

Simultaneous Diagnosis of Hodgkin's Disease and Chronic Lymphocytic Leukemia

G. Bonadonna *, S. Monfardini *, and F. Pizzetti **

National Cancer Institute, Milano, Italy

Lymphology 1, 88-95 (1968)

The coexistence of Hodgkin's disease and chronic lymphocytic leukemia seems from the literature to be a very rare association reported in no more than 30 cases (3, 4, 8, 9, 10, 11, 12, 14, 15, 16, 17, 20, 23, 24, 25, 26, 27, 28, 29). The so-called Richter's syndrome (22) includes also the association of chronic lymphocytic leukemia with reticulum cell sarcoma (7).

In one patient we were able to document ante-mortem and simultaneously the diagnosis of both lymphoproliferative disorders, while in almost every case previously reported the diagnosis of combined occurrence was made at post-mortem examination. The simultaneous diagnosis at the time of initial work up allowed a proper treatment for both diseases.

Case Report

M. T., a 68-year old house wife was admitted on October 21st, 1967 to the National Cancer Institute of Milan because of a painless adenopathy in the right cervical region of one month duration. The lymph nodes were progressively increasing in size without constitutional symptoms (fever, pruritus, night sweats) and loss of weight. The past medical history was essentially unremarkable with the exception of typhoid fever at the age of fifteen.

Physical examination revealed a well-developed, well-nurished female in no acute distress. The blood pressure was 210/110 mm Hg.; pulse 100/min; temperature 36.8 °C; and respirations 21/min. Examination of the head, ears, eyes, nose and throat showed no abnormalities. The thyroid gland and the breasts revealed the absence of nodules. A freely movable, non tender 5 x 4 cm adenopathy was palpable in the right cervical region. There was no other palpable lymphadenopathy. Examination of the heart, lungs, and nervous system was within normal limits. The liver, spleen and kidneys were not palpable. No other masses were palpated.

Laboratory studies on admission revealed: hemoglobin 11.0 gm/100 ml; red blood cells 3.700.000/mm³; white blood cells 25.000/mm³ (neutrophils 20%, lymphocytes 80%) (Fig. 1); platelets 200.000/mm³; erythro sedimentation rate 40/hr. Bone marrow aspiration from the sternum showed slight hypercellularity; 60% of cell population was composed of small lymphocytes. Her urine was negative for glucose, acetone,

* Clinical Assistants, Division of Medicine and Surgery.

** Chief, Division of Pathology.

Correspondence and requests for reprints should be addressed to: Dr. GIANNI BONADONNA, Via Venezian 1, Milano, Italy.

blood and albumin; total bilirubin was 0.4 mg^o/_o ml (direct, 0.1 mg^o/_o ml and indirect 0.3 mg/100 ml); bromsophalein retention at 45 minutes was 15^o/_o; serum alkaline phosphatase was 3 Bodansky Units; serum electrophoresis revealed a total protein of 7.7 gm^o/_o ml (albumin 3.07 gm^o/_o ml; α_1 globulin 0.30 gm^o/_o ml; α_2 globulin 0.83 gm^o/_o ml; β globulin 1.26 gm^o/_o ml; γ globulin 2.24 gm^o/_o ml) with an albumin/globulin ratio of 0.66. Serum uric acid was 4 mg^o/_o ml. Chest X-ray showed no mediastinal adenopathy nor involvement of lung parenchyma. Skeletal survey revealed a severe spondylarthrosis in the cervical and lumbar vertebrae. Foot lymphangiography revealed pathological nodes with filling defects bilaterally in both iliac and para-aortic chains. Flat plate of abdomen showed no enlargement of liver and spleen.

