Virchows Arch [Pathol Anat] (1982) 396:247–277

Virchows Archiv A

Editorial

What's in a name? That which we call a rose,
By any other name would smell as sweet.

William Shakespeare
Romeo and Juliet II.2

The Differential Diagnosis of Testicular Germ Cell Tumors in Theory and Practice

A critical Analysis of two Major Systems of Classification and Review of 389 Cases

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Summary. To better appreciate the conflicts and controversy surrounding the classification of testicular tumors, and to reappraise their morphologic substrate under the advent of tumor markers, 389 of our own cases are reviewed, classified according to the systems advocated by the World Health Organization (WHO) and the Testicular Tumour Panel and Registry (TTPR) of Great Britain, and evaluated statistically.

While many cases fit easily into either classification, the following difficulties were manifest: 1) Discrepancies in definitions and diagnostic criteria are the reason that considerably more germ cell tumors could be classified as mixed choriocarcinomas (WHO) than as trophoblastic teratomas (TTPR). It was found that tumor markers supply histochemical data that often conflict with rather than supplement morphologic ones in diagnosis and differential diagnosis. Similarly, the incidence of yolk sac structures, as yet not recorded separately by the TTPR, varies as either morphologic or histochemical criteria are applied. 2) The division of the morphologic spectrum of teratomatous differentiation by criteria of distinction that are unequal in the two systems yield comparable but non-congruent tumor entities. Consequently, borderline cases may undergo shifts to noncorresponding groups as they are translated from one system to the other. 3) Criteria separating teratoma with malignant transformation and polyembryoma (WHO) from closely allied lesions proved impractical. 4) Diagnostic labels that incorporate not only a morphologic pattern but a definite level in the histogenetic hierarchy generate a climate of incompatibility between systems whose histogenetic

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The cooperation of our documentation group PADOK is gratefully acknowledged

0340-1227/82/0396/0247/$06.20

perspectives differ. Embryonal carcinoma's claim to totipotence, in particular, leads to a conceptual split with the teratomas and brings the WHO system by itself into theoretic difficulties. Moreover, as the morphologic criteria for embryonal carcinoma are not in keeping with its histogenetic premise, the rigid separation is difficult to enforce in practice.
Once the air is cleared, a resolution is easily reached. In the combined use of both classifications their real difference, splitting vs lumping, becomes a true asset.

Key words: Testicular tumors – Germ cell tumors – Classifications

Introduction

The continuing controversy concerning the classification of testicular tumors now centers around two principal systems that have emerged from those of previous years.

The one system, referred to as the WHO (World Health Organization) classification (Mostofi and Sobin 1977), has penetrated in essence from the works of Friedman and Moore (1946), as modified by Dixon and Moore (1952), Melicow (1955), and Mostofi and Price (1973). These authors postulate a close histogenetic relationship between testicular germ cell tumors, whereby a precursor germ cell may give rise to a seminoma cell on the one hand, or to an undifferentiated, totipotent cell of the embryonal carcinoma group on the other hand (Fig. 1). The latter may undergo embryonic and/or extra-embryonic differentiation, giving rise to teratomas with varying participation of ectoderm, endoderm, and mesoderm, and/or to choriocarcinoma and yolk sac tumor respectively. Since a good percentage of cases display a mixture of such histologic types, each component is cited individually in the diagnosis, e.g. immature teratoma and embryonal carcinoma with choriocarcinomatous foci.

The other system of classification, advanced by the Testicular Tumour Panel and Registry of Great Britain (TTPR), proposes relative simplicity in nomenclature and application (Collins and Pugh 1964; Pugh 1976). While heeding Willis' view that the only definitive method of classifying tumors is on the basis of histogenesis (Willis 1960), the panel prefers morphologic lines of distinction primarily, in view of the disputed issues involved in testicular tumor origin. Thus, there are seminomas and teratomas, the latter being subdivided according

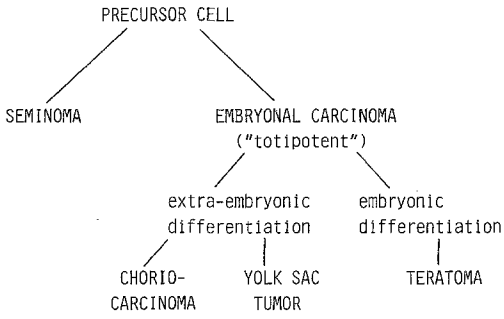

Fig. 1. Histogenetic flow diagram of "germ cell" tumors of the testicle, adapted from Dixon and Moore (1952) and Pugh and Cameron (1976)

to their degree of morphologic maturation into differentiated, intermediate, and undifferentiated types. A fourth group of teratomas containing trophoblastic elements and fulfilling specific histologic criteria is termed trophoblastic, irrespective of what other teratomatous features may be displayed. In the example of the previous paragraph, the malignant teratoma of intermediate type with an undifferentiated and trophoblastic component would be summarized accordingly as malignant teratoma, trophoblastic.

The question of histogenesis has unfortunately become the bone of contention in the controversy about the relative value of the two systems of classification. "Divergent histogenetic views" are considered ample justification for the plea of incompatibility between the two (Skinner 1978; Mostofi 1979). The theory, adhered to by the American school and the WHO system, that testicular tumors arise from germ cells is traditionally at variance with the one postulating that teratomas develop rather from displaced blastomeres, cells that early in embryonic life escaped the influence of primary organizers. The germ cell theory has gained wide acceptance under the weight of accumulated experimental evidence and the British school confirms its "conceptual correctness... in the experimental animal" (Pugh and Cameron 1976). But after nearly a century of controversy the issue is still not definitively settled: on the basis of chromosomal, clinical and histological considerations, Ashley (1973), for instance suggests that gonadal teratomas arise from germ cells by parthenogenesis but extragonadal ones from displaced blastomeres; and studies in murine tumor models can be interpreted to support both theories (Fraley et al. 1979). The problems underlying these histogenetic premises are amply discussed in the literature and will be dealt with here only as far as they determine nomenclature and classification. For the sake of simplicity then, the neoplasms under discussion shall be referred to as germ cell tumors.

While a genealogic tree is any taxonomist's ideal, a pathologist's classification is based primarily on what is at hand. In dealing first with the morphologic substrate, it need not suffer unduly from the vicissitudes of histogenetic perspectives. What the difference in perspective has created, however, is conflicting terminology and hence problems in translation. These are amplified when some diagnostic labels unite both a morphologic pattern and a histogenetic premise. Nevertheless, the two classifications are far from incompatible. Comparisons have been made in the past (Meienberg 1971; Payot 1971; Hedinger 1973, 1977, 1980; Nochomovitz and Rosai 1978; Mikuz 1979), and more than ever is there evidence that the two shall meet.

The aim of this paper is to compare the two systems of classification, not so much with the intent to investigate claims of superiority, but rather to show up similarities and differences, as well as their bearing on borderline cases. Moreover, in view of the impact that tumor markers are having on diagnosis, treatment, follow-up and finally on the classification of testicular neoplasms, it is of benefit to take another look at the morphologic substrate. For this purpose, 389 of our own cases are reviewed.

Material and Methods

Our investigations are based on 389 neoplasms of scrotal contents registered at our Institute from the beginning of 1971 to the end of 1980. Space occupying lesions, clinically suspect but non-neoplastic in nature, were discarded. Referral cases were included provided sufficient histologic material had been retained.

Routine histologic slides, stained with hematoxylin-eosin, van Gieson, and PAS, were available in each of our cases from an average of 4–5 paraffin blocks of tumor tissue. From about two-fifths of our germ cell tumors, particularly those of heterogeneous tissue constituents, many additional blocks were taken. Histochemical techniques, such as the immunoperoxidase method for visualizing alpha-1-fetoprotein and β-chorionic gonadotropin, were employed when required.

All cases were re-examined and classified according to both the AFIP/WHO and the TTPR systems.

Results

The group of 389 specimens comprises 365 testicular and 24 paratesticular tumors. Their numerical and percent distributions are given in Table 1.

Non-germ cell tumors of the testis are listed in Table 2. Their percent distribution is expressed in terms of all testicular tumors ($n=365$) and compared to the figures given by Mostofi (1973); Mostofi and Price (1973); Pugh (1976).

Germ cell tumors, i.e. neoplasms thought to arise from the germinal epithelium, were seen in 324 cases (88.8%) of all our testicular tumors. Classified according to the WHO system, the separate tumor groups of this large body are shown in Table 3 with their numerical and percent distributions. Figures taken from Mostofi (1973) and Mostofi and Price (1973) are adjusted here to express percentages in terms of germ cell tumors rather than of all testicular tumors, the former making up at least 93% of the latter.

Similarly, our 324 cases of germ cell tumors were classified according to the TTPR system. Numerical and percent distributions are listed in Table 4.

Before numerical data are invested with meaning, however, the diagnostic difficulties inherent in both taxonomic systems need to be investigated. Morphologic criteria in each are of primordial importance as they reflect definitions

Table 1. Numerical and percent distribution of 389 tumors of the scrotal contents

	n	%
Testicular tumors		
Germ cell tumors	324	88.8
Interstitial cell tumors	16	4.4
Sertoli cell/mesenchyme tumors	2	0.5
Lymphoma	17	4.7
Metastasis	3	0.8
Unclassified	3	0.8
Total	365	100.0
Paratesticular tumors		
Adenomatoid/mesothelioma/ Rete testis tumors	7	29.2
Soft tissue tumors[a]		
benign	3	12.5
malignant	8	33.3
Plasmacytoma	1	4.2
Epidermoid cyst	2	8.3
Unclassified	3	12.5
Total	24	100.0

[a] Lymphangioma 1
Chondroma 1
Leiomyoma 1
Rhabdomyosarcoma 5
Leiomyosarcoma 1
Fibrosarcoma 1
Liposarcoma 1

Table 2. Non-germ cell tumors of the testicle. Numerical and percent distributions compared to the series of the Armed Forces Institute of Pathology (AFIP) and the British Panel (TTPR)

	von Hochstetter and Hedinger		Mostofi (1973) Mostofi and Price (1973)		Pugh (1976)	
	n	%	*n*[a]	%	*n*	%
Interstitial cell tumors (ICT)	16	4.4		3	43	1.6
Sertoli cell/mesenchyme tumors (SMT)	2	0.5		<2	32	1.2
Lymphoma[b]	17	4.7		5[c]	186	6.7
Metastasis	3	0.8			24	0.9
Unclassified	3	0.8		–	82	3.0
Total	41	11.2		ca. 10	366	13.4

[a] Number of cases not indicated by the authors

[b] In this study, no attempt was made to distinguish primary from secondary involvement of the testicle by lymphoma

[c] Although lymphomas are represented by 1% according to Mostofi (1973) the figure is 5% in Mostofi and Price (1973) where they are considered as secondary tumor deposits together with metastases

and diagnostic boundaries and in the end determine prognosis and therapy. In the following, both AFIP/WHO and TTPR systems of classification will be looked at closely from the perspective of differential diagnosis with the intent to compare corresponding tumor groups through the criteria that define and demarcate them.

