, hepatoma was present in the cirrhotic livers, excised at the time of transplantation. The diagnosis of hepatoma had been made pre-operatively in 1 instance, but in the other the finding of a tumour in the specimen was a surprise.

The occurrence of primary liver cell carcinoma in livers with pre-existing cirrhosis due to congenital biliary atresia is unusual. Absolon first mentioned this association in a report on thoracic duct lymph drainage for bile duct atresia.[1] Three cases were subsequently reported by Okuyama,[9] Fish[10] and Deoras.[7]

This communication reports on the 2 above-mentioned cases of congenital biliary atresia with concomitant hepatoma treated by hepatic replacement.

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CASE REPORTS

Case 1

A 12-year-old girl was admitted to the University of Colorado Medical Centre in May 1969, with a history of persistent jaundice, which had started in the neonatal period. At an exploratory laparotomy shortly after birth, a choledochoduodenostomy was performed for congenital biliary altresia of the correctable type. She was relatively symptomfree during the 10 years that followed but developed severe upper gastro-intestinal bleeding from oesophageal varices in 1966, for which a meso-caval shunt was performed. Her subsequent clinical course indicated a slowly progressive deterioration, with fluctuation between mild asymptomatic jaundice and severe exacerbations associated with malabsorption, liver and spleen enlargement and bilirubin levels of up to 35 mg/100 ml. A liver biopsy in early 1967 showed marked parenchymal bile stasis with absence of bile in the large ducts.

A hepatic arteriogram (Fig. 1), inferior vena cavagram and technetium scan of the liver showed what appeared to be a large tumour in the right lobe of the liver, which was highly suspicious of a hepatoma. At operation on 11 May 1969, a liver replacement procedure was done and the mesocaval shunt was ligated. The immediate post-operative course was uncomplicated and normal liver function, as measured by serum protein levels, bilirubin, transaminase, alkaline phosphatase and liver scans, remained satisfactory for 2 weeks after operation.

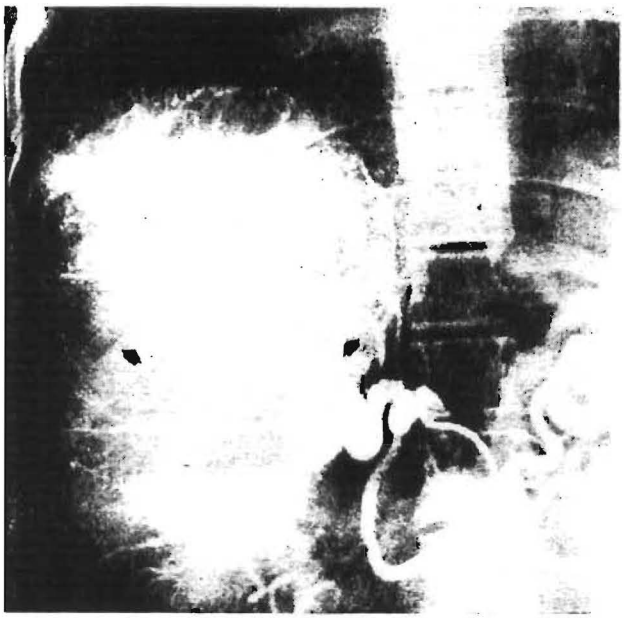

Fig. 1. Hepatic arteriogram, Case 1, showing large intra-hepatic tumor mass in the right lobe.

An occlusion of the left renal vein, secondary to thrombosis of the ligated meso-caval shunt, caused a transient loss of left renal function. This complication resolved spontaneously. After an episode of hepatic rejection had been successfully treated, the transplanted liver underwent a second rejection which was accompanied by severe gastro-intestinal bleeding episodes. The patient died on 26 July 1969, with terminal bronchopneumonia and respiratory insufficiency. A small nodule had appeared on chest X-ray in the upper lobe of the left lung approximately 2 weeks prior to her death (Fig. 2). This was interpreted as a pulmonary metastasis from the pre-existing hepatoma.

Fig. 2. Tomogram showing a small metastatic nodule in the upper lobe of the left lung, case 1.

Alpha-feto-proteins which have proven to be of a diagnostic[1,2] and prognostic[3] value in cases of liver-cell carcinoma were elevated before transplantation and during the 76 days of survival.

Pathological findings: Recipient's own liver weighed 2 025 g and appeared diffusely but unevenly nodular. On section, it contained a 10 × 10 × 8 cm grey, streaked, encapsulated mass in the middle of the right lobe. Several smaller masses 3 - 12 mm in diameter were found in the capsule of the right lobe. The vasculature was normal, but the common bile duct could not be identified.