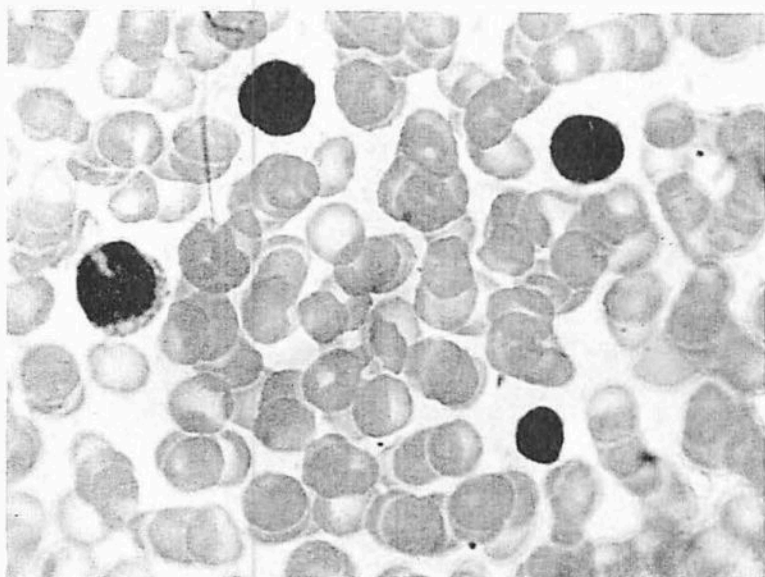


Fig. 1 Smear of peripheral blood where 80% of the cells were small lymphocytes (May Gruenwald-Giemsa, x 1100).

A biopsy of one of the lymph nodes in the right cervical area revealed Hodgkin's disease with lymphocytic and histiocytic predominance (Figures 2a and 2b). A few days later multiple lymph node biopsies of both iliac and para-aortic lymph chains through an exploratory laparotomy were performed. At the time of surgery liver, spleen and mesenteric nodes appeared macroscopically within normal limits. The histologic findings were compatible with the diagnosis of Hodgkin's disease in the para-aortic nodes (Figure 3) and of lymphocytic lymphosarcoma in the iliac nodes (Figure 4).

The patient was then started on a course of radical radiation therapy with a Cobalt 60 Unit to all lymphoid regions above the diaphragm (mantle port) and to the retroperitoneal node chains (inverted Y port) with deliverance of 3200-3600 rads (tissue dose). The spleen was not irradiated. A fall in the total leucocyte count was observed after 3 weeks from the beginning of radiation therapy. A leukopenia

