REFERENCES

Dacie, J. V. (1956). *Practical Haematology*, 2nd ed. Churchill, London.
Ebaugh, F. G., jun., Emerson, C. P., and Ross, J. F. (1953). *J. clin. Invest.*, **32**, 1260.
Falco, E. A., Goodwin, L. G., Hitchings, G. H., Rollo, I. M., and Russell, P. B. (1951). *Brit. J. Pharmacol.*, **6**, 185.
—— Hitchings, G. H., Russell, P. B., and VanderWerff, H. (1949). *Nature (Lond.)*, **164**, 107.
Frenkel, J. K., and Hitchings, G. H. (1957). *Antibiot. and Chemother.*, **7**, 630.
Frost, J. W., and Jones, R., jun. (1954). *Lancet*, **1**, 1063.
Hamilton, L., Philips, F. S., Clarke, D. A., Sternberg, S. S., and Hitchings, G. H. (1952). *Fed. Proc.*, **11**, 225.
Hitchings, G. H., Elion, G. B., VanderWerff, H., and Falco, E. A. (1948). *J. biol. Chem.*, **174**, 765.
——Falco, E. A., VanderWerff, H., Russell, P. B., and Elion, G. B. (1952). Ibid., **199**, 43.
Isaacs, R. (1954). *J. Amer. med. Ass.*, **156**, 1491.
Schmidt, L. H., Hughes, H. B., and Schmidt, I. G. (1953). *J. Pharmacol. exp. Ther.*, **107**, 92.
Vincke, I., and Lips, M. (1952). *An. Inst. Med. trop. (Lisboa)*, **9**, 563.
Wasserman, L. R. (1955). *Blood*, **10**, 659.
Wetherley-Mein, G., Hutt, M. S. R., Langmead, W. A., and Hill, M. J. (1956). *Brit. med. J.*, **1**, 1445.

SEASONAL INCIDENCE OF CLINICAL ONSET OF HODGKIN'S DISEASE

BY

MARION D. CRIDLAND, M.B., B.S., B.Sc.(Med.)
Chester Beatty Research Institute, London

In reviewing 269 cases of histologically proved Hodgkin's disease seen at the Royal Marsden Hospital since 1945, a high incidence of clinical onset in the month of December was observed.

Criteria for Selection

Since the mode of onset is so variable and the presenting symptoms may appear long after the true onset of the disease, a seasonal association could have significance only if the clinical onset were closely related in time to the apparent onset of the disease. In 106 cases there is reason to suppose this was so, and the following criteria were used in selecting them: (1) the month of onset was definitely stated; (2) lymphadenopathy was localized to one peripheral site at onset; (3) no evidence of generalized disease was present; (4) disease was confined to superficial lymph nodes with no clinical or radiological evidence of deeper involvement within six months of onset; and (5) patients were living in England at the time of onset.

Time of Onset.—In many cases the time of appearance of the first enlarged lymph node was remembered precisely by the patient, sometimes to within a few days. If the onset was remembered to within one calendar month the case was accepted for analysis, but when the description was less precise, as, for example, "about nine months ago," the case was excluded.

Site.—In 70 of the 106 patients the disease remained strictly localized to one region for six months or more. Of the remaining 36 patients, some developed enlarged nodes in the corresponding region on the opposite side, and a few had axillary involvement on the same side after initial cervical-node involvement. Provided the disease remained localized to these sites for at least six months, the case was included in the series. If the mediastinum, for instance, was the true site of onset, although the appearance of enlarged cervical nodes was the first clinical evidence of disease, some evidence of a mediastinal lesion might have been expected to be manifest within six months.

Cases Excluded from the Series

Criteria for exclusion of cases were as follows. (1) Generalized peripheral lymphadenopathy at the time of clinical onset (3 cases). (2) Evidence of intrathoracic or intra-abdominal involvement at the time of presentation or within six months (37 and 9 cases respectively), or of paravertebral involvement (3 cases). (3) Localized disease for six months or more, but the month of onset not stated (24 cases). (4) Cases lost to follow-up within six months of the onset of the disease (1 case). (5) Onset of disease outside England (30 cases).

Constitutional symptoms such as fevers, sweats, lassitude, pruritus, or loss of weight were present in some cases, sometimes for several months, before Hodgkin's disease was diagnosed. These symptoms did not occur prior to the lymphadenopathy in the cases selected for the series.

