Virchows Arch (Pathol Anat) (1985) 407:387–405

*Virchows Archiv A*


# Primary malignant hepatic tumours in childhood*

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**Summary.** Twenty-four cases of hepatoblastoma, 14 cases of hepatocellular carcinoma and three cases of malignant mesenchymoma out of a total of 54 primary liver tumours were studied by light microscopy and immunohistochemistry. A remarkable finding in one case of hepatoblastoma and one case of hepatocellular carcinoma was a sarcoid-like reaction in the tumour tissue. Three cases of hepatoblastoma presented a macrotrabecular pattern. Among hepatocellular carcinomas, three cases corresponded to the fibrolamellar variant. By immunohistochemistry, the proportion of cases with positive staining for alpha$_1$-fetoprotein was higher in hepatoblastoma than in hepatocellular carcinoma. HB$_s$-antigen could be demonstrated in non-neoplastic liver cells in two cases of hepatocellular carcinoma, but not in the tumour cells. No strong correlation between histological pattern and prognosis could be established in hepatoblastoma. However, there was a tendency to more aggressive biological behavior in cases with pronounced mitotic activity. The number of mitoses in hepatoblastoma varied widely. As in previous studies, patients with the fibrolamellar variant of hepatocellular carcinoma fared better than those with the classical type of this tumour. Prognosis in malignant mesenchymoma was not as poor as suggested from previous studies.

**Key words:** Hepatoblastoma – Hepatocellular carcinoma – Malignant mesenchymoma – Histology – Immunohistochemistry

## Introduction

Owing to the rarity of primary malignant hepatic tumours in children only a few large studies, mainly from institutions in the United States, have

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* This study was supported in part by a grant from the Bundesminister für Arbeit und Sozialordnung

been published on these tumours. It is evident that malignant tumours of the liver vary considerably in incidence, age and sex distribution and prognosis. Subtypes of the tumours have been defined, which differ in clinical behaviour from their more common typical counterparts. Thus, a macrotrabecular pattern in hepatoblastoma apparently accounts for a worse outcome than typical hepatoblastoma (Gonzalez-Crussi et al. 1982). Conversely, the fibrolamellar variant of hepatocellular carcinoma has a more favourable prognosis than the other histological subtypes of hepatocellular carcinoma (Berman et al. 1980; Craig et al. 1980).

It is the aim of the present study to investigate the clinicopathological and immunohistochemical features of all primary malignant tumours of the liver which have been collected at the Kindertumorregister (Paediatric Tumor Registry) in Kiel. We do not intend to duplicate the study of Dehner (1978) or the excellent review article recently published by Weinberg and Finegold (1983). Rather, we would like to contribute our experience from a relatively large number of cases seen at this registry since 1977 when it was established on behalf of the Deutsche Gesellschaft für Pädiatrische Onkologie e.V. (German Society of Paediatric Oncology).

## Material and methods

All cases which had been classified as primary malignant neoplasms of the liver were retrieved from the files of the Department of Paediatric Pathology, Kiel. Initial diagnoses were made on the basis of criteria established by Ishak and Glunz (1967) and Peters (1976).

When necessary, sections were recut and stained with haematoxylin eosin (H & E), Giemsa, periodic acid-Schiff (PAS), Goldner and Bielschowsky's reticulin stain. In the majority of cases, a minimum of one tissue block per centimeter of largest tumour diameter had been sampled. Thus, more than five paraffin blocks were available in most cases.

For immunohistochemical study we used the peroxidase-antiperoxidase (PAP) technique according to Sternberger et al. (1970). Briefly, paraffin sections were deparaffinized in xylene, rehydrated in ethanol and subsequently incubated with the primary antibody. Specific antibodies against the following antigens were used: $Alpha_1$-fetoprotein (AFP), $Alpha_1$-antitrypsin, $Alpha_1$-antichymotrypsin, human chorionic gonadotropin (all from Dakopatts, Hamburg, FRG) and neurotensin (Immuno Nuclear, USA). After incubation with the secondary antibody the PAP complex was applied. Chromogenic reaction was performed using 3,3′-diaminobenzidine and $H_2O_2$. Immunohistochemical study for $HB_sAg$ and $HB_cAg$ was kindly performed by Prof. Dr. Borchard, Düsseldorf.

In one case of hepatoblastoma the tissue had been fixed in alcohol for investigation of intermediate filaments. This study was done by PD Dr. M. Altmannsberger, Göttingen. The technical procedure has been decribed (Altmannsberger et al. 1981).

## Results

There was a total of 54 benign and malignant hepatic tumours excluding metastatic lesions (Table 1). Among these cases we encountered 24 cases of hepatoblastoma, 14 cases of hepatocellular carcinoma, three cases of malignant mesenchymoma and one case of unclassifiable malignant mesenchymal tumour. In another case no definite diagnosis of either hepatoblastoma or hepatocellular carcinoma could be made, since features of both types of tumour were present.

**Table 1.** Primary liver tumours collected at the Paediatric Tumour Registry Kiel

| Type of tumour | *n* |
|---|---|
| Hepatoblastoma | 24 |
| Hepatocellular carcinoma | 14 |
| Malignant mesenchymoma | 3 |
| Haemangioendothelioma | 6 |
| Cavernous haemangioma | 1 |
| Haemangiomatosis | 2 |
| Nodular hyperplasia | 2 |
| Unclassifiable malignant tumours | 2 |
| Total | 54 |

## *Hepatoblastoma*

The clinical and histopathological data of the 24 cases are shown in Table 2. The patient's age ranged from 2 to 85 months (average age: 21 months, mean age: 14 months). There were 17 males and 7 females (2.4:1). In 23 of 24 patients serum AFP levels were elevated. Except for one case, all tumours stained positively for AFP by immunohistochemistry. Three patients presented with special symptoms: A 14-month-old boy (case 10) presented with sexual precocity. Biochemical tests revealed elevated serum levels of chorionic gonadotropin and luteinizing hormone. The other patient (case 15) suffered from alcohol embryopathy, cleft lip and cleft palate. Cleft palate was also found in case 18, a 24-month-old boy. In addition, this patient had macroglossia, dysplasia of ear lobes and a broad nasal root.

Thirteen tumours were confined to the right lobe, five to the left lobe, and four extended into both lobes of the liver. In two cases the exact site could not be determined.

