Chapter 25: Tumours of the head and neck

P. N. Plowman and J. Pritchard

Although malignancy is the commonest non-accidental cause of death of children in most 'developed' countries, recent advances in treatment mean that well over 50% of children are now cured. The leukaemias (30-35% of the total), brain tumours (20-25%), lymphomata (10%) and sarcomata (10%) are the most common tumour types. In descending order of frequency, malignant tumours presenting in the head and neck (excluding the brain) are non-Hodgkin's and Hodgkin's lymphomata, rhabdomyosarcoma, neuroblastoma, nasopharyngeal and thyroid carcinomata. Other very rare tumours and two non-malignant conditions usually treated by paediatric oncologists - Langerhans cell histiocytosis and the fibromatoses - are also discussed in this chapter.

The length of the discussion apportioned to the various tumours will not necessarily correspond with their rank order of incidence as this would not be appropriate for an otolaryngological text. For example, children with lymphoma may well present first in the otolaryngology clinic as cervical lymphadenopathy, but they are not subsequently managed there; only the broad staging and treatment strategies will therefore be outlined. Conversely, although much more rare in childhood, salivary tumours and squamous cancer (notably nasopharyngeal carcinoma) have been reviewed more extensively. Ocular and brain primary tumours are omitted but pituitary tumours, craniopharyngiomata and clivus chordomata are reviewed. Angiofibromata are discussed in Chapter 19.

These days, there is general agreement that the management of children with cancer should be coordinated at regional paediatric oncology centres. Here, patients can benefit from the medical, nursing and psychosocial expertise that naturally develops when relatively large numbers of children are seen and treated. There is not no case for treatment of the 'occasional' child in an adult unit. Families usually feel that the inconvenience resulting from long-distance referral is offset by the feeling that their child is receiving the 'best possible' treatment. The inconvenience can be moderated by establishing 'shared care' arrangements with the local paediatric and/or otolaryngology units.

Lymphoma

Non-Hodgkin's lymphoma and Hodgkin's disease

Lymphomata constitute around 10% of malignancy in the 0-14-year-old age group and non-Hodgkin's lymphomata are rather more common than Hodgkin's disease. In both cases, boys are affected more frequently than girls. These and other contrasting features are listed in Table 25.1. Of particular clinical importance is that, although Hodgkin's disease usually presents with enlargement of lymph nodes, most often in the cervical or supraclavicular regions, the presentation of non-Hodgkin's lymphoma is more commonly extranodal.

Non-Hodgkin's lymphoma

The histopathological classification of non-Hodgkin's lymphoma in children is a good deal less complicated than in adults. Most tumours have a 'diffuse' (rather than a 'follicular')
pattern and, at the cellular level, are 'lymphocytic/lymphoblastic' or 'undifferentiated' (rather than histiocytic). There is so much clinical and laboratory overlap between lymphoblastic non-Hodgkin's lymphoma and acute lymphoblastic leukaemia in children that the convention of distinguishing between the two conditions, based on the percentage of bone marrow blast cells (>25%), is arbitrary and of little real value. Instead, there is an increasing tendency to classify tumours by immunological subtype, for instance 'B-cell disease' or 'T-cell disease'. As Table 25.2 indicates, sites of presentation correlate with the immunological subtype. Most T-cell lymphomata arise in the mediastinum (30-40% of all non-Hodgkin's lymphomata), probably in the thymus gland, while gastrointestinal (25-30%) and nasopharyngeal (10-15%) tumours are of B-cell origin. Distinction between T, B and null lymphoid cells is easily made because of the ready availability of panels of specific antibodies which have replaced older techniques such as 'E rosetting' (sheep red cell rosetting). Using these antibodies, 'undifferentiated' cells in fact type as mature immunoglobulin-producing B cells.

Table 25.1 Contrasting features of non-Hodgkin's lymphoma and Hodgkin's disease in children

<table>
<thead>
<tr>
<th>Feature</th>
<th>Non-Hodgkin's lymphoma</th>
<th>Hodgkin's disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex male:female</td>
<td>2.5:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Age at presentation (years)</td>
<td>5-10</td>
<td>5-35*</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Extranodal, eg nasopharynx, abdomen, mediastinum, jaw</td>
<td>Nodal</td>
</tr>
<tr>
<td>Spread</td>
<td>Non-contiguous</td>
<td>Contiguous</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>Relatively common</td>
<td>Rare</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td>Relatively common</td>
<td>Rare</td>
</tr>
<tr>
<td>Cells of origin</td>
<td>Lymphoid</td>
<td>Reed-Sternberg cell, lymphoid?, histiocytic?</td>
</tr>
</tbody>
</table>

* Second peak in later adult life.

The term 'Burkitt's lymphoma' is applied, for historical reasons, to B-cell lymphomata arising in areas of the world where there is holoendemic malaria. The high incidence of jaw tumours is the most striking difference between endemic (Burkitt) and sporadic B-cell lymphoma, but histologically and immunologically the tumours are identical. Studies on Burkitt's lymphoma cell lines and on native tumours consistently show one of three chromosomal translocations within the tumour cells; one break point always involves chromosome 8 while the other variably affects chromosome 2, 22 or 14, precisely at the respective locations of the kappa and lambda light chain and heavy chain genes. In the process, the \( c\)-myc oncogene is translocated from chromosome 8 to an area of the genome, adjacent to the immunoglobulin (Ig) genes, that is transcriptionally active in B cells. Overproduction of the \( c\)-myc protein almost certainly contributes to the generation of malignancy.

Around 15% of non-Hodgkin's lymphoma presents with nasopharyngeal symptoms (Traggis et al, 1975). The short history (at most, a few weeks and usually a few days) helps distinguish non-Hodgkin's lymphoma from other nasopharyngeal tumours. Increasing nasal
or pharyngeal obstruction, especially at night, is sometimes associated with painless enlargement of nodes in the anterior triangles of the neck. Endoscopy reveals a pinkish-white fleshy mass arising from one of the structures of Waldeyer's ring, though it is often impossible (and unimportant) to define the exact site of origin. Since results of haematoxylin and eosin stained sections, as well as confirmatory immunohistological studies, can be available within 24 hours, frozen section studies are particularly not recommended because they can be misleading. Usually, clinical suspicion of tumour is high and, to save further trauma to a child already frightened by a compromised airway, bone marrow and cerebrospinal fluid sampling should be carried out under the same anaesthetic. Chest X-ray and abdominal ultrasonography (to seek evidence of hepatic, splenic and renal involvement) complete the staging procedures.

Nasopharyngeal non-Hodgkin's lymphoma is usually clinically localized. Stage I tumours (Murphy, 1978) are those limited to a single site and stage II those where there is also local node involvement; in 10% (stage IV) the bone marrow and/or central nervous system are infiltrated. Histopathologically, tumours consist of sheets of small or medium-sized round cells containing round or oval-shaped nuclei and interspersed with 'host' histiocytes (the so-called 'starry-sky' appearance, which is not specific for Burkitt's lymphoma. Immunohistological studies confirm the B-cell origin of most tumours and, because tumour cells react only with kappa or lambda light chain antisera and not both, the clonal origin can readily be demonstrated.

Table 25.2 Non-Hodgkin's lymphoma subtypes - clinical, immunological and histological features

<table>
<thead>
<tr>
<th>T-cell</th>
<th>B-cell</th>
<th>'Null' ALL (including pre-B cell)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediastinum</td>
<td>Nasopharynx</td>
<td>Bone marrow</td>
</tr>
<tr>
<td>Gut and mesentery</td>
<td>Bone</td>
<td></td>
</tr>
<tr>
<td>Jaw</td>
<td>Diffuse</td>
<td>Diffuse</td>
</tr>
<tr>
<td>lymphoblastic</td>
<td>'undifferentiated'</td>
<td>lymphoblastic</td>
</tr>
<tr>
<td>Percentage</td>
<td>30-40</td>
<td>5</td>
</tr>
</tbody>
</table>

Lower airway obstruction, when caused by non-Hodgkin's lymphoma, is much more commonly associated with T-cell disease than with other subtypes. Chest X-ray shows an anterior mediastinal mass, sometimes of an alarming size and often associated with pleural fluid. The trachea may be compressed to a diameter of 1-2 mm but, since the obstruction is invariably intrathoracic, tracheostomy is contraindicated. The dangers of anaesthesia or even sedation are such that biopsy is often a hazardous undertaking. Bone marrow or pleural fluid aspiration shows lymphoblasts and yields a diagnosis in 20-30% of cases but sometimes urgent, empirical chemotherapy (vincristine and prednisone) must be started without delay; patients should be observed, day by day, and mediastinotomy or thoracotomy carried out as soon as acceptable relief of obstruction has been achieved. Hodgkin's disease is the most important differential diagnosis. For 24 hours before and around one week after the start of
chemotherapy, patients should receive allopurinol and undergo alkaline diuresis to reduce the risk of urate nephropathy. They should also be monitored carefully for hyperkalaemia and hyperphosphataemia - the other two major features of the life-threatening 'tumour lysis syndrome'.

Since the introduction of combination chemotherapy in the early 1970s, the prognosis for children with non-Hodgkin's lymphoma has improved dramatically. Children with stages I and II (clinically localized) disease have an 80+%, expectation of disease-free survival. In an American Children's Cancer Study Group (CCSG) study, the 'COMP' regimen (cyclophosphamide, oncovin, methotrexate and prednisolone) was found to be superior to a more complex multidrug rotating schedule (LSA$_2$L$_2$) (Anderson et al, 1983). Two randomized studies, including one in the UK (Murphy and Hustu, 1980; Mott, Eden and Palmer, 1984) have shown that local irradiation, to the site of initial 'bulk' tumour, does not improve disease-free survival, a finding that is not surprising in view of the fact that local recurrence of non-Hodgkin's lymphoma is the exception rather than the rule. Most current protocols aim at reducing the duration of chemotherapy to around six months and early results (Murphy et al, 1983) are encouraging.

Stage IV B-cell disease is more difficult to eradicate, although some encouragement can be derived from excellent early results using 'massive chemotherapy' (Philip et al, 1984). Autologous bone marrow transplantation is needed to aid haematological recovery after massive therapy and the results of such treatment may, in part, be due to the use of monoclonal antibodies which can be used to 'purge' the reinfused marrow of any residual tumour. Eradication of central nervous system disease is the outstanding problem in the management of non-Hodgkin's lymphoma. Methods of central nervous system 'prophylaxis' that seem successful in 'common' acute lymphoblastic leukaemia are far less successful in B-cell malignancy, perhaps because of the high 'growth fraction' of these tumours.