The comparative nature of our study is rendered precarious by the fact that the figures cited by Mostofi (1973) and Mostofi and Price (1973) are approximate (Table 3). More precise data are essential before significant correlations can be drawn and definite statements made. Hence, our numerical comparisons pertain particularly to the results of the British panel's series. Statistical data follow most sections on those groups that on the whole are comparable in the two systems: 1) seminoma; 2) the group comprising teratoma, embryonal carcinoma, polyembryoma, teratocarcinoma; 3) extra-embryonic tumors, i.e. yolk sac tumor and choriocarcinoma; and 4) neoplasms uniting different histologic types, i.e. mixed or combined tumors.

Non-germ cell tumors, listed in Tables 1 and 2, will not be dealt with further.

1. Seminoma

Least controversial among tumor groups of both systems of classification, seminomas present occasional diagnostic difficulties when histologic and cytologic appearances are less than typical. Although the various forms of seminomas, i.e. the classical, the spermatocytic, and the one with syncytiotrophoblastic giant cells, are clearly defined, there may be some overlap between them, as between a classical seminoma with slight cellular polymorphism and a spermato-

Table 3. Testicular germ cell tumors. Numerical and percent distributions of 324 neoplasms, classified according to the World Health Organization (WHO) system

	von Hochstetter and Hedinger		Mostofi (1973) Mostofi and Price (1973)	
	n	%	*n*[a]	%[b]
I. Tumors of one histologic type	*224*	*69.1*		
Seminoma				
typical	162			
spermatocytic	6	52.8		35–71
with STGC[c]	3			
Embryonal carcinoma	35	10.8		20
Polyembryoma	–	–		
Yolk sac tumor (YST)[d]	5	1.5		
Teratoma				
mature	6			
immature	6	4.0		4–9
with malignant transform.	1			
Choriocarcinoma[e]	–	–		<1
II. Tumors of more than one histologic type	*100*	*30.9*		
Embryonal carcinoma and teratoma (teratocarcinoma)	33	10.2		24
Seminoma and teratoma				
mature	3			
immature	1			2
with malign. transform.	3	14.8[f]		
Seminoma and teratocarcinoma	15			6
Seminoma and embryonal carcinoma	24			5
Choriocarcinoma and teratoma				
mature	–			
immature	1			
with malign. transform.	–	6.5[f]		4
Chorioca. and teratocarcinoma	13			
Chorioca., teratoca. and seminoma	2			
Chorioca. and embryonal carcinoma	5			
Total	324	100	>6,000	108–152

[a] Number of cases in each separate tumor group is not indicated by the authors. Total number (*n* 6000) includes all testicular tumors

[b] Figures calculated to express percent of germ cell tumors rather than of all testicular tumors, the former making up at least 93% of the latter (Mostofi and Price 1973)

[c] Syncytiotrophoblastic giant cell

[d] Only the pure forms are listed separately. YST found together with embryonal carcinoma is included in that group

[e] For the distinction between pure and mixed choriocarcinoma see text

[f] Percent of all mixed tumors with seminoma or choriocarcinoma as constant feature. The 2 cases of choriocarcinoma, teratoma and seminoma are thus contained in both figures

Table 4. Testicular germ cell tumors. Numerical and percent distributions of 324 neoplasms classified according to the TTPR system

	von Hochstetter and Hedinger		Pugh (1976)	
	n	%	*n*	%[a]
Seminoma	*171*	*52.8*	*1,082*	*45.6*
typical	162			
spermatocytic	6	3.5		3.7[b]
with STGC	3			
Teratomas	*100*	*30.9*	*869*	*36.6*
differentiated (TD)	6	6.0	28[d]	4.9[d]
intermediate (MTI)	37	42.0	312	54.8
intermediate with STGC[c]	5			
undifferentiated (MTU)	38	44.0	208	36.6
undifferentiated with STGC	6			
trophoblastic (MTT)[e]	8	8.0	21	3.7
Combined Tumors	*48*	*14.8*	*369*	*15.6*
Seminoma and TD	3	6.3	7[f]	2.7[f]
Seminoma and TD with STGC	–	–		
Seminoma and MTI	19	41.7	132	51.0
Seminoma and MTI with STGC	1			
Seminoma and MTU	24	52.1	107	41.3
Seminoma and MTU with STGC	1			
Seminoma and MTT			13	5.0
Yolk sac tumor (YST)[g]	*5*	*1.5*	*53*	*2.2*
Total	324	100	2,373	100

[a] Figures taken from Pugh (1976) are calculated to express percent of germ cell tumors rather than of all testicular tumors

[b] Figures given by Thackray and Crane (1976)

[c] Syncytiotrophoblastic giant cell

[d] Figures in *n* and % columns refer to a smaller group of 569 teratomas and are taken from Pugh and Cameron (1976)

[e] The distinction between tumors with STGC and those with syncytio- and cytotrophoblastic foci is discussed in the text

[f] Figures in N and % columns refer to a smaller group of 259 combined tumors and are taken from Pugh (1976)

[g] Only pure forms are listed separately. YST found together with malignant teratomas is included there

cytic one with weak or focal variations in cellular and nuclear size. Some blending of these forms within the group of seminomas may be of significance what therapy is concerned, but in the individual case the diagnostic problem can usually be resolved. More striking are occasional morphologic similarities between seminoma, embryonal carcinoma (malignant teratoma undifferentiated: MTU), and even yolk sac tumor (Raghavan et al. 1981). In some cases (Fig. 2), the light optical resemblance suggests a relationship closer than is indicated

by the histogenetic premises (Fig. 1). Similar observations have been made on electron microscopic studies (Tomoyoshi 1962; Pierce 1966; Holstein and Körner 1974). The morphologic resemblance easily leads to the idea of transitional forms and to the concept of a stem-cell as missing link between them. It may well be that those tumor forms that lie on the morphologic treshold between seminoma and embryonal carcinoma (MTU) are the ones that have been designated in the literature as anaplastic, atypical, or aggressive seminomas, and are evaluated by their mitotic rate (Mostofi 1973; von Hochstetter 1981). Further clinico-pathologic studies are required to clarify the point.

These considerations pertain to but a few of our seminomas and such differences in interpretation would certainly go unnoticed in the bulk of examined cases. Our 52.8% of seminomas are higher than the 45.6% of the TTPR series, although they certainly fit within the 33–66% of Mostofi and Price's material. However, since our share of MTU's more than covers that of the TTPR, a possible shift from MTU to seminoma through misinterpretation is improbable.

2.1 Teratoma

According to all classifications, a teratoma is a tumor composed of several types of tissues representing different germinal layers. Since these ecto-, endo-, and mesodermal components may vary in degree of maturation, teratomas present a spectrum of morphologic patterns. The systems under study differ in the tissues admitted to be teratomatous, and in the classification of teratoma subgroups.

As to what is or is not teratomatous, the WHO classification regards embryonal carcinoma as a separate histologic type, representing a distinct tumor entity. A teratoma with adjoining foci of embryonal carcinoma is considered a mixed tumor, teratocarcinoma, stressing the contention that embryonal carcinoma is not teratomatous in nature and that two histologic types are present. In the TTPR system, however, embryonal carcinoma is regarded as the undifferentiated form of malignant teratomas (MTU); hence, a teratocarcinoma is classified not as a tumor combining two histologic types, but rather as a teratoma of variable or intermediate differentiation (MTI). Mirroring a difference in histogenetic perspective, this discrepancy between the systems is expressed semantically. Irrespective of terminology, the difficulties in the differential diagnosis between groups remain, whether the line be drawn between a carcinoma and a teratoma (WHO) or between 2 kinds of teratomas (TTPR). But first let us consider the subgroups of neoplasms unanimously accepted to be teratomatous in nature and the diagnostic problems encountered in discriminating between them.

Describing stages of progressive maturation, the authors of the AFIP atlas first mention the *immature teratoma,* an entity they reserve for neoplasms composed of primitive neuroectoderm, endoderm, or mesoderm and offer an example by their Fig. 51. Then, there is *maturation to tissue level,* where formation of cartilage, bone, mucous glands, various types of epithelia, smooth or striated muscle may be seen. Although immature as well, these teratomas are clearly a step beyond the embryonic immaturity of the preceding immature teratomas.

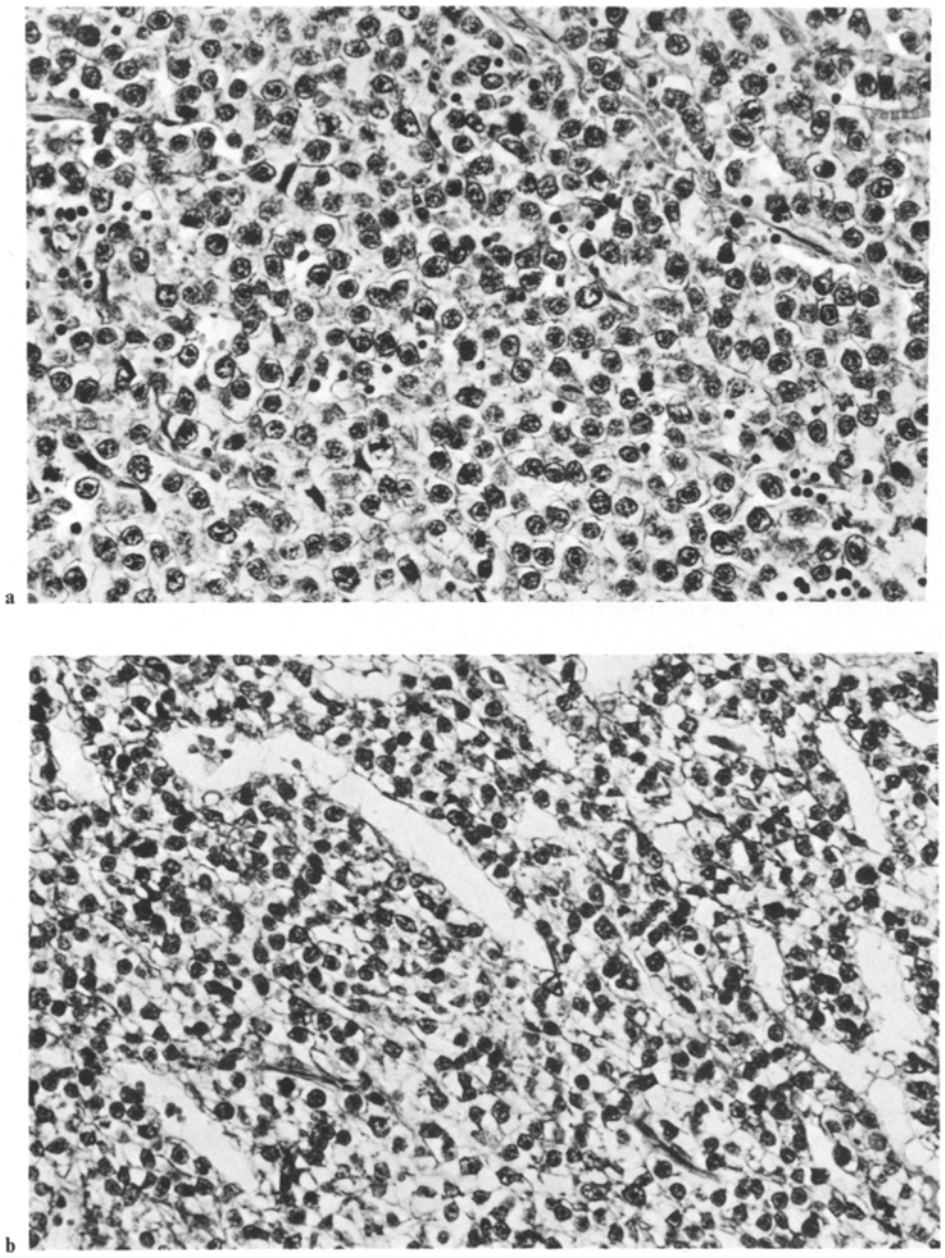

Fig. 2. Morphologic similarities between some forms of (**a**) seminoma and (**b**) embryonal carcinoma. Both HE × 250