Microscopically the lobular pattern was distorted by broad and thin bands of dense fibrous connective tissue. There was an absence of normal bile ducts in many portal regions but in some there were proliferated bile ducts peri-

pherally. There was lymphatic and histiocytic infiltration of the portal zones as well as periportal and pericentral bile stasis (Fig. 3).

The large tumour mass was a well-differentiated hepatoma. There was a disorganized pattern of liver cords and sinusoids without a lobular pattern and portal zones. The nuclei were hyperchromatic and a few rare mitoses were noted (Fig. 4). The subcapsular nodules showed a similar appearance except for the nuclear changes.

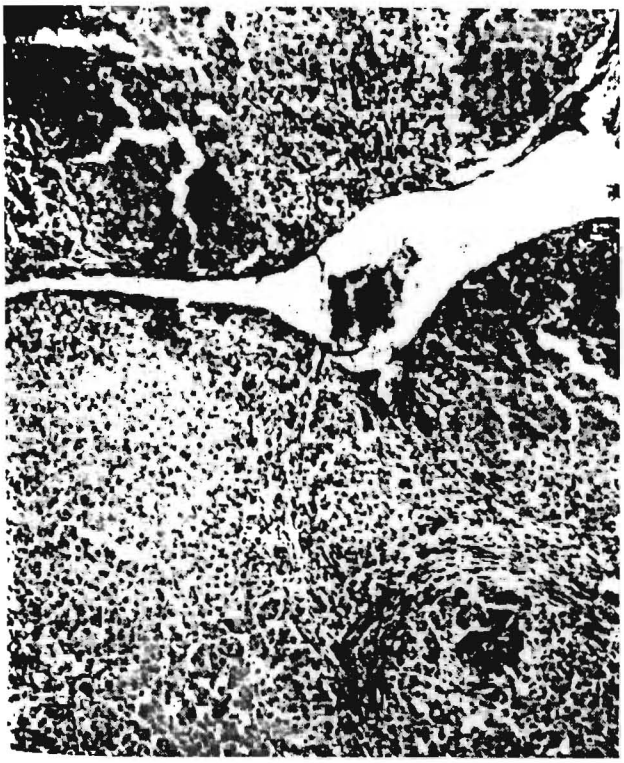

Fig. 3. Photomicrograph of the cirrhotic changes in the liver with extra hepatic biliary atresia, case 1.

The transplanted liver weighed 1 300 g and was soft, flabby and reddish-brown. On the cut surface a thick white fluid, apparently from the duct system, was exuding from many points.

Microscopically the lobular pattern was preserved. The interstitium was oedematous and contained mononuclear cells. Minimal bile duct proliferation was seen, and all the hepatocytes showed severe damage with foamy cytoplasm and degenerate nuclei. Reticulin-staining showed focal collapse and there was much bile stasis.

Evidence of cytomegalo virus involvement was widespread throughout the gastro-intestinal tract and elsewhere.

Case 2

A four-year-old girl was first admitted to the University of Colorado Medical Centre on 22 January 1970. Five weeks after a normal birth, an exploratory laparotomy and operative cholangiogram at another hospital showed an uncorrectable biliary atresia. A liver biopsy showed portal fibrosis, bile duct proliferation and bile stasis. During her first 3 years of life, she bled on several occasions from oesophageal varices and developed gross ascites. An orthotopic hepatic homotransplantation and splenectomy were carried out on the day of admission to our centre. The postoperative course was uncomplicated, and the liver function tests returned to normal levels shortly after operation. The patient is in good health at the time of writing, 18 months post-transplantation.

Fig. 4. Photomicrograph of a section of the hepatoma in case 1.

Alpha-feto-protein was present in the patient's serum at the time of operation but disappeared after a few months (Fig. 5). The findings in this case have been reported by Alpert *et al.*[5]

Pathological findings: Recipient's own liver weighed 1 080 g. On examination the liver had a dark green lobulated capsule and a dark green cut surface, marked by soft nodules delineated by white-grey firm strands of tissue. There was also a 27 × 18 mm white-yellow soft nodule present.

On microscopic examination there was pseudolobule formation, the ducts were absent to scanty, but bile ductules were increased at the edges of the pseudolobules. There was bile stasis in the parenchymal and Kupffer cells and bile canaliculi.

The large nodule was made up of cords and tubular structure, consisting of polyhedral cells, some of which contained mitoses.

The histological diagnoses were bile duct atresia, biliary cirrhosis and hepatoma.