Recurrences of non-Hodgkin's lymphoma occur relatively early, and the child who reaches 2 years off treatment can almost always be considered cured. Thus a 'typical' patient with head and neck non-Hodgkin's lymphoma is a 7-10-year-old boy with a brief history of pharyngeal obstruction and no clinical evidence of metastatic spread; his symptoms resolve within a few days of starting combination chemotherapy with a COMP-type regimen which continues for 6 months. Between courses he is able to attend school and undertakes almost all normal activities. He has no surgery or radiotherapy. Hair regrows within a few months of stopping treatment and there are not other obvious after effects of therapy although he will probably be subfertile. The chance of disease-free survival is around 90%.

**True histiocytic lymphoma ('malignant histiocytosis')**

This rare condition, quite distinct from Langerhans cell histiocytosis, most commonly presents with cervical node enlargement. In some cases, 'waxing and waning' of node swelling may induce a false sense of security, by suggesting an infectious aetiology. Liver, spleen, lungs, bones and central nervous system may be involved and bone marrow infiltration is characterized by pancytopenia, because the malignant cells phagocytose normal marrow components. Treatment is with combination chemotherapy and central nervous system 'prophylaxis'. At least 50% of patients are curable.
Hodgkin's disease

Hodgkin's disease accounts for approximately 5% of paediatric cancer, occurring as frequently as non-Hodgkin's lymphoma and with an annual incidence of approximately 7 per 10^6 per year. The disease is rare below the age of 5 years and there is a male predominance (M:F, 1.7:1.0), especially in the younger ages. Supradiaphragmatic, particularly neck, disease is the most common presenting site, as in the adult practice - usually as painless lymphadenopathy. Lymphocyte-predominant histology is more common than in adults although the majority of cases still fall into nodular sclerosing or mixed cellularity subtypes; lymphocyte-depleted Hodgkin's disease is rare in children in the UK.

The Ann Arbor staging system maintains its relevance for paediatric Hodgkin's disease. Staging procedures echo the adult practice, although the 'pick-up rate' from bone marrow trephine biopsy is very low indeed and the interpretation of lymphograms is difficult in children due to the frequent occurrence of lymphoid hyperplasia. The staging laparotomy, with splenectomy, alters staging in approximately 30% of cases and most American groups still consider this an important procedure, accepting the small morbidity and a risk of postsplenectomy sepsis. Standard, megavoltage, extended field radiotherapy (mangle, inverted Y and total nodal irradiation) for stage IA, IIA (IIIA) disease gives high relapse-free survival figures, but significant growth stunting occurs in the axial skeleton. Many UK centres prefer to avoid laparotomy and splenectomy in children, and accept clinical staging.

Childhood Hodgkin's disease has a better overall prognosis than adult Hodgkin's disease and, in recent years, many workers have attempted to decrease the intensity of first therapy. Such workers argue that with very effective modern salvage chemotherapy, relapse after conservative therapy matters less than the infliction of extra morbidity by 'over-treatment' of the majority of patients who would never relapse. This argument runs counter to the 'traditional' approach to cancer management namely the absolute necessity for disease-free survival in order to obtain high overall survival, but the good salvage capacity of chemotherapy in childhood Hodgkin's disease is an exceptional situation. The consequence of these arguments has been moves towards involved field radiotherapy, but usually supplemented by chemotherapy (Sullivan et al, 1982; Tan et al, 1983). In recent years, the St Bartholomew's/Royal Marsden Children's Solid Tumour Group has also explored chemotherapy together with a less than radical dose, involved field radiotherapy for early stage Hodgkin's disease (Robinson et al, 1984), with excellent disease-free and 95% overall survival rates. The logic of systemic therapy is of course greatest in a clinically staged population. However, as chemotherapy has an unquantifiable late morbidity (for example possible infertility and second malignancy), some groups have returned to a therapeutic recommendation from the past, that is for pathologically staged I-IIA disease, involved field radiation and careful follow-up only (Tan et al, 1983; Robinson et al, 1984). This real challenge to the 'traditional' approach to cancer may have more proponents in the future.

Chemotherapy alone is employed for children presenting with more advanced stages of disease and MOPP (mustine, vincristine, procarbazine, prednisolone) remains the most commonly used regimen, although vinblastine substituting vincristine and chlorambucil substituting mustine represent minor variants. Such chemotherapy causes complete remission in 80% of patients of whom two-thirds will enjoy prolonged disease-free remission and probably cure. Relapse after radiotherapy alone is not disastrous as patients can often be
'salvaged' by chemotherapy. Relapse after chemotherapy is more serious but improved 'second-line' regimens such as 'ABVD' or Adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine, are now available and can cure some patients. In fact, early results of studies in children and in adults indicate that 'ABVD' is very effective in newly diagnosed patients and, because 'ABVD' contains neither an alkylating agent nor procarbazine, it is less likely than 'MOPP' to produce infertility or 'secondary' leukaemia. If these impressions are confirmed, 'ABVD' and variants are likely to replace 'MOPP' as first-line treatment for Hodgkin's disease in children.

_Pseudolymphoma_

While minor degrees of cervical lymphadenopathy associated with upper respiratory tract and tonsillar infections are accepted as part of the normal childhood spectrum, there are other infections causing greater degrees of cervical lymphadenopathy, for example infectious mononucleosis, or AIDS. Preservation of normal lymph node architecture, albeit with follicular hyperplasia, readily allows distinction from malignant conditions.

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) is a non-malignant disease predominantly of Negro children who develop large, sometimes massive, cervical lymphadenopathy (Rosai and Dorfman, 1972). Other node groups are less frequently involved. Clinically, the condition presents indolently with usually bilateral, painless and often gross cervical node enlargement. Histologically, the involved lymph nodes show pericapsular fibrosis, dilated sinuses, plasma cells (often in abundance) and numerous intrasinusoidal histiocytes containing engulfed lymphocytes and other haemopoietic cells. The cause of this disease is not known and the majority of cases spontaneously remit without treatment. Deaths that occur may be due to progression of the disease locally or distantly or due to complications of a deranged immune system (Foucar, Rosai and Dorfman, 1984).

_Rhabdomyosarcoma_

Rhabdomyosarcoma is the most common variety of soft tissue sarcoma in childhood and more than one-third of cases arise in the head and neck region. There are no known predisposing factors, although there seems to be a familial association between childhood rhabdomyosarcoma and maternal carcinoma of the breast. Three-quarters of all children with rhabdomyosarcoma are aged less than 10 years at diagnosis, the sex incidence being equal and there being no racial predilection. Surgery, radiotherapy and chemotherapy all have important roles in management but the emphasis on which of the two modalities of 'local' therapy is appropriate depends on site and stage.

Tumours can arise in the orbit (commonest symptoms are proptosis and visual difficulty), anterior facial structures (painless swelling), middle ear (deafness, bloody aural discharge), nasopharynx (difficulty with phonation, upper airway obstruction), palate (painless swelling), pterygopalatine region and paranasal sinuses. When the tumour arises below a mucus-secreting epithelium, the mass may have a 'botryoid' appearance that is almost diagnostic of rhabdomyosarcoma.

The major prognostic factors are: (a) the site of the primary tumour, (b) whether or not the disease is confined to the tissue of origin and (c) its histological subtype. Thus, in one
recent study, children with 'confined' primaries, that is no evidence of extensive local, nodal or metastatic spread, had a 5-year survival of 86%, whereas children with tumour extensions outside the tissue of origin had a 5-year survival of 21% (Kingston, McElwain and Malpas, 1983). Within the head and neck region there are well-recognized relatively 'good' prognostic primary sites (orbit, parotid, anterior facial, oral cavity, larynx - all without bone erosion), and 'bad' prognostic primary sites (nasopharynx, nasal cavity, paranasal sinuses, middle ear - mastoid, pterygopalatine region, infratemporal fossae or any other sites with bone erosion). Thus, children presenting to St Bartholomew's Hospital or the Royal Marsden Hospital between 1974 and 1981 with primary orbital rhabdomyosarcoma had a predicted 5-year survival rate of 94%, whereas in the other head and neck sites survival was 50% (Kingston, McElwain and Malpas, 1983). In the same study, children with tumours of embryonal histology (the commonest variant in the head and neck region) had a better prognosis than those whose tumours were of alveolar type, as had previously been reported by others (Sutow et al, 1970; Grosfield et al, 1977). It should be emphasized that prognostic factors may vary with the type of treatment delivered. Thus, in recent studies, chemotherapy has been more intensive and successful and histology is a much less important prognostic variable.

Extension to the meninges and cerebrospinal fluid dissemination is a highly lethal complication. In a comprehensive analysis of 141 patients with tumours in head and neck sites, followed by the American Intergroup Rhabdomyosarcoma Study (IRS - Tefft et al, 1978), 57 children had primaries adjacent to the meninges (parameningeal tumours). Of these 57 children, 20 developed meningeal disease - 10 at diagnosis and 10 later on. Evidence of meningeal involvement was most commonly manifest by cranial nerve palsies and other focal neurological signs including paraparesis. Cerebrospinal fluid cytology and myelography were often diagnostic. Although plain radiology of the skull may show erosion of its base, computerized tomographic (CT) scanning is now an important staging procedure and it is well established that those children with intracranial tumour are very much more likely to develop meningeal involvement than those with little or no skull erosion. More aggressive treatment recommendations have arisen from these observations. Interestingly, none of 17 orbital rhabdomyosarcoma patients studied by Tefft et al (1978) developed meningeal disease, presumably reflecting the fact that these children rarely have evidence of spread into or beyond the optic canal.

Pretreatment staging procedures are essential to define the extent of local and distant spread. Plain X-rays of skull and CT scanning of the head delineate the extent of the primary tumour, including any intracranial extension, and are mandatory. Isotope bone scanning assists in the detection of early skull involvement by the primary tumour and of any bone metastases. Chest X-ray with CT lung scan and bone marrow examination, preferably carried out under the same general anaesthetic as the diagnostic biopsy, supplement the general physical examination for distant metastases. With parameningeal primaries, cerebrospinal fluid cell count and cytocentrifuge are absolutely necessary.

In the absence of distant metastases, a treatment programme with surgery plus or minus radiotherapy for local control, together with chemotherapy, is commenced. Although radical surgery (notably orbital exenteration) has great curative potential, orbital rhabdomyosarcoma may now be successfully managed without this mutilating procedure. Similarly, other anterior facial sites may also be managed, with a very high local control rate, without radical surgery. Unfortunately, the poor prognostic sites, where local control is much
less easily achieved with chemotherapy and radiotherapy, are also much less easily amenable
to surgery, although the opinion of a specialist head and neck cancer surgeon is always
relevant.