More differentiated yet is the *organoid* or *differentiated teratoma* in which organ formation including tissues of significant maturity is attempted. A separate subgroup of purely mature teratomas is not provided. The authors state that while organoid teratomas "may consist solely of immature, partly mature or completely mature elements, more frequently both mature and immature elements are present". Yet another group mentioned by Mostofi and Price (1973) are *teratomas with malignant change*.

The WHO classification is not congruent with the preceding. The *immature teratoma* is said to contain incompletely differentiated tissues and usually varying amounts of mature elements as well. Clearly, this covers the AFIP atlas' teratomas of tissue level maturation as well as most of the organoid ones, namely all those that harbour elements short of adult maturity. The immature teratomas of the embryonal type are not mentioned as such in the WHO fascicle but are included, as its Fig. 59 illustrates, in the immature teratoma group. The *mature teratoma* is described as being composed exclusively of well-differentiated tissues, claiming thus the smaller part of the AFIP atlas' organoid or differentiated teratomas, namely those made up solely of mature elements. Teratomas with malignant areas are again listed separately as *teratomas with malignant transformation* and are described as those forms which contain a "malignant component typically encountered in other organs or tissues" (Mostofi and Sobin 1977).

The comparison between AFIP and WHO taxonomies (Fig. 3) reveals that in the latter the mature teratoma emerges as a more clearly defined entity. As a teratoma "composed exclusively of well-differentiated tissues" (Mostofi and Sobin 1977), it is equivalent to the TTPR's teratoma differentiated (TD). The definition requires that such tumors be examined in great detail, if not by step sections, since the diagnosis is one of exclusion: the presence of an immature or malignant focus would shift the diagnosis to immature teratoma or teratoma with malignant transformation in the WHO's, and to malignant teratoma intermediate (MTI) in the TTPR's frame of reference. Thus statements that "in spite of the apparent maturity of the tissue... the clinical course in adults is unpredictable" (Mostofi and Sobin 1977), or that "even the most well-differentiated forms may metastasize and cause death" (Nochomovitz et al. 1977) invite review, since they may be prompted by insufficient sampling of the primary lesion alone. Friedman (1978) proposes that in the presence of a mature teratoma a metastasis is the result of antecedent dissemination of embryonal cells from a lesion that subsequently matured into the primary testicular teratoma. The suggestion is as attractive as it is far-reaching, to be entertained only once the primary lesion has been most meticulously and scrupulously searched for immature foci. Nevertheless, defined as above, mature or adult teratomas can be gleaned from the large body of teratomatous neoplasms by the application of unequivocal morphologic criteria.

With the mature teratoma defined by exclusion, there remains a host of incompletely differentiated tumors. These *immature teratomas* in the WHO sense "fall somewhere in between mature teratoma and embryonal carcinoma" (Nochomovitz et al. 1977) and while they must have in common some degree of maturation to tissue level, they may also contain organoid components even

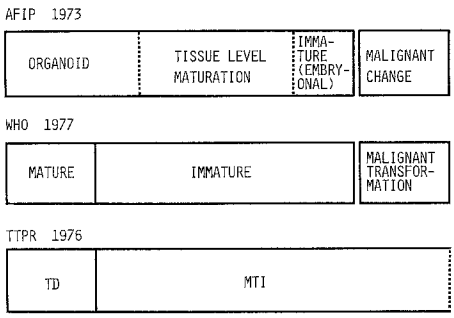

Fig. 3. Schematic representation of pure teratoma subgroups in AFIP and WHO systems and their counterparts in the TTPR classification. *TD*, teratoma differentiated. *MTI*, malignant teratoma intermediate.

of adult maturity (Fig. 3). They comprise, in addition, the rare embryonic forms, composed of primitive neuroectoderm, endoderm, or mesoderm, labelled immature in the AFIP atlas. The embryonic forms, as well as some of the mature ones with areas of ominous appearance, present a diagnostic dilemma particularly in children. Often interpreted as evidence of neoplastic anaplasia, their immaturity may well be a physiologic one, capable of maturation. Although in children ominous areas are almost invariably mesenchymal, while in the adult it is primarily the appearance of the epithelium that determines the teratoma's classification (Pugh and Cameron 1976), we have, like the TTPR, witnessed exceptions. In view of the lack of decisive morphologic criteria the diagnostic dilemma remains: embryonic tissue appears benign when its embryonic or fetal source is known, but the boundary between benign and malignant is nearly impossible to draw when dealing with similar tissue in a grown individual or even in a child. As the tumor's penchant to the malignant cannot be ignored in practice, its potential for maturation usually must be. In the WHO system, consequently, such neoplasms are considered immature teratomas and in the British they are classified as teratomas of intermediate differentiation (MTI).

In both AFIP and WHO classifications *teratomas with malignant transformation* are listed separately. Implying dedifferentiation in a previously mature neoplasm, the term is ill-chosen when "teratoma with malignant foci" would do as well. Moreover, the converse concept of maturation is neglected. In fact, the potential of teratomatous growth to differentiate in time is supported by a wealth of experimental evidence (Kleinsmith and Pierce 1964; Stevens 1967; Martin 1975), but not generally considered in practive except where metastases more mature than the primary developed during treatment (Willis and Hajdu 1973; Hong et al. 1977). Malignant transformation may involve epithelial and/or mesenchymal structures. Teratomas with carcinomatous transformation can be diagnosed as such only when a focus of malignant epithelium is part of an otherwise mature tumor formation (Fig. 4). A neighbouring but discrete area of low to medium grade carcinoma would present as an immature field adjoining an otherwise differentiated teratoma and probably lead to an overall diagnosis of immature teratoma or teratocarcinoma in the WHO sense. Similarly, an adjacent area of undifferentiated carcinoma would prompt the diagnosis of teratoma and embryonal carcinoma, i.e. teratocarcinoma. As for teratomas with sarcomatous change, mesenchymal tissues unlike epithelium display malig-

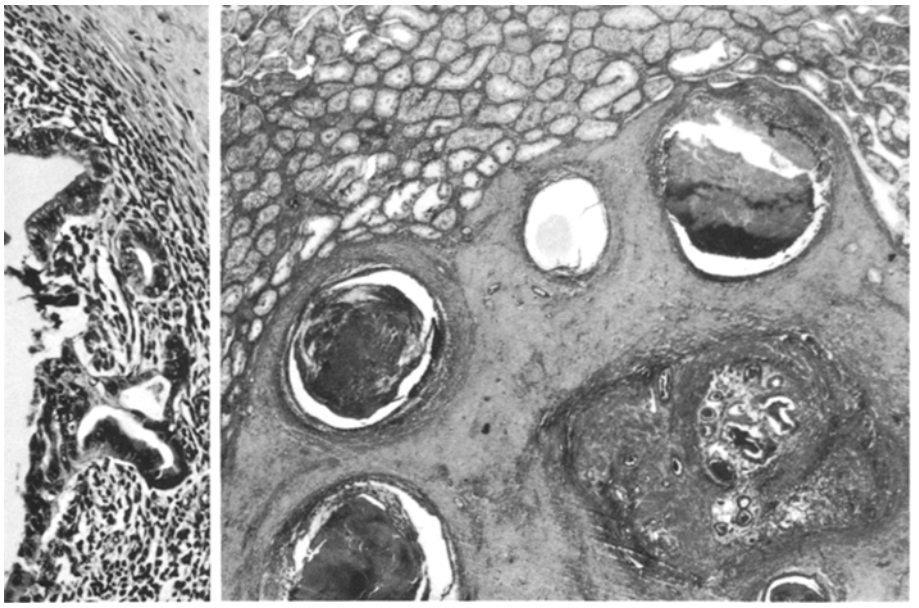

Fig. 4. Circumscribed organoid formation of well differentiated teratomatous tissues including malignant epithelial foci (*inset*). HE × 12.5, Inset × 130

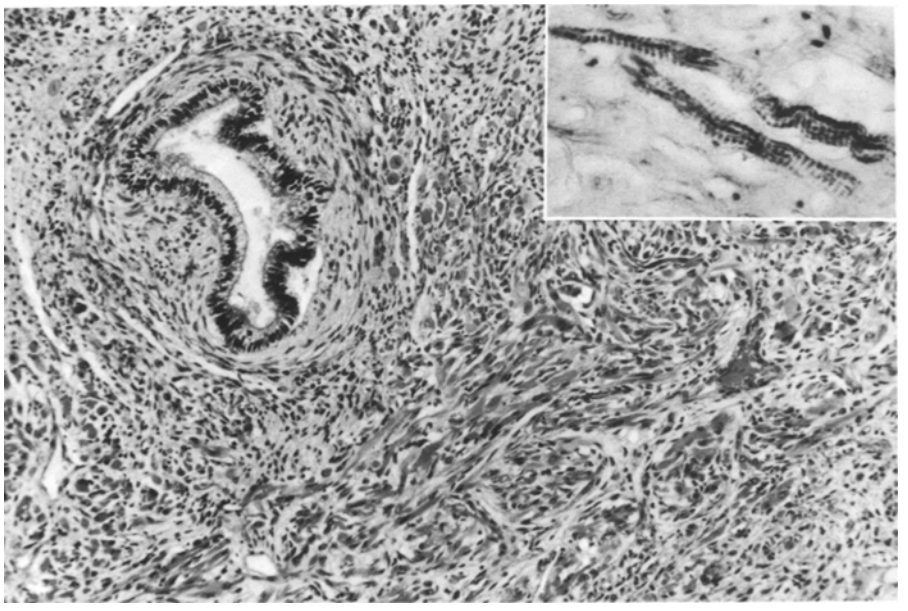

Fig. 5. Teratoma with well differentiated epithelium and numerous rhabdomyoblasts. Later metastases consisted solely of rhabdomyosarcoma. HE × 80, Inset × 400

nant characteristics over larger stretches, not focally. In practice, such tumor forms would most certainly be grouped with immature teratomas. It should be noted here that frankly malignant mesenchyme in any teratoma merits attention as it may dictate biologic behaviour: one such sarcomatous teratoma in our series harboured rhabdomyoblasts and went on to metastasize as pure rhabdomyosarcoma (Fig. 5). As far as diagnostic prerequisites are concerned, malignant transformation can be recognized only on the background of a fully differentiated or mature teratoma: the malignant area must be contained within and form an intimate part of otherwise fully mature teratomatous tissue.

