The Management of Testicular Tumours

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Preface

Since malignant tumours of the testis predominantly afflict young men, it is particularly gratifying that one of the most important advances in oncology to have occurred during the past few years should have been in the management of these hitherto lethal tumours. Until relatively recently the outlook for men with metastatic non-seminomatous germ-cell tumours was bleak and to those who experienced the frustration and feelings of helplessness when confronted by uncontrollable, rapidly progressive malignancy, the fact that many of these patients are now curable is indeed a remarkable and exciting achievement.

The success of modern therapy is tempered by its intricacy and toxicity so that delivery of optimal treatment demands the skills of a team as well as attention to detail. Progress has been good but important problems remain. A minority of patients still die of tumour and treatment may be associated with considerable toxicity.

This book is based to a great extent upon experience at the Royal Marsden Hospital and, although primarily a description of investigation and treatment methods, makes reference to some of the biological aspects of relevance and interest in germ-cell malignancy.

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MJP

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General introduction: biological diversity and predisposing factors

M. J. Peckham

Testicular tumours are uncommon but important since they predominantly afflict young men in their most productive years, often at a time of major family responsibility. During the past few years there have been major advances in clinical management, particularly the introduction of effective chemotherapy. This, together with developments in clinical staging procedures, the use of tumour markers and a better understanding of major factors influencing patient prognosis have led to striking improvements in treatment results.

Tumours of the testis are diverse with respect to histopathology, clinical evolution, age at presentation and therapeutic sensitivity. The majority of testicular tumours fall into the general category of germ-cell tumours which are divided into two broad subgroups—seminoma and malignant teratoma. To avoid terminological confusion (see Chapter 2) the latter are referred to sometimes as non-seminomatous germ-cell tumours of the testis. Seminoma and malignant teratoma may occur alone, or together in the same testis as a combined tumour. The histogenesis of seminoma and teratoma and the possible relationship between the histologically distinct components of combined tumours in terms of cellular origin, remain unsolved but fascinating problems.

Seminomas tend to present at an early stage and the cure rate with orchidectomy and radiotherapy exceeds 90 per cent (Chapter 10). Malignant teratomas can be divided into the two broad categories of early-stage and advanced-stage disease. Approximately 80 per cent of the first category can be cured by orchidectomy and radiotherapy or orchidectomy and retroperitoneal node dissection, whereas hitherto, the prognosis for patients with metastatic malignant teratoma has been poor. As described in Chapters 11 to 15, chemotherapy used alone or in conjunction with radiation and/or surgery has resulted in a major improvement in survival rates for patients with advanced disease, and the major challenge for the future is the development of treatments appropriate to each clinical situation, with particular stress on the minimization of toxicity and the preservation of normal tissue function, including potency and, where possible, fertility.

The purpose of this book is to describe current approaches to patient management, but it would be an omission not to review briefly several aspects of the biology of testicular tumours, since this provides a useful background to the better understanding of these unusual neoplasms.

The biological diversity of testicular tumours

Histology (see Chapter 2)

Figure 1.1 shows the distribution of testicular tumours by histopathological subtype, drawn from the large experience of the British Testicular Tumour Panel (Pugh and Cameron, 1976). The most common tumour type is seminoma and some 14 per cent of patients show histological evidence of both seminoma and teratoma components within the same tumour.

