Current topics**Management of Hodgkin's disease in childhood**

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Hodgkin's disease was once nearly always fatal; now with proper management most patients can look forward to long survival and probable cure. But the new techniques of management are not themselves without the risk of short- and long-term complications, and this is of particular importance in growing children. Today the challenge of treating the child with Hodgkin's disease is to design therapy which minimizes these potential hazards without in any way reducing the chance of cure.

Incidence

Hodgkin's disease is less common in children than in adults. It is exceedingly rare in the very young: of 64 children referred to the Royal Marsden Hospital in the past 20 years, only one was less than 4 years old. The incidence of the disease then gradually rises with increasing age until adulthood (Jenkin *et al.*, 1967; Fraumeni and Li, 1969; Young *et al.*, 1973). Curiously, there appears to be a higher incidence in boys than girls, particularly in the younger age groups, and this is associated with a high incidence of lymphocyte predominant histology (see below) in boys (Strum and Rappaport, 1970; Schnitzer *et al.*, 1973; Tan *et al.*, 1975; Smith *et al.*, 1977). This is much more marked than the marginally increased male incidence in adults (McMahon, 1966) and has not been satisfactorily explained.

Clinical presentation

Most children with Hodgkin's disease present with painless lymphadenopathy in the lower cervical region (Evans and Nyan, 1964; Butler, 1969; Tan *et al.*, 1975), and about half of these also have mediastinal lymph node involvement. High neck, axillary, and inguinal nodes may also be affected at presentation, but disease presenting solely in one of these sites is much less common than in the neck. In our experience clinical splenomegaly at presentation occurs in only 7% of children, whereas histological

evidence of disease in the spleen has been found in 8 out of 14 children undergoing laparotomy. Extracapsular disease at the time of presentation is nowadays rare, though involvement of lungs, liver, bone, and even skin is occasionally seen (Tan *et al.*, 1975).

Anorexia, malaise, and lassitude have been described in approximately half of children at presentation, frequently in association with weight loss. Fever has been reported in 25-50% of cases, though rarely of the classical recurrent and relapsing Pel-Ebstein pattern (Evans and Nyhan, 1964). However, in our recent experience the incidence of these complaints is much less common. This probably relates to increased awareness of the possible significance of cervical lymphadenopathy and hence earlier diagnosis. Drenching night sweats are seldom reported as a presenting complaint in children. Pruritus, usually generalized and occasionally severe enough to cause intense scratching, is sometimes reported by adults with Hodgkin's disease, but in children this is very rare.

Differential diagnosis

Clearly in most of the children who present with cervical lymphadenopathy this will be associated with a simple throat or tonsillar infection, but painless, nontender, rubbery nodes not regressing after antibiotic therapy should alert the paediatrician to the possibility of a lymphoma. At this stage other differential diagnoses need to be excluded, in particular tuberculous infection. But once simple diagnoses have been excluded it is better not to delay, and proceed directly to node biopsy. Histology of the specimen will be diagnostic if Hodgkin's disease is present (see below) and valuable time will be saved. Other malignant conditions, in particular non-Hodgkin's lymphoma, may also occur in the child with lymphadenopathy. Here the lymphadenopathy is usually more widespread and of shorter duration than in Hodgkin's disease where lymphadenopathy frequently remains localized for a fair time. Again the differential diagnosis is confirmed by histology after biopsy.

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Diagnosis and histology

Diagnosis of Hodgkin's disease must be made histologically by biopsy of the lymph node or other affected tissue. Adequacy of the biopsy sample (preferably an intact affected node) and of the technique with which it is taken are both of concern to the pathologist. Procedures that distort nodal architecture, such as needle biopsy and frozen sections, may lead to a wrong diagnosis and should be discouraged. The pathologist needs to be experienced in the diagnosis of lymphomas.

Once the diagnosis has been made the histology is subdivided into various grades. The old subdivision by Jackson and Parker (1947) of paraganuloma, granuloma, and sarcoma has now been replaced by that of Lukes and Butler (1966), in which the tumour is characterized by the presence of Reed-Sternberg cells, and graded on the basis of cellular infiltrate and the presence or absence of nodularity. Four subdivisions are identified (Table 1).

Table 1 *Hodgkin's disease—histological types, 'Rye' classification (Lukes and Butler, 1966)*

(1)	Lymphocyte predominance
(2)	Nodular sclerosis
(3)	Mixed cellularity
(4)	Lymphocyte depletion

Lymphocyte predominance broadly corresponds to the old 'paraganuloma'. In a recent analysis of children referred to the Royal Marsden Hospital this accounted for about 30% of boys and 5% of girls. This subtype frequently presents as localized disease and carries an excellent prognosis.