In five cases tumour tissue was available for gross examination. The tumours grew either as large single masses (Fig. 1) or nodules divided by fibrous tissue septae. Necrosis, cystic spaces and haemorrhage were common. Microscopically, there were 11 epithelial and 13 mixed (epithelial-mesenchymal) hepatoblastomas. In the epithelial tumours, fetal areas predominated in eight cases, and two cases were of the pure fetal type. Embryonal areas predominated in four cases, three being mixed hepatoblastomas. These occurred in young children up to 14 months of age. Fetal cells were arranged either in more or less solid sheets or forming cords and plates of 2-cell thickness separated by sinusoids (Fig. 2). In four cases the fetal tumour cells were arranged in broad trabeculae of more than 10 cells (Fig. 3). Fetal-type cells were smaller than adult-type hepatocytes and had either an eosinophilic or clear cytoplasm (Fig. 4). Foci of haemopoiesis, occasionally with megakaryocytes, were commonly found in these areas. Embryonal-type tumour cells often lacked cohesion and possessed less cytoplasm than the fetal-type cells. Nuclei were pleomorphic, hyperchromatic and occasionally contained prominent nucleoli. Frequently, embryonal-type cells were arranged in acinar or tubular configurations (Fig. 5). In one tumour several foci of squamous epithelium either with or without keratinization were ob-

**Table 2.** Clinicopathological data in patients with hepatoblastoma

| No. | Age (months) | Sex | Histological subtype | No. mitoses/10 HPF | | Therapy | Follow-up | Outcome | Special findings |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Embryonal areas | Fetal areas | | | | |
| 1 | 2 | M | E-embryonal pred. | – | – | Biopsy, CHT, RT | Lost | Unknown | |
| 2 | 4 | M | M-fetal pred. | only small foci evaluable | 5 | Op., CHT[b] | | Died postop. | Macrotrabecular pattern |
| 3 | 5 | M | M-fetal pred. | 10[a] (3 HPF) | 2 | Op. | 3 years, 6 months | NED | |
| 4 | 6 | F | E-fetal pred. | – | – | Op. | | Died intra-op. | |
| 5 | 8 | M | M-fetal pred. | 46 | 16 | Op., CHT | 2 years | NED | |
| 6 | 10 | F | E-fetal pred. | 17 | 1 | Op., CHT | 11 years | NED | |
| 7 | 11 | M | E-fetal pred. | 21 | 3 | Op., CHT | 5 years, 2 months | Died | |
| 8 | 11 | M | M-embryonal pred. | 18 | 16 | Op., CHT | 3 months | NED | Macrotrabecular pattern |
| 9 | 13 | F | M-embryonal pred. | 12 | 8 | Op., CHT | 5 months | NED | |
| 10 | 14 | M | M-embryonal pred. | 2 | 3 | Op., CHT | 5 years, 6 months | NED | Sexual precocity |
| 11 | 14 | M | M-fetal pred. | 2 | 0 | Op., CHT | 1 year | NED | |
| 12 | 16 | F | M-fetal pred. | – | – | Op., CHT | 1 year, 3 months | NED | Macrotrabecular pattern |
| 13 | 17 | M | E-fetal pred. | 18[a] (5 HPF) | 17 | Biopsy, CHT | 9 months | Died | |
| 14 | 18 | M | E-fetal pred. | – | – | Op., CHT | Lost | Unknown | |
| 15 | 21 | M | E-fetal pred. | 37 | 4 | Op., CHT | 4 years, 6 months | NED | Alcohol embryopathy, cleft lip, cleft palate |
| 16 | 22 | M | M-fetal pred. | 64 | 14 | Op., CHT | 8 months | Died | |
| 17 | 23 | M | E-fetal pred. | 69 | 29 | Biopsy, CHT | 2 months | Died | |
| 18 | 23 | F | M-fetal pred. | – | 8 | Op., CHT | 13 months | NED | |
| 19 | 23 | M | M-fetal pred. | 11 | 7 | Op., CHT | 20 months | NED | Sarcoid-like granulomas |
| 20 | 24 | M | M-fetal pred. | only small foci evaluable | 23 | Op., CHT | 2 months | NED | Macroglossia, dysplastic ear lobes, cleft palate broad nasal root |
| 21 | 30 | M | M-fetal pred. | 29 | 8 | Op. | 14 months | NED | |
| 22 | 33 | F | E-fetal pred. | 69 | 57 | Op., CHT | 19 months | NED, 1 rec. | |
| 23 | 84 | M | E-pure fetal[c] | – | 60 | Op. | | Died intra-op. | |
| 24 | 85 | F | E-pure fetal | – | 70 | Op., CHT RT | 20 months | Died | Macrotubular pattern |

[a] Less than 10 HPF counted; [b] for a short period; [c] small specimen; Op. = Operation; CHT = Chemotherapy; RT = Radiotherapy; NED = No evidence of disease; HPF = High power fields; rec. = recurrence; E = epithelial; M = mixed