A further 56 patients whose disease was clinically localized at the time of onset have been excluded from analysis because one or more of the following features were present: (1) peripheral lymphadenopathy in areas remote from the site of presentation within six months of clinical onset but without evidence of deeper involvement; (2) probable or early paratracheal or mediastinal spread not detected by serial *x*-ray films until five to six months after the first appearance of cervical nodes; (3) splenomegaly detected between three and six months after the onset of the disease; and (4) febrile episodes in the absence of other signs of spread of the disease within six months which, in retrospect, could have been due to subsequently discovered deep-seated disease not apparent at the time.

Although these 56 cases were not included in the series, they show almost exactly the same seasonal incidence as the 106 acceptable cases. If they were added to the 106, making a total of 162 cases, and the results compared with those of the 106 cases shown in Table I, the difference in incidence in any one month would be little more than $\pm 1\%$.

Many cases have thus been excluded because of the possibility that the disease was present for some time before the appearance of the first sign or symptom. Since rapidly progressive disease may develop from a focal lesion, some eligible cases might have been unnecessarily excluded.

Thus, of 269 case histories reviewed, 106 (39.5%) were regarded as suitable to be analysed for a possible seasonal association.

Results

Of the 106 patients selected, 23 (21.7%) had the clinical onset of Hodgkin's disease in the month of December. The results are shown in Table I.

Seasonal Incidence in the Two Periods 1945–53 and 1954–9.—To examine the seasonal incidence in different periods the 50 patients whose disease began in the period 1945–53 and the 56 whose disease began in 1954 to 1959 have been analysed separately. Table I shows that the seasonal incidence is essentially the same for each period and the whole period.

Incidence of Infection of the Upper Respiratory Tract at Clinical Onset of Hodgkin's Disease.—In the majority of cases the disease presented simply with painless

enlargement of a lymph node. It is possible that the high incidence of the disease in December was due to the prevalence of upper respiratory infection in that month. Patients might notice enlarged nodes for the first time if these or neighbouring nodes became tender in association with a septic throat. Of the 269 patients, 28 (10.4%) gave a history of sore throat or coryza just preceding or coincident with the finding of enlarged lymph nodes; 11 of these 28 are included in the series of 106 (10.4%). The monthly incidence of these patients presenting with respiratory infections is shown in Table II, from which it is seen that the simultaneous onset of enlarged nodes and upper respiratory infection was less common in December than in June. Five of the 11 patients have been questioned again and all are certain that enlarged nodes were not present before, but appeared during the infection and remained enlarged after it had subsided. Two cases of sore throat occurred in association with involvement of inguinal nodes only. Three patients complained of tender nodes initially. One, in December, had tenderness at the site of the presenting node several days prior to its enlargement. The two other patients, both with inguinal node involvement presenting in November and August, had rapidly enlarging tender nodes.

Possible Influence of Treatment Within the First Six Months.—The management of the 106 patients during the first six months after clinical onset of Hodgkin's disease is summarized in Table III. It is not possible in these cases to assess with certainty the influence of treatment on the recurrence rate within six months. From Table III it is seen that 38 patients were not treated within six months of the clinical onset of their disease. Their subsequent course was not less favourable than it was in the 68 patients treated sooner. It is more difficult to decide how far regional " prophylactic " irradiation or chemotherapy influenced the length of the first remission. It is, however, possible that more extensive initial treatment could have postponed recurrence which otherwise might have occurred within six months. Some of the 26 patients who received regional radiotherapy or chemotherapy or both might not have qualified for inclusion in the series if they had not received such treatment. If these 26 patients are excluded from the series, however, the percentage incidence of the time of onset is altered materially only in the month of September (7.5% instead of 11.2%).

Seasonal Recurrence Rate.—The onset of recurrence is usually impossible to establish because the majority of patients relapse with involvement of deeper regional nodes, which are often very large before their presence is detected. Nevertheless the month of relapse was noted in 89 patients, apparently in good health, who had recurrence in peripheral lymph nodes. No striking seasonal incidence was apparent.

Control Series.—A satisfactory control series is difficult to compile. In leukaemia, for example, an abnormal blood picture may have been present for a long time before symptoms arose or the disease was diagnosed. A survey has been made applying the same criteria for selection to 134 cases of lymphosarcoma (excluding those with lymphocytic leukaemia) and 50 cases of reticulosarcoma. The clinical onset could be established with precision in only 48 cases (26%). The onset of the disease in the 48 cases selected showed no particular seasonal incidence.