Nodular sclerosis, in which the lymph node is divided into nodules by bands of collagen, is commoner in girls, occurring in 80% of our series compared with 40% in boys. Nodular sclerosis also carries a good prognosis and is usually the subtype associated with mediastinal involvement.

Mixed cellularity is characterized by a pleomorphic cellular infiltrate of eosinophils, plasma cells, and mononuclear cells. In adults this subtype is commoner in males, but in our experience it occurred with equal frequency in both boys and girls (about 15% of children). In the past this subtype has often been associated with advanced disease at presentation and a rather poor prognosis. With modern techniques of management, however, its prognosis is probably no worse than that of nodular sclerosis. It is associated with a disease pattern which affects cervical nodes and the spleen, and skips the mediastinum.

Lymphocyte depletion describes a subtype in which

a paucity of lymphocytes is associated with increased numbers of mononuclear and Reed-Sternberg cells, often of pleomorphic and bizarre appearance, and is roughly equivalent to the old 'Hodgkin's sarcoma'. It carries a very much worse prognosis than the other three groups, both in children and in adults, whatever the stage at presentation. It is fortunately rare; we have seen only 2 children with this subtype in our series (3%); one of these died within a few months of diagnosis, and the other has relapsed after a remission of only 3 months.

It is notable that a much higher incidence of lymphocyte-deplete Hodgkin's disease has been reported in African children than in children from Europe and North America (Burn *et al.*, 1971).

Investigations and staging

Accurate investigation and staging of all affected sites in children with Hodgkin's disease is the cornerstone of management. Grave harm can be done to the child if local therapy is given to clinically affected sites while cryptic disease, particularly within the abdomen, remains untreated. Table 2 lists the

Table 2 *Investigations in Hodgkin's disease*

(1)	Review histology, subtype
(2)	Full blood count, ESR, liver function tests, urea, electrolytes, uric acid, protein studies
(3)	Chest x-ray; tomography if indicated
(4)	Bipedal lymphography unless contraindicated
(5)	Liver and spleen scanning (see text)
(6)	Laparotomy with splenectomy, liver and node biopsies, and bone biopsy in selected children

investigations required and these will be discussed individually. A full blood count and biochemical screen is obviously necessary.

Chest x-rays. A standard posteroanterior and lateral chest x-ray will often give enough information about the mediastinum and lungs if these are obviously affected. The paratracheal nodes are most frequently affected. Hilar node involvement is less common and is rare in the absence of paratracheal involvement (MacDonald, 1973). Lung involvement is most commonly due to extension of disease from affected mediastinal nodes into the long parenchyma, but rounded opacities which may cavitate are also seen, and occasionally patients may present with miliary deposits. A difficult radiological problem can be the differentiation between lung infiltrates and post-irradiation fibrosis. Recently it has been shown that 67-gallium citrate scanning is of great value here, in that the isotope is taken up by active Hodgkin's disease within the lung but not by irradiation fibrosis (Peckham, 1973).

Bipedal lymphography and intravenous pyelography. Lymphography was a major advance in the detection of retroperitoneal lymph node involvement, and we believe bipedal lymphography with Lipiodol to be mandatory in all children with Hodgkin's disease unless there is a specific contraindication. These include orthopnoea which is aggravated by the pulmonary oil embolism that occurs to some extent in every case, active thrombophlebitis which may increase the danger of pulmonary embolism, and therapeutic irradiation of the lungs which paralyse the pulmonary capillaries and may allow droplets of oil to pass into the systemic circulation with risk of cerebral embolism. Age is no contraindication to lymphography in experienced hands, though smaller doses of contrast medium must be used to avoid the risk of excessive pulmonary embolism (MacDonald, 1973). The procedure, for example, was recently carried out in a 4-month-old infant (for a different disease) in our unit. Obviously, in younger children a light general anaesthetic is necessary. In older children of suitable temperament, the procedure is quite feasible under local anaesthesia providing everything is carefully explained to the child beforehand.

Bipedal lymphography permits the inguinal, iliac, and para-aortic lymph nodes to be visualized. The contrast medium then passes up the thoracic duct and may opacify nodes in the mediastinum and the root of the neck, usually on the left side. Opacification of mediastinal nodes is uncommon and frequently associated with involvement of these nodes with tumour. Large masses of tumour in the abdomen may not fill with contrast medium at all, but their presence may be inferred from the displacement of the normal lymphatic architecture or ureters as seen on an intravenous pyelogram which should be done 24 hours after the lymphogram and must be regarded as an essential part of the investigation.