Local control is achieved by radiotherapy in a high proportion of cases except in those
with extensive involvement of the base of skull. Although, following a decade of experience
with a broad dose range, conventionally fractionated total doses above 55 Gy have been
recommended, it now seems likely with modern chemotherapy that doses of 50-55 Gy are
sufficient for local control of bulky disease and 40-50 Gy for control of microscopic disease.
Because of the higher normal tissue morbidity, lower doses are used for infants. For sites
where local control is known to be particularly difficult, individually planned boosts (which
may involve brachytherapy) may be appropriate. Particularly careful radiotherapeutic
technique is necessary to minimize normal tissue morbidity. These days, chemotherapy is
often used as initial treatment. Responses are often impressive, but the initial radiotherapeutic
volume should cover the whole tumour volume as assessed by CT scanning and other imaging
procedures carried out at the time of diagnosis. The final 500-1000 cGy are then delivered
through reduced portals. Where tumours are superficial, electron therapy is preferred because,
compared with photons, normal tissues are relatively 'spared'.

Results of analysis of IRS parameningeal patients, with their high incidence of fatal
meningeal relapse (Tefft et al, 1978), led to the recommendation that the skull base should
receive higher doses of radiotherapy and that radiation 'neuraxis prophylaxis' was required.
(Since the aim is to prevent the growth of occult tumour that is actually present in a
proportion of cases, the term 'central nervous system-directed therapy' is preferred.) Indeed,
the IRS group have reported that with such 'central nervous system-directed therapy' a
meningeal relapse rate of 35% is reduced to 7%. In the UK, meningeal relapse has been
relatively uncommon - a paradoxical finding not easily explained (Kingston, McElwain and
Malpas, 1983) - although relapse in the primary site around the skull base was much more
common. Our current recommendations are for maximal dose radiotherapy by an appropriate
and usually individualized technique with whole cranial radiotherapy to a prophylactic dose
(25-30 Gy) where there is CT scan evidence of intracranial tumour mass or other evidence
of meningeal disease (usually positive cerebrospinal fluid cytology). Though neither agent is
particularly active against systemic tumour, intrathecal methotrexate and cytosine arabinoside
can reduce the numbers of malignant cells in cerebrospinal fluid, and occasionally eradicate
them.

Systemic chemotherapy has greatly improved the overall survival of patients with
rhabdomyosarcoma at all sites both because of a reduction in the incidence of distant
metastases and an increase in local control rates of the primary tumours. To date, the triple
drug regimen 'VAC' (vincristine, actinomycin D and cyclophosphamide), given as bolus
injection once every 3 weeks in moderately myelosuppressive doses, has given the best
results. The treatment programme for a child with an 'unresectable' tumour often starts with
chemotherapy for 6-12 weeks, then radiotherapy to the primary site, followed by more 'VAC'
treatment. Although no good studies of the value of 'maintenance' therapy have been carried
out, chemotherapy usually continues for at least one year. The addition of doxorubicin
(Adriamycin) to 'VAC' has not led to improved survival despite being an active agent in
rhabdomyosarcoma. Other agents currently under study include the epipodophyllotoxin VP16,
cisplatin and high dose alkylating agents - especially melphalan and isophosphamide. The
prognosis for patients with detectable metastatic disease at diagnosis (stage IV) is very poor with 'VAC' alone or 'VAC' plus local irradiation, and experimental approaches similar to those used for stage IV neuroblastoma patients, such as consolidation with high dose melphalan alone or high dose melphalan plus total body irradiation, are currently under study.

The alkylating agents are now known to be relatively potent leukaemogens and are highly likely to produce infertility, especially in males. The early IRS studies showed the efficacy of two-drug (vincristine and actinomycin D) adjuvant therapy for early stage tumours and it is likely that cyclophosphamide will be omitted in future protocols for these 'good risk' patients. By contrast, in 'poor prognosis' parameningeal tumours it seems appropriate to try to find more effective regimens than 'VAC' in an attempt to improve both local and metastatic control. Because of their particularly poor prognosis and evident widespread disease, newer combination regimens are most likely to be tried first on children with stage IV disease. If effective in this context, similar regimens may be used on children with non-metastatic, but 'poor risk', tumours. If high complete response rates can be achieved, it may be possible to reduce the high doses of radiation which, in young children, lead to significant late effects.

The long-term goal of the therapist is to develop more effective therapy regimens that have less short- and long-term effects than those currently in use. In this respect, both alkylating agents and irradiation are under scrutiny.

**Neuroblastoma**

This tumour, derived from cells of the neural crest, can originate in the sympathetic neural chain, including the cervical portion, or in the adrenal gland. Around 100 new cases per annum are diagnosed in the UK, some 7-8% of all malignant disease in childhood. A closely related tumour - the olfactory neuroblastoma ('aesthesioblastoma') - is of particular concern to otolaryngologists and is discussed separately. Although recent studies showing amplification of an oncogene designated 'n-myc', may well have a bearing on tumour progression (Schaub et al, 1984), the pathogenesis of neuroblastoma is ill-understand.

Head and neck primaries account for only 5-10% of all neuroblastomata; 60-70% of tumours arise in the abdomen, one-half in the adrenal gland and one-half in the abdominal portion of the sympathetic chain; 15-20% are of cervical or thoracic origin and the remaining 5-10% arise in the pelvis. Boys are more commonly affected than girls; the median age at diagnosis is 3-4 years and some tumours are congenital. Primaries arising from the cervical sympathetic chain usually present when parents note a painless, gradually enlarging mass in the side of the neck. Differential diagnosis includes various causes of lymph node enlargement, cystic hygroma, meningomyelocoele and branchial cyst. Sometimes, there is upper airway obstruction or evidence of spinal cord compression resulting from a 'dumb-bell' intervertebral extension. Rare presentations include ipsilateral Horner's syndrome with or without iris heterochromia, opsoconus-myoconus (the so-called 'dancing eyes syndrome') and diarrhoea due to hypersecretion of vasoactive intestinal polypeptide. With cervical primaries, regional lymph nodes are rarely enlarged or involved. By contrast, metastatic spread from an abdominal primary to cervical nodes, most characteristically Troisier's node, is relatively common; under these circumstances, airway obstruction rarely occurs. Primary intracranial tumours, now more commonly known as 'primitive neuroectodermal tumours', are almost
always localized to one cerebral hemisphere and present with signs of raised intracranial pressure.

Elevated excretion of vanillylmandelic acid and homovanillic acid or their metabolites occurs in the urine of over 90% of patients with neuroblastoma. As a result, sweating is a relatively common symptom and catecholamine-induced hypertension occurs in around 10% of cases. Although usually made by histological examination of material obtained after biopsy or excision of primary or secondary tumour, the diagnosis is virtually assured if significantly elevated levels of urinary vanillylmandelic or homovanillic acids or dopamine are associated with the presence of tumour cells in bone marrow (especially if these cells react with one of several antineural monoclonal antibodies now available) or with characteristic radiological findings (Kemshead and Pritchard, 1984). Histologically, the tumour is classified as a 'small round-cell' tumour which is difficult, without other distinguishing features, to differentiate from lymphoblastic leukaemia/lymphoma or undifferentiated sarcoma. By light microscopy, however, the presence of intercellular fibrillary material and ganglion cells are virtually diagnostic, while at the ultrastructural level the identification of neurosecretory granules clinches the diagnosis.

Investigations at diagnosis relate to possible sites of spread and include multiple bone marrow aspirates and trephine biopsies, bone scan, penetrated chest X-ray (seeking paraspinal node involvement - parenchymal lung deposits are rare) and abdominal ultrasonography or CT scan (to exclude liver metastases). Because of its simplicity, the Children's Cancer Study Group staging system (Table 25.3) (Evans, D'Angio and Randolph, 1971), rather than the TNM classification system is most commonly used. Cervical tumours are usually classified as Evans stage I or stage II. The reason for the less aggressive behaviour of supradiaphragmatic tumours compared to their abdominal counterparts, most of which are stage III or IV, is uncertain although a higher proportion of cervicothoracic than abdominal tumours have a more 'mature' histological appearance (ganglioneuroblastoma). Other favourable prognostic features at diagnosis include young age, low levels of serum ferritin and neuron-specific enolase (Zelter et al, 1983), absence of amplification of the oncogene $n\text{-myc}$ and absence of local lymph node involvement (Kemshead and Pritchard, 1985). Occasionally, an infant under 6 months of age presents with a small primary tumour and metastatic disease in liver and/or bone marrow and/or subcutaneous tissues, but no bone or lymph node deposits. At one time such infants were 'successfully' treated with repeated doses of vitamin B$_{12}$, but it is now appreciated that this form of neuroblastoma, known as 'stage IVS' (Evans, Chatten and D'Angio, 1980), commonly undergoes spontaneous regression.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumour confined to organ of origin and completely excised</td>
</tr>
<tr>
<td>II</td>
<td>Tumour extends outside organ of origin but does not cross midline; lymph nodes may be involved</td>
</tr>
<tr>
<td>III</td>
<td>Tumour extends outside organ of origin and crosses midline: lymph nodes may be involved</td>
</tr>
<tr>
<td>IV</td>
<td>Metastases</td>
</tr>
<tr>
<td>IVS</td>
<td>See text</td>
</tr>
</tbody>
</table>

From Evans, D'Angio and Randolph, 1971.
Most cervical tumours are localized at diagnosis. Surgery is often indicated first in these cases and should include removal of a representative sample of regional lymph nodes, even if they appear normal. Subsequent management of each patient is individualized and dependent on prognostic variables, but some guidelines can be suggested. If complete macroscopic resection is achieved, no further therapy is given as, ironically, occult micrometastases is unusual in stage I and II neuroblastoma. If macroscopic disease remains, adjuvant chemotherapy might be advised if the child is over 2 years of age or if the concentrations of serum ferritin or neuron-specific enolase are raised. Lymph node involvement is considered by the authors to be an absolute indication for chemotherapy (Ninane et al, 1982).

When unresectable (stage III) or metastatic (stage IV) disease is present, as is the case in a majority of children with abdominal tumours and occasionally with cervicothoracic primaries, initial treatment is with chemotherapy. The regimen most often used in Europe at the time of writing is known by the acronym 'OPEC' (oncovin, cisplatin, epipodophyllotoxin (VM26) and cyclophosphamide) (Shafford, Rogers and Pritchard, 1984), while in the USA the 'COD' regimen (cyclophosphamide, oncovin, dacarbazine (Finklestein, Klemperer and Evans, 1979) is more commonly used. Most patients respond initially to chemotherapy and, if the response is sufficiently good, delayed surgical excision of the primary tumour is undertaken. Because of the nephrotoxicity, leading to a reduced glomerular filtration rate (GFR), and ototoxicity (high tone hearing loss) of cisplatin, a maximum of 8-12 courses of OPEC can be given. The majority of children with stage III and IV disease are not cured by OPEC and surgery but, nevertheless, treatment seems worthwhile in that remission often lasts over a year (median 15-18 months in one recent UK series, Shafford, Rogers and Pritchard, 1984) with good ‘quality of life’ and because some 20-30% of children (40-70% of stage III and 10-25% of stage IV) are long-term disease-free survivors.