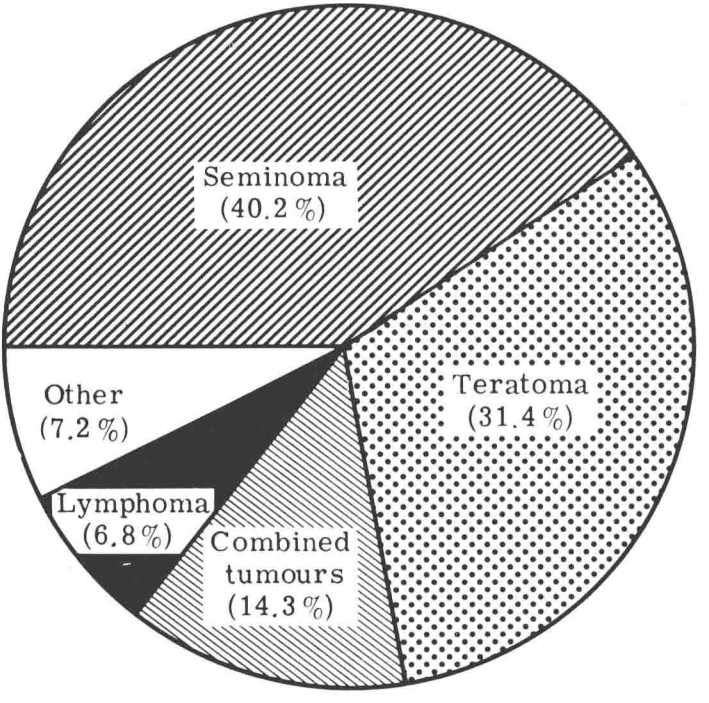

Fig. 1.1 Distribution of testicular tumours by histological subtype. (Data from Pugh and Cameron, 1976.)

Figure 1.2 (a–f) shows the differing age distributions of the major histopathological subtypes. The peak incidence of the whole group lies between the ages of 25 and 35 years (Fig. 1.2a). The initial part of the age distribution curve comprises the rare testicular tumours of childhood, including paratesticular embryonal sarcomas and the alphafetoprotein-producing yolk-sac tumour (Fig. 1.2f). Malignant lymphomas are predominantly tumours of old age (Fig. 1.2b). Seminoma (Fig. 1.2d) and teratoma (Fig. 1.2c) show peak incidences approximately one decade apart at 35 to 39 years and 25 to 29 years respectively. Combined tumours, where both seminoma and teratoma elements are identified, present within this general age range, but tend to show a peak incidence between seminoma and teratoma at 30 to 34 years (Fig. 1.2e).

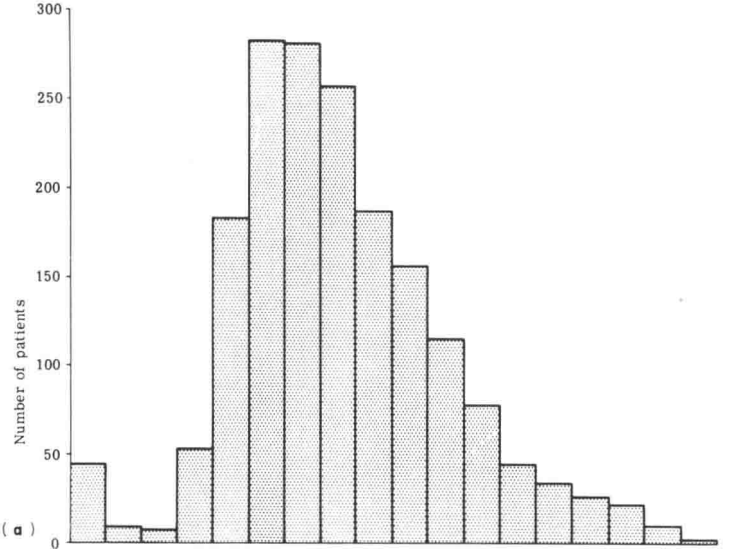

Fig. 1.2 Distribution of testicular tumour by age. **(a)** Whole group.

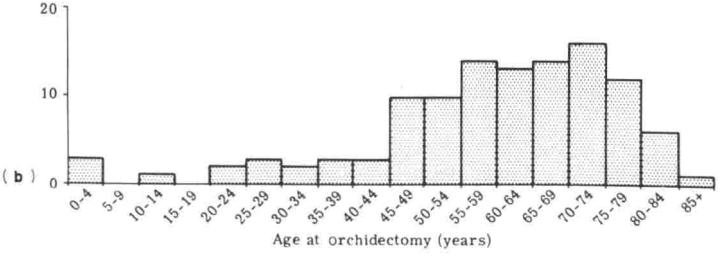

Fig. 1.2 Distribution of testicular tumour by age. **(b)** Malignant lymphoma.