There are further considerations. A carcinomatous area adjoining a teratoma, as in the examples given above, could conceivably take its origin from the mature, organoid component at a point outside the histologic plane of section. The connecting bridge of malignant transformation would be missed unless close step sections established the blending at some point of malignant and mature components. Furthermore, malignant foci are subject to growth and could easily spread beyond the confines of the mature teratoma. It seems more than likely that teratomas with malignant change on such an extensive level would present as teratocarcinomas or immature teratomas. Besides being impractical for large tumor masses, step sections would not be able to establish with certainty that dedifferentiation and outgrowth had occurred in these cases, since it could always be argued that either infiltration of the mature component by malignant elements had taken place, or that a part of the entire neoplasm had in fact differentiated to maturity. In summary, then, the diagnosis of teratoma with malignant transformation, an unfortunate term, is seen to rest largely on criteria of localization and of size, rather than of quality or kind.

Nevertheless, exemplary cases do occur and should be noted for the record. But even here some doubt remains: one of our cases was determined by close sections to fulfil the requirements of a teratoma with malignant foci but later gave rise to metastases containing teratoma and embryonal carcinoma. In consequence, our attitude is summarized by the position that teratomas with malignant foci are a morphologic peculiarity, but clinically were better classified other than on their own.

2.2 Embryonal Carcinoma

The diagnosis of pure undifferentiated carcinoma, be it solid, papillary or adenomatoid in growth, presents no great difficulty and as such embryonal carcinoma, or MTU in the British panel's nomenclature, is clearly defined. Diagnostic problems may arise on occasion in its separation from seminoma, yolk sac tumor, and not infrequently from less undifferentiated non-seminomatous neoplasms. Moreover, its criteria of distinction are not identical in the WHO and TTPR systems and merit close scrutiny.

Even though the WHO classification is firm in making a clear-cut distinction in kind between embryonal carcinoma and teratoma, there seems to be a gradual, progressive continuation in the light-optical appearance of tumor mesenchyme from the bland and non-specific of the most undifferentiated forms, to primitive

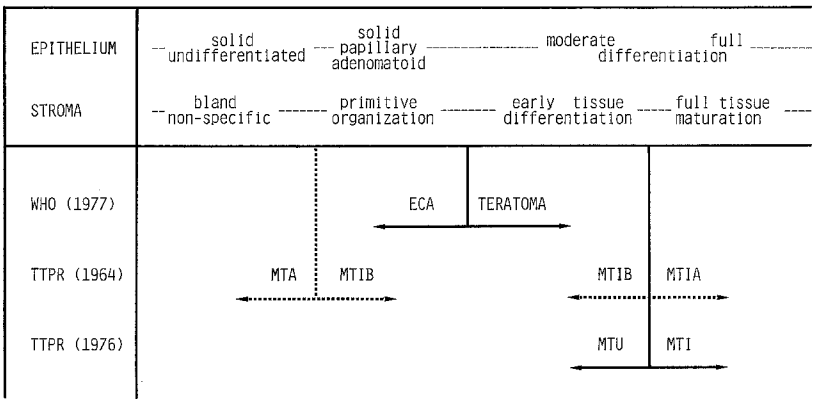

Fig. 6. Degrees of progressive epithelial and mesenchymal organization and differentiation as observed in non-seminomatous germ cell tumors: taxonomic demarcations (watershed criteria) segregating tumor groups are not identical in WHO and TTPR systems. *ECA* embryonal carcinoma. *MTA* malignant teratoma anaplastic. *MTI (A/B)* malignant teratoma intermediate (type A/B). *MTU* malignant teratoma undifferentiated

organization and differentiation. e.g. of contractile smooth muscle elements; further to early tissue differentiation, such as primitive cartilage or loose groups of muscle cells; and to the organization of tissues into organoid components that may reach even adult maturity. Consequently, the separation of pure embryonal carcinoma from teratoma, like that of MTU from MTI, necessarily focuses on the neoplastic stroma, the latter being more accessible to taxonomic incisions than an epithelial component that is either more or less undifferentiated, or mature. It is precisely in the degree of stromal organization and differentiation assigned to function as watershed criterion that the systems of classification differ.

An undifferentiated carcinomatous tumor remains an embryonal carcinoma in the WHO classification as long as its stroma does not display more than primitive mesenchymal organization and differentiation (Fig. 6). Anything beyond that, such as early tissue differentiation, would betray a definite teratomatous nature and transfer the tumor into an appropriate category. In practice, a distinction based on variable degrees of primitive stromal organization becomes delicate if not arbitrary and may, in fact, prove unnecessary. It was the same problem that confronted the diagnostician in the previous TTPR classification (Collins and Pugh 1964), in which malignant teratomas of the intermediate type B (MTIB), displaying stroma differentiation up to early tissue level, and of the anaplastic type (MTA) were separate entities. The subsequent fusion of MTIB and MTA to constitute the MTU group did much to obviate the dilemma without compromising prognosis (Pugh 1976). As a result, the criteria of distinction between MTU and MTI now are those that were applied to separate MTIB from the teratoma of intermediate type A (MTIA) in the earlier British classification. This is borne out by the fact that in 206 MTUs analyzed in detail, Pugh and Cameron (1976) found smooth muscle cells in 11%.

The watershed criterion that delimits embryonal carcinoma and MTU in their respective systems then is a particular degree of stromal differentiation: while mesenchymal organization with primitive differentiation is compatible with the diagnosis of embryonal carcinoma in the WHO system, early tissue differentiation is not; while early tissue differentiation is compatible with the

diagnosis of MTU in the TTPR system, organoid formation is not. These criteria, therefore, define similar but not congruent groups.

Mostofi and Price (1973) refer to the research of Pierce and collaborators to affirm that primitive neoplastic mesenchyme including contractile muscle elements are not incompatible with embryonal carcinoma. As much is said and shown in the WHO publication under the designation "primitive stroma" (Mostofi and Sobin 1977). In fact, Pierce regards embryonal carcinoma cells as multipotential stem cells, capable of differentiating not only into somatic but trophoblastic tissues (Pierce et al. 1960; Kleinsmith and Pierce 1964; Pierce 1966), a conclusion that concurs with the British panel's concept that non-seminomatous tumors present along a spectrum, one end of which is constituted by an undifferentiated form (MTU/embryonal carcinoma). Moreover, the British authors' view is in complete accord with Dixon and Moore (1952), who stated that embryonal carcinoma is but a transitional step toward differentiated teratoma. In the light of experimental evidence that teratomas and teratocarcinomas may be obtained by the injection of a single embryonal carcinoma cell (Kleinsmith and Pierce 1964; Damjanov and Solter 1974) the persisting strife whether embryonal carcinoma is teratomatous in nature or not is seen to derive largely from the original histogenetic premise. The nature of the problem is succinctly summarized in the statement that embryonal carcinoma is both a histologic diagnosis and a conceptual entity (Friedman 1978) and is elaborated below (Discussion).

2.3 Polyembryoma

In the AFIP and WHO nomenclatures, the term polyembryoma is reserved for tumors composed predominantly of embryoid bodies (Mostofi and Price 1973; Mostofi and Sobin 1977). The embryoid body (Fig. 7) is conceived by some authors as a fundamental formation in germ cell neoplasms, recapitulating the early human embryo in complete, imperfect, or amorphous form (Peyron 1939; Evans 1957; Marin-Padilla 1965). The variable differentiation and combinations of its three embryonic and extra-embryonic tissues are seen as the source of the great morphologic diversity that non-seminomatous germ cell tumors display (Marin-Padilla 1968). In this histogenetic sense, the embryoid body may be viewed as a precursor formation. Mostofi and Price (1973) express similar views when they compare the embryoid body to an embryo of 1–2 weeks' gestation comprising an epithelial disk, amnion and endoderm. In view of its histogenetic potential, demonstrated experimentally by Pierce and Midgley (1963), and its variable morphologic appearance, Mostofi and Price (1973) consider the embryoid formation to display totipotence and thus to be closely allied to, if not a variant of, embryonal carcinoma. It is a particularly telling example of the tenuous line drawn to separate in kind embryonal carcinoma from teratoma, suggesting that the issue is conceptual and semantic in nature. In the British classification embryoid bodies are viewed as components of MTU.

