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Endodermal Sinus Tumor or Orchioblastoma in Children and Adults

W. Woodtli and Chr. Hedinger
Department of Pathology, University of Zürich, Switzerland

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Summary. 19 "endodermal sinus tumors" of infantile testes and 5 analogous testicular tumors in adults were studied. The histopathology and prognosis of these cases are shown. As Teilum postulated, the "endodermal sinus tumor" should be a unilaterally developed teratoma mimicking embryonal yolk sac tissue. The histology seems to confirm that this tumor type is of teratomatous genesis. In one tumor specimen two dermoid cysts were found. Despite the characteristic morphology of the tumor tissue a histogenetic interpretation is not yet possible. A comparison of human embryonal yolk sac does not show any similarity to the tumor tissue. The term EDST is therefore not appropriate.

In childhood the clinical course of the EDST is relatively good, although the tumor has to be classified as an undifferentiated teratoma. At present, 12 of the 19 children with EDST are alive and without recurrences from 7 months to 26 years after orchidectomy. In one of these patients a solitary lung metastasis was diagnosed $2^1/_4$ years after operation and was removed by a lobectomy. In 7 children recurrences occurred within one year. None survived the third postoperative year. Our cases and a review of the literature show that the prognosis is aggravated by the length of symptom duration and with increasing age. Both factors may be related. In adults the clinical course is poor and may correspond to usual forms of undifferentiated teratomas in this age group. Only one of the 5 adults is alive and without metastasis 6 years after surgery.

Introduction

The most frequent tumors found n infantile testes are differentiated teratomas and undifferentiated carcinomas of predominantly adenomatous structure. The latter tumors were first documented histologically by Clark (1900) and White (1910). Current reports estimate that these neoplasms account for one ithird to one half of all prepuberal testicular tumors (Willnow *et al.*, 1970a; Woodtli and Hedinger, 1974). Magner *et al.* (1956), studying 7 cases of "adenocarcinomas with clear cells" described them as a distinct histological group characterized group as having a better prognosis than malignant teratomas.

Today 3 general views regarding the histogenetic classification of these tumors can be distinguished:

1. Teoh *et al.* (1960) contend that the "adenocarcinoma with clear cells" is a neoplasm of the immature testicular tubules in which neither Sertoli cells nor germ cells are differentiated. The term "orchioblastoma" proposed by this group has gained a certain popularity as a result of its use in the nomenclature of the British Testicular Tumour Panel (Collins and Pugh, 1964).

2. Other authors (Abell and Holtz, 1963; Bhargava and Reddy, 1966; Gangai, 1968) believe that this adenocarcinoma is a germ cell tumor which takes on a distinctive histological form in children. Abell and Holtz (1963), Young *et al.* (1970), Wurster *et al.* (1972) and Mostofi (1973a, b) state that similar

tumor patterns can be found in embryonal carcinomas and malignant teratomas of adults, and that teratomatous elements are recognizable in infantile adenocarcinomas. Considering the relatively good prognosis of this tumor, these authors distinguish it from the undifferentiated adult teratomas, and classify it merely as carcinoma or adenocarcinoma *of infants*.

In support of this view Houser *et al.* (1965) and Bachmann and v. Grawert (1972) point out that low malignancy is typical for all infantile testicular tumors irrespective of their morphology.

3. Huntington (1963) presents the view that the infantile adenocarcinoma is related to the "endodermal sinus tumor" of Teilum (1959), which occurs in the ovary of younger women. Teilum (1950, 1959) postulates that this highly malignant ovarian tumor could be a teratomatous neoplasm resembling an extraembryonal membrane, namely the yolk sac, in the same way as choriocarcinoma of the testis mimics chorionic epithelium. He compares the papillary proliferations in this tumor with perivascular formations described by Duval (1891) in the yolk sac of rodents. Although morphological comparison among species must be judged cautiously, the similarity of this typical tumor pattern to the "endodermal sinus" of the rodent yolk sac is indeed striking. The term "endodermal sinus" or "yolk sac tumor" (Pierce *et al.*, 1970a) is therefore today much in use.

The present study deals with some of the questions regarding the pathological and clinical characteristics of the "endodermal sinus" tumor (EDST) in males. It is based on 19 surgical samples of EDST of infants and 5 samples of identical adult tumors.

Material and Methods

Our investigation is based on 24 biopsy samples of "endodermal sinus" tumors (EDST). Fourteen tumors, 9 infantile and 5 adult ones, were taken from a systematic schedule of 448 testicular tumors that have been examined between 1949 and 1973 at the Department of Pathology at the University of Zürich (Meienberg, 1971; Woodtli and Hedinger, 1974). Two cases of infantile EDST originated from earlier records of this Institute and 8 more were courteously provided by colleagues. Four cases of infantile tumors were previously analyzed extensively by Karly (1968) and a report on another case will be published soon (Frei). In adults we have confined ourselves to definite cases of EDST, which fulfill the histological and cytological criteria described below.

In 18 cases, paraffin-blocks in addition to histological slides were available and most of them have been serially sectioned. Unfortunately, only once was there wet material at our disposal. Autopsies of 3 children and 4 adults dying of this type of tumor were carried out. Furthermore, biopsy material of metastases from 3 other children could be examined.

The following staining methods were used: hematoxylin-eosin, van Gieson, elastin, Giemsa, PTAH, iron (Turnbull's), sudan red, Best's carmine, Foot's reticulum, Goldner's trichrome, Alcian blue with and without hyaluronidase treatment, PAS with and without diastase digestion.

Follow-up information on all patients was obtained from hospital records and the reports of family physicians. The examination of yolk sacs from human embryos for comparison with tumor tissue structures was made possible through Prof. G. Töndury, director of the Institute of Anatomy at Zürich University.

Results

Pathology of the "Endodermal Sinus Tumor"

Children

The size of the infantile "endodermal sinus tumor" (EDST) varies from 1,3 to 8 cm in diameter. The tumor tissue is spongious and of yellow-grey colour.