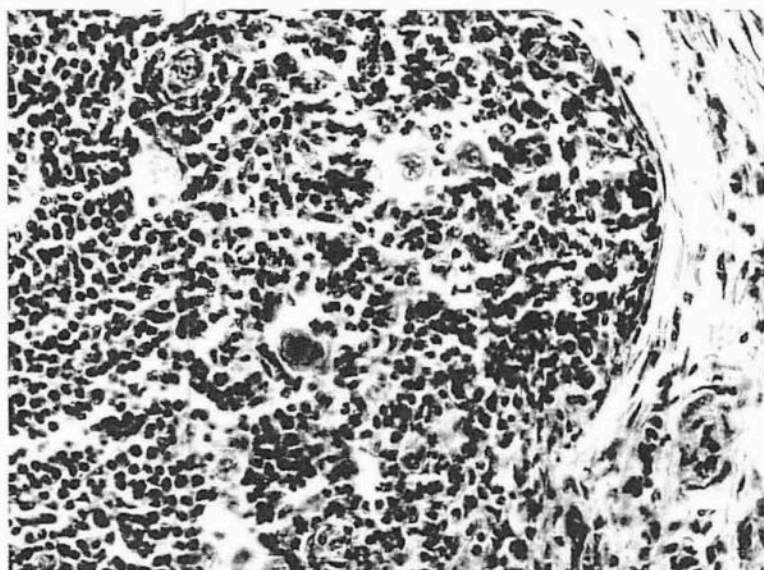


Fig. 2 a

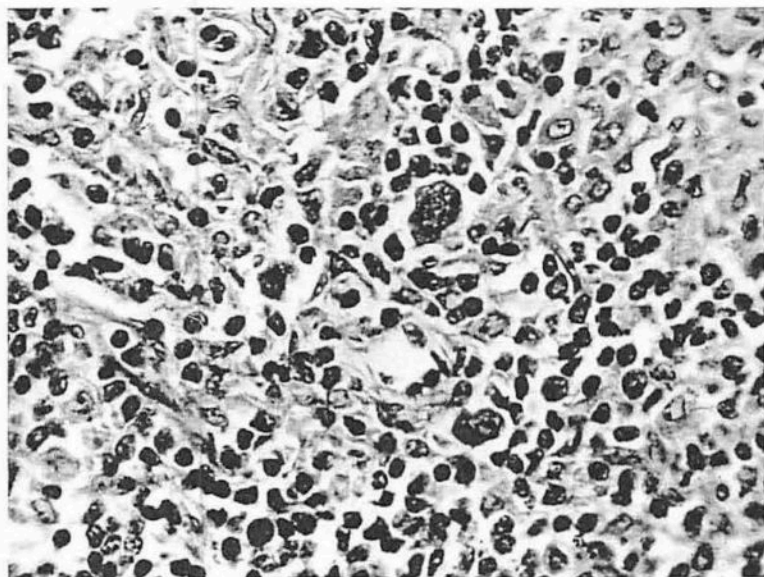


Fig. 2 b

Fig. 2 a and 2 b Sections of a cervical lymph node showing Hodgkin's disease with lymphocytic and histiocytic predominance (H. and E., x 340 and x 550).

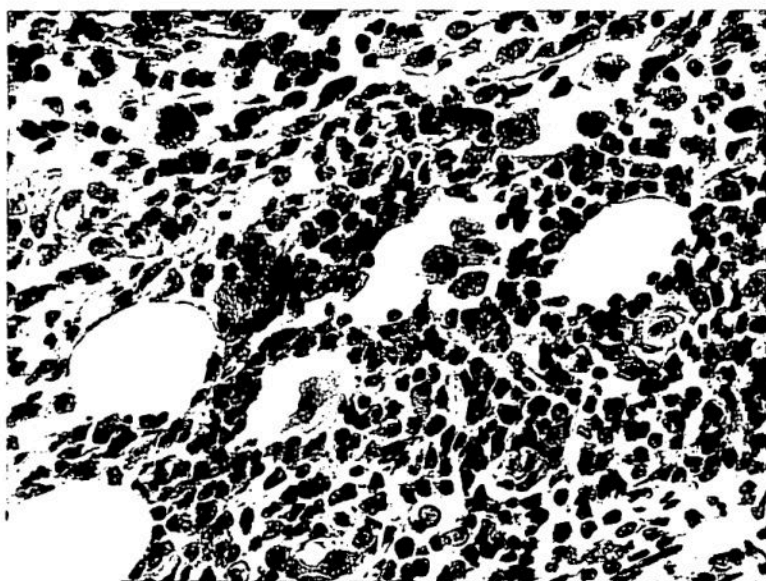


Fig. 3 Section of a para-aortic node showing Hodgkin's disease with an histologic pattern similar to that observed in the cervical node (H. and E., x 420).