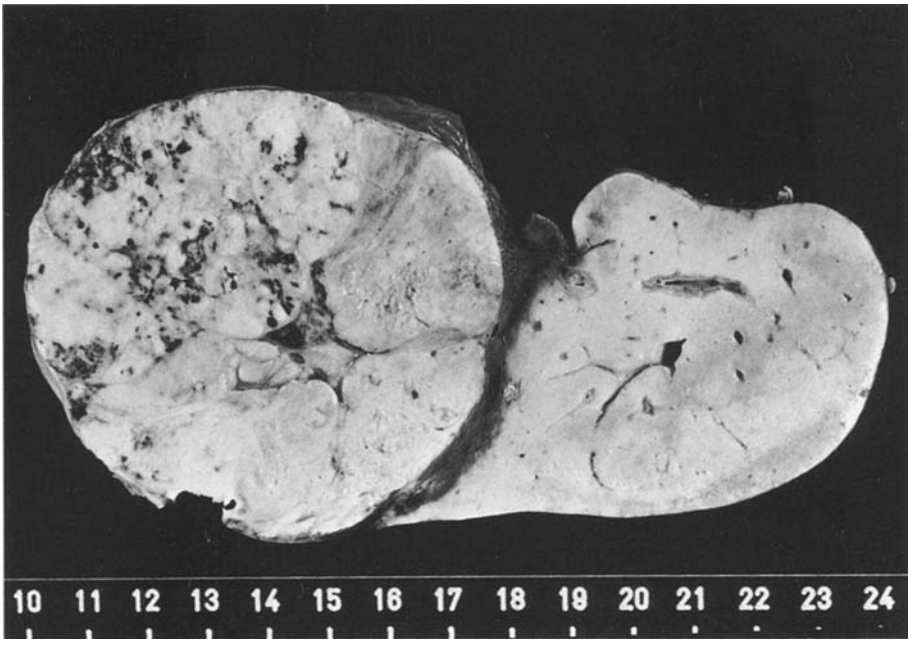


**Fig. 1.** Macroscopic appearance of hepatoblastoma growing as a large circumscribed mass

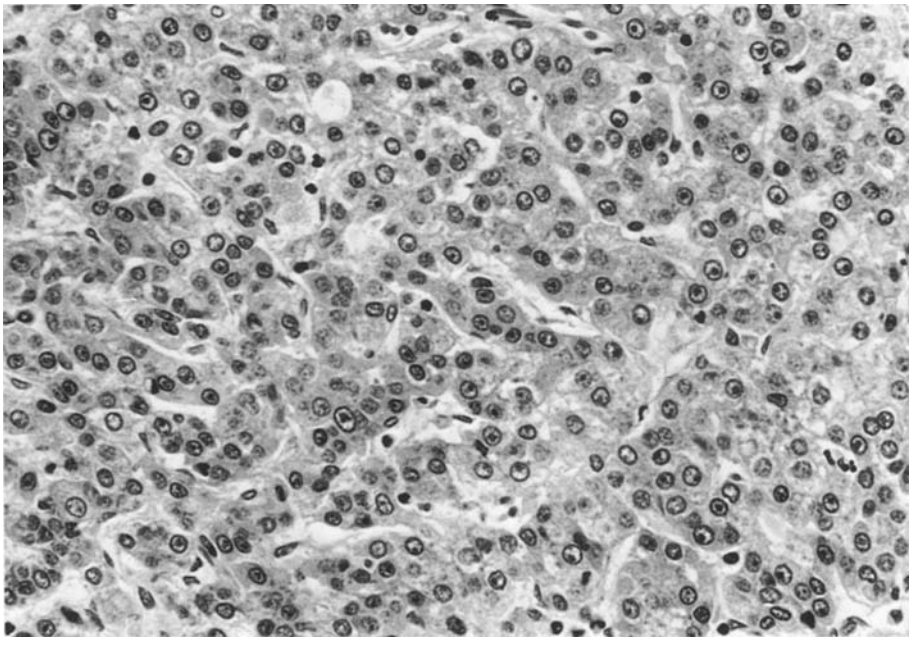

**Fig. 2.** Epithelial hepatoblastoma. Fetal-type tumour cells are arranged in cords and plates (HE, ×350)

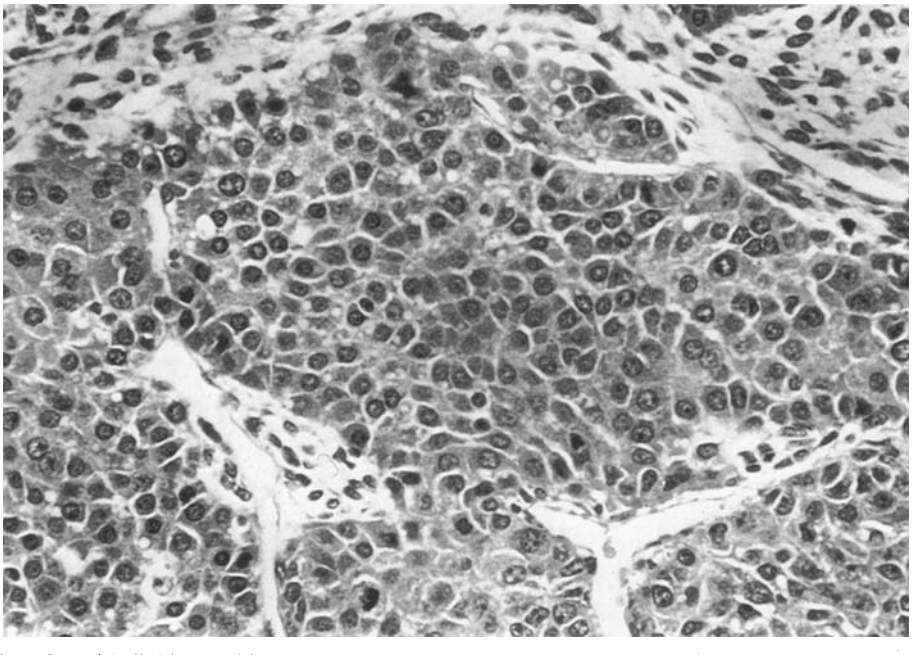

**Fig. 3.** Epithelial hepatoblastoma. Macrotrabecular pattern (HE, × 350)

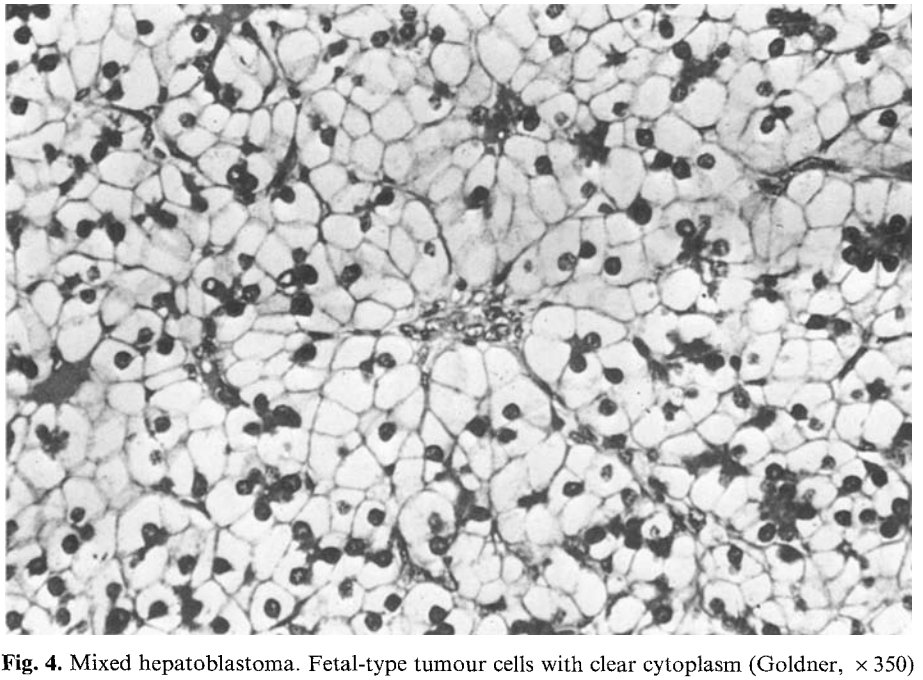

**Fig. 4.** Mixed hepatoblastoma. Fetal-type tumour cells with clear cytoplasm (Goldner, × 350)

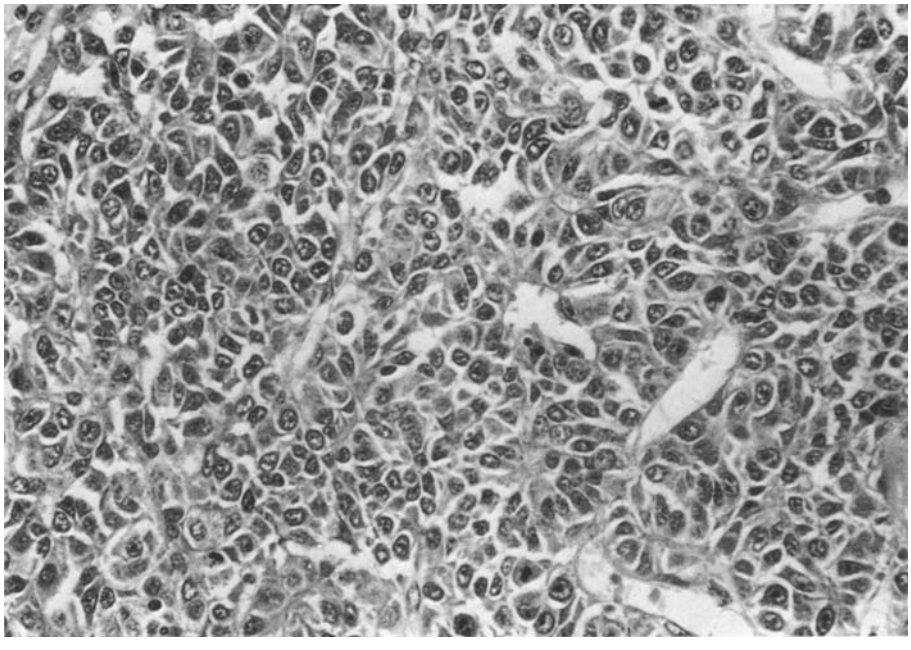

**Fig. 5.** Epithelial hepatoblastoma. Embryonal-type tumour cells, occasionally forming acinar and tubular structures (HE, ×350)

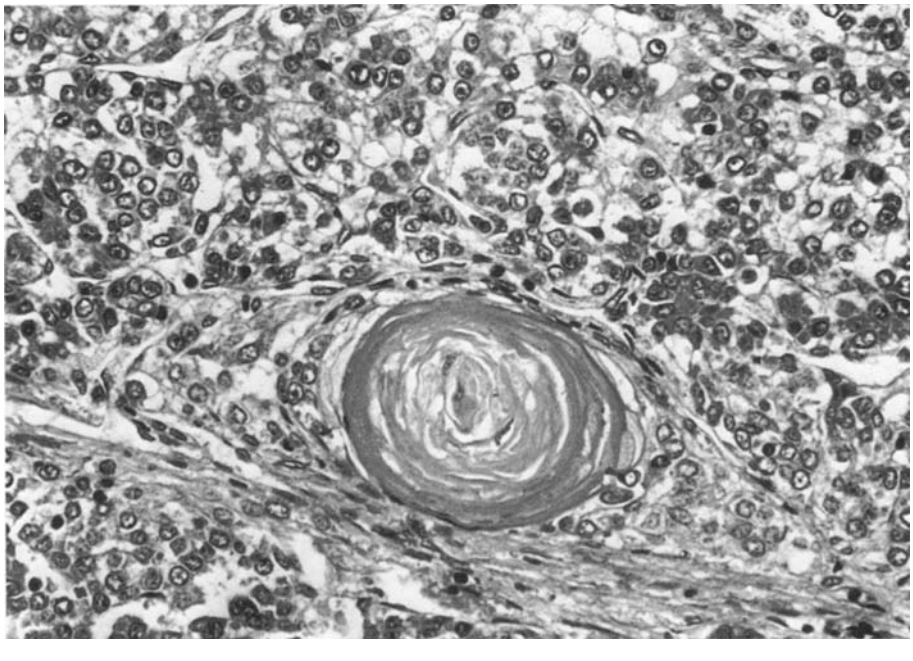

**Fig. 6.** Mixed hepatoblastoma. Focus of squamous epithelium (Goldner, ×350)

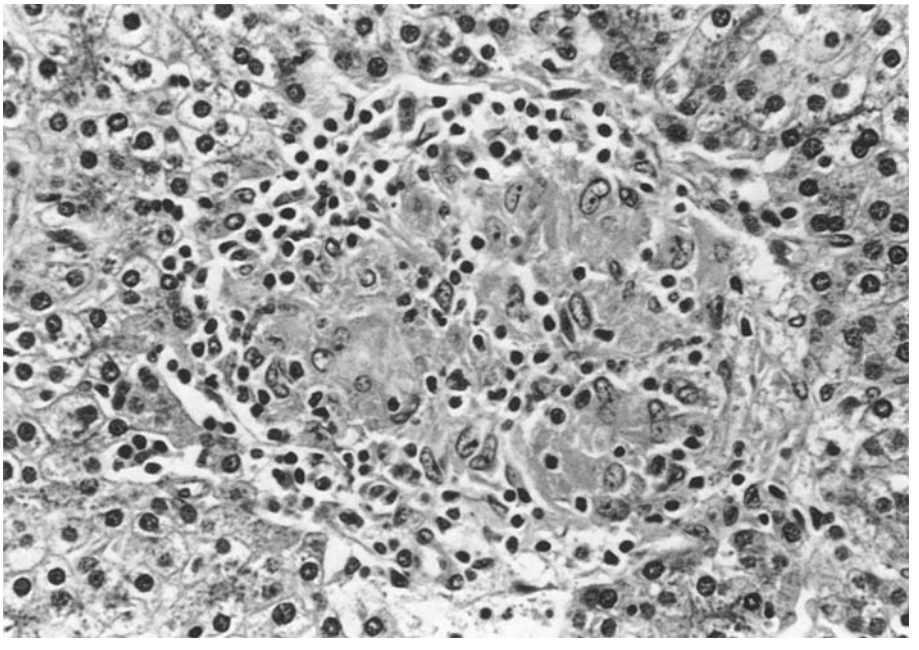

**Fig. 7.** Epithelial hepatoblastoma. Granuloma consisting of epithelioid cells surrounded by fetal-type tumour cells (HE, ×350)

served (Fig. 6). In another case, foci of haemopoiesis also occurred within the embryonal areas.

The number of mitoses varied to a great deal from tumour to tumour, but also from embryonal to fetal areas (Table 2). Generally, the number of mitoses was lower in the fetal areas. One tumour did not show any mitotic activity in the fetal areas, and only two mitoses/10 high power fields were counted in the embryonal portion. Fetal-type cells in this case had clear cytoplasm containing large amounts of glycogen. In six cases a large number of mitoses could be detected. Almost all of these patients died. Moreover, most of the patients with actively proliferating tumours, especially those exhibiting strong mitotic activity in the fetal areas, died of neoplastic disease. Mixed hepatoblastomas consisted of epithelial and mesenchymal elements. Areas of immature spindle-shaped cells in a myxomatous background surrounded fetal or embryonal areas. Formation of osteoid substance occurred in six of 11 mixed hepatoblastomas. One case of epithelial hepatoblastoma contained several granulomas of epithelioid cells (Fig. 7).