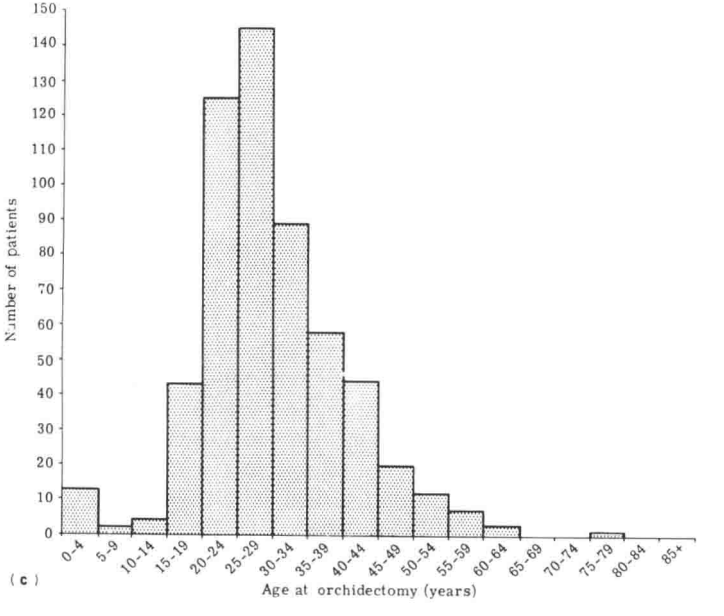

Fig. 1.2 Distribution of testicular tumour by age. **(c)** Malignant teratoma. (Data from Pugh and Cameron, 1976.)

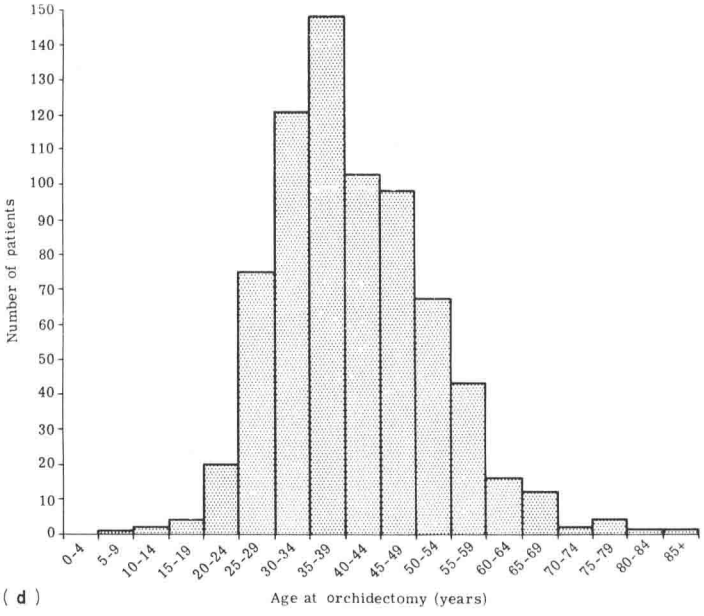

Fig. 1.2 Distribution of testicular tumour by age. **(d)** Seminoma.

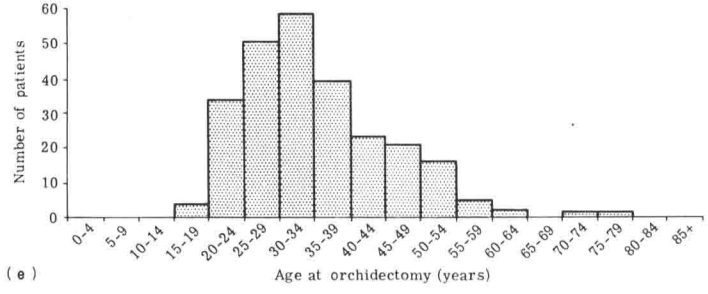

Fig 1.2 Distribution of testicular tumour by age. **(e)** Combined tumours.

The heterogeneous nature of testicular teratomas is emphasized by the range of histological appearances which may be seen in different metastases from the individual patient. However, data bearing on this important point are limited.

Information from two sources is summarized in Table 1.1. In the series from Ray *et al.* (1974), in 37 of 108 (34 per cent) of patients with embryonal carcinoma (malignant teratoma undifferentiated) primary tumours, the metastases in the abdominal nodes showed other associated histological elements. Of 32 patients with combined teratoma and seminoma primary tumours, 2 had pure seminoma metastases without an identifiable teratoma component.