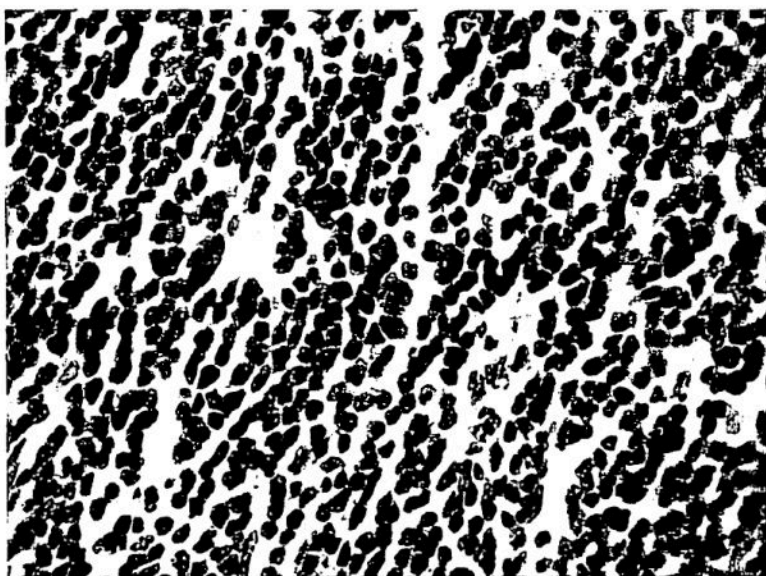


Fig. 4 Section of an external iliac node showing the histologic pattern of lymphocytic lymphoma (H. and E.; x 550).

eventually developed and the course of radiation therapy was interrupted for about 2 weeks (Figure 5). A fall in the hemoglobin value was also observed (from 11.0 gm^o/ml to 7.9 gm^o/ml). Two days before discharge the hemogram was as follows: hemoglobin 7.9 gm^o/ml; red blood cells 3.000.000/mm³; white blood cells 4.000/mm³ (neutrophils 67%, lymphocytes 32%, monocytes 1%); platelets 180.000/mm³; erythro-sedimentation rate 98/hr. Bone marrow aspiration from the posterior iliac crest showed severe hypocellularity probably secondary to radiation therapy effects. Bromsulphalein retention at 45 minutes was 23.9%, serum alkaline phosphatase was 12 Bodansky Units; serum electrophoresis revealed a total protein of 7.8 gm^o/ml (albumin 2.88 gm^o/ml; α_1 globulin 0.55 gm^o/ml; α_2 globulin 0.89 gm^o/ml; β globulin 1.14 gm^o/ml; γ globulin 2.34 gm^o/ml) with an albumin/globulin ratio of 0.58. Follow up films showed a good shrinkage of retroperitoneal nodes. Physical examination failed to detect palpable nodes in the right cervical region as well as enlargement of liver and spleen. Blood pressure on discharge returned to normal values (120/80) after treatment with Serpasil.

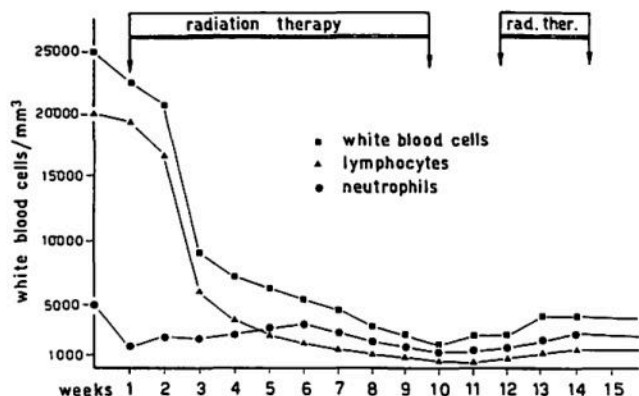


Fig. 5 White blood cell levels during radiation therapy and immediately thereafter.

Six months after discharge physical examination was essentially unremarkable. The hemogram showed: a hemoglobin of 11 gm^o/ml; white blood cells 3.700/mm³ (neutrophils 60%; lymphocytes 34%; monocytes 6%). Total bilirubin was 0,27 mg^o/ml (direct 0,12 mg^o/ml and indirect 0,15 mg^o/ml). Bromsulphalein excretion was 10% and serum alkaline phosphatase was 4,5 Bodansky Units. Serum iron concentration was 118% ml.

Comment

This case is another example of a patient with Hodgkin's disease associated with chronic lymphocytic leukemia. From reviewing the literature this case is to our knowledge the first in which the diagnosis of both diseases was clearly documented simultaneously at the time of initial work-up.