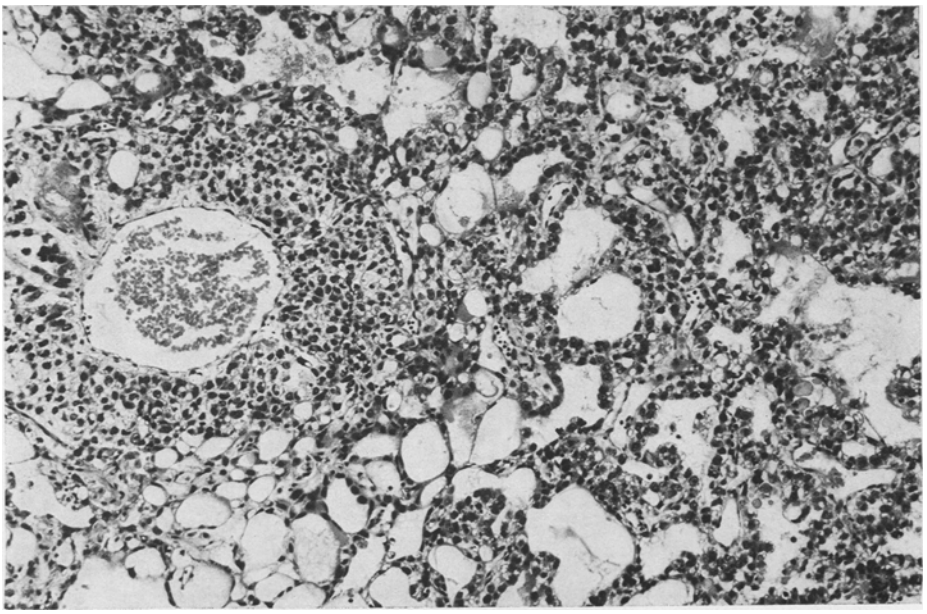

Fig. 1. The 3 basic patterns in an infantile "endodermal sinus tumor": 1. adenomatous area (in the center), 2. mesenchym-like small cystic part (at the bottom, left side), 3. solid part forming a multilayered cuff around a vessel (at the left). (Case 19, BW 4416/66) HE, × 80

In no case had the tumor grown through the tunica albuginea, or infiltrated the epididymis. A small sheet of atrophic testicular tissue is visible on the border of most tumors.

The histology of all 19 cases is uniform. Basically 3 structural patterns can be discerned: 1. adenomatous areas with large and irregular tubules. 2. small cystic, web-like sections where the cells are connected by tiny cytoplasmic processes. 3. smaller solid regions of epithelial appearance. In the latter regions the cell borders are generally less prominent than in solid anaplastic teratomas (MTA) of adults. Each tumor may demonstrate these 3 basic patterns to variable degrees, and there is considerable overlapping (Fig. 1). The gland-like formations seem to arise from the small cystic regions. The frequency of typical, papillary proliferations around capillary vessels, reminiscent of the rodent "endodermal sinus", is generally low (Fig. 2). In addition, similar proliferations are found around connective tissue septa and occasionally around testicular tubules. Larger vessels sometimes carry multilayered cuffs of tumor cells (Fig. 1).

In the glandular areas the arrangement of the tumor cells is loose and irregular. The cells frequently grow into the lumen in a coral-like fashion and occasionally seem to "bud". Cubic or cylindric epithelium of differentiated appearance are seldom found. Large cavities are lined by flattened cells. The cell borders are indistinct. The medium sized nuclei contain a dense chromatine structure in which one or more nucleoli are visible. Even though the nulcei are often vacuolated they keep the coarse chromatine structure. The frequency of mitoses and giant cells varies from one specimen to another. The granular cytoplasm contains

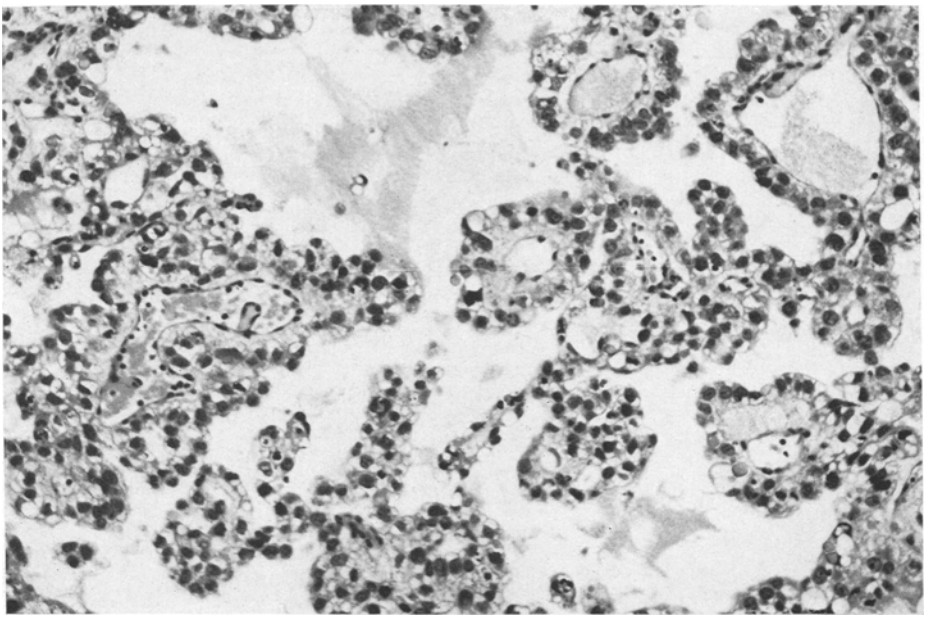

Fig. 2. Perivascular proliferations with vacuolated cells containing eosinophilic globules. (Case 19, BW 4416/66)He, × 140

randomly distributed vacuoles of varying sizes. They appear optically empty or are filled with eosinophilic granular masses and globules as well as sudanophilic droplets. The same esosinophilic, PTAH positive substances are found in the lumen and scattered in the stroma. They give a positive reaction with PAS and Best's carmine. This reaction is strongly reduced by diastase treatment, with the exception of the eosinophilic globules and the larger masses in the stroma. Slightly Alcian blue positive substances are found in some cells and in the lumen. These substances disappear following hyaluronidase treatment. Tumor cells which react positive with Turnbull's dye are occasionally observed in hemorrhagic regions.