Lymphographically-involved nodes show a foamy or reticular pattern and are frequently enlarged. Filling defects may be present, and a less common pattern is for the nodes to look more dense than normal. It is important to take adequate follow-up films when interpreting lymphograms, as this considerably increases the accuracy of interpretation. Affected nodes enlarge if not treated and shrink on treatment, whereas unaffected nodes remain static when no treatment is given. Sometimes unaffected nodes will become smaller with treatment but they do so symmetrically, whereas affected nodes will shrink more than their normal counterparts. Once the oily contrast medium is in the nodes it usually remains there for about 1 year and sometimes longer, so that follow-up abdominal x-rays can be taken without any further discomfort to the child.

It is not uncommon for the first evidence of relapse in a treated child to be enlargement of an opacified abdominal lymph node before any other clinical features of reactivation of disease are detected. This permits further treatment to be started early.

Liver and spleen scanning. Isotopic scanning of the liver and spleen has been used for some years as a means of detecting occult Hodgkin's disease, but results in both adults and children have been disappointing. Hodgkin deposits can occasionally be seen as filling defects, but more often the only information obtained is the size of the organs. The inclusion of scanning in the standard investigation is probably no longer warranted, though it may be indicated in specific instances where involvement of these organs is suspected for other reasons but laparotomy is not planned.

Diagnostic laparotomy. This procedure currently presents the most difficult problem in the investigation of children with Hodgkin's disease. In planning treatment it is of great importance to know not merely which lymph node groups are affected, but whether occult intra-abdominal or bone disease is also present. Laparotomy with splenectomy, liver biopsy, lymph node biopsy, including nodes from the splenic hilum and porta hepatis, and open iliac crest biopsy have been increasingly done in adults with clinical stage I, II, and III disease (see below) in recent years. The rationale is that no other accurate techniques are available for detecting early focal disease in these organs. Approximately one-third of patients in whom intra-abdominal disease is not suspected clinically are found to have involvement at laparotomy, particularly in the spleen (Glatstein *et al.*, 1969). The operation in adults is safe in experienced hands (Gazet, 1973), and the more accurate staging leads to more appropriate treatment with increased disease-free survival in patients whose disease remains confined to lymph nodes after operation (Peckham *et al.*, 1975).

In children, however, there appears to be an increased risk of serious postoperative complications compared with adults. Severe and often fatal infections have recently been reported (Rosenberg, 1971; Hays *et al.*, 1972; Jenkin *et al.*, 1975), and in particular Chilcoate and Baehner (1975) have documented 20 episodes of septicaemia and meningitis in 200 children after diagnostic laparotomy and splenectomy for Hodgkin's disease; 11 of these children died. These tragedies, which occurred at intervals varying between 8 days and 3 years after operation, were not confined merely to the very young, the average age of children affected being 10 years.

It would be easy to argue on the basis of this

experience that no child with Hodgkin's disease should undergo this operation. Yet we have recently seen 4 children with intra-abdominal relapse after complete clinical staging but without laparotomy, and conceivably occult disease might have been diagnosed and eradicated in some of these at presentation had they undergone this procedure. Furthermore, it is particularly important to minimize radiation therapy to unaffected normal tissues in growing children (see below) and the increased accuracy of a staging laparotomy permits limited radiation fields to be planned with greater confidence.

At present there seems to be no easy solution to this dilemma. We feel that children of 10 years and under should not undergo the procedure. In children of 11 and over the advantages of laparotomy and splenectomy seem to outweigh the possible risks, and in these children the procedure should be carried out where radiotherapy, which includes possible intra-abdominal sites of disease, is contemplated. In the infections reported by Chilcoate and Baehner (1975) *Diplococcus pneumoniae* and other penicillin-sensitive organisms were frequently isolated, and we strongly support their recommendation that splenectomized children should receive prophylactic penicillin until the age of 15. These recommendations may have to be modified in the light of future experience, and this problem is being closely looked at in centres throughout the world.