The cervical nodes showed the typical morphological pattern of Hodgkin's disease with Reed-Sternberg cells and with diffuse lymphocytic-histiocytic predominance. Furthermore the histologic appearance of some of the para-aortic nodes resembled

closely to that observed in the cervical area. The cervical and the paraaortic regions are known to be among the preferential sites of involvement for Hodgkin's disease (2). The bone marrow as well as the peripheral blood pictures were consistent with the diagnosis of chronic lymphocytic leukemia. A leukemoid reaction was excluded since the histologic examination of the iliac nodes showed the classical picture of lymphocytic lymphosarcoma. It can be concluded that the clinical and morphological diagnosis is that of a chronic lymphocytic leukemia in its benign asymptomatic form as defined by DAMESHEK and GUNZ (5): "The patient is ordinarily 60 years or over in age and feels well. Usually in the course of a routine check-up, blood counts demonstrate leukocytosis of 15,000 to 50,000 per mm³ with a well defined mature lymphocytosis. Ordinarily, the patient looks well and has no pallor. There is little, if any, lymphadenopathy or splenomegaly."

The exploratory laparotomy was performed mainly to obtain more precise information about the histopathological aspects of the retroperitoneal adenopathies in order to plan the proper treatment. Since no apparent involvement by Hodgkin's disease was found outside of the lymph nodes (stage 3° A) we decided to treat the malignant lymphoma with radiation therapy above and below the diaphragm. The rationale for this approach was due to the fact that extensive radiotherapy is presently accepted as the treatment of choice for Hodgkin's disease in stage 3° A and chronic lymphocytic leukemia usually runs a prolonged course even without chemotherapy. The extensive irradiation to most of the lymph node-bearing areas yielded to a marked fall in the peripheral blood and bone marrow smears with improvement in the differential counts.

We have no definite explanation for the changes in the BSP retention and alkaline phosphatase. Since both these tests persist slightly elevated without concomitant hepatomegaly and abnormal bilirubin at the present moment a microscopic infiltration of the liver by chronic lymphocytic leukemia cannot be excluded. A liver involvement by Hodgkin's disease seems a less convincing hypothesis since usually it is associated with systemic symptoms. The electrophoretic pattern with elevation of the globulin fraction and a reversed albumin-globulin ratio is usually seen during the course of chronic lymphocytic leukemia. Hypoglobulinemia involving chiefly the gamma globulins occurs in the terminal phases of the disease.

The coexistence of two different types of malignant lymphoproliferative disorders seems to be a rare condition (7). In particular the association of chronic lymphocytic leukemia and of Hodgkin's disease with a clearcut diagnosis has been reported in the literature in no more than 18 documented cases. The patients were predominantly elderly. In some cases there are doubts about the diagnosis of either the leukemia or of Hodgkin's disease (6, 11, 14, 15, 16, 17, 26, 27, 28). With one or two exceptions (10, 29) the diagnosis of Hodgkin's disease was made at post-mortem examination. Apparently in almost all cases reported in the literature the first diagnosis was that of chronic lymphocytic leukemia and after different lengths of time Hodgkin's disease was documented. Since in almost every instance this was recognized at post mortem examination Hodgkin's disease was already generalized.

The interpretation of the coexistence of chronic lymphocytic leukemia and Hodgkin's disease varies according to the different authors. Most of them believe that the

combined occurrence of these lymphoproliferative disorders represents the occurrence of two separate diseases (13), while others do not exclude the possibility of a transformation from one histologic type of malignant lymphoma to another.

Based principally on the work in mice and chicken modern concepts of the development of immune system and of the immunological disturbances of lymphoproliferative disorders (18, 19, 21) imply that there are two different populations of lymphocytes. The first is a thymus-dependent population (small lymphocytes) responsible for delayed hypersensitivity reaction which occurs principally in patients with Hodgkin's disease. The second is a non-thymus dependent population (large lymphocytes and plasma cells) responsible for the production of immunoglobulins and circulating antibodies. This immunoglobulin producing tissue is known to be impaired in the large majority of patients with chronic lymphocytic leukemia (hypogammaglobulinemia).