Although regional radiation therapy has often been used in the past, there is little evidence that it adds to surgery and chemotherapy in the curative treatment of neuroblastoma. However, there is no doubt of its value in the management of bone pain, proptosis and other complications during the terminal phase of metastatic disease.

Currently, major efforts are underway to design more effective 'induction' chemotherapy regimens and to investigate the use of high dose chemotherapy or chemoradiotherapy consolidation (including total body irradiation as a systemic agent), in combination with autologous or allogeneic bone marrow transplantation (August et al, 1985). High dose melphalan therapy, combined with autologous bone marrow transplantation (Pritchard, McElwain and Graham-Pole, 1982) has, for instance, increased the disease-free survival time in a current, randomized clinical trial. Another promising new approach is the use of 'targeted' radiation therapy using meta-iodobenzylguanidine (an adrenaline analogue) as a vector for the radioisotope $^{131}$I.

For children with stage I and II tumours, the prognosis is reproducibly good (5-year survival of 90+% and 80+%, respectively). Recurrences usually occur within 2 years of diagnosis so follow-up can be relaxed after this time. Survivors of advanced disease with cisplatin-induced hearing loss are greatly helped by the use of high frequency hearing aids (see below).
Aesthesioneuroblastoma (olfactory neuroblastoma)

This rare tumour, thought to arise from the embryonal olfactory placode, is clinically distinct from neuroblastoma. It occurs more commonly in males than females, is rare in black races and has a broad peak incidence in the second to fourth decades of life (Bailey and Barton, 1975), although cases have been recorded in children as young as 4 years. Presentation is with nasal obstruction sometimes with epistaxis, rhinorrhoea, epiphora and, rarely, distortion or loss of sense of smell. Because of the slow natural history, symptoms may have been present for several months before diagnosis. If the base of skull is invaded, there may be headache, diplopia or a malar mass (Lewis et al, 1965).

Histopathologically, the tumour shows features similar to neuroblastoma but can, nevertheless, easily be misdiagnosed (Oberman and Rice, 1976). Small round cells are set in a neurofibrillary matrix with pseudo-rosette formation and, rarely, true rosettes. Electron microscopy reveals neurosecretory granules and tumour cells may stain positively for dopamine beta-hydroxylase and catecholamines. There is no systematic study of urinary catecholamine excretion but, although increased homovanillic acid/vanillylmandelic acid excretion has been reported in a single case, the frequency is probably lower than in neuroblastoma. Differential diagnosis is from other malignant tumours especially rhabdomyosarcoma, non-Hodgkin's lymphoma, nasopharyngeal carcinoma and glioma, and benign masses such as meningocoele, encephalocoele and hydroencephalocele.

The staging system suggested by Kadisch, Goodman and Wang (1976) may be helpful for prognosis and treatment planning, but has not yet won general approval. Local invasion is usually too extensive to permit complete surgical removal and metastasis occurs in up to 60% of cases, particularly to cervical lymph nodes, lungs and bones. Tumour extension into the frontal lobes, best delineated by CT scanning, can occur but seeding into the cerebrospinal fluid is rare.

Radiation therapy with or without surgery gives a local control rate of 60-70%. Though no formal dose-response studies have been carried out, doses of at least 60 Gy are usually recommended (Ahmad and Fayos, 1980). There is sufficient evidence of the chemoresponsiveness of aesthesioneuroblastoma (Wade, Smith and Johns, 1984) to justify the use of chemotherapy in every case. Response rates to single agents such as vincristine, cyclophosphamide and dacarbazine are similar to those achieved in neuroblastoma so combinations, such as 'OPEC' or 'COD', are now recommended. With surgery and radiotherapy alone, 5-year survival is around 60-70%, with half of these patients being disease free. There is hope that, with chemotherapy, results will be better although it should be emphasized that at least 10 years follow-up is needed before cure can be assured.

Nasopharyngeal carcinoma

In a series of 248 patients presenting to the Royal Marsden Hospital (London) with nasopharyngeal carcinoma, six patients (2.4%) were less than 15 years of age, 10 (4%) less than 20 and 28 (11%) less than 30 years of age (Lederman, 1961). In North America, the age incidence curve for nasopharyngeal carcinoma is bimodal with a first (albeit smaller) peak incidence between 15 and 25 years (Greene, Fraumeni and Hoover, 1977). This bimodal incidence has also been observed in Puerto Rico (Morales et al, 1984) and several other
countries (India, Israel, Tunisia, Greece, Kuwait), but there is no early peak in people of Chinese extraction. The male predominance of nasopharyngeal carcinoma, so obvious in the adult population, is much less apparent in childhood. The very much higher incidence of nasopharyngeal carcinoma in Hong Kong Chinese, southern China and south-east Asian countries, compared with that encountered in the West, is attributed to racial predisposition, smoked and salted dietary fish and Epstein-Barr virus infection (Ho, 1978), but is mainly among adults. Jenkin et al (1981) pointed out that the aetiology of the disease in children and young adults may be different from that encountered in later life. However, Naegeli et al (1982) demonstrated Epstein-Barr virus antibody titres suggestive of infection and Epstein-Barr nuclear antigen-positive carcinoma cells in seven American children with nasopharyngeal carcinoma. Furthermore, the pattern of spread and prognosis of nasopharyngeal carcinoma in childhood and adults appear to be similar.

The clinical presentation and pattern of spread is similar in all ages. The primary nasopharyngeal carcinoma may be 'silent' and the disease presents clinically with upper deep cervical neck node masses at a time when mirror examination of the nasopharynx is negative. Indeed, symptoms and signs may appear only when the primary tumour has spread to involve adjacent structures, often at the base of skull. Lesions of the lateral wall may be associated with Trotter's triad of symptoms: (a) hypoacusia; (b) paresis of the soft palate; (c) pain in the territory of the mandibular division of the trigeminal nerve. Larger growths may produce nasal obstruction or bleeding and a 'nasal twang' to the voice. Invasion of the base of the skull leads to severe pain which may presage cranial nerve paresis.

The diagnosis is made by biopsy under general anaesthesia at which time the palpable extent of the primary is assessed. The histological picture is of squamous carcinoma (often poorly differentiated) and tumours previously described as lymphoepithelioma are now recognized to be poorly differentiated squamous carcinomata. Blind adenoidal region biopsy may be positive in occult cases presenting with cervical adenopathy. Nasopharyngeal carcinoma must be distinguished from nasopharyngeal angiofibroma (see Chapter 19) and from an anteriorly sited rhabdomyosarcoma arising in the nasopharynx.

The TNM staging system for nasopharyngeal carcinoma is shown in Table 25.4. Plain skull radiology, including a submentovertical view, and CT scanning of the head and neck are essential staging procedures. In the Children's Cancer Study Group (CCSG) analysis, 41 children presented with T1, or T2 lesions, 19 with T3 and 43 with T4 lesions - indicating the high frequency of skull invasion at presentation (of great prognostic importance). In the same CCSG series, 14 cases were N0, 9 cases N1, 42 N2 and 49 N3 demonstrating the high frequency of clinically obvious node metastases at presentation (Jenkin et al, 1981). Distant metastases are present at diagnosis in only 2-3% of cases, most commonly in bone but also in lung, liver and even bone marrow. Staging investigations should therefore include bone scan, posteroanterior and lateral chest X-rays and abdominal ultrasound.

Nasopharyngeal carcinoma is not amenable to surgical attack, but as the lesion is radiosensitive, treatment is based on high dose, modern megavoltage radiotherapy. Although the world's largest experience and excellent survival results come from Ho's group (Ho, 1978) this group's radiation technique is not ideal. In particular, the dissimilarly canted nasopharyngeal and neck fields produce awkward field junctions in the region of Rouvière's node and the uppermost deep cervical nodes. The radiation technique employed and
recommended for children presenting to the Hospital for Sick Children, London, commences with the supine child in an individually made shell with a dental splint keeping the tongue downwards and the floor of the mouth low and outside the radiation portals. The orbitomeatal line (Reid's baseline) is vertical and all planning (including field junctions) is parallel or perpendicular to this plane. Planning and treatment then continue in a fashion similar to a previously published technique (Lederman and Mould, 1968). The recommended tumour dose to the nasopharynx is 55-60 Gy (50 Gy to children less than 4 years, 60 Gy to children over 12 years old), conventionally divided into 175-190 cGy daily fractions. There is no evidence that total doses of more than 50 Gy are more effective, in children and young adults, than doses in the 40-50 Gy range (Jenkin et al, 1981). Therefore, the authors avoid the 70-Gy total dosage to the nasopharynx recommended for adults by many therapists. By using a three-field boost to the nasopharynx, the incidence of treatment-induced late trismus is low. Even if clinically normal, the neck nodes down to the clavicles receive a conventionally fractionated dose of 50 Gy. A good, reproducible radiation technique for nasopharyngeal carcinoma is a technically demanding exercise.

Table 25.4 TNM staging classification of nasopharyngeal carcinoma (UICC)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour limited to one region</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour extending into two regions</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour extending beyond the nasopharynx without bone involvement</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour extending beyond the nasopharynx with bone involvement, including the cartilaginous portion of the eustachian tube</td>
</tr>
<tr>
<td>N0</td>
<td>No palpable cervical nodes</td>
</tr>
<tr>
<td>N1</td>
<td>Mobile ipsilateral cervical lymphadenopathy</td>
</tr>
<tr>
<td>N2</td>
<td>Mobile bilateral cervical lymphadenopathy</td>
</tr>
<tr>
<td>N3</td>
<td>Fixed cervical lymphadenopathy</td>
</tr>
<tr>
<td>M0</td>
<td>No metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Metastases.</td>
</tr>
</tbody>
</table>

Recently, several chemotherapeutic agents have been shown to have at least partial efficacy against this tumour. Although single agent data are scanty, there is published evidence of tumour response to the 'VAC' (vincristine, actinomycin D, cyclophosphamide) regimen and personal, albeit anecdotal, experience of response to the 'BEP' (bleomycin, the epipodophyllotoxin VP16, cisplatin) combination. Although a delay to radiotherapy of more than 3 months is not advised, combination chemotherapy is included in the treatment protocol of at least the more advanced cases presenting to the Hospital for Sick Children, London.