It is of interest to note that during the collection of data on Hodgkin's disease the preponderance of patients presenting in December was apparent when records of only 50 of the 106 selected cases had been examined.

TABLE I.—*Seasonal Onset of Hodgkin's Disease in* 1945–59 *and During* 1945–53 *and* 1954–9

Month of Onset	1945–59 (106 Cases)		1945–53 (50 Cases)		1954–9 (56 Cases)	
	No.	%	No.	%	No.	%
January ..	14	13·2	7	14·0	7	12·4
February ..	6	5·7	1	2·0	5	8·9
March ..	4	3·8	3	6·0	1	1·8
April ..	9	8·5	4	8·0	5	8·9
May ..	7	6·6	4	8·0	3	5·4
June ..	7	6·6	4	8·0	3	5·4
July	4	3·8	2	4·0	2	3·6
August ..	6	5·7	3	6·0	3	5·4
September ..	12	11·2	5	10·0	7	12·4
October ..	5	4·7	2	4·0	3	5·4
November ..	9	8·5	3	6·0	6	10·7
December ..	23	21·7	12	24·0	11	19·6

TABLE II.—*Incidence of Infection of the Upper Respiratory Tract at Clinical Onset of Hodgkin's Disease*

Month	No. Presenting with Hodgkin's Disease	With Upper Respiratory Infection	
		No.	%
January	14	1	7·1
February	6	1	16·7
May	7	1	14·3
June	7	2	28·5
August	6	1	16·7
December	23	5	21·8

TABLE III.—*Management of Patients in First Six Months*

	No. of Patients
Local radiotherapy (also surgery in 3)	40
Local and "prophylactic" regional radiotherapy ..	10
Local radiotherapy and chemotherapy	8
Local radiotherapy and "prophylactic" regional radiotherapy and chemotherapy	3
Chemotherapy only	5
Surgery only	2
Treated more than six months after onset	38

Discussion

No observations on a seasonal incidence of Hodgkin's disease have been recorded in the literature so far reviewed.

Hodgkin's disease is rare and few new patients are seen each year at any one centre. The present analysis has been made on 269 patients with histologically proved Hodgkin's disease who attended one hospital in the 15 years 1945 to 1959. In 106 of these the disease began with the enlargement of a superficial lymph node and remained localized for at least six months. In 23 (21.7%) the clinical onset of the disease occurred in the month of December. The same monthly incidence throughout the year was also found in the nine years 1945–53, and in the six years 1954–9.

A series of cases such as this cannot be regarded as unselected. For the purpose of the analysis, patients with superficial and localized disease initially have been deliberately chosen. Nevertheless, there is no obvious feature in the group to suggest that it is unrepresentative of Hodgkin's disease. The ratio of males to females is 2:1 for the whole group of 269 and for the selected 106 patients. Among these 106 patients the seasonal incidence is essentially the same for both sexes. The age distribution is also the same in each group for both males and females, with males presenting at a rather younger age. The subsequent course of the illness in the selected group has been typical of Hodgkin's disease, with no features to distinguish it from the course in the 163 patients excluded from the series.

One obvious explanation for a seasonal presentation is that the attention of patients would be drawn to

previously unrecognized enlarged nodes by a coincidental infection of the upper respiratory tract. More patients with Hodgkin's disease would be likely to present when these infections are commonest—namely, the winter months. It was therefore of particular interest to find that only 10.4% of all the patients presented with coincidental or recent upper respiratory infection and that these were not most prevalent in the month of the highest incidence of Hodgkin's disease. It is concluded that the high incidence of Hodgkin's disease in December was independent of the incidence of infection of the upper respiratory tract.

Some infections characteristically show a seasonal incidence. It would be of interest to compare with Table I the monthly prevalence of known infective agents. If, in fact, the pattern of seasonal occurrence of Hodgkin's disease is confirmed, it might support the view that Hodgkin's disease is caused by an infective agent or that its onset is precipitated by such an agent.

Summary

Of 106 cases of localized Hodgkin's disease in the period 1945–1959, 23 (21.7%) had a clinical onset in the month of December.

The same seasonal incidence is seen in the two groups of 50 and 56 patients whose disease commenced in the periods 1945–1954 and 1955–1959 respectively.

The same pattern of seasonal occurrence is observed in both sexes.

The occurrence of upper respiratory tract infection in 11 patients did not lead to the discovery of lymphadenopathy nor was the relative incidence of sore throat greater in the month of December.