Positive staining for AFP was noted in 10 of 12 cases (Fig. 8). Of these cases four reacted positively for alpha$_1$-antitrypsin and alpha$_1$-antichymotrypsin. No staining for AFP was found in two cases of epithelial hepatoblastoma with predominating embryonal areas. Neoplastic cells in the case which could be investigated for intermediate filaments stained positively

**Table 3.** Clinicopathological data in patients with hepatocellular carcinoma

| No | Age (months) | Sex | Location | Therapy | Follow-up | Outcome | Special findings |
|---|---|---|---|---|---|---|---|
| 1 | 79 | F | Diffuse | Op. | 3 weeks | Died | Lung and lymph node metastases |
| 2 | 86 | F | Right I. | Biopsy | 2 months | Died | Chronic aggr. hepatitis, $Hb_sAg$ +liver cells |
| 3 | 110 | M | Diffuse | Op., CHT | 4 months | Died | $Hb_sAg$ +liver cells |
| 4 | 119 | F | Right I. | Op. | | Died intraop. | |
| 5 | 120 | M | Unknown | Unknown | Lost | Unknown | |
| 6 | 120 | F | Unknown | Op., CHT | 6 years, 6 month | NED | |
| 7 | 123 | M | Diffuse | Op., CHT | 1 year | Died | Lung and lymph node metastases |
| 8 | 168 | F | Right I. | Op., CHT | 1 year, 1 month | NED | |
| 9 | 127 | M | Diffuse | Op., preop. CHT | 5 months | Died | Lung and bone metastases |
| 10 | 172 | F | Diffuse | Biopsy, CHT liver trans-plantation | 2 years 1 month | Died | |
| 11 | 175 | M | Right I. | Unknown | Lost | Unknown | |
| 12 | 176 | F | Right I. | Op. | 2 years | NED | Epithelioid granulomas |
| 13 | 192 | M | Left I. | Op. (incomplete) | 9 months | NED (spontaneous regression) | |
| 14 | 209 | M | Left I. | Op., CHT[a] | 10 months | NED | |

[a] In conjunction with hyperthermia; CHT = Chemotherapy; NED = No evidence of disease; Op. = Operation

for keratin. Initial treatment in 20 of the 24 patients was tumour resection. In one patient local preoperative chemotherapy was given to reduce tumour size. Twenty patients received postoperative chemotherapy and two patients additional radiotherapy. Four patients developed metastatic disease. In three patients metastases were located in the lungs, and in one patient a single metastasis was found in the diaphragm. Fourteen patients are alive and well. Five patients died of progressive disease. All of these patients had been treated with adjunct chemotherapy, and one patient in addition with radiotherapy. Three patients died of complications during operation or shortly thereafter. Two patients were lost to follow-up.

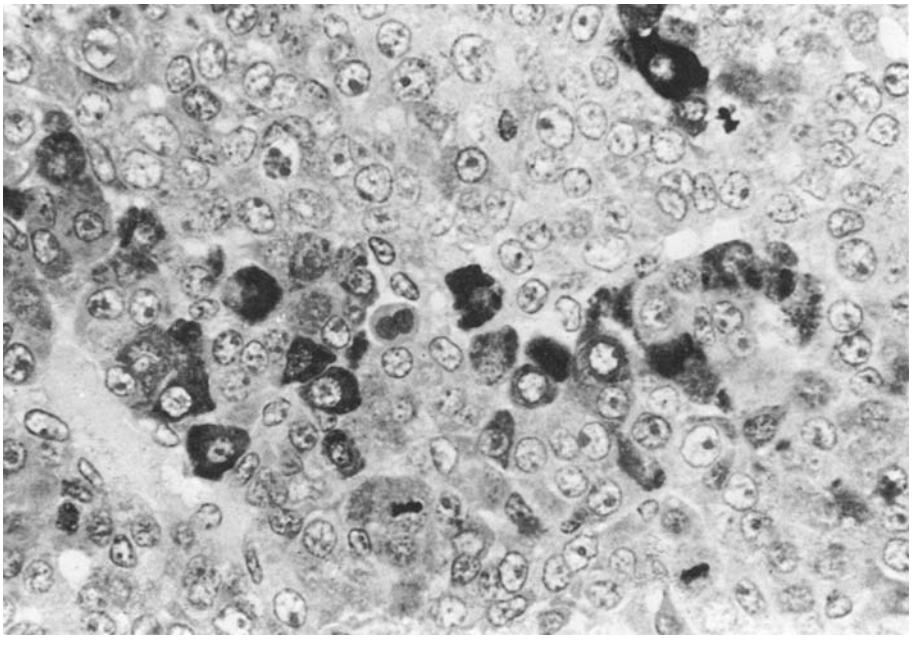

**Fig. 8.** Mixed hepatoblastoma. Several fetal-type tumour cells are positive for alpha$_1$-fetoprotein (PAP, × 540)

*Hepatocellular carcinoma*

Clinical and histopathological data of the 14 cases are summarized in Table 3. The patient's age ranged from 15 months to 17 years (average age: 11.4 years, mean age: 10 years). Ten of the 14 patients were 10 years or older than 10 years at time of diagnosis. The male-to-female ratio was 1:1 (7 males, 7 females). Serum AFP levels were elevated in five of five patients. $HB_s$-antigen was present in the serum of two patients. In both cases, non-neoplastic hepatocytes stained positively for $HB_sAg$, but were negative for $HB_cAg$. The neoplastic cells were negative for both antigens. One of these two patients, a 7 year-old boy, developed chronic aggressive hepatitis at age 3 weeks.

On the basis of the classification of Peters (1976) the following subtypes of hepatocellular carcinoma were encountered:

Macrotrabecular ($n=5$), microtrabecular ($n=2$), giant cell ($n=2$), acinar ($n=1$) and clear cell ($n=1$). Three tumours corresponded to the fibrolamellar variant (Fig. 9). Cells in these cases were large, polyhydral and possessed eosinophilic cytoplasm with occasional PAS-positive globules. In addition, one tumour presented large hyaline cytoplasmic inclusions which were PAS-negative (Fig. 10). Tumour cell complexes were separated by broad parallel bands of collagen. A remarkable finding in one of these tumours was the presence of several granulomas of epithelioid cells. Mitoses were rare. Three of eight tumours were positive for alpha$_1$-fetoprotein. Both cases of fibrola-

**Fig. 9.** Fibrolamellar variant of hepatocellular carcinoma. Tumour cells are separated by bands of connective tissue (HE, × 140)