Whatever their development significance, embryoid bodies are too variable in differentiation and too frequently present in a variety of non-seminomatous germ cell tumors to serve as criterion of morphologic distinction. Polyembryoma is characterized by an aggregate of embryoid bodies and is distinctive on a quantitative level. As there are no indications that either its biologic behaviour

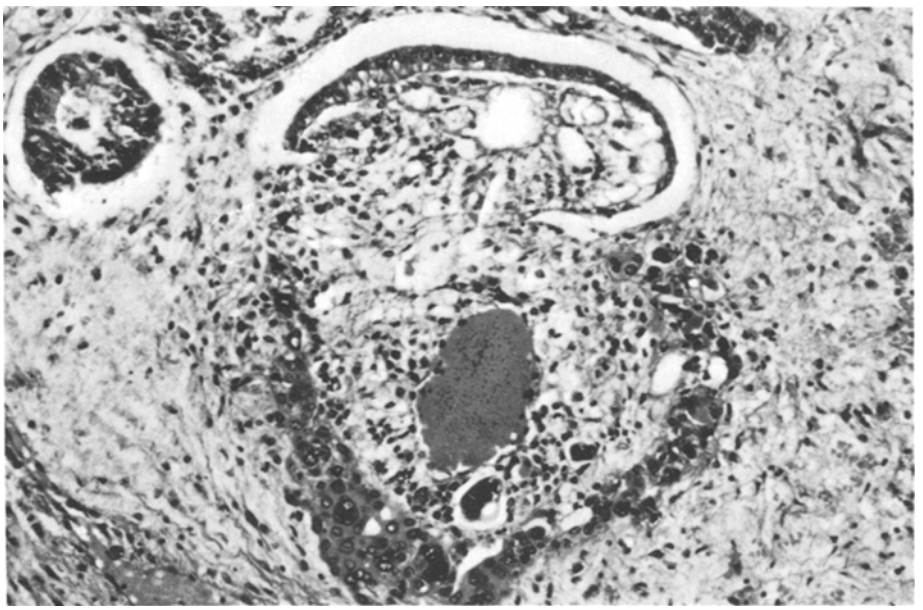

Fig. 7. Resembling an early embryo with an epithelial disc, amnion, and endoderm, the embryoid body appears as a prototype of teratoma. HE × 140

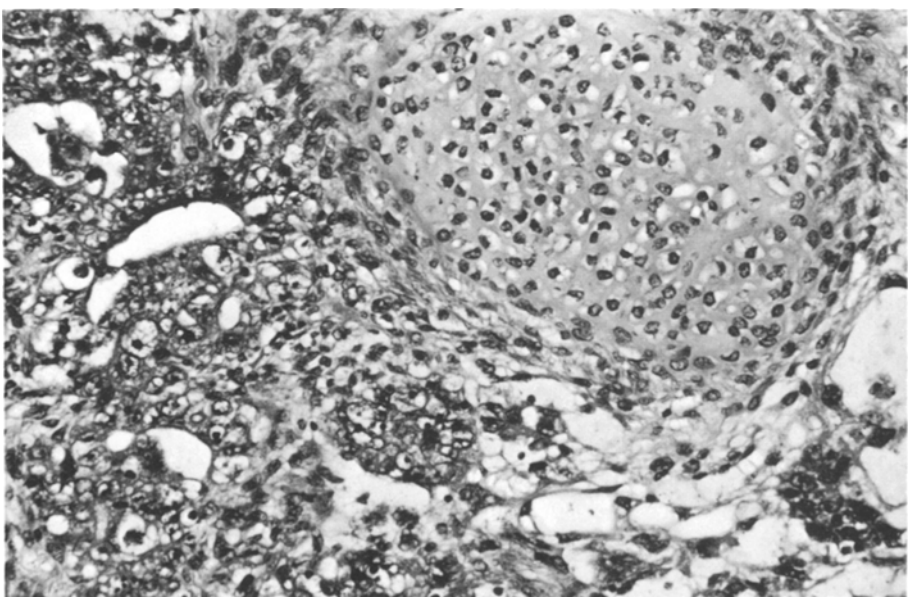

Fig. 8. Cartilage and undifferentiated carcinoma is regarded by the WHO to unite teratomatous and non-teratomatous tissues (teratoma and embryonal carcinoma), by the TTPR to be the expression of unequal differentiation in a teratoma. HE × 200

or prognosis is distinct from those of embryonal carcinoma, polyembryoma lacks qualitative distinction to rank as a separate clinicopathologic entity. The rarity of its morphologic pattern, however, merits note. In our series, only one case presented on first examination as a polyembryoma, but the subsequent examination of more tissue revealed large areas of more common embryonal carcinoma and teratoma.

2.4 Teratocarcinoma

Although listed in AFIP and WHO classifications as a neoplasm of more than one histologic type, teratocarcinoma is considered here, since it represents a morphologic step in the differential diagnosis between the pure tumors of either histologic type involved. Consisting of both teratomatous and embryonal carcinomatous components, an association reflected by its contracted name, it must be distinguished from immature teratoma, teratoma with malignant transformation, as well as from pure embryonal carcinomas displaying mesenchyme of primitive organization.

While the tumor entity which corresponds to teratocarcinoma in the British classification, i.e. malignant teratoma intermediate (MTI), affords a common ground for teratomatous tissue of variable differentiation, teratocarcinoma represents a meeting ground for tissue of two histologic types. A special case is said to exist when a single type of differentiated tissue, such as cartilage, is associated with embryonal carcinoma. As stated in the WHO fascicle, that tissue should then be considered to be teratomatous and the entire neoplasm diagnosed as teratocarcinoma (Fig. 8) (Mostofi and Sobin 1977). Strictly speaking, of course, a nodule of cartilage is not a teratoma and it is odd that its association with non-teratomatous embryonal carcinoma should make it one. In the uninitiated observer the entire neoplasm of two germinal layers should in fact evoke the diagnosis of teratoma, albeit with an undifferentiated epithelial component, or with extensive malignant transformation. According to the school of thought represented by the AFIP and WHO, however, an immature teratoma in its pure form cannot contain undifferentiated carcinoma. This special case illustrates that the conceptual division of teratoma and embryonal carcinoma into strictly separate histologic lineages further complicates the classification of the naturally diverse and colorful testicular tumors, while forcing the definition of teratoma onto precarious grounds. Moreover, it leads to a situation whereby a teratoma by itself cannot be more dedifferentiated than immature or malignantly transformed, unless it were to acquire another tissue type, i.e. embryonal carcinoma. In practice, the limits between teratoma, teratocarcinoma, and embryonal carcinoma are gradual and fluid, not abrupt and saltatory as should be expected from tumors composed of different tissue lineages and mosaics thereof. Such conflicts are essentially conceptual, arising from different histogenetic perspectives (see Discussion).

To review briefly, the spectrum of non-seminomatous germ cell tumors considered so far is grouped according to the WHO system into embryonal carcinoma and the teratomas. Gleaning the differentiated, mature teratomas and those with malignant transformation from the bulk of the latter groups leaves the immature teratomas. Neoplasms containing teratomatous elements together with embryonal carcinoma are considered to combine two separate histologic types and are classified accordingly as teratocarcinomas.

The TTPR system divides the same morphologic spectrum into 3 types of teratomas, according to the degree of differentiation. At the most mature end of the spectrum lies the differentiated form (TD), at the other end, the malignant teratoma undifferentiated (MTU). The latter corresponds to all embryonal carcinomas plus the few immature teratomas, pure or mixed with embryonal carcinoma, that display no more than early tissue differentiation. Between TD and MTU lies the group of malignant teratomas intermediate (MTI), comprising all remaining immature teratomas and teratocarcinomas, as well as teratomas with malignant transformation. In the British system, the diagnosis is reached in the manner of the devil's advocate: if a teratoma appears fully differentiated and mature (TD), it must be carefully searched for foci of immaturity; if it seems carcinomatous or poorly differentiated (MTU), more differentiated foci must be looked for as diligently. Thus the use of criteria defining neoplastic entities on either end of the morphologic spectrum divides non-trophoblastic teratomas into three mutually exclusive groups. It is this the reason for the odd situation that a teratoma of heterogenous maturity should be classified according to its more differentiated parts.

That in the subdivision of a morphologic spectrum the application of varying criteria of distinction leads to comparable but non congruent entities, is depicted schematically in Fig. 9. While teratomas with malignant transformation always fall within the limits of MTI, not all immature teratomas and hence not all teratocarcinomas are MTIs, nor are all MTUs embryonal carcinomas. Borderline cases in these groups may undergo translational shifts into a "non-corresponding" group as they are translated from one system of classification to the other. Specifically, immature teratomas, pure or mixed with embryonal carcinoma, that would previously have been regarded as MTIBs, are classified as MTU. In our material, 5 cases or 7.1% of immature teratomas/teratocarcinomas were so affected. Since the criteria of distinction involve mesenchymal organization that is difficult to assess particularly when primitive or early, errors in translation and hence in communication may easily become appreciable.

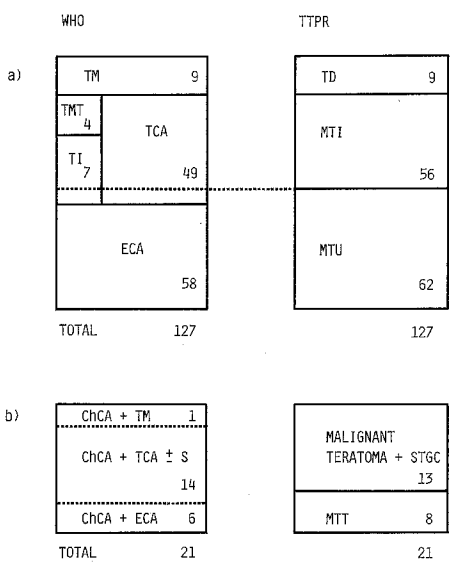

Fig. 9. Distribution of **(a)** teratomatous and/or embryonal carcinomatous neoplasms without trophoblastic components, and of **(b)** neoplasms with trophoblastic components to illustrate translational shift. *TM, TD,* teratoma mature, differentiated. *TMT,* teratoma with malignant transformation. *TI,* teratoma immature. *TCA,* teratocarcinoma. *MTI,* malignant teratoma intermediate. *MTU,* malignant teratoma undifferentiated. *ChCA,* choriocarcinoma. *MTT,* malignant teratoma trophoblastic. *STGC,* syncytiotrophoblastic giant cells. *S,* seminoma

The percent distribution of our non-seminomatous nontrophoblastic tumors is quite comparable to that of the TTPR (Table 4), with the exception that our 42% of MTI is considerably lower and our 44% of MTU higher than the British panel's 54.8% and 36.6% respectively. The discrepancy is due more to a shift of MTIs to the trophoblastic group of teratomas (MTT) for reasons elaborated below, than to the difficulty of distinguishing MTI from MTU. However, percent differences with the AFIP material (Table 3) are not so readily explained. While our 4% of pure teratomas fall into the AFIP's 4–10% range, our embryonal carcinomas and teratocarcinomas are each half or less of Mostofi and Price's figures. Since there is no compensatory elevation in any other of our tumor groups, the discrepancy can be ascribed only to the fact that, adding up to a total average of 130%, the authors' percentages are too elevated to render any interpretation significant.

3.1 Yolk Sac Tumor

Following an early documentation by Clark (1900) and by White (1910) and a description by Magner et al. (1956) as an unusual adenocarcinoma or carcinoma myxomatodes of the infantile testis, yolk sac tumor (YST) has in the last decades gone through several changes in name and status (mesonephroma, adenocarcinoma with clear cells, orchioblastoma, endodermal sinus tumor, embryonal carcinoma juvenile type). To a large degree, these reflect varying histogenetic premises (Teoh et al. 1960; Abell and Holtz 1963), the most popular to date being that YST, given its histologic resemblance to Teilum's endodermal sinus tumor of ovary and testis (1950, 1959), is derived from extra-embryonic yolk sac structures (Huntington et al. 1963; Pierce et al. 1969). In more recent years, the reliability of elevated serum alpha-1-fetoprotein (AFP) levels in the presence of gonadal and extragonadal YST (Ballas 1974; Ito et al. 1974; Burri et al. 1977; Horn et al. 1980; Talerman et al. 1980), as well as the localization on histologic slides of AFP within YST components by the immunoperoxidase method (Engelhardt et al. 1973; Abelev 1974; Nørgaard-Pedersen et al. 1975; Kurmann et al. 1977) have proved valuable indeed in establishing diagnosis and monitoring therapy (Lange et al. 1976; Scardino et al. 1977; Talerman et al. 1978; Javadpour 1980). Irrespective of histogenetic beliefs, the advent of tumor markers has elevated YST to a widely accepted entity of its own standing.