The scanty and loose stroma consists mainly of small spindle cells with few collagen fibres. There are small areas of necrosis and hemorrhage. The tubules often contain erythrocytes. Vascular invasion is demonstrable in 5 tumors.

A few tiny testicular tubules can be seen within the neoplastic tissue. Sometimes these tubules seem to communicate with the glandular tumor structures. In other areas they are disrupted by tumor tissue. They show atrophic epithelium or vacuolated Sertoli cells.

In 3 tumors the frequency of mitoses and multinucleated giant cells is high. Some regions in these samples are reminiscent of choriocarcinomatous tissue, but cytotrophoblast-like cells are missing. In two other tumors there are small islands of spindle cells resembling sarcomatous structures (Fig. 3). Muscular fibrils are not demonstrable. Seven tumors show irregular clusters of deeply stained

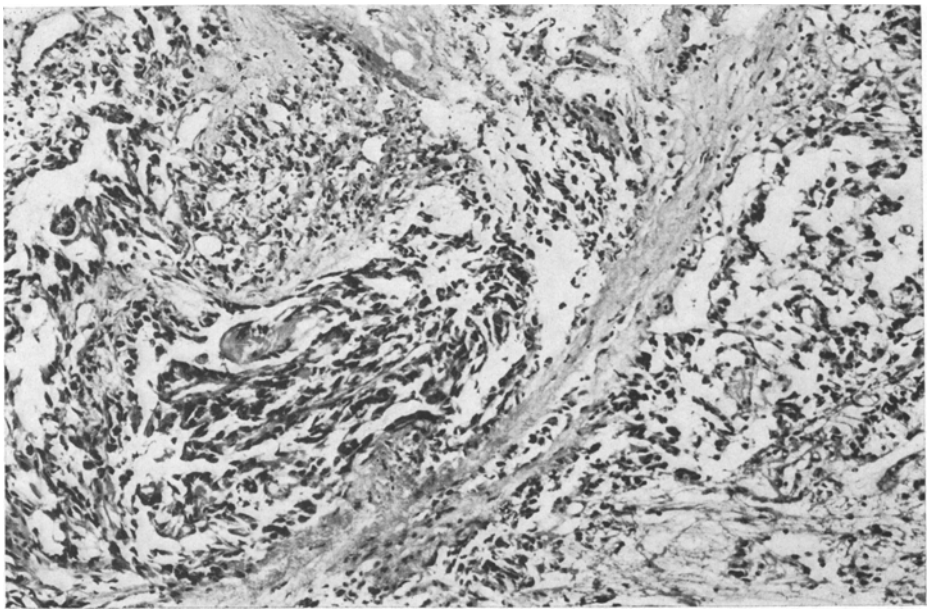

Fig. 3. Area in an infantile "endodermal sinus tumor" of "sarcomatous" aspect. (Case 13, HZ 23573/70) HE, × 100

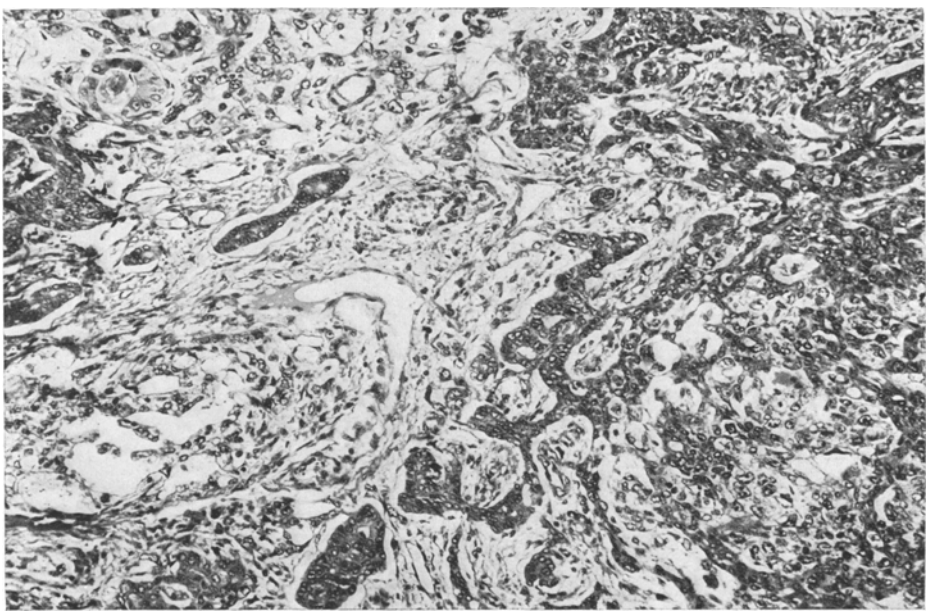

Fig. 4. Clusters of eosinophilic cells with some tubular formations. (Case 9, EL 2953/70 HE, × 140