Thus there is a rather convincing experimental evidence (1) to postulate that Hodgkin's disease and chronic lymphocytic leukemia may arise from two different populations of lymphocytes. Therefore they can coexist in the same patient as two separate diseases, although this condition seems to be rare. This hypothesis as well as recent concepts on the nature of chronic lymphocytic leukemia (5) would exclude the possibility of a transformation of one disease to another.

In conclusion the combined occurrence of chronic lymphocytic leukemia and Hodgkin's disease is in accordance with the experimental evidence of two populations of lymphocytes.

Summary

A case of Hodgkin's disease associated with chronic lymphocytic leukemia is reported. The coexistence of these two lymphoproliferative disorders has been reported in no more than eighteen documented patients. This case is the only one in which the diagnosis of both diseases was made simultaneously at the time of initial work-up. The combined occurrence of Hodgkin's disease and chronic lymphocytic leukemia probably represents the occurrence of two separate diseases. The possibility that Hodgkin's disease and chronic lymphocytic leukemia may arise from two different populations of lymphocytes is discussed.

References

- 1 Auerbach, R.: Experimental analysis of the origin of cell types in the development of the mouse thymus. *Develop. Biol.* 3 (1961), 836
- 2 Bonadonna, G., A. Banfi, G. Carnevali, F. Milani, E. Salvini: Preferential sites and mode of spread of Hodgkin's disease and lymphoreticular sarcomas on the basis of clinical evaluation of 500 cases. *Tumori* 53 (1967), 551
- 3 Boggs, D. R., S. A. Soffer, M. M. Wintrobe, G. E. Curtwright: Factors influencing the duration of survival of patients with chronic lymphocytic leukemia. *Amer. J. Med.* 40 (1966), 243
- 4 Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 28. *New Engl. J. Med.* 274 (1966), 1433
- 5 Dameshek, W., F. Gunz: *Leukemia*. Grune and Stratton, New York 1964
- 6 Epstein, R. D.: An apparent case of chronic lymphocytic leukemia terminating as Hodgkin's disease (sarcoma) *N. Y. J. Med.* 56 (1956), 3518
- 7 Givler, R. L.: Lymphocytic leukemia with coexistent localized reticulum cell sarcoma. *Cancer* 21 (1968), 1184
- 8 Holler, G.: Beobachtungen über die Wechselwirkung zwischen Leukämie und Tuberculose im menschlichen Organismus. *Klin. Wschr.* 10 (1931), 1663
- 9 Krasznai, G., S. Keresztury, L. Szűcs: Granulomatous giant cell reticulosis associated with cases of treated leukaemia. *J. Clin. Path.* 20 (1967), 841
- 10 Keiser, G., E. Uelinger, C. Virieux: Zwei Fälle von chronisch-lymphatischer Leukämie und Morbus Hodgkin. *Acta Haematologica* 26 (1961), 29
- 11 Krim, M., L. M. Meyer, J. Rosenthal, N. D. Ritz: Conversion of lymphocytic leukemia to Hodgkin's disease. *Arch. Int. Med.* 89 (1952), 297
- 12 Jackson, H., F. Parker jr.: *Hodgkin's disease and allied disorders*. Oxford University Press, New York, 1947, p. 177
- 13 Lacher, M. J., L. N. Sussman: Leukemia and Hodgkin's disease. *Ann. Int. Med.* 59 (1963), 369