Staging. The extent of disease at the time of diagnosis is staged according to the Ann Arbor system (Carbone *et al.*, 1971). This is shown in Table 3, and

Table 3 Ann Arbor staging of Hodgkin's disease

Stage I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (x)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II), or localized involvement of extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (x)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III) ± involvement of the spleen (III _s), or localized extralymphatic organ or site (III _x)
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues, e.g. liver, marrow, pleura, lung, bone, and skin
Systemic symptoms	Weight loss, fever, sweating; if absent = 'A' if present = 'B'

a few points can be added here. The first is that the use of the suffix E is used to denote involvement of an extranodal site, either where the disease is confined to that site or where there has been direct extension from an adjacent affected lymph node. The implication is that this extranodal disease is still localized and can be treated with radiotherapy. As

soon as there is widespread extranodal spread which is not treatable with radiotherapy the disease becomes stage IV. The second point concerns 'B' symptoms, defined on the basis that their presence worsens the prognosis. Pruritus, classically associated with Hodgkin's disease, does not on its own worsen the prognosis and therefore is not categorized as a 'B' symptom. Thirdly, clinical staging and pathological staging must be differentiated. The term *clinical staging* is applied to a patient who has been fully investigated as described above, but without laparotomy. *Pathological staging* refers to a patient whose investigation has included laparotomy. This allows more accurate comparisons of treatment results to be made between different centres and also allows the influence of laparotomy on the outcome of treatment to be more readily assessed.

Treatment

Radiotherapy. Gilbert (1939) takes credit for showing that Hodgkin's disease was potentially curable with radiotherapy. His success was based on the concept that lymph node areas adjacent to nodes clinically affected with disease are also potentially affected and should therefore also be irradiated. Peters (1950) and later Kaplan (1962) further developed this principle. Kaplan first described the 'mantle' technique in which cervical, axillary, and mediastinal lymph nodes were irradiated in a single field, and the 'inverted Y' technique in which the para-aortic iliac and inguinal nodes are irradiated in a single field. 'Total nodal' radiotherapy, in which both these techniques were sequentially combined in patients with stage III disease, was developed by Kaplan and Rosenberg (1966). This approach is known as extended field radiotherapy, and its use in adults with stage I to stage IIIA disease has led to 5-year disease-free survivals and probable cures in the large majority of patients. Similar results with extended field radiotherapy have recently been reported in children (Young *et al.*, 1973; Jenkin *et al.*, 1975) and an analysis of children treated by us in this way suggests that about two-thirds of them will remain disease free, and therefore probably cured, after 5 years.

In children, however, extended field radiotherapy carries with it the potential hazard, not seen in adults, of bone growth impairment and organ maldevelopment. Retardation of spinal growth is a common complication of complete spinal irradiation in children, albeit in doses considerably higher than those used for Hodgkin's disease (Probert *et al.*, 1974). Young *et al.* (1973) noted retardation in vertebral body growth after extended field radio-

therapy, particularly in younger children; one child treated in our unit has developed thoracic deformity and impaired lung function after mantle irradiation. Furthermore in children as in adults, hypothyroidism may result from mantle irradiation to the thyroid, while gonadal irradiation may result in infertility, but does not appear to interfere with the other change occurring at puberty.

It is important, therefore, to question the routine use of this extended field approach, particularly in early childhood, and to examine whether other techniques might be more pertinent in this age group. There is no doubt that *local* radiotherapy given merely to clinically affected sites, without prior adequate clinical staging, is associated with a very high relapse rate outside the treated field, and there is no place for this whatever in the modern management of Hodgkin's disease. However, a very different situation arises in children with clearly localized stage I disease after adequate staging as described above. Here it is possible that a more limited irradiation field might provide effective disease control without the risk of relapse in other sites. For example, a few children with stage IA disease restricted to one group of upper cervical nodes have recently been treated in our unit with local radiotherapy limited to both sides of the neck, rather than with a full 'mantle' field, and these are so far doing well. Our experience is too small to allow us to draw conclusions. But Fuller *et al.* (1973) have reported a large group in which local radiotherapy given to children adequately staged by lymphography and laparotomy proved to be as effective as extensive field radiotherapy with less risk of growth complications. Again the importance of adequate staging where such therapy is to be complicated must be emphasized; lymphography is an essential part of staging procedure and there is a good argument for laparotomy and splenectomy before irradiation at least in children 11 years and older.

A second potential approach to the management of early stage disease in children is with combination chemotherapy, at present restricted mainly to patients with more advanced disease.