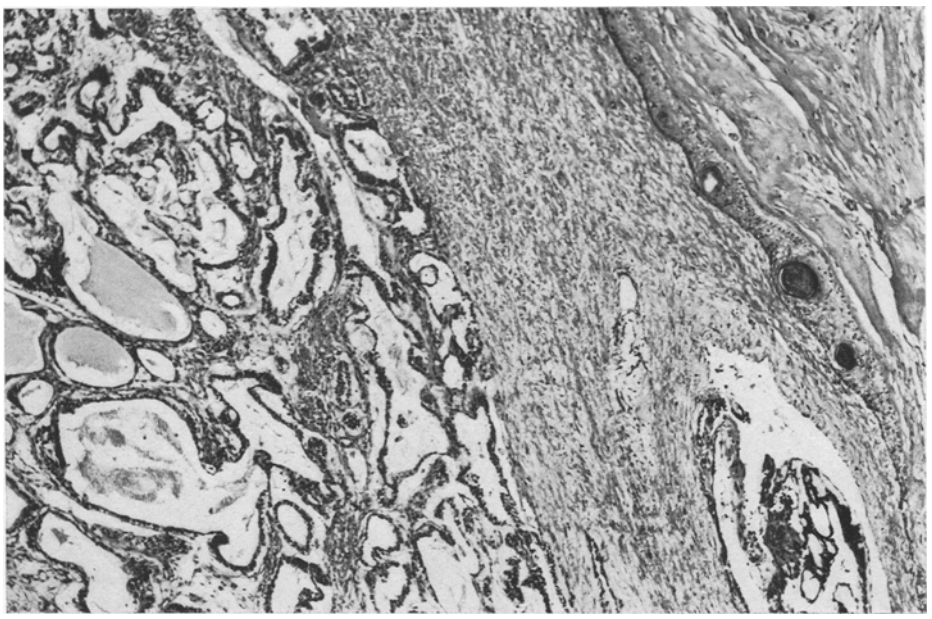

Fig. 5. Squamous epithelial cyst on the border of an "endodermal sinus tumor" (upper right). The adjacent part consists of large glandular spaces lined by an embryonal cylindric epithelium, which does not correspond to typical "endodermal sinus" patterns. Vascular invasion (at the bottom, right side). Case 14, EL 15866/71) HE, × 50

eosinophilic cells which appear cylindric, cubic and occasionally spindle shaped (Fig. 4). They differ from other tumor cells by the absence of vacuoles. The cytoplasm contains fine PAS-positive granules, which are homogenously dispersed. In 3 of these cases small single layered tubules are formed within these clusters. They sometimes can hardly be distinguished from atrophic testicular tubules.

Of special interest is case 14 which has two squamous epithelial cysts (Fig. 5) in addition to eosinophilic cell clusters and cavities lined by an irregular cylindric epithelium. These dermoid cysts are separated from the undifferentiated tumor part by a small layer of corium-like connective tissue.

Adults

In adults the EDST has produced a conspicuous testicular enlargement (5–10 cm in diameter), with the exception of one case in which metastases have been responsible for the first symptoms. The tumor shows occasionally nodular infiltration of the testis. Extensive hemorrhages and necroses are apparent in all tumors. The adenomatous areas are less prevalent than the small cystic and solid parts. The cells are generally less ballooned and the PAS-positive globules scantier (Fig. 6). In one case, a definite sarcomatous area with densely packed spindle cells is observed.

In adults and in children the histological pattern of *metastases* is identical to that of the primary tumor. Perivascular papillae are particularly prominent

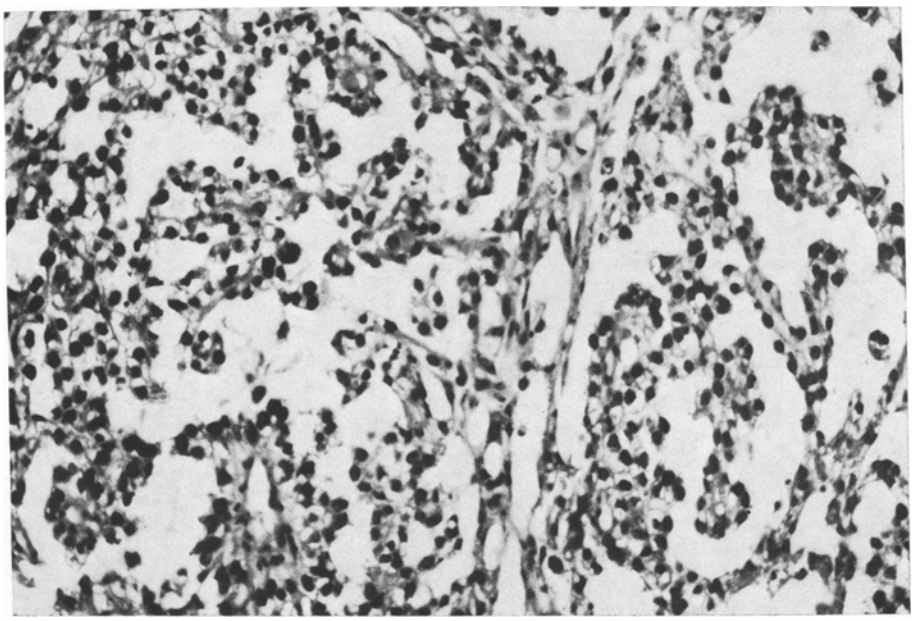

Fig. 6. Adenomatous area of an adult "endodermal sinus tumor". (Case 3, HP 5340/52) HE, × 160

features. In no case could eosinophilic cell clusters or teratomatous elements be identified.

Clinical Course of the "Endodermal Sinus Tumor"

Children

All 19 children with EDST were younger than 4 years and 14 were younger than 2 years (Table 1). Painless testicular enlargement was the only symptom. All tumors occurred in descended testes, in 10 cases on the left, in 9 on the right side. A hydrocele was diagnosed in 4 infants. Two patients demonstrated inguinal herniae on the same side as the tumor. A third had a spina bifida occulta and a dysplasia of the right hip joint. Metastases were never found clinically at the time of definitive diagnosis. The serum levels of gonadotropin were assayed in 3 patients and testosterone in 2. The values were never elevated. α-1-fetoprotein was not determined.

In one child the tumor was detected during a routine examination. In the other patients the time interval between the first observation of testicular enlargement and orchidectomy ranged from 1 week to 20 months (Table 1). Nine children were treated by surgery alone. Postoperative radiation therapy of the inguinal and abdominal lymph nodes was applied to 4 patients. An additional 4 children received chemotherapy after the orchidectomy and one child was treated with radiation therapy and chemotherapy. Retroperitoneal lymph node dissection was done in one patient. There was no evidence of tumor tissue.

Table 1. Clinical course of 19 children with endodermal sinus tumor

Case	Age at orchidectomy (months)	Symptom duration (months)	Course after orchidectomy	Diagnosis of 1st metast. and recurr. (months after operation)	Therapy additional to orchidectomy[a]
1	7	1	alive: 7 years	—	—
2	8	3	dead: 15 months	4	—
3	9	$2^1/_2$	dead: 9 months	?	—
4	11	3	dead: 8 months	5	—
5	13	1	alive: 11 years	—	R
6	13	~6	dead: 14 months	12	R
7	16	3	alive: 26 years	—	R
8	16	$^1/_4$	alive: 4 years	—	—
9	16	1	alive: 4 years	—	LD
10	16	$^1/_4$	alive: 1 year	no metast.	C
11	16	12	alive: 7 months	no metast.	C
12	19	0	alive: 5 years	—	C
13	19	$1^1/_2$	dead: 3 years	11	—
14	20	~20	dead: $3^1/_4$ years	10	—
15	22	1	alive: 14 years	—	—
16	25	$^1/_2$	alive: 3 years	—	C + R
17	28	$^1/_2$	alive: 1 year	no metast.	C
18	37	$^1/_4$	alive: 11 years	27[b]	R
19	41	$1^1/_2$	dead: 8 months	?	—

[a] R = Radiation therapy, C = Chemotherapy, LD = Lymph node dissection.
[b] Lobectomy.