- 14 Lortholary, P., M. Boiron, P. Ripault, J. P. Levy, A. Manus, J. Bernard: Leucémie lymphoïde chronique secondairement associée à une réticulopathie maligne, syndrome de Richter. *Nouv. Rev. Franc. Hémat.* 4 (1964), 621
- 15 McCartney, J. S. jr.: Malignant lymphoblastoma. A report of two cases. *Amer. J. Cancer* 12 (1928), 195
- 16 Mac Mahon, H. E., F. Parker jr.: A case of lymphoblastoma, Hodgkin's disease and tuberculosis. *Amer. J. Path.* 6 (1930), 367
- 17 Marshal, G., G. Duhamel, J. C. Weil-Face, Blamoutier: Maladie de Hodgkin avec tableau initial de leucémie lymphoïde et association de tuberculose. *Bull. Soc. Med. Hop. Paris* 69 (1953), 734
- 18 Miller, D. G.: Patterns of immunological deficiency in lymphomas and leukemias. *Ann. Int. Med.* 57 (1962), 703
- 19 Miller, D. G.: Immunological deficiency and malignant lymphoma. *Cancer* 20 (1967), 579
- 20 Oberfield, R. A.: Coexistence of chronic lymphocytic leukemia and Hodgkin's disease. A case report. *J. Amer. med. Ass.* 195 (1967), 865
- 21 Peterson, R. D. A., M. D. Cooper, R. A. Good: The pathogenesis of immunologic deficiency diseases. *Amer. J. Med.* 38 (1965), 579
- 22 Richter, M. N.: Generalized reticular cell sarcoma of lymph nodes associated with lymphatic leukemia. *Amer. J. Path.* 4 (1928), 285
- 23 Seife, M., C. Reich, J. R. Lisa: Chronic lymphatic leukemia associated with Hodgkin's disease. *Acta Haemat.* 5 (1951), 65
- 24 Storti, E., C. Mauri, T. Artusi, A. Traldi, G. L. Vaccari: Sur l'association de leucémie et de lymphopathie néoplasique de type différent chez le même individu. Contribution clinique. *Europa Medica* 4 (1966), 225
- 25 Tornoyos, K., C. R. Macossay, F. Gyorkey: Chronic lymphocytic leukemia and Hodgkin's disease in the same patient. *Cancer* 20 (1967), 552
- 26 Warthin, A. S.: A case of lymphatic leukemia with histological picture resembling of Hodgkin's disease. *Trans. Ass. Amer. Physicians* 21 (1906), 465
- 27 Warthin, A. S.: Genetic neoplastic relationships of Hodgkin's disease, aleukemic and leukemic lymphoblastoma and mycosis fungoides. *Ann. Surg.* 93 (1931), 153
- 28 Watson, C. J.: Lymphosarcoma and leukosarcoma. In *Handbook of Hematology*, Vol. 4, New York, Hoeber Co., 1938, pages 3049-3106
- 29 Wildhak, R.: Über gleichzeitiges Vorkommen von Leukose und Lymphogranulomatose. *Folia Haemat.* 7 (1963), 303

Dr. Gianni Bonadonna, Dr. Silvio Monfardini, Dr. Federico Pizzetti, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan/Italy, via Venezian 1

"Tell us... About the Lymphatic System" Comment

A. E. Dumont

Lymphology 1, 95 (1968)

A delightful passage in Thomas Mann's masterpiece *The Magic Mountain* has long been destined for the pages of a journal devoted to lymph. How appropriate that the story is set in Davos, only 3 hours by train from the editorial offices of the *Journal of Lymphology* in Zurich.

In response to Hans Castorps request "Tell us about the lymphatic system", the Hof-rat replies (in part) "Lymph is the most refined, the most rarefied, the most intimate of the body juices. It is the juice of juices, the very essence, you understand." Although Thomas Mann considered these words "lively and whimsical", viewed in the light of current knowledge there was little need for apology. The insight reflected by the contents of the entire passage is remarkable.

A vast amount of information about lymph has become available since 1924, the year *The Magic Mountain* was published. Now new knowledge seems to be accumulating at an unprecedented rate and the simple purpose of the *Journal of Lymphology* is to answer the plea for information voiced by young Castorp. Whether or not the *Journal* succeeds depends upon the willingness of a small but growing coterie of investigators to use it for sharing their enthusiasm, interest and results with others.