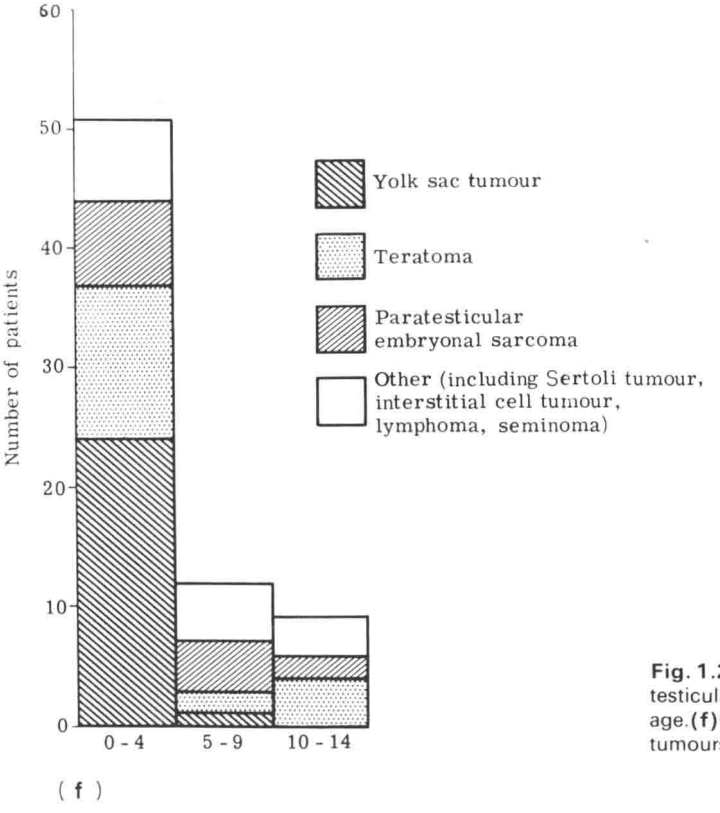

Fig. 1.2 Distribution of testicular tumour by age. **(f)** Childhood tumours.

Table 1.1 Histology of metastases in relation to histology of primary testicular tumour

References	*Histology of primary tumour*	*Total patients*	*Histology of metastases* *TD*	*MTI*	*MTU*	*MTT*	*Sem*
Pugh and Cameron (1976)	MTI + Sem	15	1	2	9	1	2
	MTU + Sem	17			15	2	
	MTT + Sem	2				2	
Ray *et al.* (1974)	Sem	2					2
	EC	34			34 (5)*		
	TC	1			1 (1)		
	Chorio	1			1 (1)		
	YS	1			1		
	EC + Sem	32			30 (5)		2
	EC + TC ± Sem	32		1	30 (20)		
	EC + TC + Chorio ± Sem	13		2	11 (5)		

* Figures in parentheses indicate metastases containing elements other than MTU. EC, embryonal carcinoma (taken as synonymous with MTU); TC, teratocarcinoma (taken as synonymous with MTI); Chorio, choriocarcinoma; YS, yolk-sac tumour; TD, teratoma differentiated; MTI, malignant teratoma intermediate; MTU, malignant teratoma undifferentiated; MTT, malignant teratoma trophoblastic; Sem, seminoma.

Functional pathology

In approximately two-thirds of men with testicular tumours, elevated serum levels of alphafetoprotein (AFP) or human chorionic gonadotrophin (HCG), or both, are present and provide a useful means of monitoring the course of the disease and the effectiveness of treatment (see Chapter 4). The identification of these tumour products, using immunocytochemical techniques on tissue sections, has provided a further indication of the complexity and heterogeneity of malignant teratomas and seminomas. This aspect is discussed in Chapter 3. Recently, it has been possible to grow human testicular teratoma tissue as xenografts in immune-suppressed mice. Production of AFP and HCG has been demonstrated by the identification of both markers in mouse serum and in fluid from the cystic centre of the xenografted tumour. The combined use of immunocytochemistry and in-vitro tumour cell cloning methods should provide the means whereby the functional elements of the tumour can be dissected apart and studied separately (see Chapter 5).

Tumour growth rate

Testicular teratomas are rapidly growing tumours, whereas most, but not all, seminomas tend to follow a more indolent course. Tumour growth rates are calculated readily in teratomas by measuring the dimensions of pulmonary metastases on sequential chest radiographs. When this is done a volume doubling time can be calculated and this tends to be short—10–30 days (Fig. 1.3).