At present, 12 of the 19 patients are alive and free of metastases from 7 months to 26 years after surgery (Table 1). In one of these children a solitary lung metastasis was removed. This case is briefly summarized below.

Case 18. The 3 year old boy was seen at the hospital with a one week history of painless swelling of the right testis. A tumor measuring $3 \times 2 \times 2$ cm was extirpated. The diagnosis was "orchioblastoma". No metastases were detectable. Two and a quarter years later the patient had persistent fits of coughing following an influenza infection. He lost weight. X-ray examination revealed a metastasis in the right upper lung. A lobectomy was performed and a tumor of about 12 cm in diameter was removed. The boy is now alive and without recurrence 10 years after lobectomy.

Seven patients showed early metastases or local relapses within 12 months after orchidectomy. None survived the third postoperative year (Table 1). The following 2 cases demonstrate typical courses of the disease and the route of metastasizing.

Case 14. In this patient an enlargement of the left testis was said to be present since birth. The initial diagnosis was an hydrocele. As the swelling increased slowly, orchidectomy was performed only at the age of 20 months. At this time no metastases were detectable. Ten months later, however, lung metastases were diagnosed. Since the parents first refused a lobectomy, radiation and chemotherapy was tried. The metastases regressed but relapsed after 10 months. At this time a lobectomy was performed. Ten months later, an extensive pleural carcinomatosis occurred and bone metastases were diagnosed by X-ray examination. The patient died 3 years after orchidectomy, at the age of 5 years.

Case 8. A 13 months old child, having a left testicular enlargement for more than 6 months, was admitted to the hospital. At this time the patient was also suffering from diarrhea

accompanied by weight loss and anemia. The clinical examination revealed no metastases. Twelve months later, diarrhea with mucinous, sanguinous stools and vomiting occurred. No lung metastases were diagnosed by X-ray examination, but at laparotomy a huge hemorrhagic retroperitoneal tumor with extensive peritoneal carcinomatosis was found. A surgical extirpation of the tumor was not possible and the patient died 2 months later.

Adults

The 5 adults with EDST were 23 to 57 years old (Table 2). In 2 patients the tumor occurred in an undescended inguinal testis. The duration of symptoms up to the time of orchidectomy ranged from 2 weeks to more than 2 years. Two patients were referred to the hospital with the symptoms of an acute abdomen. In 4 of the 5 adults, extensive metastases were already manifest at the time of diagnosis. Disseminated, painful bone metastases as well as lung and lymph node secondaries appeared in one of these 4 patients. A carcinoma of the prostata was suspected. In 2 patients peritoneal carcinomatosis was present. Lung, lymph node and kidney metastases were found in another patient. All 4 patients succumbed within a few months despite semicastration and subsequent radiation and chemotherapy.

Only one patient, whose tumor in an undescended testis was removed before appearance of metastases, is still alive and without recurrences, 6 years after surgery.

Serum levels of choriogonadotropin examined in 3 patients at diagnosis were normal. In one patient the test was repeated in an advanced stage of the disease and a highly elevated serum level was detected. The metastases, however, showed no evidence of choriocarcinomatous elements.

Table 2. Clinical course of 5 adults with endodermal sinus tumor

Case	Age at operation (years)	Symptom duration (months)	Course after orchidectomy	Diagnosis of 1st metast.	Therapy additional to orchidectomy[a]
1	23	24	dead: 3 months	at diagnosis	R/LD
2	29	5	dead: 3 months	at diagnosis	C
3	32	1/2	dead: 4 months	at diagnosis	—
4	41	1	alive: 6 years	—	R/C
5	57	4	dead: 6 months	at diagnosis	R

[a] R = Radiation therapy; C = Chemotherapy; LD = Lymph node dissection.

Discussion

Pathology of the "Endodermal Sinus Tumor"

The "endodermal sinus tumor" (EDST) is most prevalent in childhood, but occurs, although infrequently, also in adults. This tumor is characterized histologically by loose tissue structures consisting predominantly of adenomatous, mesenchym-like, papillary and occasionally solid areas. The cytoplasm of the tumor cells is abundant, vacuolated and contains conspicuous eosinophilic globules. The

EDST does not resemble the sex cord/gonadal stroma tumors (Sertoli cell-, Leydig cell tumor, androblastoma), nor does it show transitional forms to this tumor group. Therefore, the suggestion that the EDST might be an "orchioblastoma" (Teoh *et al.*, 1960), i.e. a blastoma arising from the undifferentiated testicular tubules, is unconvincing. On the other hand, the perivascular proliferations observed in this infantile tumor suggest a relationship to the highly malignant EDST in the ovary (Huntington *et al.*, 1963). The papillary growth in the infantile EDST, however, seems to be less frequent than in its ovarian counterpart (Huntington *et al.*, 1963, 1972). Histochemical characteristics found in our testicular tumors are identical to those described in the EDST of the ovary by Neubecker and Breen (1962). In all tumor samples, variable quantities of neutral and basic mucopolysaccharides, glycogens and lipids were detected. While few mucopolysaccharides and glycogen have also been demonstrated in undifferentiated teratomas, PAS-positive and diastase-resistent globules in the EDST appear to be relatively specific features. In addition, small amounts of hyaluronidase-sensitive acid mucopolysaccharides were present in the tumor cells. These observations, together with the histological characteristics, corroborate the view that the ovarian EDST and the embryonal carcinoma of the infantile testis are analogous tumors. As the EDST of the ovary is considered to be a teratoma of germ cell origin, the same may be true for the embryonal carcinoma of the infantile testis.