Pure YST constitutes the most frequently testicular tumor in children (Woodtli and Hedinger 1974; Brown 1976) and as such is treated as a separate tumor form in all classifications. In a large percentage of non-seminomatous germ cell tumors of the adult, similar yolk sac structures are encountered as components of variable size (Wurster et al. 1972; Talerman 1980). The TTPR classification includes them in the morphologic spectrum of MTUs, although the significant association with AFP should merit their explicit mention. While Mostofi and Price (1973) consider yolk sac components as embryonal carcinoma of a juvenile type, the WHO treats them as a separate histologic type, in keeping with the neoplastic tissue's distinctive property of elaborating AFP.

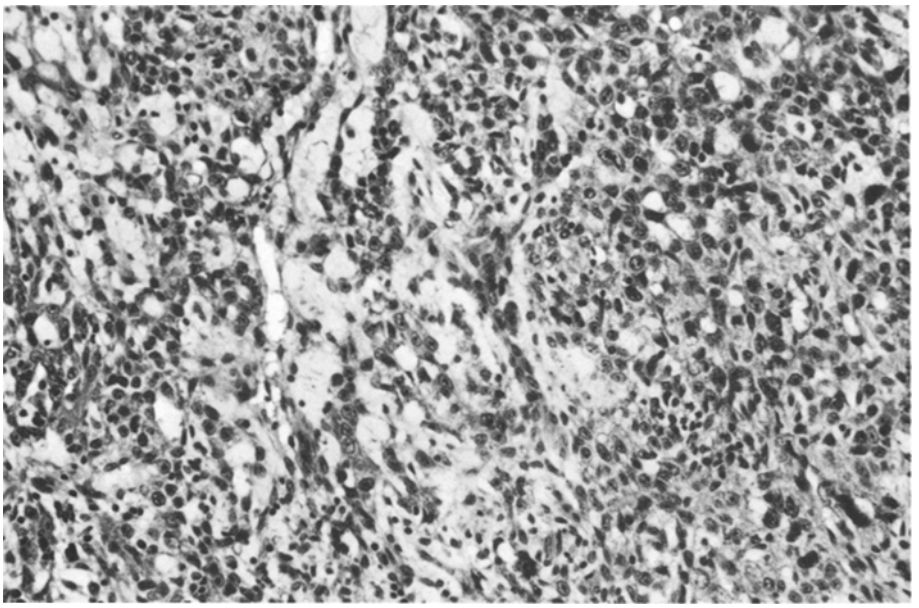

Fig. 10. Reticular yolk sac structures intermingling and blending with embryonal carcinoma/MTU. HE × 160

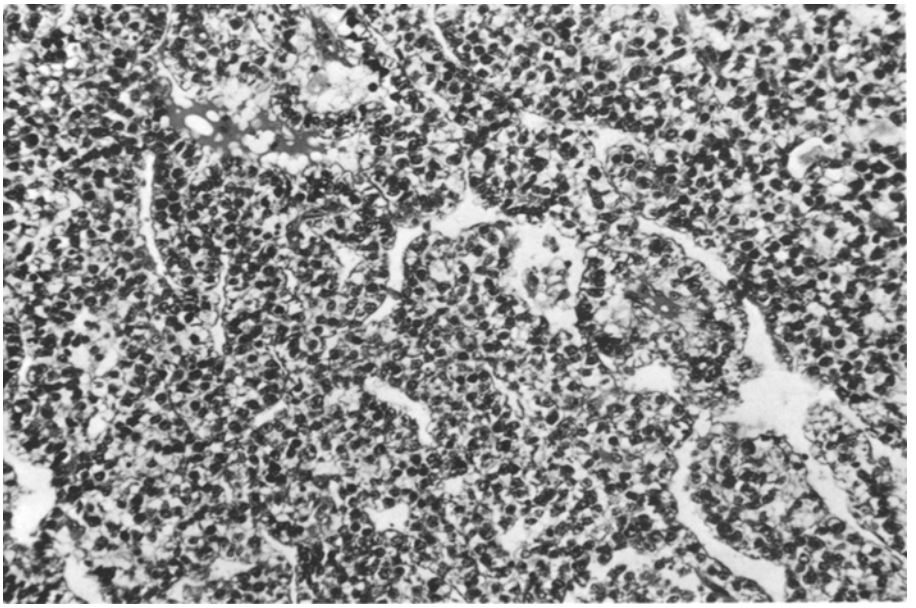

Fig. 11. Clear cell carcinoma with papillary and adenomatoid formations suggestive of yolk sac tumor. Neither the tissue preparation nor the patient's serum was positive for AFP. HE × 120

The morphologic features particular to YST have been amply described and illustrated; ultrastructural details of gonadal, extra-gonadal and murine forms are given by Pierce et al. (1969), Teilum (1971) and Nogales-Fernandez et al. (1977). While flat, cuboidal or hobnailed, often vacuolated cells are distinctive and larger areas of characteristic reticular, tubulo-acinar, or papillary patterns with or without typical Schiller-Duval bodies are easily recognized, small foci within adult tumors may escape detection, especially since they almost invariably occur together with and blend into areas of embryonal carcinoma (MTU) (Fig. 10). The intermingling of typical YST structures with undifferentiated carcinoma, as well as the localization of AFP by immunohistochemical means in cells of both components has led to the interpretation that either embryonal carcinoma cells themselves are capable of producing AFP, or that others, indistinguishable from embryonal carcinoma cells and positive for AFP, represent yolk sac precursor elements (Kurmann et al. 1977; Talerman et al. 1980; Mostofi 1980). The latter stance is taken to bolster the concept that embryonal carcinoma may be the totipotent neoplastic progenitor of other germ cell tumors including YST. Similar staining properties have recently been described in some unusual seminomas, morphologically close to embryonal carcinomas (Raghavan et al. 1981). On the other hand, one may see YST-like neoplasms that do not elaborate AFP (Fig. 11). As applied to small foci in testicular tumors, the matter is for the moment a question of definition: either YST is recognized on histomorphologic grounds alone and AFP is not tumor-type specific, or all that produces AFP is in fact YST or a precursor thereof. It should be reminded in passing, however, that the histochemical localization of intracellular AFP is spotty and notoriously unreliable when formalin-fixed material is used. As the influence of YST components on overall biologic behaviour and prognosis remains controversial (Teoh et al. 1960; Pierce et al. 1969; Wurster et al. 1972; Woodtli and Hedinger 1974; Brown 1976; Parkinson and Beilby 1977), the problem of assigning diagnostic priorities to either morphologic or biochemical criteria remains a moot point. At present, the trend is to rely increasingly on tumor marker properties for the diagnosis (Nørgaard-Pedersen and Raghavan 1980), leading thus to increased recognition and higher incidences of this neoplastic component (Talerman 1980; Sesterhenn and Mostofi 1981).

3.2 Choriocarcinoma

The diagnosis of trophoblastic tumors presents difficulties on several levels. The definition itself is not clear as to what may be included in this group of highly malignant neoplasms. Although the presence of cyto- and syncytiotrophoblastic elements is unanimously accepted as a necessary prerequisite for the diagnosis of trophoblastic tumor components, there is disagreement as to the importance of their combined morphologic patterns. While Mostofi and Price (1973) call the arrangement of cyto- and syncytiotrophoblastic elements "atypical" when villus formation is absent, the WHO classification goes so far as to consider villi non-essential for the diagnosis of choriocarcinoma. To the British panel, however, a definite papillary or villous pattern is indispensable for the definition and diagnosis of malignant teratoma, trophoblastic (MTT). It must be remembered that in the diagnostic terms of the British classification, trophoblastic components assume priority over other concomitant teratoma types.

We have thus in our series a number of tumors with areas of choriocarcinoma in the WHO terminology, that must, strictly speaking, be regarded as teratomas with syncytiotrophoblastic giant cells (STGC) rather than as MTTs in the British panel's terminology (Fig. 12). It has been our experience, however, that such primary tumors may metastasize as typical MTTs, i.e. with villus formation. Since β-HCG can be localized in STGCs of both primary and metastatic lesions, we are led to suspect that villus formation is not an essential criterion for

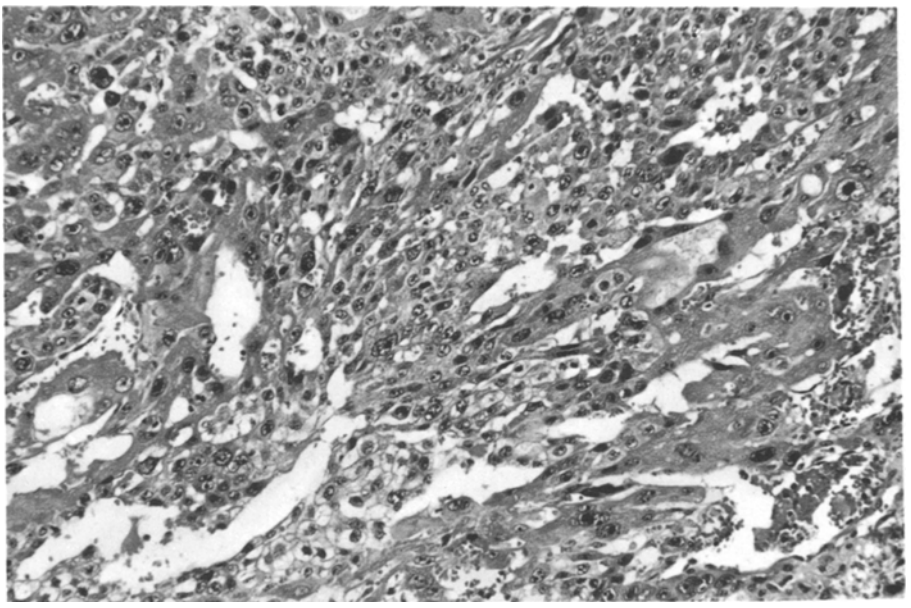

Fig. 12. Syncytiotrophoblastic giant cells positive for β-HCG by immunohistochemical staining admixed to undifferentiated mononuclear cells. The lack of obvious villus formation precludes the diagnosis of trophoblastic teratoma according to the TTPR, but is compatible with choriocarcinoma, formerly "atypical", by the AFIP/WHO's definition. HE × 120

the diagnosis of throphoblastic tumors. The presence or absence of villi may well represent different stages in the development and differentiation of trophoblastic proliferation (Marin-Padilla 1965, 1968).

