HODGKIN'S DISEASE IN CHILDREN*

By R. D. T. JENKIN, M.B., F.R.C.P.(C), M. V. PETERS, M.D.,
and J. M. M. DARTE, M.D., F.R.C.P.(C)
TORONTO, ONTARIO, CANADA

THIS review concerns those children up to and including the age of 15 years with Hodgkin's disease who presented during the years 1930–1958 at The Department of Radiotherapy, Toronto General Hospital and from 1958–1965 at The Princess Margaret Hospital, Toronto. This is a group of patients referred for radiation therapy, the majority from The Hospital for Sick Children, Toronto.

In this 36 year period, 75 children presented (Fig. 1). Fifty-five were diagnosed in the years 1950–1965.

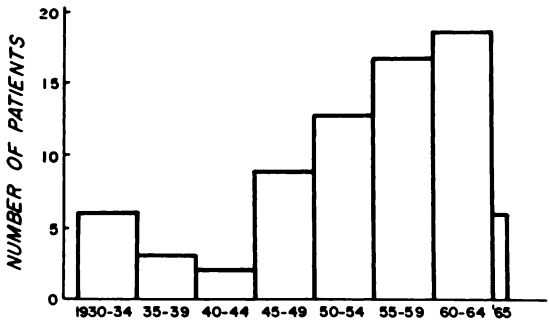

FIG. 1. Year of diagnosis. Temporal distribution.

AGE INCIDENCE

No patient was seen younger than 3 years of age. In the age range 5–15 years and within the limits set by the small total number seen, there was a fairly uniform age incidence (Fig. 2). We find no peak in the 5–9 year range as indicated by Pitcock *et al.*[7] It appears from accumulated publications[1,2,6] that in childhood the age incidence slowly increases to whatever age is taken as the arbitrary cut-off and as such represents no more than the lower tail of the complete age distribution curve.[5]

The disease is nearly twice as common in boys, the sex ratio favoring boys 7:4, and

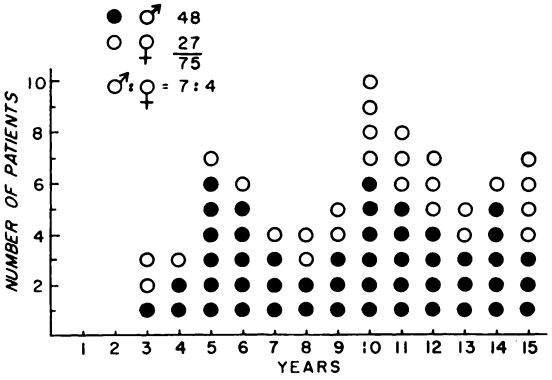

FIG. 2. Age and sex incidence.

as such does not differ from our total experience.[5]

STAGE AND SURVIVAL

Using the Toronto method of staging the disease,[3] it is seen that survival is highly stage dependent (Table 1). Those children with localized disease in Stage I and IIA do equally well with an over-all 62 per cent 5 year survival and a fair proportion of survivors at 10, 15 and 20 years. The children with widely disseminated disease in Stage III do very poorly with only 1 of 22 surviving 5 years. The 5 year survival rate for the whole group is 33 per cent.

There is no evidence that age at onset or sex had a bearing on the chance of surviving 5 years or longer.

Comparing the present series with a group of 319 patients of all ages from the same hospitals seen during the period 1928–1954,[4] we see that the children do not do quite as well (Fig. 3). The 5 and 10 year survival rates for children at 33 per cent and 24 per cent compare with 40 per cent and 26 per cent for the whole series. Whilst these differences are not statistically sig-

* Presented at the 29th Annual Meeting of The Canadian Association of Radiologists, March 2–6, 1966.
From The Princess Margaret Hospital, 500 Sherbourne Street, Toronto, Ontario, Canada.

nificant, in a stage by stage survival analysis, we find that this apparent disadvantage can be entirely accounted for by the especially bad prognosis of Stage III disease in children and in this stage it is the first year after diagnosis that sees the excess toll taken (Fig. 4). Indeed, rather more than 1 child in 4 presented with disseminated disease which ran a fulminating course with death in the first year.