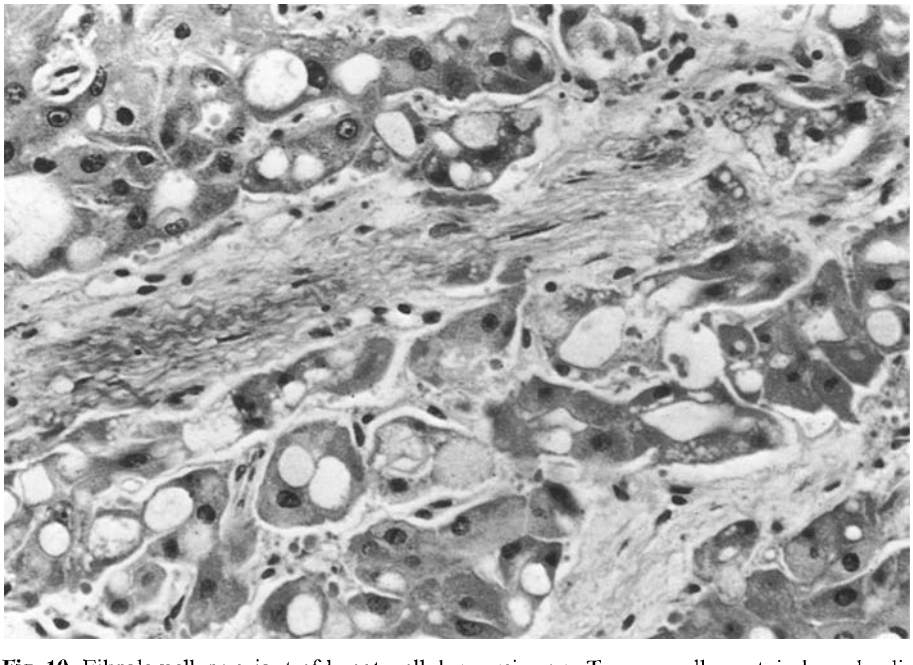

**Fig. 10.** Fibrolamellar variant of hepatocellular carcinoma. Tumour cells contain large hyaline cytoplasmic inclusions (HE, × 540)

mellar carcinoma were also among the negative cases. Seven of eight cases exhibited positive granular staining for alpha$_1$-antitrypsin and alpha$_1$-antichymotrypsin. In the case of fibrolamellar hepatocellular carcinoma with large hyaline globules the reaction product was confined to the periphery of the cytoplasm. The large hyaline inclusions were negative for both substances, whereas the PAS-positive globules stained positively for both alpha$_1$-antitrypsin and alpha$_1$-antichymotrypsin. In both cases of fibrolamellar hepatocellular carcinoma staining for neurotensin was negative.

Pertinent information on treatment and survival was available in 12 patients. All underwent surgical treatment. Because of extensive disease, one patient received a liver transplant. Postoperative chemotherapy was given in six patients, in one of these in conjunction with hyperthermia. Three patients developed metastases to the lungs. In addition, two patients had lymph node metastases. All patients with the fibrolamellar variant are alive and well, the longest survival being six years and six months. Seven patients died, one because of complications during operation. One patient (case 13) had been treated with androgens for six years because of aplastic anemia. At age 16 years, a large tumour was noted in the left lobe of the liver which could not be completely removed. Androgen therapy was stopped at that time. At laparoscopy six months later there was no evidence of tumour in the remaining liver. A biopsy was also negative. Details on this case have been published previously (Treuner et al. 1980).

*Malignant mesenchymoma*

The age of the three patients (2 boys, 1 girl) with this type of tumour was 50, 63 and 82 months. In two of them information on clinical symptoms was available. Both complained of pain in the right abdomen, and abdominal distension had developed rapidly. In addition, one had fever. Other findings were unremarkable. In particular, no increase of serum AFP level was recorded.

Two tumours were located in the right lobe and one in the left lobe. On cut section, they revealed a nodular appearance and were distinctly separated from the uninvolved liver tissue. Large areas of necrosis and haemorrhage were present. In addition, several cystic spaces were found, mostly in the central portion of the tumour.

Histologically, these lesions were highly cellular and exhibited large areas of necrosis and haemorrhage. Between the tumour tissue and the adjacent liver parenchyma there was a thick fibrous pseudocapsule which was not infiltrated by tumour cells in any case. The hepatic parenchyma was atrophic. Tumour cells varied considerably in size and shape. Many had a stellate appearance possessing long eosinophilic cytoplasmic extensions, whereas others were polygonal with ample eosinophilic cytoplasm. Despite extensive search, no cross-striations could be detected. The cytoplasm of many large cells contained eosinophilic, PAS-positive, diastase-resistant globules which resembled those in hepatocellular carcinoma and endodermal

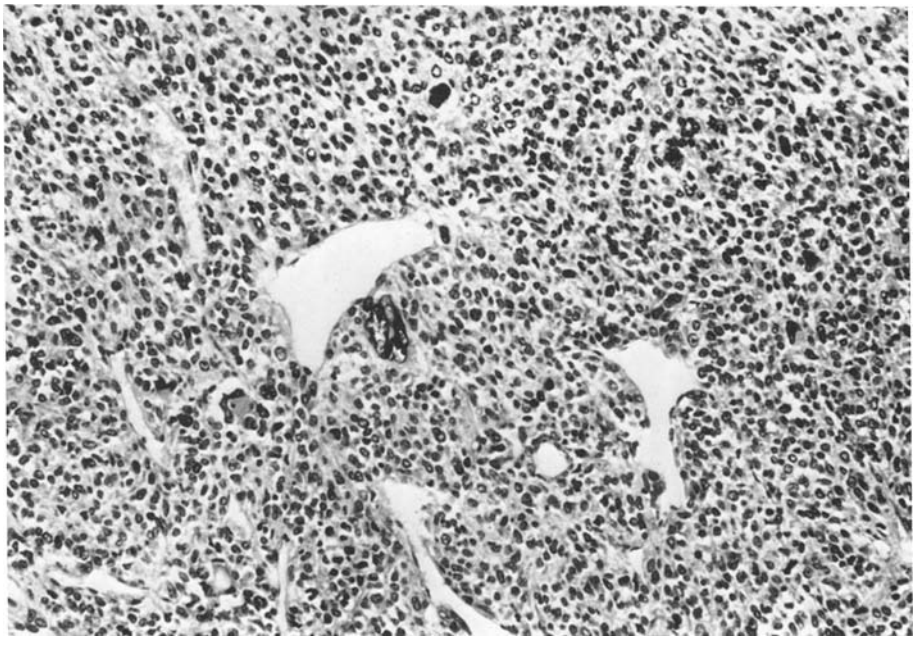

**Fig. 11.** Malignant mesenchymoma of the liver. Haemangiopericytoma-like arrangement of blood vessels (HE, ×140)

sinus tumour. They did not stain for alpha$_1$-fetoprotein, alpha$_1$-antitrypsin and alpha$_1$-antichymotrypsin. Globules were occasionally also present outside the tumour cells. These cells, however, appeared to be degenerating. Nuclei were often large and bizarre. There were numerous mitoses, some of them being atypical. Portions of the tumours contained large amounts of acid mucopolysaccharides. The number of blood vessels was highly variable; occasionally they were arranged in a haemangiopericytoma-like pattern (Fig. 11). Along the periphery of the tumour nodules duct-like structures were frequently observed, which were lined by low cuboidal to flat epithelial cells with hyperchromatic nuclei (Fig. 12).