The distinction in the WHO classification between pure choriocarcinomas and those mixed with embryonal carcinoma raises other diagnostic difficulties. Pure forms obviously contain only cyto- and syncytiotrophoblastic elements. But as Mostofi and Price (1973) themselves observe, "the cells of some embryonal carcinomas are indistinguishable from cytotrophoblastic cells seen in choriocarcinoma. With light microscopy, it is impossible to identify cytotrophoblastic cells with certainty, unless accompanied by syncytiotrophoblastic cells". On the electron microscopic level, the situation is similar (Pierce and Midgley 1963). In consequence, the limit between pure choriocarcinomas and mixed forms, be they embryonal carcinomas with choriocarcinomatous foci, with atypical choriocarcinomatous foci, or simply with STGCs, cannot be drawn on a morphologic basis.

As cytotrophoblasts merge into the morphologic background of undifferentiated tumor cells, diagnostic attention necessarily focuses on STGCs. But first, these must be identified unequivocally among tumor giant cells and those of the Langhans, foreign body, or even osteoclast type. Most are found in the vicinity of hemorrhage and necrosis. Recent techniques for the visualization of human chorionic gonadotropin (HCG) on histologic slides by indirect immunohistochemical methods (Kurman et al. 1977; Javadpour et al. 1978) are used to discern STGCs in their differential diagnosis. The method, however, reveals a great variety of β-HCG-positive cells in testicular as well as in non-testicular tumors (McManus et al. 1976) including mononuclear cells in embryonal

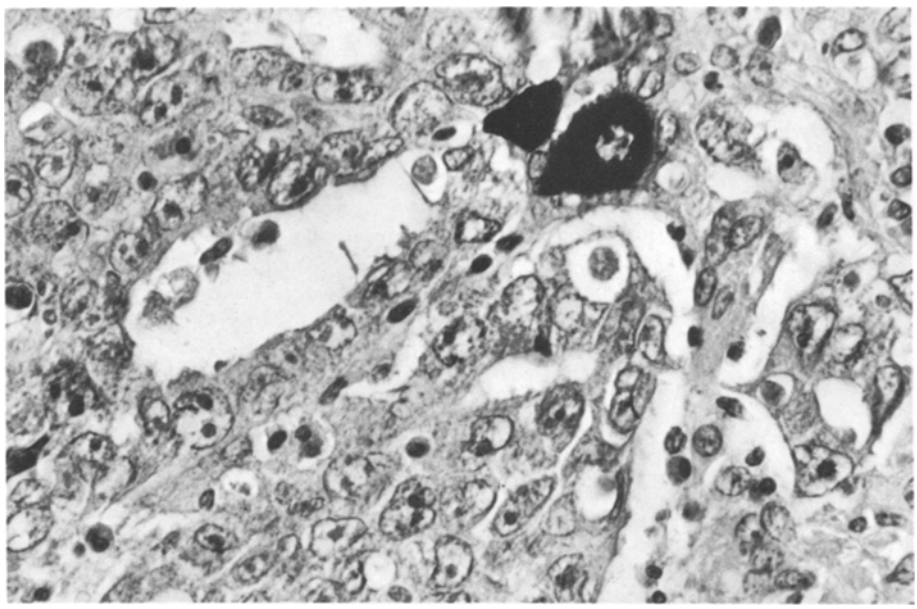

Fig. 13. β-HCG positive mononuclear cells within epithelial formation of embryonal carcinoma/MTU, following peroxidase immunohistochemical staining. $\times 400$

carcinomas (Fig. 13), or multinucleate ones that would not be considered as STGC's on morphologic grounds alone (Fig. 14).

Thus, the use of tumor markers adds histochemical data to disparate morphologic criteria without aiding in the diagnosis and distinction of trophoblastic components. As in YST, histochemical and morphologic criteria may conflict and it is unclear which is to take precedence; applied together they may lead to a widening of the diagnostic spectrum and dilution of the clinico-pathologic entity.

Our figures reflect some of these difficulties. Unable to adhere to the TTPR's definition of trophoblastic tumors in practice, we have, as it were, overdiagnosed MTT (Table 4): 8% of our teratomas are found in the MTT group, compared to 3.7% of the panel's series. This corresponds to an overall incidence of 2.5% as opposed to the TTPR's 1.4% when all testicular germ cell tumors are considered. Mostofi and Price (1973), admitting the "atypical", non-villous forms, cite a figure of less than 5% for all choriocarcinomatous tumors, pure and mixed (Table 3). Our corresponding figure of 6.5% indicates a diagnostic approach comparable to the WHO's and less restrictive than the British panels's. Correlative clinico-pathologic studies are urgently required to arrive at a more realistic definition of neoplasms that are said to carry a particularly sombre prognosis.

4. Mixed/Combined Tumors

Neoplasms displaying elements of more than one histologic type are called "mixed" and "combined" tumors in WHO and TTPR classifications, respec-

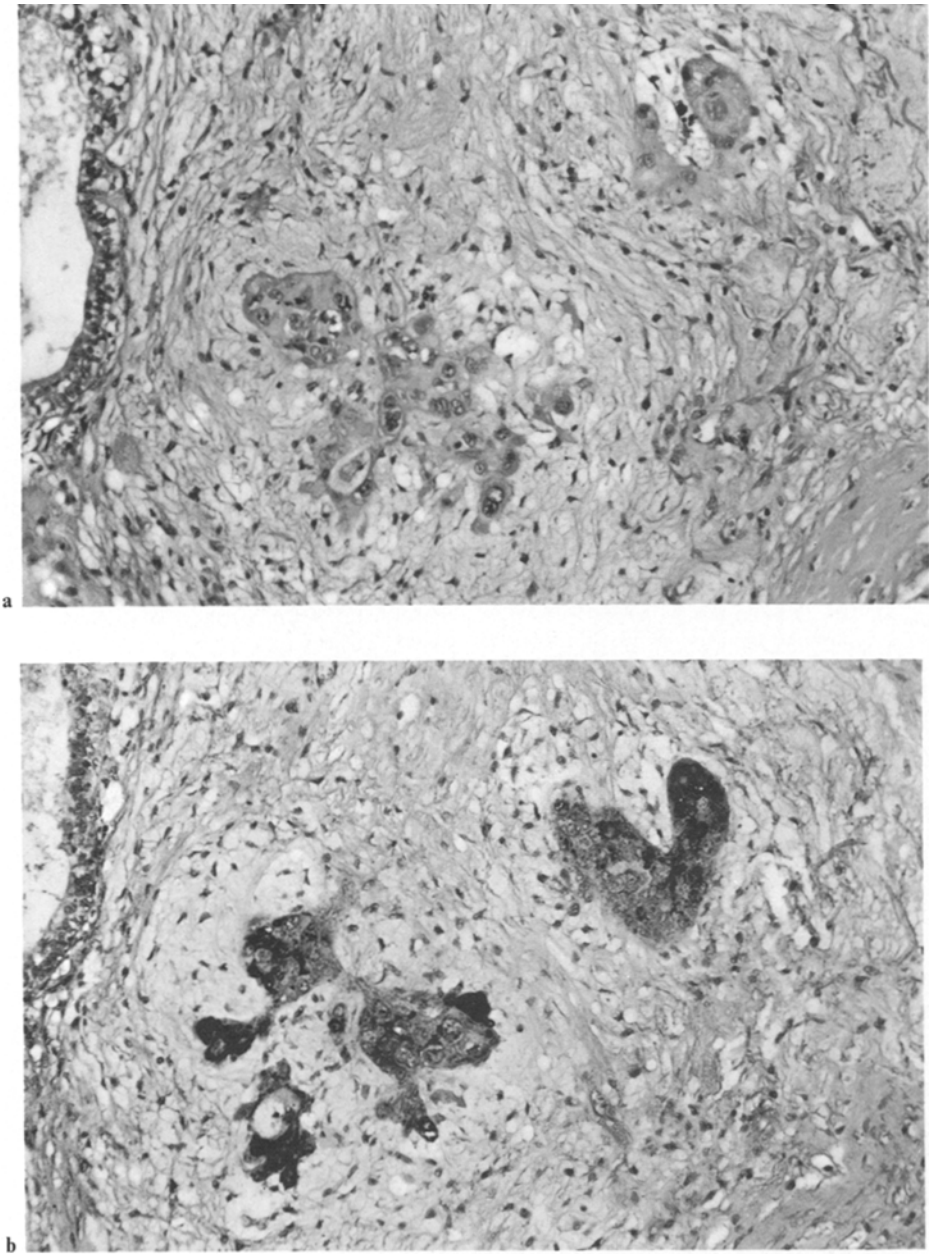

Fig. 14a, b. Multinucleate cells embedded in stroma. Although positive for β-HCG, their significance is unclear in the absence of intimately associated mononuclear cells. $\times 130$. (**a**) HE (**b**) Peroxidase immunohistochemical staining for β-HCG

tively. Care should be taken to avoid the term "compound" tumor, used by some authors to refer to simple teratomas.

It is obvious that the diversity of heterogeneous tumors is a function of the number of histologic types and their combinations. Hence, in the British system, where seminoma and teratoma are the only histologic types, there is only one type of combined tumor, although it is of course classified according to the kind of teratoma involved (Pugh 1976). The increasing recognition and rise in status of YST components in teratomas, however, is likely to change the notion of combined tumor in the British system, and hopefully will lead to a revision of its definition.

From the perspective of the WHO system, mixed patterns are multiple, given at least five different histologic types of independent standing: seminoma, embryonal carcinoma, teratoma, choriocarcinoma, and YST. Of the resulting 26 possible combinations[1], some are more frequent and/or prognostically more significant than others. In fact, only four main patterns emerge: tumors uniting teratoma and embryonal carcinoma (teratocarcinoma) with or without yolk sac components and those in which either seminomatous or trophoblastic elements are a constant feature. By comparison, the British classification modified to regard YST as a separate histologic type in adult neoplasms would yield precisely these four combinations. [1]

Our aspect of mixed or combined seminomatous tumors raises diagnostic considerations, however. The parenchyma in close vicinity to non-seminomatous neoplasms may display lesions varying in appearance from atypical spermatogonia to intratubular seminoma. While such alterations of the germinal epithelium have been recognized for some time (Wilms 1896; Peyron 1936; von Albertini 1943; Azzopardi et al. 1961; Mark and Hedinger 1965), they have recently been shown to occur frequently (Skakkebaek 1975; Sigg and Hedinger 1980). It should be noted in this context that atypical spermatogonia in testicular biopsies of infertile men have been associated with a later occurrence of germ cell tumors (Skakkebaek 1972; Nüesch-Bachmann and Hedinger 1977) and may thus by themselves constitute an in situ neoplastic lesion. In fact, some authors see in atypical germ cells the precursor elements for the spectrum of germ cell tumors (Skakkebaek 1975; Mostofi 1980; Skakkebaek and Berthelsen 1981), but ultrastructural studies so far have interpreted them as seminomatous (Holstein and Körner 1974). Since the development of a seminoma next to another germ cell tumor follows a sequence along which some steps such as atypical germ cells, intratubular seminoma, scattered groups of interstitial seminoma cells (Fig. 15), and solid tumor, may be captured morphologically, the question at which point the lesion is formally recognized as seminoma achieves importance. Stretching the term to include seminoma cells confined to an intratubular location would change statistical data considerably and render interpretation and comparisons of therapeutic results difficult. Thus, in practice we take note of in situ lesions, but diagnose combined tumors only in the presence of invasive seminoma.