Chemotherapy (see Appendix). The development of a 4-drug combination chemotherapy regimen using mustine, vincristine, procarbazine, and prednisone (MOPP) (DeVita *et al.*, 1970) revolutionized the treatment of advanced Hodgkin's disease. With this regimen, or with vinblastine substituted for vincristine (MVPP) (McElwain *et al.*, 1973), complete remissions can be achieved in up to 80% of adult patients with stage IIIB and stage IV disease, and the majority of these remain disease free 5 years later. Combination chemotherapy in children with advanced disease is

as effective as in adults and this is unquestionably the treatment of choice in children with stage IIIB and stage IV disease. Experience with adults has shown that prior treatment with single drugs is not only vastly less effective but greatly prejudices the likelihood of subsequent long-term response to combination chemotherapy. *Single agents should never be used as the initial treatment of advanced Hodgkin's disease in children.*

In our recent experience the complete remission rate and duration of remission after combination chemotherapy are as good as those in children with less advanced disease treated with radiotherapy. This suggests that chemotherapy could be used in children with less advanced disease and there are some theoretical advantages to this. First, it would eliminate the problem of possible long-term irradiation damage. Second, it would obviate the need for a staging laparotomy with splenectomy, since cryptic areas of intra-abdominal disease would be treated anyway. Third, even if relapse were to occur after chemotherapy, radiotherapy might well remain a curative treatment in many instances, and perhaps at a later stage in the child's development when growth problems were less likely.

On the other hand combination chemotherapy has its own disadvantages. Sterility in adult males, at least for a time after treatment, is inevitable (DeVita *et al.*, 1973); the extent to which this will present a long-term problem in children is so far unknown. The induction of second tumours after chemotherapy is also a risk which remains to be assessed. Nausea and vomiting are unpleasant side effects of standard MOPP and MVPP chemotherapy and these can place considerable strain on children, parents, and staff during treatment. Recently, we have explored the possibility of substituting chlorambucil for nitrogen mustard in the 4-drug regimen, and our early experience suggests that this combination is as effective as the original, but with a greatly decreased incidence of drug-associated vomiting (McElwain *et al.*, 1977).

Our current feelings on the use of chemotherapy in early stage Hodgkin's disease in children are that this approach seems sufficiently promising to warrant further study except where disease is clearly localized, and may be of particular value in children of less than 10 years, where laparotomy would not be carried out (see below).

Suggested protocol for treatment. On the basis of all these considerations we are presently treating Hodgkin's disease in children in the following way. *Children of 10 years or less* are clinically staged with lymphography but not with a laparotomy which might prove hazardous. Children with clearly

localized disease are then treated with limited field irradiation to affected nodes and to immediately adjacent sites. Full mantle or inverted-Y treatment is not given, however. All children in this age group in whom disease is not localized are treated with chemotherapy. Local radiotherapy may later be given to original sites of bulky disease.

Children of 11 years and over are pathologically staged with laparotomy and splenectomy (unless of course there is already obvious stage IV disease). Children with pathological stage I or II disease are then treated with extended field radiotherapy, unless more than three nodal areas are affected or a large mediastinal mass is present. Since these features are known to be associated with a low cure rate for radiotherapy alone (Peckham *et al.*, 1975), chemotherapy is in this situation given first to achieve good tumour regression before irradiation. In stage IIIA (with a negative spleen) treatment will depend on the age of the child. It is our policy to treat children of 13 or over with total nodal irradiation as in adults. In younger children we prefer to use chemotherapy in an attempt to minimize damage to the growing spine. In stage IIIA with splenic involvement, and in stage IIIB disease, chemotherapy is the treatment of choice, possibly followed by irradiation to sites of bulky disease. In stage IV, chemotherapy alone is given, as in adults. All splenectomized children receive oral prophylactic penicillin until aged 15.

Complications during treatment. In general complications during treatment are surprisingly rare, considering the intensity of the therapy. Of the possible infectious problems, the first is herpes zoster, which is otherwise uncommon in children. This is usually self-limiting and is treated with analgesics, though we have occasionally seen good responses to topical idoxuridine (Herpid), provided this is applied as soon as signs appear. Occasionally opportunist infections, in particular *Pneumocystis carinii* pneumonia, may occur with breathlessness, cough, and later cyanosis. These symptoms should be considered an emergency requiring urgent hospital admission, since treatment with pentamidine or sulphamethoxazole and trimethoprim (Septrin) may prove lifesaving. Bacterial infections are no more common than in normal children, unless the patient should become neutropenic as the result of therapy, in which case energetic inpatient management is again essential. Tuberculosis, once closely associated with Hodgkin's disease, is now extremely uncommon in these children.