All patients were treated by surgery. In addition, one patient was given chemotherapy according to the protocol for soft tissue sarcomas. This patient is doing well 2.5 years after cessation of treatment with no evidence of disease. Two years after surgery a floating calcified mass was noted in the right atrium on chest X-ray. Histological examination revealed nonviable tumour tissue with extensive regressive changes. In another patient an extended right hemihepatectomy had to be performed. During the interval between surgery and start of chemotherapy he developed local recurrence and massive metastatic disease to the lungs. He died 3 months later from progressive tumour disease. The parents of the third patient refused chemotherapy. Nevertheless, the girl is doing well 21 months after surgery.

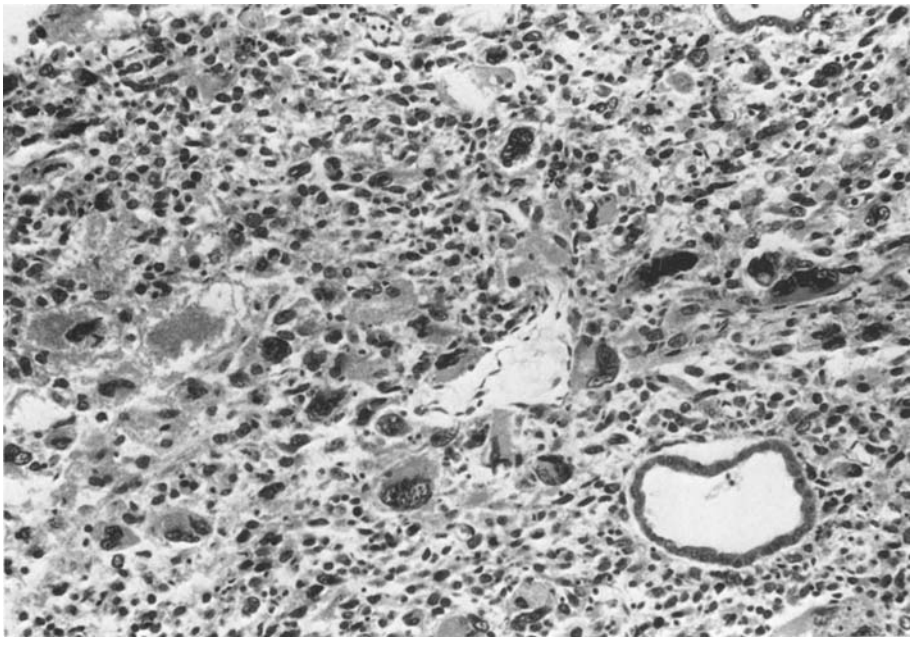

**Fig. 12.** Malignant mesenchymoma of the liver. Duct-like structures are interspersed in the tumour tissue. Tumour cells have large bizarre nuclei (HE, × 350)

## Discussion

Although the number of cases in the current study is much lower than in the two large recent reviews given by Dehner (1978) and Weinberg and Finegold (1983), the proportion of the different types of hepatic tumours is comparable attesting to the representativeness of the Paediatric Tumour Registry in Kiel. Thus, there were 21 (41%) hepatoblastomas, 14 (27%) hepatocellular carcinomas and 4 (8%) sarcomas including one case of unclassifiable malignant mesenchymal tumour.

It is evident from all studies that patients with hepatoblastoma are younger than those with hepatocellular carcinoma and liver sarcomas, although there is some overlap in age range between hepatoblastoma and hepatocellular carcinoma (Lack et al. 1982 and 1983). As in other studies (Ishak and Glunz 1967; Keeling 1972; Gonzalez-Crussi et al. 1982) patients with hepatoblastoma in the current study were usually under two years of age at diagnosis. Cases of congenital hepatoblastoma (Misugi et al. 1967) were not encountered. By contrast, the average age of patients with hepatocellular carcinoma was 11.4 years, and that of patients with malignant mesenchymoma 5.4 years.

Most studies emphasize the male predominance in hepatoblastoma, hepatocellular carcinoma and malignant mesenchymoma (see Weinberg and Finegold 1983). This sex predilection can be especially pronounced in hepatocellular carcinoma ranging from 2:1 to 11:1 (Ishak and Glunz 1967).

However, in the series of Weinberg and Finegold (1983) girls outnumbered boys by seven to four. In the present study there was an equal sex distribution in patients with hepatocellular carcinoma, but a clear male predominance in patients with hepatoblastoma.

Three of our patients with hepatoblastoma revealed clinical symptoms which are well known to occur in association with hepatocellular neoplasia (see Weinberg and Finegold 1983). One patient developed male sexual precocity secondary to ectopic gonadotropin production. However, we were not able to demonstrate HCG in the tumour tissue. Another patient suffered from fetal alcohol syndrome and a third patient presented with macroglossia and dysplasia of the ear lobes. These congenital anomalies are well known as features of the spectrum of Beckwith-Wiedemann syndrome. This syndrome has been reported in association with hepatoblastoma in one previous instance (see Sotelo-Avila and Gooch 1976). Hemihypertrophy was neither observed in that patient nor in our patient. Two of our patients with hepatocarcinoma were found to be hepatitis B virus carriers, and one of the two patients had chronic aggressive hepatitis since his third week of life. Thus, we can confirm recent observations by Weinberg and Finegold (1983) indicating that the interval between infection with hepatitis B virus and development of the hepatocarcinoma may be much shorter than had originally been suspected from the association between hepatitis B virus carrier state and hepatocarcinoma in adults. No information on previous blood infusions was available in our patients.

In accordance with the results of other studies more than 90% of our patients had elevated AFP serum levels. Interestingly, elevated AFP levels were also found in two patients having hepatoblastomas with a predominant embryonal pattern. In both cases, AFP could not be demonstrated in the embryonal-type tumour cells by immunohistochemistry.

Surprisingly, in one of our patients with hepatocellular carcinoma spontaneous regression of unresectable tumour tissue occurred. This patient had been treated with oxymetholone for 6 years because of aplastic anaemia. There are three other patients in the literature in whom spontaneous regression of the tumour has been described (for review see Treuner et al. 1980). None of our patients had liver cirrhosis. Particularly, no patients had hereditary tyrosinemia which predisposes to liver cirrhosis and may lead to development of hepatocellular carcinoma in nearly one third of patients (Weinberg et al. 1976).