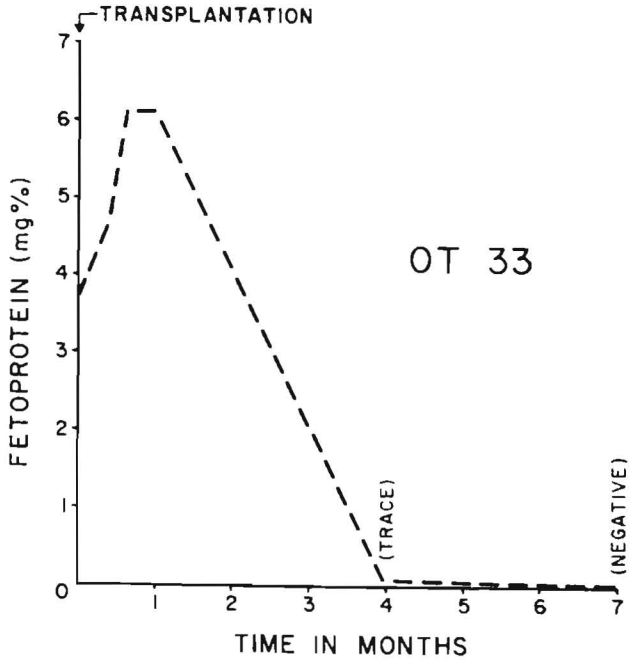

Fig. 5. Alpha-feto-protein levels in case 2. The studies were performed by Dr M. E. Alpert of Boston, who has documented his findings completely elsewhere.[4]

DISCUSSION

Environmental factors such as the presence of aflatoxin and cycasin[19,22] are strongly suspected in the aetiology of primary liver carcinoma in the adult. The frequency with which cirrhosis of various causes is associated with hepatoma varies greatly on a geographical basis.[26] For instance, the incidence of hepatoma in certain parts of Africa is much higher than the incidence of cirrhosis,[23,27] whereas liver carcinoma usually develops in longstanding, slowly-progressing cirrhosis in the European.[12]

It has been claimed by Edmondson[7] and Ishak and Glunz[15] that in those parts of the world where the frequency of hepatic carcinoma in adults is high, there is a strange absence of reported cases in children. However, Prates[23] reported that hepatoma occurs quite commonly among children in Mozambique, where the same disease is endemic in adults. Reports by Watanabe from Japan,[25] Pang from China,[21] Benson from South Africa,[4] Lin from Formosa[17] and Hoe from Vietnam,[14] have also questioned the assessment by Edmondson and Ishak *et al.*

Whatever the merits of the foregoing general controversy, it does seem clear that hepatoma in infants and children with underlying cirrhosis has not been frequently reported. In a survey of the literature by Jones[16] in 1960, only 7 patients out of 128 had carcinoma coincidental with cirrhosis. Other reports by Graser,[13] Clatworthy[6] and Bigelow[5] indicate a similar low incidence of pre-existing disease. Fraumeni[11] carried out an epidemiological study on hepatoma in childhood in the United States, and reported on 282 patients, of whom only 5 had pre-existing liver disease. In other reports[22-24] of hepatoma, associated liver pathology has included giant-cell hepatitis and cirrhosis of several causes.

In the reported cases of hepatoma associated with biliary atresia,[1,7-10,20] as well as in our own 2 cases, the initiation of oncogenesis is not understood. However, a reasonable hypothesis may be that of the triggering mechanism of liver injury, with repair and regeneration as put forward by Gall.[12] So far all hepatomas in biliary atresia have been associated with the extra hepatic variety of atresia, but have never occurred in the intrahepatic atresia victims, who tend to live much longer. On these grounds, one may speculate that the bile accumulation and stasis that is so prominent in the extrahepatic but not the intrahepatic type, is a major factor in irritation, scarring, and finally neoplasia. In our own cases, both children were subjected to laparotomy at an early stage with no suspicion of the presence of tumour. Since the natural course of hepatoma in children is a rapidly progressive and fatal one,[3,9] it seems obvious that the tumours in these patients must have developed in the months prior to transplantation. The presence of the tumour was known in advance in case 1, but in case 2, it was a completely unexpected finding.

Primary hepatic malignancy without metastases, which could not be treated by conventional subtotal liver resection, was originally considered to be the most unequivocal indication for orthotopic liver transplantation. This position has changed drastically with the observation that most patients with such extensive hepatomas developed recurrent neoplasm from which they eventually died, even after successful liver replacement.[25] Of the 2 recipients reported in this article, patient 1 illustrates the nature of the problem. Although death occurred from other causes, the development of metastases had already resulted in a hopeless prognosis in less than 3 months. In contrast, patient 2 was the exception to prove the rule. She is still well and tumour-free 18 months after liver replacement, apparently cured of an early hepatic malignancy. The outcome in this case is an argument in favour of the liver replacement procedure for presumed benign hepatic disease, instead of the alternate operation of auxiliary hepatic transplantation which would have unknowingly left the malignant process in place.