In our series we counted 48 combined tumors according to the British classifi-

[1] Mixture may involve all histologic types (n) in groups of two or more (r). Thus the total number of possible non-repetitive mixture is

$$\Sigma\binom{n}{r}=\frac{n!}{r!\,(n-r)!}$$

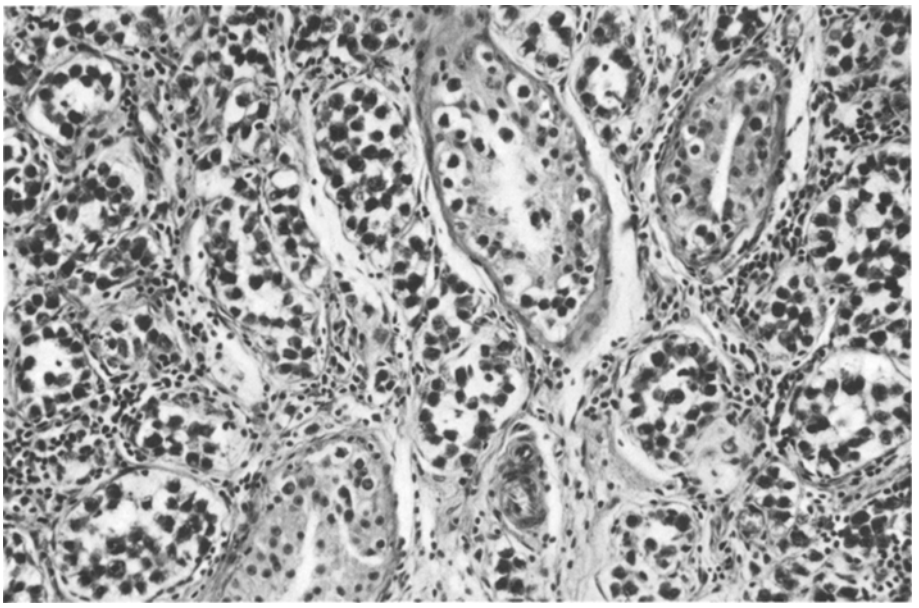

Fig. 15. Atypical spermatogonia, intratubular seminoma, and interstitial seminoma cells in the vicinity of nonseminomatous neoplasms. HE × 160

cation. These represent 14.8% of our germ cell tumors, compared to 15.6% of the TTPR's series (Table 4). In Table 3, 46 cases are found under seminomatous tumors or more than one histologic type, the remaining two in the category of mixed choriocarcinomatous tumors. Teratocarcinomas and mixed patterns incorporating yolk sac and choriocarcinomatous components are discussed above.

Discussion and Conclusion

The use of morphologic criteria in systems of classification requires the presence of precise histopathologic features that are both diagnostic and discriminatory in terms of definition and differential diagnosis, respectively. Nevertheless, in practice some criteria fall short of either aim. Imperfect criteria of definition are found in the case of trophoblastic tumors, where villus formation is attributed unequal importance and the role of STGCs is generally unclear. Similarly, the diagnosis of YST and early or in situ seminomatous lesion vary in incidence relative to what criteria are chosen to define them. In addition, the advent of tumor markers raises the fundamental question as to the roles of morphology and histochemistry in establishing criteria of diagnosis and differential diagnosis. Problems such as these obviously are found in both systems of classification independently.

Other neoplastic entities, as such properly defined, lack precise criteria to segregate them from allied lesions in a differential diagnosis: teratoma with malignant transformation cannot be separated from immature teratoma or teratocarcinoma save in exceptional cases; borderline cases between embryonal carcinoma and immature teratoma/teratocarcinoma rely on watershed criteria

of stromal organization such that the source of error can be appreciable; criteria of distinction between pure choriocarcinoma and embryonal carcinoma with choriocarcinomatous foci, or simply embryonal carcinoma with STGCs, fail in practice. In the TTPR classification similar segregations are less problematic, since here all teratomas are diagnoses of exclusion. While it may not always be easy to distinguish between an MTI and MTU, particularly a former MTIB, the criteria of distinction, i.e. watershed criteria, involve a higher degree of stroma differentiation and hence a lesser source of error.

When the two systems are superposed, it is noted that with the exception of seminoma, YST and mature teratoma (TD), the taxonomic incisions are not placed at identical points along the spectrum of morphologic appearances: watershed criteria, which stake out the territory occupied by a given diagnostic entity, differ to some degree in the two systems. Consequently, a borderline case in one system may be classified under a "non-corresponding" diagnosis in the other: in our series, immature teratomas/teratocarcinomas were grouped not as MTI but with MTUs in about 7% of cases; of all neoplasms containing choriocarcinomatous foci, 62% were diagnosed not as MTTs but as malignant teratomas with STGCs. Translational shifts such as these occur when individual borderline cases are translated from one classification to the other, reflecting different definitions and territorial claims of tumor entities in each system.

The foregoing considerations illustrate some sources of difficulty inherent in any taxonomic system. But we have seen that morphologic criteria alone account for a negligible part only of the conflicts between the two classifications. Their supposed incompatibility resides elsewhere.

A taxonomic system implies a hierarchic order. With testicular tumors, it is a histogenetic one, in the form of a precursor cell and several paths of differentiation. In the WHO's school of thought, the original cell is a germ cell that can develop into a seminoma or into a tumor of totipotent cells whose potentials are reflected by the designation embryonal carcinoma. The totipotent embryonal carcinoma cell is deemed capable of giving rise through embryonic and extra-embryonic paths of differentiation to the spectrum of non-seminomatous germ cell tumors. It is distinct from the hypothetical precursor cell only in that the latter may in addition lead to seminomatous differentiation. Moreover, the morphologic resemblance on light-optical and ultrastructural levels between some seminomas and solid embryonal carcinoma (MTU) suggests a very close relationship, as do reports of histochemical staining reactions positive for AFP in both seminoma and embryonal carcinoma (MTU). Hence, it is as easy to conceive seminoma and embryonal carcinoma (MTU) to blend into each other along a path of differentiation, as it is to adopt a concept of a stem cell common to both, but both place embryonal carcinoma in a hierarchically ambiguous position: it is either identical to or so close to the stem cell to be considered totipotent; or, as the histogenetic flow diagram would have it, clearly past the point of seminomatous differentiation, meriting rather the attribute "pluripotent". The hypothetical precursor cell has so far remained elusive to morphologic definition; its origin and nature are debated and debatable, but of no immediate concern to our taxonomies. Should it be identified, it could easily be placed on top of the histogenetic hierarchy with arrows pointing in the appropriate directions.

The claim to totipotence also defines the relation of embryonal carcinoma to the teratomas. In the WHO system embryonal carcinoma is conceptually different from teratomas since teratomatous differentiation is but one path along which embryonal carcinoma may develop: teratoma implies a commitment that the totipotent cells have not or not yet made. An embryonal carcinoma, consequently, is not a teratoma, not even a most undifferentiated one (MTU), nor is a teratocarcinoma a teratoma of intermediate differentiation (MTI) but rather a mixed neoplasm of two conceptually distinct entities. Besides creating a climate of incompatibility, the rigid separation of embryonal carcinoma and teratoma through conceptual terms of totipotence brings the system into difficulties. We have already noted the case where a nodule of cartilage and undifferentiated carcinoma together are to be diagnosed as a mixed tumor, i.e. teratocarcinoma, thereby creating a dilemma for the time-honoured definition of teratoma.

The problems surrounding totipotent embryonal carcinoma are compounded when the morphologic criteria chosen to represent it do so inadequately: conceived as a tumor uncommitted to the possible paths of differentiation, embryonal carcinoma may contain contractile muscle elements; polyembryoma is considered a variant of embryonal carcinoma, although its morphologic unit, the embryoid body, would make it a prototype of teratomas.

Embryonal carcinoma, then, emerges as a conceptual entity whose hierarchic claims and morphologic criteria of definition and distinction are not in proper relation to each other. As a tumor of totipotent cells, embryonal carcinoma takes up position of a stem cell neoplasm; uncommitted as to the various paths of possible differentiation, it claims distinction in kind from those forms to which the paths lead. Its morphologic criteria, however, stake out a wider territory, covering early embryonic and extra-embryonic differentiation. It is here the most substantial source of conflict that radiates into most reaches of the WHO classification, the repercussions being felt whenever embryonal carcinoma must be separated from other neoplastic components. These difficulties assume major proportions when in the climate of incompatibility both systems of classification are compared.

Clearly, a resolution of the conflicts must aim to reduce the tight conceptual barrier between embryonal carcinoma and teratoma. With a slight loss of status from totipotent to pluripotent, embryonal carcinoma can be viewed as harbouring cells already committed to embryonic and/or extra-embryonic differentiation. This would allow its morphologic watershed criteria to include features such as AFP- and β-HCG-positive cells or contractile muscle elements – features otherwise not compatible with a totipotent and uncommitted neoplasm. While this must in no way exclude the presence of stem cells within the embryonal carcinoma's cellular pool, the designation MTU could then be admitted on the basis that it stresses the tumor's teratomatous potential.

If the concept embryonal carcinoma is taken to depict a pool of neoplastic elements some of which may have stem-cell properties, while others may be committed to differentiation, the major conflicts with the teratomas can be resolved without compromising criteria of definition and distinction. If, in addition, YST components were to receive special mention in the TTPR system, there would remain of the major difficulties only those common to both classifications, namely the criteria for choricarcinoma (MTT). In the ensuing climate of compatibility both systems can be used effectively: while one calls for a detailed listing of all neoplastic components, essential at least to the pathologist, the other offers a more summary diagnosis and is appreciated by the clinician who prefers to act according to key diagnoses rather than select from a diagnostic mosaic those elements that are therapeutically significant. Thus, we arrive at two eminently comparable and complementary systems of classification, whose combined use will let their real difference, splitting vs lumping, emerge as valuable advantage.

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Accepted March 18, 1982