INITIAL SITE

The initial site of involvement is shown in Figure 5 for 47 children with Stage I or II disease. The left cervical or supraclavicular lymph nodes were involved in 32 compared with 21 on the right, and the mediastinum in 20. The other lymph node sites were uncommon. Only 2 children, both with Stage IIB disease, had lymph node involvement below the diaphragm. In Stage I disease, the figures for the left and right neck are 12 and 6 respectively. No patient with Stage I disease had involvement of the mediastinum alone. Assuming a unifocal disease process, the main initial pathway of spread is thus from neck to contralateral neck and/or mediastinum. All 14 Stage IIA patients had disease confined to lymph node sites above the diaphragm.

RELATIONSHIP OF RADIATION THERAPY AND SPREAD OF DISEASE

In the radiation treatment of localized Hodgkin's disease and cognizant of this possible mode of spread, the apparently uninvolved lymphatic regions above the diaphragm may be electively irradiated in the hope of eradicating microscopic foci of disease and thereby decreasing the recurrence rate and increasing the cure rate. To examine what benefit may derive from such treatment, 32 children in Stage I and II who presented with a lymph node primary site above the diaphragm are analyzed with regard to the site of first recurrence and elective irradiation (Table II).

Eleven of 32 recurred at a lymph node site above the diaphragm. Of these, only 4 had received elective radiation and in 2 the

TABLE I

THE RELATION OF SURVIVAL TO STAGE

Stage	No.	Five Year Survival	Ten Year Survival	Fifteen Year Survival	Twenty Year Survival
I	12	8	3/6	2/4	2/2
IIA	9	5	3/6	2/3	1/1
IIB	11	4	2/8	1/4	0/1
III	22	1	1/18	1/15	0/9
Total	54	18	9/38	6/26	3/13

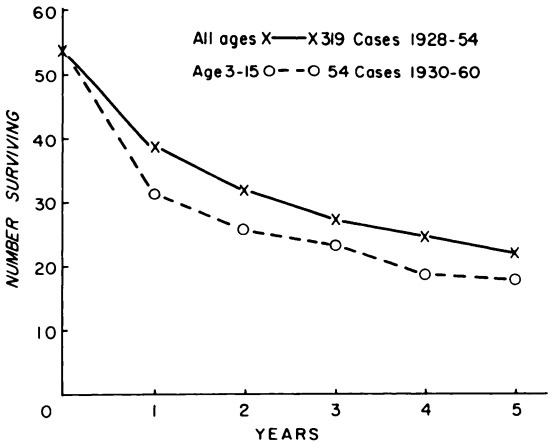

FIG. 3. All stages. Survival in children compared with the predicted survival for the same number of patients with a normal age distribution.

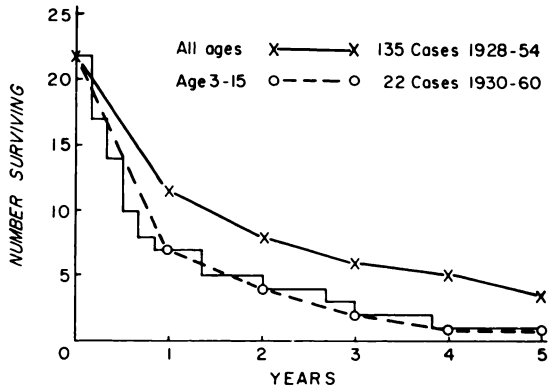

FIG. 4. Stage III. Survival in children compared with the predicted survival for the same number of patients with a normal age distribution and the same stage.