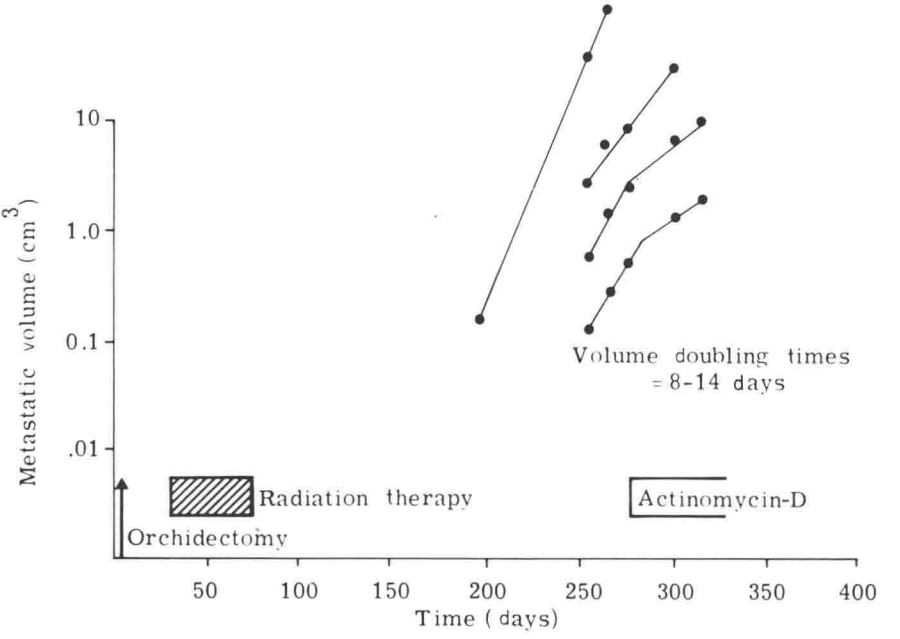

Fig. 1.3 Testicular teratoma: growth rate of pulmonary metastases detected seven months after orchidectomy and in association with failure to eradicate bulky para-aortic lymph node metastases.

Considerable variation is observed between individual patients. This is illustrated in Fig. 1.4, where the modal doubling time is approximately 20 to 25 days. However, there is a wide range of growth rates from rapidly growing tumours to indolent tumours doubling in two to three months. The rapid growth rate of malignant teratoma has important implications for clinical

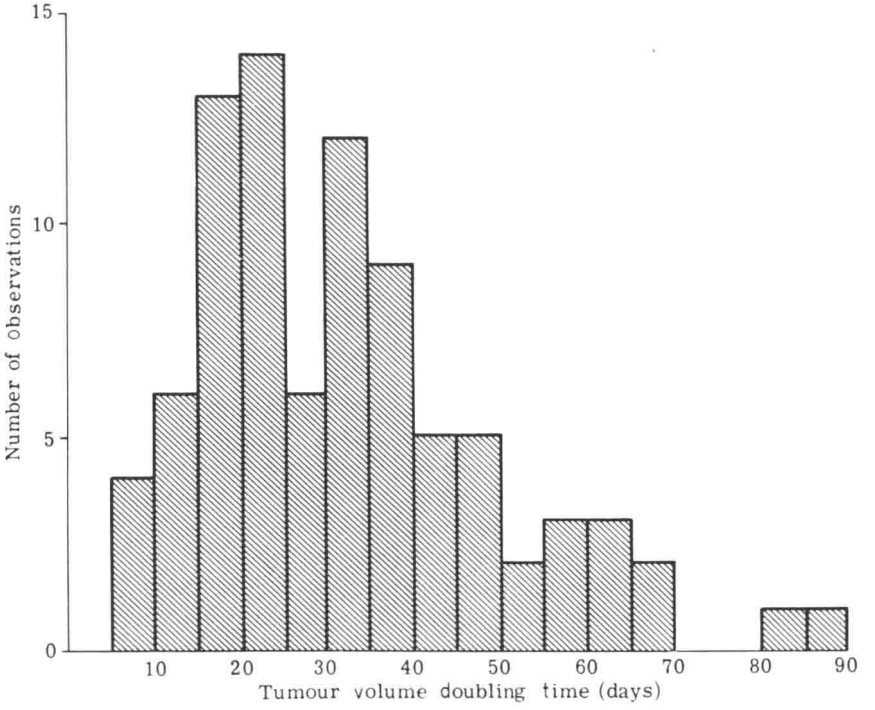

Fig. 1.4 Distribution of tumour volume doubling times in testicular teratomas. (Pooled data from Garreta *et al.* (1970) and the Royal Marsden Hospital series.)