The meticulous care of patients with congenital biliary atresia and the prolongation of their lives, and thus their cirrhotic process, in order to have them treated by hepatic transplantation, may lead to a more frequent association of hepatoma and cirrhosis in the patient with bile duct atresia.

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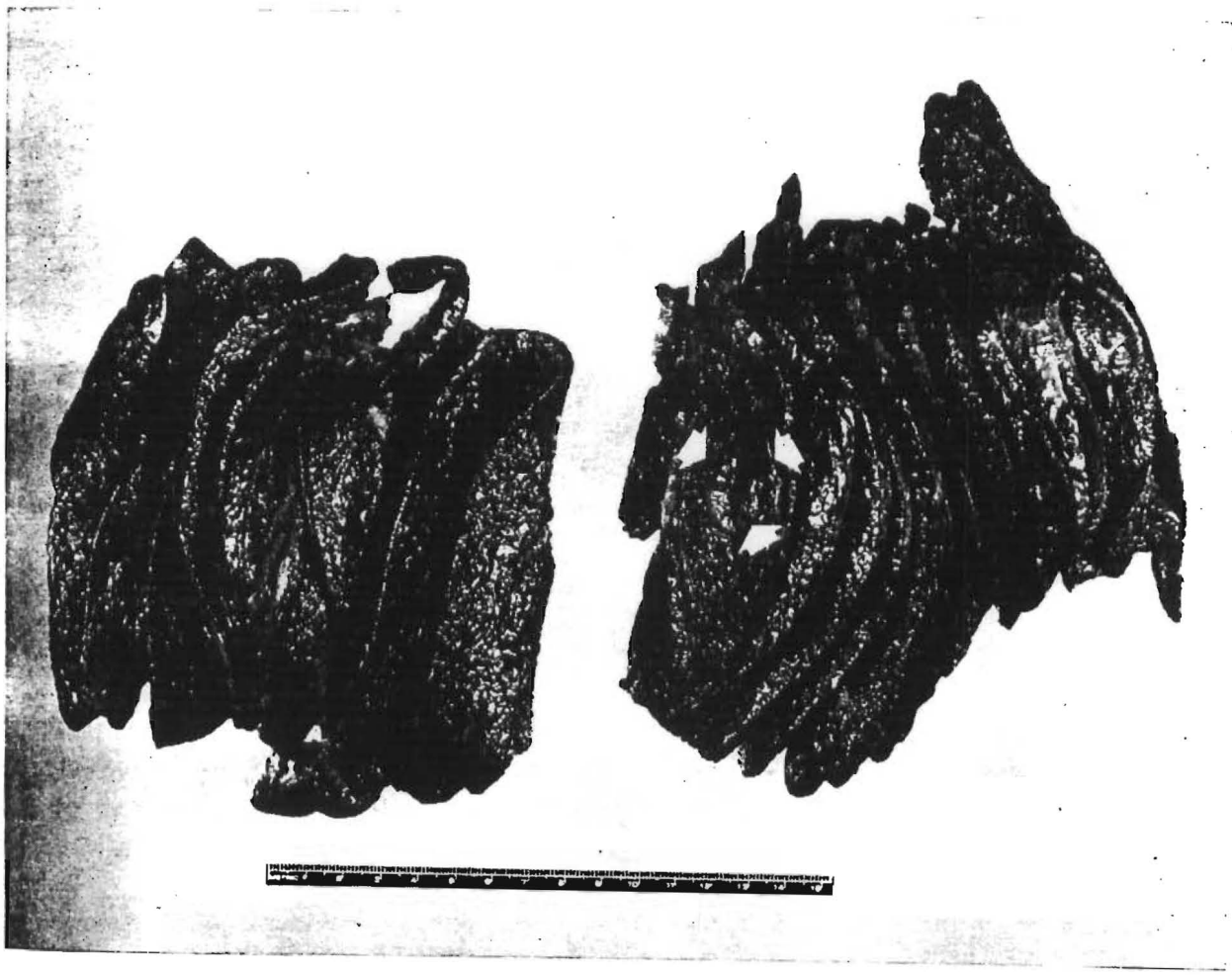

Fig. 6. Appearance of the excised liver of case 2. Hepatoma indicated by arrows.

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