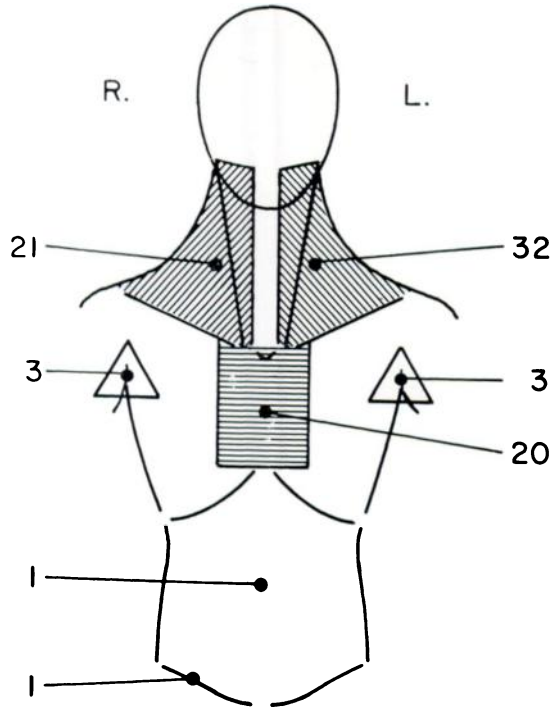

FIG. 5. Forty-seven Stage I and II cases. Lymphatic regions involved at time of diagnosis.

recurrence was outside the electively irradiated areas. In the total group of 32 patients, 16 received elective radiation with only 2 recurrences in such electively irradiated areas to date, whereas 18 have recurred at other sites. Looking at these figures another way, 8 of 12 with no recurrence received elective radiation compared with only 8 of 20 with recurrence. As far as it goes, these data support the concept of elective treatment of adjacent uninvolved areas.

TABLE III

Stage	No. of Patients	No. Recurrent At 1° Site
I	20	3
IIA	14	8
IIB	12	5

RECURRENCE AT THE PRIMARY SITE

Examining these patients for recurrence in the primary region following irradiation, we find in Stage I to date 3 recurrences in 20 patients (Table III). In 1 of these, the recurrence was outside a modest field used in the primary treatment and possibly outside in a second.

In Stage II disease, 13 of 26 patients developed recurrence. This marked difference in the chance of local recurrence compared with Stage I probably reflects a more diffuse involvement of the lymphatic regions by disease, some of which may not be included in the field of irradiation. Five of the 16 recurrent cases received a dose less than 2,500 rads. compared with 8 of 32 that did not recur. It is our opinion, certainly for doses of the order of 3,500 rads, that irradiation of an inadequate volume is the chief reason for primary recurrence.

LARGE FIELD ABDOMINAL IRRADIATION

The common indication for large field abdominal radiation therapy was disease

TABLE II

SITE OF FIRST RECURRENCE VS. ELECTIVE RADIATION THERAPY TO ADJACENT LYMPH NODE REGIONS IN 32 STAGE I AND II CASES

Site of First Recurrence	No. of Patients	No. Electively Irradiated	No. Recurrent in Region Electively Irradiated
Lymph Node Involvement above Diaphragm	11	4	2
Lymph Node Involvement below Diaphragm or Generalized	9	4	—
No Recurrence	12	8	—

mainly confined to the abdominal cavity and retroperitoneum and producing systemic symptoms.

Of 12 children treated in this manner (Fig. 6), 9 had a remission greater than 3 months and 5 greater than 12 months. This is compared with the best results obtained in the same patients with drug therapy. In most cases the drug was used after abdominal irradiation. Failure to respond to abdominal irradiation does not preclude response to drug therapy.

The best results either with irradiation or drugs were obtained in those patients who had already demonstrated a natural chronicity of disease. In such patients it is felt that where the disease is mainly confined to the abdomen, irradiation should be used before drugs.

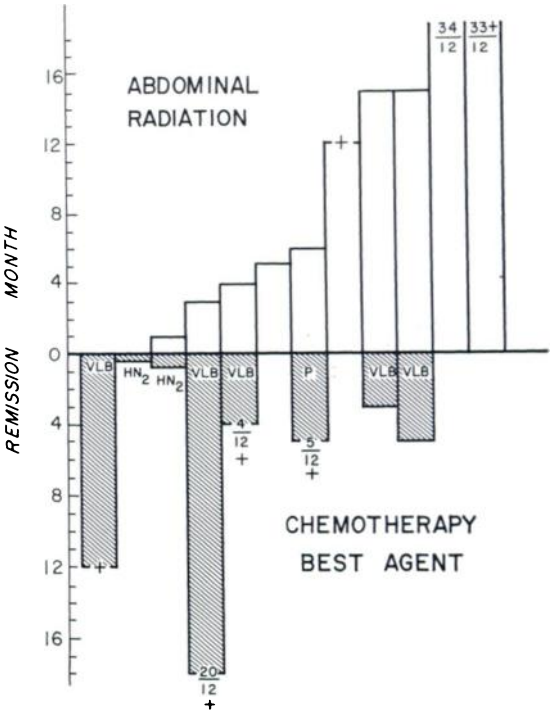

Fig. 6. Duration of remission following wide field abdominal radiation therapy compared with the best drug induced remission in the same patient.