management since, as described in Chapter 13, if relapse occurs after primary treatment, it tends to present within the first year. Similarly, uncontrolled tumour tends to lead to rapid demise of the patient. In addition to the growth rate variation seen between individual patients, sometimes different growth rates are observed between different metastases in the same patient (Fig. 1.5). Where differences in the growth rate of individual metastases are observed, this may be a reflection of differences in histology between the various deposits. Indeed, in some instances, spontaneous cessation of growth or even tumour regression may occur (*vide infra*).

Cellular origin and differentiation

Testicular teratomas are postulated to arise from gametocytes early in spermatogenesis, the pluripotency of the cell of origin being reflected in the diversity

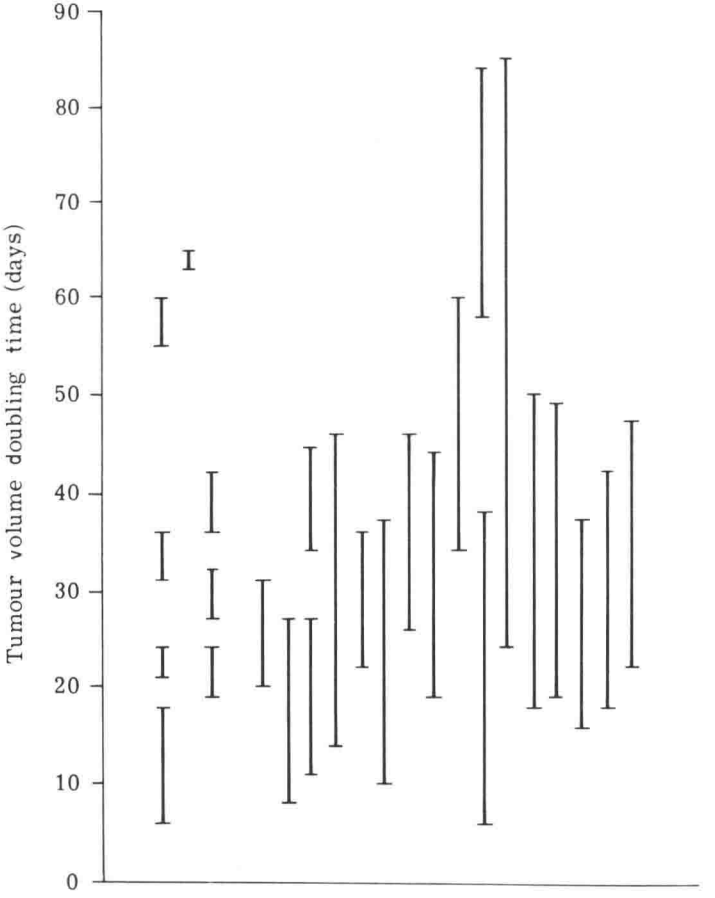

Fig. 1.5 Range of tumour volume doubling times in testicular teratoma. Each line represents the range of doubling times of different metastases within an individual patient. The figure illustrates the variation in growth rate between individual patients and between different metastases in some patients. (Data from Garreta *et al.*, 1970.)

of histological appearances of the established tumour. The rare primary teratomas and seminomas of extragonadal sites, pineal, mediastinal, retroperitoneal and sacrococcygeal (see Chapter 17), are envisaged to arise from primordial germ cells normally colonizing the gonadal ridges in embryonic life and which have failed to migrate from the primitive mesoderm (yolk sac) to the gonads during fetal development.

Teratomas and seminomas arise at an unidentified stage in the rapidly proliferating system where spermatids arising by meiotic division from spermatogonia replicate to produce spermatozoa.

Studies in a spontaneous mouse teratoma have shown that the tumour cells arise within the seminiferous tubules, at first lying within the intact basement membranes of the tubules (Stevens, 1964). Electron microscopy studies of human seminoma demonstrate cells of varying degrees of differentiation ex-

hibiting the features of spermatocytes and spermatogonia as well as undifferentiated cells (Pierce, 1966), on this basis seminoma may be regarded as a tumour of seminiferous epithelium arising from stem cells already committed to differentiate into the spermatocytic series.