Psychological and social aspects. In the child with a major illness psychological and social aspects are of

great importance. The first point concerns the physician's approach to the parents. Here there is every justification for pursuing vigorously a policy of hope and optimism about prognosis. Their justified anxiety that their child has a malignant condition can be allayed by a careful explanation of the reasons for intensive investigation and the type of treatment that will be given. They can be reassured that with modern treatment the chances for cure are high, even when the disease presents in an advanced stage.

The second point concerns management of the disease itself. Most of this can be carried out on an outpatient basis, providing there are no geographical contraindications, and the stability of the home background can thus be largely maintained for the child. For younger children the most elaborate investigation will be lymphography and this can be done under light anaesthesia if necessary. Fractionated doses of radiotherapy can also be given on an outpatient basis, and it is surprising how co-operative even young children can be in this. Treatment usually lasts only about one and a half minutes per day, with a few more minutes before this spent setting the child in position. In very young or anxious children light sedation may be desirable. Chemotherapy, given in 2-week courses at 2-week intervals can also be administered on an outpatient basis. This is mostly in tablet form with a single weekly intravenous injection of vinblastine. The combination chemotherapy used in Hodgkin's disease does not produce alopecia, which is obviously a tremendous psychological advantage, and the problem of vomiting is virtually eliminated using combinations with chlorambucil as described above. The only absolute indication for inpatient care is laparotomy with splenectomy. However, it is our recommendation that this be used only in the older child who can more readily understand the reasons for having to come into hospital.

In recent years Hodgkin's disease has become a great success story in modern cancer therapy. Many problems remain to be solved, particularly in children, and there is certainly no room for complacency. The most important point is that successful therapy and the chance of cure depend fundamentally on correct management. Inadequate staging or inappropriate therapy can still quite literally mean the difference between life and death.

Conclusions

Hodgkin's disease in childhood is essentially similar to that in adults, although boys outnumber girls before puberty. It is essential that children with this disease are fully investigated, and in older children

investigation should probably include diagnostic laparotomy and splenectomy. In younger children splenectomy is best avoided because of the subsequent danger of infection, and this dictates the need for chemotherapy in most patients in order that all potential disease is treated. Modern techniques of radiotherapy and chemotherapy are both capable of curing the majority of children. The choice of treatment should be designed to ensure the best chance of eradication of the disease with minimum damage to the patient, particularly in terms of subsequent growth and development.

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Appendix

Drug combinations in Hodgkin's disease

MOPP. (DeVita *et al.*, 1970. Complete remission rate 81%.) Mustine hydrochloride 6 mg/m² IV on days 1 and 8. Vincristine (Oncovin) 1.4 mg/m² IV on days 1 and 8. Procarbazine 100 mg/m² orally daily on days 1-14 inclusive. Prednisone 40 mg/m² orally daily on days 1-14 inclusive.

Six courses are given with 2 weeks' rest between the end of one course and the beginning of the next one. Prednisone was given in courses 1 and 4 only, but most workers now give prednisone in every course.

MVPP. (McElwain *et al.*, 1973. Complete remission rate 76·6%.) Mustine hydrochloride 6 mg/m² IV on days 1 and 8. Vinblastine 6 mg/m² IV on days 1 and 8. Procarbazine 100 mg/m² orally daily on days 1–14 inclusive. Prednisone 40 mg/m² orally daily on days 1–14 inclusive. (A total dose of 40 mg is not exceeded.)

6–10 courses are given with one month's rest between the end of one course and the beginning of the next.

Chl VPP. (McElwain *et al.*, 1977. Complete remission rate 75·7%.) Chlorambucil 6 mg/m² orally daily on days 1–14 inclusive. (A total dose of 10 mg is not exceeded.) Vinblastine 6 mg/m² IV on days 1 and 8. Procarbazine 100 mg/m² orally daily on days 1–14 inclusive. Prednisone 40 mg/m² orally daily on days 1–14 inclusive. (A total dose of 40 mg is not exceeded.)

6–10 courses are given with 2 weeks' rest between the end of one course and the beginning of the next.

MRC/DHSS Phenylketonuria Register

The attention of interested parties is drawn to the fact that the PKU Register, which hitherto has been in Liverpool, is to be moved to London. From 1 October 1977 the address will be: PKU Register Office, Department of Child Health, Institute of Child Health, 30 Guilford Street, London WC1N 1EH (Tel: 01-242 9789).

Dr. Isabel Smith will be in day-to-day charge under the Steering Committee (Chairman: Professor O. H. Wolff).