Since recurrent Hodgkin's disease so frequently involves deep-seated nodes, the inception of recurrence is impossible to establish. Peripheral node recurrence in 89 cases showed no striking seasonal incidence.

No particular seasonal incidence of onset was found in a series of 48 cases of lymphosarcoma and reticulosarcoma.

No explanation is offered for the seasonal incidence observed, but the results might support the view that Hodgkin's disease is caused by an infective agent or that its onset is precipitated by such an agent.

These results are presented in the hope that comparable studies will be made elsewhere.

This work was supported by a grant from the New South Wales State Cancer Council, Australia, and in part by a Gordon Jacobs Fellowship, The Royal Marsden Hospital, London. Thanks are extended to Dr. D. A. G. Galton for his help in the preparation of this paper, and to Professor A. Haddow, Professor D. W. Smithers, Dr. Eve Wiltshaw, and Dr. R. A. M. Case for their helpful comments.

A new British Standard (B.S. 3385) for dosimeters lays down requirements for direct-reading personal dosimeters for *x*- and gamma-radiation. These instruments—a common type of which looks like a fountain-pen—fit into the pocket. They tell the user the amount of radiation dose he has received, if any. Obviously, it is essential that these instruments should be robust and accurate, and the requirements of B.S. 3385 are intended to ensure that they are. It is the first British Standard to be prepared under the authority of the newly formed Nuclear Energy Industry Standards Committee of the British Standards Institution. Copies may be obtained from the Institution, Sales Branch, 2 Park Street, London W.1, price 3s. each, postage extra to non-subscribers.

Preliminary Communications

Intrasplenic Isotopes in Study of Portal Systemic Collateral Circulation

Investigations of the portal systemic collateral channels in patients suffering from portal hypertension have been almost restricted to the visualization of these channels, chiefly by portal venography, and by the demonstration of varices at the lower end of the oesophagus radiologically with barium. These procedures, though of value in many cases in outlining the collateral channels, do not satisfactorily reveal the true size of the "shunt" through which blood is diverted from the portal to the systemic circulation. More accurate assessment of this shunt would be of value, particularly before deciding on the surgical treatment to be followed, and postoperatively for checking the results of the various anastomotic procedures performed.

Percutaneous intrasplenic injection of radioactive materials appears to offer a method for the evaluation of the circulatory dynamics of the portal circulation and its collateral channels with the systemic circulation. The results in three normal subjects and 11 patients with portal hypertension are given.

Materials and Methods

Two identical Ekco scintillation probes, type N 559 D, attached to a low-angle collimator, are used. One probe is placed over the liver laterally and the other over the right side of the heart (Fig. 1). Both probes are adjusted so as to be in close contact with the patient's skin. The probes are connected to Ekco scalers, which record the time in seconds against a pre-set count.

Different types of radioactive isotopes were used—namely, colloidal 198Au, ^{131}I-labelled human serum albumin, and ^{131}I-labelled rose Bengal. The latter, with a short biological half-life, seems to be most satisfactory (Fellinger *et al.*, 1958 ; Baptista and Carvalho, (1958).

With a thin lumbar-puncture needle the spleen is punctured in the eight, ninth, or tenth intercostal space in the mid-axillary line. With very large spleens a subcostal approach is used. After recording the splenic pressure by means of a saline heparinized manometer,

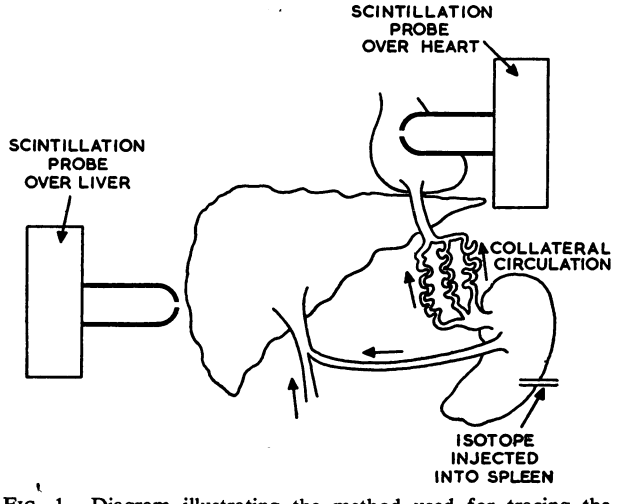

FIG. 1.—Diagram illustrating the method used for tracing the radioisotope injected into the spleen in a case of portal hypertension with a marked portal systemic circulation.