A further indication of the teratomatous genesis of the EDST is that this tumor also occurs at other anatomical sites typical for primary teratomas, i.e. epiphyseal region (Albrechtsen *et al.*, 1972), the mediastinum (Carney *et al.*, 1972; Panchaud, 1973), the retroperitoneum (Thiele *et al.*, 1971) and the sacrococcygeal region (Chretien *et al.*, 1970).

Perhaps the strongest evidence for the teratomatous genesis of the EDST is its appearance in combined form with other germinal cell tumors in gonads or in extragonadal locations. In adults the combination of EDST with a testicular teratoma has been documented by Teilum (1959) in his basic paper on the histogenesis of the EDST. EDST combined with teratomas, seminoma and dysgerminoma has been reported by Young *et al.* (1970). Wurster *et al.* (1972) found "orchioblastoma-like" areas in almost one third of undifferentiated adult testicular teratomas. Particularly frequent are islands of mesenchymal appearance reminiscent of the small cystic pattern of the EDST. Occasionally adenomatous and papillary formations can be demonstrated, but the cells are generally smaller than in the EDST and not vacuolated. However, these "orchioblastoma-like" areas in adult testicular teratomas may not always be identical to the tissue of the infantile EDST.

In infantile testicular EDST the combined forms with teratomatous elements are less conspicuous. However, Mostofi (1952) described teratomatous and, in particular, choriocarcinomatous parts in some of the embryonal carcinomas of infants. In a few of our tumors, giant cells were demonstrable, but the absence of cytotrophoblast-like cells does not allow the diagnosis of these areas as choriocarcinomatous. Bhargava and Reddy (1966) also mentioned the presence of sarcomatous lesions in infantile EDST. In two of our tumors, foci consisting of spindle cells have been found, but we were not able to exclude the possibility that these

were artefacts. The epithelial clusters of eosinophilic cells, found also in seven of our tumors, are interpreted as teratomatous elements by Abell and Holtz (1963), especially if tubules are formed. More convincing examples of combined tumors in infants are EDST with differentiated teratomatous elements described by Young *et al.* (1970) and Mostofi (1973a, b) and demonstrated by our case number 14.

A final argument in favour of the teratomatous genesis of the EDST is its production of choriogonadotropin (HCG) (Neubecker and Breen, 1962; Teilum, 1971) and α-1-fetoprotein. Although in childhood HCG has never been detected, elevated levels are found in adults with testicular and ovarian EDST. α-1-fetoprotein has been demonstrated in the serum of patients with undifferentiated teratomas (Abelev, 1968) and in children with metastasizing EDST of the testis and sacrococcygeal region (Tsuchida *et al.*, 1973). As this protein is produced in the fetal liver and the yolk sac (Gitlin *et al.*, 1972), Tsuchida suggested that its occurrence in patients with EDST supports the yolk sac theory of Teilum.

The Question of the Origin of the "Endodermal Sinus Tumor"

The hypothesis that the EDST is derived from the yolk sac of the human embryo is based on the histological comparison of the tumor tissue with similar structures in the yolk sac of the rat (Teilum, 1959, 1971). A further argument in favour of this histogenetic interpretation is given by Pierce *et al.* (1970a, b) who were able to produce a yolk sac-like tissue (resembling the parietal layer) in transplanted teratomas of the mouse strain 129.

In order to analyze the morphological relationship, we preferred to compare the histological pattern of the EDST with the human yolk sac tissue. The *human yolk sac* entoderm consists of a one- to two-layered epithelium, initially of cubic, later of high cylindric type (Jakob and Töndury, 1974). It involutes in the third fetal month (Hoyes, 1969). The large cells form a smooth, regular and continuous coat (Fig. 7). They are generally delineated distinctly against the underlying mesoderm despite the absence of a basement membrane (Hoyes, 1969; Fukuda, 1973). *Papillary proliferations around vessels are not found.* On the surface of the cells an irregular brush border is visible. The fine, honey-combed cytoplasm contains large sporadic vacuoles which always appear optically empty. The voluminous, round nuclei, with their prominent central nucleoli, are pale and surrounded by a thin membrane. The cells of the mesoderm are less than half the size of the epithelial cells and form a relatively dense layer in which vessels and hematopoietic islands are found. The parietal surface of the yolk sac has a mesothelial appearance.

In contrast to the normal human yolk sac, the club-like epithelial cells of the adenomatous areas in the EDST show a pronounced tendency to dissociate. They rarely form an organized cubic or cylindric layer. There are no cytological differences between the adenomatous and mesenchym-like parts in the EDST, whereas the epithelial and mesodermal cells in the human yolk sac are clearly distinguishable. Therefore, the small cystic areas cannot be compared with the mesodermal yolk sac layer ("magma reticulare"), as postulated by Teilum (1959, 1971). Also, the distinct vacuoles containing PAS-positive globules and the