The careful study of adults by Ho (1978) established that prognosis related to the stage of the primary tumour (base of skull invasion being a particularly bad prognostic sign), and to neck node status (fixed, bilateral and low cervical neck nodes carrying a worse outlook than high, mobile and unilateral cervical nodes). Distant metastases are almost invariably fatal. For tumours confined to the nasopharynx, the 5-year survival was 84% and for larger primaries (but without base of skull invasion) and/or mobile, high unilateral cervical nodes the survival was 62%, but where there was more extensive nodal involvement the 5-year
survival dropped to 40%. Similarly, in a more recent American study, prognosis related directly to stage of disease at presentation, initial performance status and radiation dose received (Petrovich et al, 1985). In this adult series, failure at the primary site was common (88%) when there was invasion of the base of the skull. In the study by Ho (1978) prophylactic neck node irradiation did not add to the survival of that minority of patients with small tumours localized to the nasopharyngeal mucosa. In the study by Petrovich et al (1985), radical neck dissections did not alter the outlook for patients with advanced neck node disease.

Jenkin et al (1981) analysed the results of treatment in 119 Americans under 30 years of age at diagnosis and found overall 5-year relapse-free and overall survival rates of 36% and 51%, respectively. When tumour was confined to the nasopharynx (T1 and T2), 5-year survival was 75%. These figures are similar to those reported for adults (Ho, 1978). Jenkin et al also analysed patterns of relapse in patients whose disease was initially localized. In approximately one-third of patients there was only local recurrence while in the remaining two-thirds of cases, recurrence was outside the irradiation field. Overall, just over one-half of relapses occurred at metastatic sites. Because of this statistic and because further major improvements in irradiation techniques are unlikely, the need for more effective chemotherapy regimens is re-emphasized.

**Other carcinomata of the head and neck**

Carcinoma in other head and neck sites, for example, lip, tongue, oropharynx and larynx in childhood are fortunately very rare indeed. When localized they are treated, as in adults, by radical surgery and radiotherapy.

**Thyroid cancer**

Thyroid carcinoma is rare in children and only one or two new cases are seen at the Hospital for Sick Children, each year. Of 59 paediatric cases presenting to the Mayo Clinic, 56 were papillary and only three were follicular carcinoma - a very much higher proportion of papillary to follicular than is encountered in the adult population (Woolner et al, 1961). Of 576 cases of papillary thyroid carcinoma presenting to the United States Armed Forces Institute of Pathology (AFIP), approximately 7% occurred in patients aged 6-19 years (Mazzaferri et al, 1977). Older children are more commonly afflicted and the same female preponderance exists as in adults. Papillary carcinoma usually arises from a thyroid gland with otherwise normal parenchyma but prior exposure of the neck to radiation (mean latency 16 years, Mazzaferri et al, 1977) is a recognized predisposing factor.

Thyroid cancer presents in children, as in adults, as a painless discrete thyroid mass or, less commonly as a deep cervical chain lymph node mass (the 'lateral aberrant thyroid'). Treatment recommendations have also been similar to those for adults, here summarized and have been recently and more fully reviewed (Plowman, 1986).

Following histological diagnosis by biopsy, radical thyroidectomy - preserving the recurrent laryngeal nerves and at least one parathyroid gland - is the preferred therapeutic procedure. All involved lymph nodes must be excised from one or both deep cervical chains and, if CT scan shows that mediastinal nodes are involved, mediastinal exploration to clear
such nodes is indicated. Formal block dissection of the deep cervical chain is not routinely recommended but is occasionally essential.

Following surgery, a normal thyroid remnant is almost invariably demonstrable on radioiodine tracer scanning. This iodine-avid tissue prevents the demonstration of less iodine-avid residual tumour deposits. An ablation dose of radioiodine destroys this high-avidity remnant of normal thyroid tissue and 3 months later a whole body $^{131}$I scan should reveal iodine-concentrating metastases, if present.

Papillary thyroid carcinoma in young patients is very slow growing and relapse may occur 10-20 years after diagnosis. The initial site of recurrence is most commonly in the deep cervical node chains, then in the mediastinal nodes followed by lung metastases. The overall incidence of nodal metastases in the Mayo Clinic papillary carcinoma series (all ages) was 39%, but the histological findings in the radical thyroidectomy specimen proved a strong prognosticator for subsequent nodal relapse. Thus, 32% of those patients with intrathyroidal tumours later developed nodal disease, whereas 57% of those with extrathyroidal disease later developed further nodal metastases (Woolner et al, 1961). The vast majority of papillary carcinomata actually exhibit mixed papillary and follicular architecture, although a prominent solid papillary component is more common in younger patients (Woolner et al, 1961). The microscopic architecture (notably the demonstration of a follicular element) is of relevance to subsequent radioiodine tracer studies in the follow-up of these patients and of radioiodine therapy for relapse.

Following radical thyroidectomy and radioiodine ablation of the thyroid remnant, follow-up of the patient is by clinical examination (with particularly careful palpation of the neck), augmented by chest X-rays and iodine profile scans - decreasing in frequency with time. Between radioiodine profile scans the patient is placed on fully TSH suppressive doses of thyroid hormone. Our recommendations for serial radioiodine profile scans in papillary tumour follow-up have been based on the extensive studies of Pochin (1967) who found that over 80% of differentiated thyroid cancer concentrated iodine and: "... contrary to views sometimes expressed, we have found tumours that were predominantly papillary in structure to be as likely to develop uptake and respond to treatment as those that were predominantly follicular ...'. The follicular and colloid component of a papillary tumour allows a prediction concerning iodine concentration.

More recently, serum thyroglobulin estimations have been helpful in the follow-up of patients with differentiated thyroid cancer. Serum thyroglobulin is secreted in small quantities by the cells of many follicular cell origin cancers and Black et al (1981) reported that in radically ablated patients or in those on fully TSH-suppressive doses of thyroid hormone, serum thyroglobulin estimations provided a marker for relapse detection. Since then, it has been shown that positive radioiodine tracer scans may be found in the absence of detectable serum thyroglobulin and also that circulating thyroglobulin autoantibodies may invalidate the thyroglobulin assay (Grant et al, 1984). Thus, while serum thyroglobulin estimations complement radioiodine scans in the follow-up of thyroid cancer patients, they do not reliably substitute.

When a patient with papillary thyroid carcinoma relapses in cervical or mediastinal nodes, a radioiodine tracer study must precede surgical resection of all affected nodal disease.
In those cases with a positive preoperative tracer study, a postoperative therapy dose(s) of radioiodine is given. In patients with distant metastases (usually lung), a tracer dose study will demonstrate whether or not the recurrent tumour will concentrate and be amenable to treatment by radioiodine.

The overall prognosis for patients with papillary carcinoma of the thyroid (all ages) is good. In a predominantly young adult population analysed by the AFIP, 10-year survival was 95% (Mazzaferri et al, 1977). In this particular series younger patients clearly had a better prognosis than older patients. Also noteworthy is the apparently paradoxical finding of a higher incidence of neck node recurrences in young patients than in older patients and yet better survival among younger patients. This must be due to the high curability by surgery and radioiodine of neck node recurrences. Mazzaferri et al also demonstrated a significant survival advantage among patients undergoing radical thyroidectomy, radioiodine ablation and receiving fully TSH-suppressive doses of thyroid hormone replacement compared with patients undergoing subtotal thyroidectomy.

In a series of 38 children presenting with differentiated thyroid cancer to the Gustav Roussy institute, Tubiana, Schlumberger and Rougier (1985) found an 88% survival at 15 years. However, it should be noted that there were later two extra deaths from thyroid cancer after more than 20 years of follow-up, demonstrating the long natural history of this disease. Tubiana et al concluded that there was justification for a treatment programme similar to that used in adults. At the Hospital for Sick Children, London, this viewpoint is subscribed to. A policy including radical thyroidectomy, radioiodine ablation and assiduous follow-up has been implemented and is recommended for all patients with extrathyroidal disease.

However, the recommendation for such an aggressive treatment regimen in young patients presenting with papillary cancer limited to the thyroid gland is more contentious and warrants further discussion: if a young patient with an intrathyroidal papillary cancer has the excellent prognosis indicated by Mazzaferri et al (1977), then why is it necessary to perform a radical thyroidectomy and radioiodine ablation - neither of which is without at least potential risk - and then to commit the patient to life-long thyroid hormone tablets? One school of thought argues that the best survival results in the Mazzaferri series were in the radically ablated patients, that papillary thyroid cancer is well recognized to be a multifocal disease, that modern thyroid surgery is relatively safe and lengthy experience has also proved ablative doses of radioiodine to be safe. Added to all this are the late relapses and deaths from thyroid cancer in the long-term follow-up of the less aggressively treated children in French series (Tubiana, Schlumberger and Rougier, 1985). The recommendations at the Hospital for Sick Children, London, for children with papillary carcinoma limited to the thyroid at presentation can be summarized as follows: after conservative thyroideectomy no radioiodine is administered, but daily TSH-suppressive doses of thyroxine are given to suppress the normal thyroid remnant. Clinical follow-up with careful palpation of the neck may be supplemented with CT scanning of the neck for nodal or thyroid bed recurrence. Thyroglobulin measurements (on thyroid replacement) are made. At the time of any recurrence, normal thyroid gland remnant ablation must usually precede therapeutic radioiodine treatment of disease but the 'pace' of this disease is sufficiently slow for the resultant delay in treatment not to be a practical problem.
Survivors of thyroid carcinoma developing during childhood and treated with radioiodine appear to suffer no discernible infertility or genetic damage (Sarkar et al, 1976).

**Bone tumours**

**Chordoma**

Chordomata are rare malignant tumours developing from the vestigial remnants of the notochord. Although they most commonly occur in the sacrococcygeal region, 39% of cases occur in the cranial region - particularly arising from the clivus (Utne and Pugh, 1955). Interestingly, there is a tendency for cranial cases to occur in younger age groups and there is a male predominance.

Macroscopically, chordomata are lobulated, apparently encapsulated growths and of mucoid appearance. Microscopically, large, vacuolated (physaliferous) cells are often arranged in chords in a background of mucus. Mitotic figures are sparse.

Clival chordomata usually present with a lengthy history of headaches or with focal neurological signs. Posterior extension leads to brainstem pressure while anterior extension will lead to obstruction of the nasopharynx or bleeding.

Plain skull X-rays usually show destruction of the clivus perhaps extending rostrally to involve the sella turcica or laterally to involve the sphenoid or petrous temporal bones. Computerized tomographic and magnetic resonance imaging (MR) scanning will delineate the tumour more completely.

While radical surgical resection is the treatment of choice for chordomata, this is rarely possible for intracranial lesions. High dose radiotherapy is certainly palliative and capable of causing tumour regression (Phillips and Newman, 1974).

There does appear to be radiation dose-effect relationship and, in the series of Phillips and Newman (1974), only those cases receiving high radiation doses remained disease free at 5 years. However, it must be remembered that clivus chordomata abut the central nervous system and meticulous radiation technique is required to achieve the necessary high dosage safely.

The longest survivors of clival primary chordomata are those patients amenable to surgery (including reoperation for recurrences, where possible) as well as high dose radiotherapy (Phillips and Newman, 1974). As metastases occur only in around 10% of cases, local control is of paramount importance.