Chemotherapy

The indication for drug therapy was most often inadequate control by irradiation. In severe Stage III disease, these agents are the treatment of choice to induce a remission. The optimal palliation

Table IV

Chemotherapy results in Hodgkin's disease in children

Drug	No. of Courses	Objective Response			Duration (months)
		Nil	<2 months	>2 months	
HN_2 (I)	21	6	10	5	$3\frac{1}{2}$, 5, 8, 15, 34
Procytox (M)	4	0	2	2	3+ 5+
T.E.M. (M)	8	1	4	3	$2\frac{1}{2}$, 6, 16
Leukeran (M)	3	—	1	2	2, 3
V.L.B. (M)	7	—	—	7	3+, 5, 5, 12, 12+, 15, 20+
V.L.B. (I)	5	2	3	—	

I = intermittent.
M = maintenance.
+ = Remission continuing.

TABLE V

STAGE DISTRIBUTION VS. YEAR OF DIAGNOSIS

Stage	1930–47	1948–65
I, II	7	39
III	10	19

of such cases may then be by a combination of irradiation and chemotherapy.

In the advanced phase of the disease, apparently complete remissions can be obtained with these drugs with valuable prolongation of life not otherwise obtainable.

Table IV shows the duration of remission obtained with various agents either by intermittent or maintenance therapy. We have found maintenance Vinblastine (V.L.-B.), given as an intravenous injection 0.15 mg./kg. weekly initially and then every 2–3 weeks when the remission is well established, of especial value.

CONCLUSION

It would be satisfying to demonstrate how our results have improved with the evolution of our treatment method over the years. A marked improvement is indeed noted, but this results chiefly from an almost complete reversal of the proportion presenting early rather than late (Table V) and so giving us a greater chance to cure the patient. This factor far outweighs any improvement in therapy in this small group of patients. The credit for this goes to the family doctor who realizes that in this particular child the enlarged lymph nodes of the neck are malignant rather than inflammatory.

SUMMARY

Seventy-five children with Hodgkin's disease treated mainly by irradiation are reviewed. The 5 year survival was 33 per cent, dropping to 24 per cent at 10 years.

We have no evidence that the mode of onset, natural history or response to treatment differs materially from that in the larger adult group, except that in Stage III the disease may sometimes run a more fulminating course in the child.

R. D. T. Jenkin, M.B.
The Princess Margaret Hospital
500 Sherbourne Street
Toronto 5, Ontario, Canada

REFERENCES

1. BAILEY, R. J., JR., BURGERT, E. O., JR., and DAHLIN, D. C. Malignant lymphoma in children. *Pediatrics*, 1961, *28*, 985–992.
2. KELLY, F. Hodgkin's disease in children. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1965, *95*, 48–51.
3. PETERS, M. V., and MIDDLEMISS, K. C. H. Study of Hodgkin's disease treated by irradiation. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1958, *79*, 114–121.
4. PETERS, M. V., ALISON, R. E., and BUSH, R. S. Natural history of Hodgkin's disease as related to staging. *Cancer*, 1966, *19*, 308–316.
5. PETERS, V. Résultats lointains du traitement de la maladie de Hodgkin. *Nouv. Rev. Franç. Hématol.*, 1966, *6*, 60–73.
6. PIERCE, M. I. Lymphosarcoma and Hodgkin's disease in children. *Nat. Cancer Conf. Proc.*, 1960, *4*, 559–570.
7. PITCOCK, J. A., BAUER, W. C., and MCGAVRAN, M. H. Hodgkin's disease in children: clinicopathological study of 46 cases. *Cancer*, 1959, *12*, 1043–1051.