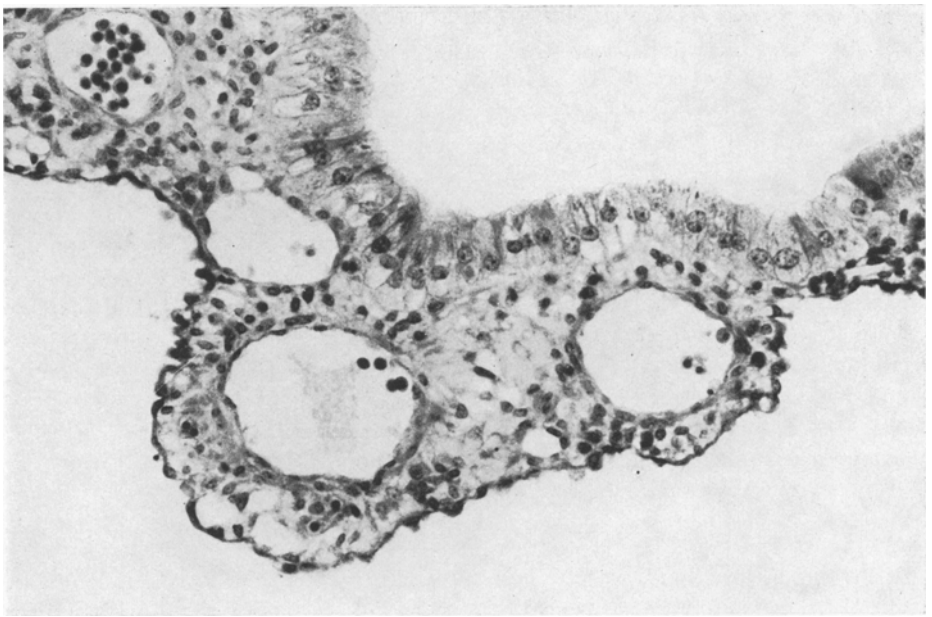

Fig. 7. Embryonal human yolk sac with the high cylindric entodermal layer, the mesodermal layer containing vessels and the mesothelial-like parietal epithelium. (Embryo of 8 mm crown-rump length, approx. 40 days after conception. Granted by Prof. G. Töndury) × 750

densely structured nuclei in the tumor cells have no equivalent in the human yolk sac.

On the basis of these observations we can exclude, with reasonable confidence, that the EDST mirrors human yolk sac structures. It is still an open question, however, from which other germ layer this tumor arises (Marin-Padilla, 1968). We believe that the clusters and tubules of eosinophilic cells often observed in these tumors (Teoh *et al.*, 1960; Abell and Holtz, 1963; Willis, 1967; Young *et al.*, 1970) should be given more attention. These cells, some cubic and some spindle shaped, are, in our opinion, more differentiated forms of the ordinary tumor cells. A close study of them may give further information on the histogenesis of the EDST.

Clinical Course of the "Endodermal Sinus Tumor"

In the majority of cases the EDST appears before the second year of life. Its occurrence in patients more than 5 years old is rare (Ravich *et al.*, 1966; Young *et al.*, 1970; Willnow *et al.*, 1970a). Three of our 5 adults with EDST were over 30 years old. Ross and Morrow (1970) described an EDST in an undescended testis and a teratoma with mainly EDST-tissue in patients aged 42 and 56 respectively. Pierce *et al.* (1970) even mentioned a pure EDST in an 82 year old man. It is noteworthy that the adult EDST seems to appear predominantly in higher age groups.

In the child, the symptoms generally consist of a relatively rapid, painless increase of testicular size (Karly, 1968). As in some of our cases, the tumor may be accompanied by a hydrocele. In children, the determination of α-1-fetoprotein

contributes little to the diagnosis of the EDST, but may be helpful in the postoperative follow-up (Gassner and Grob, 1972). The report of Tsuchida *et al.*, (1973) suggests that in children a significant increase of this protein can be expected only when metastases of a certain size are present.

In early childhood, no connection seems to exist between cryptorchism and testicular tumors. Infantile EDST in undescended testes are exceptional (Young *et al.*, 1970; Bhargava and Reddy, 1966). On the other hand, two of our infantile cases demonstrated an inguinal hernia. According to Li and Fraumeni (1972), inguinal herniae are more frequent in young children with testicular tumors than in control groups. Therefore, as in adults, a causal relation between testicular tumors and congenital defects may exist.

In children, metastases are rarely detectable at the time of operation, but they manifest themselves relatively soon after orchidectomy. In 7 of our 8 patients with metastasizing tumors, local or widespread secondaries appeared within the first postoperative year. In one patient (case 18), an already huge lung metastasis was diagnosed only 27 months after orchidectomy. Our observations are in agreement with the statement of Teoh *et al.* (1960), that new metastases arise rarely after the second postoperative year, and that children surviving 3 years without signs of metastases have a very high probability to being cured.

In childhood the main locations of metastases are the retroperitoneal lymph nodes, the lungs, and the liver. Often the tumor spreads to the homolateral kidney and, in advanced stages, to the bones, the brain, and the meninges. These locations show that the spread is possible by the lymphogenic and hematogenic route. Exclusive secondaries in the lungs are not unusual in both age groups (Teoh *et al.*, 1960; Tefft *et al.*, 1967; Young *et al.*, 1970; Skinner *et al.*, 1971). In this condition a surgical procedure can prove life-saving as our case 18 shows.

For a closer study of the natural history of the EDST we have collected 91 histologically documented cases of the literature which were followed-up for at least 3 years. The clinical course of these patients, together with the 16 of our cases, followed-up for the same period is shown in Fig. 8. The 3 + survival of these children was 60%, which is only slightly lower than the 70% figure quoted by Mostofi (1973a, b). Most deaths occurred in the first postoperative year. For comparison the survival rate of 81 adults with malignant teratomas of the intermediate type B (MTIB), out of the series of Pugh and Cameron (1964), is also plotted in Fig. 8. If the EDST is a teratomatous tumor, as has been demonstrated, it has to be classified in adults as MTIB. The graphs show that the survival rate of children with EDST is almost twice as high as that of adults with MTIB-teratomas, if metastases are not detectable at the time of diagnosis. Likewise a child surviving the first postoperative year has a much better chance of being cured than an adult.

Teoh *et al.* (1960) stated that the time between the first discovery of the tumor and operation is of decisive importance. In 5 of our 7 children dying of metastases, this interval was more than 2 months (Fig. 9). In the literature and our cases, 3/4 of all patients, irrespective of age, survived if the tumor was manifest for less than two months, but only 30% were cured if the symptoms exceeded this period. On the other hand, Houser *et al.* (1965) and many other authors made the observation that children with malignant testicular tumors, occurring before the second