The cellular origin of male malignant teratomas is unknown. Linder *et al.* (1975), using chromosome banding techniques to study ovarian teratoma tissue, concluded that since teratomas were uniformly homozygous for 17 chromosome polymorphism they had arisen by parthenogenesis from single germ cells after the first meiotic division. Early in-situ teratomas arising from germinal epithelium and confined to the lumina of the tubules have been documented in man (Waxman, 1976). The combination of both seminoma and teratoma elements within the same tumour mass suggests a common origin and chromosome studies have failed to demonstrate populations of cells with different karyotypes in combined tumours (Martineau, 1969). Large abnormal aneuploid cells are present in a proportion of men presenting with infertility, testicular atrophy or maldescent. Approximately 50 per cent of patients with these in-situ changes show progression to invasive germ-cell tumours which may be seminomas or teratomas (Skakkebaek and Berthelsen, 1978), suggesting that these tumours may arise from a common malignant stem cell.

That human teratomas can differentiate is shown by the presence in some tumours of easily identifiable adult somatic tissues such as muscle, nervous tissue, cartilage and gastro-intestinal epithelium (see Chapter 2). The spontaneous mouse teratoma referred to above has been studied extensively to provide some understanding of the spontaneous maturation process. In this tumour, which arises in the seminiferous tubules in early gestation (Stevens, 1964), the development of differentiated teratoma can be traced from undifferentiated tumour. In some strains of mice, germ-cell tumours can be produced by grafting embryonic genital ridges into adult testes. The resultant tumour cells, when grown in an ascitic form, produce embryoid bodies resembling normal five- to six-day embryos (Pierce *et al.*, 1960).

Artzt *et al.* (1973) have reported that syngeneic antisera raised against primitive cells of a rat teratoma react specifically against male germ cells and also appear to possess cell-surface antigens in common with normal cleavage stage embryos. Diwan and Stevens (1976) have reported subsequently that the primary ectoderm and endoderm of six-day mouse embryos grafted into the testes of adult mice give rise to teratocarcinoma composed of undifferentiated embryonal cells and mature derivatives of the germ layers, including respiratory and alimentary epithelia. The multipotentiality of teratoma stem cells has been investigated extensively by Kleinsmith and Pierce (1964). In cloning experiments, transplantation of single tumour cells results in tumour formation in 11 per cent of mice, the tumours showing a wide range of somatic tissues. Differentiation in the mouse teratoma system has been shown to be influenced by environmental factors. Restitution by the tumour cells of haemopoiesis and immune function in irradiated recipients has been investigated by Auerbach (1971) and, in a series of elegant transplantation experiments in which the nuclei of teratoma cells were transferred to the ova of female recipients of a different strain, Mintz and Illmensee (1975) have shown that normal offspring can be produced, bearing some of the genetic characteristics of the mouse strain from which the teratoma was derived.

So far as the clinical significance of these experimental observations is concerned, it indicates that tumour cell evolution may be influenced both by cellular control mechanisms and extracellular factors. There are parallels between the murine model and testicular tumours in man. Although human teratomas are classified for convenience into the broad categories of malignant teratoma undifferentiated (MTU), intermediate (MTI and trophoblastic (MTT), a considerable diversity of cell types is evident within individual tumours and in MTI a wide range of adult mature tissues may be juxtaposed to undifferentiated malignant components. In some cases the tumour may be composed exclusively of fully mature tissues (teratoma differentiated), yet metastases may occur which themselves show histological evidence of differentiation. 'Maturation' in metastases generally occurs as a result of therapy and may, of course, reflect the elimination of the malignant component leaving a residue of mature tissue. The possibility of spontaneous or therapy-induced differentiation, however, needs to be considered. In patients undergoing intensive chemotherapy, the presence of well-differentiated teratoma in residual tumour tissue is not uncommon. However, differentiation after minimal therapy is also well documented (Smithers, 1969). An example is shown in Fig. 1.6 in a patient with an undifferentiated primary malignant teratoma receiving minimal chemotherapy for bilateral lung metastases more than eight years ago. One large metastasis, appearing after treatment, has disappeared