Ishak and Glunz (1967) clarified the clinicopathological differences between hepatoblastoma and hepatocellular carcinoma. Using their classification scheme we classified 11 cases as epithelial and 13 cases as mixed hepatoblastoma. Epithelial tumours were composed of embryonal- and/or fetal-type cells. However, in some cases it was almost impossible to clearly define a cell as an embryonal- or fetal-type neoplastic cell. Therefore, in many cases, there was no distinct border between embryonal and fetal areas. Moreover, fetal-type cells were occasionally arranged in a manner commonly found in embryonal areas. Among the epithelial tumours two were exclusively composed of fetal cells. A fetal pattern, especially the pure form,

has been associated with a comparatively better prognosis than the embryonal or undifferentiated pattern (Kasai and Watanabe 1970; Gonzalez-Crussi et al. 1982; Lack et al. 1982). Consequently, hepatoblastomas have been divided into two groups with favorable and unfavorable histology (Weinberg and Finegold 1983). However, no clear difference in prognosis between fetal and embryonal predominant tumours was apparent in our study, although the present group of tumours is too small to draw definite conclusions. Nevertheless, it should be pointed out that some of the tumours with a large amount of fetal cells exhibited more pronounced mitotic activity than those with predominant embryonal areas. Therefore, the degree of proliferation in hepatoblastoma might influence survival more than previously recognized.

Most authors claim that extramedullary haematopoiesis is consistently associated with fetal areas (see Weinberg and Finegold 1983). However, our findings agree with those of Altmann (1978) that haematopoietic foci may occasionally also be seen in embryonal areas. The number of cases in the present study is also too small to confirm or reject the experience that hepatoblastoma with a macrotrabecular pattern has a worse prognosis than the other subtypes (Gonzalez-Crussi et al. 1982). It should be stressed, however, that all cases of hepatoblastoma with a macrotrabecular pattern in that study were stage III-tumours, and were therefore less amenable to surgical resection.

The advanced stage of disease at diagnosis has also been claimed to be the main reason for the still dismal prognosis in hepatocellular carcinoma. Due to the multicentric growth and extensive invasion of liver parenchyma in many of these tumours, only 30% of typical hepatocellular carcinomas can be resected (Exelby et al. 1975). However, a fibrolamellar variant of hepatocellular carcinoma has recently been defined, in which resection of the tumour mass is feasible in up to 50% of cases (Berman et al. 1980; Craig et al. 1980; Farhi et al. 1983; Lack et al. 1983). This type of tumour usually occurs in older children and young adults with a mean age of 26 years (Vecchio et al. 1984). In the present study the youngest patient was 10 years old. Our clinical findings support the high survival rate in these tumours. None of our three patients died, the longest survival being more than six years. Surprisingly, survival rates were relatively low in the study of Lack et al. (1983): Only one of five patients survived. The remaining four developed widespread metastases, although three of them had been treated with chemotherapy and radiotherapy.

A peculiar finding in one of our cases was sarcoid-like reaction in the tumour tissue consisting of epithelioid cells. Similar granulomas were also present in one case of hepatoblastoma, epithelial subtype. To the best of our knowledge this finding has not been reported previously.

Recently, raised serum levels of neurotensin have been reported in fibrolamellar liver carcinoma and it has been stated that neurotensin may be suitable as a marker for this type of tumour (Collier et al. 1984). We did immunostaining for neurotensin in two cases, but were unable to demonstrate this compound in the tumour cells. Alpha$_1$-fetoprotein was also ab-

sent, while alpha$_1$-antitrypsin was found in large amounts as has already been shown by Palmer and Wolfe (1976) and Stromeyer et al. (1980).

Due to its rarity – 13% of hepatic tumours in the AFIP series (Stocker and Ishak 1983) – clinical information in malignant mesenchymoma is sparse. In the first paper, reporting the clinical, angiographic and morphological features of this type of tumour, Stanley et al. (1983) gave detailed information on three male patients, age 10, 6 and 10 years, respectively. Two were treated with lobar hepatectomy and one tumour was unresectable. At time of the report, one patient had died and the remaining two were alive with locally recurrent tumour. The largest series on 31 patients was compiled by Stocker and Ishak (1978). In that study, which included 27 patients up to 15 years of age (14 males, 13 females) only six (19.4%) were free of disease. The poor prognosis of this type of tumour is also documented by the short median survival which was less than one year following diagnosis. Weinberg and Finegold (1983) reported that two of five patients died despite chemotherapy, and two had progressive disease at age six months and two years, respectively. In comparison with these data from the literature only one of our patients died after three months with metastatic lung disease. The other two are still alive with no evidence of disease after 21 and 30 months, respectively.

Although malignant mesenchymoma may histologically resemble rhabdomyosarcoma because of cells with ample eosinophilic cytoplasm, cross-striations are never present. The assumption that these tumours are not rhabdomyosarcomas is also supported by negative staining for desmin. The nature of the cytoplasmic globules which may be found in these tumours remains unknown. They stain neither for alpha$_1$-antitrypsin and alpha$_1$-antichymotrypsin nor alpha$_1$-fetoprotein. Thus, they can be distinguished from globules of similar appearance in hepatocellular carcinoma which react positively for alpha$_1$-antitrypsin (Palmer and Wolfe 1976). Since many of the cells in malignant mesenchymoma which contain globules are clearly degenerative, it may be assumed that they represent some form of degeneration product.

Cases of haemangioendothelioma were not included in the present study, because they are viewed as vascular tumours which follow a benign clinical course in the vast majority of cases. Only one patient with haemangioendothelioma has been described who developed metastatic disease (Dehner and Ishak 1971). More recently, Noronha and Gonzalez-Crussi (1984) reported on a patient with multicentric haemangioendothelioma whose tumour recurred after treatment with lobectomy. However, there were no metastases. Therefore, in individual cases, the biological behavior of haemangioendothelioma of the liver may be difficult to predict, notably in view of the fact that mitotic activity in paediatric tumours is not necessarily associated with malignancy.

*Acknowledgements.* Information on clinical follow-up was kindly provided by PD Dr. Berthold, Gießen; PD Dr. Brandeis, Heidelberg; Prof. Dr. Gadner, Wien; PD Dr. Gaedicke, Ulm; Prof. Dr. Gutjahr, Mainz; Dr. Jobke, Freiburg; Dr. Heiming, Kassel; Dr. Hieronimi, Stuttgart; Dr. Lasson, Kiel; Dr. Lux, Wuppertal; Prof. Dr. Kornhuber, Frankfurt; Prof. Dr. Kosenow,

Krefeld; Dr. Müller-Weihrich, München; Dr. Nahnsen, Bremen; Prof. Dr. Niethammer, Tübingen; PD Dr. Otte, Lübeck; Prof. Dr. Riehm, Hannover; Prof. Dr. Schellong, Münster; Dr. Spaar, Bremen; Dr. Strehl, Dortmund; Dr. Weinel, Hannover; Dr. Will, Stuttgart.

Mrs. Irene Kiekbusch and Mrs. Maren Liebig typed the manuscript. Mr. Jim Heywood reviewed the English translation.

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Accepted June 4, 1985