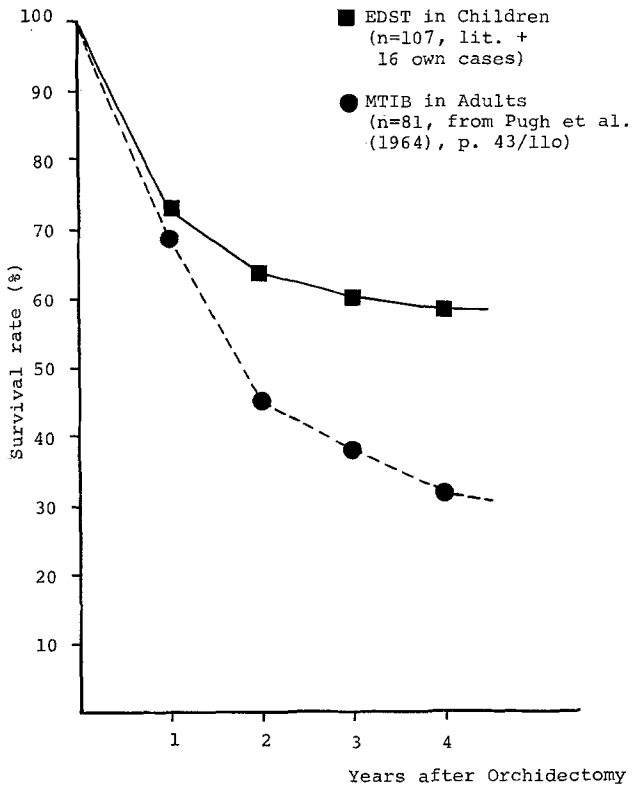

Fig. 8. Comparison of survival rate of endodermal sinus tumor in children and malignant teratomas of the intermediate type B (MTIB) in adults (literature and own cases)

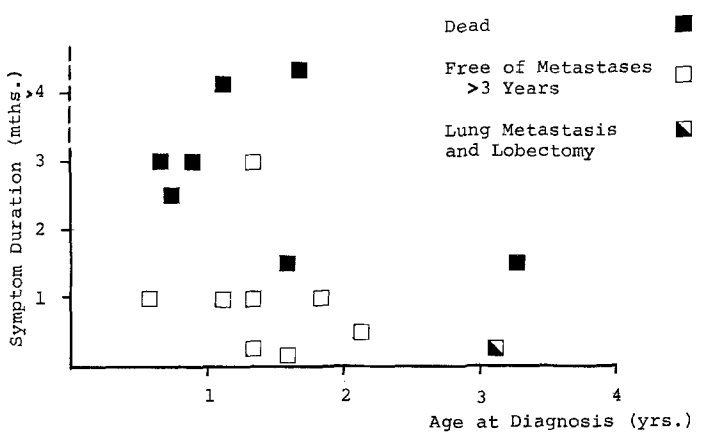

Fig. 9. Lethality in relation to symptom duration and age at diagnosis (children). 16 own cases followed up for more than 3 years

year of life, have a better prognosis than patients with a tumor appearing later. Two of our 4 patients, who were over 2 years old at the time of diagnosis, later showed metastases.

Table 3. Survival rate in relation to age at operation and symptom duration (children; Literature and own cases)

Age at orchidectomy (years)	Survival rate of n cases		Percentage of n cases with symtom duration of			
			<2	2–6	>6	months
1	75%	($n=37$)	68%	22%	10%	($n=28$)
2	51%	($n=47$)	49%	36%	15%	($n=39$)
3	36%	($n=14$)	30%	30%	40%	($n=10$)
≥ 4	56%	($n=9$)	83%	—	17%	($n=6$)

In order to estimate the influence of these two factors on the prognosis, we compared the age at diagnosis with the duration of symptoms. Table 3 shows that the number of cases with longer symptom duration increases until the third year of life. This observation may indicate that the tumor growth is less conspicuous, e.g. slower in older children than in small ones. The slower tumor growth in older children is corroborated by the fact that most patients with eventual metastases, but surviving the second postoperative year, were older than 2 years at diagnosis (Agarwal *et al.*, 1967; Pierce *et al.*, 1970; Young *et al.*, 1970). We suppose that initially latent proliferating EDST in older children and the fast growing, early diagnosed tumors in small children may arise in a relatively narrow space of time in the development. The occasional occurrence of connatal tumors in children (Rusche, 1952; Teoh *et al.*, 1960; Abell and Holtz, 1963; Tefft *et al.*, 1967), and the experiments of Stevens (1962, 1973) and Pierce *et al.* (1967, 1970b) demonstrating embryonal carcinoma cells already in the fetal testis of the mouse strain 129, indicate that the infantile testicular tumors may be malformation tumors. As the length of the presence of a manifest EDST aggravates the prognosis, its latent state also may increase the risk of metastasizing. Therefore, the influence on the prognosis of the duration of symptoms and the age at diagnosis may be related. This interpretation does not explain the good prognosis of the rare cases with EDST occurring between the fourth and tenth year of life (Willnow and Hofmann, 1970b) nor its clinical course in adults.

Four of our 5 adults with EDST and the cases cited in the literature had already widespread metastases at the time of diagnosis and died within a few months. As Teilum (1971) stated, the prognosis in adults is poor, but it is difficult to assess the clinical course in such advanced cases and to compare it with other types of malignant teratomas. Systematic examination will determine whether it is justified to classify the EDST in adults merely as teratoma of the MTIB-type or in a special group analogous to the teratomas with trophoblastic elements.

Conclusion

The EDST in children and the corresponding form in adults are most probably teratomatous tumors. The characteristic tumor tissue shows no resemblance to the human yolk sac. Therefore, the term "endodermal sinus tumor" (EDST) is not appropriate. A definite histogenetic interpretation is impossible with the present methods. It would seem of little use to introduce a new hypothesis or a new

term until further studies, for example electron-microscopic and tissue culture examinations, will be able to prove the origin of the EDST.

The clinical course observed in our patients confirms that the prognosis of the EDST is relatively favourable during the whole childhood. It becomes aggravated, however, if the tumor remains latent or develops over a longer period. In contrast, the prognosis of EDST in adults is poor and may not be very different from that of the malignant teratomas of the MTIB-type. Despite its characteristic morphology, the EDST includes almost every clinical property of the malignant testicular teratomas, i.e. the typical locations of primary tumors, the combination with other germinal cell tumors, the routes of spreading and the production of α-1-fetoprotein and choriogonadotropin. Likewise, the prognosis is not related to the EDST, as a special entity, but to the age of occurrence.

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1 Cases included in the statistical review (Table 3, Fig. 8).

Dr. W. Woodtli
Prof. Dr. Chr. Hedinger
Department of Pathology
University of Zürich
Kantonsspital
CH-8006 Zürich
Switzerland