**Ameloblastoma**

The ameloblastoma is a rare tumour of the enamel organ stem cells. It usually presents as a cystic mass, much more commonly in the mandible than the maxilla. On section there may be both cystic and solid components. Surgical resection is indicated but incomplete excision frequently leads to local recurrence. Thus wide surgical clearance is optimal.
treatment with radiotherapy reserved only for failure to achieve microscopically clear margins. Metastatic spread is exceedingly rare.

**Osteogenic sarcoma**

Osteogenic sarcoma of the craniofacial bones is rare comprising 7% of all cases of the disease. In one series, 45 of 145 cases of craniofacial osteogenic sarcoma occurred in patients below 20 years of age and the mandible followed by the maxilla were the commonest primary sites (Huvos, 1979). Clinically, such lesions present as swellings which may or may not be painful. Radiographically, abnormal areas of osteosclerosis or lysis are present and 'sunray' spiculation, emanating from the cortex may be apparent. The differential diagnosis includes osteomyelitis, reactive osseous lesions (for example ossifying fibroma, fibrous dysplasia) and other bone tumours. The lungs are the commonest site of metastatic spread and CT lung scanning, as well as 99mTc MDP bone scanning, is important in the staging of all cases.

In general, osteogenic sarcoma arising in craniofacial bones has a very poor prognosis (Caron, Hajdu and Strong, 1971), although for patients with resectable mandibular lesions the 5-year survival approaches 35% (Curtis, Elmore and Sotereanos, 1974) and published series predate the advent of more effective chemotherapy regimens.

Undoubtedly, radical surgical resection is the mainstay of treatment and hemimandibulectomy or radical maxillectomy would be appropriate operations. For unresectable lesions, high dose radiotherapy is delivered with a lesser expectation of local control. Recently, two randomized clinical trials have demonstrated the efficacy of adjuvant chemotherapy in improving the survival in childhood osteogenic sarcoma (Eilber and Eckardt, 1985; Link et al, 1986) and children with this condition would now enter chemotherapy study protocols.

**Ewing's sarcoma**

This primary bone malignancy is more radioresponsive than osteogenic sarcoma. Although surgical resection is recommended when the bone is 'dispensable', local control rates are high with radical radiotherapy combined with adjuvant chemotherapy (Pereze, Tefft and Nesbit, 1981). The most active drugs - vincristine, actinomycin D, doxorubicin (Adriamycin) and cyclophosphamide - are usually given in triple combination ('VAC' or 'VAdriaC') and can be used prior to surgery or irradiation to improve local control. Chemotherapy has also substantially increased the overall survival chance for patients presenting with localized disease (Rosen et al, 1981), but for those with metastases the prognosis, even when there is an initial response, is still poor (10-20% 2-year survival).

**Salivary gland tumours**

Of all salivary gland tumours 2-4% occur in patients under 16 year of age (Castro et al 1972; Krolls, Trodahl and Boyers, 1972). Fortunately, the majority of salivary gland swellings in children are not neoplastic and the majority of the true neoplasms are benign.

There were 430 paediatric cases in the series of salivary swellings analysed by the American Armed Forces Institute of Pathology (AFIP), (Krolls, Trodahl and Boyers, 1972).
Of these cases 262 were non-neoplastic and, of these, mucocoeles comprised the majority (185 cases). The clinical picture is of a small, smooth, unilocular and painless submucosal swelling. Mucocoeles only occur in the minor salivary glands in the mouth and the lower lip is the most common location. The condition appears to result from an injury to the secretory duct of a minor salivary gland and this tends to occur at the times of teething (both primary and secondary dentition). The other non-neoplastic salivary swellings observed in the AFIP series affected both major and minor salivary glands and were mainly inflammatory lesions - most commonly a non-specific sialadenitis, but also occasionally caused by specific diseases such as tuberculosis or sarcoidosis (Krolls, Trodahl and Boyers, 1972). Mumps is, of course, grossly under-represented in this series from a tertiary referral centre.

In the same analysis, there were 168 true neoplasms of the salivary glands, the majority (124 cases) occurring in the parotid gland (Krolls, Trodahl and Boyers, 1972; Jaques, Krolls and Chambers, 1976). Ninety of 124 parotid neoplasms were benign, including 45 pleomorphic adenomata and 40 vascular tumours.

**Pleomorphic adenoma**

Pleomorphic adenoma in children, as in adults, occurs predominantly in the parotid gland and more commonly occurs in females, the sex ratio being 2:1 in one series (Malone and Baker, 1984). The tumour occurs in teenagers more commonly than young children. In the experience of Malone and colleagues only 10% of cases occurred in the submandibular gland. As in adults, presentation is usually with a painless and very slowly enlarging mass and conservative surgery is recommended. In the AFIP series of 45 cases, there was local recurrence in six cases and further surgery was needed (Jaques, Krolls and Chambers, 1976). In the Ann Arbor experience, 18 previously untreated patients were treated by conservative parotidectomy with preservation of the facial nerve and all remained disease free at the time of reporting (Malone and Baker, 1984). However, these authors also reported 12 children referred to them with recurrent tumour following surgery elsewhere and only one of these patients had had surgery as major as superficial parotidectomy. Malone and Baker (1984) made the important points that not only is local excision followed by a high rate of local recurrence that is not so easy to cure with nerve sparing 'second-look' surgery, but also that there is a real chance of the later development of true malignancy. In their own series two of the 12 children with local recurrence developed distant metastases as a result of carcinoma ex-pleomorphic adenoma. Local recurrence of pleomorphic adenoma can occur up to 10 or more years after surgery.

The treatment of choice for pleomorphic adenoma of the parotid is parotidectomy with preservation of the facial nerve. Tumours lateral to the facial nerve or in the tail of the parotid gland are managed by a lateral (superficial) parotidectomy, while deep-sited tumours are managed by total parotidectomy with preservation of the nerve. Local excision alone or local excision and radiotherapy are inferior management schemes and wide surgical excision, as outlined above, is the optimal treatment. Similarly, local recurrences are managed by more radical surgical excisions, if necessary with sacrifice of the facial nerve. Radiotherapy is of limited usefulness in this disease and is reserved for the rare instance where radical surgery fails to produce complete microscopic clearance of disease; in this event early postoperative radiotherapy is indicated. An appositional, lateral megavoltage electron source of appropriate energy usually provides the optimal dosimetry and a conventionally fractionated prescription
of approximately 50 Gy in 6 weeks is delivered. With this technique later mouth dryness can be avoided, but some late temporomandibular joint dysfunction and mandibular ramus hypoplasia may result.

Benign pleomorphic adenomata of the submandibular gland are managed by complete excision of gland and tumour as a bloc. As with parotid lesions, preoperative incisional biopsy is to be avoided.

**Vascular tumours**

Vascular tumours are usually first noticed at birth or in infancy. They may continue to increase (occasionally rapidly) or fluctuate in size; however, later, many will spontaneously regress. Unless massive, their clinical symptomatology usually relates to their cosmetic effects. The larger ones may require surgery - usually conservative resection of the gland. These vascular tumours, although benign, also respond to low dose radiotherapy but, even with modern treatment techniques, limiting the dose to adjacent structures, radiotherapy is best avoided unless the tumour is massive (for example preventing feeding, obscuring vision and hence risking amblyopia etc). Radiotherapy is never indicated for cosmetic reasons and surgery is the preferred definitive treatment unless the operation is likely to be mutilating.

**Malignant tumours**

Of 168 paediatric true neoplasms of salivary glands assimilated for analysis by the AFIP, 54 were malignant tumours (Krolls, Trodahl and Boyers, 1972). Of these, 35 were malignant epithelial neoplasms and the rest were a heterogeneous collection of primary and secondary tumours with primary sarcoma (rhabdomyosarcoma, fibrosarcoma, anaplastic tumours) most commonly represented. Rhabdomyosarcoma arising in salivary tissue is described elsewhere in this chapter. From the Memorial Hospital series, it seems clear that undiagnosed neoplasms in the submandibular gland are more likely to be malignant than those in the parotid and the albeit rare neoplasms in the sublingual gland were all malignant (Castro et al, 1972).

Mucoepidermoid carcinoma, the commonest carcinoma of salivary tissue, accounted for 20 out of 35 cases in the AFIP series and more frequently occurred in the parotid (14 out of 20 cases; Krolls, Trodahl and Boyers, 1972). The sex incidence is equal and the peak age incidence was 10 years.

In the Memorial Hospital analysis of 288 patients (all ages) with mucoepidermoid carcinoma of the parotid, several points are worth noting (Spiro, Huvos and Strong, 1975). Mucoepidermoid carcinoma is the most common form of carcinoma encountered and usually presents clinically because of swelling; only the minority of patients experienced pain or had facial nerve dysfunction. A histological grading system (grades I-III) was found to be prognostically useful and patients with facial nerve dysfunction or positive cervical nodes were more likely to have high grade (II-III) tumours. Children were more likely to have low
grade (I) histology and, although clinically tumours were/are often mobile and discrete, histologically there is no true capsule surrounding the neoplasm. In this large study embracing all age groups, prognosis was clearly better in younger patients (Spiro, Huvos and Strong, 1975).

Treatment recommendations for childhood mucoepidermoid carcinoma are the same as in adult practice and, indeed, these apply to most true salivary neoplasms (with the exception of sarcomata and lymphomata where surgery is usually limited to biopsy). Indeed, for a well-circumscribed salivary gland swelling the histological type will usually not be known prior to definitive surgery, as both incisional or needle aspiration biopsy are to be discouraged. In general, preoperative sialography is of limited usefulness.

The recommended surgical strategy is complete removal of the neoplasm with the minimum normal tissue morbidity. The type of operation depends upon the extent of the lesion. A subtotal parotidectomy with sparing of the facial nerve is optimal if it complies with this strategy but, for more extensive growths, total parotidectomy with nerve sacrifice is necessary. Limited surgery (that is local excision) with postoperative radiotherapy is probably inferior to more radical surgery and is not recommended. Postoperative radiotherapy is indicated only where, following radical surgery, the resection margins are involved or the tumour is of high grade. Under these circumstances, postoperative radiotherapy increases the local control rate (Imperato, Weichelbaum and Ervin, 1984). Mucoepidermoid carcinoma of submandibular or sublingual glands is treated by radical gland resection, also conforming to the above strategy. Block dissection of the cervical lymph nodes is indicated either at presentation or at relapse when these nodes are clinically involved. Overall, the expected survival rate in children with mucoepidermoid carcinoma approximates 95%.

Three very rare malignant epithelial salivary tumours, in order of decreasing incidence and worsening prognosis are: acinic cell carcinoma, adenoid cystic carcinoma and adenocarcinoma. The clinical presentation and treatment recommendations are as described for mucoepidermoid carcinoma.