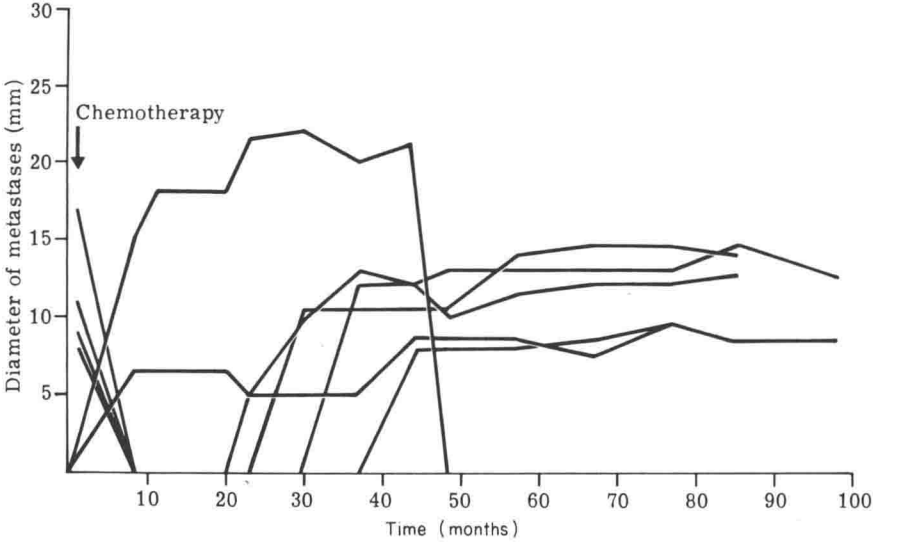

Fig. 1.6 Patient with Stage IV malignant teratoma undifferentiated (MTU) receiving one course of single-agent chemotherapy and showing simultaneous regression and progression of metastatic disease with subsequent long-term stabilization in the absence of further therapy.

spontaneously and several other lesions, after an initially rapid phase of growth, have remained unchanged for five years. The histology of the residual opacities might well show a completely differentiated structure composed of mature somatic tissues.

An unexplained and rare phenomenon of considerable interest is the apparent spontaneous regression of primary tumours in some patients. Azzopardi *et al* (1961) described a series of patients dying of widespread tumour dissemination in whom no primary tumour could be identified in the testes. In these patients the testes showed characteristic lesions composed of well-defined fibrous scars, often with ghosted remnants of seminiferous tubules. In some cases there were small foci of differentiated teratoma or microfoci of seminoma cells. The unusual appearance of these scars suggests the spontaneous resolution of the primary malignancy in the face of florid progression of metastatic disease elsewhere in the body.

Epidemiology and predisposing factors

Testicular cancer is rare in Africa and Asia and varies considerably from one European country to another (Table 1.2). The highest age-adjusted rates are encountered in Northern Europe and, interestingly, in Maoris in New Zealand. In Nordic countries there is considerable variation from 1.1 per 100 000 males in Finland to 4.9 in Denmark.

Within countries there may be marked variation in incidence between different ethnic groups. Thus, as shown in Table 1.3, the incidence rate in Negroes in the United States is approximately one-third of that of Whites. However, the incidence in Negro populations outside the United States may be considerably lower. In the African Negro, for example, it is approximately one-twentieth of the incidence observed in White populations. These observations suggest that both racial and environmental factors may be relevant in aetiology and that the observed difference between Negroes in Africa and the United States may result from exposure in the latter group to environmental agents. However, the situation may be more complex, since testicular tumours appear to be more common in the professional classes. Thus, racial differences may be explained, at least in part, by socio-economic and environmental factors.

In addition to variation between countries and between races, cancer registries in several countries have reported increasing incidence rates. Figure 1.7 summarizes data for Denmark collected by Clemmenson (1974) and shows a rise from 3.4 per 100 000 males in 1943–1947, to 5.4 in 1963–1967. Similar, and as yet unexplained, increases have been reported in this country and in the United States (Table 1.3). The increase in incidence of testicular tumours has been reported in both high and low incidence areas. Thus, age-adjusted rates rose from 3.2 to 6.7 in Copenhagen over twenty years. In Japan, a low incidence country, the rate rose from 0.15 to 0.38 during a similar period (Lee *et al.*, 1973).

The increase appears not to have changed the distribution of histological subtypes, although variability of diagnostic criteria makes intercomparison of dubious value. It is of interest that orchioblastoma (yolk-sac carcinoma) is reported to be relatively more common in Africans (Templeton, 1972). There