True neoplasms of the minor salivary glands are extremely rare in childhood but comprise the same tumours with similar relative incidence as discussed above (Budnick, 1982). Treatment principles are also similar.

Craniopharyngioma

Craniopharyngioma arise from the embryonic remains of the craniopharyngeal duct and are important, albeit uncommon, tumours of childhood. They usually arise in the suprasellar cistern but in rare instances are localized within either the sella or the third ventricle. Histologically, the craniopharyngioma is a well-differentiated tumour with sheets of squamous epithelial cells sometimes in a pallisade arrangement. Cyst formation is common.

In very young children, craniopharyngioma present with hydrocephalus due to raised intracranial pressure. Older children may present with endocrine problems (such as growth failure) or restriction of vision (bitemporal field defects and optic atrophy). Plain X-rays of the skull usually show suprasellar calcification, abnormalities of the sella turcica and/or evidence of raised intracranial pressure. The CT scan is a more sensitive imaging technique.
Although these tumours are benign, they have a propensity to recur locally. Modern neurosurgical techniques which effect total tumour excision give the best survival results, but radical removal is frequently impossible because of the attachment of the tumour or its capsule to central nervous system tissues. Although there has been controversy over its role, there are now compelling data indicating that postoperative radiotherapy decreases the risk of recurrence (Kramer, 1974; Sung et al, 1981). This decrease is not dramatic but, considering the substantial mortality from recurring craniopharyngioma over lengthy periods of follow-up and modern radiobiological understanding of the radiation tolerance of the nervous system, postoperative radiotherapy is currently recommended for all patients. For the problematic patient with the recurring cystic craniopharyngioma, beta-emitting isotope therapy is now recommended (Strauss et al, 1982; Huk and Mahlstedt, 1983) and effective.

**Pituitary tumours**

In a series of over 300 pituitary patients presenting to St Bartholomew's Hospital, less than 3% have been in children. Nevertheless, gigantism (due to acidophil adenoma), galactorrhoea or amenorrhoea (due to a prolactin secreting adenoma) or, very rarely indeed, Cushing's disease (due to a basophil adenoma) may occur in childhood. If these patients do not present with the endocrine sequelae of the tumour, then they will present with compressive symptoms from a suprasellar component, and this is how the rare functionless chromophobe adenomata present. The optic pathways are most at risk from the suprasellar growth and bitemporal hemianopia is the classic visual defect.

The investigations vary little from the adult case and high resolution CT and MR imaging techniques are essential. It has been standard teaching for many years that cases with suprasellar extension causing visual field defects require primary surgical decompression. With the greater surgical expertise in the trans-sphenoidal operation, this recommendation has many advocates. With functioning acidophil adenomata and prolactinomata it is current policy at St Bartholomew's Hospital to initiate therapy with the dopamine agonist, bromocriptine, in all patients with less than marked visual field loss, rapidly deteriorating visual fields/acuity or other complicating factors (Besser et al, 1982).

Bromocriptine therapy not only reduces growth hormone or prolactin secretion in the majority of patients but also effects tumour shrinkage, which can be dramatic. However, cure with bromocriptine therapy is very much less certain and rapid, rebound adenoma expansion has been encountered following cessation of bromocriptin (and pregnancy is probably a high risk period for the medically treated prolactinoma patients). Modern megavoltage, external beam radiotherapy is a definitive and effective treatment method which follows initial bromocriptin therapy in both acidophil adenomata (Wass et al, 1985) and prolactinomata (Grossman et al, 1984) at St Bartholomew's Hospital. Any late decline in anterior pituitary function is gradual (compare surgery). Radiotherapy also reduces the recurrence rate following surgery for macroadenomata.

**Langerhans cell histiocytosis (histiocytosis X)**

Until 1953, eosinophilic granuloma, Hand-Schüller-Christian disease and Letterer-Siwe disease were regarded a separate entities, but in that year Lichtenstein (1953), appreciating that there was much overlap between the three conditions, proposed the unifying rubric
'histiocytosis X'. Although this term is still in common use because it aptly indicates the continuing state of near-ignorance concerning the pathogenesis of the disorder, an international group of clinicians and pathologists has recently recommended that it be replaced by the more informative term 'Langerhans cell histiocytosis'.

Various children's 'tumour' registers suggest an incidence of 30-50 cases per year in the UK, but this is almost certainly an underestimate for the following reasons: (a) the disease is almost certainly underdiagnosed, mild skin involvement being mistaken, for instance, for seborrhoeic eczema (see below), (b) patients present to many 'organ specialists' (otolaryngologists, ophthalmologists, orthopaedic surgeons) and notification is not, of course, obligatory and (c) adult cases (probably between 10-20% of the total) are not taken into account. The true incidence is probably well over 100 cases per annum.

Whatever organ is involved, light microscopic appearances of Langerhans cell histiocytosis infiltrates are characterized by the presence of histiocytes and 'small round cells', in differing proportions, together with varying numbers of eosinophils. Langerhans-type histiocytes, which are normally found only in the skin and are virtually pathognomonic of Langerhans cell histiocytosis when found at other sites, can be identified if electron microscopy reveals characteristic inclusion 'granules' known as Birbeck granules (Nezelof, 1979). Less differentiated cells, however, may contain few or no granules and as normal tissue histiocytes are also found in Langerhans cell histiocytosis lesions, a prolonged search may be necessary. Immunohistochemical studies reveal that Langerhans cells stain positively with the anti-Ia, HTA-1, and OKT6 antibodies. The enzymes alpha-mannosidase, ATPase and acid phosphatase and the S-100 protein are easily detected by special techniques and can also be helpful in diagnosis. By light microscopy, the appearance of the histiocytes varies but they have no unequivocal features of malignancy and, more important, there appears to be no correlation between the histological grading of a biopsy and the clinical course of the disease.

The cause of Langerhans cell histiocytosis is unknown, but clinical and histopathological features virtually rule out a malignant process, and no infective agent has ever been identified. Some patients have evidence of partial thymic atrophy and a primary immunodeficiency state has been postulated. Though standard immunological tests (serum immunoglobulin levels, phytohaemagglutinin response) are invariably normal, a relative deficiency of suppressor (OKT8 positive) lymphocytes has been demonstrated in the blood of patients with multisystem disease. Despite evidence that suppressor cell numbers increased after incubation in vitro of blood with a crude thymic hormone preparation ('thymosin'), neither 'thymosin' nor synthetic thymic hormone preparations have been effective in clinical trials (Broadbent and Pritchard, 1985). Currently, research attention is turning to the Langerhans cells themselves. It seems likely that the underlying abnormality is one of faulty intercellular communication between lymphoid and Langerhans cells, perhaps because of abnormalities in production of lymphokines or other growth factors.

Sites of disease presentation vary enormously and, as a result, symptoms can vary. Table 25.5 lists the presenting symptoms of 30 children presenting to one large children's hospital over a 3-year period. Clinical features in adults are similar. The disease can present in the newborn period and in the elderly, but the peak age is around 2-4 years. Boys seem to be affected rather more frequently than girls (males: females, 1.5-2:1) but with the same degree of severity. In 75% of patients, many organs are obviously affected at presentation.
(multisystem disease); in the remainder only one organ or organ system is involved (single-system disease) though detailed investigation may reveal occult multisystem disease.

Table 25.5 Presenting symptoms of 30 children with Langerhans cell histiocytosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of children*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash</td>
<td>15</td>
</tr>
<tr>
<td>Recurrent aural discharge</td>
<td>8</td>
</tr>
<tr>
<td>Bone pain</td>
<td>5</td>
</tr>
<tr>
<td>Scalp lump(s)</td>
<td>5</td>
</tr>
<tr>
<td>Proptosis</td>
<td>4</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>3</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>3</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>2</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>1</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>1</td>
</tr>
</tbody>
</table>

* Numbers add up to more than 30 as some children had multiple symptoms.

As Table 25.5 indicates, recurrent or persistent aural discharge is the commonest manifestation of Langerhans cell histiocytosis in the head and neck region. When this is the consequence of otitis externa, there is usually an easily detectable rash, its distribution (scalp, eyelids and postauricular skin) being similar to that of seborrhoeic eczema. In other instances there is middle ear disease - frequently in association with mastoid involvement. In either case, secondary infection is frequent and the process is very often chronic.

Early oral involvement manifests as granularity or thickening of the gingival mucosa (Betts and McNeish, 1972). More extensive involvement may be painful and, exceptionally, a palatal fistula may develop. Dental involvement may occur in the absence of lytic lesions in the mandible or maxilla and is then presumably the consequence of direct invasion from involved oral mucosa. In severe cases, erosion of dental alveoli and gum retraction may cause premature eruption or loosening of teeth: in these patients, loss of the dental lamina dura is an important radiological sign.

Pulmonary involvement (interstitial infiltrates ± pneumothorax) is relatively common, though often subclinical. Upper airway obstruction, by contrast, is rare and although tracheal obstruction has been described (Brickman, Nogrady and Wiglesworth, 1973), involvement of Waldeyer's ring has not. Lymph node infiltration, usually painless, is more frequently localized than generalized and cervical nodes are affected more frequently than those at other sites. Occasionally enlargement may be so massive as to cause obstructive symptoms. On occasion, chronic cutaneous fistulae can develop, but cultures are negative.

Other head and neck manifestations include proptosis, the consequence of retro-orbital deposits (Moore, Pritchard and Taylor, 1985), and skull involvement. Defects in the calvarium can often be palpated and there is sometimes an overlying soft tissue swelling. Radiologically, skull lesions, in common with those in other flat bones, appear to be 'punched out'. Frequently
lesions of varying ‘ages’ are seen: those in the healing phase have a sclerotic margin. In long bones, lesions may provoke an intense periosteal reaction, sometimes mimicking malignancy.

Diabetes insipidus, due to antidiuretic hormone deficiency, occurs in 30-40% of cases (Greenberger et al, 1981) in one-half of these, the complication is manifest at diagnosis, while in the others it develops during the course of the illness. Because lytic bone defects in the region of the pituitary fossa are very uncommon, the pathogenesis was obscure but it is now known, from post-mortem studies, that there are identifiable Langerhans cell histiocytosis deposits in the posterior lobe of the pituitary gland or the infundibulum in most, if not all, of these cases. The larger deposits can be demonstrated by CT scanning (with enhancement); magnetic resonance imaging may be more sensitive. Other manifestations of Langerhans cell histiocytosis include anaemia and thrombocytopenia (due to bone marrow involvement), hepatosplenomegaly, malabsorption, and short stature (due to growth hormone deficiency). By contrast muscles (including the heart), gonads, kidneys and endocrine glands are hardly ever affected.

When several organ systems are involved, the diagnosis is relatively straightforward, but when single system disease dominates the picture or when presentation is atypical, there is often a delay. The diagnosis should certainly be considered in any child with a history of chronic aural discharge, especially if there is no history of otitis media. Distinction from other histiocytic (Groopman and Golde, 1981) disorders and from other malignancies is usually straightforward on clinical and histopathological grounds.

Initial investigation should include full blood count, liver function tests with serum albumin, prothrombin time and partial thromboplastin time, chest radiographs, skeletal survey, bone marrow aspirate and trephine, lung function tests, early morning urine osmolality and water deprivation tests.

A number of elaborate staging systems have been devised. Although such objective criteria may facilitate comparison of treatment results between centres, it is not clear that assignation of a stage is helpful in determining management of a particular patient, or in assessing prognosis. In practice, organ failure seems to be a more important prognostic factor than organ involvement; bone marrow failure, manifested by pancytopenia and liver failure, are particularly ominous.

Because the nature of the disorder is obscure there can be no scientifically rational approach to treatment, but clinical observation and clinical trials have led to development of moderately effective measures. Now that the disease is no longer regarded as a malignancy, the therapeutic strategy is a good deal more conservative than in the past; ‘aggressive’ chemotherapy, because of its immediate and delayed toxicity, is contraindicated (Broadbent and Pritchard, 1985).

When Langerhans cell histiocytosis is apparently limited to one system (single system disease), it is the skeleton that is most often involved. Spontaneous resolution often occurs and a period of observation is appropriate unless the function of a vital structure (for example, optic nerve or spinal cord) is threatened or if there is pain that cannot be controlled by simple analgesics. Intraleisonal corticosteroid injections (50-100 mg hydrocortisone (Solu-Cortef)), repeated two or three times at 2-3 weekly intervals if necessary, are often effective when
active intervention is needed. Because aural disease is usually adjacent to an open cavity it is difficult, in practice, to ensure that the steroid solution remains within the lesion but an attempt is worthwhile. Because of the risk of induction of 'second tumours', radiation therapy should be used only when a site of disease is inaccessible to the needle or when vital organs (for example, optic nerve or spinal cord) are threatened, and the dose should not exceed 10 Gy (Smith et al, 1973).

Spontaneous resolution can occur and an initial period of observation may be appropriate (Broadbent et al, 1984). Indications for systemic therapy are (a) systemic symptoms (fever, failure to thrive), (b) discomfort, especially from multiple sources, (c) organ 'failure'. Agents active against cancer are generally used and responses are often impressive. Published data suggest that steroids alone are as effective as 'cytotoxic' drugs, even when these are used in combination (Broadbent and Pritchard, 1985). By contrast there is strong evidence that 'aggressive' combination drug regimens are associated with a higher complication rate. Thus a relatively conservative approach is indicated. In most patients, there is response to daily prednisolone 2 mg/kg; after an arbitrary 4 weeks' induction therapy, and depending on the quality of the response, the regimen can be modified with the intent of controlling disease by the smallest possible dose of steroids, and preferably none at all. If maintenance treatment is needed, alternate day administration is preferable so that there is less-than-complete suppression of adrenal function. In children, growth failure and immunosuppression are the most worrying features of chronic steroid therapy and diabetes mellitus, osteoporosis and hypertension are uncommon.

When response to corticosteroids is unsatisfactory, a vinca alkaloid (vincristine or vinblastine) or an epipodophyllotoxin (VP16) can be added. Claims that methotrexate, cyclophosphamide and 6-mercaptopurine are active agents in steroid-resistant Langerhans cell histiocytosis have not yet been substantiated, and cyclophosphamide may be leukemogenic.

Other measures may be helpful where specific organ systems are involved. Steroid ear drops (Predsol) can reduce the volume of discharge from otitis externa and antibiotics are indicated when secondary infection of the middle or external ear is suspected or proven. If gingival involvement is severe, surgical curettage can be helpful and may also reduce the incidence of later dental complications. The symptoms of diabetes insipidus are completely reversed by administration of DDAVP (a synthetic form of antidiuretic hormone) intranasally 5 microg twice or three times daily. Potassium permanganate soaks are helpful topically in the management of an ulcerated skin rash. Ung. coco oil, followed by washing with a keratolytic shampoo, can be helpful in the removal of crusted lesions from the scalp; topical steroid lotion is then applied to inflamed areas. Topical nitrogen mustard can be very effective where other methods have failed to control skin rash, but expert dermatological advice is needed. Where the lungs are involved, and the patient is immunosuppressed, regular co-trimoxazole (Septrin) should be considered as prophylaxis against Pneumocystis carinii.

The prognosis for patients with single-system disease is uniformly good. Progression to multi-system involvement is rare and mortality is close to zero. Some 10-20% of patients develop chronic problems but there is a tendency for disease to 'burn itself out' over 1-5 years. Patients with multisystem Langerhans cell histiocytosis fare less well, but the prognosis is better than some publications suggest. In a few patients spontaneous regression occurs. Almost all those receiving systemic therapy show some response. In most patients
symptomatic and objective improvement is marked, sometimes with reversal of organ failure. Infections, including those with opportunistic organisms, are common treatment-related complications, especially with the more aggressive chemotherapy regimens.

Overall, 20-30% of patients enter sustained complete remission and about 10%, especially those who present with or develop organ failure, die. The remaining 60-70% enter a chronic disease phase, with involvement of new organ systems in some cases. During this phase, problems include chronic discharging ears, deafness (in 15-20% of survivors), lymph node 'suppuration' (Smith and Evans, 1984), recurrent pneumothorax and dental and orthopaedic problems (Sims, 1977; Komp, 1981). Diabetes insipidus is usually permanent and growth hormone deficiency can occur.

**Fibromatosis**

The fibromatoses are a heterogeneous collection of clinical conditions, with similar histopathological appearances, that are difficult to distinguish from fibrosarcoma (Stout and Lattes, 1967). Tumours can appear at any age, from birth onwards, and at a number of sites, including the head and neck. Patients with Gardner's syndrome (intestinal polyposis, sebaceous cysts and osteomata) are predisposed to fibromatosis, although the pathogenic link is not understood. Tumours develop slowly, and are usually firm and lobulated and can become very large. By reason of location, head and neck fibromatosis is often unresectable; anecdotal responses to 'VAC'-type chemotherapy and to irradiation have been reported (Stein, 1977) and seen by the authors and are worth considering in these cases. Sometimes, despite all efforts progression is remorseless and the condition proves fatal.

**Unwanted effects of chemotherapy and radiotherapy**

Unwanted effects of chemotherapy can be grouped into those that are non-specific and the inevitable result of the cytotoxic action of individual drugs and those that are specific to one agent or group of agents. Bone marrow and immune suppression are almost invariable, but the duration and severity depends upon the type of regimen that is used. In general, intermittent chemotherapy is less immunosuppressive than continuous treatment, while there is a direct relationship between dose and the degree of marrow damage. Thus high-dose treatments are associated with prolonged periods of myelo- and immunosuppression. Several drugs cause mucosal damage, which is aggravated because epithelial cell repopulation is prevented. Thus oropharyngeal ulceration is a common side-effect of treatment with methotrexate, actinomycin D and doxorubicin. Mucosal damage opens the way to invasion by bacterial, fungal, and viral pathogens so careful oral toilet is necessary in all such patients. If a severely neutropenic (< 0.5 x 10^9/L) child develops fever, an urgent clinical search should be made for a focus of infection - including careful examination of ears, nose and throat - and cultures taken from any suspicious site as well as from nose, throat, urine, stool, vagina and blood. Broad-spectrum antibiotics should be started without delay and continued for at least 5 days even if the patient becomes afebrile and cultures are negative. Frequent (at least daily) clinical re-examination is necessary as signs may develop and progress alarmingly fast. It is critically important to be aware that, in the absence of circulating neutrophils, pus forms slowly or not at all and that signs of inflammation may be minimal. White blood cell transfusions are only indicated when the neutrophil count shows no signs of recovery and certain organisms, especially *Pseudomonas* spp, have been isolated.
There are relatively few otolaryngology-related drug-specific side-effects. The ‘glove-stocking’ peripheral neuropathy of vincristine is usually less severe in children than in adults but mononeuropathy can sometimes occur. Facial (seventh nerve), phrenic and recurrent laryngeal palsies have all been described and recovery is usually spontaneous, albeit over several weeks or months. Jaw pain, sometimes referred to the ear, is another relatively common and unpredictable side-effect of vinca alkaloids, especially vincristine: its onset is usually within 24 hours of administration of the drug and it lasts no longer than 48 hours. Older patients and more commonly affected than infants. More persistent pain should arouse suspicion of herpes zoster infection. Cisplatin is a relatively new but important addition to the chemotherapeutic arsenal and now has an established role in the management of neuroblastoma, malignant germ cell and liver tumours and osteogenic sarcoma. However, its usefulness is limited by dose-dependent nephrotoxicity and ototoxicity. Hearing loss (McHaney et al, 1983) is unusual at an accumulative dose less than 400 mg/m² but above this dose a degree of deafness is almost invariable and appears irreversible. Hearing loss is initially in the high-tone range but extends to lower frequencies as the accumulative dose of the drug rises. Patients receiving cisplatin should not be prescribed gentamicin or other ototoxic antibiotics unless absolutely necessary. High-tone hearing aids are often invaluable to children with hearing loss. Newer cisplatin analogues (for example, carboplatin) cause less inner ear and kidney damage but their efficacy in the treatment of childhood cancers is, as yet, uncertain.

Both radiotherapy and cytotoxic chemicals have mutagenic capability and an increased incidence of second cancers has been documented in patients treated with each of these anticancer therapies. Rarely should this lead to a reduction in the chance of cure in a child with a malignancy, but the indications for any such treatment must always be carefully reviewed. In addition, radiotherapy will cause dose-dependent retardation in the growth of irradiated bone and viscera, especially in young children and consideration of the late sequelae must always be made before a radical treatment programme is initiated.

Conclusion

The striking improvement in prognosis for children with cancer has been one of the most exciting advances in paediatrics during the last 15-20 years. Improvements in chemotherapy have been central to this progress but side-effects are of major and continuing concern. Thus, attempts are underway to phase out alkylating agents, procarbazine and radiation therapy - all of which are tumorigenic and cause sterility - with agents that lack these side-effects. Exciting, though preliminary, efforts are underway to 'target' tumour deposits selectively with ¹³¹I and other tumoricidal radioisotopes and drugs, using monoclonal antibodies and other vectors. The longer the duration of chemotherapy, the greater the risk of infective complications resulting from bone marrow and immunological suppression. Therefore, there is a trend towards 'short, sharp' courses of chemotherapy rather than protracted maintenance programmes. In summary, the current objective of most paediatric oncology teams is to provide 'cure at least cost' rather than 'cure at any cost'.